Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis

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

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Executive summary

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Executive summary

Background

Psoriatic arthritis (PsA) is defined as a unique inflammatory arthritis affecting the joints and connective tissue, and is associated with psoriasis of the skin or nails, which, because it involves both skin and joints, can result in significant impairment of quality of life (QoL) and psychosocial disability. Owing to the lack of a precise definition and diagnostic marker for PsA, it is difficult to gauge its exact prevalence. The UK-adjusted prevalence of PsA in the primary care setting has been estimated to be 0.3%. Etanercept (Enbrel®), infliximab (Remicade®) and adalimumab (Humira®) are biologic agents that target tumour necrosis factor (TNF) activity in the treatment of PsA. All three agents are licensed in the UK for the treatment of active and progressive PsA in adults when the response to previous disease-modifying antirheumatic drugs (DMARDs) has been inadequate.

Objective

To determine the clinical effectiveness, safety and cost-effectiveness of etanercept, infliximab and adalimumab for the treatment of active and progressive PsA in patients who have an inadequate response to standard treatment (including DMARD therapy).

Methods

Systematic reviews of the evidence on clinical efficacy, safety and cost-effectiveness of etanercept, infliximab and adalimumab in the treatment of PsA were performed. Data for the review were sought systematically from 10 electronic databases [including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL)] up to June 2009. Industry submissions were searched for additional unpublished data. Randomised controlled trials (RCTs) (including open-label extensions) were included in the evaluation of efficacy. Safety data were sought from RCTs and observational studies reporting serious adverse events [serious infections, malignancies and activation of tuberculosis (TB)] for a minimum of 500 patients in any indication receiving one or more of the biologic agents of interest. The primary efficacy outcomes were measures of anti-inflammatory response [Psoriatic Arthritis Response Criteria (PsARC), American College of Rheumatology 20% Improvement Criteria (ACR 20)], skin lesion response [Psoriasis Area and Severity Index (PASI)] and functional status [Health Assessment Questionnaire (HAQ)]. The safety outcome was the incidence of serious adverse events. The primary measure of cost-effectiveness was incremental cost per additional quality-adjusted life-year (QALY).

Standard meta-analytic techniques were applied to efficacy data. In addition, in the absence of head-to-head comparison on the relative efficacy between the alternative biologics, an indirect comparison was undertaken using Bayesian methods. A narrative synthesis was used for adverse event data. Published cost-effectiveness studies and the economic analyses submitted to the National Institute for Health and Clinical Excellence (NICE) by the biologic manufacturers were reviewed. An economic model was developed by updating the model produced by the York Assessment Group for the previous NICE appraisal of biologics in PsA. This model was revised to

evaluate the impact of biologics on both skin and joint disease and to include new evidence from the clinical review and evidence synthesis.

Results

Efficacy

Six RCTs were identified for the evaluation of clinical efficacy (43 publications). The six RCTs comprised two RCTs in patients with PsA for each of the three agents. All trials were double-blind and placebo-controlled RCTs. All trials were rated 'good' by the quality assessment.

Pooled estimates of effect demonstrated a significant improvement in patients with PsA for all joint disease and functional status outcomes at 12–14 weeks' follow-up. The biologic treatment significantly reduced joint symptoms assessed by PsARC for etanercept [relative risk (RR) 2.60, 95% confidence interval (CI) 1.96 to 3.45], infliximab (RR 3.44, 95% CI 2.53 to 4.69) and adalimumab (RR 2.24, 95% CI 1.74 to 2.88). This was consistent with the results from the pooled estimates of ACR 20. Furthermore, the statistically significant reduction in HAQ score also indicated a beneficial effect of these biologic therapies on patients' functional status. Significant heterogeneity was observed only in the outcome of PsARC in infliximab. The 24-week data for all three biologics demonstrated that the treatment effects are maintained. Trial data demonstrate a significant effect of all three biologics on skin disease in terms of PASI response, at 12 or 24 weeks.

The results of evidence synthesis found that infliximab appears to be the most effective of the three biologics. Across all outcomes of joint and skin disease at 12 weeks, infliximab is associated with the highest probabilities of response. The response in joint disease (PsARC and ACR) is greater with etanercept than with adalimumab, whereas the response in skin disease (PASI) is greater with adalimumab than with etanercept, although these differences are not statistically significant. In those patients who achieve a PsARC response to treatment the highest mean reductions in the functional and psychological impact of the disease, measured by HAQ, are seen with infliximab and etanercept (–0.657 for infliximab and –0.630 for etanercept). For all three biologics the changes in HAQ for those patients who did not respond to treatment were below the minimum clinically significant threshold (–0.3).

