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Title: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor: a systematic review and economic evaluation

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Declared competing interests of the authors
Anne Fry-Smith was one of the authors of the technology assessment reports compiled to inform the following Technology Appraisals: TA 130 Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis; TA 36 Etanercept and infliximab for the treatment of rheumatoid arthritis. She also formed part of the Evidence Review Group for the STA of tocilizumab for rheumatoid arthritis, 2009.
Dr David Moore and Kinga Malottki are part of the Evidence Review Group for the Single Technology Appraisal of certolizumab pegol for rheumatoid arthritis currently in progress.
Dr Pelham Barton constructed the Birmingham Rheumatoid Arthritis Model (BRAM), which has been used in several NICE technology assessments/appraisals related to rheumatoid arthritis.
Angelos Tsourapas is part of the Evidence Review Group for the STA of tocilizumab for rheumatoid arthritis, 2009.
Dr Paresh Jobanputra has participated in several technology assessments/appraisals related to rheumatoid arthritis as the clinical expert of the assessment group. He works as consultant rheumatologist in a large department of rheumatology. His department has taken part in clinical trials of etanercept, adalimumab, rituximab and tocilizumab. The department receives funding for nurses from Schering Plough to administer infliximab to patients currently being treated with this drug. Currently he is the chief investigator of a clinical trial comparing adalimumab versus etanercept (ISRCTN95861172). He has in the past received support for educational purposes from Wyeth (etanercept), Abbott (adalimumab) and Roche (rituximab). He has also been involved in an advisory board for Roche in relation to tocilizumab and rituximab, and has accepted support from UCB Pharma for the purposes of study leave to attend an American College for Rheumatology in 2009. He has not been involved in any pharmaceutical company submissions to the National Institute of Health & Clinical Excellence and has no stocks or shares in any of these companies. Dr Jobanputra was also part of the Evidence Review Group for the STA of tocilizumab for rheumatoid arthritis in 2009
Dr Martin Connock is part of the Evidence Review Group for the Single Technology Appraisal of tocilizumab and certolizumab pegol for rheumatoid arthritis currently in progress.
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Contributions of authors
Kinga Malottki was the main reviewer on this report and maintained day-to-day running of the review. She participated in study selection, data extraction and analyses. She drafted the following sections: methods, results (template) and edited the report. She conducted the clinical analyses for infliximab, abatacept and comparative studies.
Dr Pelham Barton constructed and revised the Birmingham Rheumatoid Arthritis Model (BRAM), and carried out de novo modelling using the revised BRAM. He wrote the sections of the report relating to modelling and also provided senior support for all economic sections.
Angelos Tsourapas conducted the cost-effectiveness review and critique of manufacturers' submissions.
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Anne Fry-Smith devised and implemented search strategies for bibliographic databases and drafted the searching methods section.
Dr Yen-Fu Chen was the senior reviewer on this report and provided project management and advice on all aspects of the report. He compiled the study protocol, participated in study selection, data extraction and analyses, conducted subgroup analyses, drafted the summary and discussion, and takes responsibility for the whole report.

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1 GLOSSARY AND LIST OF ABBREVIATIONS

GLOSSARY

ACR20 - Defined as a twenty percent improvement in the counts of the number of tender and swollen joints and at least 3 items from the following: observer evaluation of overall disease activity; patient evaluation of overall disease activity; patient evaluation of pain; a score of physical disability; and improvements in blood acute phase responses.

ACR50 - Defined as a fifty percent improvement in the parameters described above.

ACR70 - Defined as a seventy percent improvement in the parameters described above.

ACR-N - ACR-N is a single number that describes the percentage of improvement from baseline a patient experiences, and is derived from the same clinical parameters as the ACR response. Details are provided in Appendix 10.1.

TNF inhibitors - Biological agents that block tumour necrosis factor activity.

Health Assesment Questionnaire (HAQ) - The Health Assessment Questionnaire is designed to assess the physical function of patients. Scores range from 0 (no functional impairment) to 3 (most impaired). Details are provided in Appendix 10.1.

Disease Activity Score (DAS) - Disease Activity Score. The DAS is calculated using a formula which includes counts for tender (53 joints) and swollen joints (44 joints), an evaluation by the patient of general health, and blood acute phase response. Scale 0 (best) to 10 (most active disease).

DAS28 - Disease Activity Score 28, similar to DAS above but using only 28 joints for assessment only. Scale 0 (best) to 10 (most active disease).

List of abbreviations

ABT	abatacept
ACR	American College of Rheumatology
ADA	adalimumab
anti-CCP	anti-cyclic citrullinated peptide
ARRIVE	Abatacept Researched in Rheumatoid Arthritis Patients with an Inadequate anti-TNF response to Validate Effectiveness
ASSURE	Abatacept Study of Safety in Use with other Rheumatoid arthritis thErapies
ATTAIN	Abatacept Trial in Treatment of Anti-TNF INadequate responders
AZA	azathioprine
BCP	biochemical profile
BRAM	Birmingham Rheumatid Arthritis Model
BSRBR	British Society for Rheumatology Biologics Register
CE	cost-effective
CI	confidence interval
CRP	C-reactive protein
CXR	chest X-ray
CyA	ciclosporin
CZP	certolizumab pegol
DAS	disease activity score
DMARD	disease modifying anti-rheumatic drug
ESR	erythrocyte sedimentation rate
ETN	etanercept
EULAR	European League Against Rheumatism
FBC	full blood count
GOL	golimumab
GST	injectable gold
HAQ	Health Assessment Questionnaire
HAQ DI	Health Assessment Questionnaire Disability Index
HCQ	hydroxychloroquine
hrQoL	health related quality of life
IFX	infliximab
i.m.	intramuscular
i.v.	intravenous
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
LEF	leflunomide
LTE	long term extension
MTX	methotrexate
MS	manufacturer's submission
NA	not applicable
NICE	National Institute for Health and Clinical Excellence
NR	not reported

ns	not significant
NSAID	non-steroidal anti-inflammatory drug
OPPOSITE	Open-label, Pilot Protocol of patients with rheumatoid arthritis who Switch to Infliximab after an incomplete response to Etanercept
Pall	palliation
PSA	probabilistic sensitivity analysis
QoL	quality of life
QALY	quality-adjusted life year
RA	rheumatoid arthritis
RCT	randomised controlled trial
RD	risk difference
REFLEX	Randomised Evaluation oF Long-term Efficacy of rituXimab in rheumatoid arthritis
RF	rheumatoid factor
RR	relative risk
RTX	rituximab
SD	standard deviation
SF-36	Short Form 36
SJC	swollen joint count
SUNRISE	Study for Understanding Rituximab Safety and Efficacy
TB	tuberculosis
TJC	tender joint count
TNF	tumour necrosis factor
TOC	tocilizumab
VAS	visual analogue scale

2 EXECUTIVE SUMMARY

2.1 Background

Rheumatoid arthritis is a common inflammatory condition which typically causes a symmetrical chronic arthritis that causes joint pain, swelling and in some cases a systemic illness. The cause of rheumatoid arthritis is unknown but important genetic influences are recognised. The goal of treatment is to achieve remission if patients present with early disease. In later disease key goals are to control pain and inflammation and thereby reduce functional limitations and the risk of permanent joint damage.

Timely use of disease modifying drugs anti-rheumatic drugs (DMARDs) is an essential aspect of contemporary disease management but many patients may not respond even when conventional agents are used optimally. DMARDs are defined by their ability to modify the disease process such that the risk of progressive joint damage is reduced. Biological agents designed to interrupt the inflammatory pathway have proved to be an important advance in the care of rheumatoid arthritis patients. The most widely used agents in the UK are tumor necrosis factor inhibitors (adalimumab, etanercept and infliximab) and a monoclonal antibody targeting B lymphocytes (rituximab). The use of these agents is subject to NICE guidance and all are approved for use provided specific criteria are met. Other agents such as anakinra (an interleukin-1 inhibitor), abatacept (an antibody that targets cellular interactions), and tocilizumab (an interleukin-6 inhibitor) are licensed but currently under assessment or not approved for use by NICE.

This review considers the effectiveness and cost-effectiveness of adalimumab, etanercept, infliximab, rituximab and abatacept when used in patients with rheumatoid arthritis who have tried conventional agents including methotrexate and have failed to improve after trying a first TNF inhibitor.

2.2 Objectives

The objectives of the assessment report are to assess:

- Whether significant differences in clinical and cost-effectiveness exist between adalimumab, etanercept, infliximab, rituximab and abatacept (referred to as ‘the interventions’ hereafter) when used within their licensed indications in adults with

active rheumatoid arthritis who have had an inadequate response to a first TNF inhibitor prescribed according to current NICE guidance.

- Whether the interventions are clinically effective and cost-effective compared to conventional DMARDs (such as methotrexate, sulfasalazine, leflunomide).
- Whether the interventions are clinically effective and cost-effective compared to other biologic agents (including tocilizumab, golimumab, and certolizumab pegol).
- Whether the interventions are clinically effective and cost-effective compared to supportive care.
- Whether the clinical and cost-effectiveness of the interventions differ significantly between certain subgroups of patients.

2.3 Methods

2.3.1 Clinical effectiveness

A systematic review of primary studies (excluding non-randomised studies with less than 20 patients in a treatment arm) of any of the technologies was undertaken. Databases searched included the Cochrane Library, MEDLINE, and EMBASE along with other sources up to July 2009. Further data were obtained from dossiers submitted to NICE by the manufacturers of the technologies. Inclusion decisions, quality assessment and data extraction were undertaken according to predefined criteria. Due to heterogeneity between studies and insufficient data, pooling of results was not undertaken.

2.3.2 Cost-effectiveness

A systematic review of published studies on the costs and cost-effectiveness of the technologies for RA patients who had not responded to a TNF inhibitor, and a review of the dossiers submitted to NICE by the manufacturers of the technologies were undertaken. In addition, model-based economic evaluations of the cost-effectiveness of the technologies from the perspective of the UK National Health Service (NHS) were carried out.

2.4 Results

2.4.1 Clinical effectiveness

Thirty-six studies were included in the systematic review. Five of these were randomised controlled trials (RCTs), three were comparative studies and 28 were uncontrolled studies (including two long term extensions of RCTs). Included RCTs compared one of the technologies to placebo and/or ongoing DMARDs/biologics to which the patients have inadequate response. No head-to-head trials directly comparing the five technologies against each other, or comparing the technologies to other biologics or previously untried DMARDs were identified.

Evidence from RCTs

The effectiveness of rituximab was demonstrated in a good quality RCT (REFLEX). At 6 months significantly more patients treated with rituximab achieved ACR20 (RR=2.85, 95%CI 2.08 to 2.91) and ACR70 (RR=12.14, 95% CI 2.96 to 49.86) compared to those treated with the placebo. Significant differences between groups in favour of rituximab were observed at 6 months for mean change from baseline in DAS28 score (mean difference -1.50, 95% CI -1.74 to -1.26) and mean change from baseline in HAQ score (mean difference -0.30, 95% CI -0.40 to -0.20).

The effectiveness of abatacept was demonstrated in a good quality RCT (ATTAIN). At 6 months significantly more patients treated with abatacept achieved ACR20 (RR=2.56, 95%CI 1.77 to 3.69) and ACR70 (RR=6.70, 95% CI 1.62 to 27.80) compared to those treated with the placebo. Significant differences between groups in favour of abatacept were observed at 6 months for mean change from baseline in DAS28 score (mean difference -1.27, 95% CI -1.62 to -0.93) and mean change from baseline in HAQ score (mean difference -0.34, insufficient data for calculating 95%CI).

One small RCT (OPPOSITE, n=27) compared switching to infliximab versus staying on etanercept in patients who had incomplete response to etanercept. The study population was not well defined and the comparator was considered inappropriate for this assessment. Two additional RCTs evaluated concurrent use of abatacept and TNF inhibitor which is not recommended in its licence. These studies were not further assessed.

Evidence from observational studies

One non-randomised study found greater but not statistically significant improvement in DAS28 for patients switched to rituximab compared to those who switched to an unspecified alternative TNF inhibitor (mean difference -0.35, 95%CI -0.71 to 0.01). Another prospective cohort from the British Society for Rheumatology Biologics Register showed significantly greater reduction in HAQ score for patients who switched to an unspecified alternative TNF inhibitor compared to switching to non-biologic DMARDs. Twenty-eight uncontrolled studies observed significant improvement in various measures of effectiveness compared to before switching in patients who switched to adalimumab, etanercept or infliximab after discontinued previous TNF inhibitor(s) for various reasons including lack of efficacy, adverse events and other reasons.

Subgroup analyses

Evidence from the REFLEX trial suggested that the effectiveness of rituximab does not vary significantly according to reasons of withdrawal, baseline rheumatoid factor status and number of prior TNF inhibitors tried (one vs. more than one).

No significant differences in the effectiveness of abatacept between subgroups defined by the number of prior TNF inhibitor (one vs two) and the identity of the prior TNF inhibitor received (etanercept vs infliximab) were observed in the ATTAIN trial. Some of these subgroup analyses however may be under-powered.

Evidence from observational studies showed that the proportion of patients responding to a subsequent TNF inhibitor may vary according to reason of withdrawal of the previous TNF inhibitor (higher response in patients who withdrew due to intolerance/adverse events compared to those withdrew due to lack of efficacy). The proportion of patients who respond to a subsequent treatment (including TNF inhibitors, rituximab and abatacept) decreases as the number of prior TNF inhibitor(s) that the patients have tried increases.

2.4.2 Cost-effectiveness

2.4.2.1. Systematic review

Four studies were included in the systematic review. Two studies evaluated abatacept and two rituximab. One of the rituximab studies was UK based. All but one studies carried out a cost-utility analysis and reported results in 'cost per QALY'. One study carried out a cost-effectiveness analysis and reported results in cost per additional case of 'low disease-activity state gained (DAS28<2.6) and cost per additional remission gained (DAS28≤3.2). All studies used a decision-analytic model.

Models varied in some important aspects: the type of model used, the sequence of drugs, comparator therapies, and time-horizon. There was disparity in the selection of perspectives chosen for the analyses. One study reported costs that include both those from a healthcare perspective as well as indirect costs and costs of informal care; inclusion of these costs improves the cost-effectiveness of the drug.

A direct comparison of ICERs between studies was not possible because of different approaches to modelling, in particular time-horizon, country of origin and perspective chosen.

2.4.2.2. Independent economic assessment

In the reference case all biologic agents were compared with a newly initiated DMARD and against each other. Compared to DMARDs the ICERs were: £34,300 (per QALY) for adalimumab, £38,800 for etanercept, £36,200 for infliximab, £21,200 for rituximab, and £38,600 for abatacept. Rituximab dominates the TNF inhibitors and the ICER for abatacept compared to rituximab is over £100,000/QALY. These results are subject to considerable uncertainty. Important drivers of that uncertainty were found in the scenario analysis to include the assumptions about HAQ progression on biologic treatments, the equation relating HAQ to quality of life, and for comparisons involving rituximab, the assumed time between treatments. The inclusion of adverse event costs for biologic therapy made little difference to the results.

2.5 Discussion

The limitations predominantly relate to factors outside of the control of the Assessment Group. The major limitation of the assessment was the paucity of evidence from RCTs for assessing the clinical effectiveness of the three TNF inhibitors, and a complete absence of genuine head-to head-trials comparing the five technologies against each other, against other biologics or against newly initiated, previously untried DMARDs. Many observational studies were identified. Data from these studies can be confounded by many factors such as patients' baseline disease activity, past history of therapy, and methods of selecting and following up patients and analysis of data. Pooling of data was not performed due to heterogeneity between studies on these respects.

2.6 Conclusions

There is lack of good quality evidence directly comparing the effectiveness of the five technologies against each other. This imposes significant uncertainties with regard to any assessment of their relative cost-effectiveness. Adjusted indirect comparison suggests there is no significant difference in the effectiveness between rituximab and abatacept, both of which are supported by good quality RCT evidence. Existing data do not allow reliable quantification of the effectiveness of TNF inhibitors compared to rituximab and abatacept. Independent modelling comparing each of the other four technologies to rituximab (recommended in current NICE guidance) suggests rituximab dominating adalimumab, etanercept and infliximab, and an estimated ICER of £131,000 (per QALY) for abatacept compared to rituximab.

There is lack of evidence comparing the effectiveness of the five technologies to a newly initiated, previously untried DMARDs. Independent modelling based on certain assumptions suggest the following ICERs: £34,300 (per QALY) for adalimumab, £38,800 for etanercept, £36,200 for infliximab, £21,200 for rituximab, and £38,600 for abatacept.

There is lack of evidence directly comparing the effectiveness of the five technologies to other biologic agents.

Good quality evidence from RCTs suggests rituximab and abatacept are more effective compared to supportive care (including ongoing DMARDs which had provided inadequate control of the disease). Data from observational studies suggest the use of an alternative TNF inhibitor after patients had inadequate response to a first TNF inhibitor may offer some

benefit, but there remain significant uncertainties with regard to the magnitude of treatment effects and how these translate into cost-effectiveness.

3 BACKGROUND

Summary

Rheumatoid arthritis is a common inflammatory condition which typically causes a symmetrical chronic arthritis that causes joint pain, swelling and in some cases a systemic illness. The cause of rheumatoid arthritis is unknown but important genetic influences are recognised. The goal of treatment is to achieve remission if patients present with early disease. In later disease key goals are to control pain and inflammation and thereby reduce functional limitations and the risk of permanent joint damage.

Timely use of disease modifying drugs anti-rheumatic drugs (DMARDs) is an essential aspect of contemporary disease management but many patients may not respond even when conventional agents are used optimally. DMARDs are defined by their ability to modify the disease process such that the risk of progressive joint damage is reduced. Biological agents designed to interrupt the inflammatory pathway have proved to be an important advance in the care of rheumatoid arthritis patients. The most widely used agents in the UK are tumor necrosis factor inhibitors (adalimumab, etanercept and infliximab) and a monoclonal antibody targeting B lymphocytes (rituximab). The use of these agents is subject to NICE guidance and all are approved for use provided specific criteria are met. Other agents such as anakinra (an interleukin-1 inhibitor), abatacept (an antibody that targets cellular interactions), and tocilizumab (an interleukin-6 inhibitor) are licensed but currently not approved for use by NICE.

This review considers the effectiveness and cost-effectiveness of adalimumab, etanercept, infliximab, rituximab and abatacept when used in patients with rheumatoid arthritis who have tried conventional agents including methotrexate and have failed to improve after trying a first TNF inhibitor.

3.1 Description of underlying health problem

3.1.1 Clinical features of rheumatoid arthritis

Rheumatoid arthritis (RA) typically begins in middle age and more commonly afflicts women than men. Pathologically the disease is characterised by an inflammatory reaction and

increased cellularity of the lining layer of synovial joints. Joints such as the proximal interphalangeal joints, meta-carpophalangeal joints, wrists, elbows, cervical spinal joints, knees, ankle and foot joints are commonly affected. Affected joints become stiff after periods of inactivity, for example in the morning, become swollen and are variably painful. Other organ systems may also be affected. Patients commonly experience fatigue and blood abnormalities such as anaemia and a raised platelet count. Weight loss, lymph node enlargement, lung diseases (such as pleurisy, pleural fluid, and alveolitis), pericarditis, vascular inflammation (vasculitis), skin nodules, and eye diseases (reduced tear production or inflammation) may also occur.

The severity of disease, its clinical course and individual responses to treatment vary greatly. Symptoms of RA may develop within days or evolve over many weeks and months.[1] Several distinct patterns of joint disease are recognised including: predominantly small or medium joint disease; predominantly large joint disease; flitting or transient attacks of joint pain (palindromic rheumatism); pain and stiffness of the shoulder and pelvic girdles (polymyalgic disease); and disease associated with weight loss and fever (systemic onset); or any combination of these. Pain and disability, in early RA, is linked to disease severity and to measures of psychological distress.[2] Disease progression can be relentless or punctuated by partial or complete remissions of variable and unpredictable intervals.

3.1.2 Diagnosis of rheumatoid arthritis

RA is diagnosed from a constellation of clinical, laboratory and radiographic abnormalities. Diagnosis may be obvious or may need specialist assessment or a period of clinical observation. Internationally agreed classification criteria for RA are used widely in contemporary research studies[3] but it is widely acknowledged that current criteria need to be revised. Current criteria include morning stiffness in joints exceeding 1 hour, physician observed arthritis of 3 or more areas, arthritis involving hand joints, symmetrical arthritis, rheumatoid skin nodules, a positive blood test for rheumatoid factor and radiographic changes typical of rheumatoid disease. Such criteria have limited utility in routine practice and most clinicians diagnose RA without reference to them as many patients do not meet formal disease classification criteria early in their disease.[4]

3.1.3 Epidemiology

RA affects around 0.5% to 1% of the population, three times as many women as men, and has a peak age of onset between the ages of 40 and 70. Prevalence of disease at age 65 is six times

that at age 25. Recent estimates from England and Wales show an annual incidence of 31 per 100,000 women and 13 per 100,000 men, suggesting a decline in recent decades and a prevalence of 1.2% in women and 0.4% in men.[5] The National Audit Office (NAO) estimates that around 580,000 people have RA in England and that 26,000 patients are diagnosed each year.[6]

3.1.4 Aetiology

A specific cause for RA has not been identified. There appear to be many contributing factors including genetic and environmental influences. Genetic influence is estimated at 50 to 60%.[7] The occurrence of RA in both of a pair of monozygotic twins is 12% to 15% and a family history of RA gives an individual a risk ratio of 1.6, compared with the expected population rate.[8] Many of the genes associated with susceptibility to RA are concerned with immune regulation. For example the human leukocyte antigen HLA-DRB1, which contributes the greatest risk and PTPN22, which makes the second most important genetic contribution in Caucasian populations, are both involved in T lymphocyte activation and signalling.[9,10]

Infectious agents have been suspected but no consistent relationship with an infective agent has been shown. Sex hormones have also been suspected because of the higher prevalence of RA in women and a tendency for disease to improve in pregnancy. However, a precise relationship has not been identified. A causal link with lifestyle factors such as diet, occupation, or smoking has not been shown.

3.1.5 Pathology

Synovial joints occur where the ends of two bones, covered with hyaline cartilage, meet in a region where free movement is desirable. This joint space is encapsulated by a fibrous capsule lined, on the inside, by a synovial membrane; which functions to secrete fluid to lubricate and nourish hyaline cartilage. In RA the synovial layer of affected joints becomes enlarged due to increased cellularity, or hyperplasia, infiltration by white blood cells and formation of new blood vessels. This is accompanied by increased fluid in the joint cavity which contains white blood cells and a high level of protein (an exudate) contributing to the joint swelling. Bony erosions of cartilage and bone occur where synovial tissue meets cartilage and bone. This occurs through the combined actions of synovial tissue (pannus) and resident cartilage and bone cells. Erosions, and loss of cartilage, are rarely reversible. Such damage therefore compromises the structure and function of a normal joint.

3.1.6 Pathogenesis & Biological Targets in Rheumatoid Arthritis

A detailed discussion of the pathogenesis of RA is beyond the scope of this report. This subject is reviewed comprehensively elsewhere.[11-13] The synovial membrane in rheumatoid arthritis contains activated immune cells such as B and T lymphocytes and macrophages. These cells accumulate in synovial tissue. Cells resident in normal joints including synovial fibroblasts, cartilage cells (chondrocytes) and bone cells (osteoclasts) are also activated. Different cytokines, or small proteins, are produced by particular resident and infiltrating cells and aid intercellular communication and influence cellular and tissue behaviour.

A number of cytokines involved in this inflammatory cascade are seen as potential targets for intervention in RA. Drugs that target cytokines, and which are licensed or at a late stage of development currently, include: anakinra (directed against interleukin-1); tocilizumab (targeting interleukin-6); and tumor necrosis factor inhibitors (including adalimumab, certolizumab, etanercept, golimumab and infliximab). Other agents include: abatacept (also known as CTLA4Ig) which interferes with T cell activation and rituximab which depletes B lymphocytes. Many other potential targets have been identified and a number of novel agents are in clinical trials.[14]

3.1.7 Management of rheumatoid arthritis

The current management of RA is described in detail in a recent NICE guideline.[15] An exhaustive review of management is not provided here. We focus on aspects of disease management that are relevant to the decision problem in this appraisal.

NSAIDs and analgesics are commonly used for symptom relief in RA. These drugs do not modify the disease process and key recommendations in NICE guidance centre on minimising use of NSAIDs because of the potential toxicity of these agents. Corticosteroids are used widely and in a variety of ways. High doses given orally or parenterally (by a variety of routes) are used for short term control of disease whilst waiting for the effects of DMARDs. Low dose glucocorticoids are also used commonly either as sole therapy or in combination with DMARDs. Low dose glucocorticoids have important disease modifying effects in rheumatoid arthritis.[16]

DMARDs may be divided into conventional DMARDS which include: azathioprine, ciclosporin A, gold (given by intra-muscular injection), hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine[17-19] and newer targeted biological agents described below. Conventional DMARDs such as penicillamine are now used rarely.[20] Conventional DMARDs

may be used in combination especially where there is a poor response to a single DMARD. For example in early disease methotrexate is commonly combined with sulfasalazine and hydroxychloroquine. There are few direct comparisons of individual DMARDs in early disease but methotrexate is regarded as the standard against which other drugs should be compared. Most conventional DMARDs have specific dosing and monitoring schedules which require regular visits to a health care facility and blood tests. How this is managed varies greatly in the UK for example in some centres all patients are seen in hospital clinics for drug monitoring whilst in others this occurs largely in the community.

The key objective in early RA management is to achieve remission. Many patients with early inflammatory arthritis (which often does not meet international classification criteria for RA) are able to achieve remission and treatment may be withdrawn in a proportion without relapse.[21] This occurs in randomised trials or therapeutic studies with conventional DMARDs[22-25] used as monotherapy or in combination, conventional DMARDs combined with TNF inhibitors and also in observational studies. Whilst these reports focus on the excellent outcomes achieved it is important to recall that 57% of patients with early RA treated with a protocol designed to minimise disease do not achieve remission, around a third do not achieve their treatment goal and between 31-54% of patients have progressive joint damage depending on the treatment strategy after 4 years of treatment.[26]

NICE RA guidance recommends the use of methotrexate combined with another DMARD and corticosteroids (used short-term) for disease control in early severe RA. Practice varies however and evidence for combining DMARDs is limited and controversial.[27-29] Not all rheumatologists accept the need for DMARD combinations. Some prefer to step-up therapy by adding another DMARD to methotrexate if disease is inadequately controlled and others choose to replace the first DMARD with a second drug.[30] A necessity for long term use of multiple medications plainly requires an open dialogue and shared decision making between patients and health professions[31] especially where expert opinion differs.

In England and Wales patients who have failed to respond to (or tolerate) at least two DMARDs including methotrexate at optimal doses are eligible to TNF inhibitors subject to NICE guidance. Patients who do not respond to TNF inhibitors may be treated with rituximab a monoclonal antibody which depletes B lymphocytes. Other biological therapies such as anakinra, abatacept and tocilizumab are not currently approved for use by NICE. The relevant NICE guidance concerned with biologic therapies is described briefly below (see Current Service Provision).

Controlling symptoms of joint pain and stiffness, minimising loss of function, improving quality of life and reducing the risk of disability associated with joint damage and deformity are central objectives in the management of RA at all stages. These objectives are not met with drug therapy alone: patients often need advice and support from a multi-disciplinary team including specialist nurses, podiatrists, physiotherapists and occupational therapists. Since RA is a heterogeneous disease, which may vary over time, a long-term plan with regular clinical evaluation to assess disease status, disease complications, co-morbidity, patient preferences and psychosocial factors is essential and is aided by well informed and satisfied patients and carers.[32,33] Indeed a key element of a Scottish trial reporting excellent outcomes was frequent specialist review with a focus on tight disease control.[22]

With advanced joint damage surgical intervention such as joint replacement arthroplasty, joint fusion or osteotomy may be necessary. Long-term observations show that around a quarter of patients with RA undergo a total joint arthroplasty.[34] It cannot, of course, be assumed that all such surgery is directly attributable to RA, especially as osteoarthritis is the most prevalent form of arthritis. Other surgical interventions such as removal of synovial tissues and rheumatoid nodules, peripheral nerve decompression (such as in carpal tunnel syndrome), or soft tissue procedures such as tendon release or repair may be necessary at any stage of disease.

3.1.8 Assessment of Response to DMARDs & Biologic Therapies

3.1.8.1. ACR Response Criteria

Modern clinical trials rely on composite endpoints such as the American College for Rheumatology (ACR) definition of improvement and the disease activity score (DAS). The ACR response requires an improvement in counts of the number of tender and swollen joints (using designated joints) and at least 3 items from the following: observer evaluation of overall disease activity; patient evaluation of overall disease activity; patient evaluation of pain; a score of physical disability (such as the health assessment questionnaire (HAQ) – see below); and improvements in blood acute phase responses (e.g. ESR or CRP).

Response is defined as ACR20, ACR50 or ACR70 where figures refer to percentage improvement of these clinical measures. This creates a dichotomous outcome of responders and non-responders. Achieving an ACR20 response has been regarded as a low hurdle but in clinical practice patients who achieve this hurdle often gain a worthwhile clinical response, especially in early RA. ACR response criteria are described in more detail in Appendix 10.1.

3.1.8.2. DAS Response Criteria

The DAS score is calculated using a formula that includes counts for tender and swollen joints, an evaluation by the patient of general health (on a scale of 0 to 100), and blood acute phase (usually a log of the ESR, but more recently using CRP). DAS response criteria are described in more detail in Appendix 10.1. Originally DAS was based on an assessment of 53 joints for tenderness and 44 joints for swelling. DAS28, based on an evaluation of 28 joints, is used widely in routine clinical practice, partly as a result of NICE guidance on use of TNF inhibitors. DAS28, like DAS, is a continuous scale with a theoretical range from 0 to 10. Thresholds have been suggested for the scale such that a score greater than 5.1 is regarded as indicating high disease activity, a score of less than 3.2 low disease activity and a score of less than 2.6 remission.[35,36] Achieving a DAS28 score of $\leq$3.2 and improving the score by >1.2 is regarded to be a good response whilst achieving a score of $\leq$3.2 and improving by >0.6 but less than 1.2, a moderate response. Current NICE guidance for TNF inhibitors demands that patients should improve DAS28 by 1.2 in order to justify continuing treatment. It has been suggested that NICE guidance should be altered to allow patients who have attained a moderate response to continue treatment with a TNF inhibitor.[37]

Whilst DAS28 scores are a very valuable tool for assessing treatment responses in groups of patients, scores have important limitations when used for individual patient decisions. For example, DAS28 does not incorporate ankle and foot disease. Thus a patient with disease localised here may not attain a sufficiently high score to be eligible for a TNF inhibitor. DAS28 also shows poor concordance with clinical judgment (based on a wide range of parameters).[38] In addition, the degree of measurement error in a test-retest reliability study indicates that the faith placed in DAS28 as the sole decision making tool is misplaced.[39] For example, the smallest detectable difference, which should be exceeded if a clinician is to be 95% confident that a change exceeds measurement variability, was 1.32 for DAS28.

3.1.8.3. The Health Assessment Questionnaire (HAQ)

The HAQ is a family of questionnaires designed to assess functional capacity of patients.[40] The most widely used version of HAQ is the modified HAQ (MHAQ) score which comprises eight items such as an ability to dress, get in and out of bed, lift a cup, walk outdoors and wash. MHAQ is reported as an average score across the eight categories such that 0 indicates an ability to achieve tasks without difficulty and 3 reflects an inability to achieve tasks. Scores therefore range between 0 and 3 with an interval of 0.125. Low scores indicate better function. Care in needed in the interpretation of HAQ scores in published studies because

there are several modifications to HAQ. The HAQ score is described in more detail in Appendix 10.1.

3.1.8.4. Radiographic Measures

Radiographic outcomes are believed by many to be the most important outcome measure in RA. However variation in joint inflammation has a more profound and immediate impact on disability compared with the slow and cumulative effect of radiographic damage on disability.[41] The most commonly used tools for assessing joint damage are the Sharp and Larsen methods and their modifications (see Appendix 10.1) which rely on evaluations of plain radiographs of hands and feet. Plain radiographs are rather insensitive to change but are cheap and widely available. A majority of patients show only mild or no progression on plain radiographs over periods of 1 to 2 years, highlighting one of their limitations in modern clinical trials.[42]

3.1.9 Prognosis

The impact of RA on an individual can be viewed from a variety of perspectives including employment status, economic costs to the individual or society, quality of life, physical disability, life expectancy, and medical complications such as extra-articular disease and joint deformity, radiographic damage or the need for surgery. In general, persistent disease activity is associated with poorer outcomes, although in the first five years of disease physical function is especially labile. Greater physical disability at presentation is associated with greater disability later in disease. Other factors linked with poorer function include older age at presentation, the presence of rheumatoid nodules, female sex, psychological distress, and degree of joint tenderness.[43] Continued employment is related to type of work and other aspects of the workplace such as pace of work, physical environment, physical function, education and psychological status: work disability is not necessarily linked to measures of disease activity.[44,45] Radiographic damage in RA joints is also influenced by rheumatoid factor status, age, disease duration and extent of disease and perhaps genetic factors.

Life expectancy in RA is reduced and is related to age, disability, disease severity, comorbidity and rheumatoid factor status, in particular.[46-49] For example, a 50-year old woman with RA is expected to live for 4 years less than one without RA.[50] Patients with RA have a significantly increased risk of ischaemic heart disease. Heart disease is the principal reason for an approximately 60% increased mortality risk in RA.[51] However other factors such as infection associated with aspects such as co-morbidity including lung disease, extra-

ariticular manifestations of disease, reduced white cell count and corticosteroid use also contribute.[52,53]

3.1.10 Burden of illness

Early in disease indirect costs exceed costs due to health care utilisation and medication (direct costs), by two-fold.[54] It is also clear that informal caregivers shoulder a considerable burden in terms of foregone paid employment, leisure activity and personal health.[55] Inevitably, in a disease characterised by chronic pain, discomfort and physical impairment, the burden on individuals and families is increased. Medication costs, especially in those treated with biologic agents such as TNF inhibitors, account for a majority of the direct costs of RA.[56] Some drug intervention studies have shown reduced work absence with aggressive treatment strategies[57] although only a third of employed patients cease because of disease and, unsurprisingly, manual workers are much more likely to stop work.[58] It is estimated that the total costs of rheumatoid arthritis to the UK economy is between £3.8 to 4.8 billion.[6]

3.2 Current service provision

Services for patients with RA have been reviewed in detail by the National Audit Office (NAO) in a recent report.[6] Diagnosis and management of RA is led primarily by consultant rheumatologists employed by acute hospital trusts. People who may have RA often seek help late and may suffer due to delayed treatment and referral. There are around 460 consultant rheumatologists in England giving a ratio of 1:100000 rheumatologists per head of population (the ratio in Wales is 1:106000). Consultants are supported by specialist nurses and the NAO census identified 377 specialist rheumatology nurses in England. Considerable variations and deficiencies in service provision were identified by the NAO. Specific recommendations for improving services were made by the NAO in the following areas:

- Timely diagnosis and treatment
- Better integration between primary and secondary care services
- Improved holistic care including strategies to improve self-management and providing support for maintaining employment

3.3 Description of the technologies

Five intervention technologies are considered in this report. Three are TNF inhibitors (adalimumab, etanercept and infliximab), and one each a T-cell co-stimulation modulator (abatacept) and a selective CD20 B-cell depleting agent (rituximab). The technologies are described below. Licensed indications and relevant NICE guidance are detailed in Table 1.

Table 1 EU Licensed indications related to RA for the five technologies and relevant NICE Guidance

Drug	Indications &Population	Doses & Routes of Administration	Synopsis of Relevant NICE guidance
Abatacept	Moderate to severe RA – in combination with MTX. Patients with insufficient response to DMARDs including at least one TNF inhibitor.	Intravenous infusion over 30 minutes. Dose according to weight, range 500 mg to 1000 mg. Infusions at time 0, 2 and 4 weeks followed by 4-weekly maintenance infusions indefinitely.	TA141 Not recommended
Adalimumab	Moderate to severe RA – in combination with MTX (unless MTX inappropriate). Patients with insufficient response to DMARDs including MTX.	Subcutaneous injection of 40 mg every other week indefinitely. Dose may be increased to 40 mg weekly if patients experience a decrease in their response (monotherapy).	TA130 & TA36 DAS28 score of >5.1 measured on at least two occasions, 1 month apart. Previous trial of 2 DMARDs including MTX (unless contraindicated) necessary. Normally used in combination with MTX - unless intolerant or inappropriate when monotherapy with adalimumab and etanercept may be given. Only continue after 6 months if DAS28 improves by >1.2. Alternative TNF inhibitor may be considered if treatment is withdrawn due to an adverse effect before the initial 6-month assessment of efficacy. Dose escalation above licensed starting dose is not recommended. TA36 does not recommend the consecutive use of TNF inhibitors. This recommendation is not reproduced in the NICE RA guideline. TA130 does not report on consecutive use.
Etanercept	Moderate to severe RA – monotherapy or in combination with MTX in those with an inadequate response to DMARDs. Patients with severe RA not previously treated with MTX may also be treated.	Subcutaneous injection of 25 mg twice a week or 50 mg weekly given indefinitely.	
Infliximab	Moderate to severe RA – in combination with MTX (unless contraindicated) in those with an inadequate response to DMARDs. Patients with severe RA not previously treated with MTX or other DMARDs may also be treated.	Intravenous infusion over 2 hours at a dose of 3 mg/kg at time 0, 2 and 6 weeks followed by 8-weeky maintenance infusions indefinitely. If response lost or inadequate step-wise increases in dose by 1.5 mg/kg every 8 weeks may given up to a maximum of 7.5 mg/kg. Alternatively, dosing at 3 mg/kg may be given as frequently as 4-weekly.	
Rituximab	Severe RA in combination with MTX in patients who have had an inadequate response or intolerance to other DMARDs including one or more TNF inhibitor.	Intravenous infusion given as a course of two infusions (1 gm each) two weeks apart. Further infusions may be given but a precise limit is not given. Repeat course of treatment must not be given within 16 weeks.	TA126 Use in combination with MTX in severe RA not responding to DMARDs including at least one TNF inhibitor. Continue only if DAS28 improves by >1.2 Repeat courses to be given no more frequently than every 6 months.

3.3.1 TNF inhibitors

3.3.1.1. Adalimumab (Humira® Abbott Laboratories)

Adalimumab is a recombinant monoclonal antibody, made from human peptide sequences, which neutralises the biological functions of TNFα by binding to TNF cell surface receptors. Adalimumab is licensed for use in RA, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease.

3.3.1.2. Etanercept (Enbrel®, Wyeth Laboratories)

Etanercept is a combination protein consisting of the extracellular portion of two TNFα receptors (75kd-TNF receptors) combined with a human Fc portion of human IgG1. Etanercept inhibits TNFα activity by binding soluble and cell-bound TNFα with high affinity and by competing with natural TNFα receptors. Etanercept is licensed for use in RA, psoriatic arthritis, psoriasis and ankylosing spondylitis.

3.3.1.3. Infliximab (Remicade®, Schering-Plough)

Infliximab is a recombinant chimeric human-murine monoclonal antibody that binds soluble and membrane bound TNFα thereby inhibiting the functions of TNFα. Infliximab is licensed for use in RA, Crohn's disease, ulcerative colitis, ankylosing spondylitis , psoriatic arthritis and psoriasis.

3.3.1.4. Other TNF inhibitors

Certolizumab pegol (Cimzia®, UCB) has been granted a marketing authorisation in the EU for the treatment of moderate to severe RA. It is administered by subcutaneous injection. Certolizumab pegol is currently the subject of a NICE Single Technology Appraisal with guidance expected in 2010. Golimumab (Simponi®, Schering Plough) is currently being assessed by the EMEA. A positive opinion has been given for the granting of marketing authorisation in RA. Golimumab has been referred to NICE but the appraisal has been suspended because the manufacturer was not in a position to submit evidence to NICE.

3.3.1.5. Special precautions for use of TNF inhibitors

TNFα is a key component of host defence against *M tuberculosis,* especially by forming granulomas and preventing dissemination of mycobacteria.[59,60] Inhibition of TNFα increases the risk of *M tuberculosis* and other granulomatous diseases such as *Listeria monocytogenes* (a bacterium associated with food borne diseases) and *Histoplasma capsulatum* (a fungus which, in endemic areas, causes lung disease in people with a compromised immune system). Recommendations for screening patients for TB before treatment have been published.[61] In the UK this is done most commonly by taking a medical history focusing on tuberculosis and a pre-treatment chest X-ray. Some centres also perform a tuberculin skin test[62] although interpretation of such tests is complicated by the UK's previous vaccination programme for TB prevention and also the fact that many patients with RA respond poorly to tuberculin (possibly due to current immunosuppressive therapy but also due to the disease).[63]

Routine monitoring of blood tests is not necessary for patients taking TNF inhibitors but is needed for concomitantly used DMARDs such as methotrexate. TNF inhibitors can induce anti-nuclear and anti double-stranded DNA antibodies in the blood of some patients treated with TNF inhibitors. These antibodies are associated with systemic lupus erythematosis (SLE), a potentially serious rheumatic disease. Cases of drug-induced SLE have been reported with TNF inhibitors, but are rare.[64]

3.3.2 Other Technologies

3.3.2.1. Rituximab (MabThera®, Roche)

Rituximab is a chimeric monoclonal antibody which binds the CD20 cell surface marker found on B lymphocytes and depletes these cells. CD20 occurs on normal and malignant B lymphocytes (as in non-Hodgkin's lymphomas). Normal plasma cells, an important component of host defence, and haematopoietic stem cells do not carry CD20. Rituximab is licensed for use in rheumatoid arthritis, non-Hodgkin lymphoma and chronic lymphocytic leukaemia.

3.3.2.2. Abatacept (Orencia®, Bristol-Myers Squibb)

Abatacept is a fusion protein consisting of CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) linked to a modified Fc portion of human IgG1. Abatacept works by blocking

activation of certain populations of T lymphocytes. Abatacept is currently only licensed for use in rheumatoid arthritis.

3.3.2.3. Tocilizumab (RoActemra®, Roche)

Tocilizumab is currently the subject of a NICE Single Technology Appraisal with guidance expected in 2010. This guidance is likely to have a key impact on the treatment pathways considered in this review. Tocilizumab is a humanised monoclonal antibody that inhibits the activity of the cytokine interleukin-6 (IL-6). In the EU it is only licensed for use in moderate to severe rheumatoid arthritis patients who are intolerant, or have responded inadequately, to one or more DMARDs or TNF inhibitors. The drug is recommended for use in combination with methotrexate but may be used alone in patients intolerant of methotrexate or for whom it is contraindicated. Toculizumab is given by intravenous infusion over one hour once a month indefinitely.

3.3.3 DMARDs, Biologics, Treatment Sequences & Combinations

RA is characterised, in many patients, by an excellent initial response to a DMARD with subsequent loss of response with time. Most randomised trials are of a relatively short duration (typically less than 12 months) and do not study a treatment pathway. Trials of DMARDs sequences are increasingly common.[26,65,66] Remission is possible in early disease with methotrexate alone or in combination with other agents such as sulfasalazine, hydroxychloroquine, ciclosporin and TNF inhibitors. The optimal sequence is yet to be determined, and perhaps the choice of drug is not relevant, but the key to successful management appears to be regular patient review with a focus on optimal disease control.

NICE RA guidance is consistent with this approach although recent trials indicate that early use of methotrexate in combination with a TNF inhibitor provides better outcomes.[26,67] NICE recommends that TNF inhibitors are only used in those not responding to methotrexate and another DMARD. Delayed addition of a TNF inhibitor need not necessarily compromise medium term outcomes[24,26,67] and may be justified on health economic grounds.

What steps should be taken when a first TNF inhibitor and several DMARDs including methotrexate fail? This technology assessment report sets out to examine clinical and cost-effectiveness evidence from available randomised controlled trials, observational studies and economic evaluations. A small survey conducted as part of this technology assessment on a convenience sample of consultant rheumatologists in the West Midlands indicated

considerable variability in approach for patients who fail a first TNF inhibitor. The most common suggested approaches were to consider a second TNF inhibitor or rituximab (in combination with methotrexate). Further details of this survey can be found in Appendix 10.11.

There are many and increasing permutations of treatment sequences. Combinations of biologic agents are not licensed and where combinations have been tried there is an increased risk of serious infections. Potential drug toxicity of newly licensed agents is an important unknown. Other considerations include practical matters to do with drug delivery such as intravenous or subcutaneous administration and availability of infusion facilities. Patients with RA tend to be risk averse[68] and strategies mandating targeted disease control in late 'stable' RA are commonly resisted by doctors and patients.[69] However in those with active and progressive disease new therapies are needed. This review seeks to explore some aspects of these uncertainties as determined by a protocol agreed with NICE and interested parties.

3.4 Degree of Diffusion & Anticipated Costs

The number of RA patients currently being treated with TNF inhibitors is unknown. By July 2009, 12,626 patients who started treatment with a TNFα inhibitor were registered with the British Society for Rheumatology Biologics Registry (BSRBR). This register has stopped recruiting patients with RA starting adalimumab, etanercept and infliximab. So far 2876 (23%) have ceased taking the first prescribed TNFα inhibitor and switched to a second TNFα inhibitor (1881 switched due to lack of efficacy and 995 due to an adverse event). Of these the mean and maximum observed duration of treatment with a second TNFα are currently 18 months and 64 months respectively. By August 2009 the BSRBR had registered 442 patients treated with rituximab from a target of 1100.[70]

The drug costs of biologic agents are similar for the agents given by subcutaneous injection at around £9K per annum. Costs of intravenously administered drugs vary depending on patient weight and frequency of treatments courses (with rituximab). Likely drug costs for these agents range between £7K and £10K per annum.

4 DEFINITION OF THE DECISION PROBLEM

4.1 Decision problems

According to the final scope issued by the National Institute for Health and Clinical Excellence (NICE) for this technology appraisal, the decisions to be made are:

Decision problem 1: Whether there are significant differences in clinical and cost-effectiveness between adalimumab, etanercept, infliximab, rituximab and abatacept (referred to as 'the interventions' hereafter), when used within their licensed indications in adults with active rheumatoid arthritis who have had an inadequate response to a first TNF inhibitor prescribed according to current NICE guidance.

Decision problem 2: Whether the interventions are clinically effective and cost-effective compared to conventional DMARDs (such as methotrexate, sulfasalazine, leflunomide, ciclosporin A).

Decision problem 3: Whether the interventions are clinically effective and cost-effective compared to other biologic agents (including tocilizumab, golimumab, and certolizumab pegol).

Decision problem 4: Whether the interventions are clinically effective and cost-effective compared to supportive care.

Decision problem 5. Whether the clinical and cost-effectiveness of the interventions differ significantly between certain subgroups of patients (see section 4.2).

The assessment report set out to address these decision problems as they apply to potential patient pathways in the UK. The nature of evidence and the timelines for this technology appraisal constrain the focus of the assessment report to key clinically relevant questions.

4.2 Definition of the interventions

The interventions being considered are:

Adalimumab (Humira®, Abbott Laboratories), a TNF inhibitor, administered by subcutaneous injection and usually prescribed in combination with methotrexate, except in cases where methotrexate is not tolerated or contraindicated.

Etanercept (Enbrel®, Wyeth Pharmaceuticals), a TNF inhibitor, administered by subcutaneous injection in combination with methotrexate, except in cases where methotrexate is not tolerated or contraindicated.

Infliximab (Remicade®, Schering-Plough), a TNF inhibitor, administered by intravenous infusion in combination with methotrexate.

Rituximab (MabThera®, Roche Products), a monoclonal antibody directed at CD20+ B cells, administered by intravenous infusion in combination methotrexate.

Abatacept (Orencia®, Bristol-Myers Squibb), a T-cell co-stimulation modulator, administered by intravenous infusion in combination with methotrexate.

4.3 Population and relevant subgroups

The population being considered is adults with active rheumatoid arthritis who have had an inadequate response to a first TNF inhibitor.

Potentially relevant subgroups are numerous and include:

- Patients having had primary or secondary (had initial response but subsequently lost the response over time) failure of response to the first TNF inhibitor or having withdrawn from the first TNF inhibitor mainly due to adverse effects;
- Subgroups defined by auto-antibody status (e.g. presence or absence of rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies);
- Subgroups defined by different doses of the intervention (within licence);
- Patients with co-morbidities for which some treatments may be contraindicated (e.g. heart failure).

The specific subgroups examined in the effectiveness review of this report were determined in light of available evidence and in consultation with clinical experts. Subgroups were not considered in economic modelling as compelling evidence of differential effectiveness between subgroups was lacking from the effectiveness review.

Clarification of population of interest

NICE guidance states that an alternative (second) TNF inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial 6-month assessment of efficacy. This group of patients (withdrawal due to an early adverse event) is strictly speaking outside the remit of this technology appraisal and should ideally be excluded from the technology assessment. However in practice the reason for the withdrawal of a TNF inhibitor may not be clear-cut since a decision to withdraw may be related to both efficacy and adverse effects (and the balance of risk and benefit for the patient).

4.4 Relevant comparators

Potential comparators include:

Supportive care (including corticosteroids and ongoing or re-instated conventional DMARDs such as methotrexate, sulfasalazine to which the patients have had inadequate response previously).

Conventional DMARDs which have not been tried prior to trying a TNF inhibitor for example azathioprine, ciclosporin A and gold injections either as monotherapy or combined with other DMARDs or corticosteroids.

Biologic agents including tocilizumab, golimumab and certolizumab pegol.

The interventions being considered compared with each other.

Clarification of comparators

The assessment report focuses on key clinically relevant questions, including where data allows comparing each of the interventions to supportive care and comparing each of the interventions against each other. This was based on the following considerations:

- The majority of patients considered in this technology appraisal may have already had inadequate response to at least two conventional DMARDs including methotrexate tried for an adequate length of time and at adequate doses, as indicated in current NICE guidance. These DMARDs may still be continued in the comparator (and intervention) arm(s) of trials in patients who have responded inadequately to these options. In such cases continued use of these DMARDs was regarded as supportive

care rather than as a credible alternative treatment option. Therefore a clear distinction was made between conventional DMARDs depending on whether the patients had tried them before and if there was a history of inadequate response to the DMARD tried.

- Only conventional DMARDs to which the patients have not had inadequate response or have not tried were to be regarded as separate comparators. The evidence for use of conventional DMARDs in patients who have failed to respond to TNF inhibitors was expected to be very limited.
- Although conventional DMARDs which are continued and to which the patients had an inadequate response were regarded as supportive care, subgroup analysis was considered (where relevant and evidence permits) to assess whether the presence or absence of these (failed) DMARDs in the control and intervention groups influenced the estimated treatment effects of the interventions.
- Tocilizumab, golimumab, and certolizumab pegol were potentially relevant comparators. These drugs are not yet available in the UK but all are (or are potentially) the subject of single technology appraisals by NICE. The inclusion of these three drugs in the final scope as comparators means there was no formal submissions from their manufacturers for this technology appraisal. This may have had implications with regard to the acquisition of evidence for these comparators. It was proposed that tocilizumab, golimumab and/or certolizumab pegol could have been reviewed in the assessment report as a comparator if marketing authorisation of the technology was obtained before the submission of the protocol for this assessment report. This condition was not met.

4.5 Relevant outcomes

Key outcomes considered appropriate to the decision problem were:

- Withdrawals (with reason)
- Treatment response (ACR)
- Disease activity (DAS)
- Physical Function (HAQ)
- Joint damage/radiological progression
- Pain

- Fatigue
- Serious adverse events (including death)
- Other adverse events potentially associated with treatment
- Health related quality of life

4.6 Key issues

Key issues have been mentioned where relevant earlier in this section and also in the background section of this report.

Further key issues predominately concern the limited availability of evidence from controlled trials and the impact this has on the assessment of clinical and cost-effectiveness of each of the interventions compared to the potential comparators (and the other interventions), and the ability to identify relevant subgroups in whom the technologies are more or less beneficial.

4.7 Place of the intervention in the treatment pathway(s)

Based on the final scope, the interventions are to be used when patients have had an inadequate response to a TNF inhibitor.

4.8 Overall aims and objectives of assessment

The overall aims and objectives were to address the decision questions outlines in section 4.1. These aims were to be achieved by:

- A systematic review of RCTs of the efficacy, tolerability and safety of adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of RA in adults who have had an inadequate response to a first TNF inhibitor.
- As the volume of RCT evidence was expected to be relatively small, relevant non-randomised comparative studies and uncontrolled studies were also reviewed.
- As systematic review of published studies on the cost and cost-effectiveness of the technologies in the treatment of RA in adults who have had an inadequate response to a first TNF inhibitor.

- A review of economic evaluations included in any manufacturers submissions for this appraisal
- A focused, model-based economic evaluation of the cost-effectiveness of the technologies from the perspective of the UK NHS.

5 ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

5.1.1 Search strategy

The following resources were searched for relevant studies:

- Bibliographic databases: Cochrane Library (CENTRAL) 2009 Issue3, MEDLINE (Ovid) 1950 – July week 1 2009, MEDLINE In-Process & Other Non-Indexed Citations (Ovid) 13 July 2009, EMBASE (Ovid) 1980 - 2009 week 28. Searches were based on index and text words that encompassed the condition: rheumatoid arthritis and the interventions: adalimumab, infliximab, etanercept, rituximab and abatacept.
- Citations of included studies were examined.
- Reference lists of identified systematic reviews were checked.
- Further information was sought from contacts with experts.
- Research registries of ongoing trials including NIHR Clinical Research Network Portfolio Database, Current Controlled Trials and Clinical Trials.gov using terms for the particular drugs.
- Manufacturer submissions.

The searches were not limited by date of publication or language.

Search strategies can be found in Appendix 10.1.

5.1.2 Study selection

All articles identified in the searches were imported into a Reference Manager database (Reference Manager v.11, Thomson ResearchSoft). Duplicate entries were allowed to be removed by the inbuilt feature in Reference Manager and also removed when encountered by reviewers. Titles and abstracts were independently checked for relevance based on the population and intervention by two reviewers. If articles were considered relevant by at least one of the reviewers a full paper copy was ordered.

Full papers were assessed for relevance by two independent reviewers using an inclusion/ exclusion checklist (Appendix 10.6) based on the following criteria:

- Population: a majority of adults with active rheumatoid arthritis who have had an inadequate response to a TNF inhibitor
- Intervention: adalimumab, etanercept, infliximab, rituximab, or abatacept
- Outcomes: clinical outcomes related to efficacy, safety or tolerability
- Study design: primary study (except case reports) or a systematic review
- Study duration: at least 12 weeks
- Participant numbers: for non-randomised studies - at least 20 patients in one arm

Disagreements were resolved by discussion with involvement of a third reviewer when necessary.

Conference abstracts were not sought. If they were identified as relevant in the first stage of study selection an attempt was made to match them with journal publications. If this was not possible, contact with authors was not attempted due to time constraints and they were not included in the analysis.

A list of excluded studies and the reason for exclusion were recorded (see Appendix 10.4).

Included systematic reviews were not themselves systematically reviewed but were utilised to identify further primary studies.

Additional references identified from systematic reviews or industry submissions were entered into the Reference Manager database. The same process was applied to them as to the references identified from initial searches.

5.1.3 Data extraction

Data was extracted into a standard form (see Appendix 1.1) for all included studies by one reviewer. A second reviewer checked the accuracy of extracted information. Disagreements were resolved by consensus or by referral to a third reviewer if necessary.

Information regarding study design and characteristics of study participants was extracted. Data on the following outcomes was sought from included studies:

- Treatment withdrawal (and reasons for withdrawal),
- ACR20, ACR50, ACR70,
- Disease activity (e.g. DAS28 or DAS),

- Physical function (e.g. Health Assessment Questionnaire),
- Joint damage / radiological progression (measured by a scoring system),
- Pain,
- Fatigue,
- Extra-articular manifestations of the disease,
- Serious adverse events (including death),
- Other adverse effects potentially associated with treatments,
- Health-related quality of life.

Data for any outcomes other than those listed above was also extracted if it was considered relevant to this report.

Additional data from industry submissions was extracted by only one reviewer due to time constraints.

5.1.4 Quality assessment

Quality of included studies was assessed independently by two reviewers. Any disagreements were resolved by discussion and if necessary a third reviewer was consulted.

For randomised trials the following criteria were considered:

- Randomisation – whether allocation was truly random. Randomisation using computer or random number table was considered adequate whereas the use of alternation, case record numbers, or dates of birth and day of the week was considered inadequate.
- Allocation concealment – whether allocation concealment was adequate. Any of the following methods was considered adequate: centralised (e.g. allocation by a central office unaware of subject characteristics) or pharmacy-controlled randomisation; pre-numbered or coded identical containers which are administered serially to participants; on-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered; sequentially numbered, sealed, opaque envelopes.

- Blinding – use of blinding and who was blinded (patients, study investigators/ outcome assessors, data analysts).
- Patients withdrawn - what was the percentage of patients withdrawn from the study.
- Intention to Treat (ITT) analysis – whether ITT analysis was used.

For non-randomised studies the following criteria were considered:

- Study design – if the study was controlled or uncontrolled, prospective or retrospective.
- Inclusion criteria – if inclusion criteria were clearly sated.
- Consecutive patients – if consecutive patients were included in the study.
- Patients withdrawn - what was the percentage of patients withdrawn from the study.

The results of quality assessments are reported in relevant sections of the report.

5.1.5 Data analysis/ synthesis

5.1.5.1. Outcomes of interest

Selected outcomes of interest were specified in the review protocol, based upon the final scope issued by NICE for this technology appraisal. These were:

- Treatment withdrawal (and reasons for withdrawal)
- ACR20, ACR50, ACR70
- Disease activity (e.g. DAS28 or DAS)
- Physical function (e.g. Health Assessment Questionnaire)
- Joint damage / radiological progression (measured by a valid scoring system)
- Pain
- Fatigue
- Extra-articular manifestations of the disease
- Serious adverse events (including death)
- Other adverse effects potentially associated with treatment
- Health-related quality of life

5.1.5.2. Handling of data and presentation of results

Comparisons with supportive care

Studies were considered to compare interventions with supportive care if they:

- had an arm receiving supportive care,
- had a placebo arm.

Due to the paucity of evidence from controlled studies for the TNF inhibitors, evidence from uncontrolled studies (i.e. single group before-and-after studies) is also considered in this section.

Studies were considered separately for each of the interventions. In addition TNF inhibitors were discussed together as a class of drugs. Results were presented in figures and discussed in the main text of the report for the following outcomes:

- Withdrawals (for any reason, due to lack of efficacy and due to adverse events),
- ACR20, ACR50 and ACR70,
- DAS,
- EULAR response,
- HAQ,
- Quality of life,
- Joint damage,
- Serious adverse events,
- Infections and serious infections,
- Injection/ infusion reaction.

For other outcomes only figures were created and these can be found in Appendix 10.10.

For dichotomous measures data is presented as relative risks (for RCTs) and percentages (for other study designs). For continuous outcomes mean differences (for RCTs) and means (for other study designs) were used.

Where available, data was analysed for 3, 6, 9, 12 etc. months duration of follow-up. It was assumed to be 3 month data if it was collected between 3 and 4 months from the initiation of

treatment, 6 month data if it was collected between 5 and 7 months. If more than one estimate was available for a time interval, the value nearest to the assumed follow-up was used.

Pooling of results was not attempted for the assessment of effectiveness of individual technologies because the majority of included studies had no control group and there is substantial methodological and clinical heterogeneity between included studies. Given the relatively small number of patients that can be analysed in subgroup analyses, some pooling of data using random effects model was attempted. The results were presented with I^2 statistics mainly for demonstrating consistency of findings between studies (see section 5.7).

Comparisons with newly initiated and previously untried conventional DMARDs

No studies were identified and therefore analyses were not undertaken.

Comparisons with other biologic agents

No studies were identified and therefore analyses were not undertaken.

Comparisons between technologies (head-to-head comparisons)

No studies were identified and therefore direct comparisons were not undertaken.

Indirect comparison was undertaken when data was available from RCTs. It was conducted using the method by Bucher et al.[71] Results of the analyses are presented in a tabular format.

Subgroup analyses

The following subgroups were specified in the review protocol:

- Patients having withdrawn from the first TNF inhibitor due to lack of response (primary failure), loss of response (secondary failure), or adverse events/intolerance;
- Subgroups defined by auto-antibody status (e.g. presence or absence of rheumatoid factor or anti-cyclic citrullinated peptide antibodies);
- Subgroups defined by different doses of the intervention (within licence);
- Patients with co-morbidities for which some treatments may be contraindicated (e.g. heart failure).

No subgroup data concerning the latter two categories (varied doses; co-morbidities) were identified and thus no subgroup analysis was performed for these. Subgroup analyses relating to reasons of withdrawal from the first TNF inhibitor were carried out as two separate comparisons:

(1) withdrawal due to lack of response versus withdrawal due to loss of response;

(2) withdrawal due to lack of efficacy (which includes both lack of response and loss of response) versus withdrawal due to adverse events/intolerance.

In addition to the above, subgroup data in relation to the identity of the first TNF inhibitor which the patients received before discontinuation, and the number of prior TNF inhibitor(s) that the patients had tried before switching were reported in some studies. These were considered potentially of clinical relevance and thus subgroup analyses on these were also performed where data was available. [redacted]

Ongoing studies

Ongoing primary studies were identified in the searches. They were not included in the systematic review, but discussed in Section 1.1.

5.1.5.3. Assessment of publication bias

All manufacturers of the interventions provided a list of all company-sponsored RCTs and other non-randomised or uncontrolled studies that are relevant to this appraisal. Requests of clarification of trial data that are potentially available but not reported in published papers were also made to the manufacturers of rituximab and abatacept.

The number of relevant studies for individual technology was too small to allow formal assessment of publication bias.

5.1.5.4. Sensitivity analyses

The protocol specified that if evidence permits sensitivity analyses may be carried out taking into account the following factors:

- Quality measures of studies such as blinding and randomisation,
- Factors associated with the characteristics of the study population,
- Factors associated with study design such as study duration and drug doses,
- Exclusion of data supplied as commercial/academic in confidence.

However, sensitivity analyses were not performed as no pooling of study results was undertaken.

5.1.5.5. Changes to the original protocol

During the study selection process, several potentially relevant studies including mixed proportion of patients with or without prior treatment with a TNF inhibitor were identified. No criterion relating to inclusion or exclusion of these studies was specified in the original protocol. It was agreed by consensus within the project team that studies which included less than 50% of patients with RA who have failed a TNF inhibitor were excluded unless results from these patients were described separately and the number of these patients was ≥ 20..

5.2 Results – quantity and quality of research available

The searches resulted in the identification 10281 records and additional 17 were identified from industry submissions and 15 from reference lists of included studies.

Nine relevant systematic reviews[72-80] were identified in addition to the reports conducted for previous NICE appraisals in RA. Examination of these nine reviews did not identify any further primary studies that met all the criteria for inclusion in either the effectiveness or cost-effectiveness sections of this report.

7486 records were left after duplicates had been removed. Screening of the title and abstract of these articles indicated that 174 were directly relevant to the clinical effectiveness section of this report. Full paper copies of these articles were ordered. Five of them were unobtainable.[81-85] Inclusion criteria were applied to the remaining 169 articles. Of these 113 were excluded for not meeting at least one of the inclusion criteria. Three articles were identified as conference abstracts[86-88] and since these could not be matched to full publications, they were excluded. Details of excluded studies together with reasons for exclusion can be found in Appendix 10.4.

A flow diagram presenting the process of identification of relevant studies can be found in Appendix 10.3.

There were 35 studies described in 44 papers meeting the inclusion criteria. Five of the studies were RCTs, one was a comparative study, one was a non-randomised controlled study and 28 uncontrolled studies (including one long term extension of an RCT).

A randomised study on rituximab (SUNRISE) that was not yet published in full was identified. Data from this study was requested from the manufacturer, however the clinical study report[89] was received too late to be included in the analyses.

Table 2 presents mapping of studies to relevant interventions and comparators.

The assessment of effectiveness of the technologies is reported below in six sections, one for each of the technologies and one for TNF inhibitors as a class (See sections 5.3.1-0). Studies comparing technologies and indirect comparisons are reported in Sections 5.6.1 and 1.1.1.

Table 2 Mapping of identified studies

Comparators	**Interventions (newly initiated)**					
	Adalimumab	Etanercept	Infliximab	TNF inhibitors	Rituximab	Abatacept
None [a]	• Bennett 2005 [90] (n=26, 52 wks), • Wick 2005 [91] (n=27, 24 wks) • Nikas 2006 [92] (n=24, 52 wks), • Bombardieri 2007[93,94] (n=899, 12 wks) • van der Bijl 2008 [95] (n=41, 16 wks)	• Haroui 2004[96] (n=25, 12 wks) • Buch 2005[97] (n=207, 12 weeks) • Cohen 2005[98] (n=24, 13 wks) • Buch 2007[99] (n=95, 12 wks) • Iannone 2007[100] (n=37, 24 weeks) • Laas 2008[101] (n=49, >36 wks) • Bingham 2009[102] (n=201, 16 wks)	• Ang 2003 [103] (n=24, unclear) • Hansen 2004 [104] (n=20, unclear) • Yazici 2004 [105] (n=21, unclear)	• Gomez-Reino 2006[106] (n= 488, 104wks) • Solau-Gervais 2006[107] (n=70, >13 wks) • Hjardem 2007[108] (n=235, 13 wks) • Duftner 2008[109] (n=109, up to 208 wks) • Karlsson 2008 [110] (n=337, 13 wks) • Blom 2009[111] (n=197, 48 wks)	• Bokarewa 2007 [112] (n=48, 52 wks) • Jois 2007 [113] (n=20, 26 wks)* • Keystone 2007[114] (n=158, 24 wks) • Assous 2008 [115] (n=50, 26 wks) • Thurlings 2008[116] (n=30, 24 weeks)	• ATTAIN LTE [117] (n=317, up to 260 wks) • ARRIVE[118] (n=1046, 24 wks)
Supportive care [b]				• Hyrich 2009[119-121] (n=736, >24 wks)	• **REFLEX**[122-124] (n=517, 48 wks) • ***SUNRISE,***[89] (n=559, >48 weeks)	• **ATTAIN**[125-130] (n=391, 26 wks)
Ongoing biologics[c]			• **OPPOSITE**[131] (n=27, 16 wks)			• **Weinblatt 2007**[132] (n=121, 52 wks) • **ASSURE** [133] (n=167, 52 wks)
Newly initiated DMARD						
Adalimumab						
Etanercept						
Infliximab						
TNF inhibitors						
Rituximab				• Finckh 2009[134,135] (n=318, >44 wks)		
Abatacept						
Tocilizumab						
Golimumab						
Certolizumab pegol						

[a] Studies listed in this row are uncontrolled observational studies [b] Including ongoing DMARDs to which the patients have had inadequate response and the control treatments in placebo-controlled trials. [c] Ongoing biologics to which the patients have had inadequate response: OPPOSITE – ongoing etanercept, ASSURE – abatacept plus ongoing biologics (not specified) versus ongoing biologics (not specified)
Bold type indicates the study was an RCT. *Majority of patients had failed two or more TNF inhibitors.
Weinblatt 2007 and ASSURE: with ongoing biologic therapy in both arms; *SUNRISE* has not yet been published

5.3 Effectiveness of the technologies compared to supportive care

This section describes evidence relating to each of the technologies compared to supportive care, which includes treatments received by the placebo group in placebo-controlled trials and ongoing conventional DMARDs or biologics to which the patients had had inadequate response. Due to the paucity of evidence from controlled studies for the TNF inhibitors, evidence from uncontrolled studies (i.e. single group before-and-after studies) is also considered in this section.

5.3.1 Adalimumab

5.3.1.1. Overview of evidence

Five studies in six publications[90-95] met the inclusion criteria. No RCT was found. Four studies had comparator arms in which the patients were TNF inhibitor naive[90-92,94], these arms were excluded here.One of the four[91] also had a small comparator arm of 9 patients, which was beyond our inclusion criteria of at least 20 patients for a arm to be included, thus data of this arm are excluded.

One study was a multi-centred and conducted in 12 countries, 11 of which were European countries including the UK. Single studies were conducted in the UK, Sweden and Greece. It was unclear in which country the fifth study was conducted.

Table 3 Adalimumab - Characteristics of included studies

Study	Country	Design	Reason for switching	Prior TNF inhibitors (no.)	Treatment arms (no. of patients)	Duration of follow-up	Comments
Bennett 2005[90]	UK	Uncontrolled prospective	Primary (8) and secondary (13) failure, adverse events, other	IFX, ETN, anakinra (1)	ADA, (n=26)	over 52 weeks	primary and secondary failures - all IFX
Wick 2005[91]	Sweden	Uncontrolled retrospective	Secondary failure	IFX (1)	ADA, (n=27)	3, 6 months	
Nikas 2006[92]	Greece	Uncontrolled prospective	Lack of efficacy, adverse events	IFX (1)	ADA, (n=24)	12 months	Possibly one or two active TB patients (outside study inclusion criteria)
Bombardieri 2007 (RcAct)[93, 94]	Australia, Austria, Belgium, France, Germany, Greece, Italy, The Netherlands, Portugal, Spain, Switzerland, UK	Uncontrolled prospective	Primary and secondary failure, intolerance.	IFX, ETA, or both (≥1)	ADA, (n=899)	12 weeks	
Van der Bijl 2008[95]	Unclear	Uncontrolled prospective	Primary and secondary failure, intolerance	IFX (1)	ADA, (n=41)	16 weeks (follow-up to 56 wks; treatment for and efficacy measured at 16 wks)	Pre-existing antirheumatic therapy (in about 12 patients) was continued and remained stable until week 16

Sample sizes were small, ranging from 24 to 41 patients that are relevant to the review in four studies; in one study there were 899 patients. Patients included all had previous treatment with either one or two TNF inhibitors, mostly infliximab. Reasons for switching TNF inhibitor agents were lack of efficacy only in one study[91], lack of efficacy or intolerance in

two studies[94,95], and lack of efficacy or due to adverse event in two studies[90,92]. Details on adalimumab treatment were not reported in one study; in all the other studies adalimumab was given 40mg subcutaneously every other week. Study duration ranged from 12 weeks to over one year. Further details are outlined in Table 3.

5.3.1.2. Patient characteristics

Data on patient characteristics can be found in Table 4. Characteristics of the patients included in the five studies varied in some aspects:

- Where reported 81% to 92% were female;
- mean age of the patients ranged from 50 to 56.7 years;
- mean RA duration ranged from 11.6 to 16.6 years but was not reported in two studies;
- the percentage of patient rheumatoid factor positive was reported only in two studies (63% and 72%);
- concomitant DMARDs: where reported 37 to 85% patients were on MTX, other DMARDs included ciclosporin (4%), leflunonide (3% to 13%), hydroxychloroquine (3%), and azathioprine (1%);
- the percentage of patients on concurrent steroids where reported in two studies and ranged from 77% to 100%;
- where reported the mean number of previous DMARDs use ranged from 2 to 5;
- number of mean previous TNF inhibitor was ≥1 in the biggest study, but was 1 in all the other studies;
- HAQ scores ranged from 1.29 to 2.07 in four studies but were not report in one study;
- mean DAS 28 scores were very similar, ranging from 5.5 to 6.3;
- mean number of tender joint count and swollen joint count at baseline were reported in three studies and ranged from 6.1 to 15 and 8.2 to 11 respectively;
- baseline ESR was reported in only one study (41.7 mm/hour) and CRP in only two studies (25.1 and 43.9 mg/dl)

Table 4. Adalimumab - Patient baseline characteristics of included studies

Study	Number of patients/ % female	Age; mean (SD); years	RA duration; mean (SD); years	RF positive; %	% of patients on concomitant DMARDs and steroids	Number of previous DMARDs; mean (SD)	Number of previous TNF inhibitors; mean (SD)	HAQ; mean (SD)	DAS28; mean (SD)	TJC/ SJC; mean (SD)	ESR; mean (SD); mm/hr	CRP; mean (SD); mg/dL
Bennett 2005[90]‡	26, 87%	54 (range 19–77)	NR	NR	MTX (37%); leflunomide (3%); Hydroxychloroquine (3%); azathioprine (1%). All above with or without low-dose prednisone.	3.4 (range 2-7)	1 (IFX, ETN, anakinra)	2.07	6.3	NR	NR	NR
Wick 2005[91]	27, 84%¶	50.0 (14.9)	NR	NR	MTX 85%; steroids NR	2 (NR)	1 (all IFX)	1.39 (0.52)*	5.5 (1.56)*	Tender 8.2 (4.68)*; Swollen 9.5 (5.20)*	41.7 (27.54)*	43.9 (45.21)*
Nikas 2006[92]	24, 92%	56.7 (11.2)	16.6 (7.0)	63	MTX 83%; Ciclosporin 4%; Leflunonide 13%; Steroids (100%)	NR	1 (all IFX)	NR	5.6 (0.8)	Given graphically only	Given graphically only	Given graphically only
Bombardieri 2007[93,94]	899, 81%	53 (13)	12 (8)	72	DMARDS 31%, steroids 77%	5.0 (1.9)	≥1 (IFX and/or ETA)	1.85 (0.66)	6.3 (1.1)	Tender 15 (7); Swollen 11 (6)	NR	NR
van der Bijl 2008[95]	41, 88%	55 (NR)	11.6 (7.4)	NR	One DMARD 66%; Steroids NR	NR	1 (all IFX)	1.85 (0.49)	6.1 (0.9)	Tender 6.1 (0.9); Swollen 8.2 (4.8)	NR	25.1 (32.0)

‡ Female %, mean age, previous prednisone, previous DMARDs, HAQ and DAS28 given were based on the total number of 70 patients, including those patients previous TNF inhibitor naïve.
¶Female % was based on the total number of 62 patients.
* SD was calculated from standard error.

5.3.1.3. Quality assessment

The studies were all uncontrolled, four of them were prospective and one was retrospective[91]. Criteria for patient inclusion were clearly stated in four studies; however, in three of these it was unclear whether consecutive patients were included. The highest percentage of patient withdrawn among the studies was 26.8% while there was no withdrawal in the retrospective study; in general the higher withdrawal rates occurred with the longer follow-up durations. Further details on the quality assessment of the studies were outlined in Table 5.

Table 5. Adalimumab - Quality assessment

Study	Study design	Inclusion criteria clearly defined?	Were consecutive patients included in the study?	Patients withdrew (%)	Comments
Bennett 2005[90]	Prospective uncontrolled study	Yes	yes	NR*	
Wick 2005[91]	Retrospective uncontrolled	No	n/a	0	
Nikas 2006[92]	prospective cohort study	Yes	unclear	16.7	
Bombardieri 2007[93,94]	Multi-centre, uncontrolled, open-label study	Yes	unclear	9.9	
van der Bijl 2008[95]	pilot open-label uncontrolled prospective study	Yes	unclear	26.8	

* Reported based on the total patients but not those relevant to the review.

5.3.1.4. Results

Table 6and Table 7 below state what outcomes were measured in each study. Outcomes in Table 6 are reported and discussed in the main text of this report and those in Table 7 are reported in Appendix 10.10 only.

Table 6. Adalimumab - outcomes assessed in studies and reported in the main text of the report

Study	Total withdrawal	Withdrawal by reason	ACR (20/50/70)	DAS28	EULAR response	HAQ	QoL	Joint damage	Serious adverse events	Infection/ serious infection	Injection/ infusion reaction
Bennett 2005[90]				√	√ time range	√ time range					
Wick 2005[91]	√	√	√	√							
Nikas 2006[92]	√	√	√	√	√					√	√
Bombardieri 2007[93,94]	√	√	√	√	√	√			√	√	
van der Bijl 2008[95]	√	√	√	√	√	√				√	

Table 7. Adalimumab - outcomes assessed in studies and reported in the appendix only

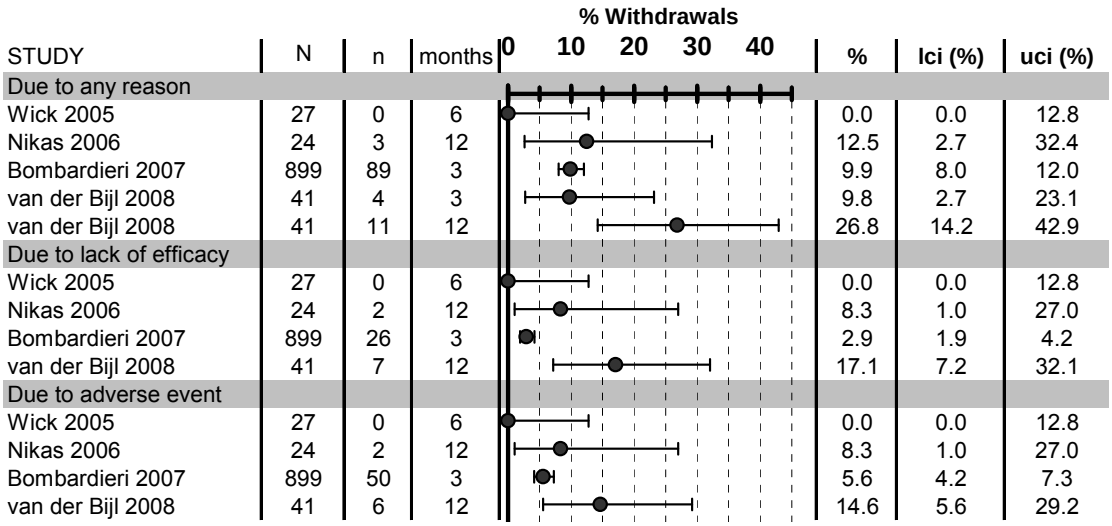
Study	Other measures of disease activity	Fatigue	Pain	TJC/ SJC	CRP/ ESR
Bennett 2005[90]					
Wick 2005					
Nikas 2006[92]			√ *	√ *	√ *
Bombardieri 2007[93,94]					
van der Bijl 2008[95]					√

*Reported graphically

Withdrawals

Withdrawal rates are presented in Figure 1. At three months follow-up the percentages of patients withdrawn were very similar in two studies that reported this outcome (9.9% / 9.8%); one of them was the biggest study. No patients withdrew in the retrospective study by 6 months. Withdrawal rate reported at one year follow-up were 16.7% and 26.8% respectively in two studies that reported this outcome. Percentages of patients withdrawn due to lack of efficacy and due to adverse events at 3 months were only reported in the biggest study and were 2.9% and 5.6% respectively. Percentages of patients withdrawn due to lack of efficacy and due to adverse events at 12 months were measured in two studies; though the rates differed between the two studies, for each outcome, the rates were initially similar (e.g. lack of efficacy : adverse event: 17.1% : 14.6%; 8.3% : 8.3%).

One study (Bennett 2005[90]) reported withdrawal data based on all the 70 patients including 44 patients received a prior TNF inhibitor as well as TNF inhibitor naïve patients; the withdrawal data were not included in this report.



STUDY	N	n	months	%	lci (%)	uci (%)
Due to any reason						
Wick 2005	27	0	6	0.0	0.0	12.8
Nikas 2006	24	3	12	12.5	2.7	32.4
Bombardieri 2007	899	89	3	9.9	8.0	12.0
van der Bijl 2008	41	4	3	9.8	2.7	23.1
van der Bijl 2008	41	11	12	26.8	14.2	42.9
Due to lack of efficacy						
Wick 2005	27	0	6	0.0	0.0	12.8
Nikas 2006	24	2	12	8.3	1.0	27.0
Bombardieri 2007	899	26	3	2.9	1.9	4.2
van der Bijl 2008	41	7	12	17.1	7.2	32.1
Due to adverse event						
Wick 2005	27	0	6	0.0	0.0	12.8
Nikas 2006	24	2	12	8.3	1.0	27.0
Bombardieri 2007	899	50	3	5.6	4.2	7.3
van der Bijl 2008	41	6	12	14.6	5.6	29.2

Figure 1 Adalimumab – Withdrawals in studies for reason

ACR 20 response

ACR20 responses were assessed in four studies (Figure 2). Two studies assessed at 3 months and the response was achieved by around half of the patients (46% and 60% respectively). In the other two studies, the percentages of patients achieved ACR20 was 70% at 6 months and 75% at 12 months respectively.

