4 June 09

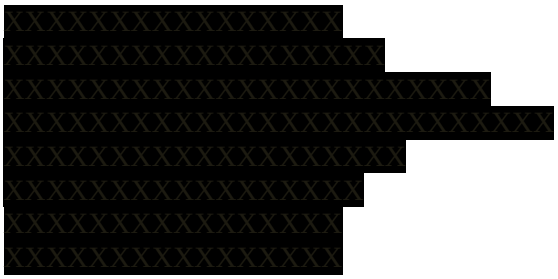
Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of NICE – Protocol

1. Title of the project

Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis

2. Name of TAR team and 'lead'

CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York



3. Plain English Summary

Psoriatic arthritis is an inflammatory disease resulting in abnormality of joints. It is closely associated with psoriasis, which is a noncontagious inflammatory skin disease characterised by recurring reddish patches covered with silvery scales. Psoriatic arthritis is diagnosed when a patient has both psoriasis and typical inflammatory arthritis of the spine and/or other joints. It has been estimated that psoriatic arthritis occurs in 5-7% of those with psoriasis.

Patients with psoriatic arthritis often have progressive joint deformity (ranging from mild inflammation of the layer of connective tissue that lines the cavities of joints to severe erosion of joints), as well as skin symptoms. Some patients have changes in the nails and small bones of the fingers or toes. All these symptoms can significantly impair a patient's health-related quality of life and social and psychological well-being.

The treatment for psoriatic arthritis is to improve arthritis, psoriasis or both. Managing severe active psoriatic arthritis is often difficult. Currently, tumour necrosis factor alpha (TNF-α) inhibitors are used for the treatment of patients with severe active psoriatic arthritis. TNF-α is involved in the damaging process that affects cartilage and joints. Etanercept, infliximab and adalimumab are the licensed medicines to inhibit the activity of TNF-α.

The purpose of this project is to assess the benefits and adverse effects of three TNF-α inhibitor treatments (etanercept, infliximab and adalimumab) for active and progressive psoriatic arthritis in patients who have an inadequate response to standard treatment. A further objective of this project is to evaluate whether these TNF-α inhibitor agents are cost-effective in these patients.

4. Decision problem

- **Objectives**

The aim of the project is to determine the clinical effectiveness, safety, and cost-effectiveness of etanercept, infliximab and adalimumab for the treatment of active and progressive psoriatic arthritis in patients who have an inadequate response to standard treatment (including disease modifying antirheumatic drug (DMARD) therapy).

- **Background**

Psoriatic arthritis is hyperproliferative and inflammatory arthritis that is distinct from rheumatoid arthritis (RA) and closely associated with psoriasis.[1, 2] Overall, because psoriatic arthritis involves both skin and joints it can result in significant quality of life impairment and joint deformity and psychosocial disability.[1, 3] Psoriatic arthritis is diagnosed primarily on clinical grounds, based on a finding of psoriasis and the typical inflammatory arthritis of the spine and/or other joints.[3] Most, but not all, of these patients will test negative for RA factor (an antibody produced by plasma cells and found in around 70% of cases of RA). Psoriatic arthritis differs from RA in that the pattern of joint involvement is commonly asymmetric, and involves the distal interphalangeal joints and nail lesions.[4] In psoriatic arthritis dactylitis, spondylitis and sacroiliitis are common whereas in RA they are not.[4] In psoriatic arthritis involved joints are tighter, contain less fluid and are less tender than those in RA. In addition to distinct clinical features psoriatic arthritis and RA show differences in the inflammatory reaction that accompanies each form of arthritis.[4] Most patients with psoriatic arthritis will have developed psoriasis first but joint involvement appears first in 19% and concurrently with psoriasis in 16% of cases.[3] There are, however, still some difficulties in defining psoriatic arthritis[2] and due to the lack of a precise definition and diagnostic marker for psoriatic arthritis, it is difficult to estimate its prevalence. Figures for the UK have estimated the adjusted prevalence in the primary care setting to be 1.7% and 0.3% for psoriasis and psoriatic arthritis respectively.[5]