Short-term radiographic measures indicate that these agents can slow disease progression in the short term (< 24 weeks). The available follow-up data, although promising, are inadequate to determine if these effects persist in the longer term.

Safety

Thirty-two relevant studies were identified for the evaluation of safety of these biologics. The rates of serious infection were etanercept 0.6%–13.2%, infliximab 0.8%–13.8% and adalimumab 0.4%–5.1%. The rates of malignancy were etanercept 1%–5.7%, infliximab 0.16%–5.1% and adalimumab 0.1%–1.1%. The rates of activation of TB for the treatment were etanercept 0%–1.4%, infliximab 0.06%–4.6% and adalimumab 0%–0.4%.

Cost-effectiveness

Six cost-effectiveness studies were identified in the literature review: three published models and three submissions from manufacturers. The published models estimated that the incremental cost-effectiveness ratio (ICER) for etanercept versus palliative care was between £26,000 and £38,000 per QALY, but did not consider the impact of biologics on the skin component of PsA. Abbott [Abbott Laboratories Ltd. Adalimumab (HUMIRA): *Multiple technology appraisal of adalimumab, etanercept and infliximab for psoriatic arthritis National Institute for Health and*

Clinical Excellence (NICE) Health Technology Appraisal. Maidenhead: Abbott Laboratories Ltd; 2009] estimated an ICER for adalimumab of £30,000, with etanercept dominated by adalimumab, and an ICER for infliximab versus adalimumab of £199,000. Schering-Plough [Schering-Plough. *REMICADE (infliximab): Remicade in the treatment of Psoriatic Arthritis (PsA) in the United Kingdom.* A submission to the National Institute of Clinical Excellence: Welwyn Garden City: Schering-Plough Ltd; 2009] concluded that the most cost-effective strategy depended on patient weight. (Since the production of this report, Schering-Plough has merged with Merck.) Wyeth [Wyeth Pharmaceuticals. *Etanercept (ENBREL): Appraisal of the clinical and cost-effectiveness of etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. An appraisal submission for the National Institute of Health and Clinical Excellence*. Maidenhead: Wyeth; 2009] estimated an ICER for etanercept of £12,000 compared with DMARDs.

The de novo York Assessment Group model evaluated the cost-effectiveness of the three biologic therapies and palliative care only. Under base-case assumptions, for patients with PsA and mild-to-moderate skin disease, the ICER etanercept versus palliative care is about £18,000 per QALY, and the ICER of infliximab versus etanercept is about £44,000 per QALY. Adalimumab is extendedly dominated. The probability that etanercept is cost-effective is 0.436 at a threshold of £20,000 per QALY and 0.475 at a threshold of £30,000 per QALY. The expected lifetime prescription costs of biologic therapies is considerably greater than offset cost savings elsewhere in the NHS.

For patients with PsA and moderate-to-severe skin disease who continue on biologics after 3 months if they respond for skin or joints, the ICER of adalimumab versus palliative care is about £16,000 per QALY, the ICER of etanercept versus adalimumab is about £21,000 per QALY and the ICER for infliximab versus etanercept is about £26,000 per QALY. If the cost-effectiveness threshold were £20,000 per QALY then all biologics have a similar probability of being cost-effective.

For patients with PsA with negligible skin involvement, the ICER of etanercept versus palliative care is about £18,000 per QALY, and the ICER of infliximab versus etanercept is about £65,000 per QALY. Adalimumab is extendedly dominated in this group.

The second-line use of biologics was explored in a sensitivity analysis. As these results are based on non-randomised comparisons they should be considered with caution. For patients with PsA and mild-to-moderate psoriasis who have failed adalimumab or infliximab as first-line therapy for either adverse events or inefficacy, the ICER for etanercept is < £20,000 per QALY. For patients who have failed etanercept as first-line therapy for either adverse events or inefficacy, the ICER for adalimumab is < £20,000 per QALY and the ICER for infliximab is < £30,000 per QALY.

These results are sensitive to several model assumptions and alternative sources of data.

Discussion

Despite the limited data, there was clear evidence of a significant improvement for all the biologic therapies on the joint disease condition and functional status of patients with PsA at short-term follow-up. There was also some evidence of beneficial effects for these agents on the skin disease response, although data on this outcome is sparse in PsA. There was a paucity of long-term data on joint disease progression. An indirect comparison of the three agents indicates that infliximab is associated with the highest probability of response on joint and skin outcomes. The range of serious adverse events did not differ considerably between agents, although there was considerable uncertainty around these estimates.

