



## Infliximab for the treatment of ulcerative colitis

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### Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of infliximab for moderately to severely active ulcerative colitis (UC) based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submission indicated that the efficacy of infliximab (5 mg/kg) had been demonstrated in terms of higher response rates and a sustained response in health-related quality of life. For the cost-effectiveness analysis, the manufacturer built a Markov model to compare infliximab with standard care. It estimated the incremental cost per quality-adjusted life-year (QALY) gained was between £25,044 and £33,866 depending on the strategy used. The ERG report generally agreed with the evidence on effectiveness of infliximab for subacute exacerbations of UC. However, there were several areas of uncertainty, of which the interpretation of the importance of the quality of life changes in the subacute situation and the assessment of the adequacy of the evidence of effectiveness of infliximab in the acute hospital-based situation were considered pre-eminent by the ERG. This challenged the estimates of cost-effectiveness offered and suggested that there should be a separate assessment of infliximab for acute exacerbations of moderately to severely active UC. The summary of the NICE guidance issued in April 2008 as a result of the STA states that: infliximab is not recommended for the treatment of subacute manifestations of moderately to severely active UC.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

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

## 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.<sup>1</sup> 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 ulcerative colitis (UC).<sup>2</sup> This STA was subsequently split into two parts, infliximab for subacute manifestations of UC and infliximab for acute exacerbations of UC. The latter is the subject of a separate STA and report (08/37/01).

## Description of the underlying health problem

Ulcerative colitis is a chronic condition in which there is inflammation of the mucosa of the large intestine. The incidence of UC is approximately 10–20 per 100,000 per year with a reported prevalence of 100–200 per 100,000 in the UK.

The symptoms of UC vary according to the extent and severity of the inflammation. The classic symptom of UC is bloody diarrhoea. Associated symptoms of colicky abdominal pain, urgency or tenesmus may be present. Mildly active UC is defined as less than four bowel movements daily. Moderately active UC is defined as more than four bowel movements daily, but when the patient is not systemically ill. Severe UC is defined as an attack in which the patient has more than six bowel movements daily and is systemically ill as shown by tachycardia, fever and anaemia. Fulminant disease correlates with more than 10 bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement and colonic dilatation (expansion).

In UC the severity of the symptoms fluctuates unpredictably over time with intervals of remission or reduced symptoms. Approximately 50% of patients with UC have a relapse in any year. A significant minority have frequently relapsing or chronic continuous disease. In total, 25% of patients with severe UC are admitted to an inpatient setting with flares of UC that are not responding to steroids. An estimated 20–30% of patients with pancolitis (disease affecting the entire colon) will require colectomy.

The British Society of Gastroenterology published guidelines for the treatment of UC in 2004. The main recommendations for the medical management of active left-sided or extensive UC are treatment with oral aminosalicylates or corticosteroids. In active distal UC (i.e. colitis confined to the rectum, or rectum and sigmoid colon) treatment options include topical mesalazine, or topical corticosteroids combined with oral mesalazine, or systemic corticosteroids. When in remission patients with UC should normally receive maintenance therapy with aminosalicylates, azathioprine or mercaptopurine to reduce the risk of relapse. Patients frequently receive combination therapies. Severe UC should be managed jointly by a gastroenterologist in conjunction with a colorectal surgeon.

Infliximab (Remicade®, Schering-Plough) is a chimeric monoclonal antibody that binds with high affinity to tumour necrosis factor (TNF)- $\alpha$ , thereby neutralising its activity. It is administered by intravenous infusion and is licensed for use in rheumatoid arthritis, active Crohn's disease, psoriasis, psoriatic arthritis and ankylosing spondylitis as well as in UC.

Infliximab is licensed for moderately to severely active UC in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or who have medical contraindications to such therapies.

## Scope of the ERG report

The purpose of the ERG report is to comment on the validity of the manufacturer's submission on the technology of interest. The scope for this submission and hence the scope for the ERG report was to appraise the clinical effectiveness and cost-effectiveness of infliximab for moderately to severely active UC.

The population considered was adults with moderately to severely active UC who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or who have medical contraindications to such therapies. The intervention was infliximab.

The standard comparators to be considered included standard care [which may include conventional therapy with a combination of 5-aminosalicylic acid (5-ASA) compounds, corticosteroids and immunomodulators (azathioprine or 6-mercaptopurine)], ciclosporin and surgery.