Effective treatment for psoriatic arthritis needs to target both skin and joint disease. Most treatments for psoriatic arthritis have been borrowed from those used for RA and non-steroidal anti-inflammatory drugs are widely used.[3] Other treatments used include local corticosteroid injections, and gold.[3] Currently, methotrexate and sulphasalazine are considered the DMARDs of choice, although the evidence for methotrexate is largely derived from non-experimental evidence and the effects of sulphasalazine appear modest.[6] Other drugs investigated for the treatment of psoriatic arthritis include: auranofin, etretinate, fumaric acid, intramuscular gold, azathioprine, and Efamol marine.[7] Ciclosporin, penicillamine and leflunomide are also sometimes used in clinical practice.

Numerous chemokines and cytokines are believed to play an important role in triggering cell proliferation and sustaining joint inflammation in psoriatic arthritis. Cytokines stimulate inflammatory processes that result in the migration and activation of T cells which then release tumour necrosis factor α (TNF-α). TNF-α is one of several pro-inflammatory cytokines that have been implicated in the pathogenesis of both psoriasis and psoriatic arthritis.[8, 9] Newer strategies for the treatment of psoriatic arthritis have focused on modifying T cells in this disease through direct elimination of activated T cells, inhibition of T cell activation, or inhibition of cytokine secretion or activity.[10] Etanercept, infliximab and adalimumab are among a number of these new biological agents that have been developed and investigated for the treatment of various diseases including psoriasis and psoriatic arthritis. Etanercept is a human dimeric fusion protein that binds specifically to TNF and blocks its interaction with cell surface receptors.[3] Infliximab is a murine/human chimeric anti-TNF monoclonal gamma immunoglobulin that inhibits the binding of TNF to its receptor.[3] Adalimumab is a fully humanised monoclonal IgG1 antibody and TNF antagonist.[15] All three agents are licensed in the UK for the treatment of active and progressive PsA in adults when the response to previous DMARD therapy has been inadequate.

5. Report methods for synthesis of evidence of clinical effectiveness

A systematic review of the evidence for the clinical effectiveness and safety of etanercept, infliximab (mono and combination therapy) and adalimumab for the treatment of active and progressive psoriatic arthritis in patients who have an inadequate response to standard treatment (including DMARD therapy) will be conducted following the general principles recommended in CRD's guidance[11] and QUOROM statement.[12]

- **Search strategy**

Searches of electronic databases will be conducted to identify relevant RCTs published since the completion of searches for the original review (2004).[13] In addition, relevant published systematic reviews and trial registers will be searched to identify any further RCTs of relevance. In the first instance, information on adverse events will be identified from searching resources of the US and European drug regulatory agencies (i.e. FDA, EMEA). Where additional information is required, additional searches for evidence on serious adverse events will not be restricted by date or study design. At the time of receiving the company submission, update searches will be conducted to ensure the review remains up-to-date and covers all relevant evidence at the time of submission. No language restrictions will be applied to the search strategy. See appendix for details of searching.

- **Inclusion and exclusion criteria**

Two reviewers will independently screen all titles and abstracts. Full paper manuscripts of any titles/abstracts that may be relevant will be obtained where possible and the relevance of each study assessed by two reviewers according to the criteria below. Studies that do not meet all of the criteria will be excluded and their bibliographic details listed with reasons for exclusion. Any discrepancies will be resolved by consensus and, if necessary, a third reviewer will be consulted.

Study design

The review of etanercept, infliximab and adalimumab will include randomised, placebo- or reference-controlled trials of efficacy (including any open-label extensions of these RCTs). If information from on serious adverse events from regulatory sources require supplementation, studies other than randomised controlled trials (RCTs) that provide these data for etanercept, infliximab and adalimumab will also be reviewed. If multiple case series are identified, inclusion will be limited to those series reporting outcomes for a minimum of 500 patients.