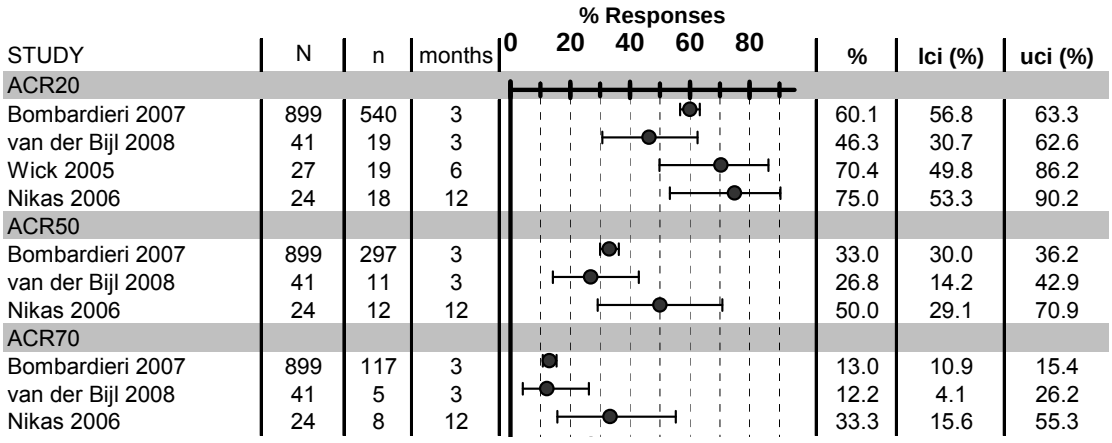
ACR 50 response

ACR50 responses were measured in 3 studies (Figure 2). Around one quarter to one thirds of the patients achieved the response. While measured at 12 month in the other study, half of the patients achieved this response.

ACR 70 response

ACR70 responses were measured in 3 studies (Figure 2). Responses at 3 months were similar in two studies that measured this outcome (13% /12%). ACR70 response at 12 months was reported in one study with 33% of the patients achieved this response.

Similar pattern was seen for ACR20, ACR50 and ACR70 that relatively higher percentage of patients achieving a response with longer duration of treatment.



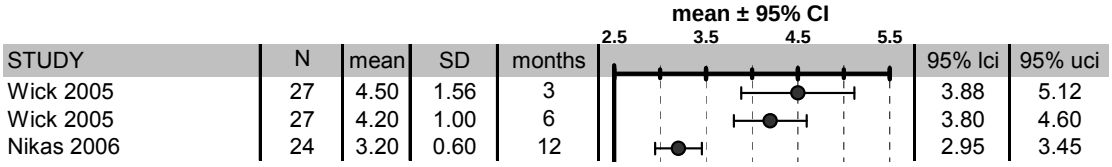
STUDY	N	n	months	%	lci (%)	uci (%)
ACR20						
Bombardieri 2007	899	540	3	60.1	56.8	63.3
van der Bijl 2008	41	19	3	46.3	30.7	62.6
Wick 2005	27	19	6	70.4	49.8	86.2
Nikas 2006	24	18	12	75.0	53.3	90.2
ACR50						
Bombardieri 2007	899	297	3	33.0	30.0	36.2
van der Bijl 2008	41	11	3	26.8	14.2	42.9
Nikas 2006	24	12	12	50.0	29.1	70.9
ACR70						
Bombardieri 2007	899	117	3	13.0	10.9	15.4
van der Bijl 2008	41	5	3	12.2	4.1	26.2
Nikas 2006	24	8	12	33.3	15.6	55.3

Figure 2. Adalimumab - ACR (20, 50, 70) responses

DAS28

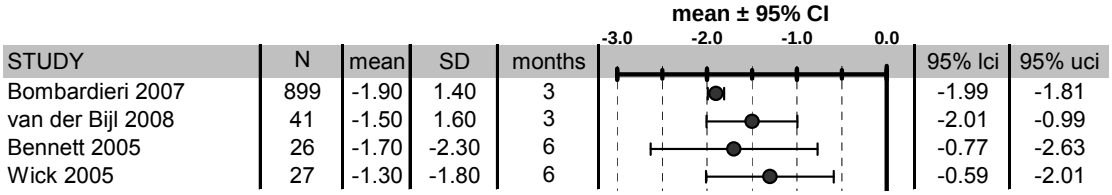
One study measured DAS28 at 3 and 6 months and another study at 12 months; the mean scores were 4.5, 4.2 and 3.2 respectively. See Figure 3 for details. The mean changes from

baseline to 3 months and to 6 months [1], were reported in four studies including the biggest study. They all showed that treatment with adalimumab significantly improved DAS28 scores (mean changes ranged from -1.30 to -1.90. See Figure 4 for details).



STUDY	N	mean	SD	months	95% lci	95% uci
Wick 2005	27	4.50	1.56	3	3.88	5.12
Wick 2005	27	4.20	1.00	6	3.80	4.60
Nikas 2006	24	3.20	0.60	12	2.95	3.45

Figure 3. Adalimumab - DAS28 scores

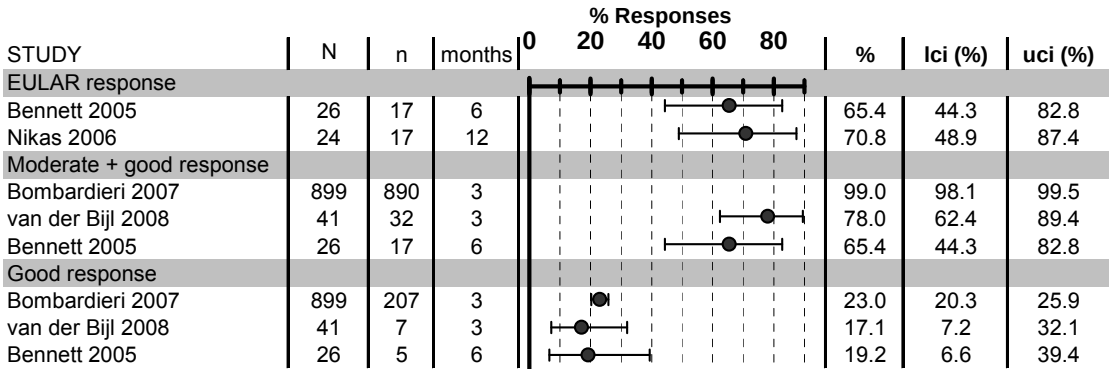


STUDY	N	mean	SD	months	95% lci	95% uci
Bombardieri 2007	899	-1.90	1.40	3	-1.99	-1.81
van der Bijl 2008	41	-1.50	1.60	3	-2.01	-0.99
Bennett 2005	26	-1.70	-2.30	6	-0.77	-2.63
Wick 2005	27	-1.30	-1.80	6	-0.59	-2.01

Figure 4. Adalimumab - Mean changes on DAS28 scores

EULAR response

Two studies reported EULAR response at 3 months; most of the patients had a moderate response (61% / 76%), with 17% to 23% had a good response. The Bennett study measured EULAR response after a mean treatment duration of 8.5 months (range 1-19); the response rate was 65%, of which 46% had moderate response and 19% had good response. See Figure 5 for details.



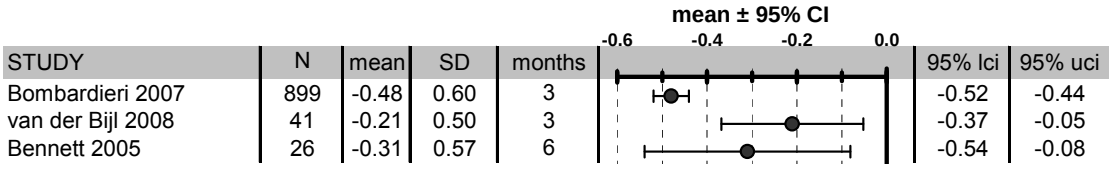
STUDY	N	n	months	%	lci (%)	uci (%)
EULAR response						
Bennett 2005	26	17	6	65.4	44.3	82.8
Nikas 2006	24	17	12	70.8	48.9	87.4
Moderate + good response						
Bombardieri 2007	899	890	3	99.0	98.1	99.5
van der Bijl 2008	41	32	3	78.0	62.4	89.4
Bennett 2005	26	17	6	65.4	44.3	82.8
Good response						
Bombardieri 2007	899	207	3	23.0	20.3	25.9
van der Bijl 2008	41	7	3	17.1	7.2	32.1
Bennett 2005	26	5	6	19.2	6.6	39.4

Figure 5. Adalimumab - EULAR response

[1] In the Bennett 2005 study it was measured after mean treatment duration of 8.5 months (range 1-19).

HAQ

Mean change on HAQ score was reported in three studies. Figure 6 shows that the mean HAQ score measured at 3 months in two studies including the biggest study, and at mean 8.5 months (range 1-19) in the Bennett study, all showed significant decrease, ranging from -0.21 to -0.48, with the largest improvement observed in the biggest study.



STUDY	N	mean	SD	months	95% lci	95% uci
Bombardieri 2007	899	-0.48	0.60	3	-0.52	-0.44
van der Bijl 2008	41	-0.21	0.50	3	-0.37	-0.05
Bennett 2005	26	-0.31	0.57	6	-0.54	-0.08

Figure 6. Adalimumab - Mean change on HAQ scores

Joint damage

None of the studies reported this outcome measure.

Quality of life

None of the studies reported this outcome measure.

Serious adverse events

One study (the largest) reported that 18% of the patients had serious adverse events; of these none was lupus-related or demyelineating disorder[93,94].

Serious infections

The largest study also reported that the serious infections rate was 10.0/100 patient years. TB infection was 0.4/100 patient years in this study; in another study (van der Bijl 2008[95]) one patient developed pulmonary TB at 11 months. In the latter study serious infection with cellulities was also reported in one patient. One patient in a 12 month study by Nikas and colleagues had to stop the study due to herpes zoster infection; it was not reported at which time point the treatment was stopped.

Injection site reaction / infusion reaction

The largest study stated that none of the patients had serious anaphylactic response during the study period of 3 months. In a 12 month study (Nikas 2005[92]) one patient had to stop the study due to immediate hypersensitivity reaction; it was not reported at which time point it was stopped.

5.3.1.5. Summary

For the assessment of effectiveness of adalimumab in comparison with standard care five uncontrolled studies were identified. Follow-up duration ranged from 3 months to over one year. All patients included in the studies were generally similar. Main results are summarised in Table 8.

Table 8. Adalimumab – summary results

Outcome	3 months	6 months	9 months or over
Withdrawals: • For any reason • Due to lack of efficacy • Due to adverse events	 9.8-9.9% 2.9% 5.6%	 0 0 0	 12.5-26.8% 8.3-17.1% 8.3-14.6%
ACR20 response	46.3-60.1%	70.4%	75.0%
ACR50 response	26.8-33.0%	NR	50.0%
ACR70 response	12.2-13.0%	NR	33.3%
EULAR response • Overall response • Moderated response • Good response • Remission	 NR 61.0-76.0% 17.1-23.0% NR	 65.4% 46.2% 19.2% 7.7%	 70.8% NR NR NR
DAS28			
• Mean change from baseline	-1.50 to -1.90 (significant improvement)	-1.30 to -1.70 (significant improvement)	NR
• Mean at time point	4.50	4.20	3.20
HAQ: mean change from baseline	-0.21 to -0.48 (significant improvement)	-0.31 (significant improvement)	NR
Quality of life	NR	NR	NR
Joint damage	NR	NR	NR
Serious adverse events	NR	NR	NR
Any infections Serious infections	NR	NR	NR
Infusion reaction	NR	NR	NR

5.3.2 Etanercept

5.3.2.1. Overview of evidence

No RCT was found. Seven uncontrolled observational studies[96-102] were identified that assessed efficacy of etanercept.

Table 9 Etanercept – characteristics of included studies

Study	Country	Design	reason for switching	prior TNF inhibitor	Treatment arms (no. of patients)	Duration of follow-up	Comments
Randomised controlled trials (none were identified)							
Non-randomised comparative studies (none were identified)							
Uncontrolled studies							
Haroui 2004[96]	USA	Uncontrolled prospective	Inefficacy + adverse events	IFX	ETN (25)	12 weeks	
Buch 2005[97]	UK	Uncontrolled prospective	Inefficacy	IFX	ETN (25)	12 weeks	This study had other subgroups not relevant for this review
Cohen 2005[98]	France	Uncontrolled retrospective	Inefficacy+ adverse events	IFX	ETN (24)	3 months	Contain a second arm with 14 patients on infliximab (switched from etanercept)
Buch 2007[99]	UK	Uncontrolled prospective	Inefficacy+ adverse events	IFX	ETN (95)	12 weeks	
Iannone 2007[100]	Italy	Uncontrolled, retrospective	Adverse events	IFX	ETN (37)	24 weeks	
Laas 2008[101]	Finland	Uncontrolled, prospective	Inefficacy, adverse events, non-medical reasons	IFX	ETN (49)	>9 months	Results > 9 months reported but duration of follow-up unclear
Bingham 2009[102]	USA & Canada	Uncontrolled, prospective	Inefficacy	IFX	ETN (201)	16 weeks	

In Buch 2005[97] and Bingham 2009[102] lack of efficacy was the primary reason for switching to etanercept. In Haraoui 2004[96] and Cohen 2005,[98] and Buch 2007[99] patients discontinued the infliximab due to lack of efficacy or safety. In Iannone 2007,[100] patients had to have responded to prior infliximab treatment but later switched to etanercept due to side effects. Patient population in this study was therefore different from the other studies. In Laas 2008 [101], patients discontinued the infliximab due to lack of efficacy, safety, or non-medical

reasons. The group of patients who discontinued infliximab due to non-medical reasons (46%, 23/49) had responded well to infliximab well but switched to etanercept for practical reasons such as convenience (e.g. no need for hospital visit to receive infusion). Two studies (Buch 2005, Buch 2007)[97,99] were carried out at the same centre (Leeds Teaching Hosptials) in the in UK. These studies were described separately in this section although it is possible that patients included in Buch 2005[97] were a subgroup of the cohort included in Buch 2007.[99] The others studies were carried out in France,[98] Italy,[100] Finland,[101], and USA.[96] One study[102] was a multicenter study that enrolled patients from both USA and Canada. The length of follow-up varied from 12 weeks to more than nine months. Further details are provided in Table 9.

5.3.2.2. Patient characteristics

Full details of patients' characteristics are reported in Table 10. The number of patients included in the studies varied from as 24 to 201. Patient characteristics differed across the seven studies:

- where reported percentage of female patients ranged from 60.0% to 88.0%;
- where reported mean age ranged from 49.0 to 57.3 years;
- where reported mean disease duration ranged from 8.3 to 12.2 years;
- where reported percentage of rheumatoid factor positive patients ranged from 44% to 75%;
- where reported concomitant DMARDs: 88% to 99% were on MTX, other DMARDs included hydroxychloroquine (9%), and sulfasalazine (5%);
- where reported 40% to 88% of patients were receiving corticosteroids;
- where reported the mean/median number of previously used conventional DMARDs varied from 4.1 to 7;
- all the studies included patients previously treated with infliximab;
- where reported the mean baseline HAQ ranged from 0.9 to 2.16;
- the mean baseline DAS28 score ranged from 5.6 to 6.6;
- one study [100] reported baseline DAS44, mean value was 2.7
- where reported the mean number of tender and swollen joints was variable (tender: 10.0 to 17.8 and swollen: 8.6 to 14.3);
- baseline ESR was only reported in two studies, 21 mm/hour and 30 mm/hour;

- where reported CRP ranged from 0.6 to 6.2 mg/dL.

The baseline values listed in Table 10 for Iannone 2007[100] were measured 8 weeks before patients switched from infliximab to etanercept (while they were still responding to infliximab) and thus the values may not be comparable to the other studies.

Table 10 Etanercept – baseline patient characteristics

	number of patients/ % female	age; mean (SD); years	RA duration; mean (SD); years	RF positive; %	concomitant DMARDs and steroids	number of previous DMARDs; mean (SD)	number of previous TNF inhibitors; mean (SD)	HAQ; mean (SD)	DAS28; mean (SD)	tender/ swollen joint count; mean (SD)	ESR; mean (SD); mm/hr	CRP; mean (SD); mg/dL
Haraoui 2004[96]	25 / 84.0	50 (38.5)	10(25.2)	NR	MTX (88%), oral corticosteroid (48%)	4.8 (3.7)	IFX	1.53	NR	10.0/ 8.6	NR	1.7
Buch 2005[97]*	34/ 71	55.9	NR	44	NR	NR	IFX	NR	6.42	NR	NR	3.8-4.2*
Cohen 2005[98]	24 / 87.5	53.6 (11.3)	12.2(9.6)	NR	MTX	4.1 (1.8)	IFX	NR	5.6(1.1)	NR	NR	NR
Buch 2007[99†]	95 / NR	57.2(1.47)	NR	71	NR	NR	IFX	2.16 (0.64)	6.41 (0.13)	14.0(1.0)/ 9.0(0.86)	NR	6.0
Iannone 2007[100]	37/81	49(12)	8.3(6)	75	MTX, prednisone	NR	IFX	0.9	2.7 (DAS44)	NR	21	0.6**
Laas 2008[101]	49 / 88.0	NR	12.2	65	MTX, prednisone (88%)	6-7**	IFX	NR	NR	NR	NR	NR
Bingham 2009[102]	201/60	57.3 (12.8)	9.1(9.5)	58	MTX (99%), sulfasalazine (5%), hydroxychloroquine (9%), prednisone (40%)	NR	IFX	1.6(0.5)	6.6(1.0)	17.8(7.1) / 14.3(6.3)	30(2 to 125)	6.2

* Only 25 of the 34 patients actually switched to etanercept after receiving infliximab. The range presented for CRP are the range of median values for the two subgroups relevant to this review (mean values not reported).

**Median value. For Laas 2008, the range presented for the number of previous DMARDs was the range of median number of previous DMARDs among the three subgroups within the study (values for the whole study population not reported).

5.3.2.3. Quality assessment

All the seven studies were uncontrolled studies. Five were prospective [96,97,99,101,102] and two were retrospective[98,100]. Full details of quality assessment are reported in Table 11. With the exception of Laas 2008[101], studies stated clearly their inclusion criteria. Only Buch 2005[97] and Buch 2007[99] clearly stated that consecutive patients were included in the studies; this information was not unclear in Bingham 2009[102] and Haraoui 2004[96]. Only study[102] reported percentage of patients lost to follow-up (0.5%).

Table 11 Etanercept – non-RCT quality assessment

	Study design	Inclusion criteria clearly defined?	Were consecutive patients included in the study?	Patients withdrawn (%)	Comments
Haraoui 2004[96]	Uncontrolled prospective	Yes	Unclear	Unclear	
Buch 2005[97]	Uncontrolled prospective	Yes	Yes	Unclear	
Cohen 2005[98]	Uncontrolled Retrospective	Yes	n/a	Unclear	
Buch 2007[99]	Uncontrolled prospective	Yes	Yes	Unclear	
Iannone 2007[100]	Uncontrolled, retrospective	Yes	n/a	Unclear	
Laas 2008[101]	Uncontrolled, prospective	No	NR	Unclear	
Bingham 2009[102]	Uncontrolled, prospective	Yes	Unclear	0.5%	

5.3.2.4. Results

Table 12 and Table 13 below state what outcomes were measured in each study. Outcomes in Table 12 are reported and discussed in the main text and in Table 13 are reported in the Appendix 10.10 only.

Table 12 Etanercept - outcomes assessed in studies and reported in the main text of the report

	Total withdrawal	Withdrawal by reason	ACR (20/50/70)	DAS 28	EULAR response	HAQ	Quality of life	Joint damage	Serious adverse events	Infection/ serious infection	Injection/ infusion reaction
Haraoui 2004[96]	√	√	√			√			√		
Buch 2005[97]	√	√	√								
Cohen 2005[98]	√	√		√	√					√	
Buch 2007[99]			√	√	√						
Iannone 2007[100]			√*	√		√					
Laas 2008[101]	√	√		√						√	
Bingham 2009[102]	√	√	√		√	√			√	√	

*The results for ACR50 and 70 reported by Iannone 2007 were measured against the baseline before the patients started prior infliximab, not before the patients switched to etanercept. The results were therefore not presented in this section.

Table 13 Etanercept- outcomes assessed in studies and reported in the appendix only

	Other measures of disease activity	Fatigue	Pain	TJC/ SJC	CRP/ ESR
Buch 2005					√
Haroui 2004	√		√	√	√
Cohen 2005	√		√		√
Buch 2007					√
Iannone 2007			√		√
Laas 2008					√
Bingham 2009	√		√	√	√

Withdrawals

Five out of seven studies reported withdrawals and the reasons for withdrawing from treatment. The percentages and reasons for withdrawing from the study after commencing etanercept are shown in Figure 7**.** The percentage of patients that withdrew due to any reason ranged from as low as 6.5% (at 3 months) to as much as 58.3% (at 12 months). The percentage of patients that withdrew due to adverse events and lack of efficacy ranged from 0% to 16.3% and 0% to 29.2% respectively.

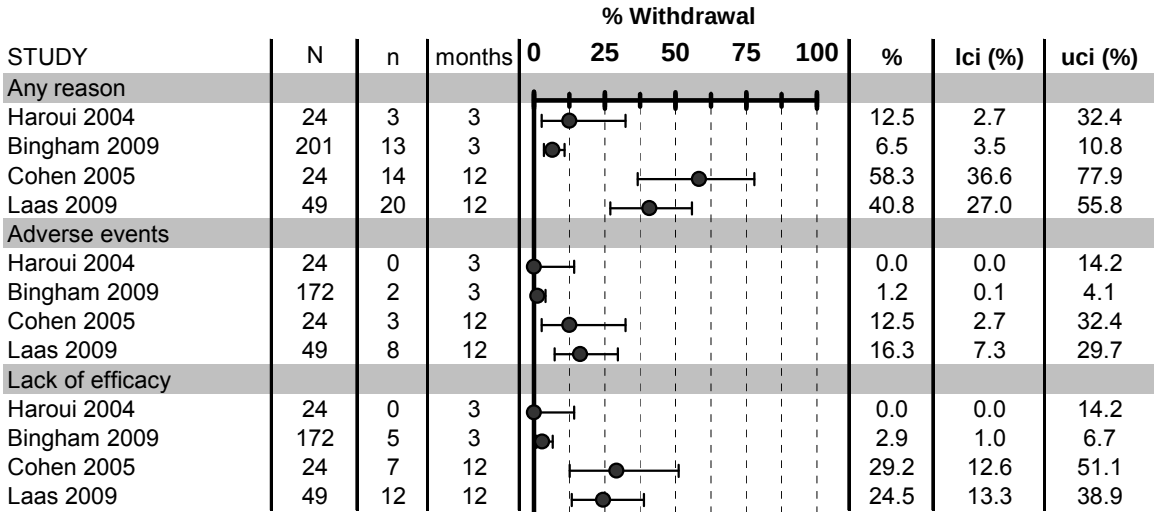


Figure 7 Etanercept withdrawals in the studies by reasons

ACR20 response

ACR20 response was assessed in four studies (Figure 8). The percentage of patients treated with etanercept after infliximab failure that achieved ACR 20 response after 3 months ranged from 37.5% to 72.0%.

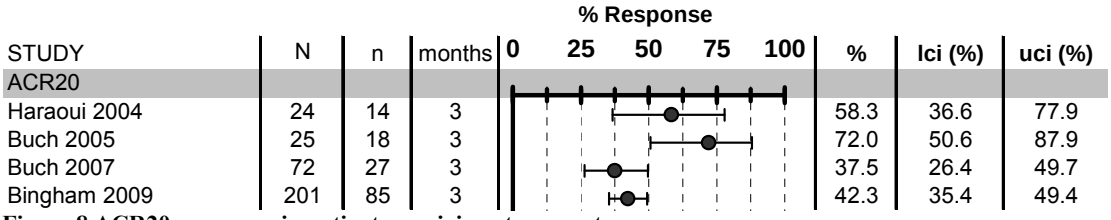


Figure 8 ACR20 responses in patients receiving etanercept

ACR50 response

ACR50 response was assessed in five studies but results from Iannone 2007 are not presented here as explained earlier (Figure 9). The proportion of patients reaching ACR50 response after taking etanercept ranged after 3 months ranged from 18.4% to 64.0%.

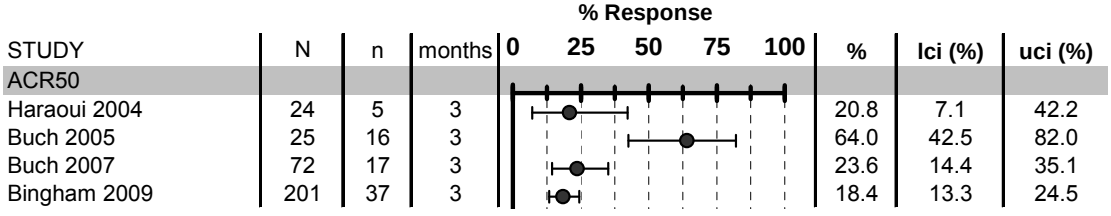
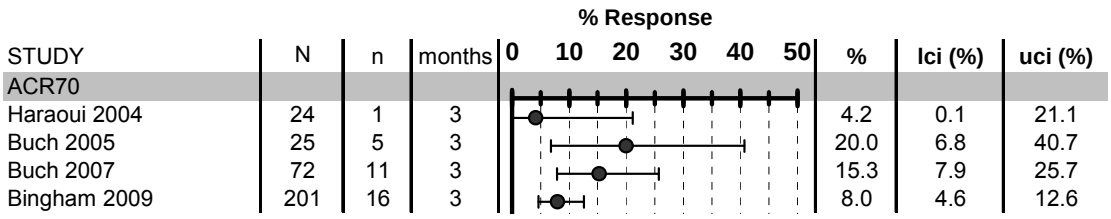


Figure 9 ACR50 responses in patients receiving etanercept

ACR70 response

ACR70 response was assessed in five studies but results from Iannone 2007 are not presented here as explained earlier (Figure 10). The proportion of patients reaching ACR70 response after taking etanercept for 3 months ranged from 4.2% to 20.0%.

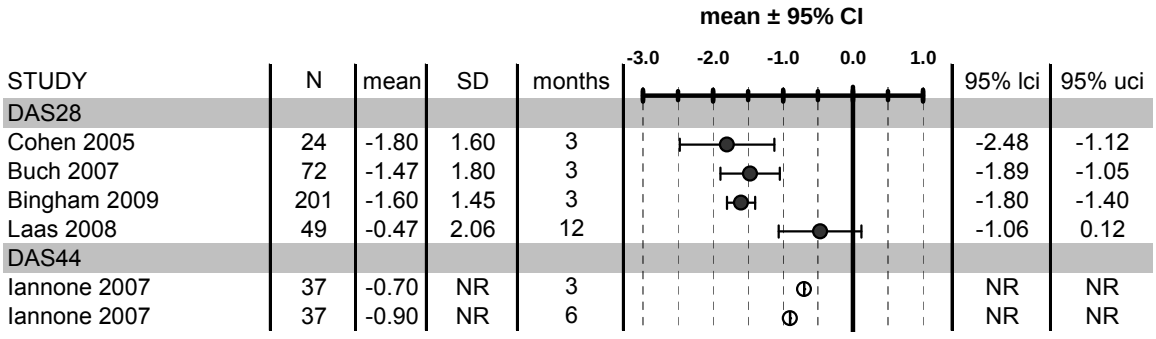


STUDY	N	n	months	%	lci (%)	uci (%)
ACR70						
Haraoui 2004	24	1	3	4.2	0.1	21.1
Buch 2005	25	5	3	20.0	6.8	40.7
Buch 2007	72	11	3	15.3	7.9	25.7
Bingham 2009	201	16	3	8.0	4.6	12.6

Figure 10 ACR70 responses in patients receiving etanercept

DAS

Figure 11 presents mean changes from baseline in DAS. Four studies [98,99,101,102] reported Disease Activity Score using 28 joint counts (DAS28). The mean decrease in DAS28 ranged from 1.6 to 1.8 at 3 months. One [100] study reported no significantly significant decrease in DAS28 score from baseline at 12 months (mean change=-0.47; 95% CI -1.06 to 0.12). One study [100] reported DAS computed on 44 joints (DAS44). Iannone 2007 [100] found no statistically significant differences in DAS44 scores when etanercept 16 and 24 weeks were compared with baseline value measured.



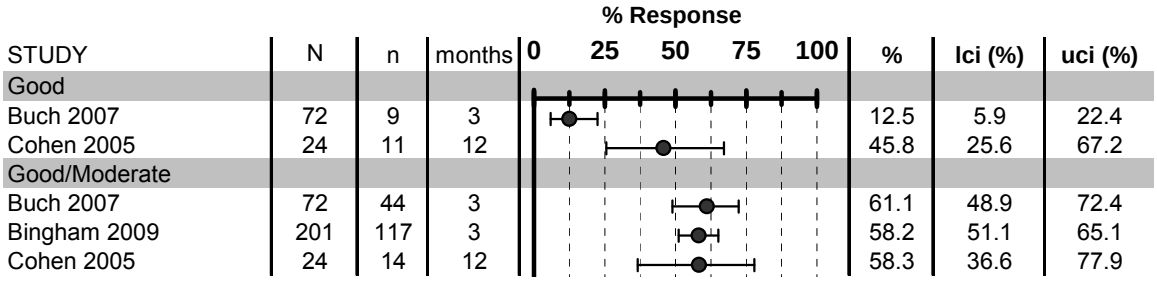
STUDY	N	mean	SD	months	95% lci	95% uci
DAS28						
Cohen 2005	24	-1.80	1.60	3	-2.48	-1.12
Buch 2007	72	-1.47	1.80	3	-1.89	-1.05
Bingham 2009	201	-1.60	1.45	3	-1.80	-1.40
Laas 2008	49	-0.47	2.06	12	-1.06	0.12
DAS44						
Iannone 2007	37	-0.70	NR	3	NR	NR
Iannone 2007	37	-0.90	NR	6	NR	NR

Figure 11 Etanercept – mean changes from baseline in DAS

EULAR response

Three studies reported EULAR responses. Figure 12 shows proportion of patients treated with etanercept that achieved good and good to moderate EULAR response after infliximab failure. The percentages of patients that achieved good EULAR were 12.5% and 45.8% at 3 and 12 months respectively. The percentage of patients that achieved good to moderate

EULAR response ranged from 58.2% to 61.1% at 3 month. One study [98] reported that 58.3% of patients achieved good to moderate EULAR response at 12 months.



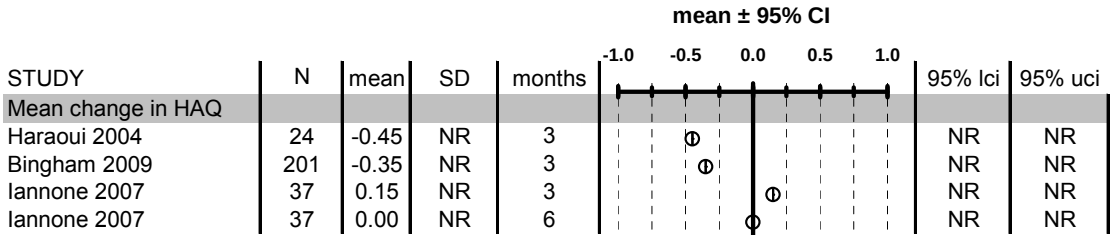
STUDY	N	n	months	%	lci (%)	uci (%)
Good						
Buch 2007	72	9	3	12.5	5.9	22.4
Cohen 2005	24	11	12	45.8	25.6	67.2
Good/Moderate						
Buch 2007	72	44	3	61.1	48.9	72.4
Bingham 2009	201	117	3	58.2	51.1	65.1
Cohen 2005	24	14	12	58.3	36.6	77.9

Figure 12 Etanercept EULAR response rates

HAQ

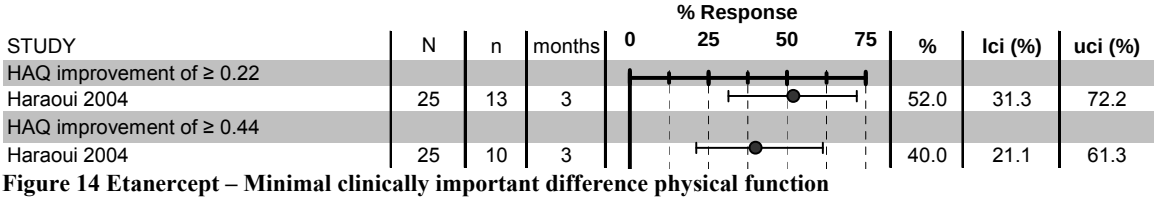
Three studies reported mean changes from baseline in HAQ score (Figure 13.In Haraoui 2004 [96], the change in HAQ score was -0.45. However, it was not reported whether this change was statistically significant or not. For Iannone 2007 [100], the value of HAQ remained substantially unchanged at 16 weeks (0.9) and 24 weeks (0.75) compared to the baseline value (0.75). In Bingham 2009 [102], there was a mean decrease in HAQ score of 0.35 at three months, this correspond to 22% decrease from baseline. This change was statistically significant.

One study[96] reported percentage of patients that achieved minimal clinically important difference (MCID) in physical function (Figure 14). Minimal clinically important difference was defined as a change of at least 0.22 in HAQ score. The percentage of patients that achieved MCID was 52%. About 40% of patients experienced physical function twice the value considered to represent MCID.



STUDY	N	mean	SD	months	95% lci	95% uci
Mean change in HAQ						
Haraoui 2004	24	-0.45	NR	3	NR	NR
Bingham 2009	201	-0.35	NR	3	NR	NR
Iannone 2007	37	0.15	NR	3	NR	NR
Iannone 2007	37	0.00	NR	6	NR	NR

Figure 13 Etanercept – mean change from baseline in HAQ score



STUDY	N	n	months	%	lci (%)	uci (%)
HAQ improvement of ≥ 0.22						
Haraoui 2004	25	13	3	52.0	31.3	72.2
HAQ improvement of ≥ 0.44						
Haraoui 2004	25	10	3	40.0	21.1	61.3

Figure 14 Etanercept – Minimal clinically important difference physical function

Quality of life

None of the studies assessed quality of life

Joint damage

None of the studies assessed joint damage

Serious adverse events

Two studies reported serious adverse events. Figure 15 presents reported serious adverse events. Haraoui 2004[96] reported that no serious adverse events occurred during the study. Bingham 2009[102] found that 5% of the patients experienced serious adverse event during the study period.

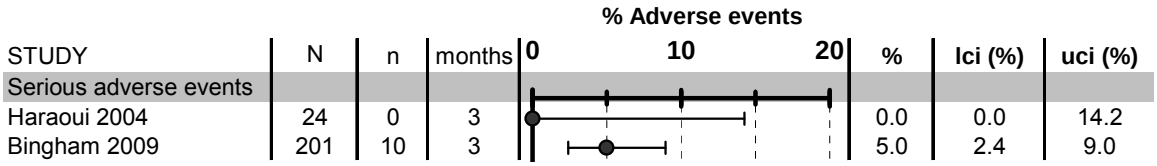


Figure 15 Etanercept reported serious adverse events

Infection and serious infection

Three studies reported infection and serious infection. Figure 16 presents reported infection and serious infection. One study[102] reported that two patients (1%) experienced serious infections events. The percentages of patients treated with etanercept who reported any infection ranged from 4.1% to 8.3%

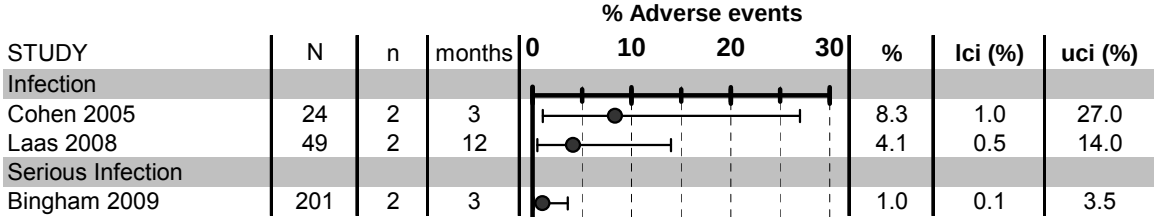


Figure 16 - Etanercept reported infection or serious infection

Injection/ infusion reaction

No study reported injection or infusion reaction

5.3.2.5. Summary

For the assessment of effectiveness of etanercept after failure of infliximab seven uncontrolled studies were identified. Follow-up duration ranged from 12 weeks to over nine months. All patients included in the studies are generally similar. Main results are summarised in the Table 14.

Table 14 Etanercept – summary results

Outcome	3 months	6 months	9 months or over
Withdrawals: • for any reason • due to lack of efficacy • due to adverse events	 6.5-12.5%. 0.0-2.9% 0.0-1.2%	 NR NR NR	 40.8-58.3% 24.5-29.2% 12.5-16.3%
ACR20 response	37.5-72.0%	NR	NR
ACR50 response	18.4-64.0%	NR	NR
ACR70 response	4.2-20.0%	NR	NR
EULAR response • Overall response • Moderated response • Good response • Remission	 58.2-61.1 12.5	 NR NR	 58.3 45.8
DAS28			
• Mean change from baseline	-1.47 to -1.60	NR	-0.47
• Mean at time point			
DAS44			
• Mean change from baseline	-0.70	-0.90	NR
HAQ: mean change from baseline	0.15 to -0.45	0.00	NR
Quality of life	NR	NR	NR
Joint damage	NR	NR	NR
Serious adverse events	0.0-5.0%	NR	NR
Any infections Serious infections	8.5 1.0	NR NR	4.1 NR
Infusion reaction	NR	NR	NR

5.3.3 Infliximab

5.3.3.1. Overview of evidence

Three studies were identified that assessed infliximab in comparison with standard care: one uncontrolled† prospective study (Yazici 2004[105]) and two uncontrolled retrospective studies (Ang 2003[103] and Hansen 2004[104]).

All included patients had tried one TNF inhibitor (etanercept) before. Reasons for discontinuation included lack of efficacy, toxicity drug shortage, patient concerns about safety and thrombocytopenia.

All studies were conducted in the USA. Duration of follow-up was unclear in all three studies.

Further details are provided in Table 15.

Table 15 Infliximab - characteristics of included studies

Study	Country	Design	Reason for switching	Prior TNF inhibitors; no.	Treatment arms (no. of patients)	Duration of follow-up	Comments
Randomised controlled trials (none were identified)							
Non-randomised comparative studies (none were identified)							
Uncontrolled studies							
Ang 2003[103]	USA	uncontrolled retrospective	Inadequate response, toxicity	ETN; 1	IFX (24)	unclear	Average treatment duration 8.2 months
Hansen 2004[104]	USA	uncontrolled retrospective	lack of efficacy, drug shortage, patient concerns about safety, thrombocytopenia	ETN; 1	IFX (20)	unclear	
Yazici 2004[105]	USA	uncontrolled prospective	Inefficacy	ETN; 1	IFX (21); IFX (41)	unclear	Group with 41 patients received 1st TNF inhibitor

† This study had a control group consisting of patients who were given their first biologic drug. This control group was not relevant to this report and therefore the study was utilised as uncontrolled.

5.3.3.2. Patient characteristics

All three studies were rather small with the number of patients treated with infliximab ranging from 20 to 24. They provided very little information about the baseline characteristics of included patients. However, based on the available information there might be some baseline differences between study populations.

- In two studies the percentage of female participants ranged from 60% to 89.6%; Yazici 2004 did not provide any information;
- In two studies the mean age was 48 years and 61 years; it was not reported in Ang 2003;
- In two studies disease duration was 9.25 and 13.4 years; it was not reported in Ang 2003;
- In two studies 34.4% to 65% of patients were RF positive; no information was provided in Yazici 2004;
- In Ang 2003 62% of patients were receiving MTX and 31% leflunomide; in Hansen 2004 all patients were receiving leflunomide and some of them also other DMARDs (azathioprine, sulfasalazine, MTX, prednisone); Yazici 2004 did not report concomitant DMARDs;
- Only one study (Hansen 2004) reported that 75% of patients were receiving concomitant prednisone;
- Two studies reported the number of previous DMARDs – it ranged from 0 to over 5; it was not reported in Hansen 2004;
- The mean number of previous TNF inhibitors was reported only in one study (Hansen 2004) – patients had tried one previous TNF inhibitor;
- None of the studies reported the baseline HAQ or DAS score;
- Only one study (Hansen 2004) reported that patients had a mean of 14 tender and 14 swollen joints at baseline;
- Only one study (Hansen 2004) reported the baseline ESR (mean 13 mm/hr) and CRP (mean 23.8 mg/dL).

Table 16 Infliximab - baseline patient characteristics

	number of patients/ % female	age; mean (SD); years	RA duration; mean (SD); years	RF positive; %	concomitant DMARDs and steroids	number of previous DMARDs; mean (SD)	number of previous TNF inhibitors; mean (SD)	HAQ; mean (SD)	DAS28; mean (SD)	tender/ swollen joint count; mean (SD)	ESR; mean (SD); mm/hr	CRP; mean (SD); mg/dL
Ang 2003[103]	24/ 89.6%*	NR	NR	34.4%*	MTX (62%), leflunomide (31%)*	0 to >5*	NR	NR	NR	NR	NR	NR
Hansen 2004[104]	20/ 60%	48 (NR)	9.25 (NR)	65%	Leflunomide (100%); azathioprine (5%); sulfasalazine (5%); MTX (10%); prednisone (75%)	NR	1	NR	NR	14 (NR)/ 14 (NR)	13 (NR)	23.8 (NR)
Yazici 2004[105]	21/ NR	61 (12.1)**	13.4 (9.8)**	NR	NR	2**	NR	NR	NR	NR	NR	NR

* including 5 patients from IFX→ETN group
** based on data for 88 patients including patients who were given IFX as the first biologic

5.3.3.3. Quality assessment

Of the three identified studies two were uncontrolled retrospective analyses. One study was uncontrolled and prospective. None of the studies reported inclusion criteria. It was unclear if consecutive patients were included in Yazici 2004 and this item was not applicable to retrospective studies. 28.6% were withdrawn from Yazici 2004 and this percentage was unclear in the remaining two studies. Details of quality assessment are reported in Table 17.

Table 17 Infliximab - non-RCT quality assessment

	Study design	Inclusion criteria clearly defined?	Were consecutive patients included in the study?	Patients withdrawn (%)	Comments
Ang 2003[103]	uncontrolled retrospective	No	n/a	unclear	
Hansen 2004[104]	uncontrolled retrospective	No	n/a	unclear	
Yazici 2004[105]	uncontrolled prospective	No	unclear	28.6%	

5.3.3.4. Results

Table 18 indicates which of the outcomes reported in the main text of the report were assessed in individual studies and Table 19 provides similar information for outcomes described in Appendix 10.10 only.

Table 18 Infliximab - outcomes assessed in studies and reported in the main text of the report

	Total withdrawal	Withdrawal by reason	ACR (20/50/70)	DAS28	EULAR response	HAQ	Quality of life	Joint damage	Serious adverse events	Infection/ serious infection	Injection/ infusion reaction
Ang 2003[103]											
Hansen 2004[104]		√								√	√
Yazici 2004[105]	√			√							

Table 19 Infliximab- outcomes assessed in studies and reported in the appendix only

	Other measures of disease activity	Fatigue	Pain	TJC/ SJC	CRP/ ESR
Ang 2003[103]					
Hansen 2004[104]	√			√	√
Yazici 2004[105]			√		

Withdrawals

Withdrawal for any reason was assessed only in Yazici 2004, withdrawal due to lack of efficacy only in Hansen 2004 and withdrawal due to adverse events was not assessed in any of the studies. Details are reported in Figure 17. Yazici 2004 reported that 28.6% of patients were withdrawn from the study due to any reason (follow-up unclear). Ten percent of patients were withdrawn from Hansen 2004 due to lack of efficacy (follow-up unclear).

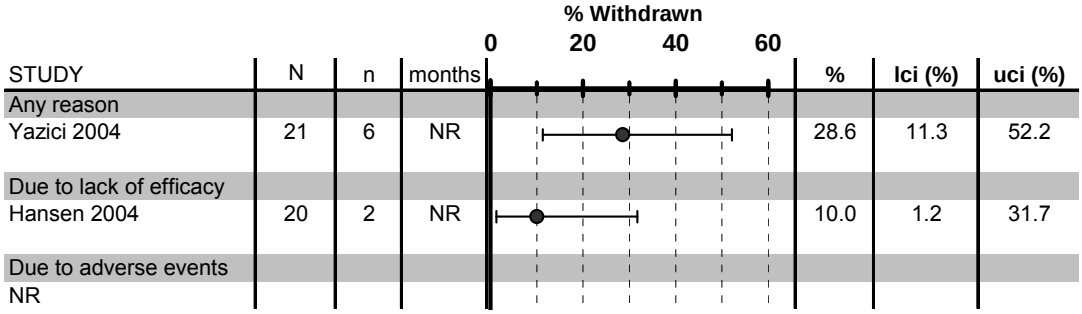


Figure 17 Infliximab - withdrawals

ACR20 response

None of the studies assessed ACR20 response.

ACR50 response

None of the studies assessed ACR50 response.

ACR70 response

None of the studies assessed ACR70 response.

DAS28

The only information on DAS28 change came from Yazici 2004 and the authors claimed that at 12 months patients “improved significantly”.

EULAR response

EULAR response was not assessed in any of the studies.

HAQ

The only information on HAQ change came from Yazici 2004 and the authors claimed that at 12 months patients “improved significantly”.

Quality of life

Quality of life was not assessed in any of the studies.

Joint damage

Joint damage was not assessed in any of the studies.

Serious adverse events

Serious adverse events were not assessed in any of the included studies.

Infections/ serious infections

Details of infections are reported in Figure 18. Fifteen percent of patients in Hansen 2004 experienced an infection (follow-up was unclear). No other studies reported infections. Serious infections were not reported in any of the studies.

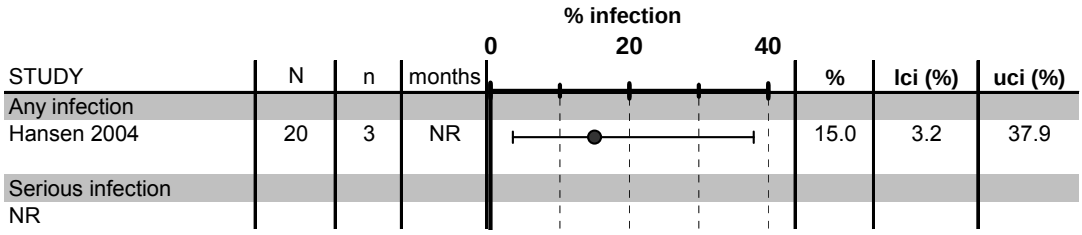


Figure 18 Infliximab - infections

Injection/ infusion reaction

There were no infusion reactions in Hansen 2004. Other studies did not report this outcome.

5.3.3.5. Infliximab in comparison with an ongoing biologic agent

One RCTs (OPPOSITE[131]) was identified that compared infliximab to ongoing etanercept. Although the study met the inclusion criteria of the systematic review, this comparison was not considered relevant to this report and therefore the study was not analysed.

It was a multicentre randomised trial and included 27 patients who had active RA and had an *"incomplete response to etanercept"*. Patients were randomised to either discontinue etanercept and receive infliximab (13 patients), or to continue etanercept treatment (14 patients). The follow-up duration was 30 weeks. Data was collected on outcomes including ACR response, HAQ, radiological progression, serum biomarker levels and safety.

5.3.3.6. Summary

Three studies compared infliximab with standard care: two uncontrolled retrospective (Ang 2003 and Hansen 2004) and one uncontrolled prospective (Yazici 2004). They included small numbers of patients ranging from 20 to 24. Follow-up was unclear in all of them. There was little information about baseline characteristics, however it seems that there may be some –if small - differences between studies. Main results of included studies are summarised in Table 20.

Table 20 Infliximab - summary of main results

Outcome	Uncontrolled studies Unclear follow-up
Withdrawals: • for any reason • due to lack of efficacy • due to adverse events	 28.6% (reported in one study) 10% (reported in one study) NR
ACR20 response	NR
ACR50 response	NR
ACR70 response	NR
DAS28	Only one study included a statement that at 12 months patients "improved significantly"
EULAR response	NR
HAQ	Only one study included a statement that at 12 months patients "improved significantly"
Quality of life	NR
Joint damage	NR
Serious adverse events	NR
Any infections Serious infections	15% (reported in one study) NR
Infusion reaction	0 (reported in one study)

5.3.4 TNF inhibitors as a class

5.3.4.1. Overview of evidence

This section reports on studies that test use of TNF-inhibitor after failure of the first as a class. No RCT was found. One controlled [119-121] and six uncontrolled observational studies[106-111] were identified. In Finckh 2007, 2009[134,135] lack of efficacy was the primary reason for switching between different TNF inhibitors. In Hyrich 2009,[119-121] Gomez-Reino 2006[106] and Blom 2009[111] patients switched to another TNF inhibitor due to lack of efficacy or adverse events. In Hjardem 2007,[108] Duftner 2008,[109] and Karlsson 2008[110] patients switched to other TNF inhibitors due to lack of efficacy, adverse events or any other reason. The reason for changing from one TNF inhibitor to another was unclear in Solau-Gervais 2006[107]. Hyrich 2009[119-121] used data from the British Society of Rheumatology Biologic Registers. The others studies were carried out in Switzerland, Spain, France, Denmark, Austria, Sweden, and the Netherlands. The length of follow-up ranged from 3 months to up to 4 years. Further details are provided in Table 21.

Table 21 TNF inhibitors as class – characteristics of included studies

Study	Country	Design	Reason for switching	Prior TNF inhibitors (no.)	Treatment arms (no. of patients)	Duration of follow-up	Comments
Randomised controlled trial (none were identified)							
Non-randomised comparative studies							
Hyrich 2009[119-121]	UK	Cohort	inefficacy, adverse event	etanercept, infliximab, adalimumab	TNF inhibitor (all switchers: n=534; stoppers: n=202)	>6 months	
Uncontrolled studies							
Gomez-Reino 2006[106]	Spain	uncontrolled, prospective	adverse events, lack of efficacy	infliximab, etanercept	TNF inhibitor (n=448)	2 years	Including other forms of arthritis (ankylosing spondylitis, psoriatic arthritis and other chronic arthritis; n=385 for RA)
Solau-Gervais 2006[107]	France	Uncontrolled prospective	Unclear	any	TNF inhibitor (n=70)	>3 months	
Hjardem 2007[108]	Denmark	Uncontrolled retrospective	inefficacy, adverse event, other	etanercept, infliximab, adalimumab	TNF inhibitor (n=235)	3 months	
Duftner 2008[109]	Austria	Uncontrolled retrospective	inefficacy, adverse event, other	Infliximab, etanercept, adalimumab	TNF inhibitor (n=109)	up to 4 years	length of follow-up including 1st line; reported 12-month drug continuation rate for 2nd, 3rd and 4th line
Karlsson 2008[110]	Sweden	Uncontrolled retrospective	inefficacy, adverse event, other	any	TNF inhibitor (n=337)	3 months	2 and 3 line separately
Blom 2009[111]	The Netherlands	Uncontrolled retrospective	Nonresponse, loss of response, and adverse events	IFX, ETN,ADA	IFX, ETN,ADA (n=197)	6 months	
Finckh 2009[134 135]	Switzerland	Prospective cohort	Inadequate response	Any (≥1)	Rituximab (n=155) Alternative TNF inhibitor (n=163)	11 months (median)	Based on the Swiss Clinical Quality Management program for RA (SCQM-RA).

5.3.4.2. Patient characteristics

Full details of patients' characteristics are reported in Table 22. The number of patients included in the studies ranged from 70 to 818. Patient characteristics were generally similar across the eight studies:

- percentage of female patients ranged from 67% to 89%;
- where reported mean age ranged from 50.6% to 58 years;
- where reported mean disease duration ranged from 8.0 to 14.7 years;
- where reported percentage of rheumatoid factor positive patients ranged from 51.5% to 81%;
- where reported concomitant DMARDs: 61% to 75% were on MTX; 55% to 68% of patients were receiving corticosteroids;
- where reported the number of previously used conventional DMARDs varied from 4.0 to 4.7;
- where reported most studies included patients on previous infliximab, etanercept, and adalimumab;
- where reported the mean baseline HAQ ranged from 1.4 to 1.9;
- where reported the mean DAS28 score ranged from 4.1 to 6.5;
- the mean number of tender and swollen joints was only reported in one study (tender: 9.3 and swollen: 8.4);
- where reported mean baseline ESR ranged from 34 to 36 mm/hour;
- the baseline CRP was only reported in one study (2.8 mg/dL).

Table 22 TNF inhibitor as a class – baseline patient characteristics

	Number of patients/ % female	age; mean (SD); years	RA duration; mean (SD); years	RF positive; %	concomitant DMARDs and steroids	number of previous DMARDs; mean (SD)	number of previous TNF inhibitors; mean (SD)	HAQ; mean (SD)	DAS28; mean (SD)	tender/ swollen joint count; mean (SD)	ESR; mean (SD); mm/hr	CRP; mean (SD); mg/dL
Hyrich 2009 [119-121]	818/79.9 %	58(11.1)	10(8.9)			4(1.5)	NR	1.9 (0.63)	6.47(0.97)	NR	NR	NR
Gomez-Reino 2006[106]	448/67%	NR	NR	NR	NR	NR		NR	NR	NR	NR	NR
Solau-Gervais 2006 [107]	70/86%	56.5	14.7	81		4.3	ETN(30-48), IFX(40-60), ADA(10-12)	NR	5.98	NR	NR	NR
Hjardem 2007 [108]	235/75	55(11.85)	8(9.6)	NR	MTX(75%), prednisone, corticosteroids	4(1.5)	IFX, ETN, ADA	NR	5.2(1.33)	NR	NR	NR
Duftner 2008 [109]	109/89	50.6(12.4)	8.0(7.5)	NR	NR	NR	IFX(27), ETN(22.3), ADA(36.5)	NR	NR	NR	NR	NR
Karlsson 2008 [110]	337/82	56(13)	14(10)	NR	MTX, corticosteroid (68%)	4.7(1.9)	First TNF inhibitor: ETN(20), IFX(73), ADA(7.7);Second TNF inhibitor : ETN(58), IFX(8.3), ADA(34)	1.4(0.6)	5.5(1.3)	9.3(6.8)/ 8.4(5.9)	36(25)	28 (35)
Blom 2009[111]	197/71.3 %	54.8	7.9	51.5	MTX, steroid	NR	IFX(37-60), ETN(16-33), ADA(23-33	NR	5.09(1.18)	NR	NR	NR
Finckh 2009 [134 135]	163 / 78%	55 (13)	11 (7)	77%	MTX 61% Steroids 55%	NR	1 (1 to 1)	1.4 (10.67)	4.1 (1.3)	NR	NR	NR

5.3.4.3. Quality assessment

One study was comparative [119-121].. Two studies [106,107] were uncontrolled and prospective. Four studies were uncontrolled and retrospective[108-111]. Although Finckh 2009 [134,136] was a non-randomized comparative study, the control arm was inappropriate for this section and as such the data from this are not considered. Full details of quality assessment are reported in Table 23. Most studies stated clearly their inclusion criteria. The inclusion criteria were unclear in two studies [106,108]. It was unclear in most studies whether consecutive patients included in the study met inclusion criteria. Percentage of patients withdrawn was not applicable in most studies as they were based on retrospective analysis of registries.

Table 23 TNF inhibitors as class – non-RCT quality assessment

Study	Design	Inclusion criteria clearly defined?	Were consecutive patients included in the study?	Patients withdrawn (%)	Comments
Hyrich 2009 [119-121]	Prospective Cohort	Yes	Unclear	Unclear	
Gomez-Reino 2006 [106]	Uncontrolled, prospective	Unclear	n/a	Unclear	
Solau-Gervais 2006 [107]	Uncontrolled prospective	Yes	Unclear	Unclear	
Hjardem 2007 [108]	Uncontrolled retrospective	Unclear	Unclear	n/a	
Duftner 2008 [109]	Uncontrolled retrospective	Yes	n/a	n/a	
Karlsson 2008 [110]	Uncontrolled retrospective	Yes	No	n/a	
Blom 2009 [111]	Uncontrolled retrospective	Yes	n/a	n/a	
Finckh 2009[134] [135]	Prospective cohort	Yes	Unclear	n/a	

5.3.4.4. Results

Table 24 and Table 25 below state the outcomes were measured in each study and whether they are reported in the main text or appendix of this report.

Table 24 TNF inhibitors as class - outcomes assessed in studies and reported in the main text of the report

	Total withdrawal	Withdrawal by reason	ACR (20/50/70)	DAS 28	EULAR response	HAQ	Quality of life	Joint damage	Serious adverse events	Infection/ serious infection	Injection/ infusion reaction
Hyrich 2009 [119-121]						√					
Gomez-Reino 2006 [106]											
Solau-Gervais 2006 [107]											
Hjardem 2007 [108]	√	√		√	√				√	√	
Duftner 2008 [109]	√									√	
Karlsson 2008 [110]			√	√	√						
Blom 2009[111]	√	√		√	√						
Finckh 2009[134 135]				√							

Table 25 TNF inhibitors as class - outcomes assessed in studies and reported in the appendix only

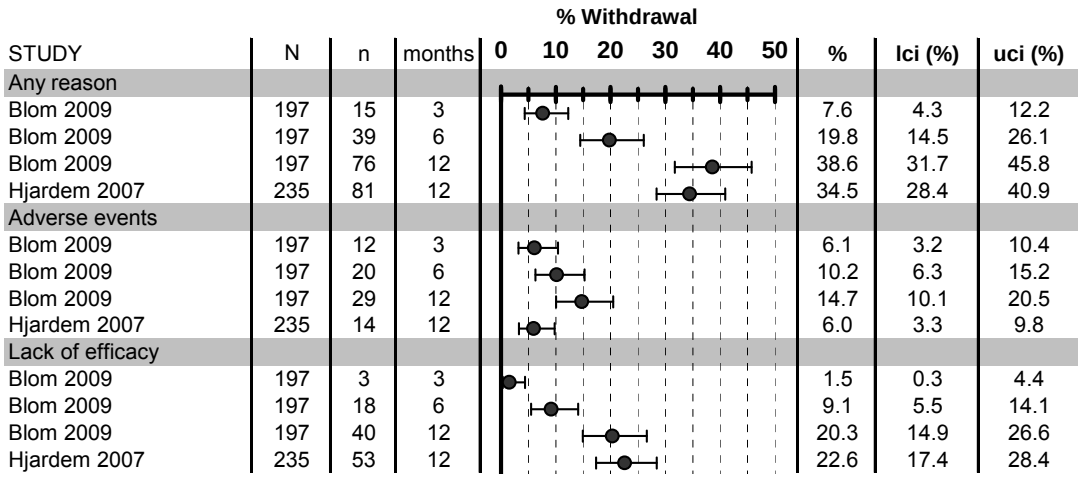
	Other measures of disease activity	Fatigue	Pain	TJC/ SJC	CRP/ ESR
Hyrich 2009[119-121]					
Gomez-Reino 2006 [106]					
Solau-Gervais 2006 [107]					
Hjardem 2007 [108]					
Duftner 2008 [109]					
Karlsson 2008 [110]					
Blom 2009 [111]					
Finckh 2009[134 135]				√	√

Withdrawals

Two studies reported withdrawals and the reasons for withdrawing from treatment (Figure 19). The percentage of patients that withdrew due to any reason ranged from 7.6% (at 3 months) to 38.6% (at 12 months). The percentage of patients that withdrew due to adverse events ranged

from 6.1% (at 3 months) to 10.2% (at 6 months), At 12 months, the percentage of patients that withdrew to adverse events ranged from 6.0% to 14.7%. The percentage of patients that withdrew due to lack of efficacy ranged from 1.5% (at 3 months) to 22.6% (at 12 months).

One study reported 1-year drug survival[106]. Gomez-Reino[106] reported that 1-year drug survival was 0.79 (95% CI 0.74 to 0.83). Two studies reported median drug survival[108,109]. Hjardem 2007[108] and Duftner 2008 reported that the median drug survival was 37 weeks and 8.0 months (range: 0 to 43.7 months).

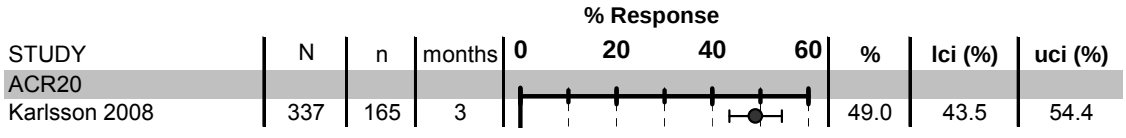


STUDY	N	n	months	%	lci (%)	uci (%)
Any reason						
Blom 2009	197	15	3	7.6	4.3	12.2
Blom 2009	197	39	6	19.8	14.5	26.1
Blom 2009	197	76	12	38.6	31.7	45.8
Hjardem 2007	235	81	12	34.5	28.4	40.9
Adverse events						
Blom 2009	197	12	3	6.1	3.2	10.4
Blom 2009	197	20	6	10.2	6.3	15.2
Blom 2009	197	29	12	14.7	10.1	20.5
Hjardem 2007	235	14	12	6.0	3.3	9.8
Lack of efficacy						
Blom 2009	197	3	3	1.5	0.3	4.4
Blom 2009	197	18	6	9.1	5.5	14.1
Blom 2009	197	40	12	20.3	14.9	26.6
Hjardem 2007	235	53	12	22.6	17.4	28.4

Figure 19 TNF-inhibitor as a class - withdrawals in the studies by reasons

ACR20 response

ACR20 response was assessed in one study (Figure 20). Karlsson 2008 [110] reported that 3 months ACR20 response rate was 49.0% (95% CI 43.5% to 54.4%).



STUDY	N	n	months	%	lci (%)	uci (%)
ACR20						
Karlsson 2008	337	165	3	49.0	43.5	54.4

Figure 20 TNF-inhibitor as a class – ACR20 response

ACR50 response

ACR50 response was assessed in one study (Figure 21). Karlsson 2008 [110] reported that 3 months ACR50 response rate was 25.8% (95% CI 22.3% to 32.1%).

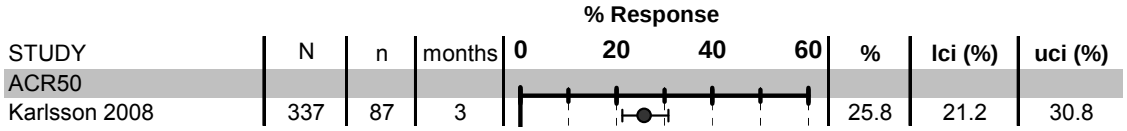


Figure 21 TNF-inhibitor as a class – ACR50 response

ACR70 response

ACR70 response was assessed in one study (Figure 22). Karlsson 2008 [110] reported that 3 months ACR70 response rate was 7.1% (4.6% to 10.4%)

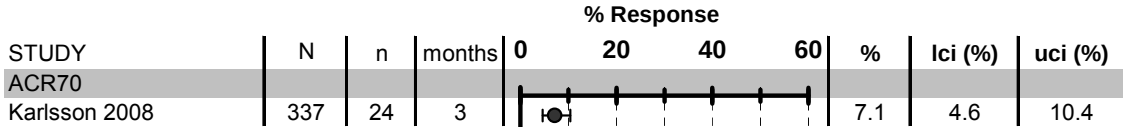


Figure 22 TNF-inhibitor as a class – ACR70 response

DAS

Three studies reported mean changes from baseline in DAS28 score (Figure 23). The mean decrease in DAS28 ranged from 0.88 (at 6 months) to 1.00 (at 3 months). Two studies[110,111] reported low disease activity (DAS28 <3.2) (Figure 24). At 3 months the percentage of patients with low disease activity ranged from 14.2% to 29.1%. One study reported DAS28 remission (DAS28 <2.6) (Figure 24). Karlsson 2008[110] reported that 15.4% (95% CI 11.7% to 19.7%) of patients were in remission.

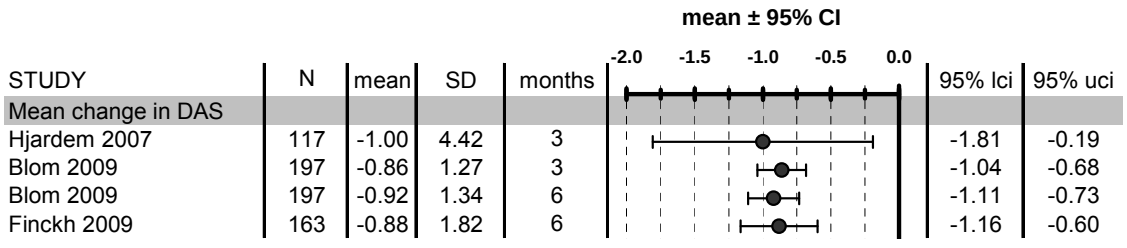


Figure 23 TNF inhibitor as a class – mean changes from baseline in DAS

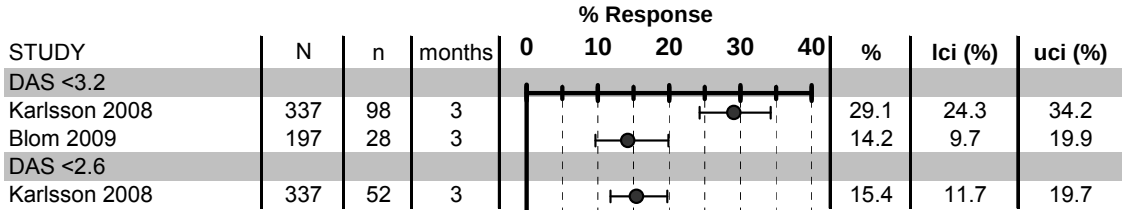


Figure 24 TNF inhibitor as a class – low disease activity (DAS28 <3.2) and remission (DAS28 <2.6)

EULAR response

Three studies[108,110,111] reported percentages of patients that achieved good and good to moderate EULAR responses (Figure 25). The percentage of patients that achieved good EULAR response ranged from 9.8% (at 3 months) to 36.7% (at 6 months). The percentage of patients that achieved good to moderate EULAR response ranged from 31.5% to 64.7% at 3 months. Only one study reported good to moderate EULAR response at 6 months (32.5%).

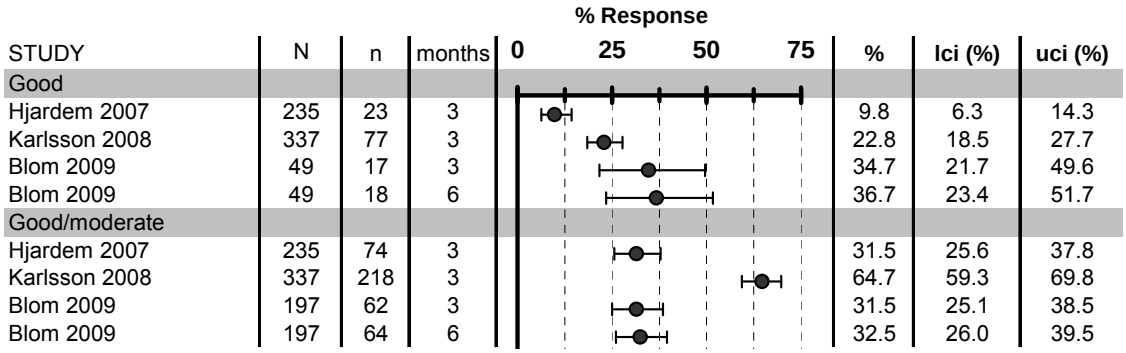


Figure 25 TNF inhibitor as a class EULAR response rates

HAQ

Only one study reported mean changes from baseline in HAQ score (Figure 26). Hyrich 2009 [119-121] compared patients that discontinued TNF inhibitor within the first 12 months and did not start a subsequent TNF inhibitor or other biologic drug during the next 12 months ('Stoppers') with patients that stopped their first TNF inhibitor within the first 12 months of therapy due to lack of efficacy but started a second TNF inhibitor during the subsequent 12 months (Switchers). The mean changes in HAQ score was adjusted for differences in age, gender, disease duration, HAQ score at first failure, DAS28 at start of first TNF inhibitor, and DAS28 score at first failure. 'All

Switchers' (adjusted mean change=-0.11; 95% CI -0.18 to -0.04) had significant greater improvement in HAQ score than 'Stoppers' (Figure 26).

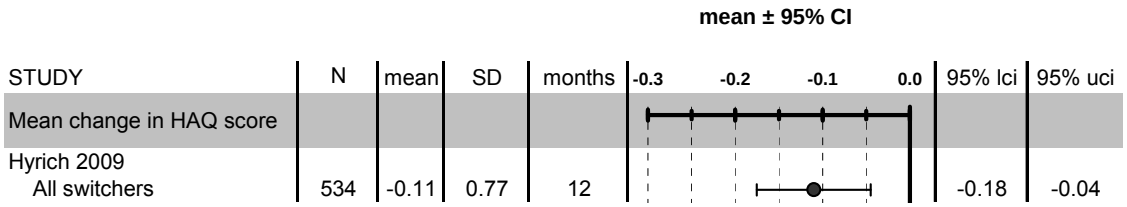


Figure 26 TNF inhibitor as a class – adjusted[c] mean change from baseline in HAQ score

Quality of life

No study reported quality of life

Joint damage

No study reported joint damage

Serious adverse events

Only one study reported serious adverse events (Figure 27). Hjardem 2007[108] reported that 6.0% (95% CI 3.3% to 9.8%) of the patients experienced serious adverse event during the study period.

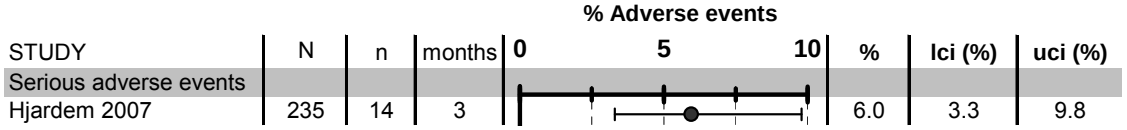


Figure 27 TNF inhibitor as a class reported serious adverse events

Infection and serious infection

Two studies reported infection and serious infection (Figure 28). At 3 months the percentage of patients that experienced infection ranged from 27.2% to 28.1%. One study[109] reported that 13.9% (95% CI 9.1% to 19.9%) of the patients experienced serious infections events at 3 months.

[c] adjusted for age, gender, disease duration, HAQ score at first failure, DAS28 at start of first TNF inhibitor, and DAS28 score at first failure

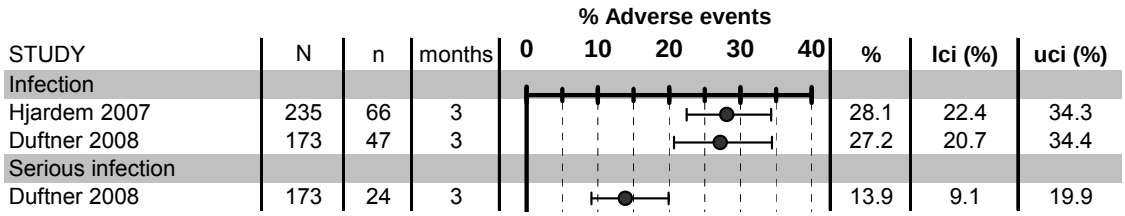


Figure 28 - TNF inhibitor as a class reported infection or serious infection

Injection / infusion reaction

No study reported injection or infusion reaction

5.3.4.5. Summary

For the assessment of effectiveness of TNF inhibitor after failure of the first as a class three nonrandomised comparative and six uncontrolled studies were identified. Follow-up duration ranged from 3 months to 4 years. All patients included in the studies are generally similar. Main results are summarised in the Table 26.

Table 26 TNF inhibitor as a class – summary results

Outcome	3 months	6 months	9 months or over
Withdrawals:			
• for any reason	7.6%	19.8%	34.5-38.6%
• due to lack of efficacy	1.5%	9.1%	20.3-22.6%
• due to adverse events	6.1%	10.2%	6.0-14.7%
ACR20 response	49.0%	NR	NR
ACR50 response	25.8%	NR	NR
ACR70 response	7.1%	NR	NR
EULAR response			
• Overall response	NR	NR	NR
• Moderated response	31.5-64.7%	NR	NR
• Good response	9.8-36.7%	NR	NR
• Remission	NR	NR	NR
DAS28			
• Mean change from baseline	-1.00 to -0.86	-0.92 to -0.88	NR
• Mean at time point			
DAS28 <3.2	14.2-29.1%	NR	NR
DAS28 <2.6	15.4%	NR	NR
HAQ: mean change from baseline	NR	NR	-0.11*
Quality of life	NR	NR	NR
Joint damage	NR	NR	NR
Serious adverse events	6.0%	NR	NR
Any infections	27.2-28.1%	NR	NR
Serious infections	13.9%	NR	NR
Infusion reaction	NR	NR	NR

* adjusted for age, gender, disease duration, HAQ score at first failure, DAS28 at start of first TNF inhibitor, and DAS28 score at first failure

5.3.5 Rituximab

5.3.5.1. Overview of evidence

Seven studies were identified that assessed rituximab in comparison with standard care: one RCT (REFLEX[122-124]), six uncontrolled studies[112-116,134,135]. One of these (Finckh 2009[134,135]) contained a comparative arm with an alternative TNF inhibitor; the comparative data is described in section 5.6.1. In one study (Keystone 2007[114]) analysing pooled data from patients of which nearly a half were prior TNF inhibitor naïve, only data reported separately for those who had prior TNF inhibitor were included in this report. In another study (Thurlings 2008[116]) at 6 months 17 patients (including five TNF inhibitor naïve at original baseline) started a second course of TNF inhibitor; data for this group of patients was excluded from the report.

Data from one cohort analysis of the REFLEX RCT extension and one pooled analysis of all rituximab development studies from the manufacturer's[137] submission are also described. The REFLEX extension was a long-term follow up analysis of repeated treatment data of the original RCT; it included patients who had responded to an initial course of rituximab during the RCT and received open-label treatment of the same rituximab regimen for up to 3 repeat treatment courses[‡]. Placebo patients in the RCT were also included and received their first course of rituximab within the extension study. A total of 480 patients from the RCT (308 from the rituximab and 172 from the placebo) entered the extension phase.

The manufacturer's pooled analysis combined data of patients from the REFLEX RCT, together with data from its open-label extension study, and also from other studies in manufacturer's rituximab development programme[*]. It is unclear how many patients from the REFLEX trial were included in the pooled analysis.

The Keystone uncontrolled study[114]also reported data for up to two treatment courses; these data are presented with those from the REFLEX extension and the rituximab pooled analysis.

The REFLEX trial was a multi-centre RCT conducted in 114 counties in the US, Europe, Canada and Israel. Of the six uncontrolled studies one was conducted in Switzerland, one in

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[‡] Responding patients in the initial RELFLEX RCT after reaching the primary endpoint at week 24 requiring further courses of rituximab treatment entered the open-extension study.

[*] Data were pooled for patients who only received the expected licensed dose of rituximab 2 x 1000 mg plus MTX regimen for first and subsequent courses and who received prior TNF inhibitor therapy.

the UK, one in Sweden, one in Netherlands and one in France. For the studies included in the Keystone analysis[114], and for those included in the manufacturer's pooled analysis except the REFLEX trial[137] it is unclear in which country the studies were conducted.

Further details are provided in Table 27.

5.3.5.2. Patient characteristics

Data on patient baseline characteristics can be found in Table 28. Patient characteristics were not reported for the manufacturer's pooled analysis, and were not reported separately for the patients who had prior TNF inhibitor in the Keystone 2007 analysis.

The number of patients included in the REFLEX RCT was 517 and ranged from 20 to 155 in the six uncontrolled studies. Where reported, characteristics of the patients included in the studies varied in some aspects but are generally similar:

- 77% to 86% were female;
- mean age ranged from 52 to 58 years in four studies and median 54 to 55 in two studies.
- mean disease duration ranged from 10 to 15 years in four studies and median 12-16 years in two studies;
- the percentage of rheumatoid factor positive patients ranged from 79 to 90% and it was lowest in the REFELX study; one study and both analyses from the manufacturer's submission did not report this;
- concomitant DMARDs were reported in five studies: 30 to 100% patients were on MTX; all the patients in the REFLEX RCT were on concomitant DMARDs;
- 55 to 100% of patients were receiving concurrent steroids; one study did not report this;
- mean number of previously used conventional DMARDs reported in three studies ranged from 2.4 to 4.2, and median reported in the other two ranged from 3 to 4;
- where reported the mean number of previous TNF inhibitors was 1 or >1, and the median number reported in two uncontrolled studies was 2;
- the mean baseline HAQ was reported only in the REFELX study was 1.9, and the median baseline HAQ reported in two uncontrolled studies ranged from 1.6 to 2.6;

- where reported the mean DAS28 score ranged from 5.0 to 6.9 and it was the highest in the REFELX study;
- the mean number of tender joints was 34 and swollen joints was 23 in the REFLEX trial; the median was 26 and 13 respectively in Jois 2007; other studies did not reported baseline number of tender and swollen joints;
- baseline mean ESR was 48 mm/hr in REFLEX and median value 37 mm/hr and 56 mm/hr in other two studies;
- mean CRP was 3.7 mg/dl in the REFELEX trial and 3.2 in another study; median CRP was 1.9 and 2.9 in other two studies.

Table 27 Rituximab - characteristics of included studies

Study	Country	Design	Reason for switching	Prior anti-TNFs (no.)	Treatment arms (no. of patients)	Duration of follow-up	Comments
Randomised controlled trial							
REFLEX [122-124]	North America, Europe, Israel	Prospective, randomised controlled parallel,	Inadequate response or intolerance	Any (≥1)	RTX (n=308) PL (n=209)	24 weeks; 48 weeks**	Pivotal trial for anti-TNF inadequate responders
Uncontrolled studies							
Bokarewa 2007[112]	Sweden	Prospective Uncontrolled	lack of response	Any biologic (no. unclear)	RTX (n=48)	12 months	Dosing schedule different from licence; Not only TNF inhibitor failures; a few patients tried other biologics (anti-thymocyte globulin treatment, IL-1 receptor antagonist); 64% had experienced more than one biologic drug prior to rituximab treatment.
Jois 2007[113]	UK	Prospective Uncontrolled	lack of response	Any (≥2)	RTX (n=20)	6 months	All patients had failed at least two TNF inhibitors: 10 had failed all three TNF inhibitors (5 of them also failed anakinra), the others had failed at least two TNF inhibitors. Patients were offered re-treatment with a second cycle of RTX if they had responded to the earlier one but flared.
Keystone 2007[114]	Unclear	Retrospective Uncontrolled	Unclear	All had TNF inhibitor (no unclear)	RTX (n=155 to 158 §)	6 months §	A pooled analysis of 1039 patients who received ≥1 courses of RTX, 427 (41%) of whom were prior TNF inhibitor naïve. 570 of these patients had≥2 courses of RTX, 255 (45%) of whom were prior TNF inhibitor naïve. Only data that were reported separately for those who had prior TNF inhibitor were included in our report.
Assous 2008[115]*	France	Retrospective Uncontrolled	lack of response; contraindication	Any (no. unclear)	RTX (n=50)	6 months	20/50 patients had contraindication to TNF inhibitors; previous exposure to TNF inhibitor treatment was not clear in these patients
Thurlings 2008[116]	Netherlands	Prospective Uncontrolled	Side effects; inefficacy	Any (=1; >1?)	RTX (n=30)	6 months	Five patients were TNF inhibitor naïve; at 6 months 17 patients including the 5 TNF inhibitor naïve were retreated with a second RTX course, 7 patients (unclear how many of then were TNF inhibitor naïve at the beginning of the study) were retreated later with a third RTX course.

Finckh 2009[134,135]	Switzerland	Prospective cohort	Inadequate response	Any (≥1)	RTX (n=155)	11 months (median)	Based on the SCQM-RA.
REFLEX extension[137]	North America, Europe, Israel	Uncontrolled retrospective	Inadequate response or intolerance	Any (≥1)	RTX (n=480)		308 were from the RIX arm and 172 were from the placebo arm. Of these, 307 received two courses, 235 received three courses, 146 received four courses, and 58 received five courses.
Rituximab pooled analysis[137] ‡	NA	Uncontrolled retrospective	NR	Any (≥1)	RTX		A pooled analysis of data derived primarily from REFLEX RCT and its extension study, and also other studies in Roche's rituximab development programme. Data included only for patients who received prior TNF inhibiter treatment and who had received the licensed dose of RTX for first and subsequent courses.

*Only 30/50 patients who had inadequate response to previous anti-TNF treatment were included in the main analysis in this report. The remaining 20 patients were included only in sensitivity analyses.

§ Evaluable patients 24 weeks after two courses of RTX treatment and who had prior TNF inhibitor.

**REFLEX – data of long term efficacy from a single course of rituximab from the Roche submission [137]

‡ Data from the Roche submission [137]. Included were patients from the primary REFLEX study, its open-label extension study, and other studies in the rituximab development programme, data have been pooled for patients who only received the expected licensed dose of rituximab 2 x 1000 mg + MTX regimen for first and subsequent courses and who received prior TNF inhibitor therapy.

