NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after failure of a different TNF-α inhibitor

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the committee meeting. This overview summarises the additional work that has been commissioned by the Institute following an appeal from consultees, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the meeting, it has been prepared before the Institute receives consultees' comments on the additional work. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

NICE appraised the use of the tumour necrosis factor-α (TNF-α) inhibitors adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. Preliminary guidance did not recommend the use of a second TNF-α inhibitor after the first had failed except if the first had been discontinued in the first 6 months because of an adverse event. This aspect of the guidance was appealed against and the appeal panel requested that NICE carry out further analyses considering the use of a second TNF-α inhibitor. Analyses requested by the appeal panel were:

- sensitivity analyses that consider a wider possible range of effectiveness for conventional disease modifying anti-rheumatic drugs (DMARDS)
- a wider possible range of doses of infliximab
- an examination of the minimum effectiveness that would be required of a second TNF-α inhibitor treatment for it to be marginally cost effective.

The guidance on the use of a first TNF-α inhibitor was published ('Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis', NICE technology appraisal guidance 130), and additional analyses about the use of a second TNF-α inhibitor were commissioned. Further changes since the appeal hearing include, firstly, the publication of 'Rituximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 126), which recommends rituximab for the treatment of severe active rheumatoid arthritis after the failure of at least one TNF-α inhibitor, and secondly, a change to the marketing authorisation for infliximab to allow the use of higher dose regimens.

1.1 The condition

Rheumatoid arthritis (RA) is a chronic and progressive disabling condition characterised by inflammation of the synovial tissue of the joints. It causes tenderness, stiffness and progressive destruction of joints, and other symptoms such as pain and fatigue. It affects between 0.5% and 1% of the population, or approximately 400,000 people, in England and Wales. Of these, approximately 15% have severe disease. RA affects three times as many women as men and has a peak age of onset of 40–70 years.

In RA, the synovium becomes enlarged because of an increase in the number of synovial cells (hyperplasia), infiltration by white blood cells and formation of new blood vessels. There is an increase in fluid-containing inflammatory cells in the joint cavity (effusion) and, secondary to this, thinning of the bone around the joint (periarticular osteoporosis). Erosion of the bone occurs where synovial tissue meets cartilage and bone, and this, together with the periarticular bone thinning, leads to long-term irreversible damage of the structure and function of the joint.

The course of RA is heterogeneous and variable. However, there are several factors associated with poor prognosis. These include the presence of rheumatoid factor or anti-cyclic citrullinated peptide (CCP) antibodies, high erythrocyte sedimentation rate or C-reactive protein (CRP) levels, early

radiographic evidence of erosions and the presence of swollen and tender joints. Within 2 years of diagnosis, patients usually experience moderate disability and after 10 years 30% are severely disabled. Approximately a third of patients stop work because of disease. Life expectancy in people with RA is also reduced. For example, a 50-year-old woman with RA is expected to die 4 years earlier than a woman without RA.

1.2 Current management

There is no cure for RA; conventional treatment aims to control pain and inflammation, and to reduce joint damage, disability and loss of function, thereby improving quality of life. It involves a combination of pharmacological and non-pharmacological interventions. Conventional drug therapy relies on various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and DMARDs. DMARDs act to ameliorate symptoms and slow progression of structural damage; they are used as monotherapy or in combination, often with steroids. DMARD treatment is started soon after diagnosis, with an aim of trying to achieve remission. Methotrexate and sulfasalazine are DMARDs often used as initial therapy. Non-drug therapies include surgery, physiotherapy and occupational therapy.

Not all people respond to all DMARDs and if there is a response to treatment, the response may reduce over time. This means that people with RA usually require a series of treatments. In NICE technology appraisal guidance 130, NICE recommends the use of one of the TNF-α inhibitors: adalimumab, etanercept and infliximab after the failure of two conventional DMARDs including methotrexate. If the first TNF-α inhibitor has to be stopped because of an adverse event in the first 6 months, NICE recommends that a second TNF-α inhibitor may be tried. For people for whom a TNF-α inhibitor has failed, NICE technology appraisal guidance 126 recommends the use of rituximab, a treatment that depletes B cells. The full recommendations for the use of first TNF-α inhibitors and rituximab are included in appendix B. In addition to completed technology appraisal guidance there is a NICE clinical guideline on RA in development and an ongoing technology appraisal of

abatacept for the treatment of RA after the failure of a TNF-α inhibitor. Preliminary guidance does not recommend abatacept for the treatment of RA. This guidance is currently subject to an appeal.

2 The technologies

Table 1 Summary description of technologies

Non-proprietary name	Adalimumab	Etanercept	Infliximab
Proprietary name	Humira	Enbrel	Remicade
Manufacturer	Abbott Laboratories Ltd	Wyeth Pharmaceuticals	Schering-Plough Ltd
Dose	40 mg adalimumab given every other week as a subcutaneous injection.	25 mg Enbrel twice weekly; alternatively, 50 mg once weekly. Given as a subcutaneous injection.	3 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.
Acquisition cost ex. VAT (BNF 54)	Net price for a 40-mg prefilled syringe = £357.50	Net price for a 25-mg vial = £89.38.	Net price for a 100-mg vial = £419.62.

Adalimumab (Humira, Abbott Laboratories) is a human-sequence antibody that binds specifically to TNF-α and neutralises its biological function by blocking its interaction with cell-surface TNF-α receptors. It also modulates biological responses that are induced or regulated by TNF-α, including changes in the levels of adhesion molecules responsible for leukocyte migration. Adalimumab is licensed for the treatment of moderate to severe, active RA in adults when the response to DMARDs, including methotrexate, has been inadequate, and for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate. Adalimumab is licensed in combination with methotrexate, except where methotrexate is not tolerated or is considered inappropriate. During monotherapy if a patient experiences a loss of response, the dose can be increased to 40 mg adalimumab every week.

