Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation

N Woolacott,[1*] Y Bravo Vergel,[2] N Hawkins,[2] A Kainth,[1] Z Khadjesari,[1] K Misso,[1] K Light,[1] C Asseburg,[2] S Palmer,[2] K Claxton,[2] I Bruce,[3] M Sculpher[2] and R Riemsma[1]

[1] Centre for Reviews and Dissemination, University of York, UK
[2] Centre for Health Economics, University of York, UK
[3] ARC Epidemiology Unit, University of Manchester, UK

* Corresponding author

Executive summary

Health Technology Assessment 2006; Vol. 10: No. 31

Health Technology Assessment
NHS R&D HTA Programme

Executive summary

Objective

The aim of this review was to evaluate the clinical effectiveness, safety, tolerability and cost-effectiveness of etanercept and infliximab for the treatment of active and progressive psoriatic arthritis (PsA) in patients who have inadequate response to standard treatment, including disease-modifying antirheumatic drug (DMARD) therapy.

Background

PsA is defined as an inflammatory arthropathy associated with psoriasis, which is usually negative for rheumatoid factor (RF) [an antibody produced by plasma cells and found in around 70% of cases of rheumatoid arthritis (RA)]. It is a hyperproliferative and inflammatory arthritis that is distinct from RA and closely associated with psoriasis. Overall, because PsA involves both skin and joints, it can result in significant quality of life impairment, joint deformity and psychosocial disability. Owing to the lack of a precise definition and diagnostic marker for psoriatic arthritis, it is difficult to gauge its prevalence. The UK adjusted prevalence of PsA in the primary care setting has been estimated to be 0.3%. In the UK both etanercept (Enbrel®) and infliximab (Remicade®) are recently licensed drugs for the treatment of adults with active and progressive PsA in patients who have responded inadequately to DMARDs. Both etanercept and infliximab are new biological agents, which target pathological T cell activity (anti-tumour necrosis factors drugs). Other therapies available for the treatment of psoriatic arthritis are DMARDs such as sulfasalazine, methotrexate and ciclosporin, all of which have limitations to their use owing to limited efficacy or serious long-term adverse effects. There is also a new DMARD, leflunomide, which is the only drug other than etanercept and infliximab licensed for the treatment of psoriatic arthritis.

Methods

A systematic review, based on literature searches conducted between April and July 2004, evaluated the clinical efficacy and adverse effects of etanercept and infliximab. The efficacy of DMARDs in the treatment of PsA was also reviewed and, where data allowed, treatments were compared utilising Bayesian evidence synthesis methods. Following evaluation of existing economic evaluations of etanercept and infliximab in psoriatic arthritis, a new economic model was developed (the York Model). This utilised the results from the evidence synthesis and data from a range of other sources.

Results

Number and quality of studies

The review of the clinical evidence identified 40 studies: three trials of the efficacy of the interventions of interest (two for etanercept and one for infliximab), 23 studies of the adverse effects of the interventions and 14 trials of the efficacy of the DMARDs.

The trials of the efficacy of the interventions were all double-blind and placebo-controlled trials and were rated 'Good' by the quality assessment. A total of 265 patients were included in the etanercept trials and 104 in the infliximab trial.

Efficacy of the interventions

Across the two trials, at 12 weeks, around 65% of patients treated with etanercept achieved an American College of Rheumatology (ACR) 20 {pooled relative risk (RR) 4.19 [95% confidence interval (CI) 2.74 to 6.42]}, demonstrating a basic degree of efficacy in terms of arthritis-related symptoms. In addition, around 45% of patients treated with etanercept achieved an ACR 50 [pooled RR 10.84 (95% CI 4.47 to 26.28)] and around 12% achieved an ACR 70 [pooled RR 16.28 (95% CI 2.20 to 120.54)], demonstrating a good level of efficacy. The subgroup analyses conducted in one trial revealed that the effect of etanercept was not dependent upon patients' concomitant use of methotrexate. In addition, almost 85% of patients treated with etanercept achieved a Psoriatic Arthritis Response Criteria (PsARC) [pooled RR 2.60 (95% CI 1.96 to 3.45)], which is the only joint disease outcome measure that has been specifically defined for psoriatic arthritis. The Psoriatic Area and Severity Index (PASI) results indicate ▶

some beneficial effect on psoriasis at 12 weeks; however, the data are sparse. The statistically significant reduction (improvement) in Health Assessment Questionnaire (HAQ) score with etanercept compared with placebo indicates a beneficial effect of etanercept on function. Similar results were seen at 24 weeks, except that the results for PASI 75 and PASI 50 now achieved statistical significance and data for Total Sharp Score (TSS) annualised rate of progression were available; this was statistically significantly lower in etanercept-treated patients than in placebo-treated patients. Uncontrolled follow-up of patients indicated that treatment benefit may be maintained for at least 50 weeks.

