Infliximab for the treatment of adults with psoriasis

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of infliximab for the treatment of moderate to severe plaque psoriasis, in accordance with the licensed indication, based on the evidence submission from Schering-Plough to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The outcomes stated in the manufacturer's definition of the decision problem were severity [Psoriasis Area and Severity Index (PASI) score], remission rates, relapse rates and health-related quality of life. The main evidence in the submission comes from four randomised controlled trials (RCT) comparing infliximab with placebo and eight RCTs comparing either etanercept or efalizumab with placebo. At week 10, patients on infliximab had a significantly higher likelihood of attaining a reduction in PASI score than placebo patients. There were also statistically significant differences between infliximab and placebo in the secondary outcomes. In the comparator trials both the efalizumab and etanercept arms included a significantly higher proportion of patients who achieved a reduction in PASI score at week 12 than the placebo arms. No head-to-head studies were identified directly comparing infliximab with etanercept or efalizumab. The manufacturer carried out an indirect comparison, but the ERG had reservations about the comparison because of the lack of information presented and areas of uncertainty in relation to the included data. The economic model presented by the manufacturer was appropriate for the disease area and given the available data. The cost-effectiveness analysis estimates the mean length of time that an individual would respond to infliximab compared

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

with continuous etanercept and the utility gains associated with this response. The base-case incremental cost-effectiveness ratio (ICER) for infliximab compared with continuous etanercept for patients with severe psoriasis was £26,095 per quality-adjusted life-year. A one-way sensitivity analysis, a scenario analysis and a probabilistic sensitivity analysis were undertaken by the ERG. The ICER is highly sensitive to assumptions about the costs and frequency of inpatient stays for non-responders of infliximab. The guidance issued by NICE in August 2007 as a result of the STA states that infliximab within its licensed indication is recommended for the treatment of adults with very severe plaque psoriasis, or with psoriasis that has failed to respond to standard systematic therapies. Infliximab treatment should be continued beyond 10 weeks in people whose psoriasis has shown an adequate response to treatment within 10 weeks. In addition, when using the Dermatology Life Quality Index (DLQI), care should be taken to take into account the patient's disabilities, to ensure DLQI continues to be an accurate measure.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of infliximab for the treatment of moderate to severe plaque psoriasis in adults.

Description of the underlying health problem

Plaque psoriasis is the most common type of psoriasis and is characterised by exacerbations of thickened, erythematous, scaly patches of skin that can occur anywhere on the body. The disease impacts on health-related quality of life. The severity of plaque psoriasis can differ in individuals; it can be split into mild, moderate and severe psoriasis.

Clinical opinion is that the prevalence of moderate to severe psoriasis in the UK is around 2%, which the ERG would estimate to mean that approximately 267,000 people in England and Wales have moderate to severe disease.

The accepted system for classifying the severity of psoriasis is the Psoriasis Area and Severity Index (PASI). The PASI is not an ideal measure of the severity of psoriasis; the limits of PASI are well documented,[2] but it is the measure used in most clinical trials. The guidance for the use of biological therapies in psoriasis issued by NICE in July 2006 defines severe psoriasis as a PASI of ≥ 10 combined with a Dermatology Life Quality Index (DLQI) of > 10.[3] A 2005 review of the PASI as an instrument for determining the severity of chronic plaque-type psoriasis defines severe psoriasis as a PASI of > 12 and moderate psoriasis as a PASI ranging from 7 to 12.[4] Body surface area (BSA) and the DLQI are also commonly used as systems for classifying the severity of psoriasis.

Scope of the ERG report

The ERG critically evaluated the evidence submission from Schering-Plough for the use of infliximab for the treatment of moderate to severe plaque psoriasis, in accordance with the licensed indication (see below). Infliximab is a tumour necrosis factor-alpha (TNF-α) inhibitor which affects T-cell functions that involve the release of TNF-α and which binds to free TNF-α receptors on cell surfaces.

Infliximab is licensed for the treatment of adults with moderate to severe psoriasis who have not responded to (or who are intolerant of) other systemic therapies.

The outcomes stated in the manufacturer's definition of the decision problem were severity, remission rates, relapse rates and health-related quality of life.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's submission to NICE as part of the STA process. The ERG checked the literature searches and applied the NICE critical appraisal checklist to the included studies, and checked the quality of the manufacturer's submission with the Centre for Reviews and Dissemination (CRD) quality assessment criteria for a systematic review. In addition, the ERG checked and provided commentary on the manufacturer's model using standard checklists. A one-way sensitivity analysis, a scenario analysis and a probabilistic sensitivity analysis (*Figure 1*) were undertaken by the ERG.