Table 28 Rituximab – baseline patient characteristics

	Number of patients, % female	Age; mean (SD); years	RA duration; mean (SD); years	RF positive; %	Concomitant DMARDs and steroids	Number of previous DMARDs; mean (SD)	Number of previous TNF inhibitors; mean (SD)	HAQ; mean (SD)	DAS28; mean (SD)	Tender/ swollen joint count; mean (SD)	ESR; mean (SD); mm/hr	CRP; mean (SD); mg/dl
REFLEX[12] 2-124	517, 81%	52 (12)	12 (8)	79%	MTX 100% Steroids 63.4%	2.5 (1.8)	1.5 (0.7)	1.9 (0.6)	6.9 (1.0)	34 (15) / 23 (12)	48 (27)	3.7 (3.9)
Bokarewa 2007 [112]	48, 79%	58 (11)	10 (7)	83%	MTX 77% Steroids 42%	4.2 (range 3 - 8)	64% had had >1 biologic previously	NR	6.1 mean (range 4.0 to 7.8)	NR^^	NR^^	NR^^
Jois 2007 [113]	20, 80%	54 (33 - 80)**	16 (5 to 39)**	90%	MTX 30% Steroids 60%)	3 (2 - 8)**	2 (2 - 4)**	2.6 (0.75 - 3)**	7.2 (5.3 - 9.0)**	26 (2-28)** / 13 (0 -26)**	56 (14 - 125)**	3.2 (0.3 - 17.4)
Keystone 2007 [114]‡	NR	NR	NR	NR	100% MTX Steroids 100%	NR	NR	NR	NR	NR	NR	NR
Assous 2008 [115]	50, 86%	58 (10)	15 (9)	90%	NR	3.5 (1.4)*	NR	NR	5.7 (4.2 - 8.7) **	NR	NR	1.9 (0.1 - 29.2)**
Thurlings 2008 [116]	24, 80%	55 (22 - 75)**	12 (1-50) **	NR	MTX 100% Steroids 100%	4 (2-9) **	1 (≥ 1?) (ETA; ADA; IFX)	NR	6.5 (1.1)	NR	37 (22-52) ^	2.9 (1.2-6.4)^
Finckh 2009[134,135]	155, 77%	55 (13)	12 (9)	88%	MTX 67% Steroids 58%	Not reported	2 (1 - 2)^	1.6 (1.1 - 2.0)^	5.0 (1.3)	NR	NR	NR
REFLEX extension [137]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rituximab pooled analysis[137]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

^Median and inter-quartile range

^^ Data presented separately in graphs for 'responders' and 'non-responders'

* Number of previous DMARDs excluding MTX. All patients had previously been treated with MTX.

**Median (range)

***Calculated using the following information: 30 patients had had TNF inhibitors; of them 10 had three anti-TNFs and 14 had two TNF inhibitors.

****One patient had vasculitis during previous etanercept treatment.

¶ Proportion of person-time MTX was taken during follow-up.

‡ Baseline data were reported based on all-exposure population and patients receiving >=2 courses RTX, nearly half of which were TNF naïve.

§ Baseline data prior to course 2 were available on only 559 patients for swollen joint count, 599 patients for tender joint count, and 558 patients for DAS28.

5.3.5.3. Quality assessment

(1) RCTs

The only RCT (REFLEX) was of good quality. Full details of quality assessment are reported in Table 29. Randomisation was appropriate and allocation concealment was not described in the paper but the allocation was likely concealed. Patients and outcome assessors were blinded. It was not clear if data analysts were aware of to which group patients were assigned. Withdrawal rate from the rituximab group and the placebo group was 18% and 46% respectively at week 24, and 63% and 89% respectively at week 48. ITT analysis was not used, as twenty one patients were excluded from analysis due to protocol violations.

Table 29 Rituximab - RCT quality assessment

Study	Was method of randomisation appropriate?	Was allocation adequately concealed?	Blinding			Patient withdrawal (%)	Was ITT used?	Comments
			patients	investigators/ outcome assessors	data analysts			
REFLEX 122-124	Yes	Unclear*	Yes	Yes**	Unclear	Week 24: rituximab 18%; placebo 46%. Week 48 ‡: rituximab 63%; placebo 89%	Yes***	21 of the randomised patients were excluded from the ITT population. See footnote.***

‡ Data from the Roche submission.
* Information not described in the papers but likely to be yes.
** Blinding of the efficacy assessor was potentially compromised in one of the centres. Patients enrolled in this centre were excluded from ITT analysis.
***A total of 21 patients were excluded from the ITT population, including those for whom treatment was unblinded due to rituximab vial breakage, those who never received treatment, those treated prior to randomisation, and those enrolled at a centre where the blinding of the efficacy assessor was potentially compromised. The authors stated that 'sensitivity analyses that included these patients demonstrated no change in the significance of the results'.

(2) Non-RCTs

All the non-RCTs were uncontrolled; four of these were prospective and two were retrospective. Full details of quality assessment are reported in Table 30. All stated clearly their inclusion criteria; however only in one study was it clear that consecutive patients were included. The percentage of patients withdrawn reported in one study was 25% (at 6 months), was unclear in two studies and not applicable in two retrospective studies as only patients with follow-up assessment were included.

(3) REFLEX extension and rituximab pooled analyses

Although some inclusion criteria were stated, in both analyses information on the study characteristics, patient characteristics and methodological appropriateness were insufficient, in particular in the pooled analysis. Outline details of quality assessment are reported in Table 30

Table 30. Rituximab – non-RCT quality assessment

Study (duration of follow-up)	Study design	Inclusion criteria clearly defined?	Were consecutive patients included in the study?	Patients withdrawn (%)	Comments
Bokarewa 2007 [112]	Prospective Uncontrolled	Yes	Unclear	NR	
Jois 2007 [113]	Prospective Uncontrolled	Yes	n/a	25% at 6 months	
Keystone 2007 [114]	Retrospective Uncontrolled	Yes	NR	n/a	
Assous 2008 [115]	Retrospective cohort	Yes	Yes	Unclear	
Thurlings 2008 [116]	Prospective Uncontrolled	Yes	NR	Unclear	Unclear for those who had subsequent courses at what time point the outcomes were assessed
Finckh 2009[134,135]	Prospective Uncontrolled	Yes	NR	n/a (only those with follow up assessment were included)	
REFLEX extension [137]	Prospective Uncontrolled	Yes	n/a	n/a	
Rituximab pooled analysis[137]	Retrospective Uncontrolled	Unclear	NR	NR	

5.3.5.4. Results

Table 31 and Table 32 present what outcomes were measured in the studies. Outcomes in Table 31 are reported and described in the main text of this report and those in Table 32 are reported in the Appendix 10.10 only. Outcome data from the rituximab arm in the RCT will be included in section on uncontrolled studies for comparison purposes. As data from the REFLEX extension cohort and the rituximab pooled analyses were analysed according to rituximab treatment courses, results of these analyses are described separately from the uncontrolled studies.

Table 31. Rituximab - outcomes assessed in studies and reported in the main text of the report

	Total withdrawal	Withdrawal by reason	ACR (20/50/70)	DAS28	EULAR response	HAQ	QoL	Joint damage	Serious adverse events	Infection/ serious infection	Injection/ infusion reaction
REFLEX[1] 22-124	√	√	√		√	√	√	√	√	√	
Bokarewa 2007[112]									√	√	
Jois 2007[113]	√					√			√		
Keystone 2007[114]			√	Reported graphically	√	√					
Assous 2008[115]	√				√						
Thurlings 2008[116]				√	√				√	√	√
Finckh 2009[134,137]		√				√					√
REFLEX extension[137]	√	√	√	√	√	√					
Rituximab pooled analysis[137]	√	√	√	√	√	√					

Table 32. Rituximab - outcomes assessed in studies and reported in the appendix only

	Other measures of disease activity	Fatigue	Pain	TJC/ SJC	CRP/ ESR
REFLEX[122-124]	√	√	√	√	√
Bokarewa 2007[112]				Reported graphically	Reported graphically
Jois 2007[113]				√	√
Keystone 2007[114]					
Assous 2008[115]					√
Thurlings 2008[116]					
Finckh 2009[134,135]				√	√
REFLEX extension[137]					
Rituximab pooled analysis[137]					

Withdrawals

(1) RCTs

Withdrawal rates are presented in Figure 29. At week 24, there were significantly less withdrawals for any reason in the rituximab arm than in the placebo arm of the REFLEX RCT (RR=0.39; 95%CI: 0.29, 0.51). Risk of withdrawal due to adverse events tended to be higher in the rituximab group than in the placebo, however, the difference was not statistically significant (RR=2.71; 95% CI: 0.58, 12.65).

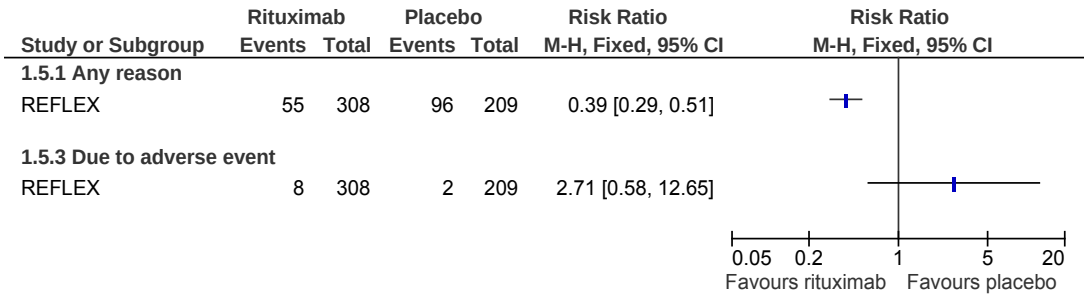


Figure 29. Rituximab withdrawals in the REFLEX RCT at 24 weeks by reason

(2) Non-RCTs

Withdrawal rate for any reason at six months was reported in only one uncontrolled study (Jois 2007[113]) as 10%; while 17.9% of patients in the rituximab arm in the REFLEX RCT withdrew at 6 months due to any reason and 2.6% due to adverse event. See Figure 30 below for details. In one study (Bokarewa 2007,[112] n=48) the total number of patients withdrawn by reason was not reported, but it stated that one patient discontinued rituximab treatment after second infusion (week 4) due to severe headache and stomach pain, and two who had a medical history of chronic myocardial ischemia died of myocardial infarction within the first month and the 13 months respectively.

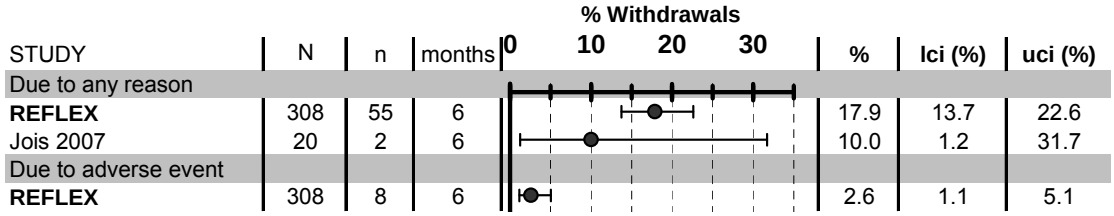


Figure 30 Rituximab withdrawals in uncontrolled cohorts by reason

ACR20

(1) RCTs

In the REFLEX trial, the percentage of patients that achieved ACR20 response at week 24 in the rituximab group was nearly three times of that in the placebo group and the difference was significant (RR=2.85, 95%CI: 2.08, 3.91). At week 48, the response rate based on observed data of small patient group favoured rituximab group but the difference was not significant (RR=1.53, 9% CI: 0.84, 2.76); when analysed based on non-responder imputation data the response rate in the rituximab group was nearly five times of that in the placebo group and the difference was significant (RR=4.92, 95% CI: 2.40, 10.09). Details can be found in Figure 31.

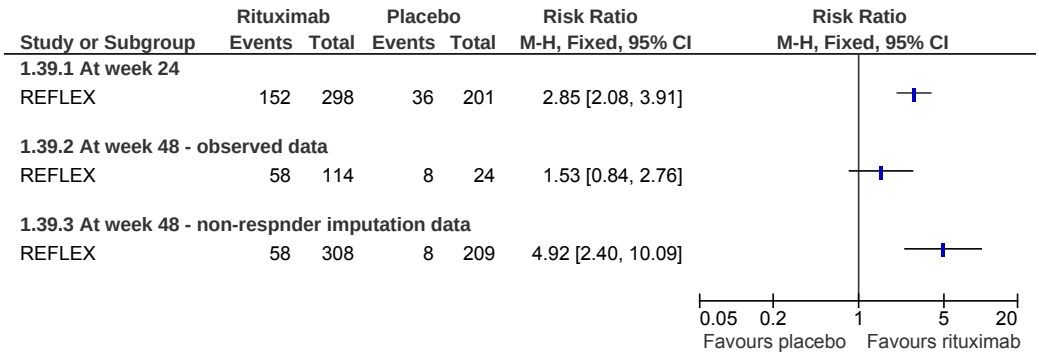


Figure 31 Rituximab – ACR20 response in REFLEX study (observed data and non-responder imputation data are from MS)

(2) Non-RCTs

In the Keystone pooled analysis ACR20 responses 24 week after the first course of rituximab for 155 evaluable patients who had prior TNF inhibitor was 65.2%, while the ACR20 at week 24 in the rituximab arm of the REFLEX trial was 51% (Figure 32). None of the other uncontrolled studies reported ACR20 responses.

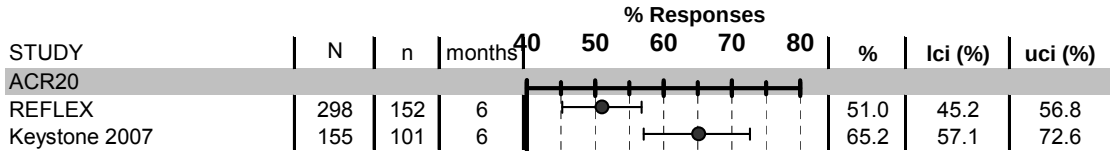


Figure 32 Rituximab – ACR 20 response in cohorts 24 weeks after first course of rituximab

ACR50

(1) RCTs

At week 24 the percentage of ACR50 responders in the rituximab group was nearly five and half times of that in the placebo group in the REFLEX trial and the difference was statistically significant (RR=5.40, 95%CI: 2.87, 10.16). The effect constantly favoured the rituximab group at week 48, analysed based on either observed data (RR=4.11, 95% CI: 1.06, 15.85) or non-responder imputation data, and based on non-responder imputation data the response rate in the rituximab group was over thirteen times of that in the placebo group (RR=13.23, 95% CI: 3.23, 54.20). Details are presented in Figure 33.

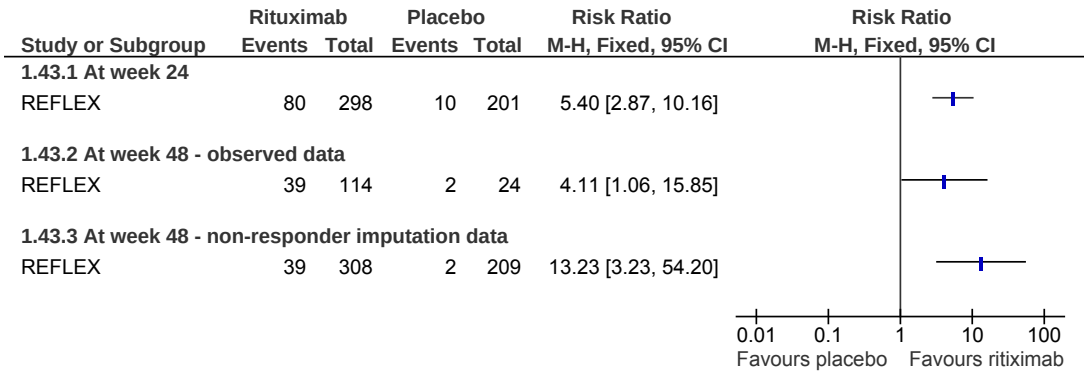


Figure 33 Rituximab – ACR50 response in REFLEX study (the observed data and non-responder imputation data were from MS)

(2) Non-RCTs

In the Keystone 2007 pooled analysis ACR50 responses 24 week after the first course of rituximab for 155 evaluable patients who had prior TNF inhibitor was 32.9%, while ACR50 reported in the rituximab arm of the REFLEX trail was 26.8% (Figure 34). None of the other uncontrolled studies reported ACR50 responses.

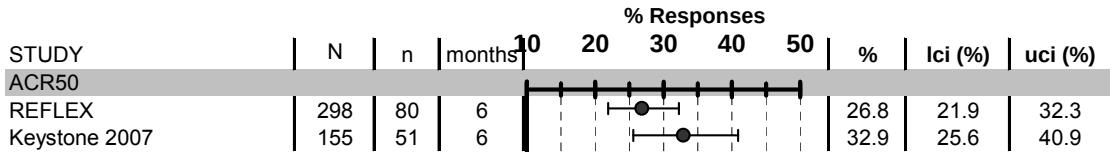


Figure 34 Rituximab – ACR 50 response in cohorts 24 weeks after first course of rituximab

ACR70

(1) RCTs

At week 24 the percentage of patients achieving ACR70 response in the rituximab group in the REFLEX trial was over twelve times of that in the placebo group and the difference was statistically significant (RR=12.14, 95%CI: 2.96, 49.86). At week 48 the beneficial effect with rituximab was not significant based on observation data of much smaller patient group (RR=3.37, 95% CI: 0.47, 24.2) but significant based on non-responder imputation data (RR=10.86, 95% CI: 1.45, 81.24). See Figure 35 for details.

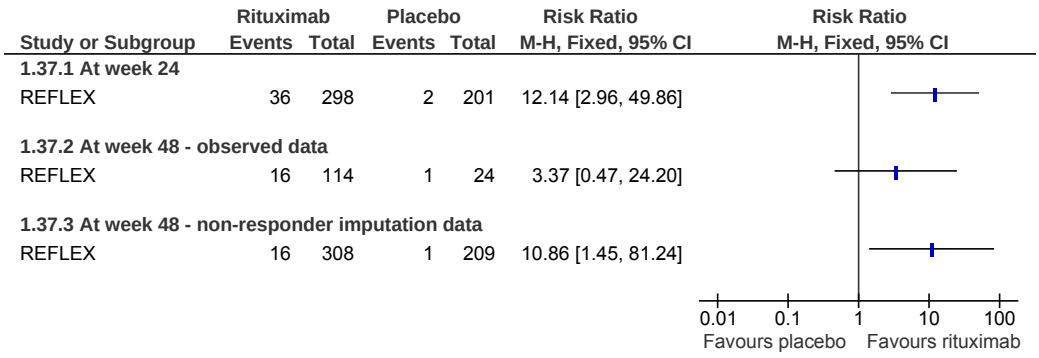


Figure 35 Rituximab – ACR70 response in REFLEX study (those based on observed data and non-responder imputation data were from MS)

(2) Non-RCTs

In the Keystone 2007 pooled analysis ACR70 responses 24 weeks after the first course of rituximab for 155 evaluable patients who had prior TNF inhibitor was 12.3%; it was very similar as that reported in the rituximab arm of REFLEX trial (12.1%) (Figure 36). None of other uncontrolled studies reported ACR70 responses.

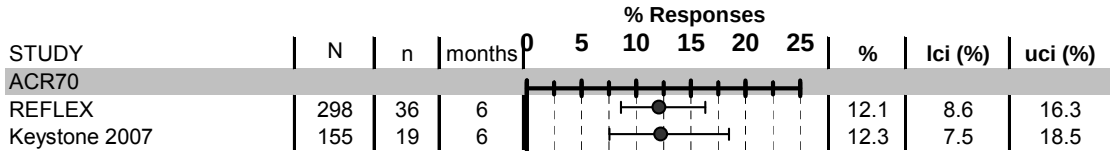


Figure 36 Rituximab – ACR 70 response in cohorts 24 weeks after first course of rituximab

EULAR response

(1) RCTs

EULAR responses were presented in Figure 37 and Figure 38. In the REFLEX trial at week 12 the percentage of patients achieving good and moderate response in the rituximab group was over twice of that in the placebo group, with also over twice having a good response; the effects were statistically significant (RR=2.02, 95%CI: 1.64, 2.49, and RR=2.23, 95%CI: 1.12, 4.41, respectively). At week 24 the percentage of patients achieving a EULAR good and moderate response in the rituximab group was nearly three times of that in the placebo group and the effect was significant (RR=2.96, 95%CI: 2.25, 3.89); the rate of achieving good response favoured the placebo group, however the difference was not significant (RR=0.76, 95%CI: 0.52, 1.12).

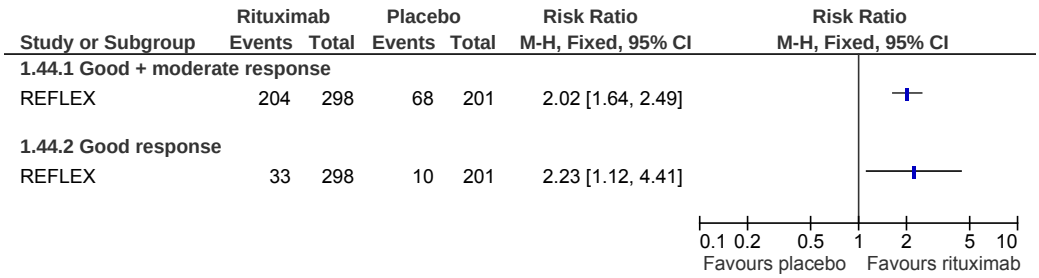


Figure 37 Rituximab – EULAR response at week 12 in REFLEX study (Data from the MS)

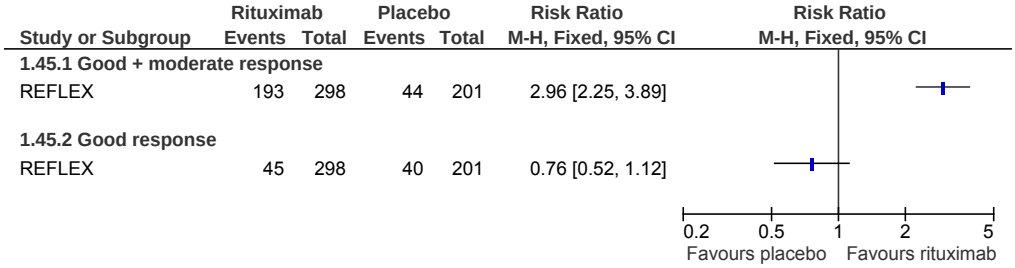
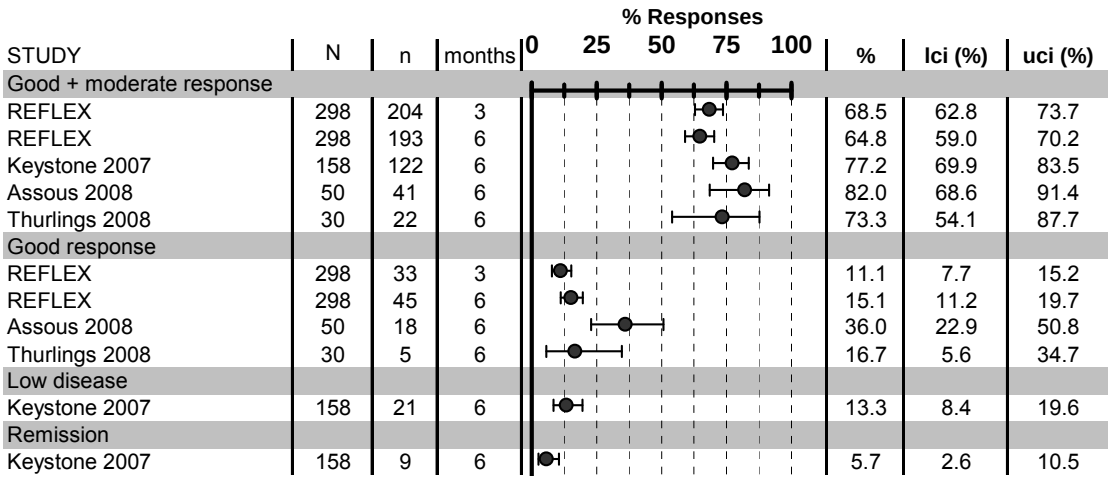


Figure 38 Rituximab – EULAR response at week 24 in REFLEX

(2) Non-RCTs

None of the uncontrolled studies reported EULAR response at 3 months while three reported at 6 months. At 3 months in the rituximab arm of the REFLEX RCT 68.5% of the patients had moderate and good response, with 11.1% had good response; at 6 months the rates did not change very much (64.8% / 15.1%). At 6 months good and moderate EULAR response in four cohorts including the RXT arm of the REFLEX trial ranged from 64.8% to 82%, and good response from 15.1% to 36%, with the REFLEX trial had the lowest for both. One study also reported EULAR low disease activity and remission at 6 months (13.3% / 5.7%). See Figure 39.



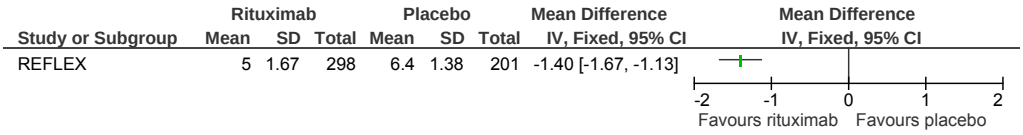
STUDY	N	n	months	%	lci (%)	uci (%)
Good + moderate response						
REFLEX	298	204	3	68.5	62.8	73.7
REFLEX	298	193	6	64.8	59.0	70.2
Keystone 2007	158	122	6	77.2	69.9	83.5
Assous 2008	50	41	6	82.0	68.6	91.4
Thurlings 2008	30	22	6	73.3	54.1	87.7
Good response						
REFLEX	298	33	3	11.1	7.7	15.2
REFLEX	298	45	6	15.1	11.2	19.7
Assous 2008	50	18	6	36.0	22.9	50.8
Thurlings 2008	30	5	6	16.7	5.6	34.7
Low disease						
Keystone 2007	158	21	6	13.3	8.4	19.6
Remission						
Keystone 2007	158	9	6	5.7	2.6	10.5

Figure 39 Rituximab – EULAR response in uncontrolled cohorts (data at 3 months for the REFLEX trial were from the MS)

DAS28

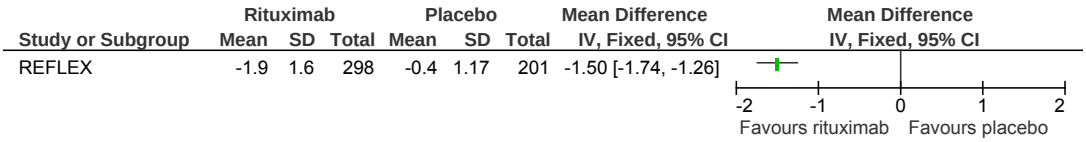
(1) RCTs

In the REFLEX trial at week 24 the rituximab arm had a significantly smaller mean DAS28 score and significantly greater reduction in mean DAS28 score from baseline than the placebo arm (-1.40, range -1.67 to -1.13; and - 1.50, range -1.67 to -1.13, respectively). At week 24 the proportion of patient with mean DAS28 score reduction in the rituximab group was over 5 times of that in the rituximab group and the difference was statistically significant. See Figure 40, Figure 41, and Figure 42 for details.



	Rituximab			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
REFLEX	5	1.67	298	6.4	1.38	201	-1.40 [-1.67, -1.13]	

Figure 40 Rituximab – DAS28 score at week 24 in REFLEX trial (LOCF data from MS)



	Rituximab			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
REFLEX	-1.9	1.6	298	-0.4	1.17	201	-1.50 [-1.74, -1.26]	

Figure 41 Rituximab – DAS28 score change from baseline at week 24 in REFLEX trial (LOCF, data from MS)

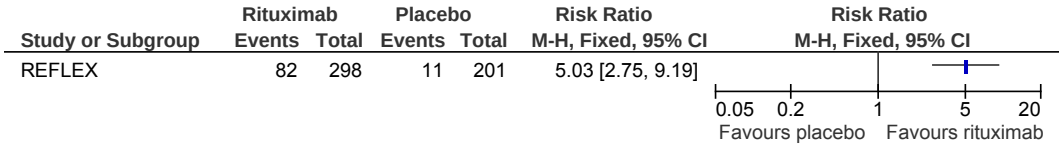


Figure 42 Rituximab – percentage of patients with DAS28 improvement from baseline at week 24 in REFLEX trial (LOCF, data from the MS)

(2) Non-RCTs

DAS28 score at 3 months was available in only one uncontrolled study (median DAS28 = 5.60). DAS28 score at 6 months were measured in three studies, as a mean score of 5.0 in one study which was the same as that in the rituximab arm of the REFLEX trial, and median score of 5.50 and 3.97 respectively in the other two studies. See Figure 43 for details*.

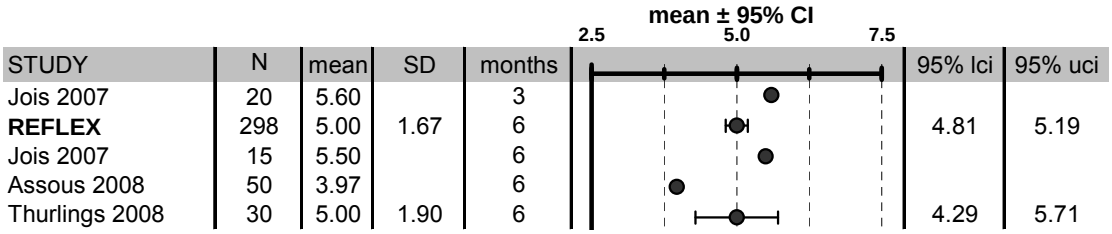


Figure 43 Rituximab – mean DAS28 scores in uncontrolled studies

The change on mean DAS28 score from baseline at 6 months was reported only in an analysis of Finckh 2009[134] including 50 patients. It was similar to that reported for the rituximab arm of the REFLEX trial and both showed significant improvement (mean= -1.90, 95% CI: -2.08, -1.72, and mean= -1.61, 95%: -1.98, -1.24 respectively). See Figure 44 for details.

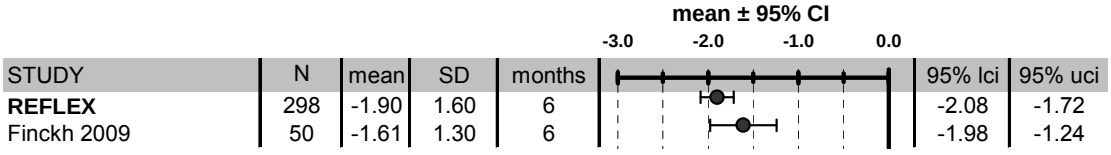


Figure 44 Rituximab – DAS28 scores change from baseline in uncontrolled cohorts (Data for REFLEX from MS)

HAQ

(1) RCTs

In the REFELX trial the rituximab group had significantly more reduction in mean HAQ score from baseline at week 24 compared to the placebo group (mean difference= -0.30, 95% CI: -0.40 to -0.20; Figure 45).

* For the Jois and Assouss study scores were reported as median.

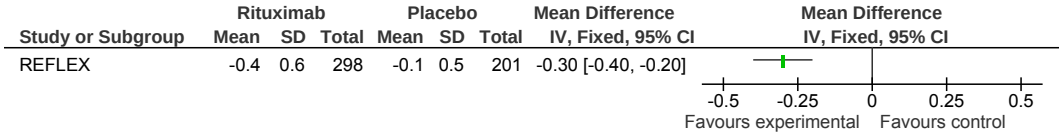


Figure 45 Rituximab – mean change in HAQ scores from baseline at week 24 in REFLEX trial

The percentage of patients with HAQ improvement, defined as a change of score < -0.22 from baseline, in the rituximab group of the REFLEX trial was nearly twice of that in the placebo group at week 12, and over two and a half times at week 24; both effects were statistically significant (RR=1.63, 95% CI: 1.29 to 2.07 and RR=2.55, 95% CI: 1.89 to 3.43, respectively. Figure 46).

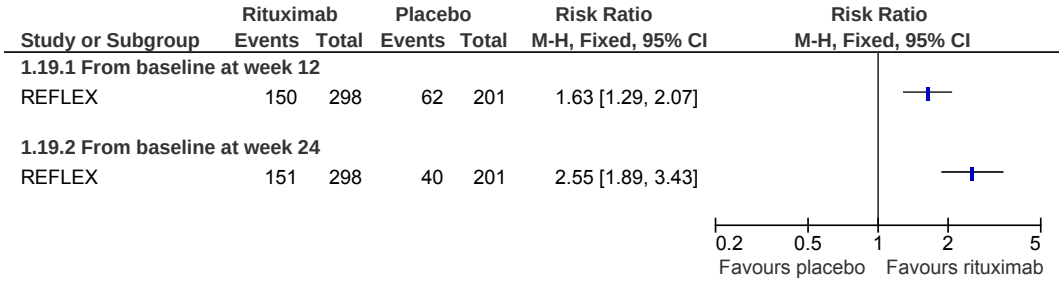


Figure 46 Rituximab – percentage of patients with a change of HAQ < - 0.25 from baseline in REFLEX study (Data from MS)

At week 24, the observed percentage of patients with minimal clinically improvement in HAQ, defined as a decrease of 0.22 in HAQ score, in the rituximab group of the REFLEX trial was over 1.6 times and of that in the placebo groups and the difference was significant; while observed at week 48 there was no significant difference (Figure 47).

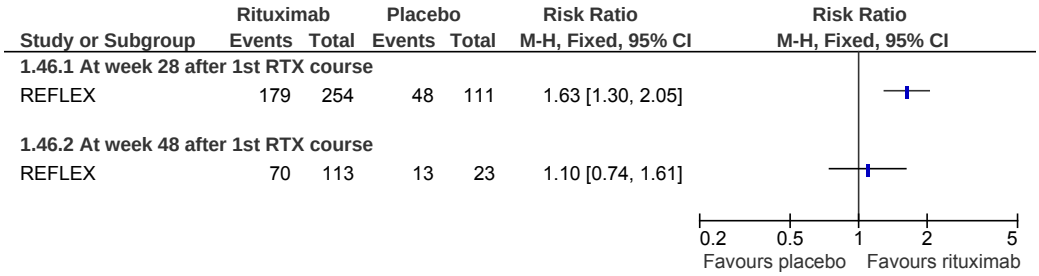


Figure 47 Rituximab –percentage of patients with a clinically significant improvement in HAQ 24 weeks after first course of RIX (data from MS)

When analysed based on non-responder imputation data, the percentage of patients with minimal clinically improvement in HAQ at week 24 and week 48 was over two and a half and over three and a half times in the rituximab group of that in the placebo group (58% versus 23%; and 23% versus 6%) respectively, and both differences were statistically significant (Figure 48).

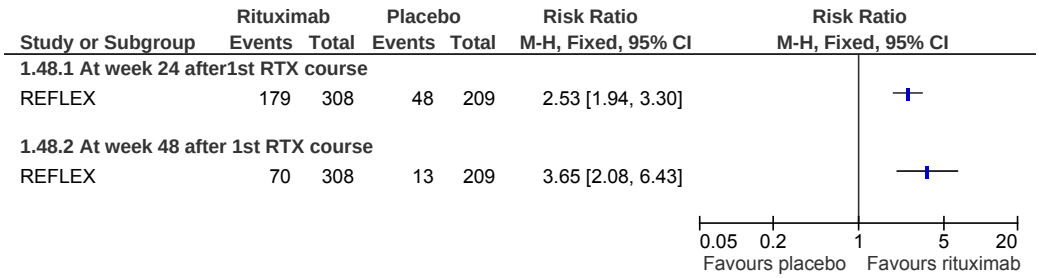


Figure 48 Rituximab – percentage of patients with a clinically significant improvement in HAQ 48 weeks after first course of rituximab (NRI data from MS)

(2) Non-RCTs

Two uncontrolled studies reported HAQ score. The median HAQ score in one study (Jois 2007) was 2.13 (range 0.63 – 2.88) at 3 months and reduced to 1.86 (range 1 – 3) at 6 months; however, both were not significant versus baseline. In the Keystone study, the percentage of patients with a decrease of means HAQ score ≥ 0.22 from baseline at week 24 after one course of RTX treatment was 71.8%, which is very similar as the observed rate reported in the rituximab arm of the REFLEX trial (70.5%) (Figure 49).

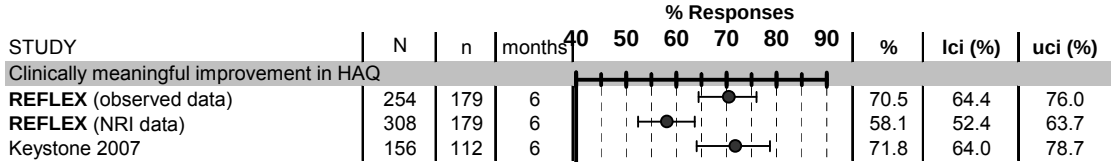


Figure 49 Rituximab – Percentage of patients with clinically meaningful improvement in HAQ score from baseline at week 24.

Joint damage

(1) RCTs

The rituximab group of the REFLEX trial had significantly less changes in Sharp-Genant total score from baseline at both week 56 (mean difference= -1.12, 95% CI: -2.13, -0.11) and week 104 (mean difference= -1.67, 95% CI: -2.67, -0.67) than the placebo group. At week 56 the percentage of patients in the rituximab group with no worsening Sharp-Genant total score from baseline nearly one and a half times of that in the placebo group and the difference was statistically significant; however, the change at week 104 became not significant. Sharp-Genant total score measured at week 104 favoured the rituximab group but the effect was not statistically significant (mean difference= 3.53, 95% CI: 9.21, 2.15). See Appendix 10.10 for details.

There were significantly less change in erosion score in the rituximab group than in the placebo group from baseline at week 56 (mean difference= -0.75, 95%CI: -1.43, -0.07) and at week 104 the significant difference became bigger (mean difference= -1.08, 95%CI: -1.73, -0.43). Erosion score at week 104 favoured rituximab arm but the effect was not statistically significant (mean difference= -2.48, 95%CI: -5.55, 0.59). Percentage of patients with no erosive progression from baseline at week 104 in the rituximab group was nearly one and a half times of those in the placebo group and the difference was statistically significant (RR=1.38, 95%CI: 1.14, 1.66).

Joint space narrowing score change from baseline was less in the rituximab group than in the placebo group both at week 56 and week 104; the difference was not statistically significant at week 56 but became significant at week 104, though at week 104 joint space narrowing score was not significantly lower in the rituximab group than that in the placebo group.

(2) Non-RCTs

None of the uncontrolled studies reported outcome on joint damage.

Quality of life

(1) RCTs

Mean SF-36 mental and physical health scores measured at week 24 in the REFLEX trial were both significantly higher in the rituximab group than in the placebo group (Figure 50). The rituximab group increased mean SF-36 physical health score by 5.16 and mean SF-36 mental health score by 3.07 more than the placebo group, and the differences were statistically significant (Figure 51).

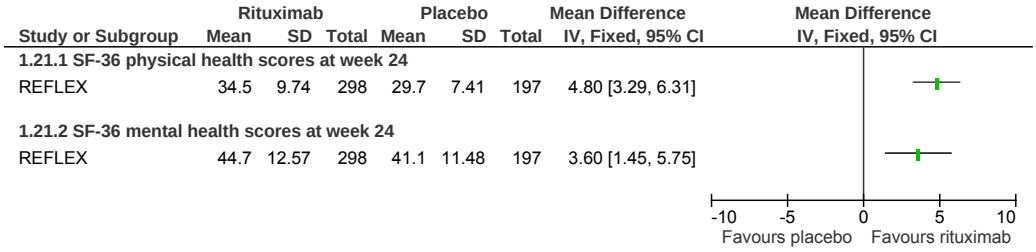


Figure 50 Rituximab – mean SF-36 scores at week 24 in the REFLEX RCT (LOCF; data from MS)

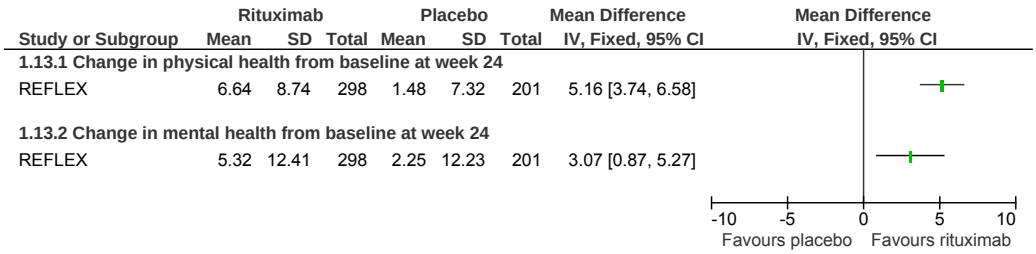


Figure 51 Rituximab – change in SF-36 scores from baseline to week 24 in REFLEX trial

(2) Non-RCTs

None of the uncontrolled studies reported outcome on quality of life.

Serious adverse events

(1) RCTs

In the REFLEX trial the percentage of patients with serious adverse events was less in the rituximab group than in the placebo group; the difference was not statistically significant (RR=0.74, 95%CI: 0.42, 1.31). See Figure 52 for details.

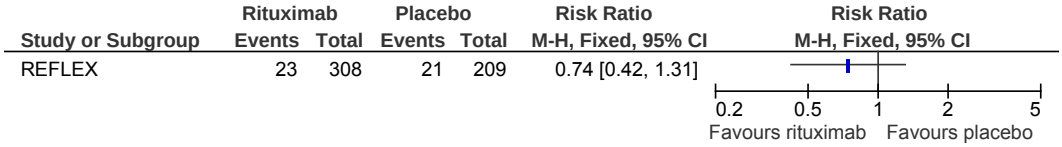


Figure 52 Rituximab – serious adverse event at week 24 in REFLEX trial

(2) Non-RCTs

In one 12 month study (Bokarewa 2007 [112]) one patient (2%) had severe headache and stomach pain the day after rituximab infusion and this lead to discontinuation of treatment. A 6 month study (Jois 2007 [113]) stated no major side effects were found during the study. During a 6 month period the Thurlings study reported 5 serious adverse events (16.7%), including 2 severe infusion reactions, 1 arterial embolism, 1 pulmonary embolism and 1 toxic hepatitis. The other studies did not report information on serious adverse events.

Serious infections

(1) RCTs

In the REFLEX trial the percentage of patients with serious infections was greater in the rituximab group than in the placebo group; the difference was not statistically significant (RR=1.58, 95%CI: 0.41, 6.05). See Figure 53 for details.

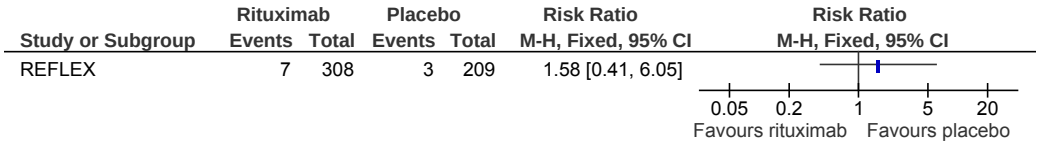


Figure 53 Rituximab – serious infection at week 24 in REFLEX trial

(2) Non-RCTs

In the Bokarewa study[112] 3 months after the treatment with rituximab pneumonia, which requiring hospitalization, was reported in one patient (2.0%). In the Thurlings study infections per patient-year was 0.9 and one serious infection requiring intravenous antibiotics occurred (3.0%).

Injection site reaction / infusion reaction

(1) RCTs

In the REFLEX trial the percentage of patients with acute infusion reactions did not differ significantly between groups (RR=1.24, 95%CI: 0.90, 1.83 for the first and RR=0.74, 95%CI: 0.43, 1.24 for the second course). See Figure 54 for details.

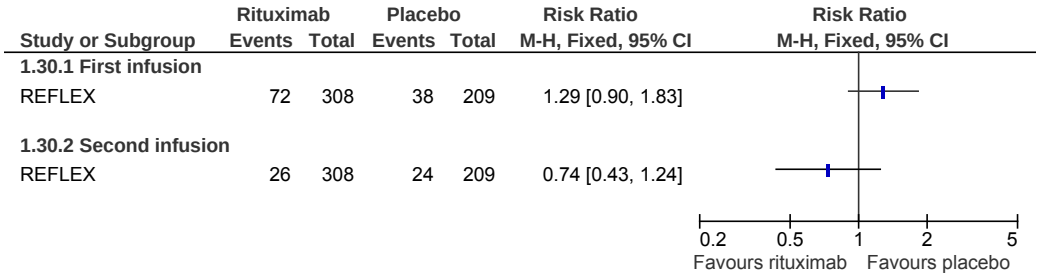


Figure 54 Rituximab – percentage of patients had acute infusion reactions from the first and second rituximab infusions

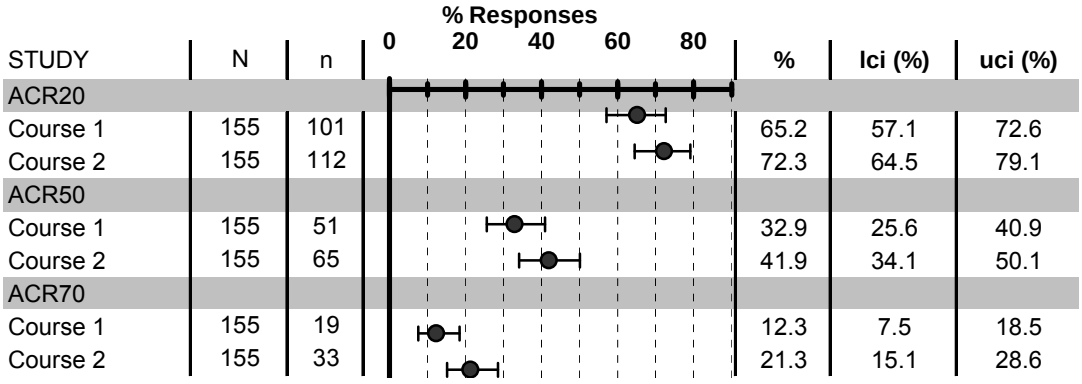
(2) Non-RCTs

One study (Finckh 2009, subgroup of 50 patients) reported three mild to moderate infusion reactions. Another study (Thurlings 2008) reported two severe infusion reactions. The other studies did not report information on injection site reaction or infusion reaction.

5.3.5.5. Data reported by treatment course

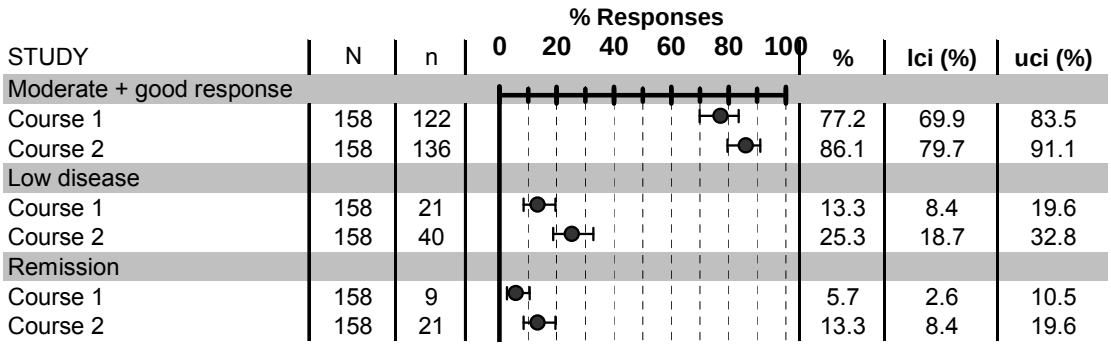
Pooled analysis (data from Keystone)

In the Keystone study, based on evaluable data the percentage of patients achieving ACR responses increased from course 1 to course 2 treatment of rituximab measured 24 weeks after each course (Figure 55). Similar pattern was seen for the percentage of patients with EULAR response 24 weeks after course 1 and course 2 (Figure 56).



STUDY	N	n	%	lci (%)	uci (%)
ACR20					
Course 1	155	101	65.2	57.1	72.6
Course 2	155	112	72.3	64.5	79.1
ACR50					
Course 1	155	51	32.9	25.6	40.9
Course 2	155	65	41.9	34.1	50.1
ACR70					
Course 1	155	19	12.3	7.5	18.5
Course 2	155	33	21.3	15.1	28.6

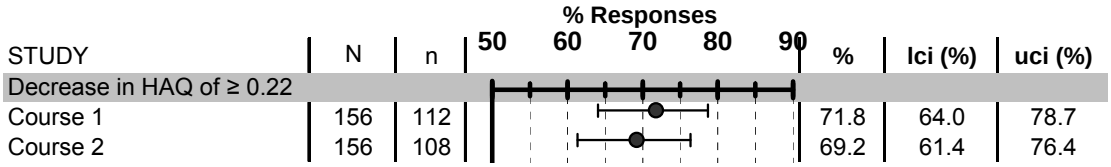
Figure 55 Percentage of patients achieving ACR responses 24 weeks after course 1 and course 2 – based on evaluable patients who had prior TNF inhibitor



STUDY	N	n	%	lci (%)	uci (%)
Moderate + good response					
Course 1	158	122	77.2	69.9	83.5
Course 2	158	136	86.1	79.7	91.1
Low disease					
Course 1	158	21	13.3	8.4	19.6
Course 2	158	40	25.3	18.7	32.8
Remission					
Course 1	158	9	5.7	2.6	10.5
Course 2	158	21	13.3	8.4	19.6

Figure 56 Percentage of patients with EULAR responses 24 weeks after course 1 and course 2 – based on evaluable patients who had prior TNF inhibitor

Percentage of patients achieving meaningful improvement in HAQ, i.e. had a decrease of HAQ scores at least 0.22 from baseline, were similar 24 weeks after course 1 and course 2 of rituximab treatment (Figure 57).



STUDY	N	n	%	lci (%)	uci (%)
Decrease in HAQ of ≥ 0.22					
Course 1	156	112	71.8	64.0	78.7
Course 2	156	108	69.2	61.4	76.4

Figure 57 Percentage of patients with a decrease of HAQ score ≥ 0.22 from baseline at week 24 after course 1 and course 2 - based on evaluable patients who had prior TNF inhibitor

Data from manufacturer's submission

Data analysis based on the manufacturer's submission can be found together wit all additional analyses in Appendix 10.10.

5.3.5.6. Summary

For the assessment of effectiveness of rituximab in comparison with standard care, one RCT and six uncontrolled studies were identified. Follow-up duration ranged from 3 months to 24 months. All patients included in the studies were generally similar. Main results of the seven studies are summarised in the Table 33.

Table 33 Rituximab – summary results

Outcome	RCT	Uncontrolled studies	
	6 months	3 months	6 months
Withdrawals: • For any reason • Due to lack of efficacy • Due to adverse events	 RR=0.39 (0.29,0.51), favours RTX NR RR=2.71 (0.58, 12.65), ns	 NR NR NR	 10% NR NR
ACR20 response	RR=2.85 (2.08, 3.91), favours RTX	NR	65.2%
ACR50 response	RR=5.40 (2.87, 10.16), favours RTX	NR	32.9%
ACR70 response	RR=12.14 (2.96, 49.86), favours RTX	NR	12.3%
EULAR response • Good + moderate response • Good response	 RR=2.96 (2.25, 3.89), favours RTX RR=0.76 (0.52, 1.12), ns	 NR NR	 73.3-82.0% 16.7-36.0%
DAS28:mean change from baseline	Mean difference=-1.40 (-1.67, -1.13), favours RTX	NR	-1.61
HAQ: mean change from baseline	Mean difference=-0.30 (-0.40, -0.20), favours RTX	NR	NR
patients with an improvement in HAQ >0.25 from baseline	RR=2.55 (1.89, 3.43), favours RTX	NR	71.8%
Joint damage	NR	NR	NR
Quality of life Change in SF-36 physical health score Change in SF-36 mental health score	 Mean difference=4.80 (3.29, 6.31), favours RTX Mean difference=3.60 (1.45, 5.75)	 NR NR	 NR NR
Serious adverse events	RR=0.74 (0.42, 1.31), ns	NR	0-16.7% (2% for 12 months)
Serious infections	RR=1.58 (0.41, 6.05), ns	2%	3%
Infusion reaction 1st infusion reaction 2nd infusion reaction	 RR=1.29 (0.90, 1.83), ns RR=0.74 (0.43, 1.24), ns	 NR NR	 NR NR

5.3.6 Abatacept

5.3.6.1. Overview of evidence

Three studies were identified that assessed abatacept in comparison with standard care: one RCT (ATTAIN[127-129]), an extension of this RCT (ATTAIN LTE[117]) and an uncontrolled study (ARRIVE[118]).

Patients were included in the ATTAIN LTE after completing six months of the RCT. It was reported that in total 74.4% of the placebo group and 86.4% of the abatacept group were included in the extension.

Table 34 Abatacept - characteristics of included studies

Study	Country	Design	Reason for switching	Prior TNF inhibitors; no.	Treatment arms (no. of patients)	Duration of follow-up	Comments
Randomised controlled trials							
ATTAIN[127-129]	North America and Europe	Parallel prospective	Primarily lack of efficacy	Any; 1-2	ABA (258) PL (133)	6 months	
Non-randomised comparative studies (none were identified)							
Uncontrolled studies							
ATTAIN LTE[117]	North America and Europe	Uncontrolled prospective LTE of RCT	Primarily lack of efficacy	Any; 1-2	ABA (317)	Up to 5 years	Some patients have not yet completed the five year follow-up; published data only up to two years; data beyond that from MS
ARRIVE[118]	USA, EU, Mexico	Uncontrolled prospective	Lack of efficacy, safety, intolerability	Any; 1-3	ABA (1046)	6 months	Two main subgroups: patients switched to ADA after a washout period and those who switched directly

Included patients were non-responders to at least one TNF inhibitor. In the ATTAIN RCT and LTE lack of efficacy was the primary reason for switching biologic agents. In ARRIVE patients discontinued the previous TNF inhibitor due to lack of efficacy, safety or intolerability.

All studies were carried out in North America and Europe. ARRIVE additionally included Mexican patients. No information was provided if these studies included UK patients. Follow-up was six months for the ATTAIN RCT and ARRIVE study. In the ATTAIN LTE

patients were followed up for up to five years, however there was no published data beyond two years. Further details are provided in Table 34.

5.3.6.2. Patient characteristics

Full details of patient characteristics are reported in Table 35.

The number of patients included in the studies was 391 in the ATTAIN RCT, 317 in its LTE and 1046 in the ARRIVE study. Patient characteristics were generally similar across studies and study arms:

- percentage of female patients ranged from 77.9% to 81.2%;
- mean age ranged from 53.0 to 54.4 years;
- mean disease duration ranged from 11.6 to 11.9 years;
- in two studies the percentage of rheumatoid factor positive patients ranged from 61.3% to 73.2%; it was not reported in the ATTAIN LTE;
- concomitant DMARDs were reported in detail in ATTAIN and ARRIVE: 69.8 to 77.7% patients were on MTX, other DMARDs included hydroxychloroquine (8.9 to 15.0%), leflunomide (8.7 to 12.8%) and sulfasalazine (8.0 to 9.8%); in the ARRIVE study azathioprine (4.1%) and gold (0.5%) were also used;
- in two studies 58.4 to 68.3% of patients were receiving corticosteroids; this was not reported in detail in the ATTAIN LTE;
- the number of previously used conventional DMARDs was not reported in any of the studies;
- the number of previous TNF inhibitors ranged from one to two in the ATTAIN and ATTAIN LTE studies and one to three in the ARRIVE study;
- the mean baseline HAQ ranged from 1.7 to 1.8;
- the mean DAS28 score ranged from 6.2 to 6.5;
- the mean number of tender and swollen joints ranged from 17.8 to 31.8 and 13.6 to 22.3 respectively;
- baseline ESR was not reported in any of the studies;
- CRP ranged from 2.1 to 4.4 mg/dL.

Table 35 Abatacept - baseline patient characteristics

Study	Number of patients/ % female	age; mean (SD); years	RA duration; mean (SD); years	RF positive; %	concomitant DMARDs and steroids	number of previous DMARDs; mean (SD)	number of previous TNF inhibitors; mean (SD)	HAQ; mean (SD)	DAS28; mean (SD)	tender/ swollen joint count; mean (SD)	ESR; mean (SD); mm/hr	CRP; mean (SD); mg/dL
ATTAIN[127-129]	391/ 78%	53.2 (12.0)	11.9 (8.6)	73.2%	MTX (77.8%); hydroxychloroquine (8.9%); leflunomide (8.7%); sulfasalazine (8.0%); corticosteroids (68.3%)	NR	1-2	1.8 (0.6)	6.5 (0.9)	31.7 (13.1) of 68/ 22.2 (10.1) of 66	NR	4.4 (3.9)
ATTAIN LTE[117]	317/ 77.9%	53.0 (11.7)	11.8 (8.6)	NR	Continued MTX, DMARDs and corticosteroids allowed	NR	1-2	1.8 (0.6)	6.5 (0.8)	31.8 (13.4)/ 22.3 (10.4)	NR	4.2 (3.7)
ARRIVE[118]	1046/ 81.2%	54.4 (12.4)	11.6 (9.5)	61.3%	MTX (69.8%), azathioprine (4.1%), gold (0.5%), hydroxychloroquine/ chloroquine (15.0%), leflunomide (12.8%), sulfasalazine (8.8%), corticosteroids (58.4%)	NR	1-3	1.7 (0.6)	6.2 (0.7)	17.8 (6.0)/ 13.6 (5.5)	NR	2.1 (3.0)

5.3.6.3. Quality assessment

(1) RCT

The only RCT (ATTAIN) was of high quality. Full details of quality assessment are reported in Table 36. Randomisation and allocation concealment were appropriate. Patients and investigators/ outcome assessors were blinded. It was not clear if data analysts knew to which group patients were assigned. 13.6% of patients were withdrawn from the abatacept group and 25.6% from the placebo group. ITT analysis was not used, as only data from patients who received at least one dose of the study drug was analysed. Two patients were excluded from analysis due to protocol violations, possibly *post hoc*. The potential impact on the results is likely to be small.

Table 36 Abatacept - RCT quality assessment

Study	Was randomisation appropriate?	Was allocation adequately concealed?	Blinding			Patients withdrawn (%)	Was ITT used?	Comments
			patients	investigators/ outcome assessors	Data analysts			
ATTAIN[127-129]	Yes	Yes	Yes	Yes	unclear	ABA 13.6%; PL 25.6%	no; modified ITT used (patients who were given at least one dose of the drug)	Two patients excluded from analysis because of protocol violation

(2) Non-RCTs

Both non-randomised studies were uncontrolled and prospective. Full details of quality assessment are reported in Table 37. Both studies stated clearly their inclusion criteria, however it was not clear if consecutive patients were included in ARRIVE. The percentage of patients withdrawn from the study was 18% for the ARRIVE study at six months and 30% in the ATTAIN LTE at two years.

Table 37 Abatacept - non-RCT quality assessment

Study	Study design	Inclusion criteria clearly defined?	Were consecutive patients included in the study?	Patients withdrawn (%)	Comments
ATTAIN LTE[117]	Uncontrolled long term open-label extension of RCT	Yes	n/a	30%	Data for 2-year follow-up
ARRIVE[118]	Uncontrolled prospective	Yes	Unclear	18%	

5.3.6.4. Results

The RCT and non-randomised studies were analysed separately. Data from the abatacept arm of the ATTAIN RCT is included in all figures referring to uncontrolled studies for comparison.

Table 38 indicates which of the outcomes reported in the main text of the report were assessed in individual studies and Table 39 provides similar information for outcomes described in Appendix 10.10 only.

Table 38 Abatacept - outcomes assessed in studies and reported in the main text of the report

	Total withdrawal	Withdrawal by reason	ACR (20/50/70)	DAS28	EULAR response	HAQ	Quality of life	Joint damage	Serious adverse events	Infection/ serious infection	Injection/ infusion reaction
ATTAIN[127-129]	√	√	√	√		√	√		√	√	√
ATTAIN LTE[117]	√	√	√	√		√			√	√	
ARRIVE[118]	√	√		√			√		√	√	√

Table 39 Abatacept- outcomes assessed in studies and reported in the appendix only

	Other measures of disease activity	Fatigue	Pain	TJC/ SJC	CRP/ ESR
ATTAIN[127-129]			√		
ATTAIN LTE[117]	√	√	√		
ARRIVE[118]					

Withdrawals

(1) RCTs

There were significantly less withdrawals for any reason in the abatacept arm than in the placebo arm of the ATTAIN RCT (RR=0.53; 95%CI: 0.35, 0.81). There were also significantly less withdrawals in the abatacept group due to lack of efficacy (RR=0.27; 95%CI: 0.15, 0.49). The risk of withdrawal due to adverse events was similar in both groups (RR=0.93; 95%CI: 0.32, 2.71). Details of the analysis are presented in Figure 58.

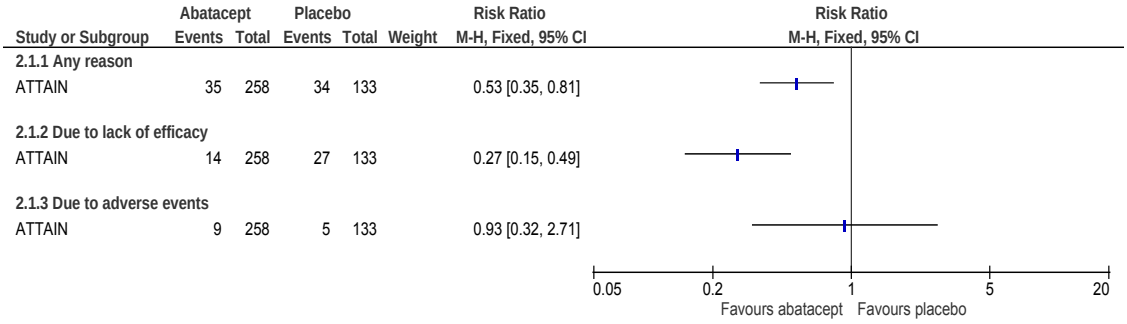
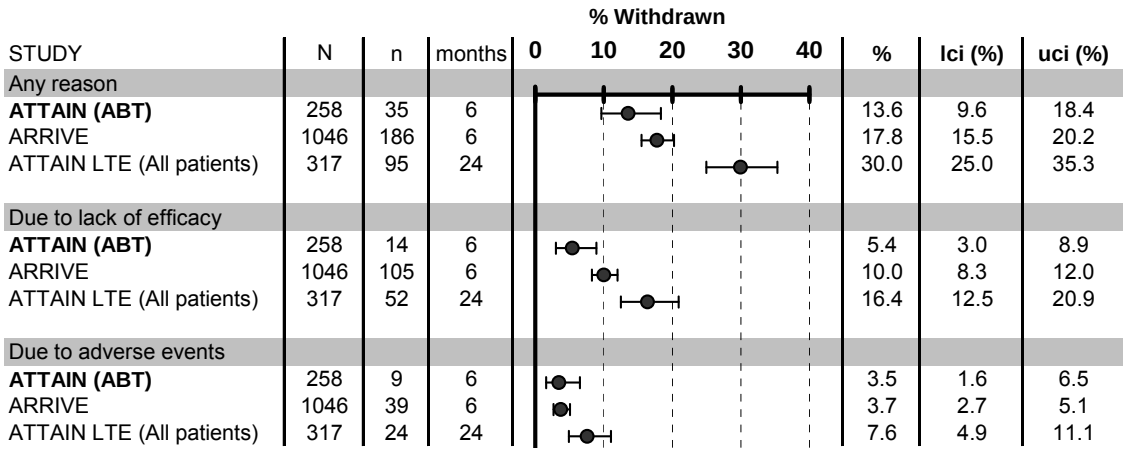


Figure 58 Abatacept withdrawals in the ATTAIN RCT at six months by reason

(2) Non-RCTs

At six months 17.8% patients withdrew from the ARRIVE study. This percentage was slightly higher than in the abatacept-treated arm of the RCT. At two years 30% patients withdrew from the ATTAIN LTE. In both studies more patients withdrew due to lack of efficacy than due to adverse events. A similar relationship was observed in the abatacept arm of the RCT. Full details are presented in Figure 59.



STUDY	N	n	months	%	lci (%)	uci (%)
Any reason						
ATTAIN (ABT)	258	35	6	13.6	9.6	18.4
ARRIVE	1046	186	6	17.8	15.5	20.2
ATTAIN LTE (All patients)	317	95	24	30.0	25.0	35.3
Due to lack of efficacy						
ATTAIN (ABT)	258	14	6	5.4	3.0	8.9
ARRIVE	1046	105	6	10.0	8.3	12.0
ATTAIN LTE (All patients)	317	52	24	16.4	12.5	20.9
Due to adverse events						
ATTAIN (ABT)	258	9	6	3.5	1.6	6.5
ARRIVE	1046	39	6	3.7	2.7	5.1
ATTAIN LTE (All patients)	317	24	24	7.6	4.9	11.1

Figure 59 Abatacept - withdrawals in uncontrolled studies by reason

ACR20 response

(1) RCT

ATTAIN reported ACR20 response at three and six months. At both follow-up times the risk of an ACR20 response was over two and a half times higher in the abatacept group than in the placebo group and the difference was statistically significant (for three months RR=2.53, 95%CI: 1.72, 3.73; for six months RR=2.56, 95%CI: 1.77, 3.69). Details can be found in Figure 60.

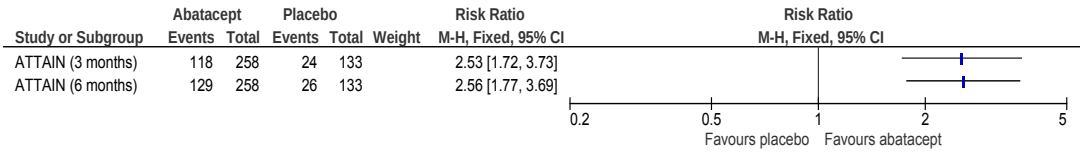


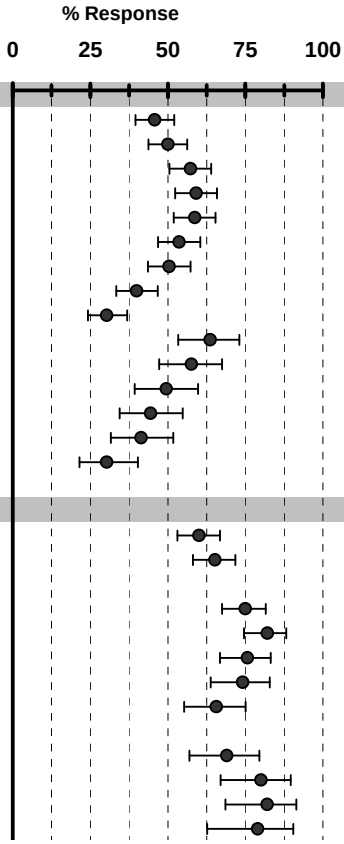
Figure 60 Abatacept - ACR20 response in the ATTAIN RCT at 3 and 6 months

(2) Non-RCTs

Of the uncontrolled studies only the ATTAIN LTE reported ACR20 response. Results are reported by subgroup based on whether patients were originally randomised to abatacept or placebo in the randomised phase (see Figure 61). After six months of abatacept treatment 57.3% patients in the group initially randomised to abatacept and 63.6% in the group initially

randomised to placebo achieved an ACR20 response. This was slightly more than in the abatacept arm of the RCT (50.0%). After six months there was a further increase in the percentage of ACR20 responders at 12 months in those initially randomised to abatacept followed by a decrease up to five years (30.3%). In those initially randomised to placebo there was a decrease in the percentage responders from 12 months onwards and at 54 months 30.3% of patients were ACR20 responders.

If only patients for whom data was available at different time points were analysed, the increase in percentage of ACR20 responders continued to three years (82.1%) and than decreased to 65.6% at five years for patients initially randomised to abatacept. In the same analysis for patients initially randomised to placebo there was an increase in the percentage of ACR20 responders up to 42 months (82.0%) and at 54 months 78.9% were ACR20 responders.



STUDY	N	n	months	%	lci (%)	uci (%)
ITT analysis						
ATTAIN (ABT)	258	118	3	45.7	39.5	52.0
ATTAIN (ABT)	258	129	6	50.0	43.7	56.3
ATTAIN LTE (ABT)	218	125	6	57.3	50.5	64.0
ATTAIN LTE (ABT)	218	129	12	59.2	52.3	65.8
ATTAIN LTE (ABT)	218	128	18	58.7	51.9	65.3
ATTAIN LTE (ABT)	218	117	24	53.7	46.8	60.4
ATTAIN LTE (ABT)	218	110	36	50.5	43.6	57.3
ATTAIN LTE (ABT)	218	87	48	39.9	33.4	46.7
ATTAIN LTE (ABT)	218	66	60	30.3	24.3	36.8
ATTAIN LTE (PL before ABT)	99	63	6	63.6	53.4	73.1
ATTAIN LTE (PL before ABT)	99	57	12	57.6	47.2	67.5
ATTAIN LTE (PL before ABT)	99	49	18	49.5	39.3	59.7
ATTAIN LTE (PL before ABT)	99	44	30	44.4	34.5	54.8
ATTAIN LTE (PL before ABT)	99	41	42	41.4	31.6	51.8
ATTAIN LTE (PL before ABT)	99	30	54	30.3	21.5	40.4
Non-ITT analysis						
ATTAIN LTE (ABT)	208	125	6	60.1	53.1	66.8
ATTAIN LTE (ABT)	198	129	12	65.2	58.1	71.8
ATTAIN LTE (ABT)	NR	NR	18	n/a	n/a	n/a
ATTAIN LTE (ABT)	156	117	24	75.0	67.4	81.6
ATTAIN LTE (ABT)	134	110	36	82.1	74.5	88.2
ATTAIN LTE (ABT)	115	87	48	75.7	66.8	83.2
ATTAIN LTE (ABT)	89	66	60	74.2	63.8	82.9
ATTAIN LTE (PL before ABT)	96	63	6	65.6	55.2	75.0
ATTAIN LTE (PL before ABT)	NR	NR	12	n/a	n/a	n/a
ATTAIN LTE (PL before ABT)	71	49	18	69.0	56.9	79.5
ATTAIN LTE (PL before ABT)	55	44	30	80.0	67.0	89.6
ATTAIN LTE (PL before ABT)	50	41	42	82.0	68.6	91.4
ATTAIN LTE (PL before ABT)	38	30	54	78.9	62.7	90.4

Figure 61 Abatacept - ACR20 response in non-RCTs

ACR50 response

(1) RCT

At six months the percentage of ACR50 responders was over five times higher in the abatacept group than in the placebo group of the ATTAIN trial and the difference was statistically significant (RR=5.36, 95%CI: 2.19, 13.10). Details are presented in Figure 62.

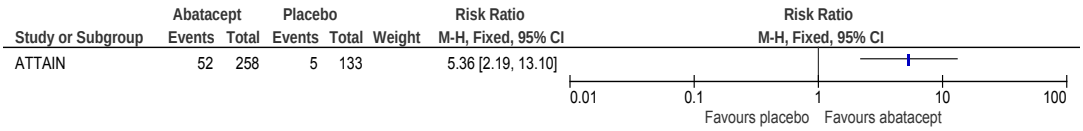
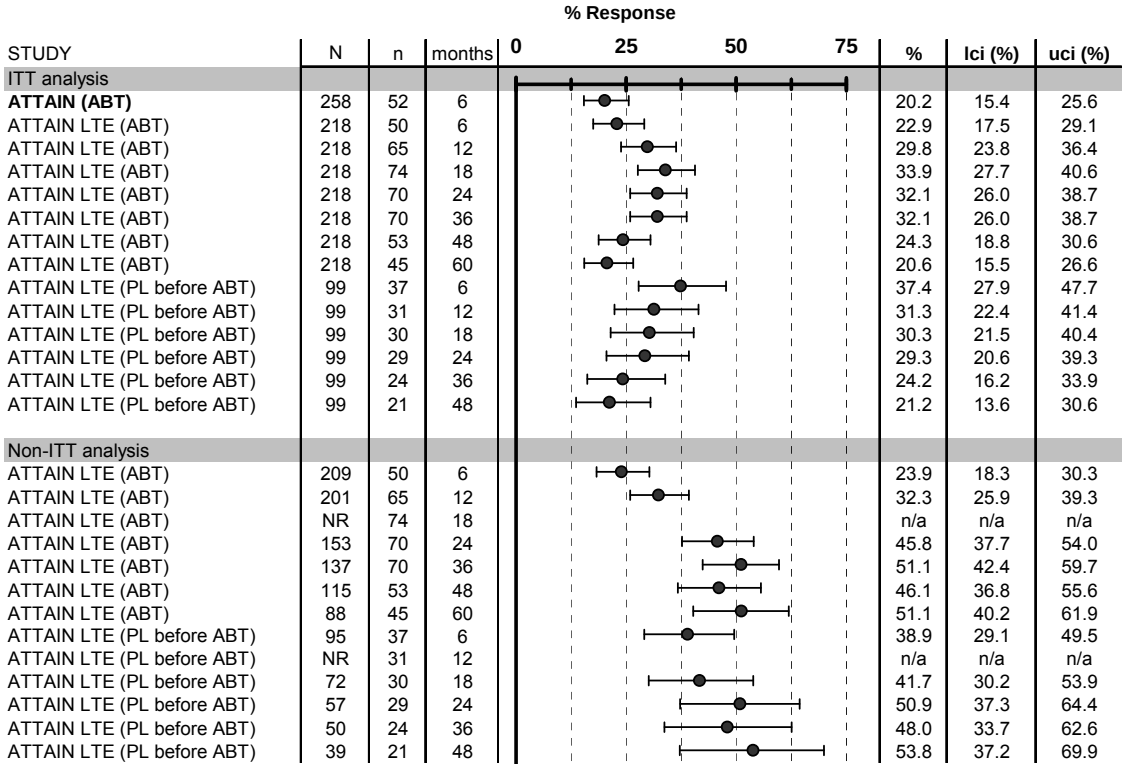


Figure 62 Abatacept – ACR50 response in the ATTAIN RCT at 6 months

(2) Non-RCTs

Of the uncontrolled studies only the ATTAIN LTE reported ACR50 response. Results are reported by subgroup based on whether patients were originally randomised to abatacept or placebo in the randomised phase (see Figure 63). This outcome was achieved at six months by 22.9% patients in those initially randomised to abatacept and 37.4% in the arm initially randomised to placebo. For comparison, this outcome was achieved by 20.2% patients in the abatacept arm of the RCT. In the arm initially randomised to abatacept the percentage of ACR50 responders increased up to 18 months (33.9%) and then decreased to 20.6% at five years. In the arm initially randomised to placebo there was a decrease after six months to 21.2% achieving ACR50 response at 48 months.

In non-ITT analysis the percentage of ACR50 responders increased in those initially randomised to abatacept increased up to three years (51.1%) and than it was 46.1% at four years and 51.1% at five years. In those initially randomised to placebo there was an almost constant increase up to 48 months (53.8%).



STUDY	N	n	months	%	lci (%)	uci (%)
ITT analysis						
ATTAIN (ABT)	258	52	6	20.2	15.4	25.6
ATTAIN LTE (ABT)	218	50	6	22.9	17.5	29.1
ATTAIN LTE (ABT)	218	65	12	29.8	23.8	36.4
ATTAIN LTE (ABT)	218	74	18	33.9	27.7	40.6
ATTAIN LTE (ABT)	218	70	24	32.1	26.0	38.7
ATTAIN LTE (ABT)	218	70	36	32.1	26.0	38.7
ATTAIN LTE (ABT)	218	53	48	24.3	18.8	30.6
ATTAIN LTE (ABT)	218	45	60	20.6	15.5	26.6
ATTAIN LTE (PL before ABT)	99	37	6	37.4	27.9	47.7
ATTAIN LTE (PL before ABT)	99	31	12	31.3	22.4	41.4
ATTAIN LTE (PL before ABT)	99	30	18	30.3	21.5	40.4
ATTAIN LTE (PL before ABT)	99	29	24	29.3	20.6	39.3
ATTAIN LTE (PL before ABT)	99	24	36	24.2	16.2	33.9
ATTAIN LTE (PL before ABT)	99	21	48	21.2	13.6	30.6
Non-ITT analysis						
ATTAIN LTE (ABT)	209	50	6	23.9	18.3	30.3
ATTAIN LTE (ABT)	201	65	12	32.3	25.9	39.3
ATTAIN LTE (ABT)	NR	74	18	n/a	n/a	n/a
ATTAIN LTE (ABT)	153	70	24	45.8	37.7	54.0
ATTAIN LTE (ABT)	137	70	36	51.1	42.4	59.7
ATTAIN LTE (ABT)	115	53	48	46.1	36.8	55.6
ATTAIN LTE (ABT)	88	45	60	51.1	40.2	61.9
ATTAIN LTE (PL before ABT)	95	37	6	38.9	29.1	49.5
ATTAIN LTE (PL before ABT)	NR	31	12	n/a	n/a	n/a
ATTAIN LTE (PL before ABT)	72	30	18	41.7	30.2	53.9
ATTAIN LTE (PL before ABT)	57	29	24	50.9	37.3	64.4
ATTAIN LTE (PL before ABT)	50	24	36	48.0	33.7	62.6
ATTAIN LTE (PL before ABT)	39	21	48	53.8	37.2	69.9

Figure 63 Abatacept - ACR50 response in non-RCTs

ACR70 response

(1) RCT

In the ATTAIN RCT the percentage of patients achieving ACR70 response at six months was almost seven times higher in the abatacept group than in the placebo group (RR=6.70, 95%CI: 1.62, 27.8). This difference was statistically significant, however it needs to be highlighted that confidence intervals were very wide (see Figure 64).

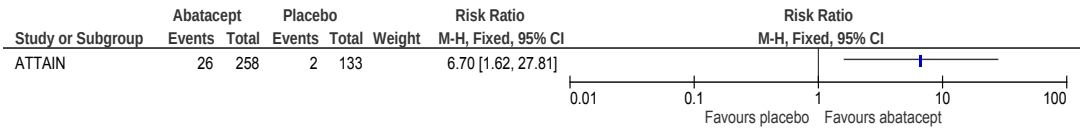
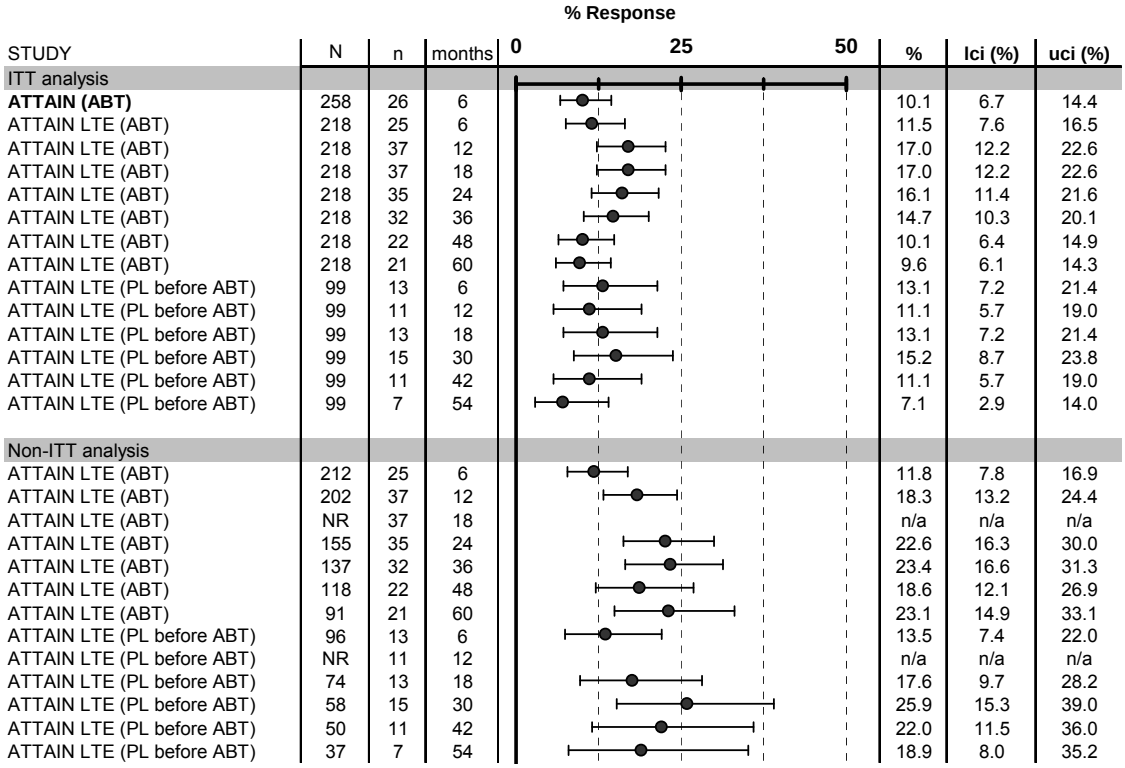


Figure 64 Abatacept - ACR70 response in the ATTAIN RCT at 6 months

(2) Non-RCTs

Of the uncontrolled studies only the ATTAIN LTE reported ACR70 response. After six months of treatment the percentage of ACR70 responders was: 11.5% in patients initially treated with abatacept and 13.1% in patients initially treated with placebo. For comparison, it was 10.1% in the ATTAIN RCT . In the arm initially randomised to abatacept there was a further increase to 17.0% at 12 months followed by a decrease to 9.6% at five years. In the arm initially randomised to placebo there was an increase up to 15.2% at 30 months followed by a decrease to 7.1% at 54 months. Non-ITT analysis provided results more favourable results with the highest percentage of ACR70 responders of 23.4 at 36 months in the arm initially randomised to abatacept and 25.9 at 30 months in the arm initially randomised to placebo.