Interventions

Etanercept, infliximab and adalimumab will be reviewed. Comparators will be placebo, another of the three listed agents, or conventional management strategies for active and progressive psoriatic arthritis that has responded inadequately to previous DMARD therapy excluding TNF-α inhibitors.

Participants

For the evaluation of the effectiveness of etanercept, infliximab and adalimumab, the reviewed studies will be of adults with active and progressive psoriatic arthritis with an inadequate response to previous standard therapy (including at least one DMARD). Trials of effectiveness must specify that the patients have psoriatic arthritis, with the definition and/or the inclusion criteria for psoriatic arthritis stated. For the assessment of adverse effects, studies of patients with other conditions will be included in the review.

Outcomes

Data on the effectiveness, adverse effects, patient-centred outcome measures, costs to the health service, and cost-effectiveness will be extracted. The outcomes of effectiveness will be overall global assessments, functional measures (e.g. HAQ), quality of life assessments (e.g. DLQI), measures of the

anti-inflammatory response (e.g. PsARC, ARC20/50/70), response of psoriatic skin lesions (e.g. PASI) and where appropriate, radiological assessments of disease progression or remission. Baseline data will be extracted where reported. Any unfavourable or dangerous reaction to these TNF-α inhibitor agents will be defined as an adverse event. This review will specifically focus on the known serious adverse events of these agents: malignancies, severe infections (i.e those that require IV antibiotic therapy and/or hospitalisation or cause death) and reactivation of latent tuberculosis. If additional serious adverse events have been reported to regulatory bodies, then the incidence of these will also be assessed. Data relating to serious adverse events in indications other than psoriatic arthritis will also be considered, provided it is clinically appropriate to do so.

- **Data extraction strategy**

Data relating to both study design and quality will be extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements will be resolved through consensus, and if necessary, a third reviewer will be consulted. If time constraints allow, attempts will be made where possible to contact authors for missing data. Data from studies with multiple publications will be extracted and reported as a single study.

- **Quality assessment strategy**

The quality of RCTs and other study designs will be assessed using standard checklists.[11] In the case of non-randomised studies, tools used by the TAR group in previous reviews will be employed.[14] The assessment will be performed by one reviewer, and independently checked by a second. Disagreements will be resolved through consensus, and if necessary, a third reviewer will be consulted.

- **Methods of analysis/synthesis**

The analysis and synthesis of clinical data in this review will be conducted in distinct sections.

In the initial analysis/synthesis of data on etanercept, infliximab and adalimumab, the results of the data extraction and quality assessment will be presented in structured tables and as a narrative summary. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques. Clinical, methodological and statistical heterogeneity will be investigated. If necessary, sensitivity analyses will be undertaken when permitted by sufficient data. The potential short and long-term benefits of etanercept, infliximab and adalimumab on both the psoriasis and arthritis components of psoriatic arthritis will be investigated. The serious adverse effects of these agents will also be explored. If the evidence allows, the appraisal will attempt to identify criteria for selecting patients for whom treatment with etanercept, infliximab or adalimumab would be particularly appropriate.

It is anticipated that trials conducting head-to-head comparisons of etanercept, infliximab and adalimumab will not yet be available. Therefore, if feasible and appropriate, indirect and/or mixed treatment comparisons will be conducted to provide information on the benefits of etanercept, infliximab and adalimumab relative to the appropriate comparators and each other. Mixed treatment comparisons are useful analytic tools when direct evidence on comparisons of interest is absent or sparse.[15] Meta-analysis using mixed treatment comparisons enables data from several sources to be combined, while taking into account differences between the different sources, in a similar way to, but distinct from, how a random effects model takes into account between-trial heterogeneity.

6. Report methods for synthesising evidence of cost-effectiveness

Identifying and systematically reviewing published cost-effectiveness studies

The sources detailed in Section 5 will be used to identify studies of the cost-effectiveness of etanercept, infliximab and adalimumab. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside trials, modelling studies and

analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The quality of the cost-effectiveness studies will be assessed according to a checklist updated from that developed by Drummond *et al.*[16] This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Health and Clinical Excellence (NICE).[17] This information will be tabulated and summarised within the text of the report. In particular information will be extracted on the comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of life, direct costs (medical and non-medical) and productivity costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic / probabilistic sensitivity analysis).