Etanercept (Enbrel, Wyeth Pharmaceuticals) is a recombinant human TNF-α-receptor fusion protein. It interferes with the inflammatory cascade by binding to TNF-α , thereby blocking its interaction with cell-surface receptors. Etanercept is licensed for use in adults with active RA whose disease has responded inadequately to DMARDs including methotrexate. Etanercept is also indicated in the treatment of severe, active and progressive RA in adults not previously treated with methotrexate. The summary of product characteristics (SPC) states that for people whose disease has responded inadequately to conventional DMARDs, etanercept should be given in combination with methotrexate, except if methotrexate is not tolerated or is considered inappropriate.

Infliximab (Remicade, Schering-Plough Ltd) is a chimeric monoclonal antibody that binds with high affinity to TNF-α , thereby neutralising its activity. It is licensed for the treatment of active RA if the response to DMARDs including methotrexate has been inadequate, and for patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs. The SPC specifies that infliximab must be used in combination with methotrexate. It also states that clinical response is usually achieved within 12 weeks of treatment. If a patient's disease responds inadequately or response is reduced after this period, consideration may be given to increasing the dose stepwise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. If adequate response is achieved, patients should be continued on the selected dose or dose frequency.

3 The evidence

This section focuses on evidence on the use of a second TNF-α inhibitor after the first has failed either because of no response or because the response has reduced over time. The clinical and cost effectiveness of a first TNF-α inhibitor are summarised only briefly in sections 3.1.1 and 3.2.2 (full details of the evidence on a first TNF-α inhibitor are included in NICE technology

appraisal guidance 130, as well as other supporting documents for that appraisal).

3.1 Clinical effectiveness

Evidence for the clinical effectiveness of a second TNF-α inhibitor and of comparator treatments is taken from a systematic review completed by the Institute's Decision Support Unit (DSU). Data from the British Society of Rheumatology Biologics Register (BSRBR) are also included for conventional DMARDs and for second TNF-α inhibitors.

3.1.1 Effectiveness of a first TNF-α inhibitor

Twenty randomised controlled trials (RCTs) were identified that investigated the use of adalimumab, etanercept or infliximab and included comparisons of interventions when given at licensed doses or equivalents. Four of these studies included only people with early RA (duration of less than 3 years), and are not reported here. Studies including people for whom previous DMARDs had failed showed statistically significant benefits of TNF-α inhibitors in comparison with placebo across a range of outcomes including physical function and disease activity. A summary of the pooled results from the assessment report (published as Chen et al. 2006) is shown in table 2.

Table 2 Clinical effectiveness of a first TNF-α inhibitor

Outcome	ACR20 (%)[c]	ACR50 (%)[c]	ACR70 (%)[c]	Change in HAQ score
Adalimumab[a]				
Intervention	53	33	17	-0.52
Control	26	9	3	-0.21
Etanercept[a]				
Intervention	61	32	11	[b]
Control	18	7	1	[b]
Infliximab				
Intervention	55	30	13	-0.41
Control	24	9	4	-0.14

ACR: American College of Rheumatology, HAQ: Health Assessment Questionnaire.

[a] Includes studies in which TNF-α inhibitors were given with and without methotrexate. TNF-α inhibitors are considered to have greater efficacy when coadministered with methotrexate.

[b] Not calculable from assessment report, difference between groups in HAQ score at end of study = –0.50.

[c] Categories not mutually exclusive.

3.1.2 Effectiveness of a second TNF-α inhibitor

Twenty nine studies were identified that investigated the efficacy of the use of a second TNF-α inhibitor after a first TNF-α inhibitor has failed; three of these studies were written up only as letters. Data for one or more of the specified outcomes (American College of Rheumatology [ACR] response, disease activity score [DAS28], European League Against Rheumatism [EULAR] response and Health Assessment Questionnaire [HAQ] improvement) could be extracted from 18 of these studies, with a further four studies reporting these outcomes for the TNF-α inhibitors as a group rather than for the individual drugs. Only one of the studies (n = 28) was a randomised controlled trial that compared switching to a different TNF-α inhibitor (infliximab) with staying on the same TNF-α inhibitor (etanercept). The follow-up period for the majority of studies was short, at 12 weeks. The outcomes for the studies investigating the use of a second TNF-α inhibitor are included in appendix C.

Comparisons between the outcomes of use of first and second TNF-α inhibitors must be undertaken cautiously because of limitations in study

design and short-term follow-up. Studies show high rates of response to a second TNF-α inhibitor. Studies that included a control group of different people who had not previously had a TNF-α inhibitor suggest that the rate of response for the second TNF-α inhibitor was lower than for the first. However, this is not consistent across studies. Where studies distinguished between no response and loss of response to the first TNF-α inhibitor, results suggested that 'no response' to the first TNF-α inhibitor may be associated with lower response to a second TNF-α inhibitor. However, again this is not consistently demonstrated across studies.

Two studies compared the response to a second TNF-α inhibitor with the response to rituximab. Both reported DAS28 scores at 12 weeks. In one study the reduction in DAS28 score was –0.8 and –1.48 in the TNF-α inhibitor and rituximab groups, respectively. In the second study the reduction in DAS28 score was –0.8 and –1.28 for the TNF-α inhibitor and rituximab groups, respectively. Both studies suggest that switching to rituximab may be more effective than switching to a second TNF-α inhibitor. The randomised controlled trial of switching to infliximab compared with staying on etanercept suggested that switching treatments was more effective than staying on the same treatment.

Data from the British Society of Rheumatology Biologics Register

The BSRBR was established in 2001 with the aim of studying the long-term efficacy and safety of biological drugs. It includes people treated with TNF-α inhibitors and also a control group of people not treated with TNF-α inhibitors. The register provides an estimate of efficacy of the use of a second TNF-α inhibitor in people with RA of long duration.

Results for the effectiveness of the use of a second TNF-α inhibitor are summarised in Table 3. These data have been collected from the British Society for Rheumatology (BSR) submission, their appeal documents (Arthritis and Musculoskeletal Alliance, 2006) and a published article (Hyrich et al. 2007). The 'predicted' EULAR response measure is the probable

likelihood of response for an 'average' person in the BSRBR rather than observed response data.