STUDY	N	n	months	%	lci (%)	uci (%)
ITT analysis						
ATTAIN (ABT)	258	26	6	10.1	6.7	14.4
ATTAIN LTE (ABT)	218	25	6	11.5	7.6	16.5
ATTAIN LTE (ABT)	218	37	12	17.0	12.2	22.6
ATTAIN LTE (ABT)	218	37	18	17.0	12.2	22.6
ATTAIN LTE (ABT)	218	35	24	16.1	11.4	21.6
ATTAIN LTE (ABT)	218	32	36	14.7	10.3	20.1
ATTAIN LTE (ABT)	218	22	48	10.1	6.4	14.9
ATTAIN LTE (ABT)	218	21	60	9.6	6.1	14.3
ATTAIN LTE (PL before ABT)	99	13	6	13.1	7.2	21.4
ATTAIN LTE (PL before ABT)	99	11	12	11.1	5.7	19.0
ATTAIN LTE (PL before ABT)	99	13	18	13.1	7.2	21.4
ATTAIN LTE (PL before ABT)	99	15	30	15.2	8.7	23.8
ATTAIN LTE (PL before ABT)	99	11	42	11.1	5.7	19.0
ATTAIN LTE (PL before ABT)	99	7	54	7.1	2.9	14.0
Non-ITT analysis						
ATTAIN LTE (ABT)	212	25	6	11.8	7.8	16.9
ATTAIN LTE (ABT)	202	37	12	18.3	13.2	24.4
ATTAIN LTE (ABT)	NR	37	18	n/a	n/a	n/a
ATTAIN LTE (ABT)	155	35	24	22.6	16.3	30.0
ATTAIN LTE (ABT)	137	32	36	23.4	16.6	31.3
ATTAIN LTE (ABT)	118	22	48	18.6	12.1	26.9
ATTAIN LTE (ABT)	91	21	60	23.1	14.9	33.1
ATTAIN LTE (PL before ABT)	96	13	6	13.5	7.4	22.0
ATTAIN LTE (PL before ABT)	NR	11	12	n/a	n/a	n/a
ATTAIN LTE (PL before ABT)	74	13	18	17.6	9.7	28.2
ATTAIN LTE (PL before ABT)	58	15	30	25.9	15.3	39.0
ATTAIN LTE (PL before ABT)	50	11	42	22.0	11.5	36.0
ATTAIN LTE (PL before ABT)	37	7	54	18.9	8.0	35.2

Figure 65 Abatacept - ACR70 response in non-RCTs

DAS28

(1) RCT

The mean change from baseline in DAS28 was -1.98 in the abatacept group and -0.71 in the placebo group. The difference between these values was –1.27 (95% CI: –1.62, –0.93, p<0.001).

This data was provided in the industry submission only. No further information was provided and therefore analyses could not be undertaken.

As indicated in Figure 66, there were over twice as many patients who achieved a clinically meaningful DAS28 improvement (defined as ≥1.2) in the abatacept arm than in the control arm (RR=2.15, 95%CI: 1.54, 2.99).

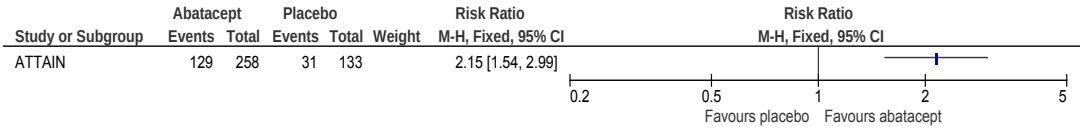


Figure 66 Abatacept - patients with clinically meaningful (≥1.2) DAS28 improvement in the ATTAIN RCT at 6 months

The ATTAIN study also reported percentages of patients who based on DAS28 achieved a low score (DAS 28≤3.2) or remission (DAS28 <2.6). At six months patients in the abatacept arm were over five times more likely to have a DAS 28≤3.2 than those in the placebo arm and the difference was statistically significant (RR=5.67, 95%CI: 2.08, 15.44). They were also over 13 times more likely to have a DAS28 <2.6 than the placebo group and the difference was also statistically significant (RR=13.40, 95%CI: 1.84, 97.69).

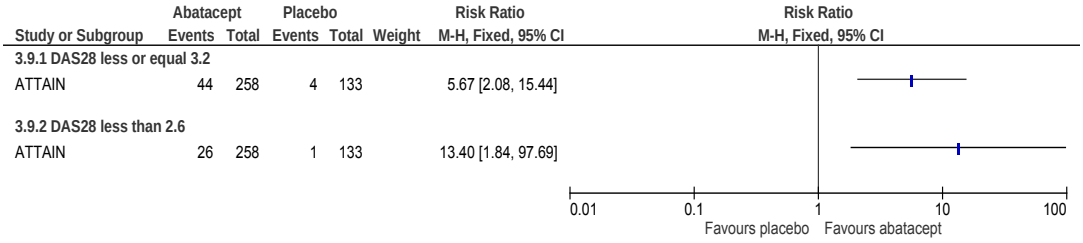
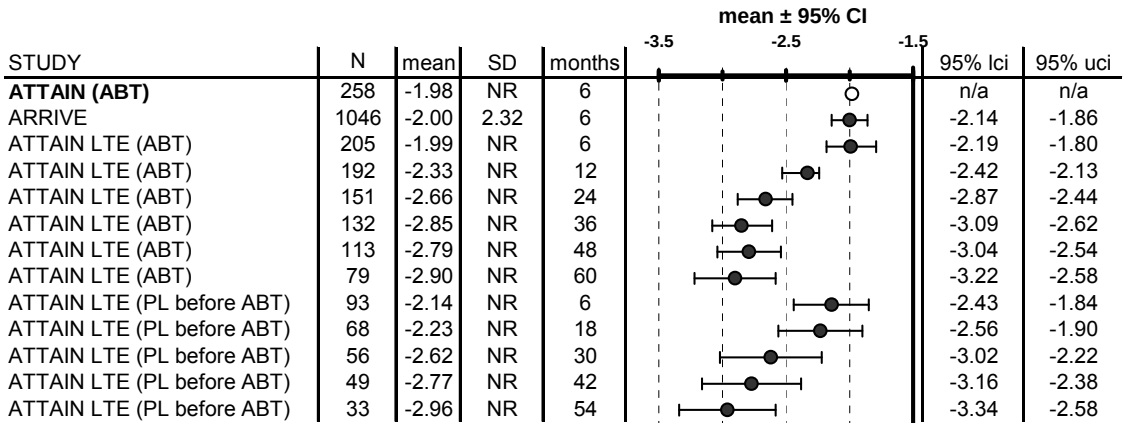


Figure 67 Abatacept - patients with final DAS28 values less or equal 3.2 and less than 2.6 in the ATTAIN RCT at 6 months

(2) Non-RCTs

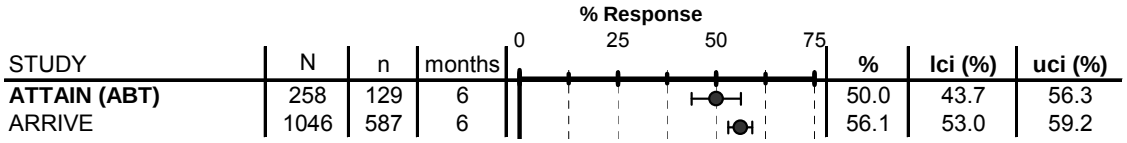
Change in the DAS28 score was assessed in both uncontrolled studies. Details are presented in Figure 68. After six months of treatment there was a mean change of -1.99 in the arm initially randomised to abatacept and -2.14 in the arm initially randomised to placebo in the ATTAIN LTE and -2.00 in the ARRIVE study. This was similar in the RCT. In the ATTAIN LTE DAS28 further decreased with time and the mean change was -2.90 at five years in the arm initially randomised to abatacept and -2.96 at 54 months in the arm initially randomised to placebo.



STUDY	N	mean	SD	months	95% lci	95% uci
ATTAIN (ABT)	258	-1.98	NR	6	n/a	n/a
ARRIVE	1046	-2.00	2.32	6	-2.14	-1.86
ATTAIN LTE (ABT)	205	-1.99	NR	6	-2.19	-1.80
ATTAIN LTE (ABT)	192	-2.33	NR	12	-2.42	-2.13
ATTAIN LTE (ABT)	151	-2.66	NR	24	-2.87	-2.44
ATTAIN LTE (ABT)	132	-2.85	NR	36	-3.09	-2.62
ATTAIN LTE (ABT)	113	-2.79	NR	48	-3.04	-2.54
ATTAIN LTE (ABT)	79	-2.90	NR	60	-3.22	-2.58
ATTAIN LTE (PL before ABT)	93	-2.14	NR	6	-2.43	-1.84
ATTAIN LTE (PL before ABT)	68	-2.23	NR	18	-2.56	-1.90
ATTAIN LTE (PL before ABT)	56	-2.62	NR	30	-3.02	-2.22
ATTAIN LTE (PL before ABT)	49	-2.77	NR	42	-3.16	-2.38
ATTAIN LTE (PL before ABT)	33	-2.96	NR	54	-3.34	-2.58

Figure 68 Abatacept - DAS28 change from baseline in uncontrolled studies

ARRIVE measured clinically meaningful DAS28 improvement. It was defined as a decrease ≥ 1.2 or a score ≤ 3.2. At six months 56.1% of patients in ARRIVE achieved this outcome. This was slightly more compared to the abatacept group of the RCT (although in ATTAIN this was defined as a decrease ≥1.2 only).



STUDY	N	n	months	%	lci (%)	uci (%)
ATTAIN (ABT)	258	129	6	50.0	43.7	56.3
ARRIVE	1046	587	6	56.1	53.0	59.2

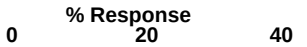
Figure 69 Abatacept - clinically meaningful DAS28 improvement in non-randomised studies at six months

Both uncontrolled studies reported percentages of patients who, based on DAS28, achieved a low score (DAS 28≤3.2) or remission (DAS28 <2.6). Full details are reported in Figure 70.

At six months a DAS28 score ≤3.2 was achieved by 10.6% of patients initially randomised to abatacept in ATTAIN LTE, 22.2% of patients initially randomised to placebo in the ATTAIN LTE and 22.4% of patients in ARRIVE. For comparison, this was 17.1% of patients in the abatacept arm of ATTAIN. Percentage of patients initially randomised to abatacept in ATTAIN LTE who achieved DAS 28≤3.2 increased up to 18 months (28%) an than decreased up to five years (15.1%). In the arm initially randomised to placebo the percentage of patients with low DAS decreased up to 54 months (7.1%).

A DAS28 score <2.6 was achieved at six months by 10.6% and 17.2% in ATTAIN LTE (initial abatacept and placebo respectively) and 13.0% in ARRIVE. For comparison, 10.1% of the abatacept arm of the RCT achieved this outcome. In the ATTAIN LTE arm initially randomised to abatacept the highest percentage of patients with DAS28<2.6 was recorded at 18 months

(17.0%) and afterwards it decreased to 9.6% at five years. In the arm initially randomised to placebo the highest percentage of patients with DAS28<2.6 was recorded after six months of treatment and at 54 months it was 6.1%.



STUDY	N	n	months	%	lci (%)	uci (%)
DAS28 ≤ 3.2	0	0	0			
ATTAIN (ABT)	258	44	6	17.1	12.7	22.2
ARRIVE	1046	234	6	22.4	19.9	25.0
ATTAIN LTE (ABT)	218	23	6	10.6	6.8	15.4
ATTAIN LTE (ABT)	218	47	12	21.6	16.3	27.6
ATTAIN LTE (ABT)	218	61	18	28.0	22.1	34.4
ATTAIN LTE (ABT)	218	49	24	22.5	17.1	28.6
ATTAIN LTE (ABT)	218	50	36	22.9	17.5	29.1
ATTAIN LTE (ABT)	218	46	48	21.1	15.9	27.1
ATTAIN LTE (ABT)	218	33	60	15.1	10.7	20.6
ATTAIN LTE (PL before ABT)	99	22	6	22.2	14.5	31.7
ATTAIN LTE (PL before ABT)	99	NR	12	n/a	n/a	n/a
ATTAIN LTE (PL before ABT)	99	7	18	7.1	2.9	14.0
ATTAIN LTE (PL before ABT)	99	15	30	15.2	8.7	23.8
ATTAIN LTE (PL before ABT)	99	13	42	13.1	7.2	21.4
ATTAIN LTE (PL before ABT)	99	7	54	7.1	2.9	14.0
	0	0	0			
DAS28 < 2.6	0	0	0			
ATTAIN (ABT)	258	26	6	10.1	6.7	14.4
ARRIVE	1046	136	6	13.0	11.0	15.2
ATTAIN LTE (ABT)	218	23	6	10.6	6.8	15.4
ATTAIN LTE (ABT)	218	27	12	12.4	8.3	17.5
ATTAIN LTE (ABT)	218	37	18	17.0	12.2	22.6
ATTAIN LTE (ABT)	218	31	24	14.2	9.9	19.6
ATTAIN LTE (ABT)	218	31	36	14.2	9.9	19.6
ATTAIN LTE (ABT)	218	23	48	10.6	6.8	15.4
ATTAIN LTE (ABT)	218	21	60	9.6	6.1	14.3
ATTAIN LTE (PL before ABT)	99	17	6	17.2	10.3	26.1
ATTAIN LTE (PL before ABT)	99	NR	12	n/a	n/a	n/a
ATTAIN LTE (PL before ABT)	99	7	18	7.1	2.9	14.0
ATTAIN LTE (PL before ABT)	99	8	30	8.1	3.6	15.3
ATTAIN LTE (PL before ABT)	99	8	42	8.1	3.6	15.3
ATTAIN LTE (PL before ABT)	99	6	54	6.1	2.3	12.7

Figure 70 Abatacept - patients with final DAS28 values less or equal 3.2 and less than 2.6 in uncontrolled studies

EULAR response

EULAR response was not assessed in any of the studies.

HAQ

(1) RCTs

At six months the HAQ changes from baseline in the ATTAIN RCT were-0.45 in the abatacept group and -0.11 in the placebo group and the difference between the two groups was reported to be statistically significant (p<0.001). No data on uncertainty of individual assessments was provided in the study and therefore further analyses could not be undertaken.

This study also assessed clinically meaningful HAQ improvement defined as a decrease in HAQ score of at least 0.3 (details are reported in Figure 71). Clinically meaningful HAQ increase was over two times more frequent in the abatacept group than in the placebo group and the difference was statistically significant (RR=2.01; 95%CI: 1.44, 2.81).

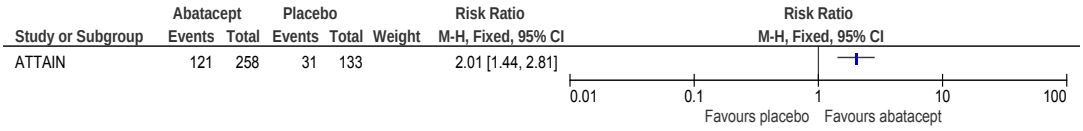
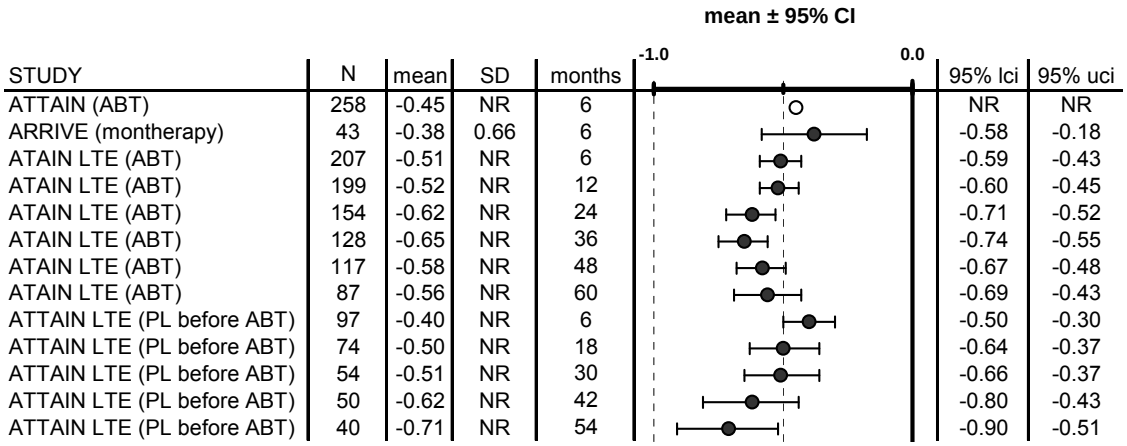


Figure 71 Abatacept - clinically meaningful improvement (≥0.3) in HAQ score

(2) Non-RCTs

Change in HAQ score was assessed in both uncontrolled studies (however for ARRIVE only data for a subgroup of 43 US patients receiving monotherapy was reported[§]). Figure 72 presents the mean changes from baseline in HAQ score. The mean change from baseline at six months was -0.51 in the arm of ATTAIN initially randomised to abatacept, -0.40 in the arm of ATTAIN initially randomised to placebo and -0.38 in the monotherapy subgroup of ARRIVE. The results for the abatacept arm of the RCT were similar. In the arm initially randomised to abatacept in the ATTAIN LTE the change decreased up to three years (-0.65) and then started slowly increasing (to -0.58 at four years and -0.56 at five years). In the group initially randomised to placebo there was a decrease up to 54 months of treatment (-0.71).

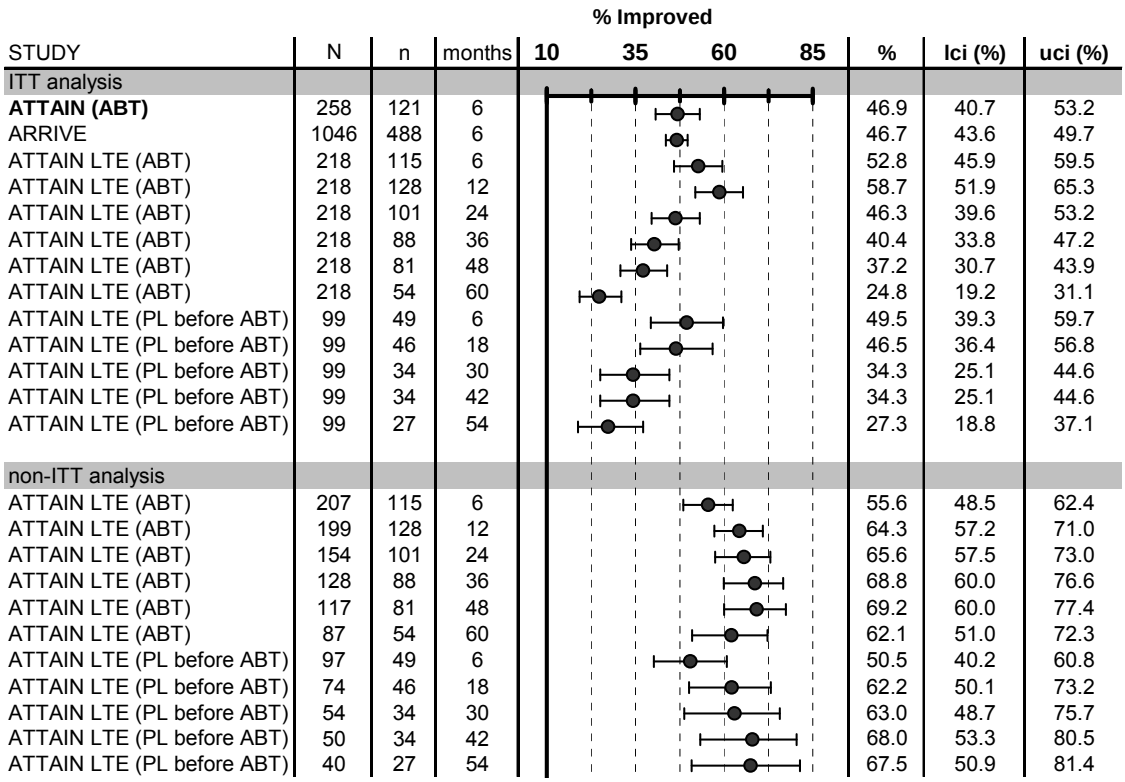
[§] abatacept as monotherapy is licensed in the USA, but not in Europe



STUDY	N	mean	SD	months	95% lci	95% uci
ATTAIN (ABT)	258	-0.45	NR	6	NR	NR
ARRIVE (montherapy)	43	-0.38	0.66	6	-0.58	-0.18
ATAIN LTE (ABT)	207	-0.51	NR	6	-0.59	-0.43
ATAIN LTE (ABT)	199	-0.52	NR	12	-0.60	-0.45
ATAIN LTE (ABT)	154	-0.62	NR	24	-0.71	-0.52
ATAIN LTE (ABT)	128	-0.65	NR	36	-0.74	-0.55
ATAIN LTE (ABT)	117	-0.58	NR	48	-0.67	-0.48
ATAIN LTE (ABT)	87	-0.56	NR	60	-0.69	-0.43
ATTAIN LTE (PL before ABT)	97	-0.40	NR	6	-0.50	-0.30
ATTAIN LTE (PL before ABT)	74	-0.50	NR	18	-0.64	-0.37
ATTAIN LTE (PL before ABT)	54	-0.51	NR	30	-0.66	-0.37
ATTAIN LTE (PL before ABT)	50	-0.62	NR	42	-0.80	-0.43
ATTAIN LTE (PL before ABT)	40	-0.71	NR	54	-0.90	-0.51

Figure 72 Abatacept - mean changes from baseline in HAQ score

Both uncontrolled studies reported the number of patients who achieved a clinically meaningful improvement in HAQ (details are provided in Figure 73). The ATTAIN LTE defined this outcome as an improvement of at least 0.3 in the HAQ score, while in ARRIVE it was an improvement of at least 0.22. After six months of treatment with abatacept the percentage of patients who achieved this outcome was 52.8% in ATTAIN LTE arm including patients initially randomised to abatacept, 49.5% in ATTAIN LTE arm including patients initially randomised to placebo and 46.7% in the ARRIVE study. For comparison, it was 46.9% in the abatacept arm of the RCT. ITT analysis of the data from the ATTAIN LTE showed a decrease in percentage of patients who achieved a clinically meaningful HAQ over time with 24.8% of patients initially randomised to abatacept achieving clinically meaningful HAQ improvement at 5 years and 27.3% of patients initially randomised to placebo achieving clinically meaningful HAQ improvement at 54 months. When the analysis included only patients in whom HAQ improvement was measured at different time points, there was a slight increase in the percentage over time.



STUDY	N	n	months	%	lci (%)	uci (%)
ITT analysis						
ATTAIN (ABT)	258	121	6	46.9	40.7	53.2
ARRIVE	1046	488	6	46.7	43.6	49.7
ATTAIN LTE (ABT)	218	115	6	52.8	45.9	59.5
ATTAIN LTE (ABT)	218	128	12	58.7	51.9	65.3
ATTAIN LTE (ABT)	218	101	24	46.3	39.6	53.2
ATTAIN LTE (ABT)	218	88	36	40.4	33.8	47.2
ATTAIN LTE (ABT)	218	81	48	37.2	30.7	43.9
ATTAIN LTE (ABT)	218	54	60	24.8	19.2	31.1
ATTAIN LTE (PL before ABT)	99	49	6	49.5	39.3	59.7
ATTAIN LTE (PL before ABT)	99	46	18	46.5	36.4	56.8
ATTAIN LTE (PL before ABT)	99	34	30	34.3	25.1	44.6
ATTAIN LTE (PL before ABT)	99	34	42	34.3	25.1	44.6
ATTAIN LTE (PL before ABT)	99	27	54	27.3	18.8	37.1
non-ITT analysis						
ATTAIN LTE (ABT)	207	115	6	55.6	48.5	62.4
ATTAIN LTE (ABT)	199	128	12	64.3	57.2	71.0
ATTAIN LTE (ABT)	154	101	24	65.6	57.5	73.0
ATTAIN LTE (ABT)	128	88	36	68.8	60.0	76.6
ATTAIN LTE (ABT)	117	81	48	69.2	60.0	77.4
ATTAIN LTE (ABT)	87	54	60	62.1	51.0	72.3
ATTAIN LTE (PL before ABT)	97	49	6	50.5	40.2	60.8
ATTAIN LTE (PL before ABT)	74	46	18	62.2	50.1	73.2
ATTAIN LTE (PL before ABT)	54	34	30	63.0	48.7	75.7
ATTAIN LTE (PL before ABT)	50	34	42	68.0	53.3	80.5
ATTAIN LTE (PL before ABT)	40	27	54	67.5	50.9	81.4

Figure 73 Abatacept - clinically meaningful improvement in HAQ score (≥0.3 in ATTAIN studies and ≥0.22 in ARRIVE)

Quality of life

(1) RCT

The ATTAIN RCT assessed patients' quality of life using the SF-36 scale. Patients in the abatacept arm improved significantly more both in the physical component (mean difference=5.50, 95%CI: 3.74, 7.26) and in the mental component (mean difference=3.70, 95%CI: 1.45, 5.95). Details are presented in Figure 74.

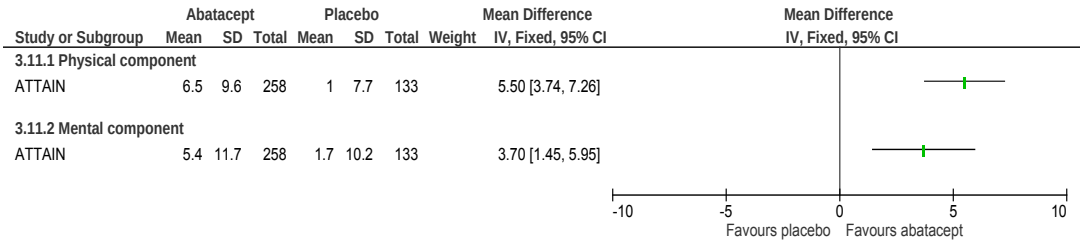


Figure 74 Abatacept - SF-36 changes from baseline in components in the ATTAIN RCT at six months

For all individual SF-36 items there was a significantly higher improvement in the abatacept arm than in the placebo arm. Details for each item are presented in Figure 75.

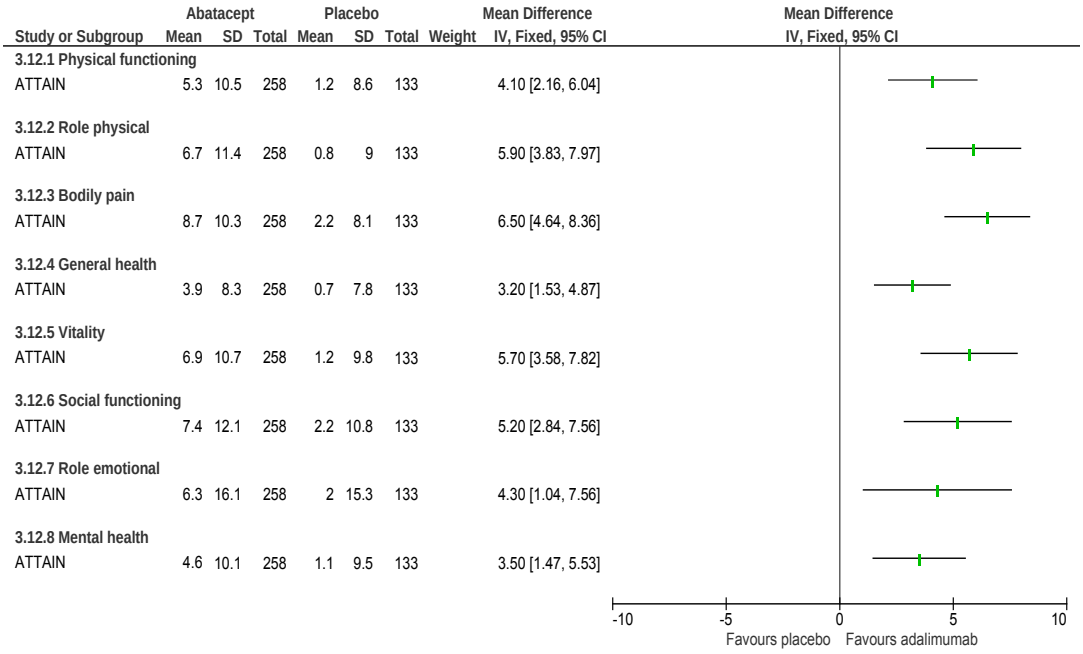


Figure 75 Abatacept - SF-36 changes from baseline in items at six months in the ATTAIN RCT

(2) Non-RCTs

Of the uncontrolled studies, change in SF-36 was assessed only in the ARRIVE study (however only for a subgroup of 43 patients receiving monotherapy[**] was reported). For the physical component of the SF-36 scale there was improvement of 7.41 for the monotherapy subgroup of ARRIVE. For the mental component the improvement was 12.66. For comparison, in the abatacept arm of attain it was 9.60 and 11.70 respectively. Further details are provided in Figure 76. Data for individual items was not reported in ARRIVE.

[**] abatacept as monotherapy is licensed in the USA, but not in Europe

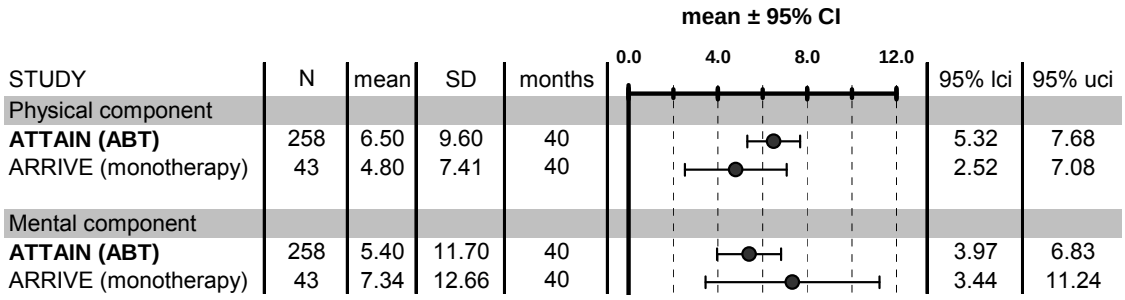


Figure 76 Abatacept - SF36 changes from baseline in components

Joint damage

Joint damage was not assessed in any of the studies.

Serious adverse events

(1) RCT

In ATTAIN there was no significant difference at six months between abatacept and placebo in the risk of experiencing a serious adverse event (RR=0.93, 95%CI: 0.51, 1.68). Details are presented in Figure 77.

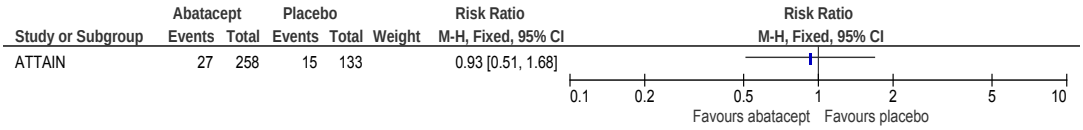


Figure 77 Abatacept - serious adverse events in the ATTAIN RCT at 6 months

(2) Non-RCTs

Serious adverse events were assessed in both uncontrolled studies. At six months the percentage of patients experiencing a serious adverse event was 10.4% respectively. It was similar in the abatacept arm of the ATTAIN RCT (10.5%). At two years 32.5% of patients in the ATTAIN LTE experienced a serious adverse event. Full details are presented in Figure 78.

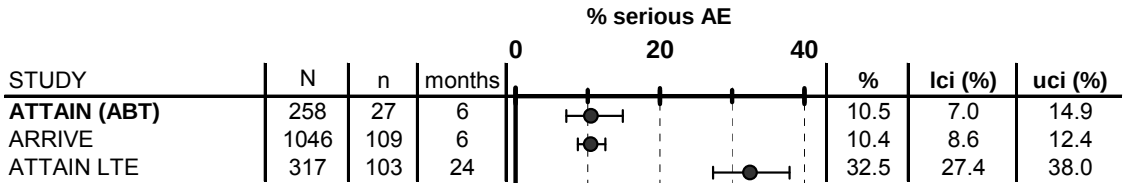


Figure 78 Abatacept - serious adverse events in non-randomised studies

Infections/ serious infections

(1) RCT

At six months there was no statistically significant difference between abatacept and placebo in the risk of infection (RR=1.16, 95%CI: 0.87, 1.56) or serious infection (RR=1.03, 95%CI: 0.26, 4.06). Details are presented in Figure 79.

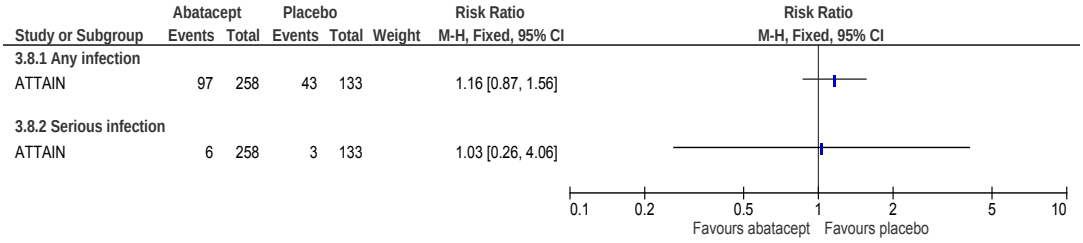


Figure 79 Abatacept - infections in the ATTAIN RCT at 6 months

(2) Non-RCTs

Both uncontrolled studies reported infections. The percentages of patients who experienced any infection were similar at six months in the abatacept arm of ATTAIN and in the ARRIVE study (37.6% and 38.9% respectively). Of these 2.3% and 2.4% were serious. At two years 73.8% of patients in the ATTAIN LTE experienced any infection and 7.9% a serious infection. Details are reported in Figure 80.

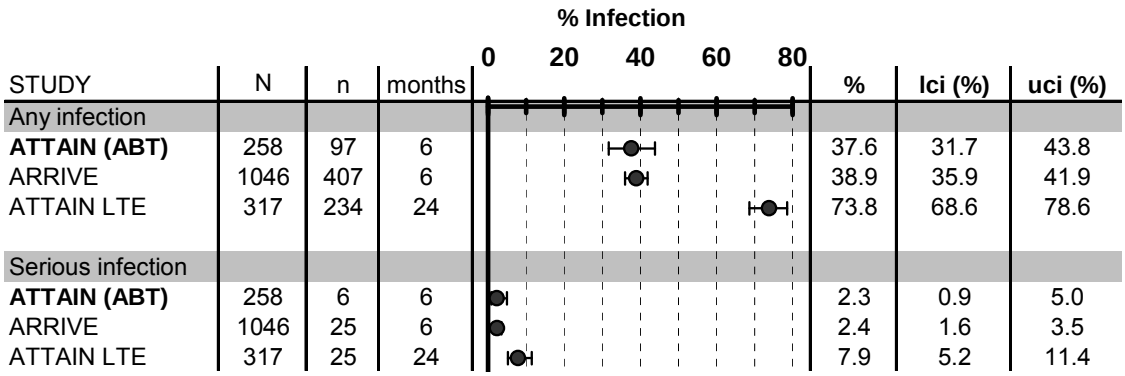


Figure 80 Abatacept - infections in non-randomised studies

Injection/ infusion reaction

Injection reactions were not assessed in any of the studies, as abatacept is administered as an intravenous infusion.

(1) RCT

At six months there was no statistically significant difference between abatacept and placebo in the risk of infusion reaction (RR=1.68, 95%CI: 0.56, 5.04). Details are reported in Figure 81.

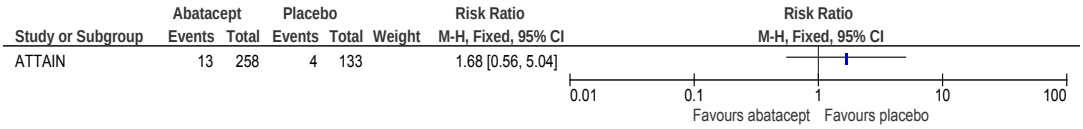


Figure 81 Abatacept - infusion reactions

(2) Non-RCTs

Of the uncontrolled studies, infusion reactions were reported only in ARRIVE. At six months 5.4% patients experienced infusion reactions. For comparison it was 5.0% in the abatacept arm of ATTAIN. Details are provided in Figure 82.

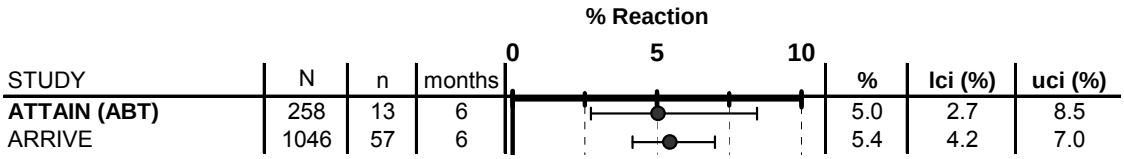


Figure 82 Abatacept - infusion reactions

5.3.6.5. Abatacept in combination with other biologic drugs

Two RCTs (Weinblatt 2007[132] and ASSURE[133]) was identified that assessed abatacept in combination with previously tried biologic drugs. Although the studies met the inclusion criteria of the systematic review, combination therapy was not considered relevant to this report and therefore they were not analysed.

Weinblatt 2007 was a multicentre placebo controlled randomised trial and included 121 patients who had active RA despite treatment with etanercept. Patients were randomised to receive etanercept and abatacept or etanercept and placebo and followed-up for one year. Afterwards they could enter a long term extension (data provided for 2 years of the extension study). Data was collected on outcomes including ACR response, HAQ, SF-36 and safety.

ASSURE was a multicentre placebo controlled randomised trial and included 167 patients who had active RA in spite of receiving therapy with biologic agents[††] (etanercept, infliximab, adalimumab and anakinra), "*warranting additional therapy at the discretion of the investigator.*" Patients continued their treatment and in addition to that were randomised to receive abatacept or placebo. They were followed-up for one year. The study assessed outcomes including HAQ DI, pain, patient and physician global assessment and safety.

[††] It also included 1274 patients who received background DMARDs and probably were biologic naïve

5.3.6.6. Summary

Three studies assessed abatacept in comparison with standard care: one RCT (ATTAIN) and two uncontrolled studies (ATTAIN LTE and ARRIVE). Follow-up ranged from six months to five years. All studies included patients with similar baseline characteristics. Main results of included studies are summarised in Table 40.

Table 40 Abatacept - summary of main results

Outcome	RCT (result (95%CI))	Uncontrolled studies	
	6 months	6 months	4.5-5 years
Withdrawals:			24 months (longer follow-up NA)
• for any reason	RR=0.53 (0.35, 0.81); less in ABT	17.8%	30%
• due to lack of efficacy	RR=0.27 (0.15, 0.49), less in ABT	10%	16.4%
• due to adverse events	RR=0.93 (0.32, 2.71), no difference	3.7%	7.6%
ACR20 response	RR=2.56 (1.77, 3.69), favours ABT; similar results for 3 months	57.3-63.6%	30.3%
ACR50 response	RR=5.36 (2.19, 13.10), favours ABT	22.9-37.4%	20.6-21.2%
ACR70 response	RR=6.70 (1.62, 27.81), favours ABT	11.5-13.1%	7.1-9.6%
DAS28			
• change from baseline	mean difference = -1.27 (-1.62, -0.93), favours ABT	–1.99 to -2.14	-2.00 to -2.90
• clinically meaningful	RR=2.15 (1.54, 2.99), favours ABT	56.1%	NA
• ≤ 3.2	RR=5.67 (2.08, 15.44), favours ABT	10.6-22.4%	7.1-15.1%
• <2.6	RR=13.40 (1.84, 97.69), favours ABT	13.0-17.2%	6.1-9.6%
EULAR response	NA	NA	NA
HAQ			
• change from baseline	Only reported that favours ABT (p<0.001)	-0.38 to -0.51	-0.56 to -0.71
• clinically meaningful	RR=2.01 (1.44, 2.81), favours ABT	46.7-52.8%	24.8-27.3
Quality of life (SF-36)			
• physical component	mean difference = 5.50 (3.74, 7.26), favours ABT	7.41	NA
• mental component	mean difference = 3.70 (1.45, 5.95), favours ABT	12.66	NA
Joint damage	NA	NA	NA
Serious adverse events	RR=0.93 (0.51, 1.68), ns	10.4%	32.5%
Any infections	RR=1.16 (0.87, 1.56), ns	38.9%	73.8%
Serious infections	RR=1.03 (0.26, 4.06), ns	2.4%	7.9%
Infusion reaction	RR=1.68 (0.56, 5.04), ns	5.4%	NA

5.4 Effectiveness of the technologies compared to newly initiated and previously untried conventional DMARDs

No study addressing the comparison was found.

5.5 Effectiveness of the technologies compared to other biologic agents

No study addressing this comparison was found.

5.6 Comparison of effectiveness between technologies (head-to-head comparisons)

5.6.1 Evidence from comparative studies

5.6.1.1. Overview of evidence

One prospective cohort study was identified to compare rituximab with TNF inhibitors as a class (Finckh 2009[134,135]).

Included patients had tried at least one TNF inhibitor (adalimumab, etanercept or infliximab) before and discontinued their treatment due to inadequate response. The study was conducted in Switzerland and the median duration of follow-up was 11 months. Full details of this study are provided in Table 41.

Table 41 Comparative studies - characteristics of included studies

Study	Country	Design	Reason for switching	Prior TNF inhibitors; no.	Treatment arms (no. of patients)	Duration of follow-up	Comments
Randomised controlled trials (none were identified)							
Non-randomised comparative studies							
Finckh 2009[134,135]	Switzerland	Prospective cohort	Inadequate response	Any (≥1)	TNF (163) RTX (155)	11 months (median)	Based on the Swiss Clinical Quality Management program for RA (SCQOM-RA)
Uncontrolled studies (n/a)							

5.6.1.2. Patient characteristics

Full details baseline characteristics are reported in Table 42. The study included 318 patients and:

- 77.5% of them were female;
- Mean age was 55 years;
- Mean disease duration was 11.3 years;

- 82.4% were RF positive;
- Concomitant DMARDs used were: methotrexate (63.9%), leflunomide (18%) and other (4.5%);
- 56.5% of patients were receiving steroids;
- The number of previous DMARDs was not reported;
- The number of previous TNF inhibitors ranged from one to over two;
- The mean baseline HAQ score was 1.5;
- The mean baseline DAS28 score was 4.5;
- No information was provided on CRP and ESR;

Table 42 Comparative studies - patient characteristics

	number of patients/ % female	age; mean (SD); years	RA duration; mean (SD); years	RF positive; %	concomitant DMARDs and steroids	number of previous DMARDs; mean (SD)	number of previous TNF inhibitors; mean (SD)	HAQ; mean (SD)	DAS 28; mean (SD)	tender/ swollen joint count; mean (SD)	ESR; mean (SD); mm/hr	CRP; mean (SD); mg/dL
Finckh 2009[134,135]	318/ 77.5 %	55 (12.85)	11.3 (8.1)	82.4 %	MTX (63.9%), LEF (18.0%), other (4.5%), steroids (56.5%)	NR	1 to >2	1.5 (2.9)	4.5 (1.3)	NR	NR	NR

5.6.1.3. Quality assessment

Full details of quality assessment are reported in Table 43. The study was a prospective cohort. It had clearly defined inclusion criteria. It was however unclear if consecutive patients were included in the study and what percentage of patients were withdrawn.

Table 43 Comparative studies - non-RCT quality assessment

Study	Study design	Inclusion criteria clearly defined?	Were consecutive patients included in the study?	Patients withdrawn (%)	Comments
Finckh 2009[134,135]	Prospective cohort	Yes	Unclear	Unclear	

5.6.1.4. Results

Table 38 indicates which of the outcomes reported in the main text of the report were assessed in the Finckh 2009 study. No other outcomes apart from the ones reported in the table below were assessed.

Table 44 Comparative study - outcomes assessed and reported in the main text of the report

	Total withdrawal	Withdrawal by reason	ACR (20/50/70)	DAS28	EULAR response	HAQ	Quality of life	Joint damage	Serious adverse events	Infection/ serious infection	Injection/ infusion reaction
Finckh 2009[134,135]				√							√

Withdrawals

Withdrawals were not assessed in this study.

ACR20/50/70 response

ACR response was not assessed in this study.

DAS28

There was a trend favouring TNF inhibitors over rituximab for change from baseline in DAS28, however this difference was not statistically significant (mean difference=-0.35, 95%CI: -0.71, 0.01). The follow-up for this outcome was unclear. See Figure 83 for details.

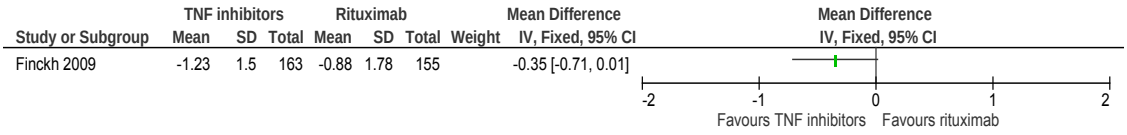


Figure 83 TNF inhibitors vs. rituximab - DAS28 change from baseline

EULAR response

EULAR response was not reported in this study.

HAQ

HAQ score was reported only for baseline in this study.

Quality of life

Quality of life was not reported in this study.

Joint damage

Joint damage was not reported in this study.

Serious adverse events

Serious adverse events were not reported in this study.

Infections/ serious infections

Infections were not reported in this study.

Injection/ infusion reaction

Data for injection/infusion reactions was reported only for a subgroup of 116 patients.[134] It reported dermatological complications (mainly injection site reactions) that occurred in one rituximab patient and nine TNF inhibitor patients. Infusion reactions were reported in 3 rituximab and none of the TNF inhibitor patients. Data from both categories were analysed together to compare adverse events associated with drug administration (see Figure 84). There was no statistically significant difference between groups (RR=1.70, 95%CI: 0.56, 5.22).

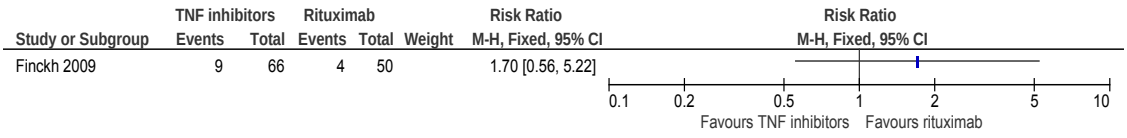


Figure 84 TNF inhibitors vs. rituximab - injection/infusion site reactions

5.6.1.5. Summary

One prospective cohort study (Finckh 2009) compared TNF inhibitors with rituximab. The median follow-up was 11 months, however it was not clearly stated when outcomes were assessed. Main results of the study are summarised in Table 45.

Table 45 TNF inhibitors vs. rituximab - summary of results

Outcome	Results (TNF inhibitors vs. rituximab)
	Unclear follow-up
Withdrawals:	NR
ACR20 response	NR
ACR50 response	NR
ACR70 response	NR
DAS28 - change from baseline	mean difference=-0.35, 95%CI: -0.71, 0.01, ns
EULAR response	NR
HAQ	NR
Quality of life	NR
Joint damage	NR
Serious adverse events	NR
Any infections Serious infections	NR NR
Injection/infusion reactions	RR=1.70, 95%CI: 0.56, 5.22, ns

5.6.2 Indirect comparisons

Two placebo controlled RCTs were identified that were considered amenable for an indirect comparison of effectiveness of two of the drugs of interest. These trials were REFLEX and ATTAIN which investigated rituximab and abatacept respectively in similar populations with similar follow up and outcome measures.

Indirect comparison was conducted (rituximab versus abatacept) using the method of Bucher et al. [71] The following binary outcomes were examined: ACR 20, ACR 50 and ACR 70 responses and "withdrawal for any reason". The results are summarised in Table 46.

Table 46 Indirect comparison: ACR response

	COMPARISON	RR	LCI	UCI	COMMENT
ACR 20					
	RITUXIMAB v PLACEBO	2.848	2.076	3.907	favours rituximab
	ABATACEPT v PLACEBO	2.554	1.737	3.756	favours abatacept
	RITUXIMAB v ABATACEPT	1.115	0.677	1.836	favours rituximab, wide CIs
ACR 50					
	RITUXIMAB v PLACEBO	5.396	2.866	10.158	favours rituximab
	ABATACEPT v PLACEBO	5.403	2.211	13.203	favours abatacept
	RITUXIMAB v ABATACEPT	0.999	0.334	2.984	No difference
ACR 70					
	RITUXIMAB v PLACEBO	12.141	2.956	49.859	favours rituximab
	ABATACEPT v PLACEBO	6.754	1.628	28.023	favours abatacept
	RITUXIMAB v ABATACEPT	1.798	0.242	13.350	favours rituximab, wide CIs
Withdrawal any reason					
	RITUXIMAB v PLACEBO	0.389	0.294	0.515	favours rituximab
	ABATACEPT v PLACEBO	0.531	0.348	0.810	favours abatacept
	RITUXIMAB v ABATACEPT	0.733	0.441	1.217	favours rituximab, wide CIs

No indirect comparison approached statistical significance, however the indirect comparison point estimates slightly favoured rituximab for ACR 20, ACR 70 and for withdrawal for any reason.

Indirect comparison for change in HAQ score from baseline to 6 months of treatment was of potential interest. However data reporting was incomplete in Cohen et al 2006 and the uncertainty in the reported estimates could not be computed reliably. The change in HAQ score was almost the same in the two trials (see Table 47) so that it is unlikely that an indirect comparison would indicate a difference between the treatments for this outcome measure.

Table 47 Indirect comparison: change from baseline in HAQ score

	CHANGE FROM BASELINE				
	active intervention		Placebo		P
	mean	(SD)	mean	(SD)	
REFLEX (RTX)	-0.45	(NR)	-11	(NR)	<0.0001
ATTAIN (ABA)	-0.4	0.6	-0.1	0.5	<0.0001

5.7 Subgroup analyses

This section summarises results from subgroup analyses. Data from RCTs and observational studies were reported separately. Planned subgroup analyses from placebo-controlled RCTs provide least biased information with regard to whether *effectiveness* (i.e. the effects of treatment over and above what could be expected without the treatment) varies significantly between the subgroups of interest. Subgroup analyses performed post hoc were highlighted and need to be interpreted with caution.

Due to the relatively small volume of data from RCTs, results from non-randomised, uncontrolled studies were also included but were reported separately from RCT data. Because of lack of control groups in these studies, any observed differences in the observed *response* (i.e. not corrected for what would happen without treatment) between the subgroups can be due to differences in baseline characteristics before switching (and the natural course of the disease that follows) as well as genuine differences in the effectiveness between the subgroups.

In accordance with the study selection criteria for non-randomised studies, subgroup analyses were included only if the number of patients was ≥ 20 in at least one of the subgroups being compared. For studies in which some patients were excluded due to missing data, intention to treat (ITT) analyses were performed and presented for binary outcomes assuming patients with missing data did not achieve the favourable outcomes such as ACR20. Non-ITT analyses based on actually observed/reported data were presented only when the statistical significance of the results and/or the direction of effect differ from ITT analyses. For continuous outcomes, results were presented as reported in the original papers and no imputation of missing data was carried out. Where data were available from more than one study for a given outcome/time point, pooled estimates using the random effects model were presented. Given the potential differences in the populations and methods between studies, the main aim is to illustrate the existence or absence of heterogeneity between studies using the I^2 statistic.

5.7.1 Reasons for withdrawal of the previous TNF inhibitor

5.7.1.1. Lack of response (primary failure) vs loss of response (secondary failure)

(1) RCTs

No evidence from RCTs was reported.

(2) Non-RCTs

Subgroup data were available for switching to adalimumab, etanercept, an unspecified TNF inhibitor and abatacept. No subgroup data were identified for switching to infliximab and rituximab.

Adalimumab

Two uncontrolled studies reported data separately for patients who switched due to lack of response and those who had initial treatment response but later switched due to loss of response.[94,95] Results comparing these two subgroups of patients are summarised in Table 48 and Table 49 below.

Overall there was no significant difference in treatment withdrawal between the two subgroups. Patients who switched to adalimumab due to loss of response had significant higher response rates for ACR20 and 50.

Table 48 Switching to adalimumab due to lack of response versus due to loss response in observational studies – binary outcomes

Study	Switched due to lack of response		Switched due to loss of response		Relative risk* (95% CI)	Risk difference (95% CI)
	n/N	%	n/N	%		
Withdrawal for any reasons at 3 months						
Bombardieri 2007 (ReAct study) [94]	14/173	8%	24/306	8%	1.03 (0.55 to 1.94)	0.00 (-0.05 to 0.05)
Withdrawal due to lack of efficacy at 3 months						
Bombardieri 2007[94]	5/173	3%	5/306	2%	1.77 (0.52 to 6.02)	0.01 (-0.02 to 0.04)

Withdrawal due to intolerance/AE at 3 months						
Bombardieri 2007[94]	5/173	3%	16/306	5%	0.55 (0.21 to 1.48)	-0.02 (-0.06 to 0.01)
ACR20 at 3 months						
Bombardieri 2007[94]	91/173	53%	205/306	67%	**0.79 (0.67 to 0.92)**	**-0.14 (-0.24 to –0.05)**
van der Bijl 2008[95]	4/15	27%	13/21	62%	0.43 (0.17 to 1.06)	**-0.35 (-0.66 to –0.05)**
Pooled estimates (random effects)					0.69 (0.42 to 1.12) I^2 =40%	**-0.20 (-0.37 to –0.02)** I^2 =39%
ACR50 at 3 months						
Bombardieri 2007[94]	44/173	25%	111/306	36%	**0.70 (0.52 to 0.94)**	**-0.11 (-0.19 to –0.02)**
van der Bijl 2008[95]	2/15	13%	8/21	38%	0.35 (0.09 to 1.42)	-0.25 (-0.52 to 0.02)
Pooled estimates (random effects)					**0.68 (0.51 to 0.91)** I^2 =0%	**-0.12 (-0.20 to –0.04)** I^2 = 0%
ACR70 at 3 months						
Bombardieri 2007[94]	15/173	9%	41/306	13%	0.65 (0.37 to 1.13)	-0.05 (-0.10 to 0.01)
van der Bijl 2008[95]	1/15	7%	4/21	19%	0.35 (0.04 to 2.83)	-0.12 (-0.33 to 0.09)
Pooled estimates (random effects)					0.62 (0.36 to 1.07) I^2=0%	-0.05 (-0.11 to 0.00) I^2=0%
EULAR moderate/good response						
Bombardieri 2007[94]	127/173	73%	243/306	79%	0.92 (0.83 to 1.03)	-0.06 (-0.14 to 0.02)
van der Bijl 2008[95]	7/15	47%	14/21	67%	0.70 (0.38 to 1.30)	-0.20 (-0.52 to 0.12)
Pooled estimates (random effects)					0.92 (0.83 to 1.02) I^2=0%	-0.07 (-0.15 to 0.01) I^2=0%
EULAR good response						
Bombardieri 2007[94]	33/173	19%	68/306	22%	0.86 (0.59 to 1.24)	-0.03 (-0.11 to 0.04)
van der Bijl 2008[95]	1/15	7%	5/21	24%	0.28 (0.04 to 2.16)	-0.17 (-0.39 to 0.05)

Pooled estimates (random effects)					0.78 (0.42 to 1.44) I^2=11%	-0.06 (-0.17 to 0.05) I^2=28%

Bold type indicates statistically significant differences between subgroups.
*Relative risk > 1 and risk difference >0 favour switch due to loss of response for outcomes related to treatment withdrawal. Relative risk < 1 and risk difference <0 favours switch due to loss of response for ACR and EULAR responses.

Table 49 Switching to adalimumab due to lack of response versus due to loss response in observational studies – continuous outcomes

Study	**Switch due to lack of response**			**Switch due to loss of response**			**Mean difference* (95%CI)**
	N	Mean	SD	N	Mean	SD	
DAS28 change from baseline at 3 months							
Bombardieri 2007[94]	173	-1.87	1.48	306	-2.03	1.36	0.16 (-0.11 to 0.43)
van der Bijl 2008[95]	15	-1.0	0.9	21	-1.8	2.0	0.80 (-0.17 to 1.77)
Pooled estimates (random effects)							0.30 (-0.22 to 0.83) I^2=36%
HAQ change from baseline at 3 months							
Bombardieri 2007[94]	173	-0.44	0.54	306	-0.51	0.62	0.07 (-0.04 to 0.18)
van der Bijl 2008[95]	15	-0.13	0.53	21	-0.36	0.48	0.23 (-0.11 to 0.57)
Pooled estimates (random effects)							0.08 (-0.02 to 0.19) I^2=0%

*Mean difference >0 favour switching due to loss of response for DAS28 and HAQ.

Etanercept

Two uncontrolled studies reported subgroup data.[99,102] Results are summarised in Table 50 and Table 51. Overall the results were similar between the subgroups and no significant difference was observed.

Table 50 Switching to etanercept due to lack of response vs due to loss response in observational studies – binary outcomes

Study	Switched due to lack of response		Switched due to loss of response		Relative risk* (95% CI)	Risk difference* (95% CI)
	n/N	%	n/N	%		
Total withdrawal at 3 months						
Bingham 2009[102]	1/29	3%	12/172	7%	0.49 (0.07 to 3.66)	-0.04 (-0.11 to 0.04)
ACR20 at 3 months-ITT						
Buch 2007[99]	14/34	41%	13/38	34%	1.20 (0.66 to 2.19)	0.07 (-0.15 to 0.29)
Bingham 2009[102]	12/29	41%	73/172	42%	0.97 (0.61 to 1.56)	-0.01 (-0.20 to 0.18)
Pooled estimates (random effects)					1.06 (0.73 to 1.53) I^2=0%	0.02 (-0.12 to 0.17) I^2=0%
ACR20 at 3 months- non-ITT						
Buch 2007[99]	14/34	41%	13/38	34%	1.20 (0.66 to 2.19)	0.07 (-0.15 to 0.29)
Bingham 2009[102]	12/28	43%	73/160	46%	0.94 (0.59 to 1.49)	-0.03 (-0.23 to 0.17)
Pooled estimates (random effects)					1.03 (0.72 to 1.48) I^2=0%	0.02 (-0.13 to 0.16) I^2=0%
ACR50 at 3-4 months –ITT						
Buch 2007[99]	10/34	29%	8/38	21%	1.40 (0.62 to 3.13)	0.08 (-0.12 to 0.28)
Bingham 2009[102]	4/29	14%	33/172	19%	0.72 (0.28 to 1.88)	-0.05 (-0.19 to 0.08)
Pooled estimates (random effects)					1.06 (0.55 to 2.02) I^2=9%	-0.00 (-0.14 to 0.13) I^2=21%
ACR50 at 3 months - non-ITT						
Buch 2007[99]	10/34	29%	8/38	21%	1.40 (0.62 to 3.13)	0.08 (-0.12 to 0.28)
Bingham 2009[102]	4/28	14%	33/160	21%	0.69 (0.27 to 1.80)	-0.06 (-0.21 to 0.08)
Pooled estimates (random effects)					1.03 (0.52 to 2.05) I^2=19%	-0.01(-0.15 to 0.14) I^2=29%
ACR70 at 3 months-ITT						
Buch 2007[99]	5/34	15%	5/38	13%	1.12 (0.35 to 3.53)	0.02 (-0.14 to 0.18)
Bingham 2009[102]	1/29	3%	15/172	9%	0.40 (0.05 to 2.88)	-0.05 (-0.13 to 0.03)
Pooled estimate (random effects)					0.86 (0.32 to 2.33) I^2=0%	-0.04 (-0.11 to 0.03) I^2=0%
ACR70 at 3 months-non-ITT						
Buch 2007[99]	5/34	15%	5/38	13%	1.12 (0.35 to 3.53)	0.02 (-0.14 to 0.18)
Bingham 2009[102]	1/28	4%	15/160	9%	0.38 (0.05 to 2.77)	-0.06 (-0.14 to 0.02)
Pooled estimate					0.85 (0.32 to 2.31)	-0.04 (-0.12 to 0.03)

(random effects)					I^2=0%	I^2=0%
EULAR good/moderate response at 3 months –ITT						
Buch 2007[99]	23/34	68%	21/38	55%	1.22 (0.85 to 1.77)	0.12 (-0.10 to 0.35)
Bingham 2009[102]	17/29	59%	100/172	58%	1.01 (0.72 to 1.40)	0.00 (-0.19 to 0.20)
Pooled estimates (random effects)					1.10 (0.86 to 1.41) I^2=0%	0.06 (-0.09 to 0.20) I^2=0%
EULAR good/moderate response at 3 months - non-ITT						
Buch 2007[99]	23/34	68%	21/38	55%	1.22 (0.85 to 1.77)	0.12 (-0.10 to 0.35)
Bingham 2009[102]	17/28	61%	100/160	63%	0.97 (0.70 to 1.34)	-0.02 (-0.21 to 0.18)
Pooled estimate (random effects)					1.07 (0.84 to 1.37) I^2=0%	0.04 (-0.10 to 0.19) I^2=0%
EULAR good response at 3 months						
Buch 2007[99]	4/34	12%	5/38	13%	0.89 (0.26 to 3.06)	-0.01 (-0.17 to 0.14)
Serious adverse events						
Bingham 2009[102]	0/29	0%	10/172	6%	0.27 0.02 to 4.56)	-0.06 (-0.12 to 0.00)
Serious infection						
Bingham 2009[102]	0/29	0%	2/172	1%	1.15 (0.06 to 23.43)	-0.01 (-0.06 to 0.04)

Bold type indicates statistically significant differences between subgroups.
*Relative risk > 1 and risk difference >0 favour switch due to loss of response for outcomes related to treatment withdrawal and adverse events. Relative risk < 1 and risk difference <0 favours switch due to loss of response for ACR and EULAR responses.

Table 51 Switching to etanercept due to lack of response vs due to loss response in observational studies – continuous outcomes

Study	**Switch due to lack of response**			**Switch due to loss of response**			**Mean difference* (95% CI)**
	N	Mean	SD	N	Mean	SD	
DAS 28 change from baseline at 3 months							
Buch 2007[99]	34	-1.49	2.25	38	-1.53	2.16	0.04 (-0.98 to 1.06)

*Mean difference >0 favour switching due to loss of response for DAS28.

Infliximab

No studies of switching to infliximab provided subgroup data.

TNF inhibitors as a class

One observational study reported data separately for patients who switched due to lack of response and those who had initial treatment response but later switched due to loss of response.[111] Outcomes for the second TNF inhibitor were reported as an aggregated group and were not reported separately for individual TNF inhibitors. The results from the study are shown in Table 52 and Table 53.

There were no significant differences between the subgroups in withdrawal and treatment response, except for the ITT analysis for EULAR good/moderate response at 3 months. A significantly higher proportion of patients who switched due to lack of response achieved EULAR good/moderate response compared to those who switched due to loss of response. Data were missing for nearly half of the patients in the 'switching due to loss of response' for several outcomes, which may compromise the reliability of the results.

Table 52 Switching to TNF inhibitors due to lack of response versus due to loss response in observational studies – binary outcomes

Study: Blom 2009[111]	**Switched due to lack of response**		**Switched due to loss of response**		**Relative risk* (95% CI)**	**Risk difference* (95% CI)**
	n/N	**%**	**n/N**	**%**		
Withdrawal for any reasons at 3 and 6 months						
3 months	2/49	4%	5/75	7%	0.61 (0.12 to 3.03)	-0.03 (-0.10 to 0.05)
6 months	6/49	12%	16/75	21%	0.57 (0.24 to 1.37)	-0.09 (-0.22 to 0.04)
Withdrawal due to lack of efficacy at 3 and 6 months						
3 months	0/49	0%	2/75	3%	0.30 (0.01 to 6.20)	-0.03 (-0.08 to 0.02)
6 months	4/49	8%	10/75	13%	0.61 (0.20 to 1.84)	-0.05 (-0.16 to 0.06)
Withdrawal due to intolerance/AE at 3 and 6 months						
3 months	2/49	4%	3/75	4%	1.02 (0.18 to 5.89)	0.00 (-0.07 to 0.07)
6 months	2/49	4%	6/75	8%	0.51 (0.11 to 2.43)	-0.04 (-0.12 to 0.04)
EULAR moderate/good response at 3 and 6 months						
3 months - ITT	25/49	51%	16/75	21%	**2.39 (1.43 to 4.00)**	**0.30 (0.13 to 0.46)**
3 months - non-ITT	25/44	57%	16/38	42%	1.35 (0.86 to 2.12)	0.15 (-0.07 to 0.36)
6 months - ITT	22/49	45%	21/75	28%	1.60 (0.99 to 2.58)	0.17 (0.00 to 0.34)
EULAR good response at 3 and 6 months						
3 months - ITT	7/49	14%	3/75	4%	3.57 (0.97 to 13.15)	0.10 (0.00 to 0.21)

6 months - ITT	4/49	8%	7/75	9%	0.87 (0.27 to 2.83)	-0.01 (-0.11 to 0.09)
DAS28 ≤ 3.2 at 3 and 6 months						
3 months - ITT	8/49	16%	7/75	9%	1.75 (0.68 to 4.52)	0.07 (-0.05 to 0.19)
6 months - ITT	5/49	10%	11/75	15%	0.70 (0.26 to 1.88)	-0.04 (-0.16 to 0.07)

Bold type indicates statistically significant differences between subgroups.
*Relative risk > 1 and risk difference >0 favour switch due to loss of response for outcomes related to treatment withdrawal. Relative risk < 1 and risk difference <0 favours switch due to loss of response for EULAR and DAS28-based responses.

Table 53 Switching to TNF inhibitors due to lack of response wersus due to loss response in observational studies – continuous outcomes

Study: Blom 2009[111]	**Switch due to lack of response**			**Switch due to loss of response**			**Mean difference* (95% CI)**
	N	Mean	SD	N	Mean	SD	
DAS28 change from baseline at 3 and 6 months							
3 months (non-ITT)	44	-1.2	1.0	38	-0.7	1.3	-0.50 (-1.01 to 0.01)
6 months (non-ITT)	33	-1.3	1.3	41	-0.6	1.3	**-0.70 (-1.30 to -0.10)**

*Mean difference >0 favour switching due to loss of response for DAS28.

Rituximab

No studies of switching to rituximab provided subgroup data.

Abatacept

Subgroup data from the long-term extension of the ATTAIN trial (ATTAIN LTE)[117] were reported in the manufacturer submission. As patients had to complete six months of treatment in the ATTAIN trial in order to enter ATTAIN LTE, the included patients were no longer representative of the randomised cohort. The results were shown in Table 54. Significant difference between the subgroups was found only in a non-ITT analysis of HAQ improvement ≥ 0.3 at 6 months. Significantly more patients who switched due loss of response achieved this criteria compared to those who switched due to lack of response.

Table 54 Switching to abatacept due to lack of response vs due to loss response in ATTAIN LTE – binary outcomes

Results at 6 months (unless otherwise	**Switched due to lack of response**	**Switched due to loss of**	**Relative risk* (95% CI)**	**Risk difference* (95% CI)**

stated)			response			
	n/N	**%**	**n/N**	**%**		
ACR20 (ITT)	73/130	56%	50/84	60%	0.94 (0.75 to 1.19)	-0.03 (-0.17 to 0.10)
ACR50 (ITT)	30/130	23%	20/84	24%	0.97 (0.59 to 1.59)	-0.01 (-0.12 to 0.11)
ACR70 (ITT)	13/130	10%	12/84	14%	0.70 (0.34 to 1.46)	-0.04 (-0.13 to 0.05)
HAQ improvement ≥ 0.3 (ITT)	77/130	59%	60/84	71%	0.83 (0.68 to 1.01)	-0.12 (-0.25 to 0.01)
HAQ improvement ≥ 0.3 (non-ITT)	77/126	61%	60/79	76%	**0.80 (0.67 to 0.97)**	**-0.15 (-0.28 to -0.02)**
DAS28 ≤ 3.2 (ITT) 3 months	11/130	8%	11/84	13%	0.65 (0.29 to 1.42)	-0.05 (-0.13 to 0.04)
DAS28 ≤ 3.2 (ITT) 6 months	21/130	16%	17/84	20%	0.80 (0.45 to 1.42)	-0.04 (-0.15 to 0.07)
DAS28 <2.6 (ITT) 3 months	8/130	6%	3/84	4%	1.72 (0.47 to 6.31)	0.03 (-0.03 to 0.08)
DAS28 <2.6 (ITT) 6 months	11/130	8%	12/84	14%	0.59 (0.27 to 1.28)	-0.06 (-0.15 to 0.03)

Bold type indicates statistically significant differences between subgroups.
*Relative risk > 1 and risk difference >0 favour switch due to loss of response for outcomes related to treatment withdrawal. Relative risk < 1 and risk difference <0 favours switch due to loss of response for EULAR and DAS28-based responses.
[a] Data were reported in the manufacturer submission to NICE and were not from the published paper.

Summary – switching due to lack of response versus due to loss of response

- No conclusion can be made with regard to whether the effectiveness of the five technologies varies according to lack of response or loss of response to the prior TNF inhibitor due to lack of RCT evidence.
- Evidence from two uncontrolled studies[94,95] of switching to adalimumab showed significant differences in favour of patients who switched due to loss of response for ACR20 and ACR50.
- Evidence from two uncontrolled studies [99,102] of switching to etanercept indicated there was no significant difference in treatment withdrawal and response between the subgroups.
- Evidence from a Dutch study (DREAM) of switching to an unspecified alternative TNF inhibitor did not find a significant difference between the subgroups.

- Evidence from the ATTAIN LTE of switching to abatacept did not find a significant difference between the subgroups except in a non-ITT analysis in which more patients who switched due to loss of response achieved HAQ improvement ≥ 0.3 at 6 months..
- No evidence from observational studies was identified for switching to infliximab and rituximab.
- Discussion: there is lack of RCT evidence. It has been speculated that patients who withdrew from a TNF inhibitor due to lack of response may not respond as well to another TNF inhibitor as those who withdrew due to loss of response. This was observed in studies of switching to adalimumab, but not in studies of switching to etanercept or an unspecified alternative TNF inhibitor. Of note, a similar trend (higher response rates for patients who withdrew due to loss of response) was seen in the ATTAIN LTE for switching to abatacept, which is not a TNF inhibitor. These observational studies were insufficiently powered to identify clinically important differences and thus the findings require further confirmation.

5.7.1.2. Switching due to lack of efficacy (lack or loss of response) vs switching due to intolerance (adverse events)

(1) RCTs

RCT evidence was available only for rituximab. Data were provided in the manufacturer submission as commercial in confidence information.

Rituximab

[redacted]

[redacted]

[redacted]

(2) Non-RCTs

Subgroup data were available for switching to adalimumab, etanercept and an alternative, unspecified TNF inhibitor.

Adalimumab

Subgroup data were reported in two uncontrolled studies and were summarised in Table 55.[94,95] The results, mainly driven by the ReAct study,[94] showed significant differences for EULAR response and change in DAS28 in favour of patients who switched due to intolerance/adverse events.

Table 55 Switching to adalimumab due to lack of efficacy vs due to intolerance/adverse event in observational studies – binary outcomes

Study	Switched due to lack of efficacy		Switched due to intolerance/AE		Relative risk* (95% CI)	Risk difference (95% CI)
	n/N	%	n/N	%		
Withdrawal for any reasons at 3 months						
Bombardieri 2007 (ReAct)[94]	38/479	8%	18/179	10%	0.79 (0.46 to 1.35)	-0.02 (-0.07, 0.03)
Withdrawal due to lack of efficacy at 3 months						
Bombardieri	10/479	2%	3/179	2%	1.25 (0.35 to 4.47)	0.00 (-0.02 to 0.03)

2007[94]						
Withdrawal due to intolerance/AE at 3 months						
Bombardieri 2007[94]	21/479	4%	12/179	7%	0.65 (0.33 to 1.30)	-0.02 (-0.06 to 0.02)
ACR20 at 3 months						
Bombardieri 2007[94]	296/479	62%	120/179	67%	0.92 (0.81 to 1.04)	-0.05 (-0.13 to 0.03)
van der Bijl 2008[95]	17/36	47%	2/5	40%	1.18 (0.38 to 3.65)	0.07 (-0.39 to 0.53)
Pooled estimates (random effects)					0.92 (0.82 to 1.05) I^2=0%	-0.05 (-0.13 to 0.03) I^2=0%
ACR50 at 3 months						
Bombardieri 2007[94]	155/479	32%	68/179	38%	0.85 (0.68 to 1.07)	-0.06 (-0.14 to 0.03)
van der Bijl 2008[95]	10/36	28%	1/5	20%	1.39 (0.22 to 8.66)	0.08 (-0.30 to 0.46)
Pooled estimates (random effects)					0.86 (0.68 to 1.08) I^2=0%	-0.05 (-0.13 to 0.03) I^2=0%
ACR70 at 3 months						
Bombardieri 2007[94]	56/479	12%	30/179	17%	0.70 (0.46 to 1.05)	-0.05 (-0.11 to 0.01)
van der Bijl 2008[95]	5/36	14%	0/5	0%	1.78 (0.11 to 28.28)	0.14 (-0.11 to 0.39)
Pooled estimates (random effects)					0.71 (0.47 to 1.07) I^2=0%	0.00 (-0.17 to 0.17) I^2=53%
EULAR good/moderate response						
Bombardieri 2007[94]	370/479	77%	151/179	84%	**0.92 (0.85 to 0.99)**	**-0.07 (-0.14 to -0.01)**
van der Bijl 2008[95]	21/36	58%	4/5	80%	0.73 (0.43 to 1.22)	-0.22 (-0.60 to 0.17)
Pooled estimates (random effects)					**0.91 (0.84 to 0.99)** I^2=0%	**-0.08 (-0.14 to -0.01)** I^2=0%
EULAR good response						
Bombardieri 2007[94]	101/479	21%	51/179	28%	**0.74 (0.55 to 0.99)**	-0.07 (-0.15 to 0.00)
van der Bijl	6/36	17%	1/5	20%	0.83 (0.12 to 5.57)	-0.03 (-0.40 to 0.34)

2008[95]						
Pooled estimates (random effects)					**0.74 (0.56 to 0.99)** I^2=0%	-0.07 (-0.15 to 0.00) I^2=0%

Bold type indicates statistically significant differences between subgroups.
*Relative risk > 1 and risk difference >0 favour switch due to intolerance/AE for outcomes related to treatment withdrawal and adverse events. Relative risk < 1 and risk difference <0 favours switch due to intolerance/AE for ACR and EULAR responses.

Table 56 Switching to adalimumab due to lack of efficacy vs due to intolerance/adverse event in observational studies – continuous outcomes

Study	**Switch due to lack of efficacy**			**Switch due to intolerance/AE**			**Mean difference* (95% CI)**
	N	Mean	SD	N	Mean	SD	
DAS28 change from baseline at 3 months							
Bombardieri 2007[94]	479	-1.97	1.40	179	-2.22	1.28	**0.25 (0.02 to 0.48)**
van der Bijl 2008[95]	36	-1.47	1.64	5	-1.40	0.60	-0.07 (-0.82 to 0.68)
Pooled estimate (random effects)							**0.22 (0.01 to 0.44)** I^2=0%
HAQ change from baseline at 3 months							
Bombardieri 2007[94]	479	-0.49	0.59	179	-0.55	0.64	0.06 (-0.05 to 0.17)
van der Bijl 2008[95]	36	-0.26	0.50	5	-0.15	0.34	-0.11 (-0.45 to 0.23)
Pooled estimate (random effects)							0.04 (-0.06 to 0.15) I^2=0%

Bold type indicates statistically significant differences between subgroups.
*Mean difference >0 favour switching due to intolerance/AE for changes in DAS28 and HAQ.

Etanercept

Subgroup data were available from one uncontrolled study.[101] The results were presented in Table 57. No significance difference between subgroups was found.

Table 57 Switching to etanercept due to lack of efficacy vs due to intolerance/adverse event in observational study – continuous outcome

Study	**Switch due to lack of efficacy**			**Switch due to intolerance/AE**			**Mean difference* (95% CI)**
	N	Mean	SD	N	Mean	SD	
DAS28 change from baseline (time not specified; between 3 months to 9 months/last observed value on treatment)							
Laas 2008 [101]	20	-1.19	2.09	6	-1.30	1.25	0.11 (-1.25 to 1.47)

TNF inhibitors as a class

Subgroup data were available from three observational studies.[108,110,111] The results are shown in Table 58 and Table 59. Patients who withdrew from the previous TNF inhibitors due to intolerance/adverse events were more likely to withdraw due to intolerance/adverse events again compared to those who withdrew from the previous TNF inhibitors due to lack of efficacy. On the other hand, patients who withdrew from the previous TNF inhibitors due to intolerance/adverse events were more likely to achieve various ACR, EULAR and other DAS28 based response criteria.

Table 58 Switching to an alternative TNF inhibitor due to lack of efficacy vs due to intolerance/adverse event in observational studies – binary outcomes

Study	Switched due to lack of efficacy		Switched due to intolerance/AE		Relative risk* (95% CI)	Risk difference (95% CI)
	n/N	%	n/N	%		
Withdrawal for any reasons at 3 and 6 months (ITT)						
Blom 2009[111] – 3 months	7/124	6%	8/73	11%	0.52 (0.19 to 1.36)	-0.05 (-0.14 to 0.03)
Blom 2009[111] – 6 months	22/124	18%	17/73	23%	0.76 (0.43 to 1.34)	-0.06 (-0.17 to 0.06)
Withdrawal due to lack of efficacy at 3 and 6 months (ITT)						
Blom 2009[111] – 3 months	2/124	2%	1/73	1%	1.18 (0.11 to 12.76)	0.00 (-0.03 to 0.04)
Blom 2009[111] – 6 months	14/124	11%	4/73	5%	2.06 (0.70 to 6.02)	0.06 (-0.02 to 0.13)
Withdrawal due to intolerance/AE at 3 and 6 months (ITT)						
Blom 2009[111] – 3 months	5/124	4%	7/73	10%	0.42 (0.14 to 1.28)	-0.06 (-0.13 to 0.02)
Blom 2009[111] – 6 months	8/124	6%	12/73	16%	**0.39 (0.17 to 0.92)**	-0.10 (-0.20 to 0.00)
ACR20 at 3 months (ITT)						
Karlsson 2008[110]	61/137	45%	78/138	57%	0.79 (0.62 to 1.00)	-0.12 (-0.24 to 0.00)
ACR50 at 3 months (ITT)						
Karlsson 2008[110]	28/137	20%	44/138	32%	**0.64 (0.43 to 0.97)**	**-0.11 (-0.22 to -0.01)**
ACR70 at 3 months (ITT)						
Karlsson 2008[110]	8/137	6%	10/138	7%	0.81 (0.33 to 1.98)	-0.01 (-0.07 to 0.04)
EULAR good/moderate response at 3 months (ITT)						

Hjardem 2007[108]	38/109	35%	19/72	26%	1.32 (0.83 to 2.10)	0.08 (-0.05 to 0.22)
Karlsson 2008[110]	80/137	58%	100/138	72%	**0.81 (0.68 to 0.96)**	**-0.14 (-0.25 to -0.03)**
Blom 2009[111]	41/124	33%	21/73	29%	1.15 (0.74 to 1.78)	0.04 (-0.09 to 0.18)
Pooled estimate (random effects)					1.02 (0.72 to 1.45) I^2=67%	-0.01 (-0.15 to 0.13) I^2=74%
EULAR good/moderate response at 6 months (ITT)						
Blom 2009[111]	43/124	35%	21/73	29%	1.21 (0.78 to 1.86)	0.06 (-0.07 to 0.19)
EULAR good response at 3 months (ITT)						
Hjardem 2007[108]	14/109	13%	5/72	7%	1.85 (0.70 to 4.91)	0.06 (-0.03 to 0.14)
Karlsson 2008[110]	24/137	18%	42/138	30%	**0.58 (0.37 to 0.90)**	**-0.13 (-0.23 to -0.03)**
Blom 2009[111]	10/124	8%	7/73	10%	0.84 (0.33 to 2.11)	-0.02 (-0.10 to 0.07)
Pooled estimate (random effects)					0.87 (0.44 to 1.70) I^2=58%	-0.03 (-0.13 to 0.08) I^2=77%
EULAR good response at 6 months (ITT)						
Blom 2009[111]	11/124	9%	7/73	10%	0.93 (0.38 to 2.28)	-0.01 (-0.09 to 0.08)
DAS28 ≤ 3.2 at 3 months (ITT)						
Karlsson 2008[110]	33/137	24%	51/138	37%	**0.65 (0.45 to 0.94)**	**-0.13 (-0.24 to -0.02)**
Blom 2009[111]	15/124	12%	13/73	18%	0.68 (0.34 to 1.35)	-0.06 (-0.16 to 0.05)
Pooled estimate (random effects)					**0.66 (0.48 to 0.91)** I^2=0%	**-0.09 (-0.17 to -0.02)** I^2=0%
DAS28 ≤ 3.2 at 6 months (ITT)						
Blom 2009[111]	16/124	13%	11/73	15%	0.86 (0.42 to 1.74)	-0.02 (-0.12 to 0.08)
DAS28 <2.6 at 3 months (ITT)						
Karlsson 2008[110]	16/137	12%	25/138	18%	0.64 (0.36 to 1.15)	-0.06 (-0.15 to 0.02)

Table 59 Switching to an alternative TNF inhibitor due to lack of efficacy vs due to intolerance/adverse event in observational study – continuous outcome

Study: Blom 2009[111]	**Switch due to lack of efficacy**			**Switch due to intolerance/AE**			**Mean difference* (95% CI)**
	N	Mean	SD	N	Mean	SD	
DAS28 change from baseline at 3 and 6 months							
3 months	82	-0.97	1.15	46	-0.80	1.40	-0.17 (-0.65 to 0.31)
6 months	74	-0.91	1.30	40	-1.00	1.40	0.09 (-0.44 to 0.62)

Summary

- Evidence [redacted] No subgroup data from RCT was identified for the other technologies.
- Evidence from observational studies was available for switching to adalimumab, etanercept and an alternative, unspecified TNF inhibitor. Evidence was not available for switching to infliximab and abatacept.
- Evidence from two observational studies of switching to adalimumab showed significant differences for EULAR response and change in DAS28 in favour of patients who switched due to intolerance/adverse events.
- No significance difference between subgroups was found in a small uncontrolled study of switching to etanercept.
- Evidence from three observational studies[108,110,111] of switching to an unspecified, alternative TNF inhibitor suggested that patients who withdrew from the previously TNF inhibitor due to intolerance/adverse event were more likely to withdraw due to intolerance/adverse events and more likely to achieve ACR, EULAR and DAS28 related response criteria compared to patients who withdrew from the previously TNF inhibitor due to lack of efficacy.
- Discussion: it is suggested that the effectiveness of a TNF inhibitor may differ between patients who withdraw from the previous TNF inhibitor due to lack of efficacy and those who withdraw due to adverse events, but the effectiveness of other technologies with different mechanism of action may not. There is a lack of RCT evidence to confirm the former. RCT evidence suggests that [redacted] RCT evidence for abatacept is also lacking. Data from observational studies appear to agree with what is expected in terms of treatment withdrawal and treatment response.