The outcome measures to be considered included health-related quality of life, survival, measures of disease activity, rates of and duration of response, relapse and remission, rates of hospitalisation, reduction in use of corticosteroids, rates of surgical intervention and adverse effects of treatment.

For the economic analysis the reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year (QALY). The time horizon should be long enough to allow reasonable estimation of expected costs (including adverse events if applicable) and benefits for each of the two clinical situations. Costs were considered from an NHS and personal social services perspective.

When evidence permitted, the appraisal of infliximab for moderate to severely active UC was to identify patient subgroups for whom the technology was most appropriate and to consider the length of treatment required when patients have responded to infliximab. Guidance was only to be issued in accordance with the summary of product characteristics.

## 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/sponsor's submission to NICE as part of the STA process.

Specific steps undertaken by the ERG included:

- discussion of the nature of the problem with a clinical expert
- reanalysis of the nature of the underlying clinical question

- rerunning searches indicated to have been carried out to inform the manufacturer's submission
- extending searches, particularly for ongoing trials
- a formal critical appraisal of the systematic review underpinning the manufacturer's submission, and a related Cochrane review
- reappraisal and checking of data abstraction on two key included studies
- detailed checking of company reports (commercial-in-confidence data) of the pivotal trials
- rerunning of meta-analyses, correcting errors in the submission
- checking the consistency of the effectiveness estimates emerging from the systematic review with the parameters used in the economic model
- rerunning of the economic model supplied by the company
- correction of an error in the reporting of the results of the economic model
- additional sensitivity analyses within the limits of the facilities of the submitted model.

The work was carried out between 20 May 2007 and 22 July 2007. Members of the ERG team attended and advised the meetings of the NICE appraisal committee where this guidance was discussed on 22 August 2007 and 20 November 2007.

## Results

### Summary of submitted clinical evidence

The submission attempted to systematically review the randomised controlled trial (RCT) evidence comparing infliximab with placebo. It used an existing Cochrane review as its starting point. The submission identified no new RCTs and included five RCTs, reported in four articles, which are well recognised. Three RCTs consider the subacute, outpatient application of infliximab and two consider the acute, hospital-based application, which is argued to be 'off-label' use.

The submission highlighted that the efficacy of infliximab at a dose of 5 mg/kg has been demonstrated, particularly by two large RCTs [ACT (Active Ulcerative Colitis Trial) I and II] in terms of higher response rates and a sustained response in health-related quality of life. Infliximab was well tolerated.

### **Summary of submitted cost-effectiveness evidence**

No published economic evaluations of infliximab in UC were identified and so the cost-effectiveness work focused almost entirely on the de novo model and economic evaluation undertaken by the manufacturer. A Markov model was built to compare two treatment strategies, infliximab versus standard care, in terms of costs and QALYs. The patient group modelled had moderately to severely active UC and included patients 'who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA (6-mercaptopurine or azathioprine respectively), or who are intolerant to or have medical contraindications for such therapies'. The main submission only considered patients in this category (although the manufacturer's clarification response included results for patients who were more severe, for whom surgery is the comparator considered). The modelling was undertaken, in part, using data from the ACT trials.

The model followed a cohort of patients with moderate or severe UC from entry through to 10 years, with patients being tracked as they moved between the nine states in the model. The cycle length was 8 weeks. The disease states in the model were defined as remission (Mayo score 0–2), mild (Mayo score 3–5) and moderate/severe (Mayo score 6–12).

Two separate treatment strategies were evaluated, which differ in the assumption made about continuation of infliximab therapy. Strategy A modelled the continuation of infliximab in treatment responders who achieved and maintained remission or mild health states. In contrast, strategy B considered a narrower therapy continuation group defined as responders who achieve and maintain remission. The results of the economic analyses indicated that the incremental cost per QALY gained was £33,866 for strategy A and £25,044 for strategy B.

### **Commentary on the robustness of submitted evidence**

#### **Strengths**

The submission comprehensively ascertained all of the available RCTs comparing infliximab with placebo. This is in agreement with other reviews in the field. Helpful additional information on the key included RCTs was made available when requested.

The submission reported a de novo model-based economic evaluation that considered the cost-effectiveness of infliximab in UC. The use of a Markov model is appropriate as the disease is characterised by progression over time and so a modelling approach that can deal with transition between states and the timing of events is required. The main transition probability inputs were derived from two relevant trials, the ACT trials, and many of the other inputs and parameters were based on appropriate data. Probabilistic sensitivity analysis (PSA) and one-way sensitivity analyses were performed.