Results

Summary of submitted clinical evidence

- The main evidence in the submission comes from four international randomised controlled trials (RCTs) comparing infliximab with placebo.[5–8] A further eight RCTs were also included: four comparing etanercept with placebo[9–12] and four comparing efalizumab with placebo.[13–16]
- Evidence in trials was presented as changes in baseline PASI scores, i.e. a PASI 75 refers to an individual who had a 75% reduction in their baseline PASI score.
- At week 10, patients on infliximab had a significantly higher likelihood of attaining a PASI 75 than placebo patients (range 75–88% versus 2–18% respectively) (four trials). It should be noted that there were wide confidence intervals around all four point estimates. There was also a statistically significant difference at 10 weeks in favour of infliximab for the proportion of patients achieving a PASI 50 and 90 (three trials).
- For both efalizumab and etanercept a significantly higher proportion of patients achieved a PASI 75 at week 12 compared with patients receiving placebo.
- In terms of secondary outcomes there were statistically significant differences between infliximab and placebo in Physician's Global Assessment (PGA) score, DLQI and Nail Psoriasis Severity Index (NAPSI). The incidence of any adverse event was slightly higher in those receiving infliximab compared with those receiving placebo, although this was not tested statistically.

Summary of submitted cost-effectiveness evidence

- The cost-effectiveness analysis estimates the mean length of time that an individual would respond to treatment and the utility gains associated with this response. The model is based closely upon the model reported in the study by Woolacott and colleagues.[2] The results are presented for infliximab compared with continuous etanercept based upon utility values for fourth quartile DLQI patients and also for all patients.

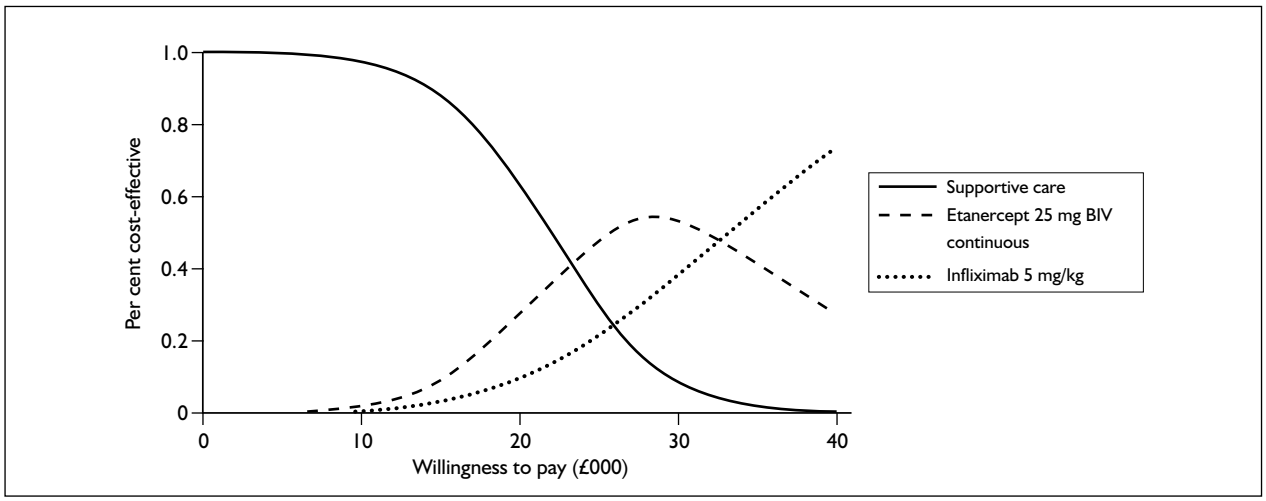

FIGURE 1 *Cost-effectiveness acceptability curve with the inclusion of uncertainty on variables previously assumed certain. BIV, twice weekly.*

- The model is generally internally consistent and appropriate to psoriasis in terms of structural assumptions. The cost-effectiveness analysis generally conforms to the NICE reference case and the scope/decision problem.
- Treatment effectiveness is reported in terms of the numbers of patients achieving PASI 50, 75 and 90 goals at 10–12 weeks and is estimated by an indirect comparison using a random-effects model.
- Patients who achieve improvements in PASI were assigned an associated improvement in quality of life with the higher responses associated with larger improvements in quality of life. These utility values have been taken from a previous report and no information was included in the manufacturer's submission on the characteristics of the individuals or the methodology used to obtain these values.
- The base-case incremental cost-effectiveness ratio (ICER) for infliximab compared with continuous etanercept for patients with severe psoriasis was £26,095 per quality-adjusted life-year (QALY).