5.7.2 Auto-antibody status

(1) RCT

RCT data for subgroups stratified by auto-antibody status were available only from the REFLEX trial of rituximab.

Rituximab

Subgroup data stratified by rheumatoid factor (RF) status from the REFLEX trial were reported in the manufacturer submission. Randomisation in this trial was stratified by RF status (RF+, defined as a value of RF ≥ 20 IU/ml at screening; or RF-, defined as RF < 20 IU/m at screening) and region (US or non-US). The results for ACR20 at 6 months are shown in Figure 87 (RR) and Figure 88 (RD) and for all the ACR response criteria are shown in Table 60. Although the proportion of patients achieving ACR criteria were generally lower in RF- patients than in RF+ patients, there was no significant difference in treatment effect between the subgroups.

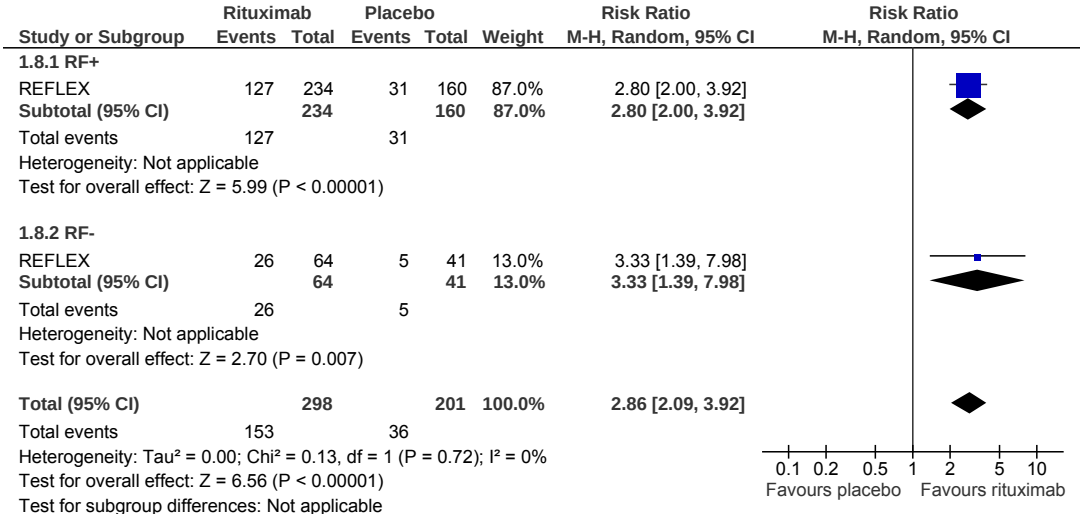


Figure 87 Subgroup analysis (switching to rituximab) for RF+ patients vs RF- patients: ACR20 at 6 months (relative risk)

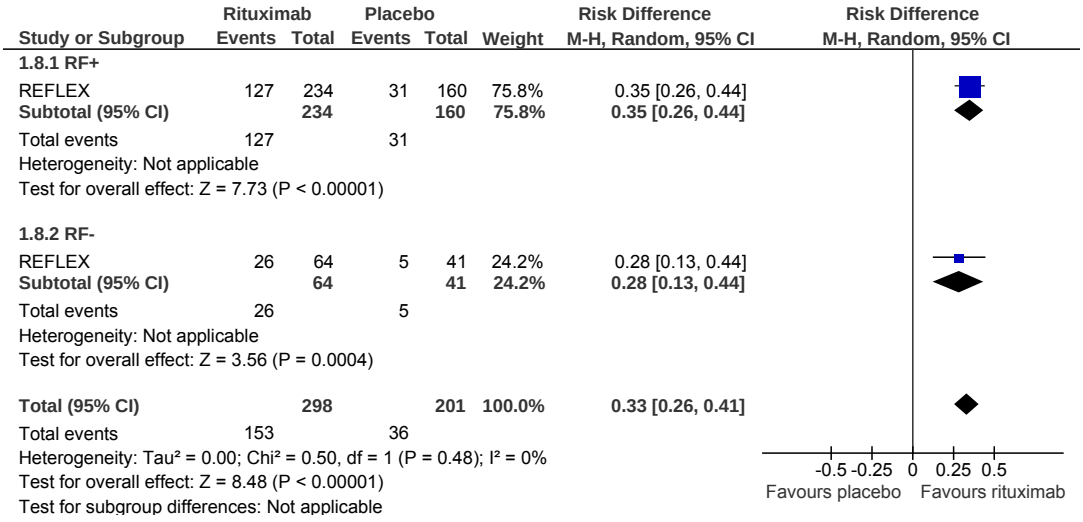


Figure 88 Subgroup analysis (switching to rituximab)by RF status: ACR20 at 6 months (risk difference)

Table 60 Subgroup analyses (switching to rituximab) for by RF status in REFLEX trial: ACR20, 50 and 70 at 6 months

Study: REFLEX	**Rituximab**		**Placebo**		**Relative risk* (95% CI)**	**Risk difference (95% CI)**
	n/N	**%**	**n/N**	**%**		
ACR20 at 6 months						
RF+	127/234	54%	31/160	19%	**2.80 (2.00 to 3.92)**	**0.35 (0.26 to 0.44)**
RF-	26/64	41%	5/41	12%	**3.33 (1.39 to 7.98)**	**0.28 (0.13 to 0.44)**
Test for interaction					p=0.72	p=0.48
ACR50 at 6 months						
RF+	69/234	29%	9/160	6%	**5.24 (2.70 to 10.19)**	**0.24 (0.17 to 0.31)**
RF-	11/64	17%	2/41	5%	3.52 (0.82 to 15.09)	**0.12 (0.01 to 0.24)**
Test for interaction					p=0.63	p=0.08
ACR70 at 6 months						
RF+	31/234	13%	3/160	2%	**7.07 (2.20 to 22.72)**	**0.11 (0.07 to 0.16)**
RF-	6/64	9%	0/41	0%	8.40 (0.49 to 145.24)	**0.09 (0.01 to 0.17)**
Test for interaction					p=0.91	p=0.67

Bold type indicates statistically significant difference between rituximab and placebo within subgroup.

Further subgroup data stratified by baseline RF and anti-cyclic citrullinated peptide (anti-CCP) status from the REFLEX trial were also reported in the manufacturer submission and were summarised in Table 61. Although test for interaction was significant for risk difference in ACR50, suggesting a greater treatment effect in patients with either RF or anti-CCP positive compared to those with both RF and anti-CCP negative, the number of patients in the latter subgroup was too small to allow firm conclusion to be drawn. This subgroup analysis was performed *post hoc* and needs to be interpreted with caution.

Table 61 Subgroup analyses (switching to rituximab) by baseline RF and anti-CCP status in REFLEX trial: ACR20, 50 and 70 at 6 months

Study: REFLEX	**Rituximab**		**Placebo**		**Relative risk* (95% CI)**	**Risk difference (95% CI)**
	n/N	**%**	**n/N**	**%**		
ACR20 at 6 months						
RF and/or anti-CCP positive	79/157	50%	19/107	18%	**2.83 (1.83 to 4.38)**	**0.33 (0.22 to 0.43)**
RF/anti-CCP negative	8/29	28%	1/16	6%	4.41 (0.61 to 32.20)	**0.21 (0.01 to 0.41)**
Test for interaction					p=0.67	p=0.33
ACR50 at 6 months						
RF and/or anti-CCP positive	46/157	29%	8/107	7%	**3.92 (1.93 to 7.97)**	**0.22 (0.13 to 0.31)**
RF/anti-CCP negative	2/29	7%	1/16	6%	1.10 (0.11 to 11.25)	0.01 (-0.14 to 0.16)
Test for interaction					p=0.31	**p=0.01**
ACR70 at 6 months						
RF and/or anti-CCP positive	20/157	13%	2/107	2%	**6.82 (1.63 to 28.55)**	**0.11 (0.05 to 0.17)**
RF/anti-CCP negative	1/29	3%	0/16	0%	1.70 (0.07 to 39.47)	0.03 (-0.08 to 0.15)
Test for interaction					p=0.43	p=0.24

Bold type indicates statistically significant difference between rituximab and placebo within subgroup or (for test for interaction) significant difference in treatment effect between subgroups.

(2) Non-RCTs

No subgroup data from observational studies was identified.

Summary

- Evidence from REFLEX trial suggested that the effectiveness of rituximab does not vary significantly according to the presence or absence of RF. There is lack of evidence for other technologies.
- Discussion: in the REFLEX trial, the proportion of patients achieving ACR criteria were generally lower in RF- patients than in RF+ patients irrespective of treatment group. The treatment effects in terms of risk differences between rituximab and placebo group were generally larger in RF+ patients than in RF- patients, but this does not hold true when relative risk is used as the measure of effect. Differences between subgroups were not statistically significant according to test for interaction, but the test may be under-powered due to the sample size. Post hoc analysis according to RF and anti-CCP status needs to be interpreted with caution.

5.7.3 Number of TNF inhibitors previously tried

(1) RCTs

RCT data stratified by the number of TNF inhibitors the patients had tried before switching were available from the REFLEX trial of rituximab and the ATTAIN trial of abatacept.

Rituximab

Subgroup data from the REFLEX trial stratified by the number of prior TNF inhibitors (one prior TNF inhibitor vs two or more prior TNF inhibitors) were reported in the manufacturer submission and were presented in Table 62. The results show that rituximab were more effective than placebo in both subgroups and there is no significant difference in treatment effects between the subgroups.

Table 62 Subgroup analyses (switching to rituximab) by number of prior TNF inhibitor in REFLEX trial: ACR20, 50 and 70 at 6 months

Study: REFLEX	**Rituximab**		**Placebo**		**Relative risk* (95% CI)**	**Risk difference (95% CI)**
	n/N	**%**	**n/N**	**%**		
ACR20 at 6 months						
1 prior TNF	104/179	58%	25/121	21%	**2.81 (1.94 to 4.07)**	**0.37 (0.27 to 0.48)**

inhibitor						
≥ 2 prior TNF inhibitor	50/119	42%	11/80	14%	**3.06 (1.70 to 5.50)**	**0.28 (0.17 to 0.40)**
Test for interaction					p=0.81	p=0.24
ACR50 at 6 months						
1 prior TNF inhibitor	54/179	30%	8/121	7%	**4.56 (2.25 to 9.24)**	**0.24 (0.16 to 0.32)**
≥ 2 prior TNF inhibitor	26/119	22%	2/80	3%	**8.74 (2.13 to 35.80)**	**0.19 (0.11 to 0.28)**
Test for interaction					p=0.41	p=0.46
ACR70 at 6 months						
1 prior TNF inhibitor	25/179	14%	1/121	1%	**16.90 (2.32 to 123.06)**	**0.13 (0.08 to 0.18)**
≥ 2 prior TNF inhibitor	12/119	10%	2/80	3%	4.03 (0.93 to 17.54)	**0.08 (0.01 to 0.14)**
Test for interaction					p=0.23	p=0.19

Bold type indicates statistically significant difference between rituximab and placebo within subgroup or (for test for interaction) significant difference in treatment effect between subgroups.

Abatacept

Subgroup data from the ATTAIN trial stratified by prior TNF inhibitors (etanercept, infliximab, or both) were reported in the manufacturer submission. For this subgroup analysis, data from patients who had received either etanercept or infliximab were combined and then were compared to data from patients who had received both etanercept and infliximab before switching to abatacept. The trial was conducted before adalimumab became widely available and thus few patients had tried more than two TNF inhibitors.

The results are shown in Table 63. Irrespective of the number of prior TNF inhibitor(s), a higher proportion of patients in abatacept group than in the placebo group achieved ACR20 and a HAQ improvement ≥ 0.3. The difference was larger and statistically significant in the subgroup of patients who had one prior TNF inhibitor, and was smaller and not statistically significant in the subgroup of patients who had two prior TNF inhibitors. Results of tests for interaction do not suggest differential treatment effects between the subgroups, although the tests may be under-powered as the number of patients in the subgroup of two prior TNF inhibitors is relatively small.

Table 63 Subgroup analyses (switching to abatacept) by number of prior TNF inhibitor in ATTAIN trial: ACR20 and HAQ improvement ≥ 0.3 at 6 months

Study: ATTAIN	**Abatacept**		**Placebo**		**Relative risk* (95% CI)**	**Risk difference (95% CI)**
	n/N	**%**	**n/N**	**%**		
ACR20 at 6 months						
1 prior TNF inhibitor	108/201	54%	22/111	20%	**2.71 (1.83 to 4.03)**	**0.34 (0.24 to 0.44)**
2 prior TNF inhibitor	21/55	38%	4/22	18%	2.10 (0.81 to 5.42)	0.20 (-0.01 to 0.41)
Test for interaction					p=0.63	p=0.23
HAQ improvement from baseline ≥ 0.3 at 6 months						
1 prior TNF inhibitor	102/201	51%	26/111	23%	**2.17 (1.51 to 3.11)**	**0.27 (0.17 to 0.38)**
2 prior TNF inhibitor	19/55	35%	5/22	23%	1.52 (0.65 to 3.56)	0.12 (-0.10 to 0.33)
Test for interaction					p=0.45	p=0.20

Bold type indicates statistically significant difference between abatacept and placebo within subgroup or (for test for interaction) significant difference in treatment effect between subgroups.

(2) Non-RCTs

Subgroup data stratified by the number of prior TNF inhibitors (or prior biologics) were available for switching to an unspecified TNF inhibitor and to abatacept.

TNF inhibitors as a class

Subgroup data (one prior TNF inhibitor vs two prior TNF inhibitors) was reported in Karlsson 2008 [110] and the results are presented in Table 64. A higher proportion of patients who previously tried one TNF inhibitor achieved various ACR and RULAR response criteria compared to those who previously tried two TNF inhibitors, although the differences were not statistically significance except for the difference in achieving EULAR good response (25% vs 8%).

Table 64 Switching to an alternative TNF inhibitor by number of TNF inhibitors previously tried (observational studies) – binary outcomes

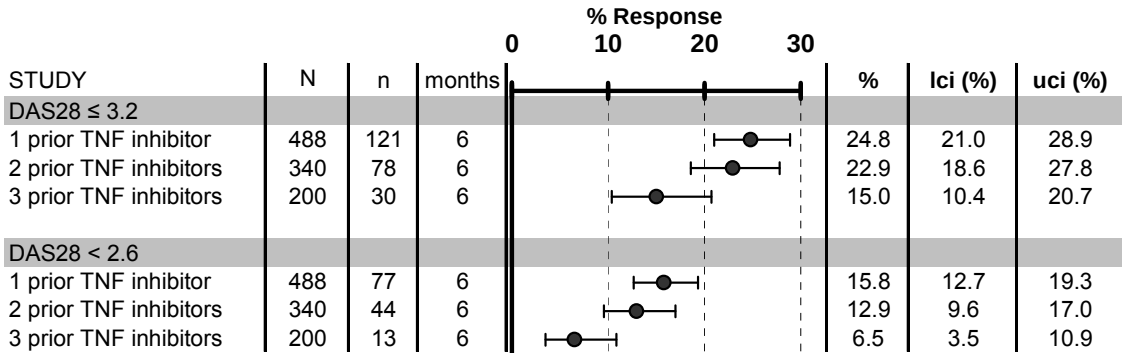
Study	1 prior TNF inhibitor		2 prior TNF inhibitors		Relative risk* (95% CI)	Risk difference* (95% CI)
	n/N	%	n/N	%		
ACR20 at 3 months						
Karlsson 2008 [110]	172/337	51%	13/36	36%	1.41 (0.90 to 2.21)	0.15 (-0.02 to 0.32)
ACR50 at 3 months						
Karlsson 2008 [110]	91/337	27%	7/36	19%	1.39 (0.70 to 2.76)	0.08 (-0.06 to 0.21)
ACR70 at 3 months						
Karlsson 2008 [110]	24/337	7%	1/36	3%	2.56 (0.36 to 18.40)	0.04 (-0.02 to 0.10)
EULAR moderate/good response at 3 months						
Karlsson 2008 [110]	240/337	71%	21/36	58%	1.22 (0.92 to 1.62)	0.13 (-0.04 to 0.30)
EULAR good response at 3 months						
Karlsson 2008 [110]	84/337	25%	3/36	8%	2.99 (1.00 to 8.98)	**0.17 (0.06 to 0.27)**

*Relative risk > 1 and risk difference >0 favours patients who had one prior TNF inhibitor for ACR and EULAR responses.

In addition to the above, Duftner et al.[109] reported 12-month discontinuation rate of 53.5%, 66.7% (n=27) and 28.6% for the first, second and third biologics (adalimumab, etanercept, infliximab and anakinra) in Austrian RA patients. This study included a mixed patient population of RA (63%, 109/173) and other rheumatic disease (37%). The exact number of patients from which the above RA specific discontinuation rates were derived was not clearly stated.

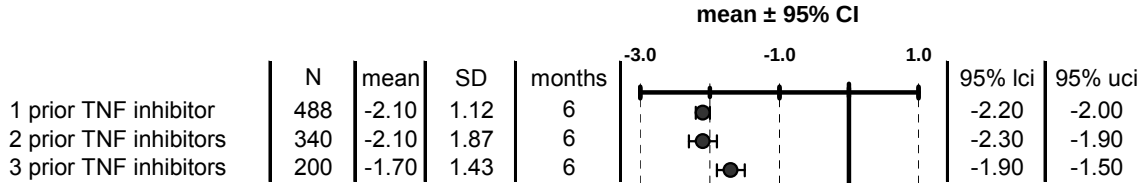
Abatacept

Subgroup data stratified by the number of prior TNF inhibitors (one, two or three) were reported by Schiff and colleagues (ARRIVE study).[118] The results were presented in Figure 89 and Figure 90. The results indicate that the proportion of patients achieving DAS28 related response criteria decreases as the number of prior TNF inhibitor(s) that the patients had tried increases (χ^2 test for linear trend, p=0.009 for DAS28 ≤ 3.2 and p=0.005 for DAS28 < 2.6). The change in DAS28 from baseline at 6 months was the same for patients who had previously tried one or two TNF inhibitors but was significantly lower for patients who had previously tried three TNF inhibitors (-2.1 vs -1.7, test for interaction, p=0.001).



STUDY	N	n	months	%	lci (%)	uci (%)
DAS28 ≤ 3.2						
1 prior TNF inhibitor	488	121	6	24.8	21.0	28.9
2 prior TNF inhibitors	340	78	6	22.9	18.6	27.8
3 prior TNF inhibitors	200	30	6	15.0	10.4	20.7
DAS28 < 2.6						
1 prior TNF inhibitor	488	77	6	15.8	12.7	19.3
2 prior TNF inhibitors	340	44	6	12.9	9.6	17.0
3 prior TNF inhibitors	200	13	6	6.5	3.5	10.9

Figure 89 Switching to abatacept – DAS28 responses at 6 months stratified by the number of prior TNF inhibitor in ARRIVE study



	N	mean	SD	months	95% lci	95% uci
1 prior TNF inhibitor	488	-2.10	1.12	6	-2.20	-2.00
2 prior TNF inhibitors	340	-2.10	1.87	6	-2.30	-1.90
3 prior TNF inhibitors	200	-1.70	1.43	6	-1.90	-1.50

Figure 90 Switching to abatacept – DAS28 change from baseline at 6 months stratified by the number of prior TNF inhibitor in ARRIVE study

Summary

- Evidence from REFLEX trial showed that the effectiveness of rituximab was similar between the subgroup of patients who had tried one TNF inhibitor and those who had tried more than one TNF inhibitor.
- Evidence from ATTAIN trial showed that effectiveness of abatacept was similar between the subgroup of patients who had tried one TNF inhibitor and those who had tried more than one TNF inhibitor, although within the latter subgroup the difference between abatacept and placebo did not reach statistical significance.
- No evidence from RCT and observational studies was available for the individual TNF
- In an observational study [110]of switching to an unspecified, alternative TNF inhibitor inhibitors, higher response rates to ACR and EULAR response criteria in patients who tried one TNF inhibitor compared to those who tried two TNF inhibitors were reported.
- One observational study (ARRIVE)[118] of switching to abatacept showed that the proportion of patients achieving DAS28 related response criteria decreases as the number of prior TNF inhibitor(s) that the patients had tried increases.

- Discussion: many of the studies included in this review covered patients who had previously tried more than one TNF inhibitor. Determining whether the effectiveness of the technologies varies depending on the number of TNF inhibitors previously tried is useful to inform the applicability of findings from these studies to the main population of interest for this appraisal, i.e. patients who had previously had inadequate response to one TNF inhibitor. Results from REFLEX and ATTAIN trials suggested that the effectiveness of rituximab and abatacept does not differ significantly between patients who tried one TNF inhibitor compared to those who tried more than one. The subgroup analyses however were limited by the relatively small number of patients and thus the possibility of differential treatment effect particularly in terms of risk difference cannot be completely ruled out. Findings from observational studies for switching to an alternative TNF inhibitor and to abatacept agree with an inverse relationship between treatment response and number of prior TNF inhibitors. To what extent the effectiveness of the technologies (in particular the TNF inhibitors) varies by prior number of TNF inhibitor remain unclear due to the small volume or complete lack of evidence from RCTs.

5.7.4 Prior TNF inhibitor

(1) RCTs

RCT data stratified by the TNF inhibitor from which the patients had switched were available only from the ATTAIN trial of abatacept.

Abatacept

Subgroup data stratified by prior TNF inhibitor (etanercept vs infliximab) from the ATTAIN trial were reported in the manufacturer submission and were presented in Table 65. Results of the subgroup analyses show that abatacept is more effective than placebo in both patients who had previously had inadequate response to etanercept and those who had previously had inadequate response to infliximab. Tests for interaction do not suggest differential treatment effects between subgroups although the tests may be under-powered.

Table 65 Subgroup analyses (switching to abatacept) by prior TNF inhibitor (etanercept or infliximab) in ATTAIN trial: ACR20 and HAQ improvement ≥ 0.3 at 6 months

Study: ATTAIN	**Abatacept**		**Placebo**		**Relative risk* (95% CI)**	**Risk difference (95% CI)**
	n/N	**%**	**n/N**	**%**		
ACR20 at 6 months						
Prior ETN	28/61	46%	8/43	19%	**2.47 (1.25 to 4.88)**	**0.27 (0.10 to 0.44)**
Prior IFX	80/140	57%	14/68	21%	**2.78 (1.70 to 4.52)**	**0.37 (0.24 to 0.49)**
Test for interaction					p=0.78	p=0.39
HAQ improvement from baseline ≥ 0.3 at 6 months						
Prior ETN	25/61	41%	11/43	26%	1.60 (0.89 to 2.90)	0.15 (-0.03 to 0.33)
Prior IFX	77/140	55%	15/68	22%	**2.49 (1.56 to 3.99)**	**0.33 (0.20 to 0.46)**
Test for interaction					p=0.25	p=0.12

Bold type indicates statistically significant difference between abatacept and placebo within subgroup or (for test for interaction) significant difference in treatment effect between subgroups.

(2) Non-RCTs

Adalimumab

Subgroup data stratified by patients who switched from either etanercept or infliximab to adalimumab was available from one study (ReAct).[94] and the results were shown in Table 66. No significant difference between the subgroups was found.

Table 66 Switching to adalimumab by prior TNF inhibitor in observational studies – binary outcomes

Study	**Switched from ETN**		**Switched from IFX**		**Relative risk* (95% CI)**	**Risk difference (95% CI)**
	n/N	**%**	**n/N**	**%**		
Withdrawal for any reasons at 3 months						
Bombardieri 2007[94]	20/188	11%	50/591	8%	1.26 (0.77 to 2.06)	0.02 (-0.03 to 0.07)
Withdrawal due to lack of efficacy at 3 months						
Bombardieri 2007[94]	5/188	3%	12/591	2%	1.31 (0.47 to 3.67)	0.01 (-0.02 to 0.03)
Withdrawal due to intolerance/AE at 3 months						
Bombardieri 2007[94]	10/188	5%	33/591	6%	0.95 (0.48 to 1.90)	0.00 (-0.04 to 0.03)

ACR20 at 3 months						
Bombardieri 2007[94]	107/188	57%	378/591	64%	0.89 (0.77 to 1.02)	-0.07 (-0.15 to 0.01)
ACR50 at 3 months						
Bombardieri 2007[94]	64/188	34%	201/591	34%	1.00 (0.80 to 1.26)	0.00 (-0.08 to 0.08)
ACR70 at 3 months						
Bombardieri 2007[94]	24/188	13%	77/591	13%	0.98 (0.64 to 1.50)	0.00 (-0.06 to 0.05)
EULAR moderate/good response						
Bombardieri 2007[94]	149/188	79%	460/591	78%	1.02 (0.94 to 1.11)	0.01 (-0.05 to 0.08)
EULAR good response						
Bombardieri 2007[94]	40/188	21%	154/591	26%	0.82 (0.60 to 1.11)	-0.05 (-0.12 to 0.02)

*Relative risk > 1 and risk difference >0 favour switching from infliximab for outcomes related to treatment withdrawal. Relative risk < 1 and risk difference <0 favours switching from infliximab for ACR and EULAR responses.

Table 67 Switching to adalimumab by prior TNF inhibitor in observational studies – continuous outcomes

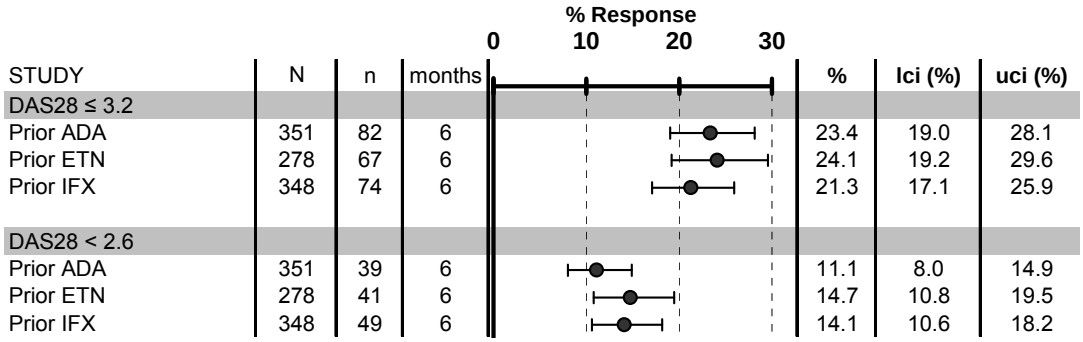
Study	**Switched from ETN**			**Switched from IFX**			**Mean difference* (95%CI)**
	N	Mean	SD	N	Mean	SD	
DAS28 change from baseline at 3 months							
Bombardieri 2007[94]	188	-2.0	1.4	591	-2.0	1.4	0.00 (-0.23 to 0.23)
HAQ change from baseline at 3 months							
Bombardieri 2007[94]	188	-0.43	0.61	591	-0.51	0.60	0.08 (-0.02 to 0.18)

*Mean difference >0 favour switching due to loss of response for DAS28 and HAQ.

In addition to the above, Gomez-Reino and colleagues reported 12-month retention on treatment of 0.75 (95%CI 0.31 to 0.93) for patients who switched from etanercept to adalimumab (n=33) and 0.69 (95%CI 0.43 to 0.85) for patients who switched from infliximab to adalimumab (n=14).[106] No statistical comparison was made.

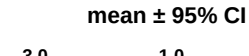
Abatacept

Subgroup data stratified by the TNF inhibitor from which the patients switched were reported by Schiff and colleagues (ARRIVE study).[118] The results were presented in Figure 91 and Figure 92. At 6 months, there was no significant difference in the proportion of patients who achieved DAS28 ≤ 3.2 (χ^2 test, p=0.67) and DAS28 <2.6 (χ^2 test, p=0.34). The mean changes from baseline in DAS28 were also similar between the groups (test for interaction, p=0.21).



STUDY	N	n	months	%	lci (%)	uci (%)
DAS28 ≤ 3.2						
Prior ADA	351	82	6	23.4	19.0	28.1
Prior ETN	278	67	6	24.1	19.2	29.6
Prior IFX	348	74	6	21.3	17.1	25.9
DAS28 < 2.6						
Prior ADA	351	39	6	11.1	8.0	14.9
Prior ETN	278	41	6	14.7	10.8	19.5
Prior IFX	348	49	6	14.1	10.6	18.2

Figure 91 Switching to abatacept – DAS28 responses at 6 months stratified by prior TNF inhibitor in ARRIVE study



	N	mean	SD	months	95% lci	95% uci
Prior ADA	351	-1.90	1.43	6	-2.05	-1.75
Prior ETN	278	-2.00	1.69	6	-2.20	-1.80
Prior IFX	348	-2.10	1.42	6	-2.25	-1.95

Figure 92 Switching to abatacept – DAS28 change from baseline at 6 months stratified by prior TNF inhibitor in ARRIVE study

Summary

- Evidence from the ATTAIN trial suggested the effectiveness of abatacept did not vary significantly according to the TNF inhibitor (etanercept or infliximab) from which the patients had switched, although the subgroup analysis may be under-powered. No RCT evidence was identified for the other technologies.
- Evidence from observational studies of switching to adalimumab[94] and to abatacept[118] suggested that treatment response does not vary significantly according to the TNF inhibitor that the patients had previously tried.

- Discussion: assuming no interaction between the technologies used sequentially, the results of this subgroup analysis provide an indication of whether patients previously treated with different TNF inhibitor represented distinctly different populations when they switch. Limited data do not suggest this is the case although the evidence is very limited in view of possible combinations of treatment sequence.

5.7.5 Other subgroups

Bold type indicates statistically significant difference between rituximab and placebo within subgroup or (for test for interaction) significant difference in treatment effect between subgroups.

5.8 Ongoing studies

5.8.1 Electronic Searches

Electronic searches for ongoing studies identified only two relevant studies. One of these looks at the extended treatment with RTX in patients who have had an inadequate response (due to toxicity or inadequate efficacy) to previous or current treatment with ETN, IFX or ADA are being entered into an open label study of two doses RTX and subsequently randomised to a third dose or placebo (if still having B-cells). The study acronym is EXTRRA and it is being conducted in the UK. It has a target sample size of 60 and the study is anticipated to finish in 2010. Parts of this study are relevant to the decision problem in this report. .

The second study is a "multicentre clinical observation real-life study" of RTX in patients with active RA whose current treatment with TNF inhibitors in combination with MTX is insufficient. The study acronym is RIRA, and it has a target sample size of 20. I appears to have been undertaken in Austria and to have been completed. This study does not as yet appear to have been published.

5.8.2 Manufacturer's Submissions

Mention of ongoing studies in the MSs were as follows:

ADA: No explicit statements are provided in the MS about on-going studies on ADA. Data from large registries are included.

ETN: No explicit statements are provided in the MS about on-going studies on ETN. Data from registries and LTEs are included.

IFX: The MS provides details on an on-going multicentre open-label RCT (RE-START; C0168Z05) that aims to assess the efficacy and safety of IFX in patients with active RA who inadequately respond to ETN or ADA. The primary outcome is EULAR response at week 10. Other outcomes will include ACR, tender/swollen joints, HAQ and hrQoL using the SF-36 instrument. Evaluations will be made up to 26 weeks. The study is being conducted in North America, EU and Israel. The sample size is indicated as ~200.

RTX: The MS lists eight ongoing studies (REFLEX open label extension, SERENE, IMAGE, MIRROR, SUNRISE, SIERRA, DANCER open label extension, WA16291 and its open label extension) and various data are presented from these studies in the submission.

ABT: No explicit statements are provided in the MS about on-going studies on ABT. Data from registries and LTEs are included.

6 ASSESSMENT OF COST-EFFECTIVENESS

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 Methods

6.1.1.1. Search strategy

Articles on the cost and cost-effectiveness of drugs for RA after the failure of a TNF inhibitor were identified from the searches for clinical effectiveness. In addition, NHS EED, Cochrane Library 2009 (Issue 3) and the internet sites of national economic units were searched.

6.1.1.2. Study selection

All articles identified in the searches were imported into the same Reference Manager database (Reference Manager v.11, Thomson ResearchSoft) as for clinical effectiveness. Titles and abstracts were independently checked for relevance based on the population and intervention by two reviewers alongside selection of papers for clinical effectiveness. If articles were considered relevant by at least one of the reviewers a full paper copy was ordered. A flow chart presenting the process of selection of studies for the systematic review can be found in Appendix 10.3.

One reviewer applied the inclusion and exclusion criteria using a standard checklist (see Appendix 10.7). Data were extracted by one reviewer using a predesigned data extraction form and were independently checked by a second reviewer. Data on the following were extracted:

- Study characteristics, such as form of economic analysis, population, interventions, comparators, perspective, time-horizon and modelling used
- Effectiveness and cost parameters, such as effectiveness data, health state valuations (utilities), resource-use data, unit cost data, and key assumptions
- Results and sensitivity analyses.

These characteristics and the main results of included economic evaluations are summarised in subsequent tables. The study population and question, selection of alternatives, form of evaluation, effectiveness data, costs, benefit measurement and valuation, decision modelling,

discounting, allowance for uncertainty and presentation of results were all evaluated as part of this process.

In addition, all five manufacturers submitted economic analyses. These submissions are reviewed in detail in Section 6.2.

6.1.2 Results

Thirty eight papers were potentially relevant and ordered. One paper[138] was unobtainable. Four studies met the inclusion criteria and the key features of these studies are summarised in Table 69. Further details of the four studies are presented in Appendix 10.9; their quality was assessed using a simplified version of the Drummond and Jefferson checklist.[139] A summary of the strategies compared and Incremental Cost-Effectiveness Ratios (ICERs) reported from these studies are provided in Table 70. A list of the excluded papers with reasons for exclusion is presented in Appendix 10.5.

Table 69 Summary of published economic analyses

Study	Drug considered	Population (patients with RA that failed to respond adequately to)	Form of economic analysis	Model used	Time-horizon
Vera-Llonch et al, 2008[140]	Abatacept	TNF inhibitors	Cost-utility	Patient-level simulation	10 years Lifetime
Russell et al, 2009[141]	Abatacept	Etanercept[∞]	Cost-effectiveness	Decision tree	2 years
Kielhorn et al, 2008[142]	Rituximab	Two non-biologic DMARDS and one TNF inhibitor	Cost-utility	Markov	Lifetime
Lindgren et al, 2009[143]	Rituximab	One or more TNF inhibitors	Cost-utility	Patient-level simulation	Lifetime
[∞] a strategy of abatacept as first biologic was also modelled but this is not relevant to the current review					

The review identified two abatacept studies, and these differed in how abatacept was modelled. Vera-Llonch and colleagues[140] considered abatacept with methotrexate compared with methotrexate alone while Russell and colleagues[141] considered abatacept first, then switch to infliximab if there was no response, then switch to conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs) compared with infliximab first, then switch to adalimumab if there was no response, then switch to conventional DMARDs.

Table 70 Summary of published ICERs

Drug	Study	Time-horizon	Strategies compared	ICER
Abatacept	Vera-Llonch[140] 2008	10 years	ABT+MTX vs. MTX	$50,576 (US) per QALY
		Lifetime		$45,979 (US) per QALY
	Russell[141] 2009	2 years	ABT→ IFX→ DMARDs vs. IFX→ADA→ DMARDs	$12,514 (CAN) per additional case of 'low disease-activity state' gained $16,829 (CAN) per additional remission gained
Rituximab	Kielhorn[142] 2008	Lifetime	RTX→DMARDs vs. DMARDs	£14,690 per QALY
			RTX→ADA→IFX→DMARDs vs. ADA→IFX→DMARDs	£11,601 per QALY
	Lindgren[143] 2009	Lifetime	RTX→TNF inhibitors vs. TNF inhibitors	RTX dominates TNF inhibitors

The review also identified two rituximab economic evaluations, and these differ in how rituximab was modelled. Kielhorn and colleagues[142] considered two different rituximab pathways (rituximab followed by traditional DMARDs compared to traditional DMARDS only and rituximab first, then switch to adalimumab if there was no response, then switch to infliximab if there was no response, then switch to traditional DMARDs, compared to adalimumab first, then switch to infliximab, then switch to conventional DMARDs). Lindgren and colleagues[143] considered rituximab first, followed by a series of TNF inhibitors compared with a series of TNF inhibitors.

Data source

Both abatacept studies[140,141] used the ATTAIN trial as their source for abatacept effectiveness. Russell and colleagues[141] also extracted the effectiveness of TNF inhibitors in patients with an inadequate response to TNF inhibitors from the ATTAIN trial, assuming a 10% reduction after each switch. The same study also used the TEMPO trial as the source for etanercept effectiveness, when etanercept appears in the sequence for the first time in patients with an inadequate response to DMARDs.

The two rituximab studies[142,143] used data from the REFLEX trial as their source for rituximab effectiveness. Kielhorn and colleagues[142] calculated the mean drop in HAQ for each of the responder groups from the REFLEX trial. Utilities were mapped from the HAQ score and their model uses the equation as estimated by Bansback and colleagues[144] (QoL = 0.76 – 0.28 x HAQ + 0.05 x Female). Lindgren and colleagues[143] in their model mapped utilities from an equation as

estimated by patient level data from the Southern Swedish Arthritis Treatment Group Registry (SSTAG) (QoL = 0.915 – 0.252 x HAQ - 0.05 x Male – 0.107 x DAS28). The SSATG data were also used to estimate the HAQ progression [HAQ progression = 0.106 + 0.241 x (HAQ at treatment start) + 0.002 x (Months on treatment) – 0.087 x (2^{nd} line) – 0.192 x (3^{rd} line) – 0.007 x (Disease duration)]. It is unclear though what type of regression was used; the text suggests linear while table suggests logistic.

Study type

Three studies were cost-utility analyses, with the cost-effectiveness ratio reported as cost per QALY gained.[140,142,143] Russell and colleagues[141] used the DAS28 response and reported results in cost per additional case of 'low disease-activity sate' gained (DAS28<2.6) and cost per additional remission gained (DAS28≤3.2).

Perspective

Kielhorn and colleagues[142] carried out the analysis from the UK healthcare perspective. Lindgren and colleagues[143] carried out the analysis from a societal perspective, including direct and indirect costs as well as informal care, therefore results are not directly relevant to a UK healthcare perspective. Vera-Llonch and colleagues[140] carried out the analysis from a third party payer perspective, including medical treatment only. Finally, Russell and colleagues[141] carried out the analysis from the Swedish healthcare perspective. Therefore, results from Russell and colleagues[141] cannot be applied directly to the UK.

Modelling approach

Each study used a different modelling approach. Russell and colleagues[141] used a simple decision-tree structure and modelled cost and outcomes over 2 years. Vera-Llonch and colleagues[140] used a patient-simulation model exploring two time horizons; 10 years and lifetime. Kielhorn and colleagues[142] used a Markov model structure with a lifetime time horizon and a 6-month cycle length. Lindgren and colleagues[143] used a patient-level simulation model. The time horizon of the model appears to be lifetime although this was not explicitly stated in the paper. The model runs for continuous time with no fixed cycle length.

Findings

Russell and colleagues[141] conclude that abatacept (followed by infliximab, then switch to DMARDs) is a cost-effective strategy in patients with an inadequate response to etanercept when compared to infliximab (followed by adalimumab, then switch to DMARDs). The ICER was $12,514 (CAN) per additional case of 'low disease-activity state' gained and $16,829 (CAN) per additional remission gained. Vera-Llonch and colleagues[140] concluded that abatacept (combined with methotrexate) is cost-effective when compared to methotrexate alone with an ICER of $50,576 (US) per QALY in the 10-year time horizon analysis and an ICER of $45,979 (US) per QALY in the lifetime time horizon. Results of the abatacept studies are not comparable since one study[141] is a cost-effectiveness analysis while the other is a cost-utility analysis[140], the studies do not have the same time horizon, and finally do not apply the same perspective.

Kielhorn and colleagues[142] concluded that rituximab is highly cost-effective for patients who have failed to respond adequately to one biologic DMARD. The ICER for rituximab followed by DMARDs was £14,690 per QALY compared to conventional DMARDs only, while the ICER for rituximab first, then switch to adalimumab, then to infliximab, then to DMARDs, compared to adalimumab first, then switch to infliximab, then to DMARDs, was £11,601 per QALY. Lindgren and colleagues[143] concluded that the rituximab strategy (followed by a series of TNF inhibitors) was dominant (i.e. cheaper and provided a QALY gain) when compared to a TNF inhibitor strategy. This was explained by the lower price and better effect of rituximab than the mix of second line TNF inhibitors. Both studies favour rituximab and their results could be comparable since both studies are cost-utility analyses with a lifetime horizon. However, the study by Lindgren and colleagues[143] uses a societal perspective which could give a more favourable ICER (in this instance the rituximab strategy dominates the TNF inhibitors strategy) as the difference in costs is driven by the indirect costs and the costs of informal care.

6.1.2.1. Summary

- A direct comparison of ICERs between studies is not possible because of different approaches to modelling, in particular time-horizon, country of origin and perspective chosen

- All studies used a decision-analytic model. Published models vary in some important aspects: the type of model used, the sequence of drugs, comparator therapies, and time-horizon
- Incremental analyses, to which appropriate sensitivity analyses had been applied, were reported without exception
- All but one studies carried out a cost-utility analysis and reported results in 'cost per QALY'. One study carried out a cost-effectiveness analysis and reported results in cost per additional case of 'low disease-activity sate' gained (DAS28<2.6) and cost per additional remission gained (DAS28≤3.2)
- There was disparity in the selection of perspectives chosen for the analyses. One study reported costs that include both those from a healthcare perspective as well as indirect costs and costs of informal care; inclusion of these costs improves the cost-effectiveness of the drug

6.2 Critique of manufacturers' submissions

A submission was received from each company with each submission containing an economic analysis. However, only four manufactures included a model. Table 71 provides a brief summary of the five economic analyses provided.

6.2.1 Abbott submission (Adalimumab)

A discrete event simulation model was built to evaluate the cost-effectiveness of adalimumab. The type of evaluation undertaken was a cost-utility analysis with outcomes measured in QALYs.

Adalimumab was compared to all interventions included in the scope; etanercept, infliximab, rituximab and abatarcept, all combined with methotrexate. In each of these five strategies, each drug was followed by gold, then leflunomide, then ciclosporin, then rescue therapy. A comparison was also made with a strategy of traditional DMARDs only (gold, then leflunomide, then ciclosporin, then rescue therapy) and also a strategy where adalimumab (or etanercept) is followed by rituximab, then gold, then leflunomide, then ciclosporin, then rescue therapy.

It is assumed that the population has already had an inadequate response to at least two traditional DMARDs, since these are patients who had had an inadequate response to a TNF inhibitor. Therefore, methotrexate, sulfasalazine and hydroxychloroquine are not considered as comparators in the economic evaluation.

Response rates are assumed to be equal across all TNF inhibitors. In addition, drug, administration and monitoring costs of adalimumab and etanercept are assumed to be equal. Therefore, adalimumab and etanercept are evaluated in the same treatment sequence and results for these two drugs are considered similar throughout the submission.

New biologic agents (tocilizumab, golimumab and certolizumab pegol) were excluded from the analysis since these drugs were considered not yet available in the UK.

Table 71 Summary of methods used in industry economic analyses

Submission features	**Adalimumab (Abbott)**	**Etanecept (Wyeth)**	**Infliximab (Schering-Plough Limited)**	**Rituximab (Roche)**	**Abatacept (Bristol-Myers Squibb)**
Population	Adult patients with active RA who have had an inadequate response to methotrexate, sulfasalazine, hydroxychloroquine and one TNF inhibitor	Adult patients with active RA who have had an inadequate response to etanercept	Adult patients with active RA who have had an inadequate response to two non-biologic DMARDs and one TNF inhibitor	Adult patients with active RA who have had an inadequate response to a TNF inhibitor	Adult patients with moderate to severe RA who have had an inadequate response to at least one TNF inhibitor
Interventions and comparators	**Gold**→Leflunomide→ Ciclosporin→rescue vs **ADA/ETN**→Gold→ Leflunomide→Ciclosporin →rescue vs **IFX**→Gold→ Leflunomide→Ciclosporin →rescue vs **RTX**→Gold→ Leflunomide→Ciclosporin →rescue vs **ABT**→Gold→ Leflunomide→Ciclosporin →rescue vs **ADA/ETN→RTX** → Gold→Leflunomide→ Ciclosporin→rescue	**ETN/IFX/ADA**→ DMARDs→ 'salvage therapy' vs **DMARDs**→ DMARDs→ 'salvage therapy' vs **RTX** → DMARDs→ 'salvage therapy'	**ADA**→DMARDs vs **ETN**→DMARDs vs **IFX**→DMARDs vs **ABT**→DMARDs vs **RTX**→DMARDs vs **ADA→RTX**→DMARDs vs **ETN→RTX**→DMARDs vs **IFX→RTX**→DMARDs vs **DMARDs**	**RTX**→Leflunomide→ Gold→Cyclosporine→ palliative care vs. **ETN**→Leflunomide→ Gold→Cyclosporine→ palliative care vs. **ADA**→Leflunomide→ Gold→Cyclosporine→ palliative care vs. **IFX**→Leflunomide→ Gold→Cyclosporine→ palliative care vs. **ABT**→Leflunomide→ Gold→Cyclosporine→ palliative care vs. **Leflunomide**→Gold→ Cyclosporine→ palliative care	**ABT→IFX→** Leflunomide→Gold→ Azathioprine→Ciclosporin→ Penicillamine→Palliative care vs **RTX→IFX→** Leflunomide→Gold→ Azathioprine→Ciclosporin→ Penicillamine→Palliative care **ABT→ TNF inhibitors→** Leflunomide→Gold→ Azathioprine→Ciclosporin→ Penicillamine→Palliative care vs **TNF inhibitors→TNF inhibitors**→Leflunomide→ Gold→Azathioprine→ Ciclosporin→Penicillamine→ Palliative care
Form of analysis	Cost-utility analysis	Cost-utility analysis	Cost-utility analysis	Cost-utility analysis	Cost-utility analysis

Submission features	**Adalimumab (Abbott)**	**Etanecept (Wyeth)**	**Infliximab (Schering-Plough Limited)**	**Rituximab (Roche)**	**Abatacept (Bristol-Myers Squibb)**
Model used	Discrete event simulation model	Markov model	Patient-simulation	Patient-level simulation	Patient-level simulation
Cycle length	Continuous	6-month	1-month	6-month	Continuous
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime
Base case results presented - ICERs (£/QALY)	ADA/ETN vs DMARDs: £15,962 IFX vs DMARDs: £21,529 RTX (9-months) vs DMARDs: £10,986 ABT vs DMARDs: £30,104 ADA/ETN→RTX vs DMARDs: £13,797	TNF inhibitors vs DMARDs: £14,501 TNF inhibitors vs Rituximab: £16,225	ADA vs DMARDs: £35,138 ETN vs DMARDs: £35,898 IFX vs DMARDs: £28,661 ABT vs DMARDs: £44,769 RTX vs DMARDs: £17,422 (9-month dose of RTX), £27,161 (6-month dose of RTX) ADA+RTX vs DMARDs: £27,998 (9-month dose of RTX), £32,345 (6-month dose of RTX) ETN+RTX vs DMARDs: £27,936 (9-month dose of RTX), £32,412 (6-month dose of RTX) IFX+RTX vs DMARDs: £24,236 (9-month dose of RTX), £28,617 (6-month dose of RTX)	RTX vs ETN: RTX dominates RTX vs IFX: RTX dominates RTX vs ABT: RTX dominates RTX vs ADA: £310,771 RTX vs DMARDs: £5,311	ABT→IFX vs RTX→IFX: £20,438 ABT→TNF inhibitors vs TNF inhibitors→TNF inhibitors: £23,019

Submission features	**Adalimumab (Abbott)**	**Etanecept (Wyeth)**	**Infliximab (Schering-Plough Limited)**	**Rituximab (Roche)**	**Abatacept (Bristol-Myers Squibb)**
PSA results	ADA/ETN→RTX vs DMARDs: 100% cost-effective at £30,000 per QALY RTX vs DMARDs probability of being cost-effective ~60% at £20,000/QALY ADA/ETN vs DMARDs probability of being cost-effective ~40% at £20,000/QALY	Not presented	RTX (9-month dose) vs DMARDs: probability of being cost-effective >90% IFX vs DMARDs: probability of being cost-effective ~60% at £30,000/QALY IFX+RTX vs RTX: probability of being cost-effective >40% at £30,000/QALY	RTX vs ETN: RTX is 100% cost-effective, dominating 74% of iterations RTX vs IFX: RTX is 100% cost-effective, dominating 70% of iterations RTX vs ADA: RTX is 100% cost-effective, dominating 37% of iterations RTX vs ABT: RTX is 100% cost-effective, dominating 70% of iterations RTX vs DMARDs: RTX is 100% cost-effective	PSA Probability of Abatacept being cost-effective at £30,000 per QALY: 99% when compared with Rituximab 97% when compared with TNF inhibitors
HAQ→QoL	EQ-5D=0.82-0.11*HAQ-0.07*HAQ^2	EQ-5D=0.76-0.28*HAQ	NA	EQ-5D=0.82-0.11*HAQ-0.07* HAQ^2	HUI3=0.76-0.28*HAQ +0.05*Female
Adverse events	Included. Rates of tuberculosis (for TNF inhibitors) from BSRBR. Rates of mild, moderate and serious adverse events of etanercept, infliximab and leflunomide from an observational study. Leflunomide was used as a	Included. Serious adverse events were modelled at £1,181 Adverse events of conventional DMARDs assumed to be more frequent that those of TNF inhibitors.	Although the submission provides background evidence on adverse events, they have not been included in the model.	Not included. The clinical section of the submission indicates that the incidence of adverse events is very similar across all treatments in the appraisal.	Included. Sources were mainly published sources. Abatacept has the lowest rates in all adverse events apart from sinusitis.

Submission features	Adalimumab (Abbott)	Etanecept (Wyeth)	Infliximab (Schering-Plough Limited)	Rituximab (Roche)	Abatacept (Bristol-Myers Squibb)
	proxy for all traditional DMARDs Etanercept was used as a proxy for adalimumab, abatarcept and rituximab.				
Mortality	Applied a treatment-specific mortality effect. Produced a parametric version of the mortality risk, with adjustments for treatment and HAQ.	Used a baseline mortality of 1.63 times general population mortality, with an adjustment for change in HAQ (not clear how they have implemented this as they did not supply their model electronically).	Used mortality ratios dependent on age and gender but no variation by HAQ or treatment.	Started from general population mortality and applied a multiplier of 1.33 to the power of the HAQ score, with the parameter 1.33 varied in sensitivity analysis.	Started from general population mortality and applied a multiplier of 1.33 to the power of the HAQ score, with the parameter 1.33 varied in sensitivity analysis.

Adverse events

Adverse events were included in the economic analysis. Rates of tuberculosis associated with each of the TNF inhibitors (adalimumab, etanercept, infliximab) were based on data from the BSRBR. [145] Rates of mild, moderate and serious adverse events were estimated from an observational study in Sweden, which evaluated the safety of patients receiving etanercept, infliximab or leflunomide.[146] Values for these drugs were used as proxies for other drugs. The effect of this was that the rate of adverse events was higher for conventional DMARDs than for biologics.

HAQ to Utility

A quadratic mapping mechanism was used in order to convert HAQ scores to EQ-5D scores (EQ-5D=0.82-0.11*HAQ-0.07* HAQ^2). This equation was estimated through EQ-5D data collected in tocilizumab trials (OPTION and LITHE).[147] The linear mapping mechanism reported in the same study (EQ-5D=0.89-0.28*HAQ) was explored in a sensitivity analysis.

Results

The base case results show that all drugs [adalimumab/etanercept, infliximab, rituximab and abatarcept (all followed by traditional DMARDs)] may represent cost-effective treatment options when compared with a sequence of traditional DMARDs. Rituximab had the lowest ICER (£10,986) while abatacept the highest (£30,104). The strategy of introducing rituximab after adalimumab/etanercept (i.e. as a third line biologic) had an ICER of £13,797 per QALY, when compared to traditional DMARDs. The ICERs are as follows:

- Adalimumab/Etanercept vs DMARDs: £15,962 per QALY
- Infliximab vs DMARDs: £21,529 per QALY
- Rituximab (9-month dose) vs DMARDs: £10,986 per QALY
- Abatacept vs DMARDs: £30,104 per QALY
- Adalimumab/Etanercept + Rituximab vs DMARDs: £13,797 per QALY

ICERs of Adalimumab/Etanercept (followed by DMARDs) vs DMARDs presented in the sensitivity analyses varied from £11,191 per QALY to £26,456 per QALY, with adalimumab/etanercept being cost-effective in the vast majority of the scenarios explored.

The PSA results for 100 replications (for a cohort of 20,000 patients per replication) showed that at a WTP of £30,000 per QALY, adalimumab/etanercept followed by rituximab is the most cost-effective strategy, with the probability of being cost-effective being close to 1. At a WTP of £20,000 per QALY, rituximab followed by conventional DMARDs is cost-effective, with a probability of being cost-effective at around 60%, while there is a 40% (approx) chance of adalimumab/etanercept followed by conventional DMARDs being cost-effective. The submission, however, states: 'although the CEAC shows the probability that a treatment sequence is the most cost-effective option at various willingness to pay thresholds, it does not show all treatment strategies which can be considered cost-effective at these threshold(s)'. Therefore, the submission concludes that although the strategy of adalimumab/etanercept followed by conventional DMARDs is never shown to be cost-effective (submission Figure 3.3.2.1), the deterministic results showed that it is cost-effective, with an ICER of under £16,000 per QALY. The MS fails to point out though that both rituximab followed by conventional DMARDs and adalimumab/etanercept followed by rituximab had lower ICERs (£10,986 and £13,797 respectively).

6.2.2 Wyeth submission (Etanercept)

A Markov model (6-month cycle) was built to evaluate the cost-effectiveness of etanercept. The type of evaluation undertaken was a cost-utility analysis with outcomes measured in QALYs. However, Wyeth did not provide the model that produced the results presented in the submission.

Patients in the model were assumed to receive initial treatment with methotrexate, then switch to sulfasalazine, then switch to a '1st TNF inhibitor'. It is unclear in text which TNF inhibitor this was. However, cost data suggests that it is etanercept in all strategies compared. Thereforeit is assumed that the population modelled were patients whose first failed TNF inhibitor was etanercept.

The three strategies compared are: second TNF inhibitor, DMARDs and 'Rituximab', all followed by traditional DMARDs and then the 'best supportive care' (salvage therapy). It is unclear though which TNF inhibitor is compared in the 'second TNF inhibitor' strategy. Cost

data suggests that it was an average of etanercept, adalimumab and infliximab combined with methotrexate. Similarly, in the 'DMARDs' strategy, it was unclear which DMARD was compared: cost data suggests that it was methotrexate. Finally, the DMARD following a TNF inhibitor seems to be sulfasalazine (again based on cost data).

Cost-effectiveness results were presented for a range of assumed HAQ changes of both the TNF inhibitor (etanecept/infliximab/adalimumab) and the conventional DMARDs.

Adverse events

Adverse events were included in the economic analysis. For simplicity, only serious adverse events were modelled, assuming that they last for one cycle (6 months) only. The cost of a serious adverse event was estimated at £1,181, which included 2 GP visits and 7 inpatient days. Text (submission page 33) suggests that various published sources were used for the rates of adverse events for each drug. Adverse events rates for all TNF inhibitors were assumed to be the same as etanercept. Data in the table suggest that rates of adverse events are more frequent in traditional DMARDs than in biologics.

HAQ to Utility

A linear mapping mechanism was used in order to convert HAQ scores to EQ-5D scores during each model cycle (EQ-5D = 0.76 - 0.28*HAQ).[148] It was assumed that patients experiencing serious adverse events would lose 0.05 units of utility (or 10% of a QALY) over one year.

Results

Results were presented for a range of assumed HAQ changes of both TNF inhibitor (etanecept/infliximab/adalimumab) and conventional DMARDs. The ICER for TNF inhibitors vs conventional DMARDs was £14,501, when a HAQ drop of 0.55 was assumed for the TNF inhibitors and no change was assumed for the conventional DMARDs. The ICER for TNF inhibitors vs Rituximab was £16,225, when a HAQ drop of 0.55 was assumed for the TNF inhibitors and a HAQ drop of 0.40 was assumed for Rituximab.

PSA results were not presented in the submission.

6.2.3 Schering-Plough Limited submission (Infliximab)

A patient-simulation/individual sampling model was used to evaluate the cost-effectiveness of infliximab. The type of evaluation undertaken was a cost-utility analysis with outcomes measured in QALYs.

Nine treatment sequences were compared in the cost-effectiveness analysis:

- Adalimumab/Etanercept/Infliximab/Rituximab/Abatacept each followed by a sequence of traditional DMARDs
- Adalimumab/Etanercept/Infliximab each followed by Rituximab and then a sequence of traditional DMARDs
- Sequence of traditional DMARDs

Patients in the model could receive a maximum of two biologic DMARDs followed by a maximum of three non-biologic DMARDs and were limited to a maximum of five treatments within each of the nine sequences. New biologic agents (tocilizumab, golimumab and certolizumab pegol) are excluded from the analysis since these drugs were considered not yet available in the UK.

The baseline characteristics of patients in the GO-AFTER trial where treatment with a TNF inhibitor (golimumab) following withdrawal from one or more previous TNF inhibitors (adalimumab, etanercept or infliximab) was investigated, were considered for the start of the model.

Adverse events

Adverse events were not included in the model although evidence on adverse events was included in the efficiency part of the submission.

HAQ to Utility

There was no mapping mechanism applied on EQ-5D scores. Utility gains or losses were modelled directly using a QoL measure. Each treatment was associated with an initial utility gain, which was estimated from BSRBR data.

Results

The base case results showed that adalimumab, etanercept, infliximab and rituximab (followed by traditional DMARDs) may represent cost-effective treatment options whereas abatacept (followed by traditional DMARDs) did not represent a cost-effective treatment option, when all strategies are compared with a sequence of traditional DMARDs. The ICERs were as follows:

- Adalimumab vs DMARDs: £35,138 per QALY
- Etanercept vs DMARDs: £35,898 per QALY
- Infliximab vs DMARDs: £28,661 per QALY
- Abatacept vs DMARDs: £44,769 per QALY
- Rituximab (9-month dose) vs DMARDs: £17,422 per QALY
- Rituximab (6-month dose) vs DMARDs: £27,161 per QALY

Further analysis, adding rituximab after the TNF inhibitors (adalimumab, etanercept, infliximab) was performed. Infliximab had the lowest ICER for both doses of rituximab explored (6-month/9-month) when compared to both traditional DMARDs and rituximab (both followed by traditional DMARDs). The ICERs were as follows:

vs DMARDs

- Adalimumab+Rituximab (9-month dose): £27,998 per QALY
- Adalimumab+Rituximab (6-month dose): £32,345 per QALY
- Etanercept+ Rituximab (9-month dose): £27,936 per QALY
- Etanercept +Rituximab (6-month dose): £32,412 per QALY
- Infliximab Rituximab (9-month dose): £24,236 per QALY
- Infliximab Rituximab (6-month dose): £28,617 per QALY

vs Rituximab

- Adalimumab+Rituximab (9-month dose): £41,747 per QALY
- Adalimumab+Rituximab (6-month dose): £39,084 per QALY
- Etanercept+ Rituximab (9-month dose): £42,477 per QALY
- Etanercept +Rituximab (6-month dose): £39,673 per QALY
- Infliximab Rituximab (9-month dose): £33,274 per QALY
- Infliximab Rituximab (6-month dose): £30,549 per QALY

Overall, when compared to DMARDs, rituximab had the lowest ICER for both 9-month (£17,422 per QALY) and 6-month doses (£27,161 per QALY). Among TNF inhibitors (etanercept, infliximab, adalimumab), infliximab had the lowest ICER (£28,661 per QALY).

ICERs in the sensitivity analyses varied from £16,752 per QALY (Rituximab vs DMARDS, when a HAQ improvement of 0.01 per annum was assumed for all biologic DMARDS) to £58,850 per QALY (Infliximab+Rituximab vs Rituximab, when the weight of the patient was assumed to be 120kg).

The PSA results showed that, when compared to traditional DMARDs, the probability of rituximab (9-month dose) being cost-effective was greater than 90% at a range of WTP thresholds greater than £20,000 per QALY. When a 6-month dose was assumed for rituximab, the probability of rituximab being cost-effective was marginally greater than the probability of infliximab being cost-effective, at WTP>£20,000 per QALY. The probability of infliximab (vs DMARDs) being cost-effective was ~60% at £30,000 per QALY. When compared to rituximab, the probability of infliximab followed by rituximab being cost-effective was greater than 40% at £30,000 per QALY.

6.2.4 Roche submission (Rituximab)

A patient-level simulation was built to evaluate the cost-effectiveness of rituximab. The type of evaluation undertaken was a cost-utility analysis with outcomes measured in QALYs.

Rituximax was compared to all interventions included in the scope; adalimumab, etanercept, infliximab and abatarcept. In addition, rituximab was compared to a strategy of traditional

DMARDs. In all strategies compared, the first active treatment was followed by salvage therapy consisting of leflunomide, gold and ciclosporine followed by palliative care. Response rates of leflunomide, gold and ciclosporine were assumed to be equivalent to MTX for this population. Comparison of rituximab against the new biological agents (tocilizumab, golimumab and certolizumab pegol) was not performed as these treatments were considered not used in routine clinical practice in the NHS.

Adverse events

Adverse events were not included in the economic analysis. The clinical section of the submission indicates that the incidence of adverse events was very similar across all treatments in the appraisal. Given that rituximab was compared head to head with each of the interventions in the scope, it was assumed that the costs of treating an adverse event would be the same in all strategies compared and therefore the cost-effectiveness ratios would not be affected by these costs.

HAQ to Utility

A quadratic mapping mechanism was used in order to convert HAQ scores to EQ-5D scores during each model cycle (EQ-5D=0.82-0.11*HAQ-0.07* HAQ^2). This equation was estimated through EQ-5D data collected in two Roche phase III trials (DMARD-IR) for tocilizumab. The linear mapping mechanism used by Bansback[144] (HUI3=0.76-0.28*HAQ+0.05*Female) was explored in a scenario analysis.

The model also assumed that the relationship of HAQ score to patient reported utility was independent of the number of previous biologics used. Moreover, for the base-case analysis, the model allowed for estimates of QALYs being less than one, when patients progress to very high HAQ scores. However, this relationship was not explored in the sensitivity analysis by adding a restriction to the negative QALY values.

Results

The base case results showed that rituximab dominates etanercept (Incremental Costs: -£13,246, Incremental QALYs: 0.0168), infliximab (Incremental Costs: -£10,490, Incremental QALYs:

0.0699) and abatarcept (Incremental Costs: -£16,075, Incremental QALYs: 0.0606). When compared to adalimumab, rituximab was less costly (Incremental Costs: -£13,551) but also less effective (Incremental QALYs:-0.0436) with an ICER of £310,771 per QALY. When compared to the traditional DMARDs strategy, rituximab was more costly (Incremental Costs: £6,323) but also more effective (Incremental QALYs: 1.0705), with an ICER of £5,311 per QALY.

Overall, TNF inhibitors (etanercept, infliximab, adalimumab) were dominated by rituximab, i.e. rituximab was more effective and less costly. Adalimumab was marginally more effective but also more costly than rituximab, resulting in an ICER of £310,771 per QALY. When compared to traditional DMARDs, rituximab was cost effective at £5,311 per QALY.

ICERs in the sensitivity analyses varied from £4,898 per QALY (vs traditional DMARDs when a 9-month time to retreatment was assumed for rituximab) to £326,397 per QALY (vs Adalimumab when a linear mapping mechanism was assumed for the HAQ to QoL conversion), while in most of the scenarios rituximab dominated the other strategies (i.e. rituximab was less costly and more effective).

The PSA results for 1,000 Monte Carlo simulations showed that the probability of rituximab being cost-effective is 100% at a wide range of WTP thresholds (5,000 - £400,000 per QALY).

6.2.5 Bristol-Myers Squibb Pharmaceuticals LTD submission (Abatacept)

A patient-level simulation model was built to evaluate the cost-effectiveness of abatacept. The type of evaluation undertaken was a cost-utility analysis with outcomes measured in QALYs. Baseline patients characteristics were from the ATTAIN trial. Data from ATTAIN, REFLEX and BSRBR were used for the treatment efficacy of the drugs modelled.

Abatacept was compared to all interventions included in the scope; adalimumab, etanercept, infliximab and rituximab. However, TNF inhibitors were also grouped under a ‘basket’ of TNF inhibitors and these were the base case comparator. The rationale was reported as based on the conclusions from the NICE appraisal of the sequential use of TNF inhibitors.[149] In addition, the submission argued that TNF inhibitors were grouped because there were no data available to conclude on the efficacy of different TNF inhibitors, after a failure of a first TNF inhibitor.

The ‘basket’ labelled TNF inhibitors was defined through use of market share data estimated through survey data (BMS data on file). These were: 22% etanercept, 52% adalimumab, 24% infliximab and 2% rituximab for the second line treatment, and 15% etanercept, 9% adalimumab, 37% infliximab and 38% rituximab for the third line, as presented on p. 134 of the submission. Patients in the model were randomly assigned to one of the three ‘basket’ treatments, based on these data, after excluding rituximab. Efficacy, costs and other parameters related to that therapy were applied to the proportion of patients receiving that therapy. Total costs and outcomes of the ‘basket’ treatment are the sum of the three ‘basket’ therapies.

There were two main comparisons. In the first comparison abatacept was compared to rituximab, both followed by infliximab, then traditional DMARDs, then palliative care. In the second comparison, abatacept was compared to a ‘basket’ of TNF inhibitors, both followed by another ‘basket’ of TNF inhibitors, then traditional DMARDs, then palliative care.

Traditional DMARDs were not considered as comparators in the economic analysis on the basis that this target population (RA patients with an inadequate response to TNF inhibitors) should have tried multiple traditional DMARDs, and so it was assumed that clinicians were unlikely to revert to these therapies. DMARDs were only included as part of the sequence of treatments after an insufficient response or intolerance to multiple biological therapies (after failure of three biologic DMARDs). After failing DMARDs, patients received NSAIDs only (palliative care).

Other new biologic agents were not considered as comparators for two reasons. Firstly, price information for the new biological therapies was not available at the time of writing. Secondly, new biological therapies were considered not routinely used in the NHS.

In summary, this submission did not consider a ‘non-biologic’ strategy. All strategies compared included at least two biologic DMARDs (patients with an inadequate response to one TNF inhibitor).

Adverse events

Adverse events were assumed to reduce quality of life as well as reducing costs. The following adverse events were included in the economic analysis: infusion related reaction, injection site reactions, upper respiratory tract infection and urinary tract infection, rash, nausea, neutropenia, hypotension, leucopenia, severe allergic reaction and sinusitis. The sources for the rates of the

adverse events were mainly published data.[124,128] Abatacept had the lowest rates of all adverse events apart from sinusitis.

HAQ to Utility

A linear mapping mechanism was used in order to convert HAQ scores to HUI3 scores during each model cycle (HUI3 = 0.76 - 0.28*HAQ + 0.05*Female).{8908/id] The submission discussed the available sources for conversion of HAQ to utility, and selected the formula above for the base case analysis, on the basis that this formula was used in previous RA appraisals and models[142,144,150] and was preferred over other algorithms{8902,8909/id} by the ERG in the original abatacept appraisal. The submission acknowledged that the average baseline HAQ score of 1.5 from the formula selected might not be appropriate for a population with an inadequate response to one TNF inhibitor, and therefore explored the EQ-5D approach[151] in sensitivity analysis

Results

The base case results showed that abatacept was cost-effective when compared to rituximab (both followed by infliximab as the third biologic) with an ICER of £20,438 per QALY. Abatacept was also cost-effective when compared to a 'basket' of TNF inhibitors (both followed by another 'basket' of TNF inhibitors) with an ICER of £23,019 per QALY. Overall, results showed the ICERs for abatacept were all below £30,000 whether compared with single or a 'basket' of TNF inhibitors, or rituximab.

ICERs for abatacept in the sensitivity analyses varied from £14,145 per QALY (vs rituximab, when a 1.5% discount rate was assumed for QALYs) to £40,534 (vs rituximab, when the abatacept HAQ progression rate was assumed to be 0.012 than -0.013 in the base case).

The PSA results showed that the probability of abatacept being cost-effective was 99% at £30,000 per QALY when compared to rituximab. When compared to a 'basket' of TNF inhibitors, the probability of abatacept being cost-effective was 97% at £30,000 per QALY. However, the submission failed to report any other PSA results (particularly below the £30,000 per QALY threshold). From the presented figures it seems that at £20,000 per QALY, both

rituximab and the 'basket' of TNF inhibitors were cost-effective when compared to abatacept, with the probabilities being >50% and >95% respectively.

6.2.6 Summary

A key issue is the appropriate comparator to be used. All but one submissions choose conventional DMARDs as their base case comparator. One submission has not considered a strategy of conventional DMARDs at all, assuming a switch to a third biologic in all strategies compared.

All submissions used the same type of economic evaluation, with cost per QALY being offered as efficiency measure.

There is some variation in the methods used and sources of data for important model inputs such as quality of life scores or baseline population characteristics. Three submissions considered adverse events in their model; however, methods and sources of rates and costs of adverse events varied.

6.3 Independent economic assessment

The Assessment Group's own independent analysis was carried out using the Birmingham Rheumatoid Arthritis Model (BRAM), which has been further updated to allow for a non-linear relationship between HAQ and utility. Additional coding has been added to the model to facilitate the use of probabilistic sensitivity analysis (PSA). This means putting a distribution around all parameters in the model. Unless there is a good reason to treat a parameter as fixed, some distribution has been used.

The BRAM is an individual sampling model. A large number of virtual patient histories is simulated with the accumulation of costs and QALYs. The basic model structure is shown in Figure 93. A complete description of the model follows here.

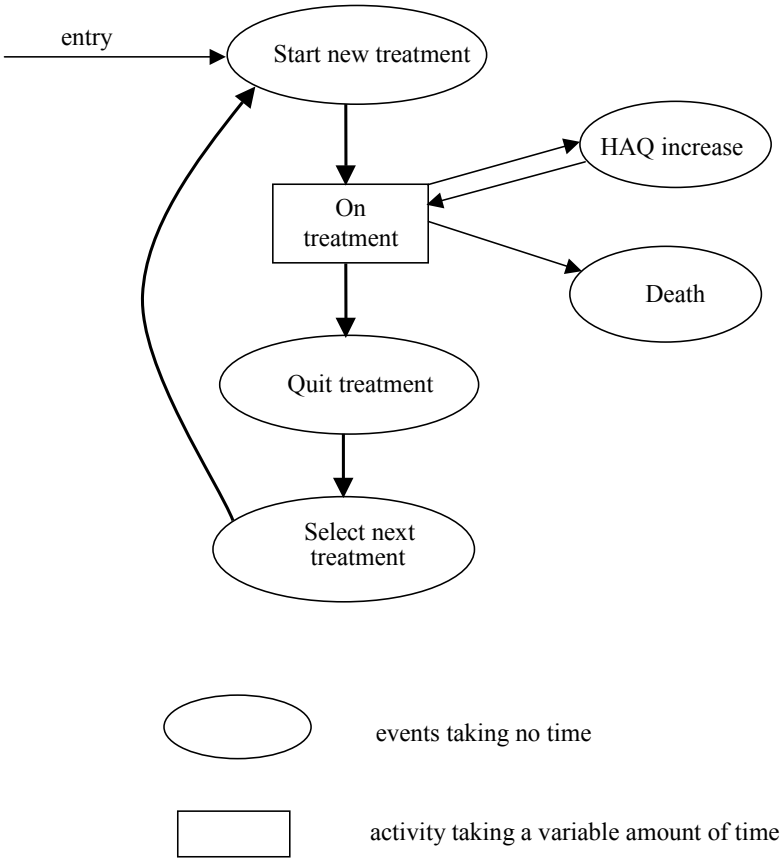
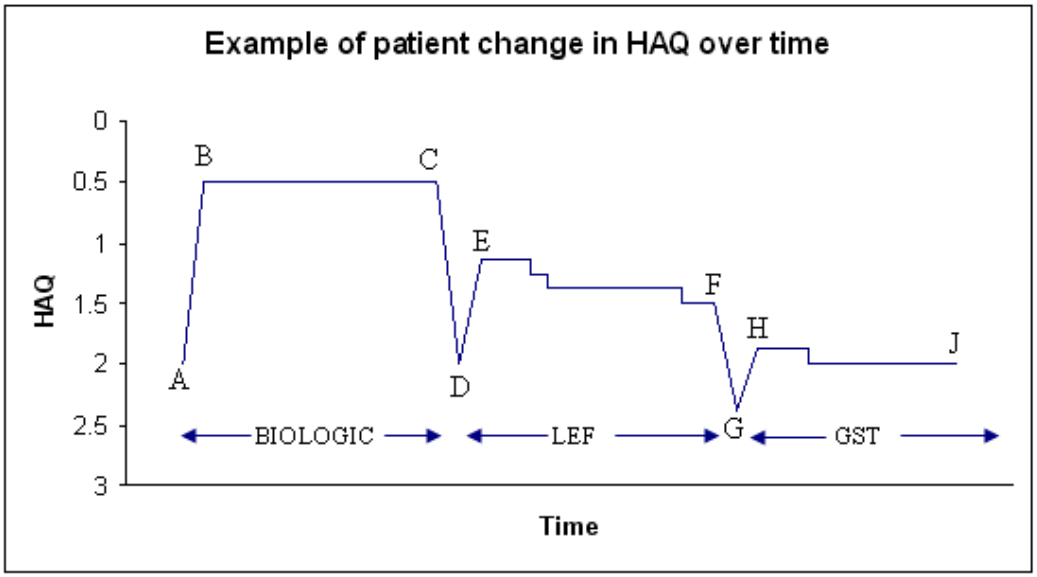


Figure 93 Basic structure of the model

6.3.1 Methods

Patients are assumed to follow a sequence of treatments. This involves: starting a treatment, spending some time on that treatment, quitting a treatment if it is toxic or ineffective, and starting the next treatment. The pattern is then repeated as long as active treatments are available. The final treatment in any strategy is palliation.

The HAQ disability index (see Appendix 10.1) is used as the marker for disease severity. Scores on this scale range from 0 (best) to 3 (worst) in multiples of 0.125. Patients' HAQ scores are assumed to improve (decrease) on starting a treatment and this improvement is lost on quitting the treatment regardless of reason for quitting. While on treatment, a patient's condition is assumed to decline slowly over time. This is modelled by occasional increases of 0.125 in HAQ score. The mean time between such increases in HAQ is allowed to vary by treatment; see Figure 94 for a possible HAQ trajectory. In the reference case analysis, HAQ is assumed to remain constant while a patient is successfully treated with a biological agent: this is modelled by a very large mean time to increase in HAQ.



Initial improvement on a biological agent (AB) is lost on quitting the treatment (CD). A smaller improvement (DE) on starting LEF is similarly lost on quitting (FG) and followed by a gain (GH) on starting GST. In this case the patient dies of other causes (J) while still responding to GST. There is a gradual deterioration in HAQ from E to F and from H to J, but not from B to C in the reference case analysis. In some cases, the time spent on a conventional DMARD is not long enough for any deterioration in HAQ to occur.

Figure 94 Possible trajectory of HAQ over time

6.3.1.1. Strategies to be compared

The current appraisal is concerned solely with the decision to be made at the point of failure of a first TNF inhibitor. Accordingly, the starting population consists of patients who have reached that point in a sequence of treatments. Table 72 shows the treatment sequences compared in this appraisal.

Table 72 Treatment sequences compared in the BRAM for this appraisal

Strategy name	ADA	ETN	IFX	RTX	ABT	DMARDs
1st	ADA	ETN	IFX	RTX	ABT	LEF
2nd	LEF	LEF	LEF	LEF	LEF	GST
3rd	GST	GST	GST	GST	GST	CyA
4th	CyA	CyA	CyA	CyA	CyA	AZA
5th	AZA	AZA	AZA	AZA	AZA	Pall
6th	Pall	Pall	Pall	Pall	Pall	

All biologics are assumed to be taken in combination with methotrexate.

Note that previous versions of the BRAM used a starting population of DMARD-naïve patients, and generated a range of different decision populations within the model. Strategies compared also allowed different choices of treatment options depending on toxicity of previous treatments. While the coding to allow this flexibility remains within the model, such flexibility is not required within the present appraisal.

The choice of DMARDs following biologic therapy has been made in line with expected practice and excludes any DMARDs that are likely to have been used before biologic therapy.

6.3.1.2. Data used in the BRAM

What follows is a detailed description of the data and sources thereof. Updated literature reviews have been used wherever possible.

Initial patient data

Table 73 and Table 74 show the information about the initial population. As stated earlier, the initial population is a population immediately following failure of a first TNF inhibitor. The values are based on the BSRBR submission to NICE.[152]

Table 73 Initial age and gender distribution

	Age (years)							
	15-24	25-34	35-44	45-54	55-64	65-74	75-84	Total
Male	0.0	0.4	1.9	5.2	6.5	3.8	1.2	19
Female	0.1	1.5	8.2	22.1	27.7	16.3	5.1	81

Table 74 Starting distribution of HAQ scores

HAQ	0.125	0.25	0.375	0.5	0.625	0.75	0.875	1
%	0.0	0.1	0.2	0.5	0.7	1.2	1.7	2.2
HAQ	1.125	1.25	1.375	1.5	1.625	1.75	1.875	2
%	2.9	3.6	4.3	5.1	5.8	6.6	7.2	7.7
HAQ	2.125	2.25	2.375	2.5	2.625	2.75	2.875	3
%	8.1	8.4	8.3	8.0	7.1	5.9	3.7	0.7

Starting treatments

As in the previous version of the BRAM, the change in HAQ on starting a new DMARD is sampled on an individual basis and takes the form of a multiplier applied to the HAQ score on starting treatment. This multiplier is sampled from a beta distribution. Full details of the method used to estimate the parameters of the beta distribution may be found in a previous report.[153] For biologic DMARDs, the parameters have been re-estimated using the best available data for use immediately after a first TNF inhibitor. For conventional DMARDs to be used after biologics, the only available data was from trials in early RA. The effectiveness was halved for use in late RA.

When a patient starts a new treatment in the model, a random number is drawn to determine the HAQ improvement for that patient. Consider for example a patient about to start leflunomide with a HAQ score of 2 and suppose that the random number drawn is 0.5. The value of 0.5 indicates that the improvement multiplier should be at the median of the relevant distribution. In the case of leflunomide, using the values from Table 75, the median is 0.358 so the HAQ should improve by $0.358 \times 2 = 0.716$. However, because HAQ is measured on a discrete scale, the improvement must be rounded to the nearest multiple of 0.125 which in this case is 0.75. The HAQ on treatment would then be $2 - 0.75 = 1.25,$ and the 0.75 improvement (reduction) would be lost on quitting treatment. Had the starting HAQ score been 1, the improvement would have been 0.375 to give a HAQ on treatment of 0.625.