At 16 weeks, 65% of patients treated with infliximab achieved an ACR 20 [RR 6.80 (95% CI 2.89 to 16.01)], demonstrating a basic degree of efficacy in terms of arthritis-related symptoms. This level of efficacy was not dependent upon patients' concomitant use of methotrexate. Almost half the patients treated with infliximab achieved an ACR 50 [RR 49.00 (95% CI 3.06 to 785.06)] and over one-quarter achieved an ACR 70 [RR 31.00 (95% CI 1.90 to 504.86)] compared with none of the placebo group, demonstrating a good level of efficacy. In addition, 75% of patients treated with infliximab achieved a PsARC [RR 3.55 (95% CI 2.05 to 6.13)]. The beneficial treatment effect on psoriasis was also statistically significant with a mean difference in percentage change from baseline in PASI of –5 (95% CI –6.8 to –3.3), as was the percentage improvement from baseline in HAQ score with infliximab compared with placebo [mean difference 51.4 (95% CI 48.08 to 54.72)], indicating a beneficial effect of infliximab on functional status.

Uncontrolled data from all measures of joint disease, psoriasis and HAQ collected at up to 50 weeks of follow-up reflect those at 16 weeks. There were no radiographic assessments, so the potential or otherwise of infliximab to delay the progression of joint disease could not be assessed.

Adverse effects

Injection site reactions appear to be the most common adverse effects of etanercept. Overall, etanercept appeared to be well tolerated in short- and long-term use, although much of the long-term data are not from patients with psoriastic arthritis. As identified in earlier reviews, the main areas of concern relate to uncommon but serious adverse events the significance of which is not readily discernible from the published reports of clinical trials.

Overall, infusion reactions, the development of antibodies and infections appear to be the most common adverse effects of infliximab, although it is unclear whether they occur more frequently than on placebo. In the long term, the possible risk of serious adverse effects requires caution and further monitoring and investigation.

Importantly, both biologics are new drugs with which there is only very limited experience and long-term monitoring. Therefore, review and further investigations of their safety are warranted.

DMARDs

The available drug treatments for psoriatic arthritis, with the exception of sulfasalazine and possibly leflunomide, have not been investigated thoroughly. The available limited data indicate some degree of efficacy for all DMARDs, but the evidence for intramuscular gold and azathroprine is particularly weak and may not be reliable.

Evidence synthesis

A Bayesian evidence synthesis was undertaken to complete the clinical evaluation and to estimate relevant parameters for the economic model. The need to populate the economic model indicated a focus on response rates to therapy in terms of PsARC and changes in HAQ conditional on whether the patient responds to therapy. The synthesis relates to etanercept, infliximab and placebo as these are the comparators in the economic model. The probability of responding to infliximab treatment was estimated to be 0.7705, and for etanercept this probability is also estimated as 0.7705. The RR of infliximab versus etanercept of 1.0 (95% CI 0.82 to 1.18) also highlighted that, as far as response rates are concerned, the evidence synthesis suggested the two treatments are very similar. The evidence synthesis showed that responders to either treatment experienced a statistically significant improvement in HAQ scores. Incremental to the natural progression baseline change in HAQ of 0.0166 (95% CI 0.002 to 0.031), responders to etanercept treatment experienced an additional change in HAQ of –0.72 (95% CI –0.83 to –0.61), and responders to infliximab treatment of –0.67 (95% CI –0.84 to –0.49). Both of these HAQ changes are significantly different from the incremental HAQ change experienced by placebo responders, of –0.28 (95% CI –0.39 to –0.18), but do not differ substantially between the two active treatments.

Cost-effectiveness

Cost-effectiveness models were submitted by Wyeth and Schering-Plough. Wyeth's model ▶

estimated the incremental cost per quality-adjusted life-year (QALY) gained for etanercept (compared with a composite comparator) to range from £28,189 for a 10-year time horizon to £66,580 for a 6-month time horizon. Schering-Plough presented two models. The 'Active Joint' model estimated an incremental cost per QALY gained for infliximab of £36,786 (5-year time horizon). The 'Chronic Active Joint' model estimated an incremental cost-effectiveness ratio (ICER) of £33,877 (30-year time horizon).

Given some potential limitations of the manufacturers' models and their failure to compare the two biological therapies directly and with palliative care, a new model was developed (the York Model). Results were estimated over a range of time horizons and based on a number of alternative assumptions. Infliximab is consistently dominated by etanercept because of its higher acquisition and administration costs without superior effectiveness. The incremental cost per QALY gained of etanercept compared with palliative care ranges from £14,818 (females, 40-year time horizon) to £49,374 (males, 1-year time horizon) if it is assumed that, when patients eventually fail on biological therapy, their disability (in terms of HAQ score) deteriorates by the same amount as it improved when they initially respond to treatment (rebound equal to gain). The ICERs of etanercept range from £25,443 (females, 40-year time horizon) to £49,441 (males, 1-year time horizon) if it is assumed that, when patients fail on therapy, their disability level returns to what it would have been had they never responded (rebound equal to natural history).