Commentary on the robustness of submitted evidence

Strengths

- The manufacturer conducted a systematic search for clinical effectiveness and cost-effectiveness studies of infliximab. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include other databases.
- The four identified infliximab trials were of reasonable methodological quality (with some limitations) and measured a range of outcomes that are as appropriate and clinically relevant as possible.
- Overall, the manufacturer's submission presents an unbiased estimate of treatment efficacy for infliximab based on the results of the placebo-controlled trials.
- The economic model presented with the manufacturer's submission used an appropriate approach for the disease area and given the available data.

Weaknesses

- The processes undertaken by the manufacturer for screening studies, extracting data and applying quality criteria to included studies are not detailed in the submission. In addition, details relating to the searches were not always thorough and were recorded inconsistently. These factors limit the robustness of the systematic review.
- The manufacturer's submission reported very limited data on the comparator trials and did not undertake a systematic review of these.
- Combining the four infliximab trials in a meta-analysis was not appropriate given the statistically significant heterogeneity between studies. Similarly, pooling data in the indirect comparison was also inappropriate given the known heterogeneity. The resulting pooled mean values should therefore be treated with caution.
- The base-case results for the economic model have been presented for fourth quartile DLQI patients. It is unclear precisely what this definition means and how representative this is of severe psoriasis patients.

Conclusions

Areas of uncertainty

- The short intervention period of 10 weeks provides limited information about the longer-term efficacy of infliximab.
- The relative risks calculated by the manufacturer have wide confidence intervals around all four point estimates for the primary outcome of PASI 75 achievement (and other outcomes), indicating a lack of certainty regarding the true effect.
- No description of the principles, assumptions or methodology behind the indirect comparison was provided, making it difficult for the ERG to check either the model or the data. Despite asking the manufacturer for clarification, a number of areas remain unclear, such as where the data come from, which trials were included and which placebo groups were included for the pooled estimates.
- A definition of moderate psoriasis was not provided in the manufacturer's submission and neither were there any inclusion/exclusion criteria for the rating of the severity of psoriasis to ensure that patients were moderate to severe. The populations of the included infliximab trials were predominantly those with severe psoriasis. In addition, it is unclear what proportion of trial participants had previously been treated with systemic therapy. This causes concern over whether the participants included in the trials reflect those in the scope.
- The PASI is not an ideal measure of the severity of psoriasis in terms of measuring the impact on patients, but it is often the best

available outcome and is the measure used most in clinical trials. This raises questions regarding the relevance of the PASI outcome to patient experience in practice.
- There is uncertainty over the appropriate group to use in terms of QALY values. The base case presents values for fourth quartile DLQI patients. It is unclear precisely what the characteristics of patients were in this group.
- It was unclear how values for the number of inpatient days per year for a non-responder were derived. There was also uncertainty over the costs associated with inpatient care and the number of outpatient stays required for an individual on supportive care.
- There may be greater variability in the cost-effectiveness of treatment than is presented in the sensitivity analyses in the manufacturer's submission.
- The dropout rate for patients who no longer respond may be underestimated in the model.

Key issues

- The trials of infliximab efficacy presented in the manufacturer's submission were placebo-controlled trials. No head-to-head studies were identified that directly compared infliximab with etanercept or efalizumab, the comparators stated in the scope. The manufacturer carried out an indirect comparison but the ERG has reservations about the comparison because of the lack of information presented and areas of uncertainty in relation to the included data. In addition, the ERG question the appropriateness of pooling data that is statistically heterogeneous.
- The ICER is highly sensitive to assumptions about the costs and frequency of inpatient stays for non-responders of infliximab.
- It is unclear what severity of psoriasis was represented by the utility values presented in the manufacturer's submission. It is also unclear to what extent moderate psoriasis would be represented in the analysis presented in the submission.

Summary of NICE guidance issued as a result of the STA

NICE issued an appraisal consultation document in August 2007 which states that:

> 1.1 Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met.
> – The disease is very severe as defined by a total Psoriasis Area Severity Index (PASI) of 20 or more **and** a Dermatology Life Quality Index (DLQI) of more than 18.
> – The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate **or** PUVA (psoralen and long-wave ultraviolet radiation), **or** the person is intolerant to or has a contraindication to these treatments.
>
> 1.2 Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to 0 treatment within 10 weeks. An adequate response is defined as either:
> – a 75% reduction in the PASI score from when treatment started (PASI 75) **or**
> – a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started.
>
> 1.3 When using the DLQI healthcare professionals should take care to ensure that they take account of a patient's disabilities (such as physical impairments) or linguistic or other communication difficulties, in reaching conclusions on the severity of plaque psoriasis. In such cases healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with section 1.2.

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