Infliximab for the treatment of acute exacerbations of ulcerative colitis

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Declared competing interests of authors: none

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis, in accordance with the licensed indication, based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The submitted clinical evidence included four randomised controlled trials (RCTs), two comparing infliximab with placebo in patients not responsive to initial treatment with intravenous corticosteroids and one comparing ciclosporin with placebo. A fourth RCT compared ciclosporin with intravenous corticosteroids as the initial treatment after hospitalisation. The manufacturer's submission concluded that infliximab provides clinical benefit to patients with acute severe, steroid-refractory ulcerative colitis and is well tolerated; it also provides additional clinical benefits over ciclosporin, particularly avoidance of colectomy. A decision tree model was built to compare infliximab with strategies involving ciclosporin, standard care and surgery. After correcting a small number of errors in the model, the revised base-case incremental cost-effectiveness ratio (ICER) for infliximab compared with standard care was £20,000. However, sensitivity analyses revealed considerable uncertainty emanating from the weight of the patient, the timeframe considered and, most importantly, the colectomy rates used. When a more appropriate mix of trials were included in the estimation of colectomy rates, the ICER for infliximab rose to £48,000.

HTA 08/37/01

Date of ERG submission:
June 2008

TAR Centre(s):
West Midlands Health Technology Assessment Collaboration (WMHTAC)

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The research reported in this article of the journal supplement was commissioned and funded by the HTA programme on behalf of NICE as project number 08/37/01. The assessment report began editorial review in November 2008 and was accepted for publication in June 2009. See the HTA programme website for further project information (www.hta.ac.uk). This summary of the ERG report was compiled after the Appraisal Committee's review.

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).

The guidance issued by NICE on 31 October 2008 states that infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient; for people who do not meet this criterion, infliximab should only be used for the treatment of acute exacerbations of severely active ulcerative colitis in clinical trials.

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, where 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 entitled 'Infliximab for the treatment of acute exacerbations of ulcerative colitis'.

Description of the underlying health problem

Ulcerative colitis (UC) is a chronic condition in which there is inflammation of the mucosa of the large intestine. The cause of UC is unknown. Hereditary, infectious and immunological factors have been proposed as possible causes.

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. This prevalence is likely to be an underestimate as this implies an average disease duration of 10 years for a condition that is known to last for life. Based on these prevalence figures there are between 52,794 and 105,587 people in England and Wales with UC. The age of onset peaks between 20 and 40 years of age, but the disease may present at all ages. The prevalence of UC in children is about six to seven 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 daily bowel movements, but where 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 or anaemia. Fulminant disease correlates with more than 10 bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement and colonic dilation (expansion). Patients in this category may have inflammation extending just beyond the mucosal layer, causing impaired colonic motility and leading to toxic megacolon (toxic dilation of the colon).

Approximately 90% of all incident cases of UC are mild or moderate in severity.

In UC the severity of the symptoms fluctuate 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. Twenty-five per cent 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.

Complications of UC may include haemorrhage, perforation, stricture formation, abscess formation, anorectal disease (e.g. fissures), arthritis, eye, cutaneous and liver abnormalities. Patients with long-standing dysplasia and extensive colitis have an increased risk of bowel cancer. UC has a slight excess of mortality in the first 2 years after diagnosis, but little subsequent difference from the general population. A severe attack of UC is a potentially life threatening illness.

The British Society of Gastroenterology published guidelines for the treatment of UC in 2004. The main recommendations for the

medical management of severe UC indicate that patients whose condition has not responded to maximal oral treatment with a combination of mesalazine and/or corticosteroids should be admitted for intensive intravenous therapy. When hospitalised, patients are usually given intravenous corticosteroids and, if there is no improvement during the first 3 days, surgical intervention or intravenous ciclosporin is considered. Following induction of remission, patients with UC should normally receive maintenance therapy with aminosalicylates and often also azathioprine or mercaptopurine and/or short-term ciclosporin 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 within a multidisciplinary team with specialist nursing support.

Infliximab (Remicade, Schering Plough) is a chimeric monoclonal antibody that binds with high affinity to tumour necrosis factor-α, thereby neutralising its activity. It is administered by intravenous infusion and 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 have medical contraindications for such therapies.

Scope of the evidence review group report

The purpose of the ERG report was 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 is shown in *Table 1*.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence 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 performed to inform the manufacturer's submission
- extending searches, particularly for ongoing trials
- formal critical appraisal of systematic review underpinning the manufacturer's submission, and two related Cochrane Reviews
- reappraisal and checking of data abstraction on the four key included studies
- rerunning of mixed treatment comparison model
- checking the consistency of the direct effectiveness evidence with the estimates emerging from the mixed treatment comparison model and the parameters used in the economic model
- rerunning of the economic model supplied by the company
- correcting minor programming errors
- additional sensitivity analyses within the limits of the facilities of the submitted model.

The work was carried out between 17 April 2008 and 18 June 2008.

Members of the ERG team attended and advised the meeting of the NICE appraisal committee where this guidance was discussed on 17 July 2008.