Table 3 BSRBR data for the effectiveness of a second TNF-α inhibitor

	Change in HAQ score	EULAR response % poor/moderate/good	% remaining on treatment
First TNF-α inhibitor	–0.30	6 months observed: 32 / 49 / 18 Predicted: 15.6 / 64.4 / 19.9	At 6 months: 79% 18 months: 61%
Second TNF-α inhibitor	Actual: –0.15 Adjusted for confounding variables: –0.21	Predicted: 44.5 / 35.6 / 19.9	Mean follow up 6 months: 73%

EULAR: European League Against Rheumatism, HAQ: Health Assessment Questionnaire, TNF: tumour necrosis factor.

Data suggest that the likelihood of response to a second TNF-α inhibitor is lower than for the first TNF-α inhibitor and that the response to the second may be less durable.

3.1.3 Effectiveness of comparator treatments

The review by the DSU sought to identify studies of the effect of conventional DMARDs in people for whom a TNF-α inhibitor had previously failed; or in the absence of such data, studies of the effect of conventional DMARDs in people with RA of long duration. The review included an update to searches carried out by the Assessment Group, and a summary of an analysis of data from the BSRBR.

Updated searches identified no new studies that measured the treatment effect of conventional DMARDs in people for whom a TNF-α inhibitor had failed. One study (the BeST study) was identified that investigated management strategies in people with early RA. This included a sequence where infliximab was used as the initial treatment followed by other conventional DMARDs. However, the BeST study presented no data on the effectiveness of individual DMARDs.

The searches identified six studies relevant to the question of the effectiveness of conventional treatments for people with RA of long duration (see below).

Conventional DMARDs

Two of the six studies were RCTs investigating the effect of conventional DMARDs in people who had an average disease duration of longer than 3 years. A third study was a review examining the impact of disease duration on HAQ score.

One of the RCTs compared intramuscular gold with placebo in patients with an average disease duration of 3.4 years and baseline Health Assessment Questionnaire Disability Index (HAQ-DI) score of 1.3. At 24 weeks, the ACR20 scores were 58% and 22% in the gold and placebo groups, respectively. The percentage reduction in HAQ was 38% and 15% in the gold and placebo groups, respectively. The second RCT was of etanercept (TEMPO), which included placebo and methotrexate arms. People in the study had average disease duration of approximately 6.5 years and had tried an average of 2.3 previous DMARDs (although not methotrexate). At 54 weeks the improvement in HAQ score was 0.6, 1.0 and 0.7 for the methotrexate, etanercept and methotrexate, and etanercept groups, respectively.

The third study was a review of DMARD studies that included HAQ as an outcome. It used multiple regression to estimate the relationship between HAQ effect at 6 and 12 months with disease duration and treatment as explanatory variables. The study concluded that disease duration was associated with lower effect in both conventional and biological DMARDs. However, the DSU highlighted a number of limitations with the methodology.

Studies of abatacept and rituximab

The fourth and fifth of the six studies identified investigated the effect of two novel treatments (rituximab and abatacept) in comparison with placebo when added to an ongoing ineffective DMARD regimen. These were the ATTAIN trial (abatacept) and the REFLEX trial (rituximab). People in both studies had

previously tried a TNF-α inhibitor that had failed. Both studies were the primary sources of evidence in the NICE appraisals of abatacept and rituximab for the treatment of RA. The 6-month data for both studies are summarised in Table 4.

Table 4 Clinical effectiveness of rituximab and abatacept

Treatment	% ACR20	% HAQ imp ≥ 0.3	% ACR70	Mean HAQ change	Mean DAS28 change
Abatacept + methotrexate	50.4	47.3	10.2	–0.45	–1.98
Placebo + methotrexate	19.5	23.3	1.5	–0.11	–0.71
Rituximab + methotrexate	51	NR	12	–0.4	NR
Placebo + methotrexate	18	NR	1	–0.1	NR

ACR: American College of Rheumatology, DAS28: disease activity score, HAQ: Health Assessment Questionnaire, NR: not reported.

The data from the control groups in which people had a placebo added to an ongoing DMARD regimen show a small improvement in 6-month outcomes; a mean change in HAQ score of –0.1 and an ACR20 response rate of just below 20%. Outcomes for the group receiving rituximab show a mean change in HAQ score of –0.4 and ACR20 score of 51%.

Data from the BSRBR on conventional DMARDs

The last of the six relevant studies was the BSRBR. The register provides an estimate of efficacy of conventional DMARDs in people with RA of long duration. Data from the BSRBR were used in a regression analysis to estimate the probability of response to a conventional DMARD as an alternative to a first TNF-α inhibitor and after the failure of the first TNF-α inhibitor, both for a person for whom an average of five DMARDs have failed (reflecting the 'average' person in the BSRBR) and for a person for whom two DMARDs have failed (reflecting NICE technology appraisal 130). Data were only available to allow regression on EULAR response. The regression suggests that the probability of response is reduced by a small amount as

disease duration and number of previous treatments increases. The results are summarised in table 5.

Table 5 BSRBR data for the effectiveness of conventional DMARDs

	BSRBR cohort (5 DMARDs failed)		NICE scenario (2 DMARDS failed)	
Probability of EULAR response to conventional DMARD	As alternative to 1st TNF-α inhibitor	After failure of 1st TNF-α inhibitor	As alternative to 1st TNF-α inhibitor	After failure of 1st TNF-α inhibitor
None	0.37	0.39	0.33	0.35
Moderate	0.51	0.50	0.53	0.52
Good	0.12	0.11	0.14	0.13

BSRBR: British Society of Rheumatology Biologics Register, DMARD: disease-modifying anti-rheumatic drug, EULAR: European League Against Rheumatism, TNF: tumour necrosis factor.

3.2 Cost effectiveness

This section describes the independent economic model developed by the Assessment Group for NICE technology appraisal guidance 130. It also summarises the Committee considerations about the cost effectiveness of the use of a first TNF-α inhibitor from NICE technology appraisal guidance 130. It goes on to describe commissioned additional work that considers the sequential use of TNF-α inhibitors after the first has failed. This includes the additional work completed before the appeal using data from the BSRBR, and that completed after the appeal.