The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the specific research question posed and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review. The presence of any data gaps (e.g. resource use data) that may need to be filled during the development of the model will be identified and additional searches may be required.

Development of a new decision-analytic model

Subject to the availability of existing models and evidence, a new decision-analytic model will be developed to estimate the cost-effectiveness of etanercept, infliximab and adalimumab. The perspective will be that of the National Health Services and Personal Social Services. Productivity costs are not included within this perspective but may be included as a secondary analysis. Both cost and QALY will be discounted at 3.5%.

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise patients' care and subsequent prognosis and the impacts of alternative therapies on joint and skin disease, in a way which is clinically acceptable.
- To relate initial and intermediate outcomes (such as response to treatment and functional status) to final health outcomes, expressed in terms of quality-adjusted life years (QALYs). This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units which permit comparison with other uses of health service resources.
- To populate this model using the most appropriate data. This is likely to be identified systematically from published literature, routine data sources and using data elicited from relevant clinical experts.
- To estimate the mean cost-effectiveness of each of the therapies compared with palliative care, based on an assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival.
- Consistent with available evidence, to report cost-effectiveness of alternative treatments for specific sub-groups of patient, such as those with severe joint and/or skin involvement at baseline.
- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this *parameter uncertainty,* is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, *decision uncertainty.* This is

presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.

- To inform future research priorities in the NHS, the model will be used to undertake analyses of the expected value of perfect information. These take the decision uncertainty associated with analysis and quantify the cost of this uncertainty in terms of health gain forgone and resources wasted by making the wrong decision. This cost of uncertainty represents the value of perfect information, and this can be estimated for the model overall and for individual parameters.

The specific details of the data to be used to populate the model will have to await the development of the structure, the systematic searches of the literature and the manufacturers' submissions. However, we expect to derive estimates of the relative effectiveness of the therapies from available randomised trials. Estimates of the natural history progression of psoriatic arthritis, and patients' prognosis if they continue or withdraw from treatment may use observational evidence relevant to UK clinical practice identified by the review of clinical effectiveness. This may be supplemented by data elicited from a sample of UK rheumatology experts using appropriate elicitation techniques.[18]

Bayesian Methods

The previous NICE appraisal of etanercept and infliximab conducted an indirect treatment comparison of treatment effects using Bayesian statistical methods (NICE 2006).[13] These parameters were used as inputs to a conventional Markov model in Excel. As this protocol is submitted we are exploring a potential collaboration with academics at the Universities of Leicester and Cambridge to carry out the analysis for this TAR, where possible, using fully Bayesian methods to explore the feasibility and added value of using such an approach over more established methods and providing an exemplar case study. If this collaboration were agreed by all parties, we would intend to carry out the evidence synthesis and decision modelling using a comprehensive one-stage approach.[19, 20] In doing this we will explore the possibility of using elicited expert opinion to inform the mapping of clinical to quality of life outcomes required for the economic decision modelling. In addition, we intend to develop and apply some dynamic and interactive presentational tools to i) present the results of the analysis, ii) explore the robustness of the modelling, and iii) allow prior beliefs about the values of key parameters be incorporated into the decision modelling in real time. It is hoped that, if sufficiently developed, these tools could be used 'live' in the appraisal meeting(s); but this would be at the discretion of both the York TAR group and NICE and a decision made nearer the time. It is intended that a further document outlining the intentions of this collaboration in more detail will be written quickly and submitted to NICE for approval within the next few weeks.

7. Handling the company submission(s)

All data submitted by the drug manufacturers will be considered if received by the review team no later than 26 August 2009. Data arriving after this date will only be considered if time constraints allow.