Results

Summary of submitted clinical evidence

The manufacturer's submission reviewed systematic reviews and randomised controlled trials (RCTs) of infliximab and ciclosporin, the main alternative treatment option. The review also examined non-RCT evidence, particularly case-series of infliximab in the patient group of interest, but this did not contribute to the conclusions and is not considered further in this summary.

The main evidence identified is well known, four RCTs, two[2,3] comparing infliximab with placebo in patients not responsive to initial treatment with intravenous corticosteroids and one[4] comparing ciclosporin with placebo. A fourth RCT[5] compared ciclosporin with intravenous corticosteroids as the initial treatment after hospitalisation. The evidence on effectiveness was combined through a mixed treatment comparison model.

TABLE 1 *Submission scope*

Component of submission scope	Detail of submission scope
Appraisal objective	To appraise the clinical effectiveness and cost-effectiveness of infliximab for the treatment of acute exacerbations of severely active UC that require hospitalisation
Intervention(s)	Infliximab
Population(s)	Adults with acute exacerbations of severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies, and whose clinical management requires hospitalisation
Standard comparators	The standard comparators to be considered include: – standard clinical management which may include surgical intervention – ciclosporin
Outcomes	The outcome measures to be considered included: – health-related quality of life – survival – rates of and duration of response, relapse and remission – rates of surgical intervention – measures of disease activity – adverse effects of treatment
Economic analysis	The reference case stipulated that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year Time horizon should be long enough to allow reasonable estimation of expected costs (including adverse events if applicable) and benefits for the intervention, but should also account for the disease specific feature, particularly fluctuation and unpredictability of symptoms Costs were considered from an NHS and Personal Social Services perspective
Other considerations	Where evidence permits, the appraisal of infliximab for the acute exacerbation of severely active UC should identify patient subgroups for whom the technology is most appropriate Where evidence permits, the appraisal of infliximab for the acute exacerbation of severely active UC should consider different posology or methods of administration, treatment continuation strategies and lengths of treatment required when patients have responded to infliximab Guidance will only be issued in accordance with the Summary of Product Characteristics
Related NICE recommendations	Related ongoing technology appraisals: Infliximab for the sub-acute manifestation of ulcerative colitis. Related guidelines: none

The review and the model contribute to the two main conclusions offered in the manufacturer's submission:

- Infliximab provides clinical benefit to patients with acute severe, steroid-refractory UC and is well tolerated.
- Infliximab provides additional clinical benefits over ciclosporin, particularly avoidance of colectomy.

Summary of submitted cost-effectiveness evidence

No published economic evaluations of infliximab in acute UC were identified and so the cost-effectiveness work focused entirely on the de novo model and economic evaluation undertaken by the manufacturer. A decision tree model was built to compare infliximab with strategies involving ciclosporin, standard care and surgery. The main evidence used to estimate some of the key probabilities in the model derived from the main trials, but data on resource use and costs were available only from an expert panel. Utility data were taken from an observational cohort (the HODaR study; Health Outcomes Data Repository). The results revealed dominance in the comparison of standard care and ciclosporin. On the basis of the results, it is clear that the move from standard care to ciclosporin is highly cost-effective given that it is associated with lower costs and higher quality-adjusted life-years. Thus, the policy question then to be addressed is the subsequent move from ciclosporin to infliximab, and so the only appropriate comparator for infliximab is ciclosporin. After correcting a small number of errors in the model, the revised base-case incremental cost-effectiveness ratio (ICER) for infliximab compared with standard care was

£20,000. However, sensitivity analyses revealed considerable uncertainty emanating from the weight of the patient, the timeframe considered and, most importantly, the colectomy rates used. When a more appropriate mix of trials was included in the estimation of colectomy rates, the ICER for infliximab rose to £48,000.

Commentary on the robustness of submitted evidence

Strengths

The review of effectiveness was generally systematic in approach, building on previous work in the area.

The submission reported a de novo model-based economic evaluation that has considered the cost-effectiveness of infliximab in UC. The use of a decision tree model was appropriate, as the focus is on the acute phase of the disease. The main probability inputs were derived from trial data.

Probabilistic sensitivity analysis and one-way sensitivity analyses were performed.

Weaknesses

Although generally systematic, the review of clinical effectiveness had some errors, most notably failing to distinguish that the effect measured by one of the included RCTs[5] is qualitatively different from the other trials and should not be combined with them. There was concern that the considerable uncertainty surrounding the estimates of effectiveness arising from the very small number of RCTs, which are themselves small, was understated. Although the mixed treatment comparison model is interesting, it is debatable whether the very limited amount of data available warranted such a sophisticated approach.

The model did not consider side-effect issues or mortality events. The resource use estimates used in the model were from an expert panel. The key model inputs on colectomy rates were derived from a small number of small trials, some of which may not be directly relevant to the policy question being addressed.

