TECHNOLOGY ASSESSMENT REPORT FOR THE HTA PROGRAMME

Efalizumab and etanercept for the treatment of psoriasis

A. Final version

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B. Full title of research question

A systematic review of the clinical effectiveness, safety, tolerability and cost effectiveness of efalizumab and etanercept for the treatment of psoriasis in adults diagnosed with moderate to severe psoriasis.

C. Clarification of research question and scope

This review will examine the clinical effectiveness, safety, tolerability and cost-effectiveness of efalizumab and etanercept in adults diagnosed with moderate to severe psoriasis. The assessment of etanercept for people with psoriatic arthritis will be part of a separate review and therefore this assessment will not include treatment outcomes for psoriatic arthritis. Studies where efalizumab and etanercept are used alone or in combination with other interventions for the treatment of moderate to severe psoriasis will be reviewed.

It is anticipated that trials in which efalizumab and etanercept have been compared with other active treatments will not yet be available. The review will therefore include a separate assessment of the effectiveness and tolerability of the other agents with which it is considered appropriate to compare efalizumab and etanercept. In addition, if feasible and appropriate, statistical techniques will be employed to conduct analyses of mixed treatment comparisons of efalizumab and etanercept with the appropriate comparators.

The systematic review of economic evaluations will include cost effectiveness analyses, cost-minimisation analyses, cost-utility analyses and cost-benefit analyses.

At the time of preparing this protocol the use of efalizumab and etanercept for the treatment of psoriasis are awaiting approval from the Medicines and Healthcare Products Regulatory Agency (MHRA).

D. Report methods

Search strategy

See Appendix. No language restrictions will be applied to the search strategy.

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 efalizumab and etanercept will include randomised, placebo- or reference-controlled trials of efficacy and full economic evaluations that compare two or more options and consider both costs and consequences. Economic evaluations will include cost-effectiveness, cost-minimisation, cost-utility and cost-benefit analysis. The review of economic studies will include economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Studies other than RCTs that provide long-term adverse events data for efalizumab and etanercept will also be reviewed, provided they have an adequate sample size and follow-up period.

The review of the appropriate comparators will use pertinent information from an existing systematic review, published as a Health Technology Assessment,[1] in addition to relevant subsequently published RCTs. In addition to RCTs, tertiary data sources (i.e. standard reference texts) will be reviewed for adverse event data for the comparators.

Interventions

Efalizumab and etanercept will be reviewed. Comparators will be placebo or any of the following

treatments: photochemotherapy (PUVA), RePUVA, and narrow-band UVB, either alone or in combination with another therapeutic agent; the Ingram regimen (daily in-hospital administration of dithranol (anthralin) and phototherapy for a period of several weeks); the Goeckerman regimen (daily in-hospital combination treatment with coal tar and phototherapy); oral systemic agents (acitretin, ciclosporin, methotrexate, hydroxycarbamide, and fumaric acid esters (fumarates)), either alone or in combination with other therapeutic agents; and the biological agent infliximab, either alone or in combination with other therapeutic agents.

Participants
The reviewed studies will be of adults with moderate to severe psoriasis. For the purposes of this review patients with moderate to severe psoriasis are considered to be those that have an inadequate treatment response to topical treatment alone. Data on psoriasis outcomes from studies of psoriatic arthritis will be used in the review if appropriate. Data relating to adverse events, safety and tolerability of efalizumab and etanercept in other indications will also be considered, provided it is clinically appropriate to do so.

Outcomes
Data on the following outcome measures will be extracted where available:
Psoriasis Area and Severity Index (PASI); Self Administered Psoriasis Area and Severity Index (SAPASI); Psoriasis Disability Index (PDI); Total Severity Score (TSS); Investigator's Assessment of Global Improvement (IAGI); Physician's Global Assessment (PGA); adverse effects; patient-centred outcome measures; quality of life (QoL); Dermatology Life Quality Index (DLQI); duration of remission; costs to the health service and to others, and cost-effectiveness.

Data extraction strategy
Data relating to both study design and quality will be extracted by one reviewer 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.[2] 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.

The quality of the cost effectiveness studies will be assessed by one reviewer and checked by a second according to a checklist updated from that developed by Drummond et al., 1997.[3] This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute of Clinical Excellence.[4]

Methods of analysis/synthesis
The analysis and synthesis of clinical data in this review will be conducted in distinct sections: an analysis/synthesis of the primary studies of efalizumab and etanercept; an analysis/synthesis of the appropriate comparator treatments; and, if feasible and appropriate, an analysis of mixed treatment comparisons.

In the analysis/synthesis of the data on efalizumab and etanercept the results of the data extraction and quality assessment will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques. Where appropriate, the possibility of publication bias will be investigated using funnel plots and Egger's test.

The analysis/synthesis of the appropriate comparators will use pertinent information from the existing systematic review[1] in addition to relevant subsequently published RCTs.