Two manufacturers (Abbott Laboratories, Wyeth Pharmaceuticals) included analyses of sequential use of TNF-α inhibitors in their submissions for the original appraisal (NICE technology appraisal guidance 130). Both assumed no reduction in effectiveness when a TNF-α inhibitor was used after the failure of another. Analyses from the manufacturer of adalimumab gave an estimate of the cost effectiveness of providing adalimumab and methotrexate as a fifth-line therapy after infliximab had failed provided an estimate of cost effectiveness of £19,841 per additional QALY gained. Analyses from the manufacturer of etanercept provided estimates of cost effectiveness ranging

from £15,000 to almost £25,500 per additional QALY gained, depending on the exact sequence of TNF-α inhibitors used.

3.2.1 Birmingham Rheumatoid Arthritis Model

The Birmingham Rheumatoid Arthritis Model (BRAM) is an individual sampling model, which assesses the cost effectiveness of adding a TNF-α inhibitor to an existing treatment pathway of DMARDs for RA when compared with the same pathway of DMARDs without a TNF-α inhibitor.

In this model, initial age and sex distribution, as well as the starting distribution of HAQ scores, were based on observational data from the Norfolk Arthritis Register, a primary-care-based cohort of patients with inflammatory polyarthritis. HAQ score improvement was modelled as a multiplier of the starting HAQ score and was set to vary in the model. Utilities were estimated based on a mapping process whereby HAQ scores in the trial were mapped via an algorithm to EQ-5D scores in order to derive estimates of utility.

People on TNF-α inhibitors were assumed to have underlying disease progression (modelled as a constant increase of HAQ score indicating worsening functional disability) commensurate with the general population (0.03 a year). People on palliative therapy (no active treatment) were assumed to have HAQ progression twice that of the general population (0.06 a year), while those on conventional DMARDs had underlying disease progression of 0.045 a year. Sensitivity analyses were carried out assuming no disease progression while on TNF-α inhibitors (modelled as a zero increase in HAQ score per year). The model included a proportion of people stopping treatment at 24 weeks due to toxicity and inefficacy. Joint replacement and associated costs were included in sensitivity analyses.

3.2.2 Cost effectiveness of a first TNF-α inhibitor

Based on the assessment report and other submissions of evidence, the Committee concluded a first TNF-α inhibitor was cost effective after the failure of two conventional DMARDs (NICE technology appraisal guidance 130). The

Committee considered that in the Assessment Group's analyses the estimate of cost effectiveness of a first TNF-α inhibitor lay somewhere between the estimates of cost effectiveness presented for 'early' RA (efficacy data taken from studies in which a proportion of people were conventional DMARD-naive) and 'late' RA (efficacy data taken from studies in which people had established RA of long duration, and for whom an average of two to three conventional DMARDs had failed). In addition the estimate lay between the estimates presented using constant annual increases in HAQ score of 0.03 and zero. Based on the evidence before it the Committee accepted an annual increase in HAQ score of less than 0.03, but in the final guidance the Committee allowed for some disease progression, shown in the guidance as a reduction in the response to treatment. The Committee noted that there was additional uncertainty about the efficacy of conventional treatments in the population considered by the appraisal. The incremental cost-effectiveness ratios (ICERs) are presented in table 6.

Table 6 Estimates of cost effectiveness of a first TNF-α inhibitor

	TNF-α inhibitor data source	
	ICER based on 'early' RA data (£/QALY)	ICER based on 'late' RA data (£/QALY)
Annual increase in HAQ score of 0.03		
Adalimumab + methotrexate	30,200	64,400
Etanercept + methotrexate	28,500	49,800
Infliximab + methotrexate	34,400	139,000
Annual increase in HAQ score of 0.00		
Adalimumab + methotrexate	19,100	30,200
Etanercept + methotrexate	17,800	24,600
Infliximab + methotrexate	19,500	39,400

HAQ: Health Assessment Questionnaire, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year, RA: rheumatoid arthritis, TNF: tumour necrosis factor.

3.2.3 Cost effectiveness of TNF-α inhibitors in comparison to DMARDs: data from the BSRBR

The first piece of additional work was conducted in response to the consultation on the appraisal consultation document for NICE technology

appraisal guidance 130. Analyses were carried out in the BRAM. For these analyses the estimate of benefit from TNF-α inhibitors was taken from BSRBR data. In the main analyses the value for change in HAQ on starting a second TNF-α inhibitor was a multiplier calculated from data in which the population had a mean change in HAQ score of 0.2146 (standard deviation [SD] 0.4216), and a mean baseline HAQ score of 2.05 (SD 0.6). In addition, in a series of speculative analyses, data from the clinical trials were adjusted downwards using the ratio of the response to the first and second TNF-α inhibitor (70%) seen in the BSRBR to represent the 'likely' benefit from the sequential use of a TNF-α inhibitor if a clinical trial were to be carried out.

Analyses were carried out assuming no disease progression while on treatment with TNF-α inhibitors (that is, an increase in HAQ score of zero) which reflected the best possible scenario for underlying disease progression. The analyses were carried out with discount rates of 6% and 1.5% for costs and benefits respectively. A sensitivity analysis was carried out, which reduced the effectiveness of conventional treatments by 50%. This was exploratory because adequate data of treatment effect was not identified to inform this parameter. The estimates of cost effectiveness are presented in table 7.

Examining the analyses the Committee considered that the data from the BSRBR suggested a reduction in response to the second TNF-α inhibitor compared with the response to the first, although there were limitations in the data because of the study design. The Committee also considered that the uncertainties in the benefits of conventional DMARDs and underlying disease progression while on treatment, which had been relevant to its decision on the use of a first TNF-α inhibitor, were still relevant to consideration of the second TNF-α inhibitor. The Committee concluded that, under the same set of assumptions as accepted for the first TNF-α inhibitor, the use of a second TNF-α inhibitor would not be cost effective.