Table 75 shows the point estimates for the parameters of the beta distributions used. However, these values are not known with certainty, so some variation must be included in the probabilistic sensitivity analysis. In the absence of any obvious way of measuring the uncertainty around the parameters, an assumption was made that each could be independently sampled from a Normal distribution with a standard deviation equal to 0.1 times the point estimate. This is still likely to underestimate the uncertainty in these parameters, but is preferable to using fixed values. Note that although the same point estimates have been used for etanercept and infliximab, separate and independent samples have been used for the two drugs in the PSA. This principle has been applied throughout the model. In such cases, it is not known in which direction the difference between the treatments should be, but it is not a reasonable assumption that the treatments should take identical values.

Table 75 Beta distributions for HAQ multipliers (point estimates)

Treatment	*A*	*b*	Mean	Source
ADA	0.32	0.92	0.26	Bombardieri 2007[93,94]
ETN	0.21	0.75	0.22	Bingham 2009[102]
IFX	0.21	0.75	0.22	Assume same as ETN
RTX	0.20	0.75	0.21	REFLEX[122-124]
ABT	0.33	0.85	0.28	ATTAIN[125-130]
LEF	0.285	0.935	0.23	Effectiveness halved from values used in previous report[153]
GST	0.225	0.925	0.20	
CyA	0.065	0.325	0.17	
AZA	0.10	0.90	0.10	

For probabilistic sensitivity analysis, the values a and b are drawn from Normal distributions with standard deviation 0.1 times the point estimate (see text).

Time on treatments

The model allows for two stages of early quitting of treatment. For conventional DMARDs, this facility has been used with parameters preserved from Chen *et al* (2006).[153] For TNF inhibitors and abatacept, a single stage of early quitting has been included in line with available data, while for rituximab no early quitting can be allowed, because it is necessary to model the full costs of each cycle of treatment. The values used are in Table 76. For long term survival on treatment, Weibull curves were fitted to the available data.

In the form used, a random variable *X* has a Weibull distribution with shape parameter *a* and scale parameter *b* if $\left(\frac{X}{b}\right)^a$ has an exponential distribution with unit mean. If $a = 1,$ the Weibull reduces to the exponential distribution with mean *b*; in any case *b* is the time until $\frac{1}{e} \approx 37\%$ of the original population remains. If $a < 1,$ then the hazard decreases with time; if $a > 1,$ the hazard increases. The values used are shown in Table 77. For convenience, the mean of the distribution is also shown for the point estimates of the parameters.

For TNF inhibitors, the same principle as for initial effectiveness has been applied: independent samples were drawn each time from the same distribution. For rituximab, the time sampled is then taken up to the nearest multiple of the assumed time between treatment cycles.

Table 76 Probability of early quitting of biologic treatment

Treatment	Parameter	Point estimate	Distribution	Source
ADA	Quit at 12 weeks	9.9%	Beta(89,810)	Bombardieri (2007)[93,94]
	Toxicity if above	56.2%	Beta(50,39)	
ETN	Quit at 13 weeks	5.2%	Beta(21,385)	Bingham (2009)[102] and Buch (2005)[97]
	Toxicity if above	16.7%	Beta(2,10)	Bingham (2009)[102]
IFX	Quit at 16 weeks	23%	Beta(3,10)	OPPOSITE[131]
	Toxicity if above	66.7%	Beta(2,1)	
RTX	No early withdrawal (see text)			
ABT	Quit at 6 months	13.6%	Beta(35,223)	ATTAIN[125-130]
	Toxicity if above	25.7%	Beta(9,26)	
LEF	Quit at 6 weeks	13%	Beta(13,87)	Geborek (2002)[146]
	Quit 6-24 weeks	30%	Beta(30,70)	
	Toxicity if above	33.3%	Beta(10,20)	
GST	Quit at 6 weeks	14%	Beta(10,62)	Hamilton (2001)[154]
	Quit 6-24 weeks	27.1%	Beta(19.5,52.5)	
	Toxicity if above	66.7%	Beta(6.5,13)	
CyA	Quit at 6 weeks	8%	Beta(16,184)	Yocum (2000)[155]
	Quit 6-24 weeks	24%	Beta(48,152)	
	Toxicity if above	50%	Beta(24,24)	Marra (2001)[156]
AZA	Quit at 6 weeks	15%	Beta(15,85)	Willkens (1995)[157]
	Quit 6-24 weeks	25%	Beta(25,75)	
	Toxicity if above	50%	Beta(12.5,12.5)	

Table 77 Times to quitting treatments

Treatment	*a*	95%CI	*b* (years)	95%CI	Mean (years)	Source
TNF inhibitors	0.701	(0.634,0.768)	3.211	(3.022,3.412)	4.06	BSRBR submission[121]
RTX	0.474	(0.403,0.545)	5.1	(3.742,6.951)	11.31	REFLEX long-term extension[137]
ABT	0.81	(0.734,0.886)	5.49	(5.166,5.834)	6.17	BMS submission[158]
LEF	1	(0.905,1.095)	5.98	(5.627,6.355)	5.98	GRPD database[159]
GST	0.48	(0.434,0.526)	1.81	(1.703,1.923)	3.91	
CyA	0.5	(0.452,0.548)	4.35	(4.094,4.623)	8.70	
AZA	0.39	(0.353,0.427)	4.35	(4.094,4.623)	15.53	

Normal distributions used for parameter a; lognormal for parameter b. Standard errors for TNF inhibitors and RTX estimated from data. For other treatments, the same proportional variability as for TNF inhibitors has been assumed. Mean team on treatment based on the point estimate of the parameters.

HAQ changes on treatment

In the reference case analysis, it is assumed that HAQ remains constant while on any biologic treatment. Mean rates of HAQ increase of 0.045/year on conventional DMARDs and 0.06/year on palliation are modelled as mean times to increase (by 0.125) of 2.7 years and 2 years respectively. In the PSA these times are sampled from normal distributions with standard deviations 0.27 years and 0.2 years respectively. Again, the times for the conventional DMARDs are sampled independently each time.

Costs

Costs are made up of drug costs plus monitoring costs. As in previous versions, the model includes an annual usage cost for each treatment, together with a "start-up" cost reflecting higher dosage and additional monitoring early in treatment, as appropriate for each treatment. Table 78 shows the unit costs for tests and visits and Table 79 the unit costs for drugs.

An administration cost of £141.83 is assumed for each dose of IFX, RTX, and ABT. This figure is inflated from the figure of £124 used in earlier versions of the BRAM. Monitoring assumptions for conventional DMARDs are shown in Table 80. It is assumed that monitoring for biologic therapies is included within the monitoring for methotrexate or administration costs, so no

additional monitoring cost is included for these. Combining the monitoring assumptions with the unit costs then leads to start-up and annual usage costs as shown in

Table 81. Note that since these costings are based on fixed prices and monitoring rules, rather than measured resource use, the prices are not varied in the probabilistic sensitivity analysis. All costs were discounted at 3.5% per annum from the start of the model.

Table 78 Unit costs for tests and visits

Test	Cost	Source
FBC	4.55	Values from Chen *et al* (2006)[153] inflated to 2008 prices using the Hospital and Community Health Services inflation index (Curtis, 2008)[160]
ESR	3.51	
BCP	4.39	
CXR	17.82	
Urinalysis	0.09	
Visit		
GP	36	Curtis (2008)[160]
Hospital outpatient	71	
Specialist nurse visit	35.50	Assumed half of outpatient visit

Table 79 Unit costs for drugs

Treatment	Cost	Assumptions
ADA	£357.50 per dose	26 doses per year
ETN	£178.75 per dose	52 doses of 50 mg per year
INF	£419.62 per vial	70 kg patient; drug wastage
RTX	£873.15 per 500mg vial	Dosage of 2×1000 mg every 8.7 months in base case
ABT	£242.17 per 250 mg	750 mg every 4 weeks
MTX	11.7p per tablet	15 mg per week
LEF	£1.70 per day	20 mg per day
GST	£11.23 per dose	50 mg ampoule administered at GP visit
CyA	£5.37 per day	225 mg per day
AZA	40.3p per day	150 mg per day

Source: BNF 58 accessed online

Table 80 Monitoring assumptions

Treatment	Pretreatment	On treatment
MTX	FBC, ESR, BCP, CXR	FBC, BCP every 2 weeks for 4 months then monthly
LEF	FBC, ESR, BCP, urinalysis	FBC every 2 weeks for 6 months, every 8 weeks thereafter. BCP monthly for 6 months, every 8 weeks thereafter.
GST	FBC, ESR, BCP, urinalysis	FBC, BCP, urinalysis every week for up to 21 injections, then every 2 weeks for 3 months, then every 3 weeks for 3 months, then monthly. Treatment given by i.m. injections
CyA	FBC, 2×BCP, ESR, urinalysis	FBC, BCP every 2 weeks for 4 months, then BCP monthly
AZA	FBC, ESR, BCP	FBC, BCP weekly for 6 weeks, then every 2 weeks for 3 visits, then monthly
Pall		Outpatient visit every 3 months

Table 81 Treatment costs

Treatment	Start-up (£)	Annual use (£)
ADA	382.03	10290.74
ETN	427.75	10290.74
IFX	1720.44	9399.88
RTX	319.75	6204.38
ABT	1188.09	12284.16
LEF	711.70	1098.42
GST	2562.08	1527.10
CyA	213.49	2859.34
AZA	479.62	1105.93
Pall	0.00	284.00

Costs for hospitalisation and joint replacement are estimated by a cost per unit HAQ score. In the base case analysis, this was set at £1120 per unit HAQ. This was inflated from the previous figure of £860 per unit included in previous versions of the BRAM. Scenario analysis includes various alternative costings here based on industry submissions.

Mortality

Basic mortality was taken from standard life tables. A relative risk per unit HAQ was applied. The point estimate for this relative risk was set to 1.33, sampling in the PSA from a lognormal distribution with 95% confidence interval (1.10,1.61).

Quality of life (QoL) scores

In the reference case analysis, a quadratic equation was used to relate HAQ score to QoL score. This was of the form $QoL = a - b_1 HAQ - b_2 HAQ^2$, where the coefficients are shown in Table 82. It is noted that this equation gives negative values (indicating a state worse than death) for high HAQ scores. While this reflects the fact that individual patients in the dataset used to generate the equation gave EQ-5D responses which map to scores below zero on the standard UK tariff, it is acknowledged that the use of negative QoL scores is controversial. Accordingly, coding was added to allow such scores to be adjusted to zero in the model. This coding was used in scenario analysis.

Table 82 Coefficients in HAQ to QoL equation

Coefficient	Point estimate	95% confidence interval
A	0.804	(0.711,0.897)
b_1	0.203	(0.054,0.351)
b_2	0.045	(-0.007,0.096)

Source: Birmingham analysis of dataset from Hurst. Note that the coefficient b2 takes a negative value in approximately 9 per cent of model replications. However, the positive value of b1 ensures that QoL decreases with increasing HAQ.

It was assumed that start and end effects could be modelled as one-off deductions proportional to the change in QoL score. The multiplier was set to a base case value of 0.2 (years), sampled from a Normal distribution with standard deviation 0.02 (separately for start and end).

Accumulated QALYs were discounted at 3.5% per annum from the starting point of the model.

6.3.2 Results

When an individual sampling model is run with a fixed parameter set, it must be run with a large number of patients to produce a precise estimate of the population mean cost and QALY differences between strategies. When such a model is run using probabilistic sensitivity analysis, the aim is to produce a distribution for the population outcomes which reflects the parameter uncertainty. This is done by sampling repeatedly from the joint distribution of parameters, and then for any parameter set, sampling a sufficient number of individuals.

Parameter set 1: $QoL = 0.7688 - 0.1723HAQ - 0.0506HAQ^2, etc$	
	Patient 1.1: Female, starting age 45.0947, starting HAQ 2.875
	Patient 1.2: Female, starting age 51.2780, starting HAQ 2.75

	Repeat up to patient 1.*M*
Parameter set 2: $QoL = 0.8209 - 0.2087HAQ - 0.0359HAQ^2, etc$	
	Patient 2.1: Female, starting age 50.6852, starting HAQ 2.625
	Patient 2.2: Female, starting age 59.4641, starting HAQ 1.625
	Repeat up to patient 2.*M*
Repeat up to parameter set *N*.	

Figure 95 shows the overall design of such a model run.

Note that a new set of patients is sampled for each parameter set, but the same patients are run through each of the possible strategies. Preliminary exploration suggested that 5000 patients per parameter set would be appropriate. For the reference case analysis, 1000 parameter sets were sampled from the parameter distributions as described in the previous section. For each parameter set, 5000 individual patient attributes were sampled and these patients were run through each of the six strategies defined in Table 72.

Parameter set 1: $QoL = 0.7688 - 0.1723HAQ - 0.0506HAQ^2, etc$	
	Patient 1.1: Female, starting age 45.0947, starting HAQ 2.875
	Patient 1.2: Female, starting age 51.2780, starting HAQ 2.75
	Repeat up to patient 1.*M*
Parameter set 2: $QoL = 0.8209 - 0.2087HAQ - 0.0359HAQ^2, etc$	
	Patient 2.1: Female, starting age 50.6852, starting HAQ 2.625
	Patient 2.2: Female, starting age 59.4641, starting HAQ 1.625
	Repeat up to patient 2.*M*
Repeat up to parameter set *N*.	

Figure 95 Running an individual sampling model under probabilistic sensitivity analysis

6.3.2.1. Reference case

The discounted lifetime costs and QALYs for each patient were calculated and the mean results for each parameter set output. The overall mean of these results forms the reference case estimate for the mean cost and QALY of each strategy: the 2.5 and 97.5 percentiles give the limits of the 95% credible interval. Note that these percentiles are likely to come from different parameter sets not just between strategies, but also for costs and QALYs for any particular strategy. These results are shown in Table 83. In each case, the lower credible limit for QALYs is negative,

reflecting the use of an equation which allowed negative quality of life scores; see the scenario analysis for the effect of changing this assumption.

Table 83 Results for single strategies in reference case analysis

Treatment	Mean Cost	95% Credible Interval		Mean QALY	95% Credible Interval	
ADA	74500	68400	80500	2.89	-2.25	7.74
ETN	74800	68700	81200	2.81	-2.29	7.75
IFX	72800	65900	79500	2.81	-2.44	7.73
RTX	69100	62400	76300	3.10	-1.91	7.88
ABT	92800	86000	99900	3.28	-1.67	7.96
DMARDs	48800	43100	54600	2.14	-3.47	7.39

Incremental results were obtained by subtraction for each parameter set, thus producing a sample of 1000 points from the incremental cost-effectiveness distribution between any pair of strategies. Again, the 95% credible interval can be found for cost and QALY differences: note that although the mean results can be inferred from the previous part of the table (subject to rounding effects), the relevant percentiles cannot. The results are shown in Table 83, which shows all pairwise comparisons. Scatterplots for the comparisons between the biologic strategies and conventional DMARDs alone are shown in Figure 96, together with the cost-effectiveness acceptability curves for these five comparisons: the remaining scatterplots are in Appendix 1.1.

Table 84 Differences between strategies in reference case analysis

Comparison	Diff Cost	95% Credible Interval		Diff QALY	95% Credible Interval	
ADA - DMARDs	25700	24000	27500	0.75	0.33	1.21
ETN - DMARDs	26000	24200	27900	0.67	0.30	1.11
IFX - DMARDs	24000	19300	26700	0.66	0.27	1.09
RTX - DMARDs	20300	17600	23000	0.96	0.39	1.58
ABT - DMARDs	44000	41100	46700	1.14	0.51	1.86
ADA - RTX	5300	2200	8600	-0.21	-0.51	0.03
ETN - RTX	5600	2500	9000	-0.29	-0.61	-0.04
IFX - RTX	3600	-1400	7400	-0.29	-0.61	-0.04
ABT - RTX	23600	19900	27400	0.18	-0.09	0.48
ADA - ABT	-18300	-21500	-15200	-0.39	-0.77	-0.11
ETN - ABT	-18000	-21300	-14400	-0.47	-0.86	-0.17
IFX - ABT	-20000	-25100	-16000	-0.48	-0.87	-0.17
ADA - ETN	-300	-2900	2200	0.08	-0.10	0.29
ADA - IFX	1700	-1500	6500	0.09	-0.11	0.29
ETN - IFX	2000	-1300	6700	0.01	-0.16	0.20

Diff = difference, calculated by subtracting the value for the strategy named second from the value for the strategy named first.

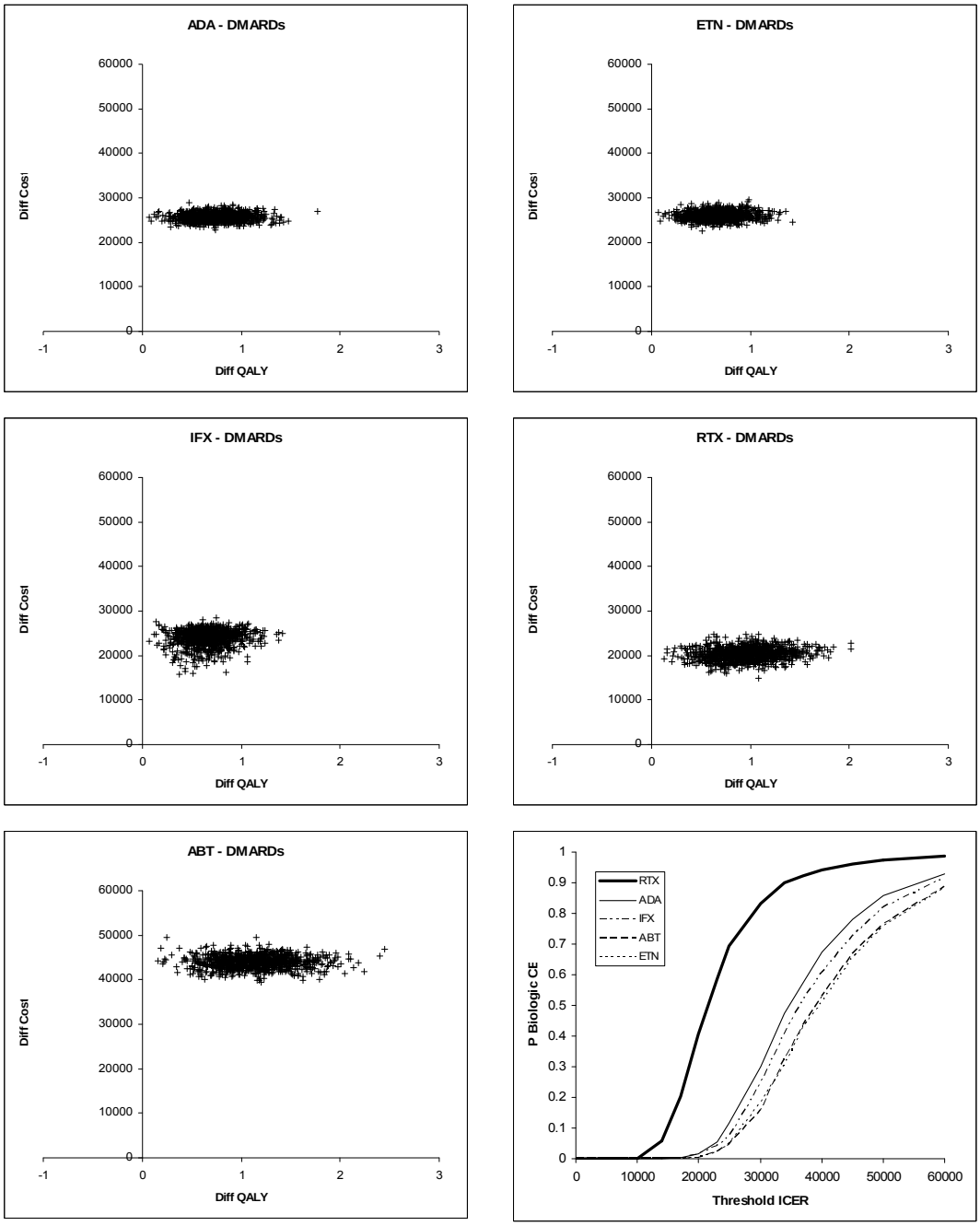


Figure 96 Cost-effectiveness scatterplots for main comparisons in the reference case

Similar remarks apply to the incremental cost-effectiveness ratio (ICER), which is found by dividing the difference in mean cost by the difference in mean QALY. Finally, the proportion of model replications for each biologic strategy appears cost-effective compared to any other is

shown, using a threshold ICER of £20,000/QALY and £30,000/QALY. These results are shown in Table 85.

Table 85 ICERs for reference case analysis

Comparison	ICER	95% Credible Interval		Proportion of cases CE at £20,000/QALY	Proportion of cases CE at £30,000/QALY
ADA - DMARDs	34300	21200	78900	0.02	0.30
ETN - DMARDs	38800	23500	88700	0.00	0.18
IFX - DMARDs	36200	21500	83100	0.02	0.25
RTX - DMARDs	21200	12800	52000	0.41	0.83
ABT - DMARDs	38600	23200	85700	0.00	0.16
ADA - RTX	RTX	Not meaningful		0.00	0.00
ETN - RTX	RTX	Not meaningful		0.00	0.00
IFX - RTX	RTX	Not meaningful		0.00	0.00
ABT - RTX	131000	49800	RTX	0.00	0.00
ADA - ABT	*47000*	*23600*	*156200*	0.99	0.90
ETN - ABT	*38400*	*20100*	*103400*	0.98	0.79
IFX - ABT	*42100*	*22400*	*114400*	0.99	0.84
ADA - ETN	ADA	Not meaningful		0.83	0.84
ADA - IFX	19900	Not meaningful		0.52	0.63
ETN - IFX	320000	Not meaningful		0.21	0.25

CE = cost-effective. The proportion of cases cost-effective relates to the strategy given first on each line. ICER in italics means that the strategy named second is more costly and more effective. Where a strategy name is given in place of an ICER, the named strategy dominates its comparator (less costly and more effective). A 95% credible interval for the ICER is not meaningful in cases where the cost-effectiveness scatterplot is not confined to one half of the plane.

6.3.2.2. Scenario analysis

A number of different scenarios have been run. Details of each scenario and the results are in Appendix 10.14, and a summary is in Table 86, Table 87 and Table 88. It should be noted that although it is always possible to give a result based on the mean of the probabilistic analysis, the results for comparison between TNF inhibitors invariably are from a distribution covering all four quadrants of the cost-effectiveness plane, and thus the mean results are subject to enormous uncertainty in that case.

Table 86 Results from scenario analysis: Comparisons against DMARDs strategy (ICER in £/QALY)

Scenario	ADA - DMARDs	ETN – DMARDs	IFX - DMARDs	RTX - DMARDs	ABT - DMARDs
Reference	34300	38800	36200	21200	38600
Vary time on TNF inhibitors	34400	38500	37700	21300	38700
Same time on all biologics	34400	38700	35900	21100	39600
RTX cycle time 6 months	34400	38800	35800	32700	38600
RTX cycle time 11.6 months	34200	38800	35900	14800	38500
HAQ change on biologics	60500	75400	68600	45300	62700
Adverse event costs included	34800	39800	36900	22600	39100
No negative QoL scores	48400	56200	51900	30600	52900
Linear equation HAQ to QoL	38400	43500	40500	23600	42300

ICER in italics means that the strategy named second is more costly and more effective. Where a strategy name is given in place of an ICER, the named strategy dominates its comparator (less costly and more effective). Small variations in results where neither strategy had changed parameters reflect the first and second order sampling in the model.

Table 87 Results from scenario analysis: Comparisons of other biologics against RTX (ICER in £/QALY)

Scenario	ADA - RTX	ETN – RTX	IFX - RTX	ABT - RTX
Reference	RTX	RTX	RTX	131100
Vary time on TNF inhibitors	RTX	RTX	*4200*	132100
Same time on all biologics	202000	RTX	RTX	131100
RTX cycle time 6 months	*1200*	RTX	*15100*	51800
RTX cycle time 11.6 months	RTX	RTX	RTX	736300
HAQ change on biologics	RTX	RTX	RTX	96200
Adverse event costs included	RTX	RTX	RTX	126700
No negative QoL scores	RTX	RTX	RTX	142000
Linear equation HAQ to QoL	RTX	RTX	RTX	131800

ICER in italics means that the strategy named second is more costly and more effective. Where a strategy name is given in place of an ICER, the named strategy dominates its comparator (less costly and more effective).

Table 88 Comparisons between biologics other than RTX (ICER in £/QALY)

Scenario	ADA - ABT	ETN - ABT	IFX - ABT	ADA - ETN	ADA - IFX	ETN - IFX
Reference	*47000*	*38400*	*42100*	ADA	19900	320000
Vary time on TNF inhibitors	*48200*	*39600*	*39500*	*72300*	28800	39000
Same time on all biologics	*85400*	*43300*	*54900*	ADA	21900	561000
RTX cycle time 6 months	*46700*	*38400*	*42600*	ADA	22100	888000
RTX cycle time 11.6 months	*46900*	*38200*	*42300*	ADA	20800	833000
HAQ change on biologics	*66200*	*50300*	*56800*	ADA	21900	IFX
Adverse event costs included	*47200*	*37900*	*42100*	ADA	18400	353000
No negative QoL scores	*60900*	*48900*	*54200*	ADA	24600	2420000
Linear equation HAQ to QoL	*49300*	*40500*	*44600*	ADA	22400	301000

ICER in italics means that the strategy named second is more costly and more effective. Where a strategy name is given in place of an ICER, the named strategy dominates its comparator (less costly and more effective). Small variations in results where neither strategy had changed parameters reflect the first and second order sampling in the model. It should be stressed that the comparisons between TNF inhibitors are based in each case on the mean values from a distribution which covers all four quadrants of the cost-effectiveness plane.

6.3.2.3. Summary of model results

The reference case model results show similar costs and QALYs for the TNF inhibitors, with somewhat lower costs and QALYs for rituximab and higher costs and QALYs for abatacept. Compared to conventional DMARDs alone, the incremental cost-effectiveness ratio for rituximab is somewhat lower than for the other biologics. Rituximab dominates the TNF inhibitors (lower cost and more QALYs). The ICER for abatacept compared to rituximab is over £100,000/QALY. These results are subject to considerable uncertainty. Important drivers of that uncertainty were found in the scenario analysis to include:

- the assumptions about HAQ progression on biologic treatments;
- the equation relating HAQ to quality of life – in particular whether negative quality of life scores can be allowed;

- for comparisons involving rituximab, the assumed time between treatments.
- The inclusion of adverse event costs for biologic therapy made little difference to the results.

7 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Wide use of biologic agents, NICE guidance on RA and the recent NAO report on services for patients with RA have profound implications for specialist rheumatology services. The NAO report suggests that acute trusts and primary care trusts have not yet met all the challenges they face. For example monthly review in patients with active disease, as recommended in NICE guidance, is only achieved by 15% of acute trusts surveyed by the NAO. Main barriers reported by trusts were: staffing; limited outpatient capacity; and pressures to improve the ratio of follow up to new patients. A majority of acute trusts reported that they were unable to provide adequate follow up for RA patients.[6] Models of shared care between primary care and secondary care exist but only around half of the GPs in the NAO survey said that they had a shared care agreement with their local acute trust.[161] Good shared care schemes with appropriate patient selection[69,162] could reduce the burden on specialists and meet some of the objectives set out in Lord Darzi's review.[163]

Increasing use of biologics, different mechanisms for obtaining funding (including appeals processes and inconsistency of response) for different PCTs and collection and submission of audit data have increased the administrative burden on specialist departments. PCTs have parallel demands with a need to monitor high cost drug use, manage the implications of burgeoning NICE guidance and increasing demands from patients and hospital doctors with varying approaches to disease management. Expert teams remain vital to the delivery of services for RA patients but pressures to provide community clinics in many locations risks fragmenting small teams and diluting expertise. Increasing complexity of care driven by new agents and more aggressive disease management means that primary care physicians are less able to take a lead role in the management of individual patients.[161] Also, the fact that prescriptions for biologics can only be issued by a specialist, means that even better links between primary and secondary care colleagues are needed to coordinate care and avoid drug interactions.

Abatacept and tocilizumab both require monthly intravenous infusions. Currently such treatment is delivered largely in a hospital day-case unit. Capacity is under pressure as newer agents arrive and indications for existing agents widen. Solutions to improve capacity are needed. It seems likely that periodic intravenous infusions, required long term, will be administered away from acute hospitals and within patients' homes or other community settings. Pilot studies exploring infliximab infusions at home in stable clients are underway.

In summary, it is imperative that acute trusts and PCTs are better placed to meet the challenges of therapeutic innovations in RA and the deficiencies of care identified by the NAO.

8 DISCUSSION

8.1 Statement of principle findings

8.1.1 Quantity and quality of evidence

Thirty-five studies described in 44 papers met the inclusion criteria. These included five RCTs, three comparative studies and 28 uncontrolled studies. Comparisons made in the included RCTs were: switching to infliximab (from ongoing etanercept) versus ongoing etanercept (OPPOSITE trial, n=27)[131]; rituximab versus placebo with ongoing traditional DMARDs (REFLEX trial, n=517) [122-124]; abatacept versus placebo with ongoing traditional DMARDs (ATTAIN trial, n=391) [125,126 127-130]; abatacept added to ongoing etanercept versus ongoing etanercept (Weinblatt 2007, n=121)[41]; abatacept added to ongoing biologics or non-biologic DMARDs versus ongoing biologics or non-biologic DMARDs (ASSURE trial, n=167). [133] No directly relevant head-to-head trial directly comparing any of the five technologies against each other, or directly comparing any of the technologies against other biologics or previously untried, newly initiated DMARDs was found.

8.1.2 Effectiveness of adalimumab

No RCT was identified. Five uncontrolled studies with duration of follow–up ranging from 3 to 12 months showed that between 46% to 75% of patients achieved ACR20 and 13% to 33% patients achieved ACR70. Mean reductions of 1.3 to 1.9 in DAS28 score and of 0.21 to 0.48 in HAQ score were observed. Results were not pooled due to substantial clinical and statistical heterogeneity.

8.1.3 Effectiveness of etanercept

No RCT was found. Seven uncontrolled studies with duration of follow-up ranging from 3 months to over 9 months showed that ACR20 was achieved in 37% to 71% of patients after switching to etanercept, ACR70 in 4% to 21% of patients. Mean reductions of 0.47 to 1.80 in DAS28, and of 0.35 to 0.45 in HAQ score were observed. Results were not pooled due to substantial clinical and statistical heterogeneity between studies.

8.1.4 Effectiveness of infliximab

One RCT (OPPOSITE trial) compared switching to infliximab (n=13) versus staying on etanercept (n=14) in patients who had incomplete response to etanercept. The study was considered not directly relevant to this report. Three uncontrolled studies with unclear length of follow-up were found but none of these reported ACR response criteria or quantitative results of changes in DAS28 and HAQ scores.

8.1.5 Effectiveness of TNF inhibitors as a class

Some of the included studies assessed switching to an alternative TNF inhibitor but did not provide data separately for individual TNF inhibitors. Two non-randomised comparative studies and six uncontrolled studies with duration of follow-up ranging from 3 months to 4 years were identified. ACR resposnses were reported in only one study, with response rates of 49% for ACR20 and 7% for ACR70 being observed. Reported mean reductions in DAS28 score ranged from -0.88 to -1.00. Only one study (using data from BSRBR) reported mean reduction in HAQ score of -0.11.

8.1.6 Effectiveness of rituximab

One good quality RCT (REFLEX) compared rituximab to placebo (with onging DMARDs in both groups) in patients who have had inadequate response to one or more TNF inhibitor. At 6 months significantly more patients treated with rituximab achieved ACR20 (RR=2.85, 95%CI 2.08 to 2.91) and ACR70 (RR=12.14, 95% CI 2.96 to 49.86) compared to those treated with the placebo. Significant differences between groups in favour of rituximab were observed at 6 months for mean change from baseline in DAS28 score (mean difference -1.50, 95% CI -1.74 to -1.26) and mean change from baseline in HAQ score (mean difference -0.30, 95% CI -0.40 to -0.20). No significant difference in the risk of servious adverse events and serious infections were observed. One non-randomised comparative study, five uncontrolled studies and two further analyses of data from rituximab RCTs were also identified. Results generally supported findings from the REFLEX trial.

8.1.7 Effectiveness of abatacept

One good quality RCT (ATTAIN) compared atatacept to placebo (with onging DMARDs in both groups) in patients who have had inadequate response to one or more TNF inhibitor. At 6 months significantly more patients treated with abatacept achieved ACR20 (RR=2.56, 95%CI 1.77 to 3.69) and ACR70 (RR=6.70, 95% CI 1.62 to 27.80) compared to those treated with the placebo. Significant differences between groups in favour of abatacept were observed at 6 months for mean change from baseline in DAS28 score (mean difference -1.27, 95% CI -1.62 to -0.93) and mean change from baseline in HAQ score (mean difference -0.34, insufficient data for calculating 95%CI). No significant difference in the risk of servious adverse events and serious infections was observed. Further data from the long-term extension of the ATTAIN trial and a large prospective uncontrolled study (ARRIVE) generally supported findings from the ATTAIN trial. Two further RCTs (Weinblatt 2007[132] and ASSURE[133]) were identified that compared abatacept added to ongoing TNF inhibitors/biologics versus ongoing TNF inhibitors/biologics. Results from these trials showed patients who received a combination of abatacept and a TNF inhibitor had increased risk of infection and serious infection. This is reflected in the licensed indication which advises against the use of such combination therapy and thus further data from combination therapy were not assessed in this report.

8.1.8 Comparative effectiveness

No RCT provided evidence on genuine head-to-head comparisons between the technologies, other biologics and newly initiated, previously untried DMARDs. One non-randomised controlled study (Finckh 2009[134,135]) compared switching to rituximab versus switching to an alternative TNF inhibitor. The mean change in DAS28 score was greater in the rituximab group compared to the TNF inhibitor group (mean difference -0.35, 95%CI -0.71 to 0.01; median follow-up 11 months) but the difference just failed to reach statistical significance.

It was possible to carry out adjusted indirect comparison between rituximab and abatacept using data from placebo controlled trials which included similar patient populations. The results showed no evidence of significant difference in their effectiveness (ACR20 for rituximab vs abatacept, RR=1.12, 95% CI 0.68 to 1.84). No further analyses for comparative effectiveness were performed due to limitation in available data.

8.1.9 Subgroup analyses

Evidence from the REFLEX trial suggested that the effectiveness of rituximab does not vary significantly according to reasons of withdrawal, baseline RF status and number of prior TNF inhibitors tried (one vs. more than one).

No significant differences in the effectiveness of abatacept between subgroups defined by the number of prior TNF inhibitor (one vs two) and the identity of the prior TNF inhibitor received (etanercept vs infliximab) were observed in the ATTAIN trial. Some of these subgroup analyses however may be under-powered.

Evidence from observational studies showed that the proportion of patients responding to a subsenquent TNF inhibitor may vary according to reason of withdrawal of the previous TNF inhibitor (higher response in patients who withdrew due to intolerance/adverse events compared to those withdrew due to lack of efficacy). The proportion of patients who respond to a subsequent treatment (including TNF inhibitors, rituximab and abatacept) decreases as the number of prior TNF inhibitor(s) that the patients have tried increases.

8.1.10 Review of cost-effectivenss studies

Four studies met inclusion criteria. All studies used a decision-analytic model. Published models vary in some important aspects: the type of model used, the sequence of drugs, comparator therapies, and time-horizon. All but one studies carried out a cost-utility analysis and reported results in 'cost per QALY'. One study carried out a cost-effectiveness analysis and reported results in cost per additional case of 'low disease-activity state' gained (DAS28<2.6) and cost per additional remission gained (DAS28≤3.2). Appropriate sensitivity analyses were carried out in all studies. A comparison of ICERs between studies is not possible because of different approaches to modelling, in particular time-horizon, country of origin and perspective chosen. There was disparity in the selection of perspectives chosen for the analyses. One study reported costs that include both those from a healthcare perspective as well as indirect costs and costs of informal care; inclusion of these costs improves the cost-effectiveness of the drug.

8.1.11 Independent modelling

The reference case model results show similar costs and QALYs for the TNF inhibitors, with somewhat lower costs and QALYs for rituximab and higher costs and QALYs for abatacept. Compared to conventional DMARDs alone, the incremental cost-effectiveness ratio for rituximab is somewhat lower than for the other biologics. Rituximab dominates the TNF inhibitors and the ICER for abatacept compared to rituximab is over £100,000/QALY. These results are subject to considerable uncertainty. Important drivers of that uncertainty were found in scenario analysis to include:

- the assumptions used about HAQ progression on biologic treatments;
- the equation relating HAQ to quality of life – in particular whether negative quality of life scores can be allowed;
- for comparisons involving rituximab, the assumed time between treatments.

The inclusion of adverse event costs for biologic therapy made little difference to the results.

8.2 Strengths and limitations of the assessment

8.2.1 Strengths of the assessment

The strengths of this assessment include:

- A comprehensive literature review was undertaken which went beyond RCT evidence. Studies were selected and assessed according to a pre-specified protocol. Additional data from manufacturers' submissions were included.
- Key data were graphically presented in a systematic way to allow easy inspection of variations between studies.
- Detailed subgroup analyses were carried out to examine factors that may influence the effectiveness of the technologies.
- The BRAM model has been further improved and modelling was carried out on various scenarios to explore uncertainties.

8.2.2 Limitation of the assessment

The limitations predominantly relate to factors outside of the control of the Assessment group. The major limitation of the assessment was the paucity of evidence from RCTs for assessing the clinical effectiveness of the three TNF inhibitors, and a complete absence of genuine head-to-head trials comparing the five technologies against each other, against other biologics or against newly initiated, previously untried DMARDs.

Given the paucity of RCT evidence, this report assessed data from observational studies which are more prone to potential bias. Most of the included studies were uncontrolled studies, which only allow the assessment of treatment response post intervention compared to before intervention. Such comparisons do not adjust for the natural course of the disease, hence any observed responses could be attributed to possible effects of the treatment as well as other factor such as different methods of follow-up and data collection, data imputation and regression to the mean for example.

As registration of observational study is not mandated, they are more prone to publication bias. In addition, the reporting of outcomes varies widely between studies, and the scope for selective reporting of outcomes is substantial. These biases are difficult to assess.

The focus of this assessment was on the patient population who have had inadequate response to a first TNF inhibitor. Many existing studies have included patient populations who withdrew from the previous TNF inhibitor due to adverse events/intolerance and/or who had already tried more than one TNF inhibitors. The subgroup analysis suggests these factors may influence the proportion of patients who respond to subsequent treatments but this does not necessarily translate into differential effectiveness measured as relative risk or risk difference. Furthermore, there is much less evidence to allow assessment of whether the magnitude of effects varies between subgroups in those patients who do respond. These require further research.

8.3 Uncertainties

Lack of good quality evidence on effectiveness for the use of an alternative TNF inhibitor after patients had an inadequate response is the source of major uncertainty for this assessment. For the assessment of cost-effectiveness, lack of evidence assessing the effectiveness of previous untried traditional DMARDs in this patient population is also an important source of uncertainty.

Additional areas of uncertainty identified in the independent modelling include assumptions about HAQ progression on biologic treatments; whether negative quality of life scores can be allowed when estimating quality of life from HAQ score, and treatment interval between courses of rituximab.

9 CONCLUSIONS

9.1 Implications for service provision

In relation to the decision problems described in Section 4, the findings of this assessment report suggest:

1. There is lack of good quality evidence directly comparing the effectiveness of the five technologies against each other. This imposes significant uncertainties with regard to any assessment of their relative cost-effectiveness. Adjusted indirect comparison suggests there is no significant difference in the effectiveness between rituximab and abatacept, both of which are supported by good quality RCT evidence. Existing data do not allow reliable quantification of the effectiveness of TNF inhibitors compared to rituximab and abatacept. Independent modelling comparing each of the other four technologies to rituximab (recommended in current NICE guidance) suggests rituximab dominating adalimumab, etanercept and infliximab, and an estimated ICER of £131,000 (per QALY) for abatacept compared to rituximab.

2. There is lack of evidence comparing the effectiveness of the five technologies to a newly intitated, previously untried DMARDs. Independent modelling based on certain assumptions suggest the following ICERs: £34,300 (per QALY) for adalimumab, £38,800 for etanercept, £36,200 for infliximab, £21,200 for rituximab, and £38,600 for abatacept.

3. There is lack of evidence directly comparing the effectiveness of the five technologies to other biologic agents.

4. Good quality evidence from RCTs suggests rituximab and abatacept are more effective compared to supportive care (including ongoing DMARDs which had provided inadequate control of the disease). Data from observational studies suggest the use of an alternative TNF inhibitor after patients had inadequate response to a first TNF inhibitor may offer some benefit, but there remain significant uncertainties with regard to the magnitude of treatment effects and how these translate into cost-effectiveness.

5. Good quality evidence from RCTs does not suggest differential effectiveness between various subgroups for rituximab and abatacept.

9.2 Suggested research priorities

The following research priorities are suggested in view of findings of this assessment:

- Head-to-head trials of adequate size and duration comparing the effectiveness and cost-effectiveness of the technologies against each other and emerging biologics.
- Good quality studies collecting information on the effectiveness and cost-effectiveness of the technologies compared to previously untried coventional DMARDs in this patient population.
- Further analysis and synthesis of existing and future RCT data to quantify the potential impact of reasons for withdrawal of first TNF inhibitor and the history of prior exposure to TNF inhibitor(s).
- An overarching synthesis of evidence for the effectiveness of treatment mordalities that can be used in various places of the treatment pathway for RA.

10 APPENDICES

10.1 Details of key outcomes used in RA trials

The Health Assessment Questionnaire (HAQ)

The HAQ now comprises a family of questionnaires designed to assess the functional capacity of patients with musculoskeletal complaints and specifically RA. The most widely used HAQ is derived from the Stanford Health Assessment Questionnaire[164] and consists of 2 or 3 questions in 8 categories:

- Dressing and grooming: dress yourself, including doing shoelaces, and shampooing your hair
- Rising: from an armless chair and in and out of bed
- Eating: being able to cut meat, lift a full cup or glass to mouth, and open a new carton of milk
- Walking: outdoors on flat ground and climb 5 steps
- Hygiene: wash and dry entire body, take a bath, get on and off the toilet
- Reaching: reach and get down a 5lb object, bend down and pick up clothing
- Grip: open car doors, open previously unopened jars, turn taps on and off
- Activities: run errands and shop, get in and out of car, do chores

The score from the most limited activity in each category is obtained. Each category is scored 0 (without any difficulty), 1 (with some difficulty), 2 (with much difficulty), or 3 (unable to do). Use of aids or devices to help with function is taken into account so that need for such assistance automatically scores 2 (unless 3 has been ticked). The maximum score in each of the 8 categories is added to give a maximum possible score of 24. This total score may be divided by 8 to give an average value in the range 0 to 3.

HAQ has several modifications:[40]

- Modified HAQ (MHAQ): is a shortened version of HAQ which uses only one question in each of the 8 categories and does not consider the use of aids and devices to assist function. It is simpler to score and has the same range as HAQ (0 to 3).
- RA-HAQ: is another shortened version of HAQ designed to overcome some of the metric limitations of MHAQ. .
- DHAQ: This uses the original 8 categories of HAQ but is based on the most difficult items in each of the categories. Neither the RA-HAQ nor DHAQ have been widely used, unlike MHAQ.

American College for Rheumatology Response Criteria[165]

In order to achieve an ACR20 response a 20% improvement in the score for tender joints and a 20% improvement in swollen joints is necessary and 20% improvement in at least 3 of the following:

- global disease activity assessed by observer
- global disease activity assessed by patient
- patient assessment of pain
- physical disability score (e.g. HAQ)
- acute phase response (e.g. ESR or CRP)

Responses may also be defined as ACR50 (50%) or ACR70 (70%) depending on degree of benefit.

ACR-N is an extension of the ACR response criteria, and is defined as the lowest of the following three values:

- Percentage change in the number of swollen joints
- Percentage change in the number of tender joints
- The median of the percentage change in the other five measures listed above

It is thus a continuous variable. For example, a patient with an ACR-N of 38 means an improvement of at least 38% in tender and swollen joint counts and an improvement of at least 38% in three of the five other parameters.[166]

Disease Activity Score (DAS)

Original DAS

DAS = 0.54(√RAI*) + 0.065(total number of swollen joints out of 44) + 0.33(ln ESR) + 0.0072(patient general health score where 0=best, 100=worst)

*RAI refers to a graded score of joint tenderness for 53 joints known as the Ritchie Articular Index.

Disease activity score based on 28 joint evaluations

DAS 28-4 = 0.56(√TJC28) + 0.28(√SJC28) + 0.7ln(ESR) + 0.014(patient general health score where 0=best, 100=worst)

Where scores for general health are not available, or not measured, the following formula is used:

DAS 28-3 = [0.56(√TJC28) + 0.28(√SJC28) + 0.7ln(ESR)]1.08 + 0.16

European League Against Rheumatism (EULAR) response criteria[167]

The EULAR response criteria are based on the DAS score. They incorporate both change from baseline and DAS or DAS28 at endpoint and based on both classify patients as good, moderate or non-responders (see Table 89).

Table 89 The EULAR response criteria using DAS and DAS28

DAS at endpoint	DAS28 at endpoint	Improvement in DAS or DAS28 from baseline		
		≤1.2	>0.6 and ≤ 1.2	≤0.6
≤2.4	≤3.2	good		
>2.4 and ≤3.7	>3.2 and ≤5.1		Moderate	
>3.7	>5.1			none

Radiographic Assessment Methods[168]

Sharp Score

The simplified Sharp system,[169] that evaluates hand and wrist images, assesses 17 areas for erosions and 18 areas for joint space narrowing. Each joint is scored on a 6-point scale as follows: 0 = no erosion; 1 = discrete erosion; 2 = two separate quadrants with erosions or 20-40% joint involvement; 3 = 3 separate quadrants with erosions or 41-60% joint involvement; 4 = all four quadrants with joint erosion or 61-80% joint involvement; and 5 = extensive destruction with >80% joint involvement. The range of erosion scores for a patient with two hands and wrists is 0 to 170. For joint space narrowing each joint is scored using a 5-point scale as follows: 0 = no narrowing; 1 = up to 25% narrowing; 2 = 26-65% narrowing; 3 = 66-99% narrowing; 4 = complete narrowing. The range for joint space narrowing is therefore 0 to 144. This gives a total joint score in the range 0 to 314.

Van der Heijde modified Sharp score

In this case 16 joints are assessed in each hand and wrist and 6 joints in each foot. Erosions are scored 0 to 5 and depending on the affected surface area and 0 to 10 in the feet yielding possible erosion scores of 0 to 160 for hands/wrists and 0 to 120 for feet (total 0 to 280). Joint space narrowing is assessed in 15 joints for each hand/wrist and 6 joints in each foot on a scale of 0 to 4. The range of possible JSN scores is in the range 0 to 168. This yields a possible total score in the range 0 to 448.[170]

The Larsen Score

In this method standard films are used to classify each joint into one of 6 possible categories (0 = normal, 5 = severely damaged). Any joint may be scored but the focus is on hands and feet. In the hands each proximal interphalangeal joint and each metacarpophalangeal joint scores 0 to 5; each wrist joint scores 0 to 25 (the basic score is multiplied by 5): this gives a maximum score of 150 for two hands and wrists. In the feet each metatarsophalangeal joint is scored 0 to 5, giving a total score of 50 for two feet. This yields a possible total score in the range 0 to 200.

Scott modified Larsen[171]

Scott and colleagues suggested minor modifications to the scale in order to improve correlation between scorers. It was proposed that grade 1 included erosions and cysts of <1 mm diameter and grade included one or more erosions of >1mm diameter.

10.2 Literature search strategies

Source – Cochrane Library (CENTRAL, DARE and NHS EED) 2009 Issue 3

#1 rheumatoid next arthritis
#2 MeSH descriptor Arthritis, Rheumatoid explode all trees
#3 (#1 OR #2)
#4 adalimumab or humira
#5 etanercept or enbrel
#6 infliximab or remicade
#7 rituximab or mabthera
#8 abatacept or orencia
#9 (#4 OR #5 OR #6 OR #7 OR #8)
#10 (#3 AND #9)

Source – MEDLINE (Ovid) 1950 – July Week 1 2009

1 rheumatoid arthritis.tw. (58668)
2 arthritis rheumatoid/ (68937)
3 or/1-2 (83478)
4 (adalimumab or humira).mp. (1199)
5 (etanercept or enbrel).mp. (2138)
6 (rituximab or mabthera).mp. (5052)
7 (abatacept or orencia).mp. (1779)
8 (infliximab or remicade).mp. (4830)
9 or/4-8 (13083)
10 3 and 9 (2759)

Source - MEDLINE(Ovid) In-Process & Other Non-Indexed Citations July 13, 2009

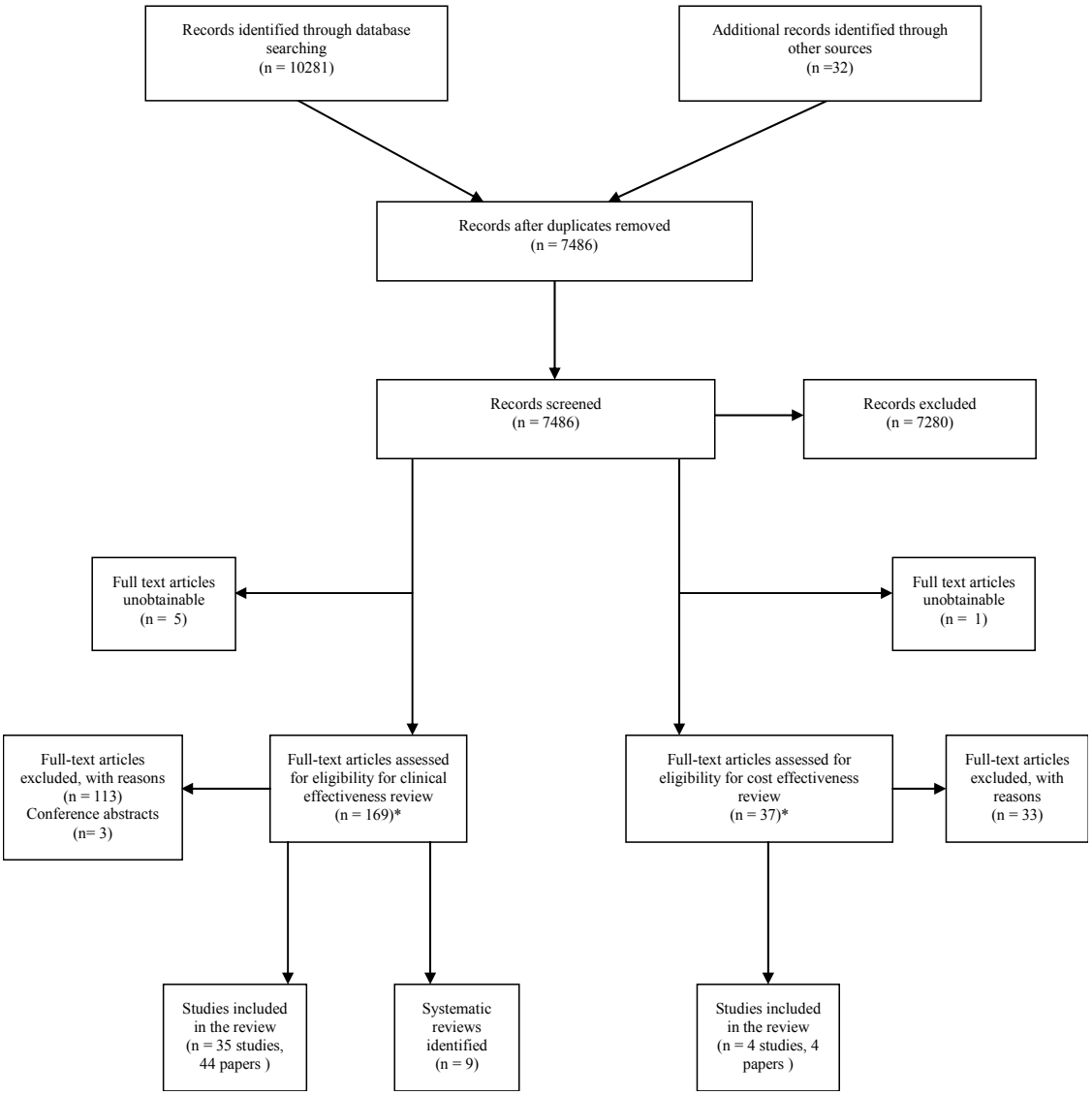
1 (adalimumab or humira).mp. (129)
2 (etanercept or enbrel).mp. (203)
3 (rituximab or mabthera).mp. (455)
4 (abatacept or orencia).mp. (39)
5 (infliximab or remicade).mp. (346)
6 or/1-5 (990)
7 rheumatoid arthritis.tw. (1987)
8 6 and 7 (220)

Source - EMBASE (Ovid) 1980 to 2009 Week 28

1 (adalimumab or humira).ti,ab,sh. (4120)
2 (etanercept or enbrel).ti,ab,sh. (8362)
3 (rituximab or mabthera).ti,ab,sh. (12634)
4 (abatacept or orencia).ti,ab,sh. (1014)
5 (infliximab or remicade).ti,ab,sh. (12117)
6 or/1-5 (26879)
7 rheumatoid arthritis/ (59837)

8 rheumatoid arthritis.tw. (47871)
9 7 or 8 (68003)
10 6 and 9 (6262)

10.3 Flow diagram



* one paper was ordered for both clinical and cost effectiveness

10.4 Clinical effectiveness -table of excluded studies with rationale

Article	reason for exclusion
Prior lack of efficacy with etanercept does not predict lack of efficacy with infliximab. *Formulary* 2005; 40(3):93.	design
Abatacept: Rheumatoid arthritis: After failure of TNF alpha antagonists and rituximab. *Prescrire International* 2008; 17(98):232.	design
[Fusion protein abatacept. Remission in every 5th TNF-alpha refractory patient]. [German]. *MMW Fortschritte der Medizin* 2008; 150(26-27):56-57.	design
The COMET study: High remission rate through the use of etanercept in early rheumatoid arthritis. [German]. *Arzneimitteltherapie* 2008; 26(11):434-435.	population
Alexander W, Han C, Giles J. American College of Rheumatology Scientific Meeting. ASPIRE: Infliximab (Remicade) plus methotrexate for rheumatoid arthritis. *P and T* 2009; 34 (1):37.	population
Allison C. Abatacept as add-on therapy for rheumatoid arthritis (DARE structured abstract). *Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA)* 2005;4.	Design
Allison C. Abatacept as add-on therapy for rheumatoid arthritis. *Issues in Emerging Health Technologies* 2005;(73):1-4.	design

Article	reason for exclusion
Alonso-Ruiz A, Pijoan J, I, Ansuategui E, Urkaregi A, Calabozo M, Quintana A. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety (DARE structured abstract). *BMC Musculoskeletal Disorders* 2008; 9:52.	population
Alten R. Costimulation with Abatacept - A new and successful therapeutic principle in rheumatoid athritis. Part 2: Efficacy and safety of Abatacept. [German]. *Aktuelle Rheumatologie* 2007; 32(5):271-277.	Design
Alten R, Musch A. Abatacept in patients with rheumatoid arthritis. [German]. *Arzneimitteltherapie* 2008; 26(1):9-16.	design
Arenere MM, Navarro AH, Cilveti SU, Allende BM, Rabanaque HM, Arrieta NR, *et al*. Etanercept use in rheumatoid arthritis patients treated previously with infliximab. [Spanish]. *Atencion Farmaceutica* 2005; 7(6):465-469.	Participant number
Assous N, Gossec L, Dougados M, Kahan A, Allanore Y. Efficacy of rituximab in patients with rheumatoid arthritis refractory or with contra-indication to anti-tumor necrosis factor-alpha drugs in daily practice: An open label observational study [3]. *Clinical and Experimental Rheumatology* 2007; 25(3):504.	Participant number
Baumgartner SW, Fleischmann RM, Moreland LW, Schiff MH, Markenson J, Whitmore JB. Etanercept (Enbrel) in patients with rheumatoid arthritis with recent onset versus established disease: Improvement in disability. *Journal of Rheumatology* 2004; 31(8):1532-1537.	population
Bazzani C, Filippini M, Caporali R, Bobbio-Pallavicini F, Favalli EG, Marchesoni A, *et al*. Anti-TNFalpha therapy in a cohort of rheumatoid arthritis patients: Clinical outcomes. *Autoimmunity Reviews* 2009; 8(3):260-265.	population

Article	reason for exclusion
Bernal RL, Guerrero A, Monzon MA, Beltran GM, Hernandez CB, Colmenero MA. Effectiveness and safety of adalimumab and etanercept for rheumatoid arthritis in a third-level hospital. [Spanish]. *Farmacia Hospitalaria* 2006; 30(4):223-229.	population
Blank N, Max R, Schiller M, Briem S, Lorenz H-M. Safety of combination therapy with rituximab and etanercept for patients with rheumatoid arthritis. *Rheumatology* 2009; 48(4):440-441.	Participant number
Blumenauer Barbara BTB, Judd M, Wells GA, Burls A, Cranney A, Hochberg MC, *et al.* Infliximab for the treatment of rheumatoid arthritis. Cochrane Database of Systematic Reviews: Reviews. Cochrane Database of Systematic Reviews 2002 Issue 3. Chichester (UK): John Wiley & Sons, Ltd; 2002.	population
Blumenauer Barbara BTB, Cranney A, Burls A, Coyle D, Hochberg MC, Tugwell P, *et al.* Etanercept for the treatment of rheumatoid arthritis. Cochrane Database of Systematic Reviews: Reviews. Cochrane Database of Systematic Reviews 2003 Issue 3. Chichester (UK): John Wiley & Sons, Ltd; 2003.	population
Braun-Moscovici Y, Markovits D, Rozin A, Toledano K, Nahir AM, Balbir-Gurman A. Anti-tumor necrosis factor therapy: 6 year experience of a single center in northern Israel and possible impact of health policy on results. *Israel Medical Association Journal* 2008; 10(4):277-281.	population
Brocq O, Plubel Y, Breuil V, Grisot C, Flory P, Mousnier A, *et al*. Etanercept - Infliximab switch in rheumatoid arthritis 14 out of 131 patients treated with anti TNFalpha. [French]. *Presse Medicale* 2002; 31(39 I):1836-1839.	Participant number

Article	reason for exclusion
Brocq O, Plubel Y, Breuil V, Grisot C, Flory P, Mousnier A, *et al*. Switch etanercept - infliximab dans la polyarthrite rhumatoide. *Presse Medicale* 2002; 31:1836-1839.	Participant number
Brocq O, Albert C, Roux C, Gerard D, Breuil V, Ziegler LE. Adalimumab in rheumatoid arthritis after failed infliximab and/or etanercept therapy: Experience with 18 patients [3]. *Joint Bone Spine* 2004; 71(6):601-603.	Participant number
Buch MH, Marzo-Ortega H, Bingham SJ, Emery P. Long-term treatment of rheumatoid arthritis with tumour necrosis factor alpha blockade: Outcome of ceasing and restarting biologicals [1]. *Rheumatology* 2004; 43(2):243-244.	population
Buch MH, Bingham SJ, Seto Y, McGonagle D, Bejarano V, White J, *et al*. Lack of Response to Anakinra in Rheumatoid Arthritis Following Failure of Tumor Necrosis Factor alpha Blockade. *Arthritis and Rheumatism* 2004; 50(3):725-728.	intervention
Buch MH, Boyle DL, Rosengren S, Saleem B, Reece RJ, Rhodes LA, *et al*. Mode of action of abatacept in rheumatoid arthritis patients having failed tumour necrosis factor blockade: a histological, gene expression and dynamic magnetic resonance imaging pilot study. *Annals of the Rheumatic Diseases* 2009; 68(7):1220-1227.	Participant number
Burmester GR, Mariette X, Montecucco C, Monteagudo-Saez I, Malaise M, Tzioufas AG, *et al*. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: The Research in Active Rheumatoid Arthritis (ReAct) trial. *Annals of the Rheumatic Diseases* 2007; 66(6):732-739.	population

Article	reason for exclusion
Burr ML, Malaviya AP, Gaston JH, Carmichael AJ, Ostor AJK. Rituximab in rheumatoid arthritis following anti-TNF-associated tuberculosis. *Rheumatology* 2008; 47(5):738-739.	design
Carmona L. Changes in anti-TNF: Is this always justified?. [Spanish]. *Reumatologia Clinica* 2008; 4(3):87-89.	design
Combe B. Switching between anti-TNFalpha agents: What is the evidence? *Joint Bone Spine* 2004; 71(3):169-171.	design
Coyle D, Judd M, Blumenauer B, Cranney A, Maetzel A, Tugwell P, *et al*. Infliximab and etanercept in patients with rheumatoid arthritis: a systematic review and economic evaluation (DARE structured abstract). *Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA)* 2006;45.	population
Davies A, Cifaldi MA, Segurado OG, Weisman MH. Cost-effectiveness of sequential therapy with tumor necrosis factor antagonists in early rheumatoid arthritis. *Journal of Rheumatology* 2009; 36(1):16-25.	design
Di PE, Perin A, Morassi MP, Del FM, Ferraccioli GF, De VS. Switching to etanercept in patients with rheumatoid arthritis with no response to infliximab. *Clinical and Experimental Rheumatology* 2007; 25(1):85-87.	Participant number
Donahue KE, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, *et al*. Systematic review: Comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Annals of Internal Medicine* 2008; 148(2):124-134.	population

Article	reason for exclusion
Emery P. Abatacept has beneficial effects in rheumatoid arthritis patients with an inadequate response to anti-TNFalpha therapy. *Clinical and Experimental Rheumatology* 2005; 23(6):767-768.	design
Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, *et al*. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIb randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis and Rheumatism* 2006; 54(5):1390-1400.	population
Emery P, Keystone E, Tony HP, Cantagrel A, Van VR, Sanchez A, *et al*. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: Results from a 24-week multicentre randomised placebo-controlled trial. *Annals of the Rheumatic Diseases* 2008; 67(11):1516-1523.	intervention
Erickson AR, Mikuls TR. Switching anti-TNF-alpha agents: What is the evidence? *Current Rheumatology Reports* 2007; 9(5):416-420.	design
Favalli EG, Arreghini M, Arnoldi C, Panni B, Marchesoni A, Tosi S, *et al*. Anti-tumor necrosis factor alpha switching in rheumatoid arthritis and juvenile chronic arthritis. *Arthritis & Rheumatism* 2004; 51(2):301-302.	Participant number
Fernandez Lison LC, Vazquez DB, Luis FJ, Moreno AP, Fruns G, I, Liso RJ. Quality of life of patients with rheumatoid arthritis undergoing out-patient treatment with TNF inhibitors. [Spanish]. *Farmacia Hospitalaria* 2008; 32(3):178-181.	population

Article	reason for exclusion
Filippini M, Bazzani C, Zingarelli S, Ziglioli T, Nuzzo M, Vianelli M, *et al*. Anti-TNF alpha agents in elderly patients with rheumatoid arthritis: A study of a group of 105 over sixty five years old patients. [Italian]. *Reumatismo* 2008; 60(1):41-49.	population
Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis (DARE structured abstract). *Journal of Rheumatology* 2006; 33:2398-2408.	population
Genta MS, Kardes H, Gabay C. Clinical evaluation of a cohort of patients with rheumatoid arthritis treated with anti-TNF-alpha in the community. *Joint Bone Spine* 2006; 73(1):51-56.	population
Gomez-Puerta JA, Sanmarti R, Rodriguez-Cros JR, Canete JD. Etanercept is effective in patients with rheumatoid arthritis with no response to infliximab therapy. *Annals of the Rheumatic Diseases* 2004; 63(7):896.	Participant number
Gomez CT. Rituximab and abatacept in rheumatoid arthritis. [Spanish]. *Reumatologia Clinica* 2009; 5(SUPPL. 1):77-81.	design
Gonzalez-Juanatey C, Llorca J, Sanchez AA, Garcia-Porrua C, Martin J, Gonzalez-Gay MA. Short-term adalimumab therapy improves endothelial function in patients with rheumatoid arthritis refractory to infliximab. *Clinical and Experimental Rheumatology* 2006; 24(3):309-312.	Participant number

Article	reason for exclusion
Gonzalez-Juanatey C, Llorca J, Vazquez-Rodriguez TR, az-Varela N, Garcia-Quiroga H, Gonzalez-Gay MA. Short-term improvement of endothelial function in rituximab-treated rheumatoid arthritis patients refractory to tumor necrosis factor alpha blocker therapy. *Arthritis Care and Research* 2008; 59(12):1821-1824.	Participant number
Haraoui B. Is there a rationale for switching from one anti-tumor necrosis factor agent to another? *Journal of Rheumatology* 2004; 31(6):1021-1022.	design
Hay EM, Thomas E, Paterson SM, Dziedzic K, Croft PR. Do etanercept-naqive patients with rheumatoid arthritis respond better to infliximab than patients for whom etanercept has failed? *Ann Rheum Dis* 2004; 63:607-612.	design
Health Q, I, Scotland. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (DARE structured abstract). *Glasgow: NHS Quality Improvement Scotland (NHS QIS)* 2007.	population
Health Q, I. Rituximab for the treatment of rheumatoid arthritis (Brief record). *Glasgow: Health Quality Improvement Scotland (NHS QIS)* 2007.	design
Heiberg MS, Rodevand E, Mikkelsen K, Kaufmann C, Didriksen A, Mowinckel P, *et al*. Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: Results from a 6-month longitudinal, observational, multicentre study. *Annals of the Rheumatic Diseases* 2006; 65(10):1379-1383.	population

Article	reason for exclusion
Higashida J, Wun T, Schmidt S, Naguwa SM, Tuscano JM. Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and anti-tumor necrosis factor-alpha treatment. *Journal of Rheumatology* 2005; 32(11):2109-2115.	population
Hoff M, Kvien TK, Kalvesten J, Elden A, Haugeberg G. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. *Annals of the Rheumatic Diseases* 2009; 68(7):1171-1176.	population
Iking-Konert C. Therapy-refractive rheumatoid arthritis: Effectiveness and reliability of abatecept and infliximab. [German]. *Aktuelle Rheumatologie* 2008; 33(5):239-240.	population
Jamal S, Patra K, Keystone EC. Adalimumab response in patients with early versus established rheumatoid arthritis: DE019 randomized controlled trial subanalysis. *Clinical Rheumatology* 2009; 28(4):413-419.	population
Kavanaugh A, Rosengren S, Lee SJ, Hammaker D, Firestein GS, Kalunian K, *et al*. Assessment of rituximab's immunomodulatory synovial effects (ARISE trial). 1: Clinical and synovial biomarker results. *Annals of the Rheumatic Diseases* 2008; 67(3):402-408.	Participant number
Kielhorn A, Porter D, Diamantopoulos A, Lewis G. Uk cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. *Current Medical Research and Opinion* 2008; 24(9):2639-2650.	design

Article	reason for exclusion
Kievit W, Adang EM, Fransen J, Kuper HH, Van De Laar MAFJ, Jansen TL, *et al*. The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data. *Annals of the Rheumatic Diseases* 2008; 67(9):1229-1234.	population
Koike T, Harigai M, Inokuma S, Inoue K, Ishiguro N, Ryu J, *et al*. Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. *Journal of Rheumatology* 2009; **36**(5):898-906.	population
Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: Results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in Southern Sweden. *Arthritis and Rheumatism* 2006; 54(2):600-606.	population
Laas K, Peltomaa R, Puolakka K, Kautiainen H, Leirisalo-Repo M. Early improvement of health-related quality of life during treatment with etanercept and adalimumab in patients with rheumatoid arthritis in routine practice. *Clinical & Experimental Rheumatology* 2009; 27(2):315-320.	population
Li S, Kaur PP, Chan V, Berney S. Use of tumor necrosis factor-alpha (TNF-alpha) antagonists infliximab, etanercept, and adalimumab in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: a retrospective record review of 11 patients. *Clinical Rheumatology* 2009; 28(7):787-791.	population
Lopez-Olivo MA, Amezaga M, McGahan L, Suarez-Almazor ME. Rituximab for rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2008;(4).	design

Article	reason for exclusion
Mease PJ, Revicki DA, Szechinski J, Greenwald M, Kivitz A, Barile-Fabris L, *et al*. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab - Results of the dose-ranging assessment: International clinical evaluation of rituximab in rheumatoid arthritis (DANCER) trial. *Journal of Rheumatology* 2008; 35(1):20-30.	population
Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: The CHANGE study. *Modern Rheumatology* 2008; 18(3):252-262.	population
Moreland L. Efficacy of costimulation blockade with abatacept in rheumatoid arthritis patients refractory to tumor necrosis factor-alpha inhibition. *Current Rheumatology Reports* 2006; 8(5):367.	design
Navarra SV, Raso A-A, Lichauco JJ, Tan PP. Clinical experience with infliximab among Filipino patients with rheumatic diseases. *APLAR Journal of Rheumatology* 2006; 9(2):150-156.	population
Navarro-Sarabia F, riza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. Cochrane Database of Systematic Reviews: Reviews. Cochrane Database of Systematic Reviews 2005 Issue 3. Chichester (UK): John Wiley & Sons, Ltd; 2005.	population
NHS Quality Improvement Scotland (NHS QIS). Abatacept for the treatment of rheumatoid arthritis (DARE structured abstract). *Glasgow: NHS Quality Improvement Scotland (NHS QIS)* 2008.	design

Article	reason for exclusion
Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumour necrosis factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons (DARE structured abstract). *Rheumatology* 2007; 46:1140-1147.	population
Olsen N. Anti-TNF switching: Effect on outcomes in patients with RA: Commentary. *Nature Clinical Practice Rheumatology* 2007; 3(8):430-431.	design
Ostergaard M, Unkerskov J, Linde L, Krogh NS, Ravn T, Ringsdal VS, *et al*. Low remission rates but long drug survival in rheumatoid arthritis patients treated with infliximab or etanercept: Results from the nationwide Danish DANBIO database [2]. *Scandinavian Journal of Rheumatology* 2007; 36(2):151-154.	population
Ostor AJK. Abatacept: A T-cell co-stimulation modulator for the treatment of rheumatoid arthritis. *Clinical Rheumatology* 2008; 27(11):1343-1353.	design
Owczarczyk KM, Hellmann M, Fliedner G, Rohrs T, Maizus K, Passon D, *et al*. Clinical outcome and B cell depletion in patients with rheumatoid arthritis receiving rituximab monotherapy in comparison with patients receiving concomitant methotrexate. *Annals of the Rheumatic Diseases* 2008; 67(11):1648-1650.	population
Palylyk-Colwell E, McGahan L. Rituximab for rheumatoid arthritis (DARE structured abstract). *Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH)* 2006;4.	design

Article	reason for exclusion
Parker CT, Rennie T, Yocum DE, Furst DE, Kaine JL, Baldassare A, *et al*. Failure to report previously used drugs and dosages in pharmaceutical company-sponsored rheumatoid arthritis trials: Comment on the article by Yocum et al [3]. *Arthritis and Rheumatism* 2004; 50(9):3051-3052.	population
Pavelka K, Gatterova J, Vencovsky J, Sedova L, Chroust K. Radiographic progression of rheumatoid arthritis in real clinical practice results in national registry attra. [Czech]. *Rheumatologia* 2009; 23(1):7-11.	population
Pedersen SJ, Hetland ML, Ostergaard M, Navarro-Sarabia F, riza-Ariza R, Hernandez-Cruz B, *et al*. Adalimumab for treating rheumatoid arthritis. [Danish]. *Ugeskrift for Laeger* 2006; 168(35):2899-2902.	population
Pisetsky DS. A landmark study on treatment strategies for rheumatoid arthritis. *Arthritis and Rheumatism* 2008; 58(2 SUPPL.):S123-S125.	population
Reynolds J, Shojania K, Marra CA. Abatacept: A novel treatment for moderate-to-severe rheumatoid arthritis. *Pharmacotherapy* 2007; 27(12 I):1693-1701.	design
Rubbert-Roth A, Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: A critical review. *Arthritis Research and Therapy* 2009; 11(SUPPL. 1).	design
Russell A, Beresniak A, Bessette L, Haraoui B, Rahman P, Thorne C, *et al*. Cost-effectiveness modeling of abatacept versus other biologic agents in DMARDS and anti-TNF inadequate responders for the management of moderate to severe rheumatoid arthritis. *Clinical Rheumatology* 2009; 28(4):403-412.	design

Article	reason for exclusion
Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, *et al*. Infections during tumour necrosis factor-alpha blocker therapy for rheumatic diseases in daily practice: A systematic retrospective study of 709 patients. *Rheumatology* 2007; 46(2):327-334.	population
Sanmarti R, Gomez-Puerta JA, Rodriguez-Cros JR, Albaladejo C, Munoz-Gomez J, Canete JD. Etanercept in rheumatoid arthritis patients with a poor therapeutic response to infliximab. [Spanish]. *Medicina Clinica* 2004; 122(9):321-324.	Participant number
Sheitanov I. Our experience with Remicade (infliximab) in patients with early and refractory rheumatoid arthritis. [Bulgarian]. *Rheumatology* 2005; 13(3):66-73.	population
Silman AJ. Available therapeutic options following failure of a first anti-TNF agent. *Nature Clinical Practice Rheumatology* 2009; 5(3):115.	design
Singh A, Ghazvini P, Honeywell M, Treadwell P, Canty. Rituximab for the treatment of refractory rheumatoid arthritis: New information from clinical trials. *P and T* 2006; 31(6):321+343.	design
Smolen JS, Weinblatt ME. When patients with rheumatoid arthritis fail tumour necrosis factor inhibitors: What is the next step? *Annals of the Rheumatic Diseases* 2008; 67(11):1497-1498.	design
Strand V, Balbir-Gurman A, Pavelka K, Emery P, Li N, Yin M, *et al*. Sustained benefit in rheumatoid arthritis following one course of rituximab: Improvements in physical function over 2 years. *Rheumatology* 2006; **45**(12):1505-1513.	population

Article	reason for exclusion
Suarez-Almazor M, Ortiz Z, Lopez-Olivo M, Moffett M, Pak C, Skidmore B, *et al*. Infliximab and etanercept in rheumatoid arthritis: systematic review of long-term clinical effectiveness, safety, and cost-effectiveness (DARE structured abstract). *Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH)* 2007;32.	population
Summers KM, Kockler DR. Rituximab treatment of refractory rheumatoid arthritis (DARE structured abstract). *Annals of Pharmacotherapy* 2005; 39:2091-2095.	population
Taylor PC. Is abatacept an effective treatment for patients with RA who do not respond to other anti-TNF treatments? Commentary. *Nature Clinical Practice Rheumatology* 2006; 2(3):128-129.	design
Van De Putte LBA, Atkins C, Malaise M, Sany J, Russell AS, Van Riel PLCM, *et al*. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Annals of the Rheumatic Diseases* 2004; 63(5):508-516.	population
Van Der Kooij SM, De Vries-Bouwstra JK, Goekoop-Ruiterman YP, Ewals JA, Han KH, Hazes JM, *et al*. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis.[see comment]. *Arthritis & Rheumatism* 2009; 61(1):4-12.	population
Van Der Kooij SM, De Vries-Bouwstra JK, Goekoop-Ruiterman YPM, Ewals JAPM, Han KH, Hazes JMW, *et al*. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. *Arthritis Care and Research* 2009; 61(1):4-12.	population

Article	reason for exclusion
Van Vollenhoven,R, Harju,A, Brannemark,S, Klareskog,L. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor alpha blockers can make sense. *Ann Rheum Dis* 62, 1195-1198.2003	Participant number
Van Vollenhoven RF. Switching between biological agents. *Clinical and Experimental Rheumatology* 2004; 22(5 SUPPL. 35):S115-S121.	design
Van Vollenhoven RF. Switching between anti-tumour necrosis factors: Trying to get a handle on a complex issue. *Annals of the Rheumatic Diseases* 2007; 66(7):849-851.	design
Van VR, Harju A, Brannemark S, Klareskog L. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: Data from the STURE registry showing that switching tumour necrosis factor alpha blockers can make sense. *Annals of the Rheumatic Diseases* 2003; 62(12):1195-1198.	Participant number
Venkateshan SP, Sidhu S, Malhotra S, Pandhi P. Efficacy of biologicals in the treatment of rheumatoid arthritis: A meta-analysis. *Pharmacology* 2009; 83(1):1-9.	population
Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O, *et al*. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to tumor necrosis factor-alpha antagonists. *Journal of Rheumatology* 2008; 35(9):1745-1753.	design
Villamayor BL, Moreno Ramos MJ, Urbieta SE, Martinez PM, Jorge V, V, Gonzalez Perez-Crespo C, *et al*. Study of adalimumab's use in rheumatoid arthritis. [Spanish]. *Atencion Farmaceutica* 2006; 8(3):157-162.	population

Article	reason for exclusion
Vital EM, Dass S, Buch MH, Rawstron AC, Ponchel F, McGonagle D, *et al*. Re-treatment of rheumatoid arthritis patients who were initial nonresponders to rituximab: Comment on the article by Thurlings et al. *Arthritis and Rheumatism* 2009; 60(6):1867.	design
Voulgari PV, Alamanos Y, Nikas SN, Bougias DV, Temekonidis TI, Drosos AA. Infliximab therapy in established rheumatoid arthritis: An observational study. *American Journal of Medicine* 2005; 118(5):515-520.	population
Walsh CAE, Minnock P, Slattery C, Kennedy N, Pang F, Veale DJ, *et al*. Quality of life and economic impact of switching from established infliximab therapy to adalimumab in patients with rheumatoid arthritis. *Rheumatology* 2007; 46(7):1148-1152.	population
Weaver AL, Lautzenheiser RL, Schiff MH, Gibofsky A, Perruquet JL, Luetkemeyer J, *et al*. Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: Results from the RADIUS observational registry. *Current Medical Research and Opinion* 2006; 22(1):185-198.	population
Weisman MH, Paulus HE, Burch FX, Kivitz AJ, Fierer J, Dunn M, *et al*. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. *Rheumatology* 2007; 46(7):1122-1125.	population
Witte F. How beneficial is switching from one anti-TNF-alpha agent to a second anti-TNF-alpha agent in patients with rheumatoid arthritis?. [German]. *Aktuelle Rheumatologie* 2007; 32(4):182.	design

Article	reason for exclusion
Yazici Y, Yazici H. Tumor necrosis factor alpha inhibitors, methotrexate or both? An inquiry into the formal evidence for when they are to be used in rheumatoid arthritis. *Clinical and Experimental Rheumatology* 2008; 26(3):449-452.	population
Yazici Y, Krasnokutsky S, Barnes JP, Hines PL, Wang J, Rosenblatt L. Changing patterns of tumor necrosis factor inhibitor use in 9074 patients with rheumatoid arthritis. *Journal of Rheumatology* 2009; 36(5):907-913.	population
Yukawa N, Mimori T. [B cell depletion therapy using anti-CD20 antibodies in rheumatoid arthritis]. [Review] [17 refs] [Japanese]. *Clinical Calcium* 2007; 17(4):569-576.	design
Zhang W, Bansback N, Guh D, Li X, Nosyk B, Marra CA, *et al*. Short-term influence of adalimumab on work productivity outcomes in patients with rheumatoid arthritis. *Journal of Rheumatology* 2008; 35(9):1729-1736.	population
Zintzaras E, Dahabreh IJ, Giannouli S, Voulgarelis M, Moutsopoulos HM. Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens (Provisional abstract). *Clinical Therapeutics* 2008; 30:1939-1955.	population

10.5 Cost effectiveness -table of excluded studies with rationale

Article	reason for exclusion
Bansback N, Ara R, Karnon J, Anis A. Economic evaluations in rheumatoid arthritis: A critical review of measures used to define health states. PharmacoEconomics 2008; 26(5):395-408.	Review of clinical measures in RA
Bansback NJ, Brennan A, Ghatnekar O. Cost effectiveness of adalimumab in the treatment of patients with moderate to severe rheumatoid arthritis in Sweden. Annals of the Rheumatic Diseases 2005; 64(7):995-1002.	Population
Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with a chronic condition: The case of antibodies against tumour necrosis factor in rheumatoid arthritis. Health Technology Assessment 2004; 8(11):iii-42.	Population
Bullano MF, McNeeley BJ, Yu YF, Quimbo R, Burawski LP, Yu EB et al. Comparison of costs associated with the use of etanercept, infliximab, and adalimumab for the treatment of rheumatoid arthritis. Managed Care Interface 2006; 19(9):47-53.	Population
Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness (DARE structured abstract). Health Technology Assessment 2006; 10:1-248.	Population

Article	reason for exclusion
Chiou C-F, Choi J, Reyes CM. Cost-effectiveness analysis of biological treatments for rheumatoid arthritis. Expert Review of Pharmacoeconomics and Outcomes Research 2004; 4(3):307-315.	Population
Davies A, Cifaldi MA, Segurado OG, Weisman MH. Cost-effectiveness of sequential therapy with tumor necrosis factor antagonists in early rheumatoid arthritis. Journal of Rheumatology 2009; 36(1):16-25.	Population
Doan QV, Chiou C-F, Dubois RW. Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. Journal of Managed Care Pharmacy 2006; 12(7):555-569.	Review of TNF inhibitors in RA
Kamal KM, Miller L-A, Kavookjian J, Madhavan S. Alternative Decision Analysis Modeling in the Economic Evaluation of Tumor Necrosis Factor Inhibitors for Rheumatoid Arthritis. Seminars in Arthritis and Rheumatism 2006; 36(1):50-60. Ref ID: 3040	Review of decision modelling in economic evaluations of TNF inhibitors in RA
Kobelt G, Jonsson L, Young A, Eberhardt K. The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. Rheumatology 2003; 42(2):326-335.	Population

Article	reason for exclusion
Kobelt G, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: Costs and outcomes in a follow up study of patients with Ra treated with etanercept or infliximab in southern Sweden. Annals of the Rheumatic Diseases 2004; 63(1):4-10.	Population
Launois R, Payet S, Saidenberg-Kermanac'h N, Francesconi C, Franca LR, Boissier M-C. Budget impact model of rituximab after failure of one or more TNFalpha inhibitor therapies in the treatment of rheumatoid arthritis. Joint Bone Spine 2008; 75(6):688-695.	Design
Lyseng-Williamson KA, Foster RH. Infliximab: A Pharmacoeconomic Review of its Use in Rheumatoid Arthritis. PharmacoEconomics 2004; 22(2):107-132.	Population
Lyseng-Williamson KA, Plosker GL. Etanercept: A pharmacoeconomic review of its use in rheumatoid arthritis. PharmacoEconomics 2004; 22(16):1071-1095.	Population
Merkesdal S, Ruof J, Mittendorf T, Zeidler H. Cost-effectiveness of TNF-A-blocking agents in the treatment of rheumatoid arthritis. Expert Opinion on Pharmacotherapy 2004; 5(9):1881-1886.	Review of TNF inhibitors in RA
Monteiro RDC, Zanini AC. Cost analysis of drug therapy in rheumatoid arthritis. [Portuguese]. Revista Brasileira de Ciencias Farmaceuticas/Brazilian Journal of Pharmaceutical Sciences 2008; 44(1):25-33.	Population
Muller-Ladner U. Cost effectiveness of biologics in the treatment of rheumatoid arthritis. [German]. Internist 2004; 45(12):1402-1406.	Population

Article	reason for exclusion
Nuijten MJ, Engelfriet P, Duijn K, Bruijn G, Wierz D, Koopmanschap M. A cost-cost study comparing etanercept with infliximab in rheumatoid arthritis. PharmacoEconomics 2001; 19(10):1051-1064.	Population
Prokes M. Effectiveness of TNF antagonists in routine clinical practice and costs. [Czech]. Vnitrni Lekarstvi 2009; 55(1):45-53.	Population
Ravasio R, Lucioni C. Economic evaluation of etanercept in AR. [Italian]. PharmacoEconomics - Italian Research Articles 2006; 8(2):129-140.	Review of etanercept
Regier DA, Bansback N, Dar SA, Marra CA. Cost-effectiveness of tumor necrosis factor-alpha antagonist in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Expert Review of Pharmacoeconomics and Outcomes Research 2007; 7(2):155-169.	Review of TNF inhibitors in RA, psoriatic arthritis and ankylosing spondylitis
Rubio-Terres C, Ordovas Baines JP, Pla PR, Martinez NC, Sanchez Garre MJ, Rosado Souviron MA. Use and cost of biological disease -modifying anti-rheumatic drugs in Spain (PRAXIS study). [Spanish]. Farmacia Hospitalaria 2007; 31(2):78-92.	Population
Rubio-Terres C, Ordovas Baines JP, Pla PR. Critical analyis of the article: <<Use and cost of biological disease-modifying anti-rheumatic drugs in Spain (PRAXIS study)>>. [Spanish]. Farmacia Hospitalaria 2008; 32(3):190-193.	Population

Article	reason for exclusion
Suka M, Yoshida K. [Economic evaluation of a new treatment for rheumatoid arthritis]. [Review] [5 refs] [Japanese]. Nippon Rinsho - Japanese Journal of Clinical Medicine 2007; 65(7):1327-1330.	Population
Tsutani K, Igarashi A. [Anti-rheumatoid biologics and pharmacoeconomic evaluation]. [Review] [4 refs] [Japanese]. Nippon Rinsho - Japanese Journal of Clinical Medicine 2005; 63 Suppl 1:711-718.	Design
Unit of Health Economics and Technology Assessment. Rituximab in patients with rheumatoid arthritis:systematic review and economic evaluation (Brief record). Budapest: Unit of Health Economics and Technology Assessment in Health Care (HUNHTA) 2006.	Population
Van Den Hout WB, Goekoop-Ruiterman YPM, Allaart CF, Vries-Bouwstra JKD, Hazes JMM, Kerstens PJSM et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis Care and Research 2009; 61(3):291-299.	Population
Virkki LM, Konttinen YT, Peltomaa R, Suontama K, Saario R, Immonen K et al. Cost-effectiveness of infliximab in the treatment of rheumatoid arthritis in clinical practice. Clinical and Experimental Rheumatology 2008; 26(6):1059-1066.	Population
Wailoo AJ, Bansback N, Brennan A, Michaud K, Nixon RM, Wolfe F. Biologic drugs for rheumatoid arthritis in the medicare program: A cost-effectiveness analysis. Arthritis and Rheumatism 2008; 58(4):939-946.	Population

Article	reason for exclusion
Walsh CAE, Minnock P, Slattery C, Kennedy N, Pang F, Veale DJ et al. Quality of life and economic impact of switching from established infliximab therapy to adalimumab in patients with rheumatoid arthritis. Rheumatology 2007; 46(7):1148-1152.	Population
Wong JB, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis. American Journal of Medicine 2002; 113(5):400-408.	Population
Wong JB. Cost-effectiveness of anti-tumor necrosis factor agents. Clinical and Experimental Rheumatology 2004; 22(5 SUPPL. 35):S65-S70.	Review of TNF inhibitors in RA
Wu EQ, Chen L, Birnbaum H, Yang E, Cifaldi M. Cost of care for patients with rheumatoid arthritis receiving TNF-antagonist therapy using claims data. Current Medical Research and Opinion 2007; 23(8):1749-1759.	Population

10.6 Clinical effectiveness – full paper inclusion/ exclusion checklist

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor – Full text inclusion checklist for clinical effectiveness

	Question	Yes	No
Q1	**Population** Did the study include a majority (>50%) of adults with active rheumatoid arthritis who have had an inadequate response to a TNF inhibitor?	Go to Q2	Exclude UD4 = excluded pop
Q2	**Interventions** Did the interventions include at least one of the following drugs: o adalimumab, o etanercept, o infliximab, o rituximab, o abatacept?	Go to Q3	Exclude UD4 = excluded int
Q3	**Outcomes** Did the study report any clinical outcomes related to efficacy, safety or tolerability?	Go to Q4	Exclude UD4 = excluded out
Q4	**Study design** Was it a primary study (except case reports) or a systematic review?	For primary study: go to Q5 For systematic review: include; UD4 = SR	Exclude UD4 = excluded des
Q5	**Study duration** Was the study at least 12 weeks duration?	Go to Q6	Exclude UD4 = excluded dur
Q6	**Participant numbers** If the study was not an RCT, did it include at least 20 patients in at least one of the treatment arms (if there was more than one arm)	Include UD4 = included	Exclude UD4 = excluded num

10.7 Cost effectiveness – full paper inclusion/ exclusion checklist

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor – Full text inclusion checklist for cost effectiveness

	Question	Yes	No
Q1	**Population** Did the study include a majority of adults with active rheumatoid arthritis who have had an inadequate response to a TNF inhibitor?	Go to Q2	Exclude UD5 = excluded pop
Q2	**Interventions** Did the interventions include at least one of the following drugs: o adalimumab, o etanercept, o infliximab, o rituximab, o abatacept?	Go to Q3	Exclude UD5 = excluded int
Q3	**Outcomes** Did the study report any quality of life estimates, cost estimates or cost effectiveness results?	Go to Q4	Exclude UD5 = excluded out
Q4	**Study design** Was it a cost-consequence analysis, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis, cost study (UK only), or quality of life study?	Include UD5 = included	Exclude UD5 = excluded des

10.8 Clinical effectiveness review - data extraction form

Adalimumab/ Etanercept/ Infliximab/ Rituximab/ Abatacept (delete as appropriate)
RCT/Controlled study (concurrent)/Controlled study (historical)/Uncontrolled study (delete as appropriate)

First author & year		Reference no.	
Trial name/protocol no.		Reviewer	
Citation		Date of abstraction	
Country & no of centres		Sponsorship	
Related references			

Inclusion criteria	***General comments and comments on exclusions***
Age: Duration of RA ≥ Prior TNF inhibitor treatment: Reason for discontinuation of TNF inhibitor:	
Disease activity parameters Tender joint count ≥ Swollen Joint count ≥ ESR ≥ CRP ≥ Morning stiffness>	
Other inclusion/exclusion criteria:	
Concomitant treatments during the trial Methotrexate: allowed / not allowed / unclear / conditional: Other DMARDs: allowed / not allowed / unclear / conditional: Steroids: allowed / not allowed / unclear / conditional: Other treatments allowed: Other treatments not allowed:	

Previous TNF inhibitor (s)
Eligibility for the previous anti-TNF:

Doses and treatment duration of previous TNF inhibitor (and concomitant DMARDs):

Wash out period from the previous TNF inhibitor:

RCT study design & quality

Was randomisation adequate: Yes / No / Unclear

Was allocation adequately concealed: Yes / No / Unclear

Blinding:
Were patients blinded from the study interventions: Yes / No / Unclear
Were study investigators/outcome assessors blinded from the study interventions: Yes / No / Unclear
Were data analysts blinded from the study interventions: Yes / No / Unclear

Was lost to follow-up stated for each treatment groups: Yes / No / Unclear

Was ITT analysis used: Yes / No / Unclear

Duration of treatment: Duration of follow-up (if different):

Study visits (outcome data available):

Comments on study design & quality (problem in study design; power of study; potential bias):

Non-RCT study design & quality

What was the study design:

Were criteria for including patients into the study stated?