The Assessment Group found that under base-case assumptions, etanercept is most likely to be the cost-effective strategy for patients with PsA and mild-to-moderate psoriasis if the threshold for cost-effectiveness was £20,000 or £30,000 per QALY. All biologics have a similar probability of being cost-effective for patients with PsA and moderate-to-severe psoriasis at a threshold of £20,000 per QALY.

A number of outstanding uncertainties include:

- Bayesian indirect comparison analyses provide evidence of the relative efficacy of these biologics; however, those findings may be considered more uncertain than would be provided in head-to head RCTs.
- The patients in most trials are not precisely representative of the population recommended for biologics in current guidelines. It is unclear whether the beneficial effects are similar in those treated in routine clinical practice.
- The adverse event data are derived primarily from patients with rheumatoid arthritis (RA) or other indications. The generalisability of these findings to patients with PsA remains unclear.
- The progression of HAQ on and off treatment, and the length of time over which biologics are assumed to be effective.
- The long-term progression of PsA with and without biologics.
- The prescription cost of biologics.
- The relationship between utility and severity of arthritis and psoriasis.
- Alternative rules about continuing therapy beyond 3 months depending on response.
- The health-care costs of treating psoriasis and arthritis of varying severity.

Conclusions

Implication for service provision

- The limited data indicate that etanercept, infliximab or adalimumab is efficacious in the treatment of PsA compared with placebo, with beneficial effects on joint symptoms, functional status and skin. Short-term data suggest that these three biologic agents can delay joint disease progression.
- Despite such limited data from PsA trials in the evaluation of efficacy of these biologics, the evidence to support their use in the treatment of PsA is convincing, given the size of treatment effect and quality of data.
- An indirect analysis found that across all outcomes at 12 weeks (PsARC, ACR and PASI) infliximab is associated with the highest probability of response. In those patients who achieve a PsARC response to treatment, the highest mean reductions in HAQ are seen with infliximab and etanercept.
- This review cannot rule out concerns about an increased risk of serious adverse events (serious infection, malignancy and activation of latent TB) of the biologics investigated.
- The Assessment Group found that, under base-case assumptions, etanercept would be considered the most cost-effective strategy for patients with PsA and minimal or mild-to-moderate psoriasis if the threshold for cost-effectiveness were £20,000–30,000 per QALY.
- All biologics have a similar probability of being cost-effective at a threshold of £20,000 per QALY for patients with PsA and moderate-to-severe psoriasis, if patients who respond at 3 months for either skin disease or joint disease continue with biologic therapy.
- In a secondary analysis, etanercept appeared most likely to be cost-effective at a threshold of £20,000 or £30,000 per QALY for patients with PsA and mild-to-moderate psoriasis who have failed adalimumab or infliximab as first-line therapy for either adverse events or inefficacy.

- For patients with PsA and mild-to-moderate psoriasis who have failed etanercept as first-line therapy for either adverse events or inefficacy, adalimumab seems most likely to be cost-effective at a threshold of £20,000 per QALY, although infliximab is most likely to be cost-effective if the threshold is £30,000 per QALY.

Recommendations for research

- Long-term observational studies with large sample sizes of patients with PsA are required to demonstrate that beneficial effects for joint and skin disease and improvement of function are maintained. In particular, data on the effects of joint disease progression (e.g. radiographic assessment), and long-term HAQ progression while responding to biologic agents and health-related quality of life are required. Withdrawal rates due to lack of efficacy and adverse events should also be reported.
- Further monitoring of the safety profiles of the biologic agents [e.g. through the British Society for Rheumatology Biologics Register (BSRBR)] is required. Future research should also establish whether long-term patterns of adverse events of these biologic agents in PsA are similar to those in RA.
- Further investigation is required to reduce uncertainties around the following parameters identified in the economic model:
  - The length of time over which biologics are assumed to be effective.
  - The change in HAQ following withdrawal from biologic drugs.
  - Evidence from general practice about the prescribing, administration and monitoring costs of biologic therapy.
  - The NHS costs of treating psoriasis and arthritis of varying severity.
  - The progression of HAQ on and off biologic treatment.
  - The effectiveness and withdrawal rates of biologics used as second-line therapy.
- Future studies should assess how the biologic treatment of both arthritis and psoriasis affects patients' QoL, using generic preference-based utility instruments.
- The cost-effectiveness of sequential use of biologic therapies should be evaluated further.
- Although indirect analysis is useful, future trials comparing one biologic agent with another in the treatment of PsA are warranted.
- The effectiveness and cost-effectiveness of biologics in patients who might not quite reach the current BSR/British Association of Dermatologists criteria for either psoriasis or arthritis, but might nevertheless benefit from biologic therapy, should also be examined.

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Publication

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