Table 7 Estimates of cost effectiveness of a second TNF-α inhibitor using data from the BSRBR

Scenario	ICER (£/QALY) for second TNF-α inhibitor					
2nd TNF-α inhibitor	Adalimumab		Etanercept		Infliximab	
1st TNF-α inhibitor	Etanercept	Infliximab	Adalimumab	Infliximab	Adalimumab	Etanercept
Using values for the second TNF-α inhibitor derived from BSRBR						
Base case	61,700	62,900	59,900	59,600	58,700	59,400
DMARDs weaker	35,800	38,800	36,100	34,600	35,400	36,700
Speculative analysis adjusting trial data						
Base case	49,400	48,400	32,200	31,000	48,000	49,000
DMARDs weaker	32,800	34,700	24,000	23,300	31,400	32,700

BSRBR: British Society of Rheumatology Biologics Register, DMARD: disease-modifying anti-rheumatic drug, QALY: quality-adjusted life year, TNF: tumour necrosis factor.

3.2.4 Cost effectiveness of TNF-α inhibitors in comparison to DMARDs: additional work following the appeal

Further analyses in the BRAM were commissioned following the appeal. The same assumptions were used in the new analyses as in the previous additional work, including no disease progression (represented as annual increase in HAQ score) while on TNF-α inhibitors. In the new analyses the only changes made were to the sources of efficacy data for TNF-α inhibitors and conventional DMARDs. But, in line with recommendations from the current 'Guide to the methods of technology appraisal' the discount rates used for costs and benefits were 3.5% and 3.5% respectively, rather than 6.0% and 1.5% respectively.

Two sources of efficacy data for TNF-α inhibitors were used in the analyses. The first source was the observed data in the BSRBR after controlling for confounding factors. This is the same as that used in the previous additional work (represented in table 8 as option A). The second source was data from a

study of the sequential use of adalimumab by Bombardieri et al. The Bombardieri study differentiated between people who had stopped their first TNF-α inhibitor because of no response and loss of response; these are represented in table 8 as options B and C, respectively. In addition, this study identified a lower rate of response for patients switching from etanercept to adalimumab than for people switching from infliximab to adalimumab. The lower rate of response was applied to any sequences of adalimumab and etanercept.

In the absence of any studies that provided an estimate of the efficacy of conventional DMARDs after the failure of a TNF-α inhibitor, two sources were used to derive data. The first source (labelled old DMARD values in table 8) reflects the estimates of cost effectiveness when modelled using the benefits of conventional DMARDs that were used in the economic modelling for NICE technology appraisal guidance 130. The sources of these benefits included studies of people with early RA and in the absence of an alternative data, a study of anakinra in people with late RA. The second source (labelled new DMARD values in table 8) is derived from the placebo arm of the abatacept clinical trial. This scenario assumes that after the failure of TNF-α inhibitors there is no active treatment effect from conventional DMARDs.

The results suggest that in a scenario in which (a) no disease progression is assumed while on treatment with TNF-α inhibitors, (b) no active treatment effect is assumed while on conventional treatments and (c) the estimates of benefits for the TNF-α inhibitors are taken from the Bombardieri study (that is, based on data for adalimumab), the estimated ICER is approximately £31,000 to £39,000 per QALY gained. The other sets of assumptions that were modelled produced higher ICERs.

Table 8 Estimates of cost effectiveness of the use of a second TNF-α inhibitor compared with conventional DMARDs

Late DMARDs	Old DMARD values[a] (ICER £/QALY)			New DMARD values[b] (ICER £/QALY)		
Second TNF-α inhibitor	A[c]	B[d]	C[e]	A[c]	B[d]	C[e]
Adalimumab following etanercept	145,000	94,500	75,700	46,700	38,700	33,400
Adalimumab following infliximab	143,000	59,600	59,500	44,500	31,300	31,300
Etanercept following adalimumab	156,000	91,600	67,100	45,900	38,600	33,600
Etanercept following infliximab	164,000	62,600	62,600	45,900	31,700	31,700
Infliximab following adalimumab	136,000	56,000	56,600	45,300	31,100	31,000
Infliximab following etanercept	152,000	59,600	63,200	47,500	32,400	32,100

BSRBR: British Society of Rheumatology Biologics Register, DMARD: disease-modifying anti-rheumatic drug, ICER: incremental cost-effectiveness ratio, TNF: tumour necrosis factor.

[a] values for conventional DMARDs as per original assessment report

[b] values for conventional DMARDs as per placebo arm of abatacept trial

[c] values for a second TNF-α inhibitor from BSRBR

[d] values for a second TNF-α inhibitor from Bombardieri et al. non responders to the first TNF-α inhibitor

[e] values for a second TNF-α inhibitor from Bombardieri et al. people who had a response to the first TNF inhibitor which subsequently reduced

The appeal panel also requested a threshold analysis that identified the minimum clinical effectiveness required for TNF-α inhibitors to be cost effective at willingness to pay thresholds of £20,000 and £30,000 per additional QALY gained. The analysis suggests that in a scenario with no disease progression while on TNF-α inhibitors and no active treatment effect of conventional DMARDs, the clinical effectiveness of TNF-α inhibitors has to be slightly greater than the values observed in the study by Bombardieri et al.

3.2.5 Cost effectiveness of second TNF-α inhibitors in comparison with rituximab

To compare the cost effectiveness of a second TNF-α inhibitor with that of rituximab, the same analyses as above (section 3.2.4) were run but rituximab was introduced into the treatment sequence after the failure of the first TNF-α

inhibitor. The same sources of efficacy data for TNF-α inhibitors and DMARDs were used. The data for rituximab were identified from the REFLEX trial (described in 3.1.3), and were the same as those used in NICE technology appraisal guidance 126. Differential rates of underlying disease progression (modelled as annual increases in HAQ score) were applied; zero was used for TNF-α inhibitors, and 0.03 was used for rituximab. The latter value was consistent with the value accepted by the Committee in the appraisal of rituximab. The estimates of cost effectiveness are summarised in table 9.