Were consecutive patients meeting the inclusion criteria (if any) entered into the study?

Was lost to follow-up stated for each treatment groups: Yes / No / Unclear

Duration of treatment: Duration of follow-up (if different):

Study visits (outcome data available):

Comments on study design & quality (problem in study design; power of study; potential bias):

Interventions & comparators

State drug name(s), dose, frequency, route of administration
A)
B)
C)
D)
E)
F)

Baseline characteristics

Tx arm	A)	B)	C)	D)	E)	F)	All patients
Patient Number							
Age (mean, yrs)							
Female %							
Disease Duration (yrs)							
Auto-antibody status							
(Comorbidity) %							
(Comorbidity) %							
(Comorbidity) %							
Previous TNF inhibitor							
No. of previous DMARDs							
(Previous DMARD) %							
(Previous DMARD) %							
On steroids (%)							
On NSAIDs (%)							
If on MTX - dose?							
% joint replm							
Comments on the presence or absence of significant differences between treatment arms: No. of patients screened: No. of patients randomized: No. of patients received at least one dose of study drug:							

Outcomes: ITT population / Efficacy population (delete as appropriate)

Measure of activity	*Values (SD or IQR)*	*Intervention – A n=*	*Intervention – B n=*	*Intervention – C n=*	*Intervention – D n=*	*Intervention – E n=*	*Intervention – F n=*
1. Withdrawal - lack of efficacy	*N° eval.* *N° withdrew*						
2. Withdrawal – adverse events	*N° eval.* *N° withdrew*						
3. Withdrawal – any reason	*N° eval.* *N° withdrew*						
4. ACR 20%	*N° eval.* *N° improved*						
5. ACR 50%	*N° eval.* *N° improved*						
6. ACR 70%	*N° eval.* *N° improved*						
7. Swollen joint count ( ) *Specify week*	N° eval						
	Pre-Rx						
	Post						
	Chge *P value*						
8. Tender joint Count ( ) *Specify week*	*N° eval*						
	Pre-Rx						
	Post						
	Chge *P value*						
9. Pain - patient ( ) *Specify week*	*N° eval*						
	Pre-Rx						
	Post						
	Chge *P value*						
10. Phys. Global ( ) *Specify week*	*N° eval*						
	Pre-Rx						
	Post						

	Chge *P value*						
11. Patient global ( ) *Specify week*	*N^{o} eval*						
	Pre-Rx						
	Post						
	Chge *P value*						
Measure of activity	*Values (SD or IQR)*	*Intervention – A* *n=*	*Intervention – B* *n=*	*Intervention – C* *n=*	*Intervention – D* *n=*	*Intervention – E* *n=*	*Intervention – F* *n=*
12. CRP *Specify week*	*N^{o} eval*						
	Pre-Rx						
	Post						
	Chge *P value*						
13. ESR *Specify week*	*N^{o} eval*						
	Pre-Rx						
	Post						
	Chge *P value*						
14. HAQ *Specify week*	*N^{o} eval*						
	Pre-Rx						
	Post						
	Chge *P value*						
15. DAS Specify week	*N^{o} eval*						
	Pre-Rx						
	Post						
	Chge *P value*						
16. Joint damage (scale: *Specify week*	*N^{o} eval*						
	Pre-Rx						
	Post						
	Chge *P value*						

(scale: *Specify week*							
	Pre-Rx						
	Post						
	Chge *P value*						
Comments: Which is/are the primary endpoint(s)? How were missing data handled (e.g. LOCF)? Were any outcome evaluation planned but not reported? Results of subgroup analysis							

Adverse Events

	Interventions:					
	A (n=)	B (n=)	C (n=)	D (n=)	E (n=)	F (n=)
Deaths						
Serious adverse events						
Serious infection (definition:						
Infections needing antibiotics						
Any infection						
Malignancy						
Injection site reaction						
Infusion reaction						
Others:						
Comments:						

10.9 Cost effectiveness review - data extraction of included studies

Table 90 Lindgren 2009 - economic evaluation data extraction form

Author	Lindgren	**Date**	2009	**Study population**	Patients with active RA and an inadequate response to one or more TNF inhibitor agents	**Type of economic evaluation**	Cost-utility analysis
Intervention 1	Rituximab	**Intervention 2**					
Clinical Effectiveness							
Source of effectiveness data	Effectiveness of treatment with TNF inhibitors is based on patient level data from the Southern Swedish Arthritis Treatment Group Registry (SSATG) (1997-2007). This data set contains baseline demographic data, disease information (all available HAQ and DAS28 scores), treatment data (biologics and DMARDs) and utility scores (EQ-5D). The data set used for this analysis contained 1,903 patients with sufficient data on up to three lines of treatment. Source for Rituximab effectiveness was the REFLEX trial, where patients with active RA and an inadequate response to one or more TNF inhibitors were randomised to receive intravenous rituximab (one course, two infusions of 1,000mg each) or placebo, both with MTX as background therapy.			**Clinical outcomes measured & methods of valuation used**	REFLEX primary efficacy point was ACR20 response at 6 months. Secondary end points were ACR50 and ACR70 response, DAS28, and EULAR response criteria at 6 months. Mean HAQ scores declined from 1.9 to 1.4 at the 4-week measurement and remained constant up to 6-months of treatment. Mean DAS28 scores declined from 6.9 to 5.4 after 4 weeks and to 5.0 after 6 months. Assuming normal distribution of the scores, 5.9% of patients would achieve a DAS28 below 3.2 at week 4, but no further change to low disease activity thereafter. Utilities are mapped from the HAQ score. The model uses the equation as estimated by SSATG data (6,860 observations for 1,787 patients). QoL = 0.915 – 0,252 x HAQ - 0.05 x Male – 0.107 DAS28 HAQ progression was estimated through the SSATG data. It is unclear though what type of regression was used; text suggests linear while table 2 suggests logistic. Also, Table		

					2 should have a clearer indication of which variable is the dependent one on all functions used. HAQ progression = 0.106 + 0.241 x (HAQ at treatment start) + 0.002 x (Months on treatment) – 0.087 x (2nd line) – 0.192 x (3rd line) – 0.007 x (Disease duration)
Cost data					
Currency used	Costs estimated in Swedish kronor (SEK) and presented in Euro (1€ = 9.45 SEK)	**Years to which costs apply**	2008	**Perspective(s)**	Societal perspective (direct and indirect costs included as well as informal care)
Cost data handled appropriately	Yes. Source for resource consumption was a survey carried out at regular intervals by the department of rheumatology at the University Hospital of Malmo (Southern Sweden). The survey covers an estimated 90% of the patient population in the area and includes all costs; direct medical and non-medical, as well as productivity losses. Costs were calculated as a function of HAQ and DAS28. The cost of TNF inhibitor treatment was a weighted mean based on usage of each drug. Unit costs were obtained from standard national (Swedish) sources. The cost of rituximab was based on the dose used in REFLEX (two infusions of 1,000mg each per course). Retreatment could take place between 4 and 12 months, at a 6-month interval. Costs of adverse events (such as hospitalisation due to severe infections or clinical investigations) were excluded from the analysis as such costs would occur in both arms. Costs are discounted at 3%.				
Cost effectiveness					
Modelling summary	A discrete event simulation model was developed. Patients in the model can be in three states: on treatment, off treatment, or dead. On treatment, a difference is made between the first, second, or third TNF inhibitors but not between the different agents. The treatment state is further divided into high or low disease activity, with the cut-off point defined as DAS28 = 3.2. Simulation starts when patients start on second line treatment, either with a second TNF inhibitor or with rituximab. Patients will stay on these treatments until discontinuation of the second line TNF inhibitor (according to SSATG data) or withdrawal from rituximab (according				

	to data from REFLEX). Patients previously on rituximab will receive their second TNF inhibitor. When patients fail again, they will switch to another TNF inhibitor again. In the absence of sufficient data to estimate the event rates for the fourth (or subsequent) TNF treatment lines, these are assumed to be the same as for the third line. Improvement in HAQ score was assumed to occur immediately and HAQ levels thereafter were assessed using linear regression (as indicated in text – not clear on the table) on the difference compared with the initial HAQ response. At treatment discontinuation, patients return to the initial HAQ score and progress at the rate of 0.03 per year while off treatment. Base case is for a 52-tear-old female patient with a HAQ of 1.9 at the start of the second biologic and disease duration of 12 years.				
Outcome measures used in economic evaluations	Incremental QALY's and ICER's	**Statistical analysis for patient-level stochastic data**	A Cox-proportional hazard model was estimated to identify covariates (age, gender, disease duration, current HAQ, current disease activity, treatment line) with a possible impact on times to event. Bootstrapping was used for parameters where patient level data were available.	**Appropriateness of statistical analysis**	Yes
Uncertainty					
Uncertainty around cost-effectiveness expressed	Yes. Model uncertainty was explored using PSA with 1000 samples by Monte Carlo simulation using all available data and patient characteristics.	**Appropriateness of method dealing with uncertainty around cost effectiveness**	Yes		

Sensitivity analysis	Sensitivity analysis for the key variables was performed. For parameters relating to rituximab and the progression of HAQ, normal distribution was assumed.	**Modelling inputs & techniques appropriate**	Yes
Author's conclusions	The strategy including rituximab in second line dominates current treatment. Total costs were €401,000 for the rituximab arm and €403,600 for current treatment. Patients in the rituximab arm gain 0.20 additional QALYs, due in part to the absence of lag-time in restarting a TNF inhibitor at withdrawal of rituximab. Changes in the individual key parameters do not affect these results. Only if rituximab was administered every 4 months or less, then costs for this strategy are higher. The results from the PSA indicate that all but one of the 1,000 simulations fall below a theoretical threshold of 500,000SEK (€53,000)		

Table 91 Russell 2009 -economic evaluation data extraction form

Author	Russell	**Date**	2009	**Study population**	Patients with moderate to severe RA and with an inadequate response to one or more DMARDs and/or TNF inhibitors	**Type of economic evaluation**	Cost effectiveness analysis
Intervention 1	Abatacept	**Intervention 2**					
Clinical Effectiveness							
Source of effectiveness data	DAS data are from various published sources, including the ATTAIN and TEMPO trials. The AIM trial was the source for: patients' inadequate response to DMARDs; safety and effectiveness of Abatacept when appearing in the sequence for the first time (TNF inhibitor inadequate responders); effectiveness of Abatacept maintained after the first cycle and for one or more subsequent 6-month cycles. The ATTAIN trial was the source for: patients' inadequate response to TNF inhibitor therapies; safety			**Clinical outcomes measured & methods of valuation used**	Treatment effectiveness was defined as either achieving disease remission (DAS28<2.6) or low disease-activity rate (DAS≤3.2). The effectiveness of TNF inhibitors in TNF inhibitor inadequate responders was extracted from the ATTAIN trial, assuming a 10% reduction after each switch.		

	of Abatacept, effectiveness of Abatacept maintained after the first cycle and for one or more subsequent 6-month cycles. The TEMPO trial was the source for: effectiveness of Etanercept when appearing in the sequence for the first time (DMARD inadequate responders); effectiveness of Etanercept maintained after the first cycle and for one or more subsequent 6-month cycles.				
Cost data					
Currency used	$ (CAN)	**Years to which costs apply**	2006	**Perspective(s)**	Public payer
Cost data handled appropriately	Abatacept is administered over a 30-min i.v. infusion at 2 and 4 weeks after the first infusion, and every 4 weeks thereafter. The analysis assumes an average dose of 750mg (3 x 250 mg vials) per infusion. However, infusion costs were not included because in Canada, infliximab and abatacept were administered in participating rheumatology and infusion clinics or at home for abatacept. Direct medical costs per DAS score categories were assessed based on a Canadian cost survey. Data were collected from 253 adult patients and the following cost categories were collected: visits to health professionals [family physician, specialist (non-surgical reported separately from surgical visits), allied health, dentist], laboratory tests or investigation (X-ray, CT, MRI, ultrasound, ECG, other laboratory, bone density), hospitalisations, prescribed drugs (arthritis [not including TNF inhibitor or co-stimulation modulator], anti-hyoertensive, gastro-protective, other), home care, transportation services, adaptive aids/other devices. The estimated annual costs of therapy were: Abatacept (250mg vial): $18,480 (Year 1), $17,160 (Year 2) Adalimumab (40mg pre-filled syringe): $17,680 (Year 1), $17,680 (Year2) Etanercept (25mg vial): $18,200 (Year 1), $18,200 (Year 2) Infliximab (100mg vial): $20,445 (Year 1), $18,330 (Year 2)				
Cost effectiveness					
Modelling summary	14 decision trees (for the various strategies) were designed and analysed as simulation models in DecisionPro software. Patients with moderate to severe RA with an inadequate response to DMARDs, eligible for biologic therapy are entering the model. Patients achieving treatment success (defined as either achieving a low disease-activity rate or remission) are maintained on existing therapy for up to 2 years. Those with an inadequate response to a biologic therapy are switched to a subsequent biologic agent, with decision to switch made at 6 months intervals in case of an inadequate response.				

	The model assesses the cost-effectiveness of abatacept used as first biologic therapy in patients with an inadequate response to DMARDs and as second biologic therapy in patients with an inadequate response to a first TNF inhibitor. The comparator was defined as a successive trial of TNF inhibitor therapies based on the most established treatment pattern in Canada at time of model development. Rituximab was not reimbursed for RA in Canada at that time, therefore it was not considered as a valid comparator. The same treatment continues as long as it is efficacious; decision to switch treatment for all causes (lack or loss of efficacy, adverse events, intolerance, etc); the model allows switches to occur every 6 months. The model calculates the overall effectiveness of each entire sequence of biologic strategies as an effectiveness outcome. Reference case was a 2-year treatment with up to three successive biologic agents (in case of an inadequate response to the previous biologic agent). Etanercept→Infliximab→Adalimumab→DMARDs The following strategies were simulated: Abatacept→Etanercept→Infliximab→DMARDs Etanecept→Abatacept→Infliximab→DMARDs				
Outcome measures used in economic evaluations	Cost per additional case of LDAS gained Cost per additional remission gained	**Statistical analysis for patient-level stochastic data**	Not undertaken	**Appropriateness of statistical analysis**	NA
Uncertainty					
Uncertainty around cost-effectiveness expressed	Probabilistic sensitivity analysis using 5000 Monte Carlo simulations was used to explore uncertainty in the model. Beta distribution was used for transition probabilities; lognormal distribution was used for costing variability	**Appropriateness of method dealing with uncertainty around cost effectiveness**	Yes		
Sensitivity analysis	One-way sensitivity analyses (scenario-based) was undertaken.	**Modelling inputs & techniques appropriate**	Yes		
Author's conclusions	*Inadequate response to DMARDs - Cost per additional case of LADS gained* The lowest cost biologic strategy was abatacept used as the first biologic agent. This strategy dominated the other two, providing 13.8% greater probability (29.4% vs. 15.6%) of achieving LDAS than sequential TNF inhibitor therapy with an overall RA-related cost-saving of $730 ($39,759 vs. $ 40,489) over 2 years.				

	Abatacept used as a second biologic after an inadequate response to one TNF inhibitor (etanercept) was cost-effective, providing 3.7% greater probability of achieving LDAS (19.3% vs. 15.6%) at an additional cost of $463 ($40,952 vs. $40,489) over the 2-year period, with an ICER of $12,514 per additional case of LDAS gained. Thus, abatacept used as first biologic appears to be less costly and to provide greater probability of achieving LDAS than using abatacept as second biologic agent. *Inadequate response to DMARDs - Cost per additional remission gained* The lowest cost biologic strategy was abatacept used as the first biologic agent. This strategy dominated the other two, providing 9.6% greater probability (14.8% vs. 5.2%) of remission than sequential TNF inhibitor therapy with an overall RA-related cost-saving of $504 ($38,061 vs. $ 38,565) over 2 years. Abatacept used as a second biologic after an inadequate response to one TNF inhibitor (etanercept) was cost-effective, providing 3.5% greater probability of achieving remission (8.7% vs. 5.2%) at an additional cost of $589 ($39,154 vs. $38,565) over the 2-year period, with an ICER of $16,829 per additional remission gained. Thus, abatacept used as first biologic appears to be less costly and to provide greater probability of achieving remission than using abatacept as second biologic agent. *Inadequate response to etanercept* After an initial 6-montha treatment failure to etanercept, all patients were switched to either abatacept or infliximab as the second biologic option, followed by infliximab and adalimumab, respectively. Abatacept used as second biologic agent was cost-effective, providing 6.9% additional treatment success rate for achieving LDAS (17.1% vs. 10.2%) and 3.5% additional treatment success rates for achieving remission (7.4% vs. 3.9%) at an ICER of £20,377 per additional case of LDAS and $26,400 per additional remission, respectively.

Table 92 Kielhorn 2008 -economic evaluation data extraction form

Author	Kielhorn	**Date**	2008	**Study population**	Patients with RA that failed to respond adequately to two non-biologic DMARDs and one TNF-α inhibitor	**Type of economic evaluation**	Cost-utility analysis
Intervention 1	Rituximab	**Intervention 2**					
Clinical Effectiveness							
Source of	The mean drop in HAQ for each of the responder groups			**Clinical outcomes**	Utilities are mapped from the HAQ score. The model uses		

effectiveness data	is calculated from the REFLEX trial.			**measured & methods of valuation used**	the equation as estimated by Bansback et al (2005). QoL = 0.76 – 0,28 x HAQ + 0.05 x Female All-cause mortality is derived by GAD (2005) and adjusted with an RA risk multiplier related to each individual's HAQ score (Barton et al, 2004)
Cost data					
Currency used	British £	**Years to which costs apply**	2004 (not explicitly stated)	**Perspective(s)**	NHS and Personal Social Services
Cost data handled appropriately	For each treatment, drug cost, administration cost and monitoring cost were considered. Drug costs were obtained from BNF 50. Administration costs are generated by bDMARDs requiring infusion or injection. For rituximab, 5 hours of administration was assumed on average, including pre-medication. For infliximab, a 3-hour infusion time for the 225mg of active substance was assumed including post-infusion observation time. A weight of 78kg was assumed (Cohen et al, 2006). No drug wastage or increase in dose was included in the calculation. Healthcare personnel attendance time was estimated according to Nuijten et al, 2001 and personnel salaries were obtained from PSSRU 2004. Monitoring costs include an outpatient visit or a GP visit, and certain examination and tests. Costs for these were obtained from NHS, PSSRU or Barton et al, 2004. Costs are linked to functional status, as measured by the HAQ score, by grouping HAQ scores into six categories (Kobelt et al, 1999, 2004). Each HAQ score category was assigned an average cost. Direct costs included the cost of the drug, drug administration, medical resource consumption (co-medication, surgery etc). All costs accruing after the first year of the evaluation were discounted at 3.5%.				
Cost effectiveness					
Modelling summary	A microsimulation Markov model was designed and analysed in Microsoft Excel. A cycle length of 6 months was used. Patients either follow the current standard treatment sequence reflecting real life clinical practice in the UK or an alternative sequence, which is identical, except for the introduction of rituximab as an additional treatment within the sequence. If patients respond they remain on the drug for a predetermined period of time. If they do not respond, they continue to the next treatment in the sequence. They remain in palliative care (MTX) until they reach 100 years of age or death. Analysis A, assumes non-sequential use of bDMARDs (NICE 36, 2002) Analysis B, assumed sequential use of bDMARDs; (based on data from the British Society of Rheumatology Biologics Registry and Hyrich				

	et al, 2006) Patients enter the model and are allocated to either of the two treatment sequences. The patients are then exposed to the first treatment in the sequence and are allocated to one of the three responder groups; ACR 20-49, 50-69, 70+, or to the non-responder group. The HAQ score is assumed to drop by 0.1 for non-respondents, 0.45 for ACR20-49, 0.85 for ACR50-69 and 1.11 for ACR70+ respondents (Kielhorn et al, 2005). While on treatment, patient HAQ scores are assumed to progress by 0.017 during each cycle of the model (Scott et al, 2000). HAQ progression for patients on palliative care is assumed to be 0.065 (Bansback et al, 2005). Time on treatment in the sequence was derived from Barton et al, 2004 and was 4.25 years for all bDMARDs apart from infliximab where, driven by a higher drop-out of patients, 2.46 years was assumed. NbDMARDs treatment duration was 1.7 years for ciclosporin, 3.85 years for gold and 4.1 years for leflunomide. For rituximab a course of 2 x 1000 mg every 9 months over the course of 4.25 years was assumed. For all other drugs the licensed dose as per the EU label was assumed. Once treatment stops, the entire initial gain in HAQ is assumed to be lost instantly (100% rebound effect). Patients are then allocated to the next available treatment option until the treatment sequence is exhausted. At this point, all patients receive palliative care, defined as single agent MTX, until death. Patients leave the model when they reach the age of 100 years or die.				
Outcome measures used in economic evaluations	Incremental QALY's and ICER's	**Statistical analysis for patient-level stochastic data**	Not undertaken	**Appropriateness of statistical analysis**	NA
Uncertainty					
Uncertainty around cost-effectiveness expressed	Yes. Model uncertainty was explored using PSA with 1000 samples by Monte Carlo simulation. Due to lack of data it was not possible to run a PSA on all variables. For these variables, one-way sensitivity analysis was applied instead. A Dirichlet distribution was fit for response rate parameters, a Weibull distribution into the time on treatment parameters and a normal distribution was fit into the inpatient day (trimmed for values [0,+∞)).	**Appropriateness of method dealing with uncertainty around cost effectiveness**	Yes		
Sensitivity analysis	Yes. One-way sensitivity analysis was applied to determine	**Modelling inputs & techniques**	Yes		

	the relative importance of different parameters to the primary outcome. The model was not sensitive with respect to changes to assumed time on treatment, or changes between adjusted and unadjusted response rates. Larger variability was observed in changes to rituximab dosing re-treatment from 9 months to 6 months and when changing the HAQ long-term progression. Variability was also observed when baseline age is increased.	**appropriate**	
Author's conclusions	Both analyses showed higher treatment cost in the sequence containing rituximab. Analysis A Total discounted QALYs were 3.051 and 2.324 for the rituximab arm and the standard of care arm, respectively, resulting in a QALY gain of 0,.727. The ICER based on total direct medical costs was £14,690 Analysis B QALY gain was 0.526 the ICER based on total direct medical costs was £11,601		

Table 93 Vera-Llonch 2008 -economic evaluation data extraction form

Author	Vera-Llonch	**Date**	2008	**Study population**	Women with moderate to severe RA with inadequate response to TNF inhibitors	**Type of economic evaluation**	Cost-utility analysis
Intervention 1	Abatacept	**Intervention 2**					
Clinical Effectiveness							
Source of effectiveness data	Source for effectiveness data was the ATTAIN trial.			**Clinical outcomes measured & methods of valuation used**	Improvement in HAQ scores during the first 6 months of therapy. For patients continuing to receive abatacept beyond 6 months, the improvement at 6 months was assumed to persist over time. For patients discontinuing abatacept, the HAQ score was assumed to return to a value equal to what it would have been in the absence of such treatment (oral DMARD only).		

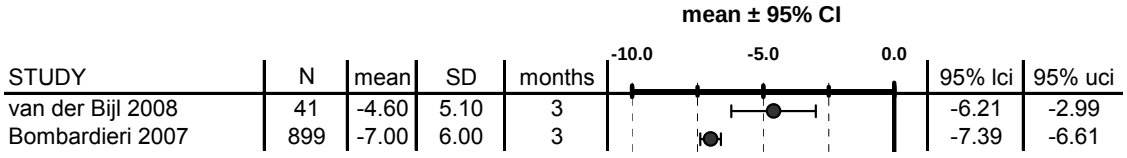
					Initial HAQ scores are randomly assigned to each patient entering the model from an assumed initial probability distribution. Future values of the HAQ score were estimated based on the assumed initial value, the expected rate of disease progression, and the expected effect of treatment. The estimated mean percentage HAQ change 3 months after therapy initiation in ATTAIN was 21%; at 6 months it was 25.5%. The distribution of the HAQ change with abatacept was assumed to be truncated normal, based on visual inspection of the data in ATTAIN. Among patients continuing to receive abatacept, the percentage reduction in the HAQ was assumed to remain constant at the level prevailing at 6 months. However, the HAQ value against which this percentage reduction was applied was increased by 0.015 annually. Health-state utility values were mapped from the HAQ score. Although mean utilities corresponding to the appropriate HAQ score are presented in a table, the exact formula that was using for this mapping is not provided. For patients receiving oral DMARD only, the HAQ score was assumed to increase by 0.065 annually to reflect disease progression. Mortality risk was estimated through age and the expected value of the HAQ score. Health-state utilities were similarly estimated based on the expected future values of the HAQ score.
Cost data					
Currency used	$ (US)	**Years to which**	2006	**Perspective(s)**	Third party payer (medical treatment only – direct non-

		costs apply			medical costs or loss productivity were excluded)	
Cost data handled appropriately	Following an initial infusion, abatacept was assumed to be administered on days 14 and 29, and every 4 weeks thereafter, for a total of 15 infusions during the first year and 13 infusions every year thereafter. Patients weighing < 60kg were assumed to receive 2 vials (500mg) per infusion; 60-100kg, 3 vials (750mg); and >100mg, 4 vials (1g). The cost of abatacept was assumed to be $450 per 250mg vial. The cost of each 30 min infusion was assumed to be $129. Oral DMARD therapy was assumed to consist of MTX. The annual cost of treatment with MTX was assumed to be $600, based on an assumed dose of 15mg weekly. Estimates of the cost of baseline and routine monitoring for patients receiving abatacept were based on product labelling, published guidelines and Medicare payment rates. Tests for abatacept patients were assumed to cost $9 (one off cost) while tests for the DMARD patients were at $181 per year. Costs were discounted at 3%.					
Cost effectiveness						
Modelling summary	A simulation model of a hypothetical cohort of 1,000 women aged 55-64 was developed. The model cycle was 3 months. Patients enter the model, at either the 'oral DMARD' state or the 'oral DMARD state plus abatacept'. Patients on abatacept are assumed to initiate treatment on day 1 [500-100mg (based on body weight) i.v. infusion over 30 min[, and receive additional infusions on day 14, day 29, and every 4 weeks thereafter. Patients with HAQ-DI improvements of -0.50 or greater at 6 months were assumed to continue to receive abatacept. Patients failing to achieve this improvement are assumed to discontinue treatment. Patients also discontinue treatment for other reasons such as side effects, intercurrent illness and surgery. All patients discontinuing abatacept are assumed to continue to receive 'oral DMARDs'. Authors justify this assumption (assuming no switch from abatacept to another biologic DMARD) on the bases that there are no data on the efficacy of the latter agents given prior failure with abatacept. Time horizons were 10 years and lifetime.					
Outcome measures used in economic evaluations	Incremental cost per QALY		**Statistical analysis for patient-level stochastic data**	Not undertaken	**Appropriateness of statistical analysis**	NA
Uncertainty						

Uncertainty around cost-effectiveness expressed	Expressed through 100 Monte Carlo simulations.	**Appropriateness of method dealing with uncertainty around cost effectiveness**	Yes
Sensitivity analysis	Yes. Selected assumptions and parameter estimates were varied, including: - Discontinuation of abatacept therapy for lack of efficacy or other reasons - Timing of therapy discontinuation due to lack of efficacy (3 vs. 6 months) - OR for mortality associated with each 1-point increase in the HAQ score - Assumption of mortality benefit with abatacept - Expected rate of disease progression - Threshold for clinical meaningful improvement in HAQ - Women aged other than 55-64 - Male population	**Modelling inputs & techniques appropriate**	Yes
Author's conclusions	Over a 10-year time horizon, the cost-effectiveness of abatacept was estimated to be $50,576 per QALY gained. On a lifetime basis, cost-effectiveness was $45,979 per QALY gained. At a threshold of $100,000 per QALY, the probability that abatacept would be cost-effective was 1. At a threshold of $20,000 per QALY, abatacept would be unlikely to be cost-effective (probability=0) At a threshold of $50,000 per QALY, the probability that abatacept would be cost-effective was 0.39 over a 10-year time horizon and 1 over lifetime.		

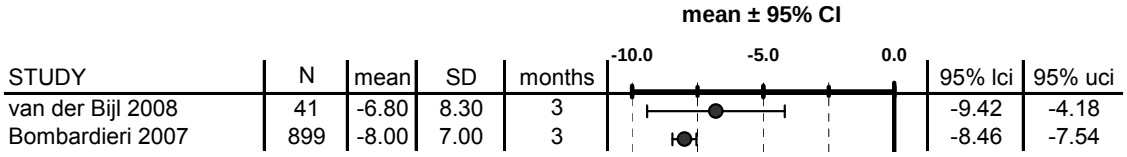
10.10 Outcomes not reported in the main text of the report

10.10.1 Adalimumab



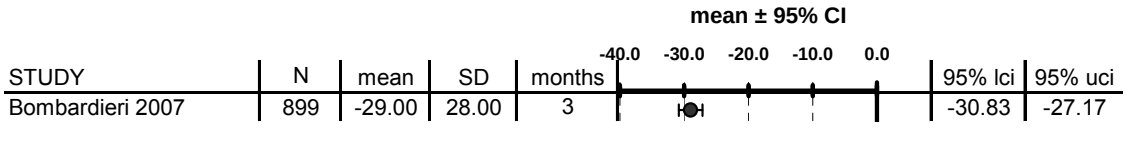
STUDY	N	mean	SD	months	95% lci	95% uci
van der Bijl 2008	41	-4.60	5.10	3	-6.21	-2.99
Bombardieri 2007	899	-7.00	6.00	3	-7.39	-6.61

Figure 97 Adalimumab - swollen joint count, change from baseline



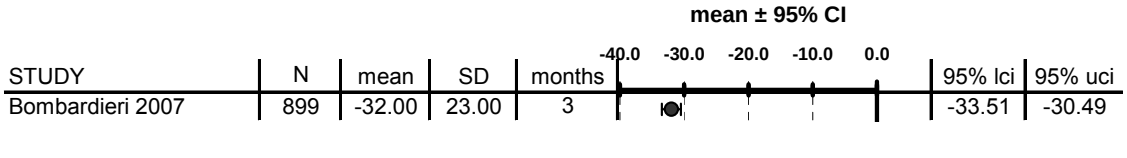
STUDY	N	mean	SD	months	95% lci	95% uci
van der Bijl 2008	41	-6.80	8.30	3	-9.42	-4.18
Bombardieri 2007	899	-8.00	7.00	3	-8.46	-7.54

Figure 98 Adalimumab - tender joint count, change from baseline



STUDY	N	mean	SD	months	95% lci	95% uci
Bombardieri 2007	899	-29.00	28.00	3	-30.83	-27.17

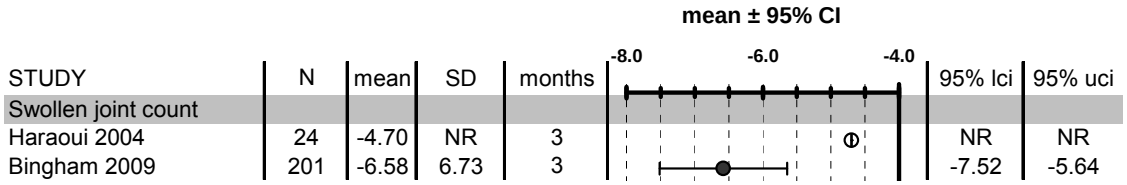
Figure 99 Adalimumab - pain (VAS), change from baseline



STUDY	N	mean	SD	months	95% lci	95% uci
Bombardieri 2007	899	-32.00	23.00	3	-33.51	-30.49

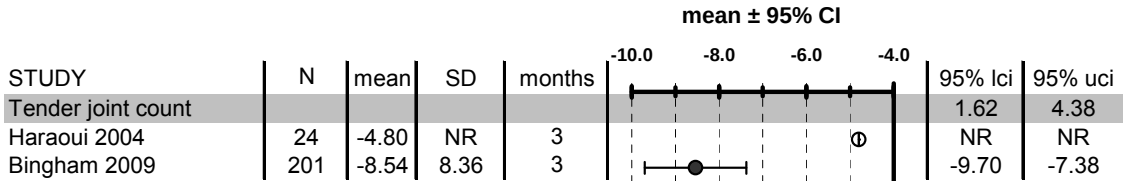
Figure 100 Adalimumab - physician global assessmen (VAS), change from baseline

10.10.2 Etanercept



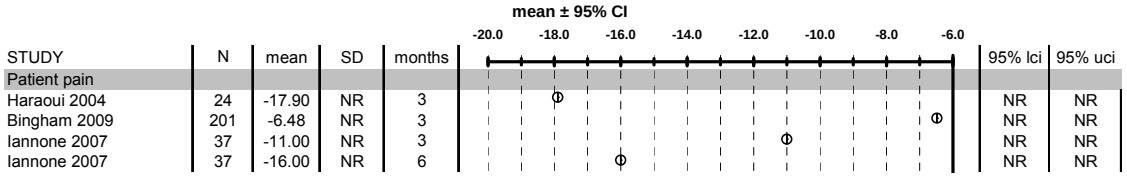
STUDY	N	mean	SD	months	95% lci	95% uci
Swollen joint count						
Haraoui 2004	24	-4.70	NR	3	NR	NR
Bingham 2009	201	-6.58	6.73	3	-7.52	-5.64

Figure 101 Etanercept: Swollen Joint Count



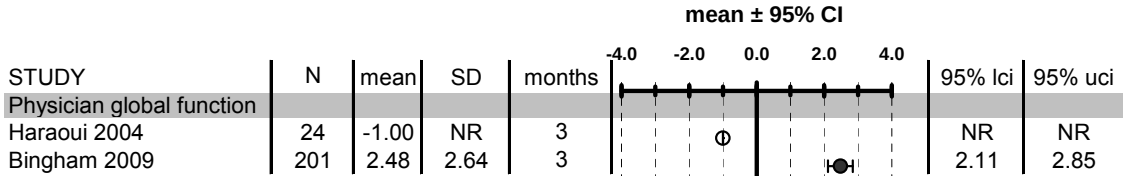
STUDY	N	mean	SD	months	95% lci	95% uci
Tender joint count					1.62	4.38
Haraoui 2004	24	-4.80	NR	3	NR	NR
Bingham 2009	201	-8.54	8.36	3	-9.70	-7.38

Figure 102 Etanercept: Tender Joint Count



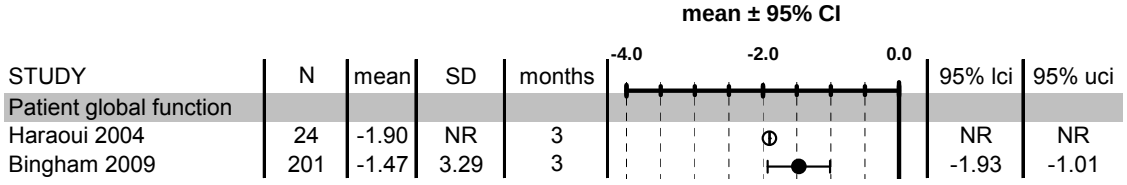
STUDY	N	mean	SD	months	95% lci	95% uci
Patient pain						
Haraoui 2004	24	-17.90	NR	3	NR	NR
Bingham 2009	201	-6.48	NR	3	NR	NR
Iannone 2007	37	-11.00	NR	3	NR	NR
Iannone 2007	37	-16.00	NR	6	NR	NR

Figure 103 Etanercept: patient pain



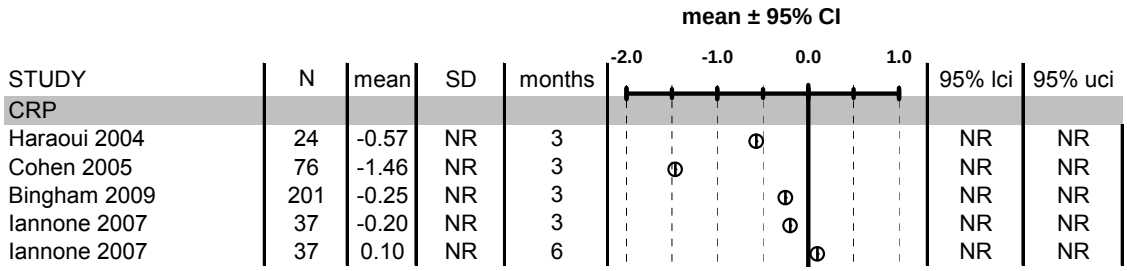
STUDY	N	mean	SD	months	95% lci	95% uci
Physician global function						
Haraoui 2004	24	-1.00	NR	3	NR	NR
Bingham 2009	201	2.48	2.64	3	2.11	2.85

Figure 104 Etanercept: Physician global function



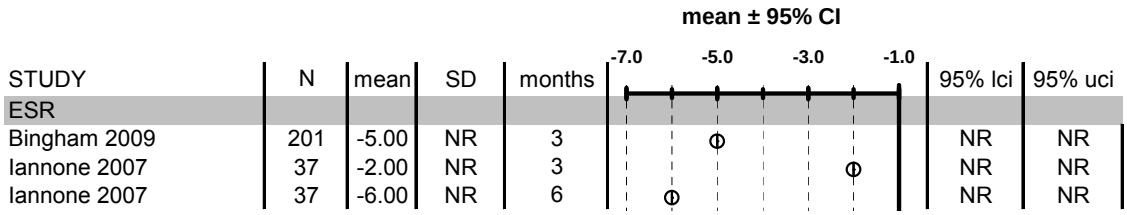
STUDY	N	mean	SD	months	95% lci	95% uci
Patient global function						
Haraoui 2004	24	-1.90	NR	3	NR	NR
Bingham 2009	201	-1.47	3.29	3	-1.93	-1.01

Figure 105 Etanercept - Patient global function



STUDY	N	mean	SD	months	95% lci	95% uci
CRP						
Haraoui 2004	24	-0.57	NR	3	NR	NR
Cohen 2005	76	-1.46	NR	3	NR	NR
Bingham 2009	201	-0.25	NR	3	NR	NR
Iannone 2007	37	-0.20	NR	3	NR	NR
Iannone 2007	37	0.10	NR	6	NR	NR

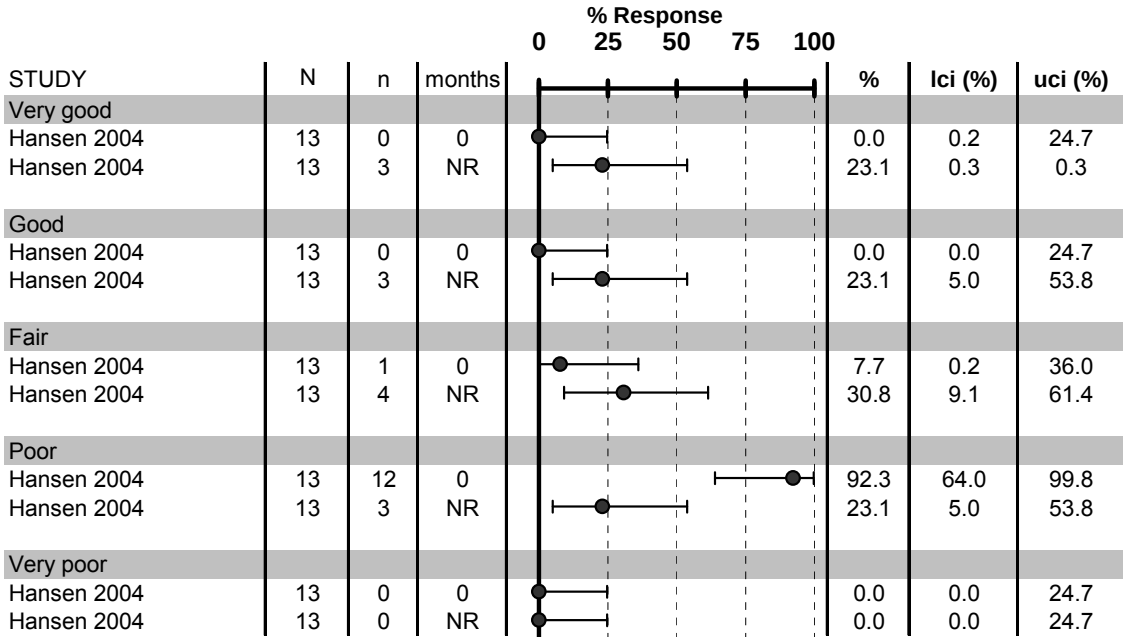
Figure 106 Etanercept - mean change from baseline in CRP



STUDY	N	mean	SD	months	95% lci	95% uci
ESR						
Bingham 2009	201	-5.00	NR	3	NR	NR
Iannone 2007	37	-2.00	NR	3	NR	NR
Iannone 2007	37	-6.00	NR	6	NR	NR

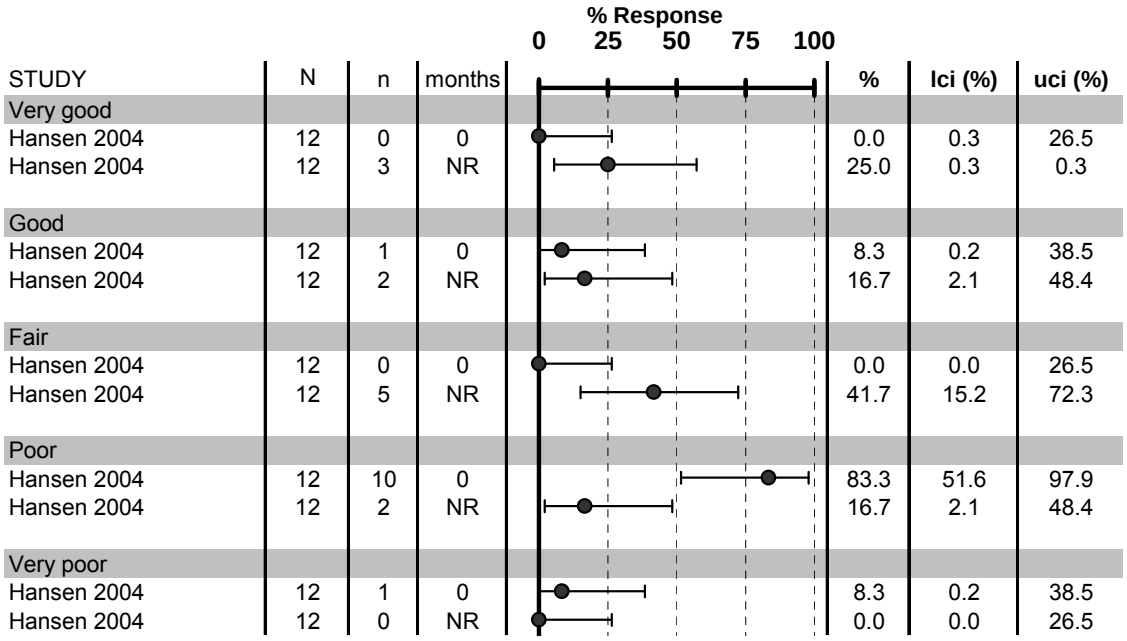
Figure 107 Etanercept - mean change from baseline in ESR

10.10.3 Infliximab



STUDY	N	n	months	%	lci (%)	uci (%)
Very good						
Hansen 2004	13	0	0	0.0	0.2	24.7
Hansen 2004	13	3	NR	23.1	0.3	0.3
Good						
Hansen 2004	13	0	0	0.0	0.0	24.7
Hansen 2004	13	3	NR	23.1	5.0	53.8
Fair						
Hansen 2004	13	1	0	7.7	0.2	36.0
Hansen 2004	13	4	NR	30.8	9.1	61.4
Poor						
Hansen 2004	13	12	0	92.3	64.0	99.8
Hansen 2004	13	3	NR	23.1	5.0	53.8
Very poor						
Hansen 2004	13	0	0	0.0	0.0	24.7
Hansen 2004	13	0	NR	0.0	0.0	24.7

Figure 108 Infliximab - physician global assessment



STUDY	N	n	months	%	lci (%)	uci (%)
Very good						
Hansen 2004	12	0	0	0.0	0.3	26.5
Hansen 2004	12	3	NR	25.0	0.3	0.3
Good						
Hansen 2004	12	1	0	8.3	0.2	38.5
Hansen 2004	12	2	NR	16.7	2.1	48.4
Fair						
Hansen 2004	12	0	0	0.0	0.0	26.5
Hansen 2004	12	5	NR	41.7	15.2	72.3
Poor						
Hansen 2004	12	10	0	83.3	51.6	97.9
Hansen 2004	12	2	NR	16.7	2.1	48.4
Very poor						
Hansen 2004	12	1	0	8.3	0.2	38.5
Hansen 2004	12	0	NR	0.0	0.0	26.5

Figure 109 Infliximab - patient global assessment

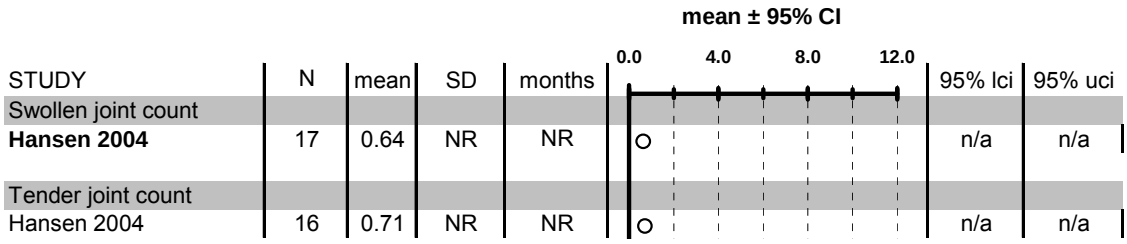


Figure 110 Infliximab - percentage change from baseline in swollen and tender joint count

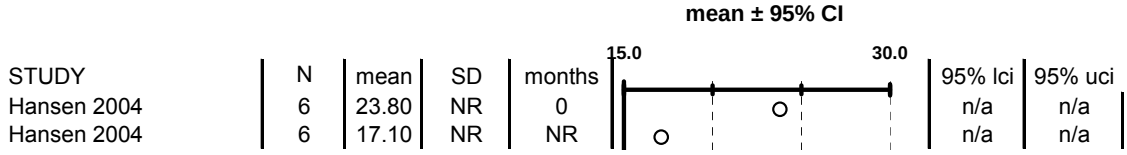


Figure 111 Infliximab - CRP

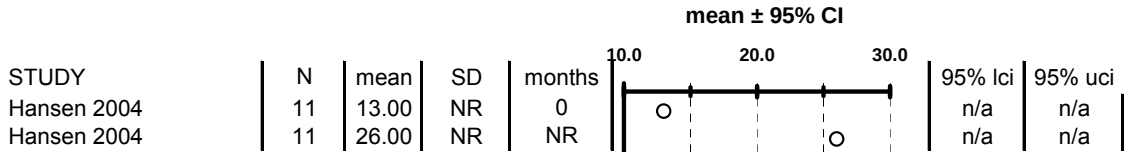
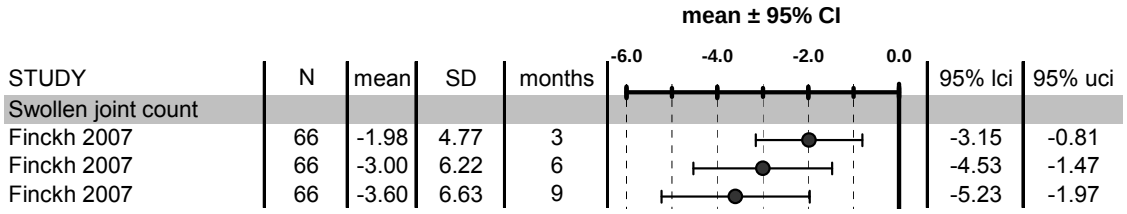


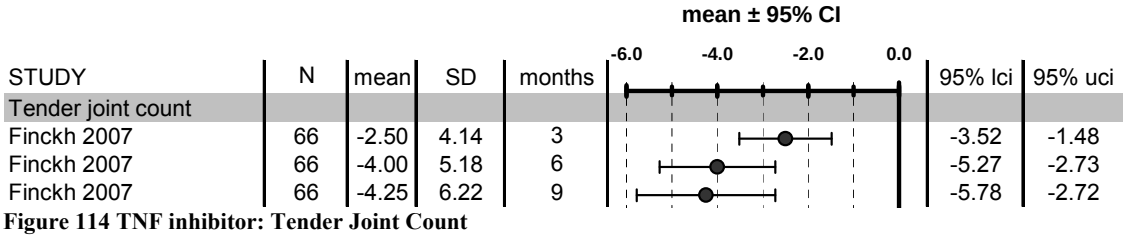
Figure 112 Infliximab - ESR

10.10.4 TNF inhibitors as a class



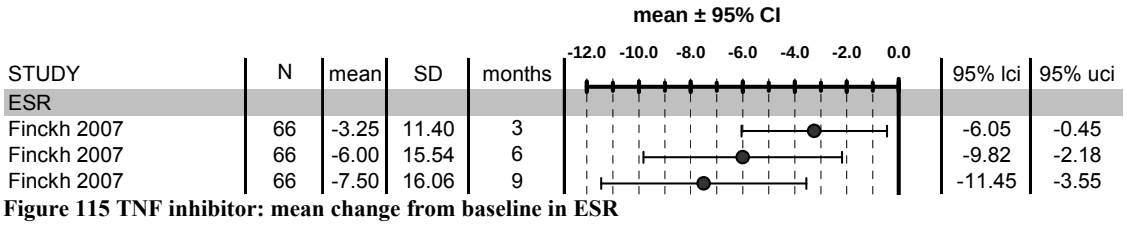
STUDY	N	mean	SD	months	95% lci	95% uci
Swollen joint count						
Finckh 2007	66	-1.98	4.77	3	-3.15	-0.81
Finckh 2007	66	-3.00	6.22	6	-4.53	-1.47
Finckh 2007	66	-3.60	6.63	9	-5.23	-1.97

Figure 113 TNF inhibitor: Swollen Joint Count



STUDY	N	mean	SD	months	95% lci	95% uci
Tender joint count						
Finckh 2007	66	-2.50	4.14	3	-3.52	-1.48
Finckh 2007	66	-4.00	5.18	6	-5.27	-2.73
Finckh 2007	66	-4.25	6.22	9	-5.78	-2.72

Figure 114 TNF inhibitor: Tender Joint Count



STUDY	N	mean	SD	months	95% lci	95% uci
ESR						
Finckh 2007	66	-3.25	11.40	3	-6.05	-0.45
Finckh 2007	66	-6.00	15.54	6	-9.82	-2.18
Finckh 2007	66	-7.50	16.06	9	-11.45	-3.55

Figure 115 TNF inhibitor: mean change from baseline in ESR

10.10.5 Rituximab

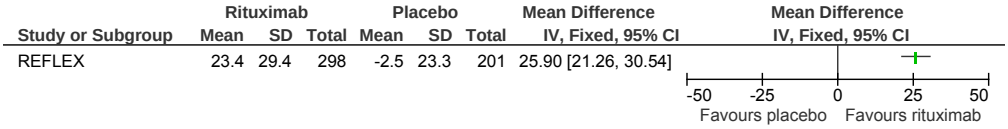


Figure 116 Rituximab - Patient pain (0-100mm VAS) change from baseline at week 24 in the REFLEX RCT

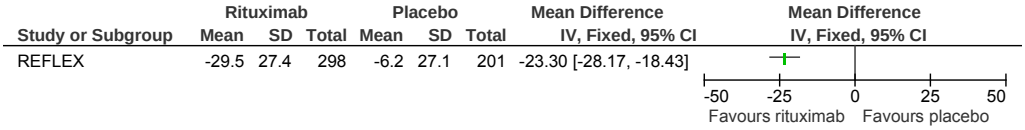


Figure 117 Rituximab - Physical global function (0-100mm VAS) change from baseline at week 24 in the REFLEX RCT

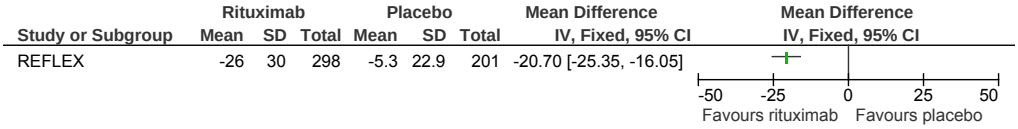


Figure 118 Rituximab - Patient global function (0-100mm VAS) change from baseline at week 24 in the REFLEX RCT

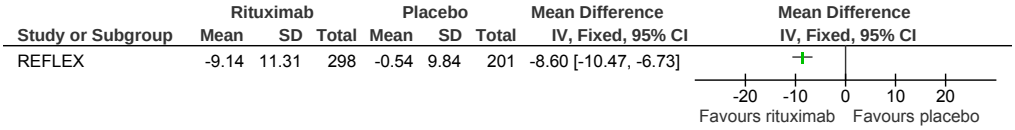


Figure 119 RTX – change in FACIT–F (range 0-52) score from baseline at week 24 in the REFLEX RCT

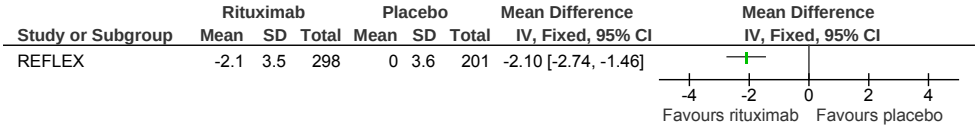


Figure 120 Rituximab – mean change in CRP (mg/l) from baseline at week 24 in the REFLEX RCT

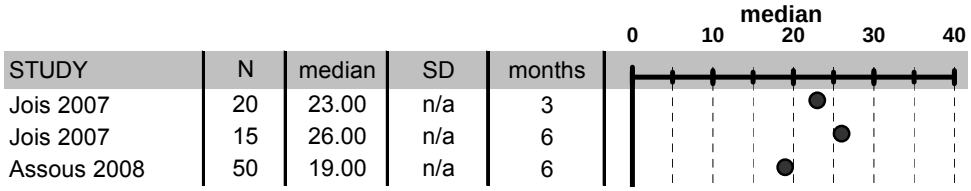


Figure 121 Rituximab – Median CRP (mg/l) in uncontrolled studies

(ns versus baseline for the Jois study and p<0.05 versus baseline for the Assous study)

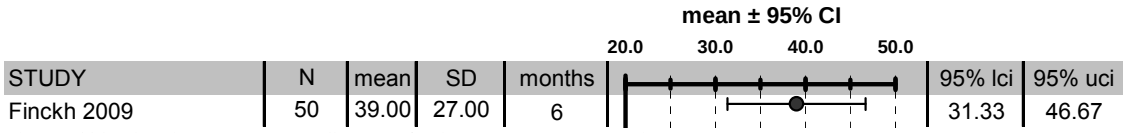


Figure 122 Rituximab – Mean ESR (mm/h) in uncontrolled studies

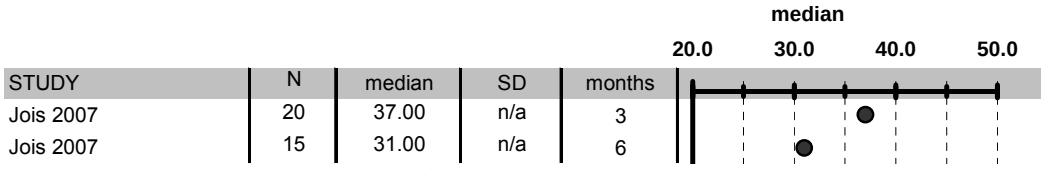


Figure 123 Rituximab – Median ESR (mm/h) in uncontrolled studies
(p<0.0001 for both at 3 months and 6 months)

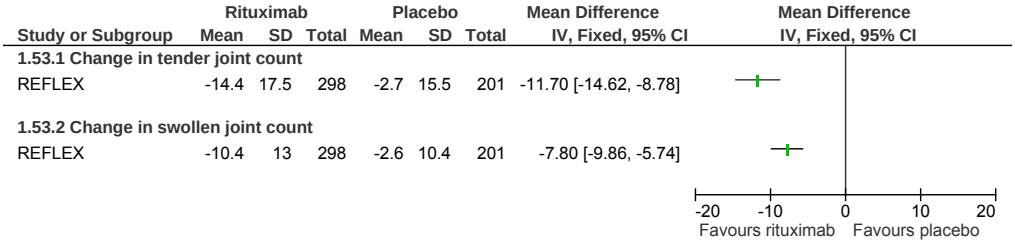


Figure 124 Rituximab - Change in tender/swollen joint count from baseline at week 24 in the REFLEX RCT

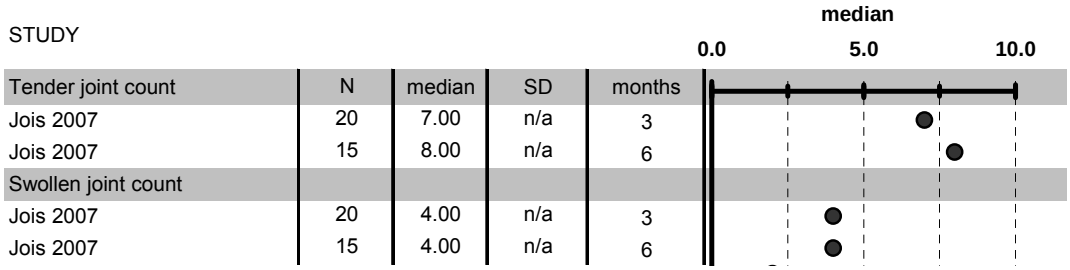


Figure 125 Rituximab – Median tender/swollen joint count in uncontrolled studies
(p<0.0001 for 3 months versus baseline and p<0.05 for 6 months versus baseline)

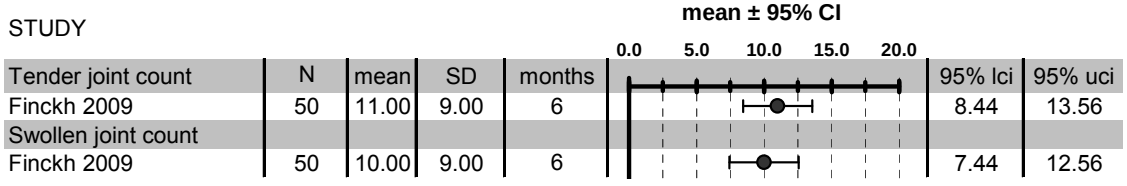


Figure 126 Rituximab – Mean tender/swollen joint count in uncontrolled studies

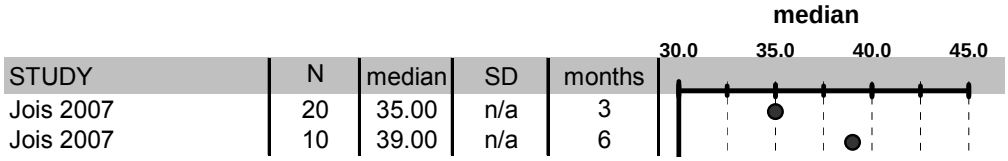


Figure 127 Rituximab – Median patient global score (VAS 0-100 mm) in uncontrolled studies

Joint damage data from MS

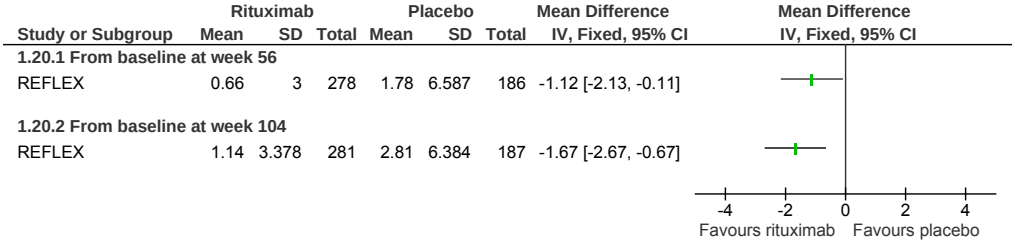


Figure 128 Rituximab – Sharp-Genant total score change from baseline in the REFLEX trial (Data from MS; the SD for that at week 56 was calculated from p value)

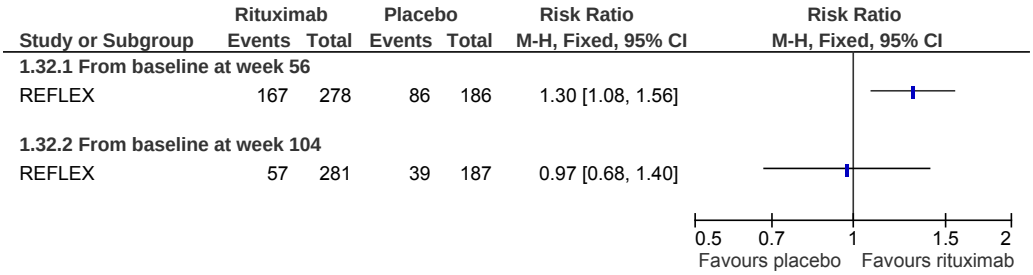


Figure 129 Rituximab – Percentage of patients with no worsening Sharp-Genant total score from baseline in the REFLEX trial (Data from MS)

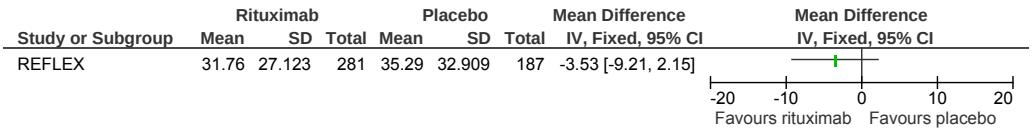


Figure 130 Rituximab – Sharp-Genant total score at week 104 in the REFLEX trial (data from MS)

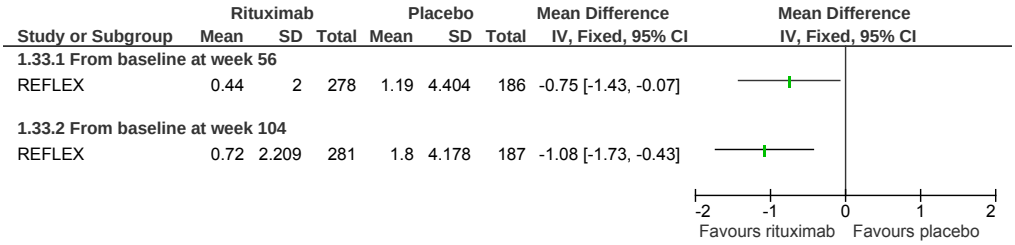


Figure 131 Rituximab – Erosion score change from baseline in the REFLEX trial (Data from MS; the SD for that at week 56 was calculated from p value)

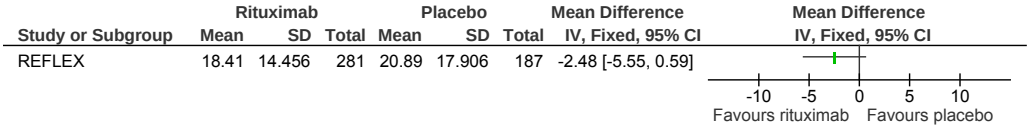


Figure 132 Rituximab – Erosion scores at week 104 in the REFLEX trial (Data from MS)

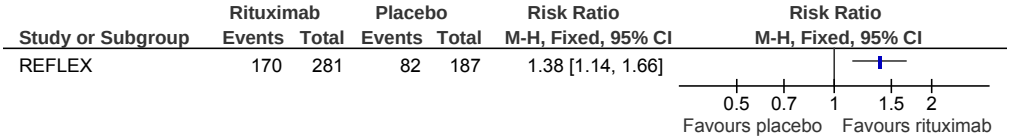


Figure 133 Rituximab – percentage of patients with no erosive progression from baseline at week 104 in the REFLEX trial (Data from MS)

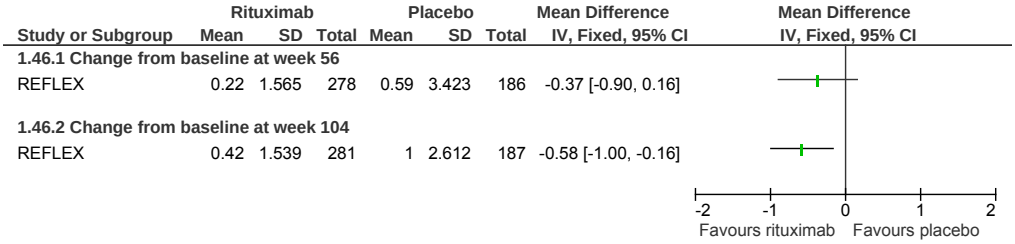


Figure 134 Rituximab – Joint space narrowing score change from baseline in the REFLEX trial (Data from MS; for the 56 week the SD was calculated from p value)

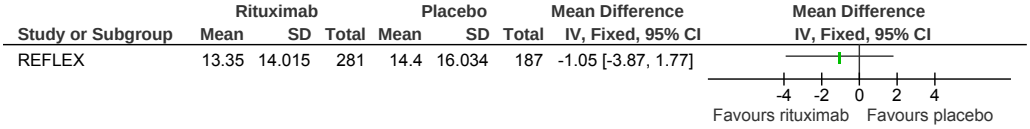
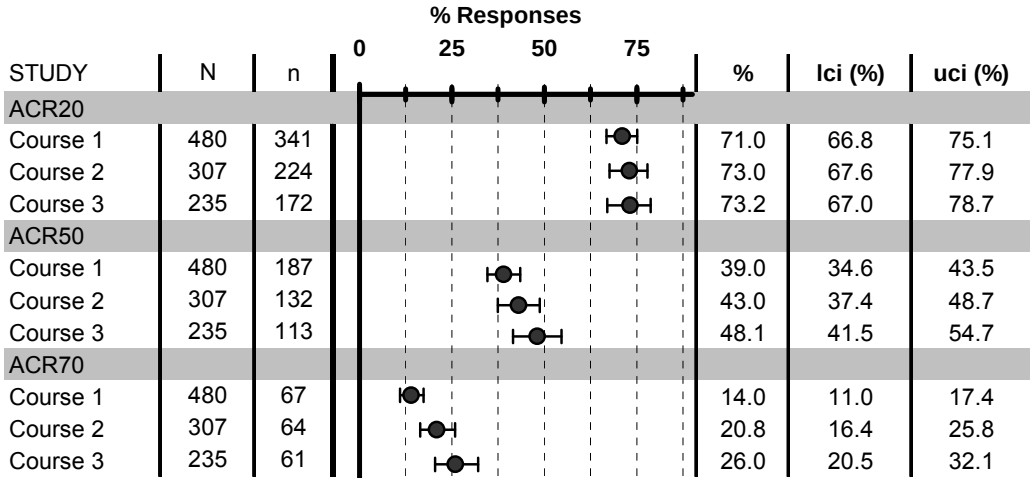


Figure 135 Rituximab – Joint space narrowing score at week 104 in the REFLEX trial (Data from MS)

REFLEX extension

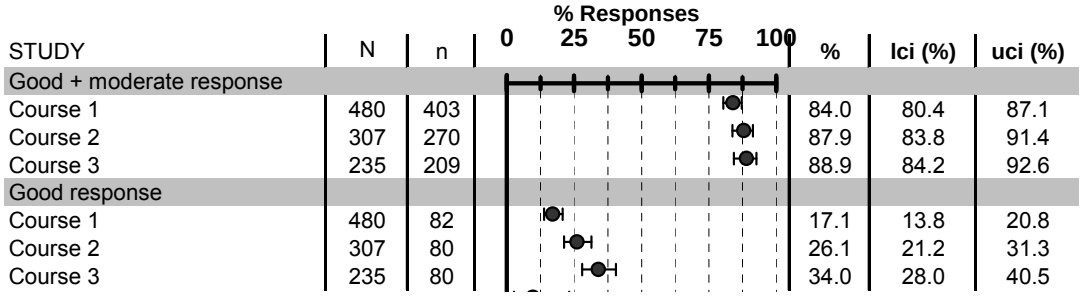
Figure 136 below presents ACR response at week 24 after 1, 2, and 3 RTX treatment courses versus original baseline in the REFLEX trial. Similar pattern was seem for each ACR responses 24 week after each course, with the ACR responses following each course were slightly increased with subsequent courses.



STUDY	N	n	%	lci (%)	uci (%)
ACR20					
Course 1	480	341	71.0	66.8	75.1
Course 2	307	224	73.0	67.6	77.9
Course 3	235	172	73.2	67.0	78.7
ACR50					
Course 1	480	187	39.0	34.6	43.5
Course 2	307	132	43.0	37.4	48.7
Course 3	235	113	48.1	41.5	54.7
ACR70					
Course 1	480	67	14.0	11.0	17.4
Course 2	307	64	20.8	16.4	25.8
Course 3	235	61	26.0	20.5	32.1

Figure 136 Rituximab - ACR response at week 24 after each course vs. original baseline (data from MS)

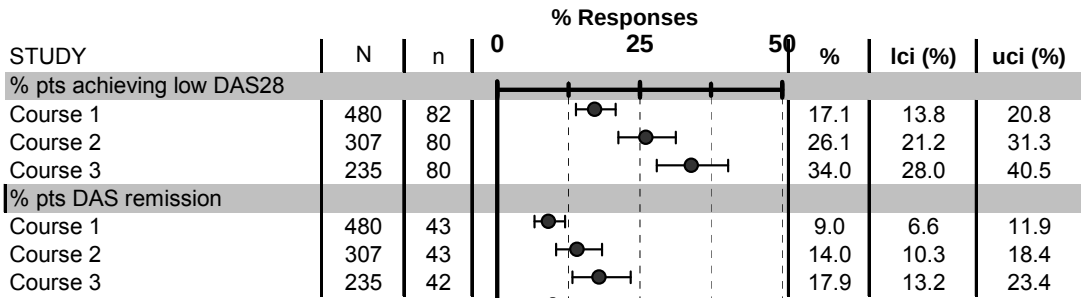
Figure 137 below presents EULAR response at week 24 after 1, 2 and 3 courses of RTX versus original baseline of the REFLEX trial. The percentage of patients achieving moderate plus good response and good response alone increased with each treatment course (from 84% to 87.9% to 88.9% and from 17.1% to 26.1% to 28% respectively).



STUDY	N	n	%	lci (%)	uci (%)
Good + moderate response					
Course 1	480	403	84.0	80.4	87.1
Course 2	307	270	87.9	83.8	91.4
Course 3	235	209	88.9	84.2	92.6
Good response					
Course 1	480	82	17.1	13.8	20.8
Course 2	307	80	26.1	21.2	31.3
Course 3	235	80	34.0	28.0	40.5

Figure 137 Rituximab - EULAR responses 24 weeks after each course vs. original baseline (data from MS)

Figure 138 below presents percentage of patients achieving DAS28 low disease activity or remission at week 24 after course 1, 2 and 3 versus original baseline of the REFLEX trial. Improvement for both was observed following sequent courses (from 17.1% to 26.1% to 34% and from 9% to 14% to 13.2% respectively).