If efficacy and/or adverse effects data meet the inclusion criteria for the review then they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any economic evaluations included in the company submission will be assessed. This will include a detailed analysis of the appropriateness of the parametric and structural assumptions involved in any models in the submission and an assessment of how robust the models are to changes in key assumptions. Clarification on specific aspects of the model may be sought from the relevant manufacturer. An assessment of any differences between the published economic evaluations, those submitted by the manufacturers and any economic evaluation developed by us will be reported.

Any 'commercial in confidence' data taken from a company submission will be clearly marked in the NICE report (*underlined and followed by an indication of the relevant company name e.g. in brackets)* and removed from the subsequent submission to the HTA.

8. Competing interests of authors

[redacted] has a financial interest in a consulting company which has undertaken work for Abbott, Schering Plough and Wyeth, but not relating to psoriatic arthritis, and he has not personally participated in this work. He has personally undertaken paid consultancy for some of the comparator manufacturers, again not relating to psoriatic arthritis.

There are no other competing interests.

9. References

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Appendix: Literature searching

Handsearching

To ensure that all newly published relevant papers not identified by database searches are considered by the review team, handsearching of key journals will also be conducted. The journals will be selected by combining a number of approaches i.e. by using the Journal Citation Reports via ISI Web of Knowledge to check for journals specific to the topic, by checking through the results of the initial searches that were carried out to develop the search strategy in the protocol, and by consulting with the clinical expert on the review.

MEDLINE (via OvidSP) was searched to inform the scope of the TAR and the protocol. For the full review, update searches will be run on MEDLINE and in addition the following databases will be searched:

For RCTs:
MEDLINE
MEDLINE In Process
EMBASE
Cochrane Central Register of Controlled Trials (CENTRAL)
Science Citation Index (SCI)

For Ongoing Trials:
ClinicalTrials.gov
Current Controlled Trials

For Economic Evaluations:
NHS Economic Evaluation Database (NHS EED)
Health Economic Evaluations Database (HEED)
EconLit

For Conference Proceedings:
Conference Proceedings Citation Index - Science (CPCI-S)

The following draft strategy was developed for MEDLINE (OvidSP) to identify RCTs. It will be revised as required on acceptance of the protocol and adapted to run effectively on the other databases listed above.

Since our previous review of etanercept and infliximab covered the period prior to April 2004,[21] the update search for these drugs covers 01 April 2004 to date. The adalimumab search was not limited by date.

1. randomized controlled trial.pt.	271221
2. controlled clinical trial.pt.	79237
3. randomized.ab.	181126
4. placebo.ab.	112190
5. drug therapy.fs.	1311670
6. randomly.ab.	131483
7. trial.ab.	188318
8. groups.ab.	905101
9. or/1-8	2395038

10. humans.sh.	10730636
11. 9 and 10	1954674
12. Arthritis, Psoriatic/	2213
13. (psoria$ adj2 (arthrit$ or anthropath$)).ti,ab.	3239 mp.
14. 12 or 13	3838
15. (etanercept or enbrel).ti,ab,rn.	2077 mp.
16. (infliximab or remicade).ti,ab,rn.	4669 mp.
17. 15 or 16	5840
18. 11 and 14 and 17	445
19. (200404$ or 200405$ or 200406$ or 200407$ or 200408$ or 200409$ or 200410$ or 200411$ or 200412$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.	3512627
20. 18 and 19	352
21. (adalimumab or humira or D2E7 or (D2 adj E7)).ti,ab,rn.	1150
).mp.	
22. 11 and 14 and 21	140
23. 20 or 22	393

Additional searches will be undertaken in the databases listed above to identify adverse events information. These additional searches will be developed and refined early in the review process.

The searches for the information to inform the economic model will be developed in collaboration with the health economists working on the project and will be designed pragmatically to capture relevant information to inform model parameters as necessary.

Where necessary, additional searches will be undertaken to identify literature on the treatment comparators.

Reference management and documentation

As several databases will be searched, some degree of duplication will result. In order to manage this issue, the titles and abstracts of bibliographic records will be downloaded and imported into Endnote bibliographic management software to remove duplicate records. Full details of the searching process will be recorded.