Table 9 Estimates of cost effectiveness of a second TNF-α inhibitor in comparison with rituximab

Late DMARDs	Old DMARD values (ICER £/QALY)[a]			New DMARD values (ICER £/QALY)[b]		
Second TNF-α inhibitor	A[c]	B[d]	C[e]	A[c]	B[d]	C[e]
Adalimumab following etanercept	758,000	138,000	89,900	74,800	50,500	39,000
Adalimumab following infliximab	362,000	56,900	56,900	68,700	34,500	34,500
Etanercept following adalimumab	298,000	115,000	72,600	58,200	44,600	35,600
Etanercept following infliximab	255,000	57,500	57,500	56,400	32,800	32,800
Infliximab following adalimumab	463,000	57,700	58,900	62,300	32,800	32,200
Infliximab following etanercept	919,000	61,400	66,700	66,600	33,700	33,800

BSRBR: British Society of Rheumatology Biologics Register, DMARD: disease-modifying anti-rheumatic drug, ICER: incremental cost-effectiveness ratio, TNF: tumour necrosis factor.

[a] values for conventional DMARDs as per original assessment report

[b] values for conventional DMARDs as per placebo arm of abatacept trial

[c] values for a second TNF-α inhibitor from BSRBR

[d] values for a second TNF-α inhibitor from Bombardieri et al. non-responders to the first TNF-α inhibitor

[e] values for a second TNF-α inhibitor from Bombardieri et al. people who had a response to the first TNF inhibitor which reduced

Results suggest that in a scenario that assumes no disease progression while on treatment with TNF-α inhibitors, no active treatment effect while on conventional treatments and uses the efficacy estimate for TNF-α inhibitors based on the Bombardieri et al. study, the ICER is approximately £32,000 to

£51,000 per QALY gained. The other sets of assumptions that were modelled produced higher ICERs.

3.2.6 Cost effectiveness of infliximab using alternative assumptions about dosing

The appeal panel requested further analyses that examined the cost effectiveness of infliximab using alternative dosing assumptions. Five analyses were completed; one that assumed that there was no wastage of infliximab when only part of a vial was used, and four that examined the impact on cost effectiveness of increasing the dose of infliximab either by giving it more frequently or through dose escalation. The analyses that investigate increasing the dose of infliximab reflect the cost effectiveness of infliximab for the subgroup of people who require an increased dose rather than the cost effectiveness of the cohort of people prescribed infliximab for whom only a proportion would require an increased dose.

In the analyses examining the impact on cost effectiveness of increasing the dose of infliximab, no additional efficacy of infliximab associated with increasing the dose was assumed. This is in accordance with the SPC, which states that dose escalation may be considered to either generate a response or to regain the initial response if it has reduced. There was no reduction in the efficacy of infliximab modelled to reflect the period of no response or the reduction in response to treatment. In addition, the analyses do not include the initial loading doses for infliximab, assuming that dose escalation will occur after the initial 12-week period.

In all the analyses the number of vials is based on a person weighing 70 kg, which is the average weight of people with RA in the General Practice Research Database (GPRD). This is a simplification as the amount of infliximab required per infusion differs depending on the weight of the person.

Table 10 shows the estimates of cost effectiveness under an assumption of no vial wastage. This analysis assumes that 2.1 vials rather than 3.0 vials are used per infliximab infusion. An assumption of no vial wastage produces an

estimate of cost effectiveness that is lower than if vial wastage is assumed. In a scenario that assumes no disease progression while on treatment with TNF-α inhibitors, no active treatment effect while on conventional treatments and that uses an estimated efficacy for TNF-α inhibitors based on the Bombardieri et al. study, the ICER is approximately £22,000 to £23,000 per QALY gained. The other sets of assumptions that were modelled produced higher ICERs.

Table 10 Cost effectiveness of infliximab compared with conventional DMARDs at a dose of 3 mg/kg assuming no vial wastage

Late DMARDs	Old DMARD values (ICER £/QALY)[a]		New DMARD values (ICER £/QALY)[b]	
Infliximab effectiveness	A[c]	B[d]	A[c]	B[d]
Infliximab following adalimumab	109,000	40,900	31,900	21,900
Infliximab following etanercept	106,000	43,500	33,300	23,000

DMARD: disease-modifying anti-rheumatic drug, ICER: incremental cost-effectiveness ratio.

[a] values for conventional DMARDs as per original assessment report

[b] values for conventional DMARDs as per placebo arm of abatacept trial

[c] values for a second TNF-α inhibitor from BSRBR

[d] values for a second TNF-α inhibitor from Bombardieri et al.

Table 11 shows the estimates of cost effectiveness using an increased dose of infliximab. This analysis assumes vial wastage and is based on 4 vials being used to deliver 5 mg/kg of infliximab and 6 vials to deliver 7.5 mg/kg infliximab. This analysis is a simplification as in clinical practice and in accordance with the SPC doses would be escalated incrementally. No additional effectiveness is assumed from increasing the dose of infliximab, as the SPC recommends dose escalation to maintain response or to produce a response in a person whose disease is not responding to treatment.

In a scenario that assumes no disease progression while on treatment with TNF-α inhibitors, no active treatment effect while on conventional treatments and estimates efficacy TNF-α inhibitors based on the Bombardieri et al. study the ICERs are approximately £40,000 to £42,000 per QALY gained for

5 mg/kg and £60,000 to £63,000 per QALY gained for 7.5 mg/kg. The other sets of assumptions that were modelled produced higher ICERs.

Table 11 Cost effectiveness of infliximab compared with conventional DMARDs: dose escalation of 5 mg/kg and 7.5 mg/kg

Late DMARDs	Old ICER values (£/QALY)[a]		New ICER values (£/QALY)[b]	
Infliximab effectiveness	A[c]	B[d]	A[c]	B[d]
5 mg/kg				
Infliximab following adalimumab	178,000	75,600	57,300	40,300
Infliximab following etanercept	211,000	80,600	61,500	42,400
7.5 mg/kg				
Infliximab following adalimumab	264,000	112,000	85,000	59,800
Infliximab following etanercept	314,000	120,000	91,100	62,800

DMARD: disease-modifying anti-rheumatic drug, ICER: incremental cost-effectiveness ratio.