Conclusions

Several areas of uncertainty were identified:

- There was considerable uncertainty about the evidence on effectiveness of infliximab and ciclosporin. Primarily this emanates from the very limited amount of RCT data, the impact of which was somewhat understated in the manufacturer submission. This was compounded by a debatable decision about 'combining' the data for an RCT with a control arm of intravenous corticosteroids with RCTs with placebo control arms and the use of a mixed treatment comparison model to generate estimates of the effect infliximab versus ciclosporin for which there is no direct evidence. This however also led to estimates of effect of infliximab and ciclosporin that differed in important respects from the original trials (*Tables 2 and 3*).
- The results consistently indicated that the move from standard care to ciclosporin is highly cost-effective. Thus, the appropriate policy question is not uncertain. The question to be addressed was: should we make a subsequent move from ciclosporin to infliximab? And so the only appropriate comparator for infliximab is ciclosporin.
- There was considerable uncertainty concerning what colectomy rates should be used.
- The weight of the patient was important – if patients tended to be 60 kg or less then the cost-effectiveness of infliximab was more attractive.
- The timeframe of the model was also important – extrapolating beyond 12 months was the approach that is consistent with the NICE methods guide. Such extrapolation indicates worsening cost-effectiveness for infliximab in general.

The key issues for consideration by the appraisal committee were thus suggested to be:

- Was the effectiveness of both infliximab and ciclosporin accurately portrayed by the manufacturer submission, particularly through the 'inclusion' of the RCT of ciclosporin by D'Haens *et al*.,[5] and through the use of the mixed treatment comparison model to summarise and estimate parameters for the economic model?
- Did the manufacturer's submitted model fully capture and convey the uncertainty arising from the problems with the effectiveness data?
- From the information available was it likely that improved estimates of effectiveness, and therefore cost-effectiveness, would arise from the ongoing trials of infliximab versus ciclosporin identified?

TABLE 2 *Colectomy 0- to 3-month results [event rates and odds ratios (ORs)] from different parts of the report*

Intervention	Jarnerot[2]	Sands[3]	Lichtiger[4]	D'Haens[5]	MTC model
Crude rates (%) [95% CI by Wilson's method]					
Infliximab	7/24 (0.29) [0.15 to 0.49]	0/3 (0.0) [0.0 to 0.56]			(0.23) [0.05 to 0.56]
Ciclosporin			3/11 (0.27) [0.10 to 0.57]	3/14 (0.21) [0.08 to 0.48]	(0.58) [0.22 to 0.88]
Placebo	14/21 (0.67) [0.45 to 0.83]	3/3 (1.0) [0.44 to 1.0]	4/9 (0.44) [0.19 to 0.73]	3/15 (0.20) [0.07 to 0.45]	(0.67) [0.46 to 0.85]
Odds ratio [95% CI]					
Infliximab vs placebo	0.21 [0.06 to 0.73][a]	0[a]			0.13 [0.03 to 0.44]
Ciclosporin vs placebo			0.47 [0.07 to 3.04][b]	1.09 [0.18 to 6.58]	0.70 [0.18 to 2.69]
Infliximab vs ciclosporin	No direct comparisons				

CI, confidence interval; MTC, mixed treatment comparison.
a Combined result from meta-analysis of Jarnerot and Sands, supplied by manufacturer in response to request for supplementary information, summary OR (fixed effects) 0.16 (0.05 to 0.53), Summary OR (random effects) 0.16 (0.04 to 0.66).
b Equivalent to relative risk of 0.61 (0.18 to 2.1).

TABLE 3 *Colectomy 3- to 12-month results [event rates and odds ratios (ORs)] from different parts of the report*

Intervention	Jarnerot[2]	Sands[3]	Lichtiger[4]	D'Haens[5]	MTC model
Crude rates (%) [95% CI by Wilson's method]					
Infliximab	3/17 (0.18) [0.06 to 0.41]				(0.27) [0 to 0.92]
Ciclosporin				3/11 (0.27) [0.10 to 0.57]	(0.18) [0.0 to 0.70]
Placebo	1/7 (0.14) [0.03 to 0.51]			3/12 (0.25) [0.09 to 0.53]	(0.14) [0.0 to 0.47]
Odds ratio [95% CI]					
Infliximab vs placebo	1.3 [0.11 to 15.0]				1.8 [0.13 to 57]
Ciclosporin vs placebo				1.1 [0.18 to 7.2]	1.1 [0.15 to 8.5]
Infliximab vs c°iclosporin	No direct comparisons				

CI, confidence interval; MTC, mixed treatment comparison.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the Final Appraisal Determination document issued by NICE on 31 October 2008 states that:

This guidance relates only to the use of infliximab within its marketing authorisation, for the treatment of acute exacerbations of severely active ulcerative colitis. It relates to an induction course of three doses of infliximab.

1.1 Infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient.

1.2 In people who do not meet the criterion in 1.1, infliximab should only be used for the treatment of acute exacerbations of severely active ulcerative colitis in clinical trials.

Key references

1. NICE. *Guide to the single technology (STA) process 19 September 2006.* 2006. URL: www.nice.org.uk/pdf/STA_Process_Guide.pdf (issued September 2006).

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