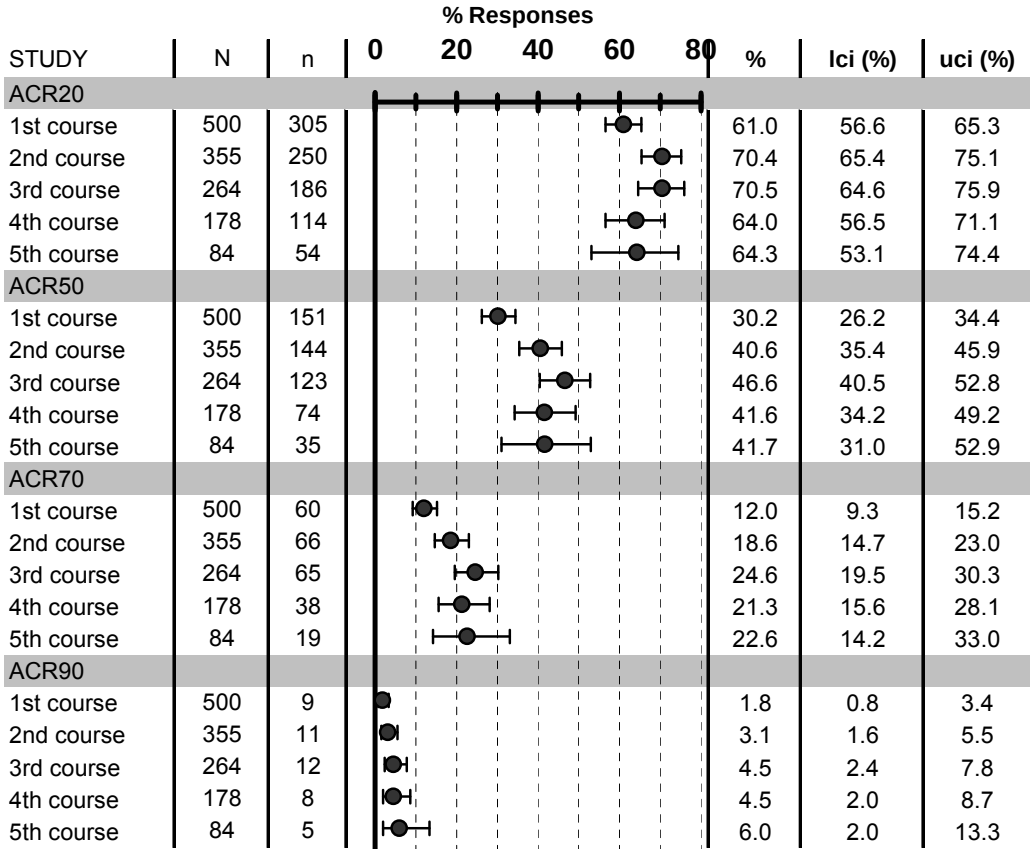


STUDY	N	n	%	lci (%)	uci (%)
% pts achieving low DAS28					
Course 1	480	82	17.1	13.8	20.8
Course 2	307	80	26.1	21.2	31.3
Course 3	235	80	34.0	28.0	40.5
% pts DAS remission					
Course 1	480	43	9.0	6.6	11.9
Course 2	307	43	14.0	10.3	18.4
Course 3	235	42	17.9	13.2	23.4

Figure 138 Rituximab - Percentage of patients achieving DAS28 low disease activity at week 24 after each course vs original baseline (data from MS)

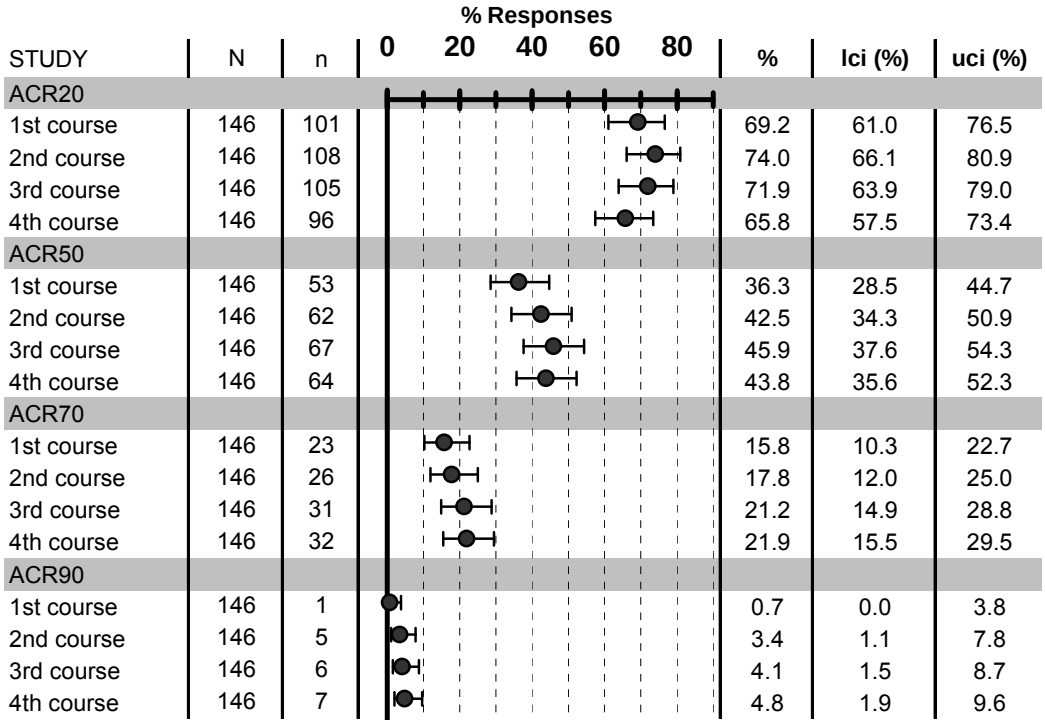
Pooled analysis data (manufacturer's submission)

Figure 139 presents ACR responses for 4 or 5 courses and Figure 140 presents ACR responses for 3 or 4 courses of rituximab 24 weeks after each course. The overall pattern was that there was an improvement from the 1st to the 2nd course and then maintained through the subsequent courses. Observed data on EULAR responses for 4 or 5 courses at 24 weeks after each course showed a similar pattern as that of ACR responses (Figure 141).



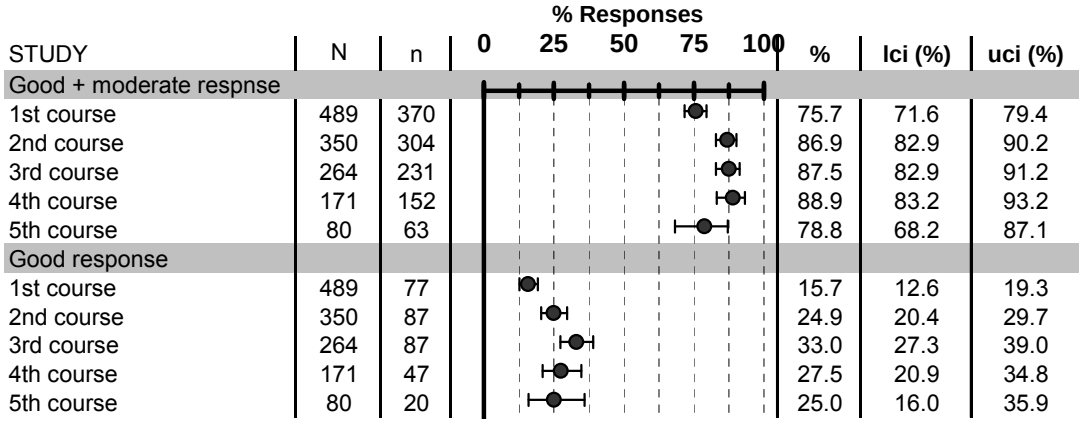
STUDY	N	n	%	lci (%)	uci (%)
ACR20					
1st course	500	305	61.0	56.6	65.3
2nd course	355	250	70.4	65.4	75.1
3rd course	264	186	70.5	64.6	75.9
4th course	178	114	64.0	56.5	71.1
5th course	84	54	64.3	53.1	74.4
ACR50					
1st course	500	151	30.2	26.2	34.4
2nd course	355	144	40.6	35.4	45.9
3rd course	264	123	46.6	40.5	52.8
4th course	178	74	41.6	34.2	49.2
5th course	84	35	41.7	31.0	52.9
ACR70					
1st course	500	60	12.0	9.3	15.2
2nd course	355	66	18.6	14.7	23.0
3rd course	264	65	24.6	19.5	30.3
4th course	178	38	21.3	15.6	28.1
5th course	84	19	22.6	14.2	33.0
ACR90					
1st course	500	9	1.8	0.8	3.4
2nd course	355	11	3.1	1.6	5.5
3rd course	264	12	4.5	2.4	7.8
4th course	178	8	4.5	2.0	8.7
5th course	84	5	6.0	2.0	13.3

Figure 139 Rituximab - ACR responses for five courses of treatment 24 weeks after each course (all patients; observed data; data from MS)



STUDY	N	n	%	lci (%)	uci (%)
ACR20					
1st course	146	101	69.2	61.0	76.5
2nd course	146	108	74.0	66.1	80.9
3rd course	146	105	71.9	63.9	79.0
4th course	146	96	65.8	57.5	73.4
ACR50					
1st course	146	53	36.3	28.5	44.7
2nd course	146	62	42.5	34.3	50.9
3rd course	146	67	45.9	37.6	54.3
4th course	146	64	43.8	35.6	52.3
ACR70					
1st course	146	23	15.8	10.3	22.7
2nd course	146	26	17.8	12.0	25.0
3rd course	146	31	21.2	14.9	28.8
4th course	146	32	21.9	15.5	29.5
ACR90					
1st course	146	1	0.7	0.0	3.8
2nd course	146	5	3.4	1.1	7.8
3rd course	146	6	4.1	1.5	8.7
4th course	146	7	4.8	1.9	9.6

Figure 140 Rituximab - ACR responses for 3 or 4 course (24 weeks) after each course (within patients within visit comparisons, observed data, n=146; data from MS)

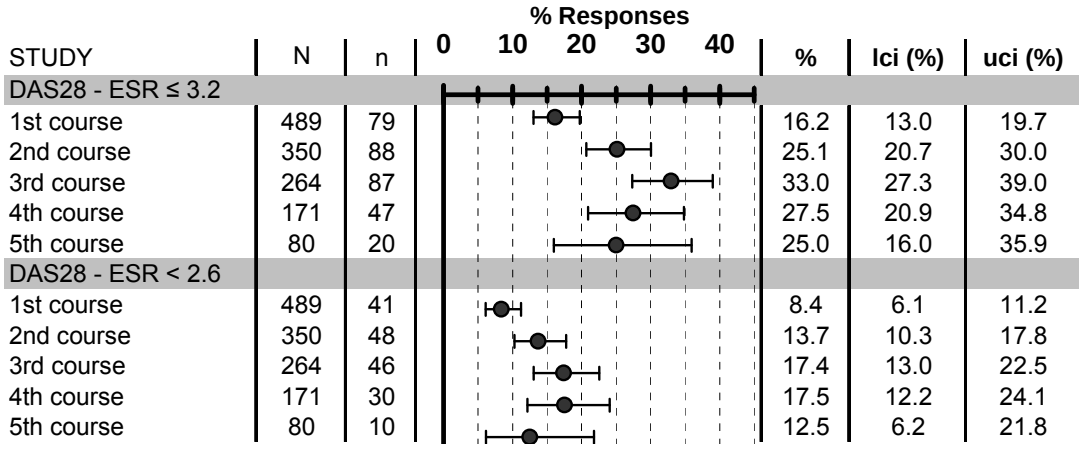


STUDY	N	n	%	lci (%)	uci (%)
Good + moderate respnse					
1st course	489	370	75.7	71.6	79.4
2nd course	350	304	86.9	82.9	90.2
3rd course	264	231	87.5	82.9	91.2
4th course	171	152	88.9	83.2	93.2
5th course	80	63	78.8	68.2	87.1
Good response					
1st course	489	77	15.7	12.6	19.3
2nd course	350	87	24.9	20.4	29.7
3rd course	264	87	33.0	27.3	39.0
4th course	171	47	27.5	20.9	34.8
5th course	80	20	25.0	16.0	35.9

Figure 141 Rituximab - EULAR response rates for 4 or 5 courses (week 24 after each course, all patients, observed data; data from ms)

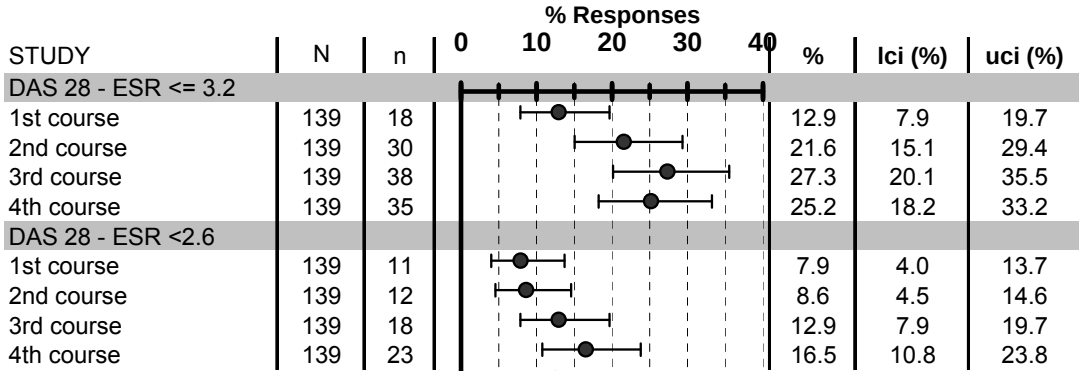
The patterns for the percentage of patients with low disease activity (defined as DAS28-ESR≤3.2) and with remission (defined as DAS28-ESR<2.6) for 4 or 5 courses at week 24 after each course, and for data on 3 or 4 courses at week 24 after each course, were similar, with a improvement

from 1st to 2nd course and to 3rd course and then generally maintained with subsequent courses (Figure 142 and Figure 143).



STUDY	N	n	%	lci (%)	uci (%)
DAS28 - ESR ≤ 3.2					
1st course	489	79	16.2	13.0	19.7
2nd course	350	88	25.1	20.7	30.0
3rd course	264	87	33.0	27.3	39.0
4th course	171	47	27.5	20.9	34.8
5th course	80	20	25.0	16.0	35.9
DAS28 - ESR < 2.6					
1st course	489	41	8.4	6.1	11.2
2nd course	350	48	13.7	10.3	17.8
3rd course	264	46	17.4	13.0	22.5
4th course	171	30	17.5	12.2	24.1
5th course	80	10	12.5	6.2	21.8

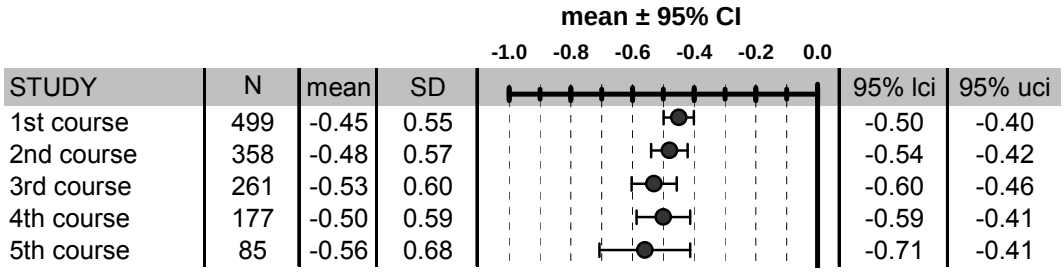
Figure 142 Rituximab - Percentage of patients with low disease activity (DAS28-ESR ≤ 3.2) and with remission of disease activity (DAS28-ESR < 2.6) for 4 or 5 courses (week 24 after each course, all patients, observed data; data from MS)



STUDY	N	n	%	lci (%)	uci (%)
DAS 28 - ESR <= 3.2					
1st course	139	18	12.9	7.9	19.7
2nd course	139	30	21.6	15.1	29.4
3rd course	139	38	27.3	20.1	35.5
4th course	139	35	25.2	18.2	33.2
DAS 28 - ESR <2.6					
1st course	139	11	7.9	4.0	13.7
2nd course	139	12	8.6	4.5	14.6
3rd course	139	18	12.9	7.9	19.7
4th course	139	23	16.5	10.8	23.8

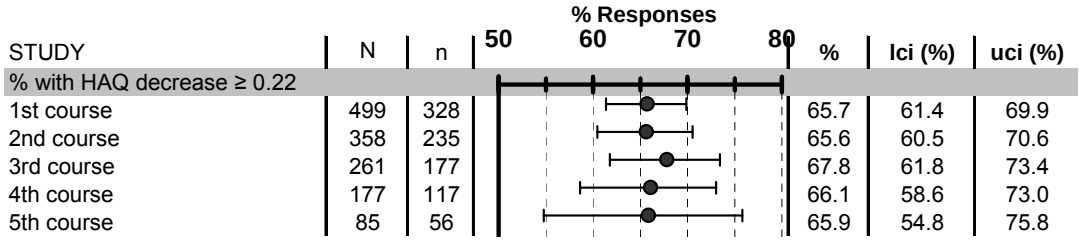
Figure 143 Rituximab - Percentage of patients with low disease activity (DAS28-ESR ≤ 3.2) and with remission of disease activity (DAS28-ESR < 2.6) for 3 or 4 course (week 24 after each course, all patients, observed data; data from MS)

Figure 144 presents the change from original baseline of the REFLEX trial in HAQ for 4 or 5 courses 24 weeks after each course and Figure 145 presents the percentage of patients achieving minimally important clinical difference, i.e. a decrease in HAQ score of ≥0.22 from baseline, for 4 or 5 courses 24 weeks after each course. Both the change in HAQ score and the percentage of patients achieving a clinically meaningful decrease in HAQ score maintained over treatment courses of rituximab.



STUDY	N	mean	SD	95% lci	95% uci
1st course	499	-0.45	0.55	-0.50	-0.40
2nd course	358	-0.48	0.57	-0.54	-0.42
3rd course	261	-0.53	0.60	-0.60	-0.46
4th course	177	-0.50	0.59	-0.59	-0.41
5th course	85	-0.56	0.68	-0.71	-0.41

Figure 144 Rituximab – Change from original baseline in HAQ endpoints for 4 or 5 courses (week 24 after each course, all patients, observed data; data from MS)



STUDY	N	n	%	lci (%)	uci (%)
% with HAQ decrease ≥ 0.22					
1st course	499	328	65.7	61.4	69.9
2nd course	358	235	65.6	60.5	70.6
3rd course	261	177	67.8	61.8	73.4
4th course	177	117	66.1	58.6	73.0
5th course	85	56	65.9	54.8	75.8

Figure 145 Rituximab - Percentage of patients with HAQ decrease ≥ 0.22 from original baseline for 4 or 5 courses (week 24 after each course, all patients, observed data; data from MS)

10.10.6 Abatacept

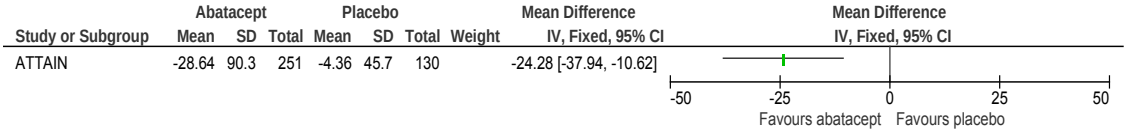


Figure 146 Abatacept - change in pain score (VAS) in the ATTAIN RCT at 6 months

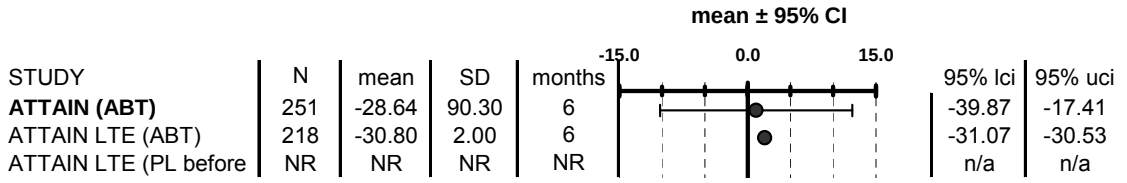


Figure 147 Abatacept - change in pain score (VAS) in uncontrolled studies

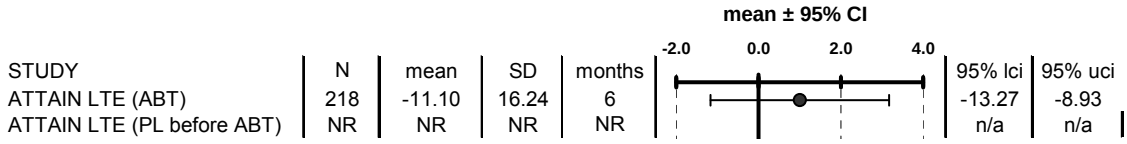


Figure 148 Abatacept - change in sleep score - uncontrolled studies at 6 months

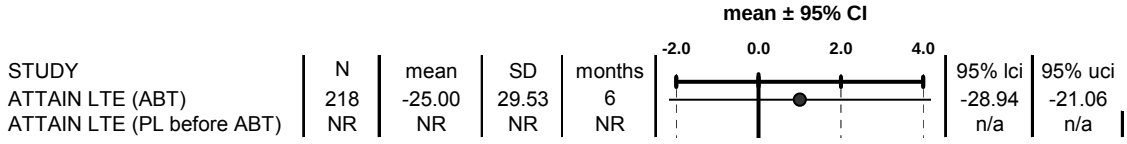


Figure 149 Abatacept - change in fatigue score in uncontrolled studies at 6 months

10.11 Survey of West Midlands rheumatologists

A survey of rheumatologists in the West Midlands was conducted in June and July 2009 to investigate current practice and clinicians' preferences for treatment options in rheumatoid arthritis.

Methods

In the beginning of June a questionnaire was sent to a convenience sample of 55 rheumatologists by email (see Figure 150)

1. Which DMARD(s), in addition to MTX, do you normally try before using a TNF inhibitor?

2. Which is your preferred 1st choice TNF inhibitor, if any?

3. In people not responding adequately to a TNF inhibitor, assuming that another TNF inhibitor, rituximab, abatacept, and tocilizumab were all available and not restricted by NICE, which DMARDs (including non-biologic agents) would you next try (jot down an ideal sequence of individual or combinations you prefer, in sequence, and ignore issues of local logistics and of patient co-morbidity)

a) first ……

b) second (if the first fails)…….

c) third (etc)…….

d) fourth ……

e) fifth (and beyond, continue as long as your imagination or patience allows)
…….

4. Please write here any general comments or thoughts

Figure 150 Survey of West Midlands Rheumatologists

Responses were collected until early July when a reminder together with the results of the survey so far was sent. Responses received afterwards were included in the results.

Due to the overall variability it was not possible to determine in any way if the three responses received after the reminder were influenced by the knowledge of the early results.

Results

Twenty four rheumatologists replied before the reminder email. Three additional responses were received after the reminder was sent out. The overall response rate was 49%.

For drugs used in addition to methotrexate before the initiation of the first TNF inhibitor responses often included combinations of multiple conventional DMARDs or different therapeutic options. Sulfasalazine alone or in combination with other DMARDs was the most frequently mentioned DMARD (in 22 responses) used before the initiation of the first TNF inhibitor. Leflunomide was mentioned in 17 responses and hydroxychloroquine in ten. Five respondents mentioned the use of steroids.

Results for the first TNF inhibitor and following treatment options are presented in Figure 151. The highest number of respondents (nine) left the choice of the first TNF inhibitor to the patient. Seven would chose adalimumab and one indicated that this drug was most often chosen by patients. Etanercept was the preferred first TNF inhibitor for six respondents, however three would ultimately leave the choice to their patient. The remaining four would choose either adalimumab or etanercept (two because of involvement in a clinical trial).

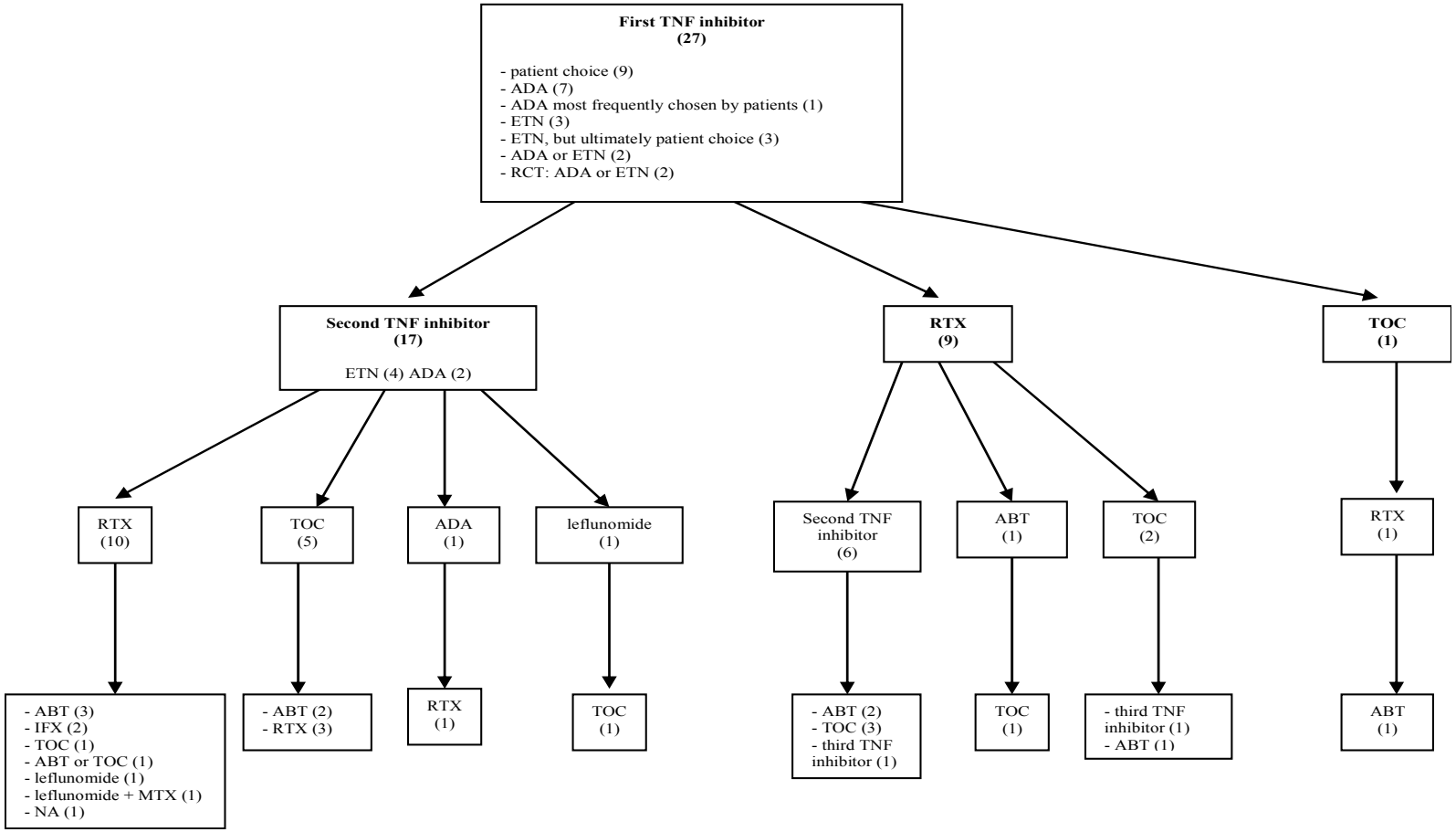
After the failure of the first TNF inhibitor 17 respondents would try a second one (only six were specific and their preferences were – adalimumab in four and etanercept in two cases). Nine respondents would try rituximab as a second line biologic agent and one – tocilizumab.

There was more variability in the following lines of treatment and preferences depended on what has been tried before. After the failure of a second TNF inhibitor ten respondents would try rituximab, five tocilizumab, one adalimumab and one leflunomide. After the failure of rituximab (following first TNF inhibitor) six respondents would try a second TNF inhibitor, two would try tocilizumab and one – abatacept. One respondents who would try tocilizumab after the failure of the first TNF inhibitor would choose rituximab as the next therapeutic option.

For the next line of treatment please see Figure 151. Results for the subsequent treatment options are not reported due to their high variability.

The comments from respondents included a number of issues referring both to current practice and proposed research:

- different factors might influence choice of drug, such as:
- previous or possible tuberculosis,
- risk of infection,
- co-morbidities,
- primary vs. secondary failure,
- sero-positive vs. –negative patients,
- intolerance vs. inefficacy,
- ethnicity (etanercept preferred in Asian patients),
- “needle-phobia”;
- practice is frequently tailored to the individual patient (pattern of disease, side-effect risks, etc.);
- going back to a TNF inhibitor already used could be considered;
- for some patients receiving biologic treatments, adjunct DMARDs other than methotrexate could be considered;
- switching TNF inhibitors before the three-month NICE deadline could be considered if the patient showed little response;
- a combination of TNF inhibitors could be considered.



Numbers in brackets are the numbers of respondents selecting an option

Figure 151 Survey of West Midlands Rheumatologists - results

10.12 Withdrawals from treatment with TNF inhibitors

Withdrawal from treatment with 2'nd line anti-TNF (BSRBR data)

Updated BSRBR data[152] provided Kaplan-Meier plots for survival in treatment for four groups of patients receiving second line anti-TNF therapy as follows: [i] withdrew from 1'st line anti-TNF for lack of efficacy and from 2'nd line anti-TNF for lack of efficacy; [ii] withdrew from 1'st line anti-TNF for lack of efficacy and from 2'nd line anti-TNF for adverse events; [iii] withdrew from 1'st line anti-TNF for adverse events and from 2'nd line anti-TNF for lack of efficacy; [iv] withdrew from 1'st line anti-TNF for adverse events and from 2'nd line anti-TNF for adverse events.

The proportion lost to treatment at 3-month time points in each category was read from the graphs in the BSRBR submission and the absolute number lost calculated using N=995 for 1'st line withdrawal through lack of efficacy and N=1882 for 1'st line withdrawal due to adverse events. The proportion of patients withdrawing for any reason was then estimated and the proportion remaining in treatment plotted (data points Figure 152). A Weibull distribution (time in years) was fitted to the data (scale parameter (lambda) 0.441555 (SE 0.00958300), shape parameter (gamma) 0.7008 (SE 0.033681) labelled BSRBR Weibull fit in Figure 152 (extrapolation to 25 years is shown in the inset).

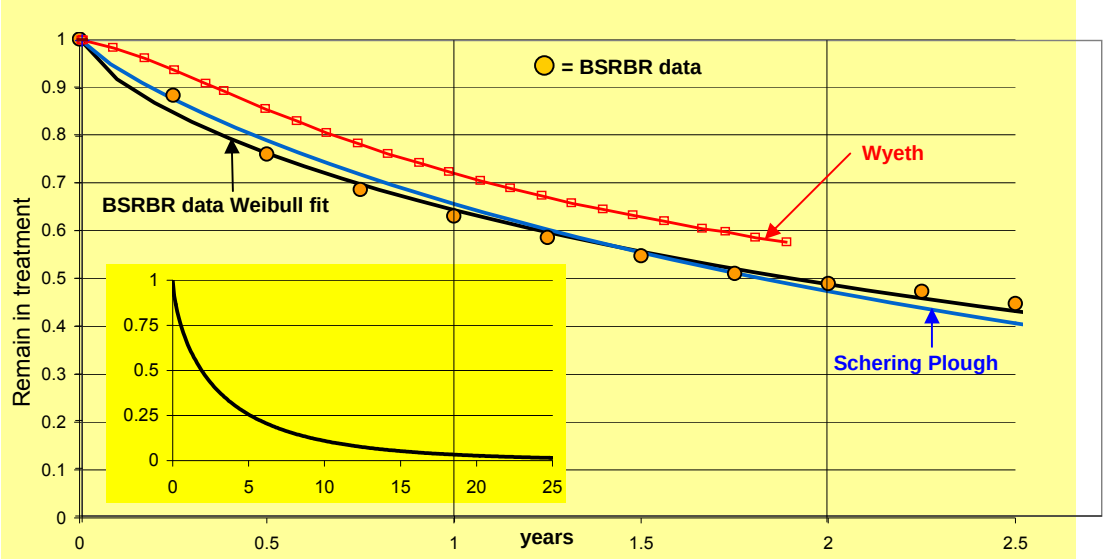


Figure 152 Continuation in 2'nd line anti-TNF therapy.

Comparison with manufacturer's submissions

The Schering Plough (infliximab) submission[172] provided Weibull parameters for treatment withdrawal that were also based on BSRBR data; the parameters are shown below.

Log(scale)	3.529	(time in months)
Log(shape)	-0.19	(time in months)

Assuming log (scale) in the table above refers to "log β" where β = (1/λ) ^[1/γ], and survival = exp(-(t* β)^ γ)), then lambda = 0.054 and gamma = 0.827 and the fitted curve labelled Schering Plough in Figure 152 is generated (and can be seen to be very similar to the review group's fit).

The Wyeth submission[173] modelled withdrawal from treatment using a "shared frailty" model and this is also represented in Figure 152.

Withdrawal from 2'nd line treatment according to anti-TNF agent

According to analysis of Danish National registry (DANBIO) data withdrawal from 1'st line anti-TNF treatment occurs at rates that are statistically significantly different between the three anti-TNFs, Table 94 provides the reported hazard ratios and 95% CIs (Hetland et al 2009 [174]).

Table 94 Hazard ratios for withdfrawal from 1'st line anti-TNFs (DANBIO data)

COMPARISON	HAZARD RATIO	HR 95% CIs	Weibull fit HR
Adalimumab v. etanercept	1.35	1.13 to 1.61	1.28
Infliximab v. etanercept	2.10	1.70 to 2.59	1.80
Infliximab v. adalimumab	1.56	1.26 to 1.94	1.41

It may be reasonable to expect that similar differences might apply for 2'nd line anti-TNF treatments.

Data was extracted from the Kaplan-Meier graph for each anti-TNF agent published for the Danish registry.[174] These were fitted with Weibull distributions (Figure 153 left) and survivors then combined for each drug (according to number of patients given each anti-TNF) so as to provide overall survival (N=2,935), and this in turn was fitted with a Weibull distribution.

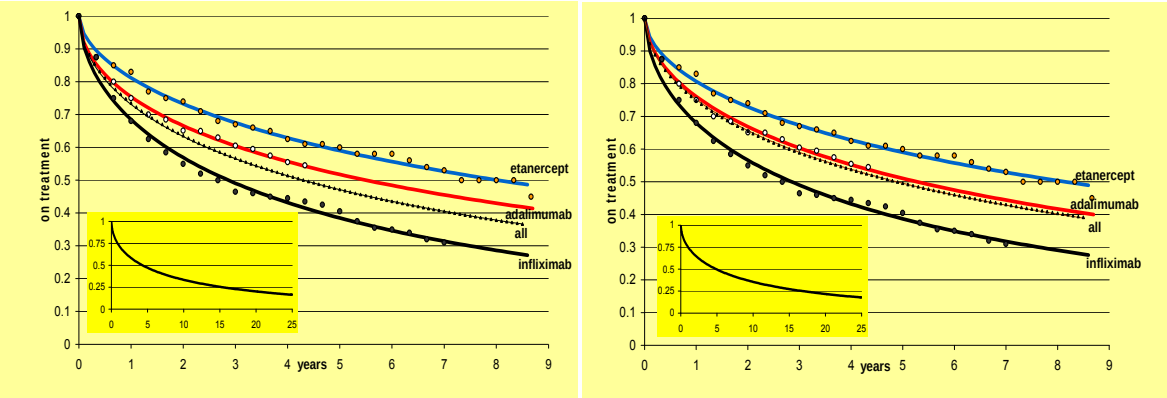


Figure 153 Withdrawal from 1'st line anti-TNFs (DANBIO data with Weibull fits).

The shape parameters for the Weibull fits were similar and therefore it was considered reasonable to average these and apply the same shape parameter for each drug and for overall survival. Because the BSRBR 1'st line withdrawal data was derived using equal numbers of patients (~4000) treated with each anti-TNF the shape parameters for the DANBIO data were combined to give an unweighted average. Using this "common" shape parameter (0.5595) the data were again fitted with Weibull distributions providing the fits shown in Figure 153 right; the overall survival then assumed equal numbers received each of the three anti-TNFs; this allows comparison of DANBIO and BSRBR 1'st line withdrawal data (see below).

The hazard ratios (ratio of scale parameters) for comparison of anti-TNFs using these Weibull fits were within the respective hazard ratio 95% CIs reported for the Danish registry data[7] (Table 94). Relative to all patients (equal mixture) the hazard ratios for each anti-TNF calculate as follows: Etanercept v all, 0.751; Adalimumab v all, 0.958; Infliximab v all, 1.353.

When these HRs are applied to the Weibull fit of BSRBR data[152] for continuation of 2'nd line treatment the drug-specific rates of withdrawal over 25 years are as shown in

Figure 154.

[7] Contact with the lead author confirmed that the published HRs were reversed for ada v etan and inf v ada; this has been corrected in the table above.

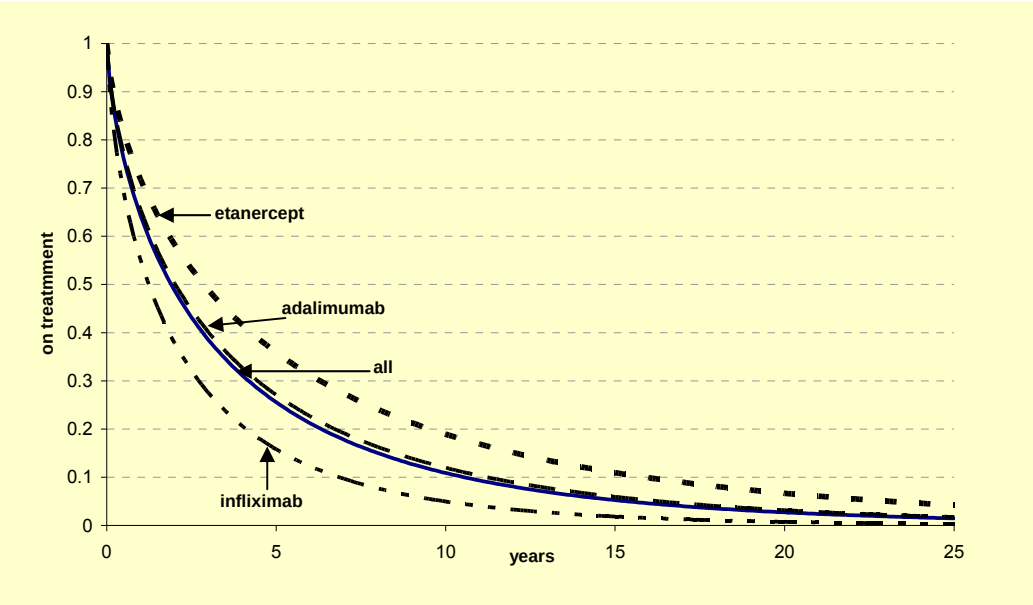


Figure 154 Estimated continuation of 2'nd line treatment according to anti-TNF agent.

DANBIO and BSRBR withdrawal rates from 1'st line anti-TNF therapy.

Data for 1'st line withdrawal were extracted from the UK BSRBR submission[152] and fitted with Weibull distributions in which the shape parameter was or was not fixed to that for overall survival derived from the Danish registry data (0.5595, see above). Extrapolations to 25 years were compared between UK and Danish 1'st line treatments and between 1'st line and 2'nd line treatments (Figure 155).

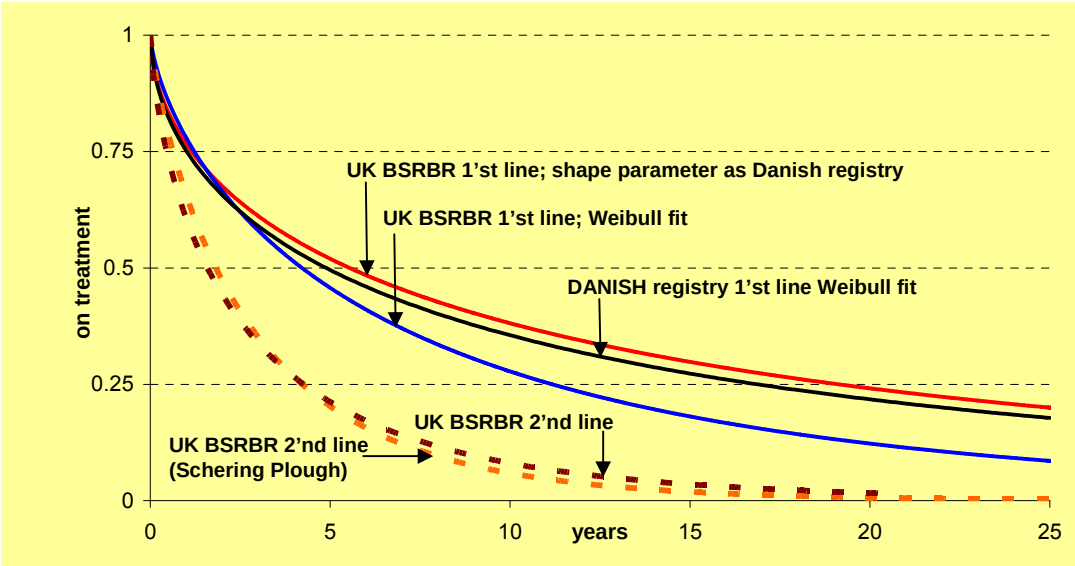


Figure 155 Modelled survival in treatment with 1'st and 2'nd line ant-TNFs.

Additional sources of evidence

Several additional sources were identified with potentially relevant information on withdrawal from the different anti-TNF agents; these are listed in Table 95.

Except for the DANBIO registry data (Hetland 2009 [174]) the studies do not provide the information required (K-M plots) to easily compare withdrawal rates between different anti-TNFs, the main reasons being: mixed analysis of 1'st and 2'nd line withdrawal, mixed populations (RA only a subpopulation), or outcome measure a combination of switching and of dose escalation (Curtis 2009 [175]). The German study[176] does provide information for etanercept and adalimumab but follow up was insufficient to see any difference developing. Wolfe & Michaud 2007[177] reported median survival in 2'nd line anti-TNF therapy. These results (Table 96) compare reasonably well with the median survival for each anti-TNF calculated as described above and shown in Figure 154.

In general the data from these studies is consistent with the DANBIO study in that continuation with etanercept appears superior to that with infliximab and continuation with adalimumab treatment being intermediate.

Table 95 Studies reporting withdrawal rates from anti-TNF treatments

Study Country	POPULATION (n) Anti-TNFs	1'st line / 2'nd line withdrawal	Findings	Comment
DANBIO Hetland 2009 [174] Denmark	RA [National registry] (2,935) Infliximab, etanercept & adalimumab	Withdrawal from 1'st line	Withdrawal more likely for infliximab than adalimumab and for ada than etan.	Separate data for withdrawal from 1'st line treatment with each anti-TNF.
Finckh 2006 [178] Switzerland	RA only (1,198) Infliximab, etanercept & adalimumab	Mixed, not differentiated	No difference between infl, etan, and ada after adjustment for RF +'ivity, baseline DAS28, HAQ, failure of previous anti-TNF.	Not useful for 1'st line or 2'nd line withdrawal for RA.
Duclos 2006 [179] France	Mix of RA [57%] & SpA [one centre]. (770) Infliximab, etanercept & adalimumab	Mixed, not differentiated	No difference between anti-TNFs. Retention longer for 1'st line v 2'nd line [HR 2.17; 95% CI) 1.82–2.58, p < 0.0001] and better if concomitant DMARD.	Not useful for 1'st line or 2'nd line withdrawal for RA.
Gomez-Reino 2006 [106] Spain	Mixed [68% RA] (4,706) Infliximab, etanercept &	Both 1'st line & 2'nd line differentiated	Retention longer for 1'st line v 2'nd line, & for 2'nd line v 3'rd line. 2'nd line retention better if 1'st line	Not useful for 1'st line or 2'nd line withdrawal for RA.

	adalimumab		failure was for AEs rather than lack of efficacy. Retention in inf influenced by availability of etan. 2'nd line retention better after switch to etan from inf than if to switch to inf from etan.	
Vollenhoven 2005 [180] Sweden	"Rheumatic diseases" (128) Infliximab, etanercept & adalimumab	2'nd line withdrawal for lack of efficacy	Less withdrawal from etan than from inf; ada data immature	Not useful for 1'st line or 2'nd line withdrawal for RA.
Kristensen 2006 [181] Sweden	RA only (1,161) Infliximab & etanercept	1'st line; separate analyses according to ± concomitant DMARD & ± MTX.	Retention better with etan than infl; Better retention if patient also receives MTX.	K-M data for three subgroups; overall withdrawal from 1'st line with each anti-TNF difficult to compute.
Zink 2005 [176] Germany	RA (854) Infliximab & etanercept	1'st line	No statistically significant difference in retention at 12 months: 65.4% for inf and 68.6% for etan	Data too immature to draw conclusions.
Curtis 2009 [175] USA	RA (11,903) Infliximab, etanercept & adalimumab	Withdrawal from 1'st line or dose escalation	HR for switch from anti-TNF (to other DMARD) OR dose escalation: inf v etan 6.29 (5.82 to 6.81) ada v etan 1.18 (1.08 to 1.30)	Combines discontinuation and dose escalation.
Wolfe & Michaud 2007 [177] USA	RA (4,915) Infliximab, etanercept & adalimumab	Mixed, & 2'nd line	Median continuation (years): For 1'st & 2'nd line: ada 3.0, etan 5.5, inf 4.5. For 2'nd line: ada 2.0, etan 2.5, inf 2.5	K-M plots not supplied.

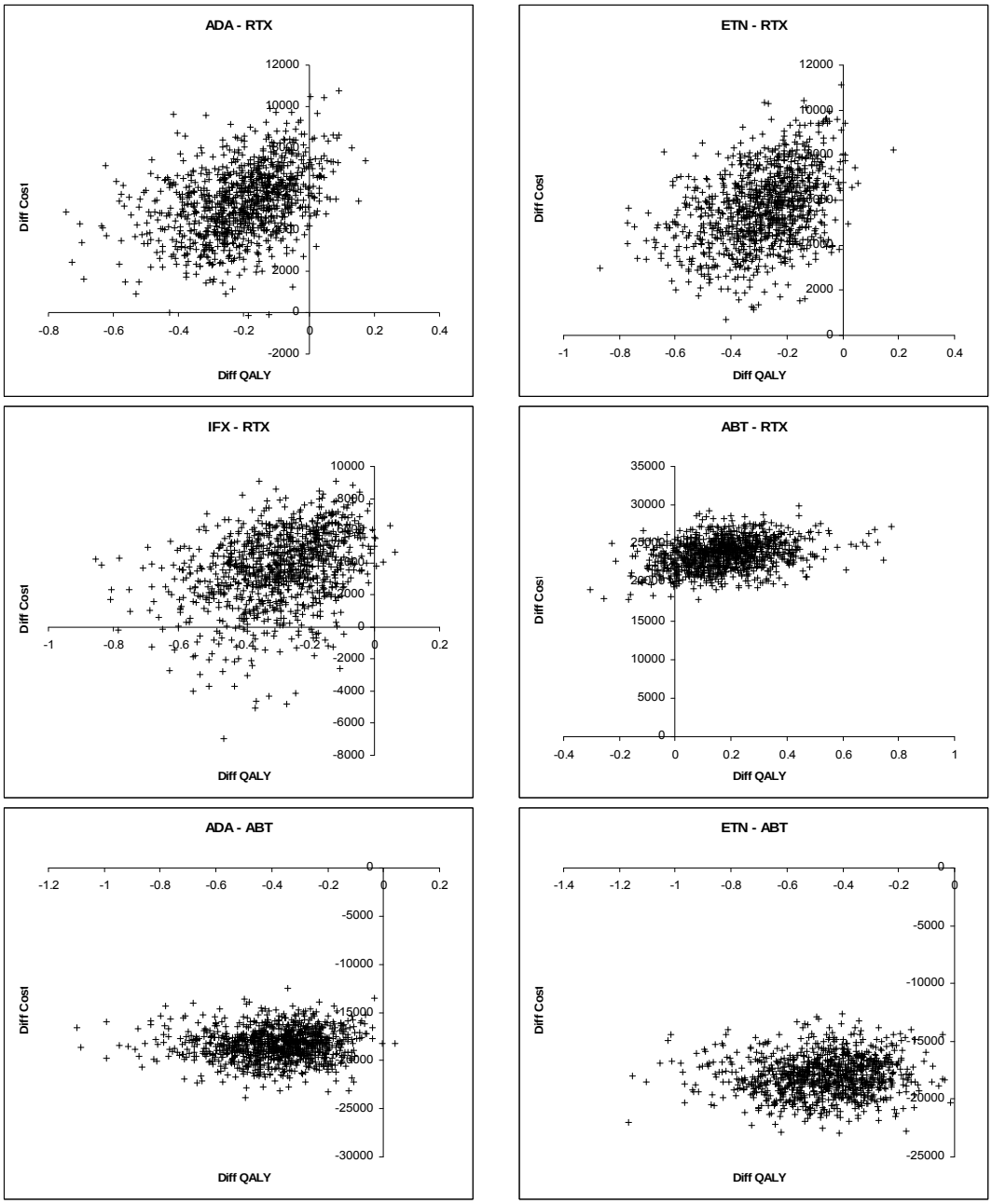
Table 96 Median survival in 2'nd line anti-TNF therapy

	Reported by Wolfe & Michaud 2007 [177]	Estimated (as Fig 3)
Anti-TNF	Median survival 2'nd line (years)	Median survival 2'nd line (years)
adalimumab	2	2.02
etanercept	2.5	2.86
infliximab	2.5	1.24
All*	2.36	1.90

* weighted average according to number of patients receiving each anti-TNF

10.13 Scatterplots for comparisons among biologics in the reference case

Figure 156 contains the cost-effectiveness scatterplots for the ten comparisons between biologic treatments in the reference case. The comparisons between biologics and conventional DMARDs are shown in Section 6.2.



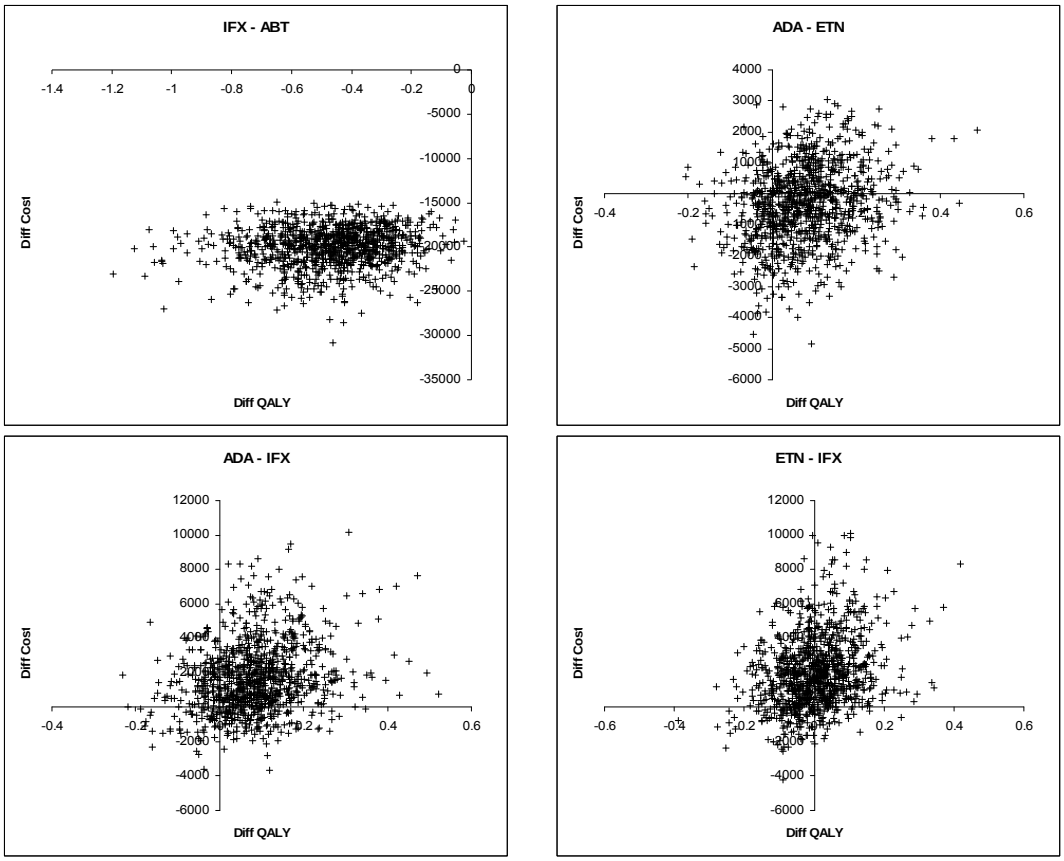


Figure 156Cost-effectiveness scatterplots for comparisons between biologic treatments in the reference case

10.14 Scenario analyses

The following scenarios were considered in addition to the reference case analysis. The section headings correspond to the abbreviated descriptions used in Section 6.2. In each case, any parameters not mentioned in the description of the scenario remain as in the reference case analysis.

Vary time on TNF inhibitors

In this case, the time to quitting treatments for TNF inhibitors was changed to give the same relative risk as for their use as first biologic agents. The *b* parameters from Table 77 were changed as follows:

Treatment	New *b* parameter (point estimate)
ADA	3.413
ETN	4.831
IFX	2.086

Results were as follows:

Treatment	Mean Cost	95% Credible Interval		Mean QALY	95% Credible Interval	
ADA	75600	69200	82000	2.92	-2.25	7.76
ETN	82400	75900	89200	3.02	-2.04	7.83
IFX	67100	60600	73500	2.63	-2.64	7.62
RTX	69100	62500	75800	3.10	-1.96	7.89
ABT	92800	86000	100300	3.28	-1.58	7.96
DMARDs	48800	43000	54800	2.14	-3.31	7.34

Comparison	Diff Cost	95% Credible Interval		Diff QALY	95% Credible Interval	
ADA - DMARDs	26800	25100	28600	0.78	0.34	1.27
ETN - DMARDs	33600	31600	35800	0.87	0.38	1.47
IFX - DMARDs	18400	14900	20600	0.49	0.21	0.79
RTX - DMARDs	20400	17500	23100	0.96	0.42	1.58
ABT - DMARDs	44000	41200	46900	1.14	0.50	1.86
ADA - RTX	6400	3200	9700	-0.18	-0.47	0.07
ETN - RTX	13300	9900	16600	-0.08	-0.37	0.17
IFX - RTX	-2000	-5900	1500	-0.47	-0.85	-0.17
ABT - RTX	23600	19800	27300	0.18	-0.09	0.51
ADA - ABT	-17200	-20500	-14100	-0.36	-0.70	-0.09
ETN - ABT	-10400	-13500	-7200	-0.26	-0.56	-0.03
IFX - ABT	-25600	-29800	-22100	-0.65	-1.11	-0.25
ADA - ETN	-6800	-9500	-4200	-0.09	-0.33	0.10
ADA - IFX	8400	5800	12000	0.29	0.08	0.56
ETN - IFX	15300	12300	19100	0.39	0.14	0.73

Diff = difference, calculated by subtracting the value for the strategy named second from the value for the strategy named first.

				Proportion of cases CE at	
Comparison	ICER	95% Credible Interval		£20,000/QALY	£30,000/QALY
ADA - DMARDs	34400	21000	77300	0.01	0.31
ETN - DMARDs	38500	22900	86900	0.00	0.18
IFX - DMARDs	37700	22600	90000	0.01	0.21
RTX - DMARDs	21300	12900	48100	0.40	0.83
ABT - DMARDs	38700	23700	88000	0.00	0.16
ADA - RTX	RTX	123900	RTX	0.00	0.00
ETN - RTX	RTX	83500	RTX	0.00	0.00
IFX - RTX	*4200*	RTX	16500	0.01	0.00
ABT - RTX	132100	48000	RTX	0.00	0.00
ADA - ABT	*48200*	*23600*	*189100*	1.00	0.90
ETN - ABT	*39600*	*17400*	*308500*	0.95	0.73
IFX - ABT	*39500*	*22100*	*99500*	0.99	0.83
ADA - ETN	*72300*	*19800*	ADA	0.97	0.88
ADA - IFX	28800	13700	101100	0.15	0.50
ETN - IFX	39000	20400	112400	0.02	0.21

CE = cost-effective. The proportion of cases cost-effective relates to the strategy given first on each line. ICER in italics means that the strategy named second is more costly and more effective. Where a strategy name is given in place of an ICER, the named strategy dominates its comparator (less costly and more effective).

Same time on all biologics

In this scenario, the distribution of long term survival time on all biologics was set to the value used for TNF inhibitors in the reference case. The results were as follows:

Treatment	Mean Cost	95% Credible Interval		Mean QALY	95% Credible Interval	
ADA	74500	68300	80700	2.89	-2.37	7.72
ETN	74800	68800	81300	2.82	-2.34	7.71
IFX	72800	65500	79700	2.81	-2.37	7.72
RTX	63400	57600	69800	2.84	-2.39	7.76
ABT	81800	75400	88400	2.98	-2.20	7.79
DMARDs	48800	43000	54800	2.14	-3.43	7.37

Comparison	Diff Cost	95% Credible Interval		Diff QALY	95% Credible Interval	
ADA - DMARDs	25700	24000	27500	0.75	0.32	1.21
ETN - DMARDs	26100	24300	27800	0.67	0.28	1.11
IFX - DMARDs	24000	19200	26700	0.67	0.29	1.11
RTX - DMARDs	14600	13600	15800	0.69	0.29	1.15
ABT - DMARDs	33000	30700	35400	0.83	0.38	1.36
ADA - RTX	11100	9200	13000	0.05	-0.12	0.25
ETN - RTX	11400	9400	13300	-0.02	-0.20	0.16
IFX - RTX	9400	4600	12300	-0.02	-0.21	0.15
ABT - RTX	18400	15900	20700	0.14	-0.06	0.36
ADA - ABT	-7300	-10000	-4600	-0.09	-0.29	0.11
ETN - ABT	-6900	-9800	-4000	-0.16	-0.40	0.02
IFX - ABT	-9000	-14100	-5400	-0.16	-0.40	0.02
ADA - ETN	-300	-2800	2200	0.08	-0.11	0.28
ADA - IFX	1700	-1600	6700	0.08	-0.11	0.29
ETN - IFX	2100	-1300	7000	0.00	-0.17	0.18

Diff = difference, calculated by subtracting the value for the strategy named second from the value for the strategy named first.

Comparison	ICER	95% Credible Interval		Proportion of cases CE at £20,000/QALY	Proportion of cases CE at £30,000/QALY
ADA - DMARDs	34400	20800	79900	0.02	0.30
ETN - DMARDs	38700	23300	92100	0.01	0.16
IFX - DMARDs	35900	20800	82400	0.02	0.26
RTX - DMARDs	21100	12600	49500	0.42	0.84
ABT - DMARDs	39600	23800	89200	0.01	0.14
ADA - RTX	202000	43800	RTX	0.00	0.00
ETN - RTX	RTX	68500	RTX	0.00	0.00
IFX - RTX	RTX	64800	RTX	0.00	0.00
ABT - RTX	131100	49900	RTX	0.00	0.00
ADA - ABT	*85400*	*23400*	ADA	0.99	0.93
ETN - ABT	*43300*	*16000*	ETN	0.92	0.76
IFX - ABT	*54900*	*21600*	IFX	0.98	0.89
ADA - ETN	ADA	Not meaningful		0.82	0.83
ADA - IFX	21900	Not meaningful		0.48	0.59
ETN - IFX	561000	Not meaningful		0.20	0.26

CE = cost-effective. The proportion of cases cost-effective relates to the strategy given first on each line. ICER in italics means that the strategy named second is more costly and more effective. Where a strategy name is given in place of an ICER, the named strategy dominates its comparator (less costly and more effective). A 95% credible interval for the ICER is not meaningful in cases where the cost-effectiveness scatterplot is not confined to one half of the plane.

RTX cycle time 6 months

In this case, it was assumed that cycles of rituximab would be given every 6 months. The assumption was that withdrawal rates per cycle would be maintained from the reference case. The results are as follows:

Treatment	Mean Cost	95% Credible Interval		Mean QALY	95% Credible Interval	
ADA	74500	68200	80700	2.89	-2.35	7.78
ETN	74800	68800	81300	2.82	-2.34	7.76
IFX	72800	65600	79700	2.81	-2.41	7.71
RTX	74600	67200	82600	2.93	-2.24	7.81
ABT	92800	86200	99900	3.28	-1.63	8.00
DMARDs	48800	43100	54700	2.14	-3.45	7.43

Comparison	Diff Cost	95% Credible Interval		Diff QALY	95% Credible Interval	
ADA - DMARDs	25700	24000	27500	0.75	0.31	1.23
ETN - DMARDs	26000	24200	27900	0.67	0.27	1.11
IFX - DMARDs	24000	19100	26800	0.67	0.27	1.08
RTX - DMARDs	25800	21800	29900	0.79	0.33	1.30
ABT - DMARDs	44000	41100	46800	1.14	0.50	1.88
ADA - RTX	-49	-4400	4400	-0.04	-0.27	0.17
ETN - RTX	300	-4100	4700	-0.12	-0.36	0.10
IFX - RTX	-1800	-7600	3100	-0.12	-0.37	0.09
ABT - RTX	18300	13400	22900	0.35	0.07	0.71
ADA - ABT	-18300	-21400	-15200	-0.39	-0.75	-0.11
ETN - ABT	-18000	-21100	-14600	-0.47	-0.85	-0.18
IFX - ABT	-20100	-25200	-16000	-0.47	-0.87	-0.18
ADA - ETN	-300	-2900	2000	0.08	-0.11	0.28
ADA - IFX	1700	-1500	6600	0.08	-0.11	0.29
ETN - IFX	2100	-1300	7200	0.00	-0.18	0.19

Diff = difference, calculated by subtracting the value for the strategy named second from the value for the strategy named first.

				Proportion of cases CE at	
Comparison	ICER	95% Credible Interval		£20,000/QALY	£30,000/QALY
ADA - DMARDs	34400	20500	79300	0.02	0.30
ETN - DMARDs	38800	23100	93300	0.00	0.18
IFX - DMARDs	35800	21600	86900	0.02	0.26
RTX - DMARDs	32700	19900	76200	0.03	0.37
ABT - DMARDs	38600	23400	88600	0.01	0.16
ADA - RTX	*1200*	Not meaningful		0.38	0.36
ETN - RTX	RTX	Not meaningful		0.13	0.11
IFX - RTX	*15100*	Not meaningful		0.40	0.29
ABT - RTX	51800	24800	211400	0.00	0.07
ADA - ABT	*46700*	*24000*	*155200*	1.00	0.90
ETN - ABT	*38400*	*20300*	*94400*	0.98	0.78
IFX - ABT	*42600*	*23400*	*109300*	0.99	0.87
ADA - ETN	ADA	Not meaningful		0.82	0.83
ADA - IFX	22100	Not meaningful		0.48	0.58
ETN - IFX	888000	Not meaningful		0.19	0.24

CE = cost-effective. The proportion of cases cost-effective relates to the strategy given first on each line. ICER in italics means that the strategy named second is more costly and more effective. Where a strategy name is given in place of an ICER, the named strategy dominates its comparator (less costly and more effective). A 95% credible interval for the ICER is not meaningful in cases where the cost-effectiveness scatterplot is not confined to one half of the plane.

RTX cycle time 11.6 months

In this case, it was assumed that cycles of rituximab would be given every 11.6 months, which was the observed mean time in the REFLEX extension study (Roche submission, p. 200). The assumption was that withdrawal rates per cycle would be maintained from the reference case. The results were as follows:

Treatment	Mean Cost	95% Credible Interval		Mean QALY	95% Credible Interval	
ADA	74500	68200	80800	2.90	-2.28	7.73
ETN	74800	68700	81200	2.82	-2.36	7.73
IFX	72800	65700	79700	2.81	-2.42	7.69
RTX	65100	59000	71700	3.25	-1.68	7.95
ABT	92800	85800	99800	3.29	-1.64	8.05
DMARDs	48800	43000	54900	2.14	-3.48	7.39

Comparison	Diff Cost	95% Credible Interval		Diff QALY	95% Credible Interval	
ADA - DMARDs	25700	24000	27600	0.75	0.31	1.21
ETN - DMARDs	26000	24300	27900	0.67	0.29	1.10
IFX - DMARDs	24000	19100	26800	0.67	0.27	1.09
RTX - DMARDs	16300	14400	18400	1.10	0.48	1.81
ABT - DMARDs	44000	41200	46800	1.14	0.52	1.85
ADA - RTX	9400	6900	12100	-0.35	-0.73	-0.07
ETN - RTX	9700	7000	12200	-0.43	-0.82	-0.14
IFX - RTX	7600	2800	11000	-0.44	-0.84	-0.13
ABT - RTX	27700	24400	31100	0.04	-0.27	0.33
ADA - ABT	-18300	-21600	-15100	-0.39	-0.74	-0.11
ETN - ABT	-18000	-21200	-14400	-0.47	-0.87	-0.18
IFX - ABT	-20100	-25600	-16100	-0.47	-0.87	-0.17
ADA - ETN	-300	-2900	2100	0.08	-0.09	0.29
ADA - IFX	1700	-1700	6400	0.08	-0.09	0.28
ETN - IFX	2100	-1500	7000	0.00	-0.18	0.19

Diff = difference, calculated by subtracting the value for the strategy named second from the value for the strategy named first.

Comparison	ICER	95% Credible Interval		Proportion of cases CE at £20,000/QALY	Proportion of cases CE at £30,000/QALY
ADA - DMARDs	34200	21200	82100	0.01	0.32
ETN - DMARDs	38800	23100	90300	0.01	0.17
IFX - DMARDs	35900	21700	85800	0.01	0.26
RTX - DMARDs	14800	9000	33700	0.80	0.96
ABT - DMARDs	38500	23300	84900	0.00	0.17
ADA - RTX	RTX	RTX	RTX	0.00	0.00
ETN - RTX	RTX	RTX	RTX	0.00	0.00
IFX - RTX	RTX	Not meaningful		0.00	0.00
ABT - RTX	736300	84800	RTX	0.00	0.00
ADA - ABT	*46900*	*24000*	*165600*	1.00	0.90
ETN - ABT	*38200*	*20300*	*97600*	0.98	0.78
IFX - ABT	*42300*	*22400*	*116600*	0.99	0.85
ADA – ETN	ADA	Not meaningful		0.83	0.84
ADA – IFX	20800	Not meaningful		0.51	0.59
ETN – IFX	833000	Not meaningful		0.19	0.23

CE = cost-effective. The proportion of cases cost-effective relates to the strategy given first on each line. ICER in italics means that the strategy named second is more costly and more effective. Where a strategy name is given in place of an ICER, the named strategy dominates its comparator (less costly and more effective). A 95% credible interval for the ICER is not meaningful in cases where the cost-effectiveness scatterplot is not confined to one half of the plane.

HAQ change on biologics

In this scenario, a deterioration of 0.03/year in HAQ was assumed on biologic treatments. This was modelled as a mean time between 0.125 unit increases of 4 years. For each treatment separately, this figure was given a Normal distribution with a standard deviation of 0.4 years. The results were as follows:

Treatment	Mean Cost	95% Credible Interval		Mean QALY	95% Credible Interval	
ADA	75200	69000	81700	2.46	-2.59	7.51
ETN	75600	69200	82100	2.38	-2.76	7.47
IFX	73500	66500	80500	2.38	-2.79	7.47
RTX	70200	63100	77300	2.49	-2.54	7.50
ABT	93600	86500	100900	2.74	-2.32	7.62
DMARDs	48900	43200	54800	2.02	-3.35	7.26

Comparison	Diff Cost	95% Credible Interval		Diff QALY	95% Credible Interval	
ADA - DMARDs	26300	24400	28300	0.43	0.16	0.78
ETN - DMARDs	26600	24800	28500	0.35	0.13	0.64
IFX - DMARDs	24600	20400	27500	0.36	0.13	0.65
RTX - DMARDs	21300	18100	24500	0.47	0.17	0.85
ABT - DMARDs	44700	42100	47600	0.71	0.32	1.22
ADA - RTX	5000	1400	8700	-0.03	-0.29	0.20
ETN - RTX	5400	2100	8600	-0.12	-0.43	0.11
IFX - RTX	3400	-2100	7400	-0.11	-0.39	0.11
ABT - RTX	23500	19800	27400	0.24	-0.03	0.61
ADA - ABT	-18500	-21400	-15600	-0.28	-0.60	-0.02
ETN - ABT	-18100	-21100	-15000	-0.36	-0.73	-0.10
IFX - ABT	-20100	-25000	-16300	-0.35	-0.72	-0.08
ADA - ETN	-400	-2800	2200	0.08	-0.11	0.31
ADA - IFX	1600	-1700	6000	0.08	-0.11	0.29
ETN - IFX	2000	-1300	6400	-0.01	-0.21	0.18

Diff = difference, calculated by subtracting the value for the strategy named second from the value for the strategy named first.

Comparison	ICER	95% Credible Interval		Proportion of cases CE at £20,000/QALY	Proportion of cases CE at £30,000/QALY
ADA - DMARDs	60500	33500	163300	0.00	0.00
ETN - DMARDs	75400	42400	213400	0.00	0.00
IFX - DMARDs	68600	36300	195100	0.00	0.00
RTX - DMARDs	45300	24600	121800	0.01	0.09
ABT - DMARDs	62700	36600	140300	0.00	0.00
ADA - RTX	RTX	Not meaningful		0.02	0.05
ETN - RTX	RTX	Not meaningful		0.00	0.01
IFX - RTX	RTX	Not meaningful		0.05	0.05
ABT - RTX	96200	39400	RTX	0.00	0.00
ADA - ABT	*66200*	*29400*	*772200*	1.00	0.97
ETN - ABT	*50300*	*23600*	*191800*	0.99	0.92
IFX - ABT	*56800*	*27800*	*242400*	0.99	0.96
ADA - ETN	ADA	Not meaningful		0.79	0.80
ADA - IFX	21900	Not meaningful		0.50	0.58
ETN – IFX	IFX	Not meaningful		0.24	0.28

CE = cost-effective. The proportion of cases cost-effective relates to the strategy given first on each line. ICER in italics means that the strategy named second is more costly and more effective. Where a strategy name is given in place of an ICER, the named strategy dominates its comparator (less costly and more effective). A 95% credible interval for the ICER is not meaningful in cases where the cost-effectiveness scatterplot is not confined to one half of the plane.

Adverse event costs included

Additional annual costs based on the BMS submission as follows

Treatment	Additional cost
ADA	117.82
ETN	224.87
IFX	162.02
RTX	273.51
ABT	110.16

When these were included, the results were as follows:

Treatment	Mean Cost	95% Credible Interval		Mean QALY	95% Credible Interval	
ADA	74800	68700	80900	2.89	-2.25	7.74
ETN	75400	69300	81900	2.81	-2.29	7.75
IFX	73200	66300	80000	2.81	-2.44	7.73
RTX	70400	63500	77700	3.10	-1.91	7.88
ABT	93200	86400	100400	3.28	-1.67	7.96
DMARDs	48800	43100	54600	2.14	-3.47	7.39

Comparison	Diff Cost	95% Credible Interval		Diff QALY	95% Credible Interval	
ADA - DMARDs	26000	24300	27900	0.75	0.33	1.21
ETN - DMARDs	26700	24800	28600	0.67	0.30	1.11
IFX - DMARDs	24500	19700	27200	0.66	0.27	1.09
RTX - DMARDs	21600	18700	24400	0.96	0.39	1.58
ABT - DMARDs	44500	41500	47200	1.14	0.51	1.86
ADA - RTX	4400	1200	7800	-0.21	-0.51	0.03
ETN - RTX	5100	1800	8600	-0.29	-0.61	-0.04
IFX - RTX	2900	-2400	6800	-0.29	-0.61	-0.04
ABT - RTX	22800	19000	26700	0.18	-0.09	0.48
ADA - ABT	-18400	-21600	-15200	-0.39	-0.77	-0.11
ETN - ABT	-17800	-21100	-14200	-0.47	-0.86	-0.17
IFX - ABT	-20000	-25100	-15900	-0.48	-0.87	-0.17
ADA - ETN	-600	-3200	1900	0.08	-0.10	0.29
ADA - IFX	1600	-1700	6500	0.09	-0.11	0.29
ETN - IFX	2200	-1200	7000	0.01	-0.16	0.20

Diff = difference, calculated by subtracting the value for the strategy named second from the value for the strategy named first.

Comparison	ICER	95% Credible Interval		Proportion of cases CE at £20,000/QALY	Proportion of cases CE at £30,000/QALY
ADA - DMARDs	34800	21500	80000	0.01	0.28
ETN - DMARDs	39800	24100	91000	0.00	0.15
IFX - DMARDs	36900	21900	84800	0.01	0.22
RTX - DMARDs	22600	13700	55200	0.32	0.79
ABT - DMARDs	39100	23400	86600	0.00	0.15
ADA - RTX	RTX	Not meaningful		0.00	0.00
ETN - RTX	RTX	Not meaningful		0.00	0.00
IFX - RTX	RTX	Not meaningful		0.00	0.00
ABT - RTX	126700	47700	RTX	0.00	0.00
ADA - ABT	*47200*	*23700*	*157100*	0.99	0.90
ETN - ABT	*37900*	*19800*	*102300*	0.97	0.78
IFX - ABT	*42100*	*22300*	*113800*	0.99	0.84
ADA - ETN	ADA	Not meaningful		0.88	0.88
ADA - IFX	18400	Not meaningful		0.55	0.64
ETN - IFX	353000	Not meaningful		0.18	0.23

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No negative QoL scores

In this case, all quality of life scores that were calculated as negative using the equation converting HAQ to QoL were replaced by zero. The results were as follows:

Treatment	Mean Cost	95% Credible Interval		Mean QALY	95% Credible Interval	
ADA	74500	68400	80500	3.79	1.65	7.74
ETN	74800	68700	81200	3.73	1.61	7.75
IFX	72800	65900	79500	3.73	1.61	7.73
RTX	69100	62400	76300	3.93	1.75	7.88
ABT	92800	86000	99900	4.09	1.93	7.96
DMARDs	48800	43100	54600	3.26	1.31	7.39

Comparison	Diff Cost	95% Credible Interval		Diff QALY	95% Credible Interval	
ADA - DMARDs	25700	24000	27500	0.53	0.28	0.74
ETN - DMARDs	26000	24200	27900	0.46	0.25	0.66
IFX - DMARDs	24000	19300	26700	0.46	0.24	0.66
RTX - DMARDs	20300	17600	23000	0.66	0.36	0.95
ABT - DMARDs	44000	41100	46700	0.83	0.48	1.12
ADA - RTX	5300	2200	8600	-0.13	-0.36	0.07
ETN - RTX	5600	2500	9000	-0.20	-0.43	0.00
IFX - RTX	3600	-1400	7400	-0.20	-0.44	-0.01
ABT - RTX	23600	19900	27400	0.17	-0.07	0.41
ADA - ABT	-18300	-21500	-15200	-0.30	-0.53	-0.09
ETN - ABT	-18000	-21300	-14400	-0.37	-0.59	-0.15
IFX - ABT	-20000	-25100	-16000	-0.37	-0.59	-0.16
ADA - ETN	-300	-2900	2200	0.07	-0.09	0.23
ADA - IFX	1700	-1500	6500	0.07	-0.11	0.24
ETN - IFX	2000	-1300	6700	0.00	-0.16	0.15

Diff = difference, calculated by subtracting the value for the strategy named second from the value for the strategy named first.

Comparison	ICER	95% Credible Interval		Proportion of cases CE at £20,000/QALY	Proportion of cases CE at £30,000/QALY
ADA - DMARDs	48400	34800	92500	0.00	0.00
ETN - DMARDs	56200	39600	102500	0.00	0.00
IFX - DMARDs	51900	34900	99600	0.02	0.25
RTX - DMARDs	30600	21700	56200	0.01	0.48
ABT - DMARDs	52900	39400	90000	0.00	0.00
ADA - RTX	RTX	Not meaningful		0.00	0.00
ETN - RTX	RTX	Not meaningful		0.00	0.00
IFX - RTX	RTX	Not meaningful		0.00	0.00
ABT - RTX	142000	59200	RTX	0.00	0.00
ADA - ABT	*60900*	*33900*	*199600*	1.00	0.99
ETN - ABT	*48900*	*29600*	*124400*	1.00	0.97
IFX - ABT	*54200*	*32100*	*128200*	1.00	0.99
ADA - ETN	ADA	Not meaningful		0.82	0.84
ADA - IFX	24600	Not meaningful		0.47	0.58
ETN - IFX	2420000	Not meaningful		0.19	0.24

CE = cost-effective. The proportion of cases cost-effective relates to the strategy given first on each line. ICER in italics means that the strategy named second is more costly and more effective. Where a strategy name is given in place of an ICER, the named strategy dominates its comparator (less costly and more effective). A 95% credible interval for the ICER is not meaningful in cases where the cost-effectiveness scatterplot is not confined to one half of the plane.

Linear equation HAQ to QoL

In this scenario, the linear equation $QoL = 0.862 - 0.327HAQ$ was used as in previous versions of the BRAM. For the probabilistic analysis, the coefficients were sampled from Normal distributions with standard deviations 0.034 and 0.0201 respectively.[182] The results were as follows:

Treatment	Mean Cost	95% Credible Interval		Mean QALY	95% Credible Interval	
ADA	74600	68500	81200	3.02	1.67	4.27
ETN	75000	68800	81800	2.95	1.63	4.20
IFX	72900	66000	79600	2.94	1.65	4.19
RTX	69300	63100	76100	3.21	1.89	4.49
ABT	92900	86100	99500	3.39	2.09	4.60
DMARDs	48900	43300	54900	2.35	1.02	3.63

Comparison	Diff Cost	95% Credible Interval		Diff QALY	95% Credible Interval	
ADA - DMARDs	25700	23900	27500	0.67	0.51	0.84
ETN - DMARDs	26100	24400	27900	0.60	0.44	0.75
IFX - DMARDs	24000	19200	26700	0.59	0.43	0.75
RTX - DMARDs	20400	17800	23300	0.86	0.65	1.12
ABT - DMARDs	44000	41400	46600	1.04	0.81	1.29
ADA - RTX	5300	2000	8500	-0.19	-0.45	0.04
ETN - RTX	5700	2600	8800	-0.26	-0.50	-0.04
IFX - RTX	3600	-1200	7400	-0.27	-0.54	-0.04
ABT - RTX	23600	19600	27600	0.18	-0.11	0.43
ADA - ABT	-18300	-21600	-15100	-0.37	-0.61	-0.14
ETN - ABT	-17900	-21200	-14700	-0.44	-0.66	-0.22
IFX - ABT	-20100	-25300	-16200	-0.45	-0.69	-0.23
ADA - ETN	-300	-2900	2100	0.07	-0.11	0.25
ADA - IFX	1800	-1500	6500	0.08	-0.10	0.25
ETN - IFX	2100	-1100	6900	0.01	-0.17	0.17

Diff = difference, calculated by subtracting the value for the strategy named second from the value for the strategy named first.

Comparison	ICER	95% Credible Interval		Proportion of cases CE at £20,000/QALY	Proportion of cases CE at £30,000/QALY
ADA - DMARDs	38400	30200	50900	0.00	0.02
ETN - DMARDs	43500	34600	57600	0.00	0.00
IFX - DMARDs	40500	30700	54000	0.00	0.02
RTX - DMARDs	23600	18700	30700	0.09	0.97
ABT - DMARDs	42300	34300	54400	0.00	0.00
ADA - RTX	RTX	122600	RTX	0.00	0.00
ETN - RTX	RTX	RTX	RTX	0.00	0.00
IFX - RTX	RTX			0.00	0.00
ABT - RTX	131800	54400	RTX	0.00	0.00
ADA - ABT	*49300*	*29400*	*126900*	1.00	0.97
ETN - ABT	*40500*	*26100*	*82400*	1.00	0.91
IFX - ABT	*44600*	*28200*	*89000*	1.00	0.96
ADA - ETN	ADA			0.82	0.82
ADA - IFX	22400			0.49	0.59
ETN - IFX	301000			0.20	0.26

CE = cost-effective. The proportion of cases cost-effective relates to the strategy given first on each line. ICER in italics means that the strategy named second is more costly and more effective. Where a strategy name is given in place of an ICER, the named strategy dominates its comparator (less costly and more effective). A 95% credible interval for the ICER is not meaningful in cases where the cost-effectiveness scatterplot is not confined to one half of the plane.

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