[a] values for conventional DMARDs as per original assessment report

[b] values for conventional DMARDs as per placebo arm of abatacept trial

[c] values for a second TNF-α inhibitor from BSRBR

[d] values for a second TNF-α inhibitor from Bombardieri et al.

Table 12 shows the estimates of cost effectiveness assuming an increased frequency of doses of infliximab. This analysis assumes vial wastage and is based on either 8 or 12 doses of infliximab a year, as opposed to 6.5 doses. This analysis is a simplification as in clinical practice and in accordance with the SPC the frequency would be increased incrementally. No additional effectiveness is assumed from increasing the frequency of the dose of infliximab, as the SPC recommends increasing the frequency of the dose to maintain response or to produce a response in a person whose disease is not responding to treatment. Increasing the frequency of dosing incurs additional drug costs and additional administration costs.

In a scenario that assumes no disease progression while on treatment with TNF-α inhibitors, no active treatment effect while on conventional treatments and estimates the efficacy of TNF-α inhibitors based on the Bombardieri et al.

study, the ICERs are approximately £41,000 to £45,000 per QALY gained for 8 doses per year and £61,000 to £64,000 per QALY gained for 12 doses per year. The other sets of assumptions that were modelled produced higher ICERs.

Table 12 Cost effectiveness of infliximab compared with conventional DMARDs assuming increased dose frequency

Late DMARDs	Old DMARD values (ICER £/QALY)[a]		New DMARD values (ICER £/QALY)[b]	
Infliximab effectiveness	A[c]	B[d]	A[c]	B[d]
Dose every 6 weeks				
Infliximab following adalimumab	180,000	76,400	57,900	40,800
Infliximab following etanercept	224,000	85,500	65,200	44,900
Dose every 4 weeks				
Infliximab following adalimumab	270,000	115,000	86,700	61,000
Infliximab following etanercept	320,000	122,000	93,000	64,100

DMARD: disease-modifying anti-rheumatic drug, ICER: incremental cost-effectiveness ratio.

[a] values for conventional DMARDs as per original assessment report

[b] values for conventional DMARDs as per placebo arm of abatacept trial

[c] values for a second TNF-α inhibitor from BSRBR

[d] values for a second TNF-α inhibitor from Bombardieri et al.

4 Issues for consideration

A number of studies consider the clinical effectiveness of sequential use of TNF-α inhibitors. However, they are associated with a number of methodological limitations and difficulties in generalising the results due to small sample sizes and poor reporting. Does the Committee consider that the efficacy of the use of a second TNF-α inhibitor has been demonstrated adequately? Is it possible to distinguish in terms of clinical effectiveness between the different TNF-α inhibitors?

The clinical effectiveness values used in the cost effectiveness analyses are observational data from the BSRBR and results from a study of adalimumab

(Bombardieri et al.). Does the Committee consider that it is appropriate to infer the efficacy estimates for all TNF-α inhibitors from a study of adalimumab? Of the sets of assumptions used in the economic analyses, which one is considered the most appropriate for decision making?

No studies were identified that examined the clinical effectiveness of conventional treatments when used to treat people for whom a TNF-α inhibitor has failed. One scenario is that there is a very limited active treatment effect; an alternative scenario is that there is only a small reduction in the probability of response as disease duration and number of prior treatments increases. Based on current evidence, which scenario does the Committee consider most plausible?

The economic analyses are sensitive to assumptions about the rate of underlying disease progression while on treatment with DMARDs, and the differences between the rates of progression for different DMARDs. What rate of underlying HAQ progression does the Committee consider is reasonable for conventional DMARDs, TNF-α inhibitors and rituximab?

Rituximab is recommended by NICE, following the failure of a TNF-α inhibitor. Therefore rituximab may be used at the same point in the care pathway as a second TNF-α inhibitor. Is a second TNF-α inhibitor cost effective in comparison with rituximab?

The licensed starting dose for infliximab is 3 mg/kg. It is sold in vials of 100 mg. This means that any infliximab left over may be wasted if the dose is anything other than a multiple of 100 mg and the vials are used for one person only. If infusions are prepared centrally (for example by a pharmacy central intravenous additive service), then it may be possible to reduce, but not completely eliminate, wastage by sharing vials between patients. Is it appropriate for the Committee to accept an assumption that there will be no vial wastage?

If there is no response to infliximab or there is a loss of response to infliximab, the dose of infliximab may be increased to up to 7.5 mg/kg, or the number of doses increased to one every 6 or 4 weeks. Does the Committee consider that for people requiring higher doses, infliximab would be cost effective in these alternative regimens?

The group of people being considered in this appraisal are heterogeneous and will have tried, at a minimum, three previous treatments (two conventional and one biological DMARD), but on average have tried five previous treatments (four conventional and 1 biological DMARD). In addition the group includes people for whom rituximab may be an alternative and those for whom rituximab may be contraindicated, or for whom methotrexate (with which rituximab must be given) is contraindicated. Do different considerations apply to different subgroups of people?

5 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The additional work for this appraisal was prepared by the Institute's Decision Support Unit and Pelham Barton, West Midlands Health Technology Consortium.

- Barton P (2008) Further cost-effectiveness analysis of sequential TNF-α inhibitors for rheumatoid arthritis. West Midlands Health Technology Assessment Consortium
- Wailoo A, Tosh J (2008) The effectiveness of non biologic DMARDs after anti TNF inhibitor failure. Decision Support Unit.
- Wailoo A (2008) The sequential use of TNF-α inhibitors: update to a report by the decision support unit. Decision Support Unit.

B Additional references used:

Chen YF, Jobanputra P, Barton P, et al. (2006) 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. Health Technology Assessment 10(42).

Hyrich KL, Lunt M, Watson KD, et al. (2007) Outcomes after switching from one anti-tumor necrosis factor α agent to a second anti-tumor necrosis factor α agent in patients with rheumatoid arthritis. Arthritis and Rheumatism 56(1): 13–20.