#### **Weaknesses**

The review was generally poorly reported. The conduct of the review was at best adequate and there were some important deficiencies. For instance, several data abstraction errors were identified. Also the summary of the results of the included studies lacked clarity and the meta-analyses attempted were incorrect. In the analysis the submission failed to clearly separate the results relating to subacute applications of infliximab from the acute applications in hospital.

Despite the errors in the review of clinical evidence offered in the submission the ERG's own summary suggests that portrayal of the effectiveness evidence in the manufacturer's submission remains reasonably faithful. Infliximab is effective in increasing clinical response, remission and mucosal healing and in improving health-related quality of life in moderate to severe UC in the outpatient setting.

In terms of the submitted evidence on cost-effectiveness there are serious concerns in relation to the appropriateness of the policy question being addressed and a judgement is required as to whether this question is the question of most interest to NICE. The manufacturer's analysis considered the use of infliximab in patients with moderate to severe UC compared with standard care including 5-ASA compounds, corticosteroids and immunomodulators (azathioprine or 6-mercaptopurine). However, the scope indicated that the question of interest for NICE was the use of infliximab in patients who have had an inadequate response to conventional therapy for whom the comparator technologies include surgery or ciclosporin.

The manufacturer chose not to make use of the health utility data available from the ACT trials,

but rather commission a new cross-sectional study to gather new health utility data. Given that much of the input data for the model were taken from the ACT trials, this decision is surprising and requires justification.

The model had a time horizon of 10 years for the base case, but the longest follow-up in the ACT trials was 54 weeks. Thus, the transition probabilities were derived from trial data up to 54 weeks and were assumed to remain constant through to 10 years.

The PSA was undertaken in a very partial manner, with distributions placed around selected parameters only. Errors in the interpretation of the PSA and calculation of the cost-effectiveness acceptability curve were identified.

## Conclusions

The key areas of uncertainty identified were:

- There is evidence on the effectiveness of infliximab in the acute hospital-based setting in terms of response and avoidance of surgery; however, the results are primarily based on one small study, even though the effect on colectomy rates is highly statistically significant.
- The evidence on colectomy and ostomy rates in the subacute setting is unclear, and indeed there are some inconsistencies between different reports of hospitalisation rates from ACT I and II.
- In ACT I and II, although the statistical significance of the differences in change in quality of life with infliximab compared with placebo are clear, the importance of these changes to the patient is less easy to define, an issue with a key bearing on the interpretation of the cost-effectiveness component of the submission.
- In common with all newly introduced drugs the long-term safety of infliximab needs to be established, particularly with respect to the risk of malignancy.
- The definition of the policy question and, depending on the answer to this question, the

appropriate trials from which to be drawing data.

- A key driver of the model results is the utility data and so a judgement on the most appropriate source of utility data is required.
- The robustness of the assumption concerning long-term follow-up to 10 years, given that this is based on trial data to 54 weeks.

Of these, the interpretation of the importance of the quality of life changes in the subacute situation and the assessment of the adequacy of the evidence of effectiveness of infliximab in the acute hospital-based situation were considered pre-eminent by the ERG.

## Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance document issued by NICE in April 2008 states that:

Infliximab is not recommended for the treatment of subacute manifestations of moderately to severely active ulcerative colitis.

For the purposes of this guidance, a subacute manifestation of moderately to severely active ulcerative colitis is defined as disease that would normally be managed in an outpatient setting and that does not require hospitalisation or the consideration of urgent surgical intervention.

## Key references

1. National Institute for Health and Clinical Excellence. *Guide to the single technology (STA) process*. 19 September 2006. URL: [www.nice.org.uk/page.aspx?o=STAprcessguide](http://www.nice.org.uk/page.aspx?o=STAprcessguide).
2. Hyde C, Bryan S, Juarez-Garcia A, Andronis L. *Infliximab for ulcerative colitis*. Birmingham: West Midlands Health Technology Assessment Collaboration, University of Birmingham; July 2007. URL: [www.nice.org.uk/nicemedia/pdf/UlcerativeColitisEvidenceReviewGroupReport.pdf](http://www.nice.org.uk/nicemedia/pdf/UlcerativeColitisEvidenceReviewGroupReport.pdf). Accessed 1 November 2008.