If feasible and appropriate, mixed treatment comparisons will be conducted to provide information on the benefits of efalizumab and etanercept relative to the appropriate comparators. Mixed treatment

comparisons are a useful analytic tool when direct evidence on comparisons of interest is absent or sparse. 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. If conducted, the mixed treatment comparisons will utilise the findings from the analyses of clinical trial data and economic evaluations.

Methods for estimating costs and cost-effectiveness
Details of each published economic evaluation, together with a critical appraisal of its quality, will be presented in structured tables. A detailed review of any published economic model will also be carried out. If models are submitted by sponsors, these will also be reviewed.

Based on the review of the published economic evaluations - and any evaluations submitted by the manufacturers - a decision analytic model may be developed to assess the cost-effectiveness of the drugs within the context of the NHS. This may require the development of a 'de novo' model or the modification and/or re-parameterisation of an existing model. 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.

E. Handling the company submission(s)

All data submitted by the drug manufacturers will be considered if received by the review team no later than 23 July 2004. 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.

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.

F. Project management

a. Timetable/milestones - submission of:

Draft protocol:	2 April 2004
Final protocol:	15 April 2004
Industry submission:	23 July 2004
Progress report:	30 July 2004
Draft report to referees and NICE:	18 January 2005
Final report to HTA:	7 February 2005

b. Competing interests
None of the research team has any competing interests to declare. Any competing interests relating to the external reviewers will be declared in the final report.

c. External reviewers
The Technology Assessment Report will be subject to external review by at least two experts acting on behalf of the NHS HTA Programme. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that the NICE secretariat and Appraisal Committee will undertake methodological review. In addition, an external methodological referee will be asked to review the report on behalf of the HTA Programme. Referees will review a complete and near final draft of the TAR and will understand that their role is part of

external quality assurance. Referees will be required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking, which we will hold on file. Comments from referees and the Technical lead, together with our responses will be made available to NCCHTA in strict confidence for editorial review and approval. In addition, the review team will invite up to two external experts to advise on the clinical content of the review.

G. Appendices

Background for NICE psoriasis

Psoriasis is a common inflammatory skin disease affecting 0.5 to 2.5% of the world population. It is a chronic condition for which there is as yet no cure, requiring life-long treatment. Psoriasis tends to be most common in Caucasian races.[5] In the UK the prevalence is 1 to 2 %.

There are different forms of psoriasis including plaque psoriasis, inverse psoriasis, guttate psoriasis, generalised pustular and erythrodermic psoriasis, all of which have different characteristics. How closely linked the different forms of psoriasis are in term of their pathophysiology and response to therapy is not fully established.[6] Plaque psoriasis or psoriasis vulgaris, characterised by clearly demarcated, red, scaling plaques, is the most common form of psoriasis, occurring in more than 80% of cases.[5]

In addition to its physical symptoms, psoriasis can cause a high degree of emotional suffering, greatly diminishing an individual's quality of life. Depression, low-self esteem and social isolation can all be associated with psoriasis.[7]

Psoriasis is usually classified as mild, moderate or severe, often according to the proportion of the skin affected, but the intensity of the condition and the effect it has on the patient's quality of life should also be taken into account. Assessment of psoriasis severity is not an exact science and the definition of 'severe' will inevitably differ, both amongst and between dermatologists and patients.[8] If one adheres to strict clinical criteria then severe psoriasis could be defined as psoriasis affecting at least 20% of skin surface area or if as determined by the Psoriasis Area Severity Index (PASI, typically scored 0-72) has an index value of at least 10. Other scoring systems have been developed which encompass a global score, usually 0 (no psoriasis) to 7 or 8 (very severe psoriasis), running through gradings such as mild and moderate. Understandably this is a subjective assessment or gestalt. It is important to realise that difficult to treat or severe psoriasis does not necessarily equate with extent of disease. For instance a patient with relatively minimal extent psoriasis may be severely psychosocially disabled by the disease and have unrealistic expectations of cure or response to treatment. Another patient with moderate disease may have failed to respond to and/or to tolerate a variety of treatments. For the purposes of this review, the definition of severe psoriasis is a clinical one applied to extensive chronic plaque, generalised pustular or erythrodermic psoriasis. If a more holistic approach to treatment is adopted, then the definition of 'severe' may change to incorporate clinical extent, psychosocial disability and historical response to treatment.[8]

Management of mild psoriasis relies on a range of topical treatments: emollients (for mild self limiting episodes), corticosteroids, salicylic acid, coal tar, vitamin D analogues, retinoids and dithranol.[9] When psoriasis is refractory to topical treatments or too widespread, phototherapy or systemic therapies are indicated.[5] The systemic drugs available include retinoids, methotrexate and ciclosporin. The activity of the immunosuppressant drug ciclosporin in psoriasis indicated a role for the immune system in the pathogenesis of psoriasis and further evidence for the role of T cells in the pathogenesis of psoriasis has come from both experimental and clinical data. Although methotrexate and ciclosporin are effective, their short and long-term side effects limit their usefulness and more specific immunosuppressant agents have been sought.[10]

Newer strategies for the treatment of psoriasis 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.[11] A number of these new biological agents have been developed and investigated. Two in particular have gained or are close to gaining approval for clinical use, these are etanercept and efalizumab. Their agent class and therapeutic strategies are summarised in the table below.