Arthritis and Musculoskeletal Alliance (2006) Appendix 1: Modellling the cost effectiveness of sequential use of TNF-α inhibitors in the management of rheumatoid arthritis: an update. Appeal documents submitted to NICE. Available from www.nice.org.uk.

Appendix B: Related technology appraisal guidance

Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 130)

1.1 The tumour necrosis factor alpha (TNF-α) inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics.

- Active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
- Have undergone trials of two disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.

1.2 TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and etanercept may be given as monotherapy.

1.3 Treatment with TNF-α inhibitors should be continued only if there is an adequate response at 6 months following initiation of therapy. An adequate response is defined as an improvement in DAS28 of 1.2 points or more.

1.4 After initial response, treatment should be monitored no less frequently than 6-monthly intervals with assessment of DAS28. Treatment should be withdrawn if an adequate response (as defined in 1.3) is not maintained.

1.5 An alternative TNF-α inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial 6-month assessment of efficacy, provided the risks and benefits have been fully discussed with the patient and documented.

1.6 Escalation of dose of the TNF-α inhibitors above their licensed starting dose is not recommended.

1.7 Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules.

1.8 Use of the TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.

1.9 Initiation of TNF-α inhibitors and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.

Rituximab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 126)

1.1 Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor α (TNF-α) inhibitor therapy.

1.2 Treatment with rituximab plus methotrexate should be continued only if there is an adequate response following initiation of therapy.

An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more. Repeat courses of treatment with rituximab plus methotrexate should be given no more frequently than every 6 months.

1.3 Treatment with rituximab plus methotrexate should be initiated, supervised and treatment response assessed by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

Appendix C: Clinical effectiveness of a second TNF-α inhibitor

Study	n	Comparison	Week	ACR (% of patients)			Mean change DAS28	EULAR (% of patients)			Mean change HAQ
				20	50	70		None	Moderate	Good	
Etanercept											
Cantini (2005)	15	None	24	90	33	10	–2.43				
Kristensen (2006)	239	Second biological	26	59							
	442	First biological (d)		63							
Cohen (2005)	24	None	12				–1.5	26	16	58	
Buch (2005[a])	12	Switching group A[a]	12	66	66	33					
	22	Switching group B		71	57	14					
	58	Staying infliximab		59	35	6					
Gomez Puerta (2004)	12	Second biological	26				–1.33	17	67	17	
		First biological (s)					not comparable	NR	NR	NR	
Haroui (2004)	22	None	12	64	23	5					–0.45
Buch (2007)	95	None	12	38	24	15	–1.47	27	61	12	
Hjardem (2007) from infliximab	57	Second biological	12				–1.2	46	30	23	
		First biological (s)						41	39	20	
Hjardem (2007) from adalimumab	17	Second biological	12				–1.6	33	33	33	
		First biological (s)						38	31	31	
Keystone (2004)	83	Switch to etanercept	26								–0.41
	72	Switch to infliximab									–0.13

Study	n	Comparison	Week	ACR (% of patients)			Mean change DAS28	EULAR (% of patients)			Mean change HAQ
				20	50	70		None	Moderate	Good	
Adalimumab											
Nikas (2006)	24	Second biological	52	75	50	33	–2.4		71 (good/moderate)		
	9	Loss/lack effect		89	56	33	–2.1		78 (good/moderate)		
	25	First biological (d)		76	56	36	–2.6		72 (good/moderate)		
Wick (2005)	27	From infliximab	26	70			–1.3				
	9	From etanercept		78			–1.9				
	26	First biological (d)		70			–2.1				
Atzeni (2006)	15	None	26				–2.7				
Bombardieri (2007)	899	Second biological	12	60	33	13	–1.9	24	53	23	–0.48
	173	No response		52	25	8	–1.9	26	55	19	–0.44
	306	Reduced response		67	37	13	–2.0	21	57	22	–0.51
	5711	First biological (d)		70	41	19	–2.2	16	35	49	–0.55
Buch (2005b)	19	No response	12				–1.3	57	36	7	
	30	Reduced response					–1.4	32	61	7	
	30	First biological (d)					NR	50	40	10	
Kristensen (2006)	165	Second biological	26	52							
	90	First biological (d)		62							
Hjardem (2007) from infliximab	73	Second biological	12				–0.9	36	46	17	
		First biological (s)					–1.3	39	39	22	
Hjardem (2007) from etanercept	5	Second biological	12				–1.0	25	50	25	
		First biological (s)					–1.5	40	20	40	
Bennett (2005)	8	No response	Mean 7.3 months				–0.7	62	25	13	–0.22
	13	Reduced Response					–2.1	23	62	15	–0.26
	44	First biological (d)					–2.4	15	30	55	–0.31
Van der Bijl	41	None	16	49	26		–1.6		65 (good/moderate)		

Study	n	Comparison	Week	ACR (% of patients)			Mean change DAS28	EULAR (% of patients)			Mean change HAQ
				20	50	70		None	Moderate	Good	
Infliximab											
Cohen (2005)	14	None	12				–1.7	33	33	33	
Keystone (2004)	67	Switching to infliximab	26								–0.13
		Switching to etanercept									–0.43
van Vollenhoven (2003)	18	Second biological	24	67			–1.6				
		First biological (s)		NR			NR				
Furst (2007)	14	Switching to infliximab	16	62	31		–2.2				
		Staying on etanercept		29	15		–1.3				
Hjardem (2007) from etanercept	4	Second biological	12				–1.4	25	50	25	
		First biological (s)					-0.2	100	0	0	
Hjardem (2007) from adalimumab	5	Second biological	12				–0.9	25	75	0	
		First biological (s)					–0.7	50	50	0	

ACR: American College of Rheumatology, CRP: C-reactive protein, EULAR: European League Against Rheumatism, HAQ: Health Assessment Questionnaire.

[a]Group A No response and CRP reduction less than 20% at week 6, group B No response and CRP reduction greater than 20% at week 6, but not at week 12

(d) = compared with a different control group

(s) = within group comparison