

Etanercept and efalizumab for the treatment of psoriasis: a systematic review

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Executive summary

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Executive summary

Background

Psoriasis is a common inflammatory skin disease, with estimates of its world prevalence ranging from 0.5 to 4.6% and UK prevalence estimated at around 1.5%. Psoriasis generally occurs in adults, with males and females being equally commonly affected by the condition. Ethnic variations have been identified and Caucasians are more likely to suffer from the disease. Psoriasis is a chronic disorder that can be physically and emotionally debilitating and which can require life-long treatment. Plaque psoriasis, characterised by clearly demarcated, red, scaling plaques, is the most common form of psoriasis, occurring in more than 80% of cases. In the UK, both etanercept (Enbrel[®]) and efalizumab (Raptiva[®]) have recently been licensed for the treatment of adults with moderate to severe plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate or photochemotherapy (PUVA). Both etanercept and efalizumab are new biological agents, which target pathologic T cell activity. Other therapies available for the treatment of moderate to severe psoriasis include phototherapy and systemic agents such as ciclosporin, methotrexate and retinoids, all of which have limitations on their use due to serious long-term adverse effects.

Objective

The objective of the study was to evaluate the clinical effectiveness, safety, tolerability and cost-effectiveness of etanercept and efalizumab for the treatment of moderate to severe chronic plaque psoriasis.

Methods

For the evaluation of efficacy, randomised controlled trials (RCTs) with a minimum of 20 participants were included. For the evaluation of safety, long-term experimental and observational studies of at least 24 weeks' duration and

including a minimum of 100 patients were eligible for inclusion. Studies or data without an explicitly stated denominator were excluded from the review. In addition, adverse event data from the trials of efficacy of etanercept and efalizumab were included. An update of an existing systematic review of the efficacy and safety of other treatments for moderate to severe chronic plaque psoriasis was also undertaken. For the efficacy evaluation, RCTs with a minimum of 20 participants were included. Information on the adverse effects of the other treatments for moderate to severe psoriasis were summarised from tertiary reference sources.

A mixed treatment comparison analysis was then carried out to enable comparisons to be made between the efficacy of all treatments (etanercept and efalizumab and other) for moderate to severe chronic plaque psoriasis.

A systematic review was then undertaken of published economic evaluations. Studies were eligible for inclusion if they assessed both costs and benefits and compared findings with an appropriate comparator treatment. The economic models supplied by the manufacturers of etanercept and efalizumab were critiqued. An economic model was then developed of etanercept and efalizumab in the treatment of moderate to severe chronic plaque psoriasis.

For the systematic reviews, relevant studies were identified through searches of the major electronic databases. All databases were searched from their inception to the date of the search. Searches were also undertaken on several Internet resources. Searches took place over the period from January to April 2004.

The primary outcome in the review was the proportion of patients achieving a 75% reduction in the Psoriasis Area and Severity Index (PASI) score ('PASI 75'). The PASI is an assessment score, representing the extent, redness, thickness and scaliness of a person's psoriasis on a single scale, usually scored from 0 (no psoriasis) to 72.



Results

Clinical evaluation

Number and quality of studies

Our review of the clinical evidence identified a total of 39 published and three unpublished studies: eight RCTs of the efficacy of etanercept (three trials) and efalizumab (five); 10 studies of the adverse effects of the interventions; and 24 RCTs of the efficacy of the other treatments for moderate to severe psoriasis.

The trials of the efficacy of the interventions were all double-blind and placebo-controlled trials and generally of good quality, but three of the five efalizumab trials were poorly reported. A total of 1347 patients were included in the etanercept trials and 2963 in the efalizumab trials.

Efficacy of etanercept and efalizumab

Data on the efficacy of etanercept 25 mg twice a week for 12 weeks were available from three RCTs. On average, active treatment resulted in 62% of patients achieving a PASI 50, 33% achieving a PASI 75, 11% achieving a PASI 90 and 40% were assessed as clear or almost clear. These figures are not adjusted for changes relative to placebo. Improvement in quality of life as assessed by mean percentage change in Dermatology Life Quality Index (DLQI) was around 59% with etanercept 25 mg twice a week compared with 9% with placebo, and all mean differences that could be calculated were statistically significantly in favour of etanercept. Data on the efficacy of etanercept 50 mg twice a week for 12 weeks were available from two RCTs. Across the two trials, the proportion of patients achieving PASI 50, 75 and 90 was 76, 49 and 21%, respectively; the pooled relative risks were all statistically significantly in favour of etanercept. The findings for mean PASI after treatment, mean percentage change in PASI from baseline and mean percentage change in DLQI also demonstrated the efficacy of etanercept treatment.