Generic name	Class	Target	Therapeutic strategy
Etanercept	Receptor antibody fusion protein	Binds the postsecretory cytokine TNFα*	
Efalizumab	Humanized monoclonal antibody	Anti CD11a subunit of LFA-1. Blocks T cell activation or migration	

* TNFα=Tumour necrosis factor α. This is one of a number of cytokines that stimulate the dendritic cells, macrophages and keratinocytes and maintains the inflammatory state.

(Adapted from Pariser 2003[12] and Gniadecki 2002.[10])

Search Strategy

Scoping Search

The scoping search has already been carried out by the National Institute of Clinical Excellence.

Main Literature Search

The following databases will be searched:

Medline
Embase
Cochrane Controlled Clinical Trials Database (CCTR)
National Research Register (NRR)
http://www.update-software.com/National/
CenterWatch Clinical Trials Listing Service
http://www.centerwatch.com/
Controlled Clinical Trials
http://controlled-trials.com
Clinical Trials.gov
http://www.clinicaltrials.gov
Web of Knowledge (current contents and ISTP)
http://wok.mimas.ac.uk/

The review team and Information Specialist plan to undertake a series of searches to identify literature. An initial search to identify relevant randomised controlled trials will be carried out using the following Medline strategy. This strategy will be translated and adapted for use in other databases.

1. randomized controlled trial.pt.
2. exp randomized controlled trials/
3. random allocation/
4. double blind method/
5. single blind method/
6. clinical trial.pt.
7. exp clinical trials/
8. controlled clinical trials/
9. clin$ trial$.ti,ab.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
11. placebo$.ti,ab.
12. placebos/
13. random$.ti,ab.
14. exp evaluation studies/
15. follow up studies/
16. exp research design/
17. prospective studies/
18. (control$ or prospectiv$ or volunteer$).ti,ab.
19. or/1-18

20. animal/
21. human/
22. 20 not (20 and 21)
23. 19 not 22
24. psoriasis/
25. psoria$.mp.
26. or/24-25
27. etanercept.mp.
28. enbrel.mp.
29. efalizumab.mp.
30. raptiva.mp.
31. or/27-30
32. 23 and 26 and 31

Additional searches will be undertaken to identify cost-effectiveness studies and modelling data and to locate literature on the treatment comparators. Additional searches of registers of ongoing trials will be undertaken. This will include the NRR and those trial registers found on the Internet listed above.

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 Reference Manager bibliographic management software to remove duplicate records.
Full details of the searching process will be recorded.

References

1 Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC. A Systematic Review of Treatments for Severe Psoriasis. *Health Technology Assessment* 2000;4.

2. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness. CRD's guidance for carrying out or commissioning reviews*. 2nd ed. York: NHS Centre for Reviews and Dissemination, 2001.

3. Drummond M, O'Brien B, Stoddart G, Torrance G. *Methods for the economic evaluation of health care programmes.* 2nd ed. Oxford: Oxford Medical Publications, 1997.

4. National Institute for Clinical Excellence. *Technical guidance for manufacturers and sponsors on making a submission to a Technology Appraisal.* London: NICE; 2001.

5. Lebwohl M. Psoriasis. *Lancet* 2003;361:1197-204.

6. Christophers E. Genotyping psoriasis. *J Invest Dermatol* 2003;120:xvii.

7. Leone G, Rolston K, Spaulding G. Alefacept for chronic plaque psoriasis: a selective therapy with long-lasting disease remissions and an encouraging safety profile. *Dermatol Nurs* 2003;15:216-20, 224-5; quiz 226.

8. Kirby B, Fortune DG, Bhushan M, Chalmers RJ, Griffiths CE. The Salford Psoriasis Index: An holistic measure of psoriasis severity. *British Journal Of Dermatology* 2000;142:728-732.

9. Mason J, Mason A, Cork MJ. *Topical Preparations for the Treatment of Psoriasis in Primary Care: A Systematic Review*: Centre for Health Economics, University of York; 2002.

10. Gniadecki R, Zachariae C, Calverley M. Trends and developments in the pharmacological treatment of psoriasis. *Acta Derm Venereol* 2002;82:401-10.

11. Prinz JC. The role of T cells in psoriasis. *J Eur Acad Dermatol Venereol* 2003;17:257-70.

12. Pariser DM. Management of moderate to severe plaque psoriasis with biologic therapy. *Manag Care* 2003;12:36-44.