Sensitivity analyses

Probabilistic sensitivity analysis showed that etanercept and palliative care have the highest probabilities of being cost-effective. At lower levels of the threshold value of cost-effectiveness, palliative care has the higher probability of being cost-effective. As the threshold increases, so does the probability that etanercept is optimal. Scenario analysis was undertaken to assess the sensitivity of the results to other assumptions in the model. The most important analysis indicates that the ICER of etanercept increases markedly if it is assumed that etanercept only improves symptoms and does not retard disease progression. We also examined an alternative specification of the prior distribution in the evidence synthesis used to reflect between-trial variation in the placebo response rate, but no substantive change in the results was observed.

Limitations of the calculations (assumptions made)

A number of parameters in the model are based on very limited evidence. This applies, in particular, to the long-term withdrawal rate (based on a non-randomised observational study and assumed to be the same for the two biological therapies), the natural history HAQ progression (based on an unpublished cohort study of 24 PsA patients reported in the Wyeth submission) and the HAQ progression in patients responding to therapy (assumed to be zero based on some evidence for the open-label continuation studies after etanercept and infliximab).

Other important issues regarding implications

The model considered the cost-effectiveness of etanercept and infliximab compared with each other and with palliative care. This is equivalent to assuming that the biological therapies would be used 'end of line' once DMARD therapies have been tried and failed. The York Model was not able to incorporate the possible quality of life impact of the biological therapies on patients' skin. This assumption also had to be made in the two manufacturers' models. The York Model uses HAQ score as the measure of disability, which drives both quality of life and costs in the model. This is consistent with both the Wyeth models in PsA and many cost-effectiveness models of biological therapies in RA, but the use of radiological measures of disease progression may be more appropriate should data become available.

Notes on the generalisability of the findings

The efficacy data used in the clinical evaluation, evidence synthesis and the economic models were very limited, being derived from just three trials and 369 patients, with only 134 patients treated with etanercept and 52 treated with infliximab. Furthermore, these trial populations were not precisely representative of those for whom etanercept and infliximab are licensed: neither population was made up exclusively of patients who had failed to respond to at least two DMARDs. Other parameters within the economic models were also based on very limited evidence.

Conclusions

The limited data available indicated that both etanercept and infliximab are efficacious in the treatment of psoriatic arthritis with beneficial effects on both joint and psoriasis symptoms and

on functional status. Short-term data indicated that etanercept can delay joint disease progression but further long-term data are required to confirm and consolidate the evidence base for this. There are no controlled data as yet to indicate that infliximab can delay joint disease progression. Further data are required to confirm the findings of the currently available trials and to demonstrate that response is maintained and that disease progression is delayed in the long term.

Treatment with both etanercept and infliximab for 12 weeks demonstrated a significant degree of efficacy, with no statistically significant difference between them.

For both etanercept and infliximab, adverse events were common with mild injection/infusion reactions being the main treatment-related effect. Concerns exist over uncommon serious and long-term adverse effects and, in the authors' opinion, further monitoring of the safety profiles of both drugs is required.

The York Model indicated that etanercept is more cost-effective than infliximab as it has a lower cost with little difference in outcomes. The incremental cost per QALY gained of etanercept compared with palliative care (i.e. to no active therapy) ranged from £14,818 (females, 40-year time horizon) to £49,374 (males, 1-year time horizon) under the assumption of rebound equal to gain. It ranged from £25,443 (females, 40-year time horizon) to £49,441 (males, 1-year time horizon) under the assumption of rebound equal to natural history progression. The cost-effectiveness of etanercept was also sensitive to assumptions made about the extent of disease progression when patients are responding to therapy. The number of years for which a patient can be safely on biologicals is uncertain so these results should be considered with caution.

Recommendations for further research

The following areas are recommended for future research (all are of equal importance).

- Long-term controlled trials are required to confirm that symptomatic benefits for joint and skin disease and improvements in function are maintained. Data on long-term HAQ progression while responding to biologics is required.
- Long-term controlled trials on the effects of biologics on joint disease progression are also required.
- Further research on the effects of biologics on both arthritis and psoriasis and their combined effects on quality of life is required, including in terms of a generic preference based (utility) instrument.
- A 2-year controlled trial of etanercept versus best care (probably methotrexate or leflunomide) is warranted; such a trial should gather comparative data on HAQ and radiographic progression with leflunomide.
- Randomised controlled trials investigating the effects of the biologics in combination with methotrexate, with reference to any synergistic effect and the possibility of tachyphylaxis, are warranted.
- Long-term monitoring studies of adverse events and regular reviews of the significance of serious adverse events are essential. Research should establish whether long-term patterns of adverse events are similar to those in RA. The setting up of a Biologics Registry for the treatment of psoriatic arthritis is advisable.
- Long-term information on withdrawal rates from biologics for lack of efficacy and adverse events is important.
- Research to establish whether intermittent biologic therapy is a reasonable option for the treatment of psoriatic arthritis would be of value.

Publication

Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2006;**10**(31).

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.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

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.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 04/04/01. The protocol was agreed in April 2004. The assessment report began editorial review in August 2005 and was accepted for publication in November 2005. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.