Evidence from one RCT indicates that the response to etanercept is maintained post-treatment, at least in the medium term, and data from uncontrolled follow-up phases reflect and extend these findings. Uncontrolled data from follow-up in one trial suggest no real evidence for severe exacerbation of psoriasis after discontinuation of treatment. There is evidence from one trial that retreatment in patients who have relapsed following an earlier treatment period does not induce a poorer response than

initial treatment. Overall, the trial populations may not truly reflect the difficult-to-treat patients for whom etanercept is licensed.

Efalizumab at a dose of 1 mg/kg once a week subcutaneously was studied in five RCTs. Across these trials, 12 weeks of active treatment resulted in an average of 55% of patients achieving PASI 50, 27% PASI 75, 4.3% PASI 90 and 27% clear or minimal psoriasis status. These figures are not adjusted for changes relative to placebo. There is no evidence from RCTs that the response to efalizumab 1 mg/kg once a week is maintained when treatment continues beyond 12 weeks, and long-term follow-up data relate to a range of doses and are poorly reported and so cannot be used to draw even tentative conclusions regarding the long-term efficacy of efalizumab. Uncontrolled data from trial follow-up suggest that time to relapse may be around 60 days. No data indicating the existence or absence of any rebound in psoriasis after discontinuation of efalizumab were identified. There is no evidence relating to the efficacy of efalizumab upon retreatment. As for etanercept, the trial populations may not truly reflect the difficult-to-treat patients for whom efalizumab is licensed.

Adverse effects of etanercept and efalizumab

Injection site reactions appear to be the most common adverse effects of etanercept. Overall, etanercept appears to be well tolerated in short- and long-term use, although many of the long-term data are not from patients with psoriasis; data derived from patients with rheumatoid arthritis may not be applicable to those with psoriasis. As identified from earlier reviews, the main areas of concern relate to uncommon but serious adverse events, but their significance is not readily discernible from the published reports of clinical trials.

Headache, chills and, to a lesser extent, nausea, myalgia, pain and fever are the common adverse events associated with efalizumab. Overall, withdrawal rates due to adverse events are low. Longer term data for efalizumab are not readily available for evaluation, but the adverse events data up to 3 years appear to reflect those over 12 weeks and to remain stable. Unfortunately, few data for serious infections and serious adverse events with efalizumab are available.

Other treatments for moderate to severe psoriasis

Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the treatments available for the

relief of moderate to severe psoriasis. Only infliximab and ciclosporin have had their efficacy demonstrated in placebo-controlled RCTs, but trials are typically short term and include small numbers of patients. Although clinical experience has demonstrated excellent efficacy of PUVA and methotrexate, no placebo-controlled trials have been conducted. In clinical trials, methotrexate appears to be as effective as ciclosporin. The trials of other treatments, acitretin, RePUVA, and NBUVB, in comparison with PUVA, provide only limited evidence, demonstrating some degree of effectiveness but making it difficult to draw firm conclusions regarding relative efficacy.

Mixed treatment comparison analysis

To enable indirect comparisons to be made between all treatments for moderate to severe psoriasis, a meta-analysis of the PASI 50, 75 and 90 response rates from the RCTs was performed. The end-points were jointly modelled using an ordered probit model. The available data permitted the inclusion of etanercept (25 and 50 mg), efalizumab, infliximab, ciclosporin, methotrexate, Fumaderm and placebo in this mixed-treatment comparison that was implemented as a Bayesian hierarchical model.

In terms of mean response rate, when response is taken as PASI 75, infliximab appears the most effective, followed by methotrexate and ciclosporin, then etanercept 50 mg. Etanercept 25 mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. As shown by the credible intervals around the mean response rates, which overlap considerably, there is uncertainty around these response rates. This is also shown in terms of the relative risks of each option (compared with placebo) and their confidence intervals. These findings for the PASI 75 level of response are mirrored in the results for the PASI 50 and PASI 90.

Cost-effectiveness

One published article examining the cost-effectiveness of biological therapy in psoriasis was identified, but its methods and US focus give it limited relevance to UK practice. Therefore, the cost-effectiveness of etanercept and efalizumab was informed by models submitted by the two manufacturers, together with a *de novo* model from the assessment team (the York Model). The company models

compare only each manufacturer's product with non-systemic therapy. In contrast, the York Model compares various therapeutic strategies based on etanercept and efalizumab, and supportive care. In a secondary analysis, the York Model also includes other systemic therapies (infliximab, ciclosporin, methotrexate and Fumaderm). The York Model uses efficacy data taken directly from the mixed treatment comparison analysis. Health effects are expressed in terms of quality-adjusted life-years (QALYs), where utilities for alternative PASI response categories are derived from a 'mapping' exercise. The focus of the York Model is to establish the most cost-effective **sequence** of therapies based on alternative threshold values for cost-effectiveness.

For the primary analysis comparing etanercept, efalizumab and supportive care, the results of the York Model suggest that the biological therapies would only be cost-effective for all patients with moderate to severe psoriasis if the NHS were willing to pay over £60,000 per QALY gained. In patients with poor baseline quality of life (fourth quartile DLQI), efalizumab, etanercept 25 mg (intermittent), etanercept 25 mg (continuous) and etanercept 50 mg (intermittent) would be cost-effective as part of a treatment sequence if the NHS were willing to pay £45,000, £35,000, £45,000 and £65,000 per QALY gained, respectively. In patients who are also at high risk of inpatient hospitalisation (21 days per annum), these therapies would be cost-effective as part of a sequence as long as the NHS were willing to pay £25,000, £20,000, £25,000 and £45,000 per QALY gained, respectively.

As part of a secondary analysis including a wider range of systemic therapies as comparators, the York Model found that it would only be cost-effective to use etanercept and efalizumab in a sequence after methotrexate, ciclosporin and Fumaderm.

Conclusions

There is good evidence that etanercept is efficacious in the treatment of moderate to severe psoriasis, and that the response is maintained up to 24 weeks. The most common adverse effect of etanercept is injection site reaction. Other serious adverse events, as identified from earlier reviews, are uncommon and not readily identified from clinical trials. ►

There is evidence that efalizumab is efficacious in the treatment of moderate to severe psoriasis, however there is no evidence from RCTs that the response to efalizumab 1 mg/kg once a week is maintained when treatment continues beyond 12 weeks. The publicly available information for efalizumab indicates that the drug is well tolerated over a 12-week period; however, few data for any longer term treatment are available for evaluation.

Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the other treatments available for the relief of moderate to severe psoriasis. All other treatments are associated with serious and possibly long-term adverse events.

In a mixed treatment comparison, including etanercept, efalizumab, ciclosporin, Fumaderm, methotrexate, infliximab and placebo, infliximab appeared the most effective, followed by methotrexate and ciclosporin, then etanercept 50 mg. Etanercept 25 mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. The pattern is consistent across the different PASI response categories.

Overall, clinical trial data indicate that both etanercept and efalizumab are efficacious in patients who are eligible for systemic therapy, but the economic evaluation demonstrates that these biological therapies are likely to be cost-effective only in patients with poor baseline quality of life and who are at risk of hospitalisation.

Recommendations for further research

The following areas are recommended for further investigation.

- Efficacy trials conducted in the specific population for which etanercept and efalizumab are licensed, that is, patients with moderate to severe chronic plaque psoriasis in whom conventional therapy has failed or is inappropriate. Trials should assess duration of remission following treatment withdrawal.
- Long-term comparisons of etanercept and efalizumab with other treatments for moderate to severe psoriasis, particularly infliximab, methotrexate and ciclosporin.
- Long-term efficacy trials, to provide data on how etanercept and efalizumab perform as maintenance therapies.
- Long-term safety/tolerability data for patients treated with etanercept or efalizumab.
- Psoriasis is a heterogeneous group of diseases; trials to identify specific subtypes that respond better to one drug than another.
- Research on the rate of inpatient hospitalisation in patients with moderate to severe psoriasis, and the effect of treatment on this rate.

Publication

Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al.* Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health Technol Assess* 2006;**10**(46).

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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