NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Use of tumour necrosis factor alpha (TNF-α) inhibitors (adalimumab and infliximab [review]) for Crohn's disease

The overview was written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee before the third committee meeting. The overview summarises the evidence and views of the Decision Support Unit (DSU) contained in their report and highlights key issues and uncertainties. This document should be read with the DSU report and comments from consultees and commentators on the DSU report.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Introduction

The purpose of this overview is to explain the history of this appraisal, as well as summarise new information available since the last Appraisal Committee meeting. This information is intended to help the Appraisal Committee in their decision about the use of adalimumab and infliximab for patients with Crohn's disease. A summary of the key points for consideration in the DSU report is also provided.

1.1 The history of the appraisal

Following referral from the Department of Health and the Welsh Assembly Government in August 2006, NICE started work on the appraisal 'Use of tumour necrosis factor alpha (TNF-α) inhibitors (adalimumab and infliximab [review]) for Crohn's disease'. This appraisal includes a review of 'Guidance on the use of infliximab for Crohn's disease' (NICE technology appraisal guidance 40, see appendix B).

Key stages in the history of this appraisal are listed in Table 1 below.

Table 1 Key stages in the history of this appraisal

Date	Event
August 2006	Topic referred to NICE by the Department of Health and the Welsh Assembly Government. Topic later amended to include the review of infliximab as part of the appraisal.
March 2007	Updated referral from the Department of Health received, requesting inclusion of natalizumab in the appraisal.
April 2007	Final scope published.
June 2007	Final protocol sent to consultees and commentators.
September 2007	Natalizumab removed from the appraisal after delay in marketing authorisation timelines. Negative Committee for Medicinal Products for Human Use (CHMP) opinion issued in November 2007.
December 2007	Certolizumab removed from the appraisal after negative CHMP opinion.
January 2008	Assessment report from the independent Assessment Group, West Midlands Health Technology Assessment Collaboration (University of Birmingham) sent for consultation to consultees and commentators.
March 2008	First Appraisal Committee meeting cancelled because of concerns about the completeness and transparency of aspects of the assessment report. Decision made that the concerns should be addressed before the Appraisal Committee met to develop its preliminary recommendations.
June 2008	Second (revised) assessment report sent for consultation to consultees and commentators.
August 2008	First Appraisal Committee meeting – ACD issued (see appendix C).
October 2008	Second Appraisal Committee meeting.
November 2008	In response to the points raised at the second Appraisal Committee meeting, the DSU was commissioned to perform a re-analysis of the evidence submitted.
January 2009	Appraisal Committee meeting cancelled because the DSU report received by NICE recommended further work. The report suggested that a full reconciliation of the economic evaluations included in the current evidence base may be required to develop reliable estimates of cost effectiveness and appropriately reflect areas of uncertainty. Structural issues and individual parameter values in the models were also areas for consideration.
April 2009	NICE commissioned the DSU to reconcile the economic evaluations taking into account their current capacity and resources.
June 2009	DSU report sent to consultees and commentators for consultation.
August 2009	Third Appraisal Committee meeting.

After consideration of the responses from consultees and commentators on the assessment report and the independent Assessment Group model at the

second Appraisal Committee meeting in October 2008, the DSU was commissioned to re-analyse the evidence submitted. The DSU was asked to determine reasons for key structural and parameter differences among the models submitted by the sponsors (Abbott Laboratories, 'Abbott'; and Schering-Plough, 'SP') and the Assessment Group (the 'Leeds' model). In January 2009 the DSU reported that it was not feasible to draw firm conclusions about the reasons for the differences between the models without further investigation and data review, and they agreed to undertake this work. Their final report was sent to consultees and commentators for consultation in June 2009.

A summary of the key issues raised by the DSU in their report is given in this document.

2 Report from the Decision Support Unit

The final report from the DSU detailed:

- the key differences in the modelling approaches adopted
- the impact of the transition probabilities used in the Leeds model, which govern patients' movements from remission to relapse while they are receiving standard care
- the impact of using revised post-remission standard care relapse rates from an updated literature review, in the Leeds model, and
- the impact of modifying the Leeds model to be consistent with the sponsors' modelling approaches.

A summary of the key outcomes from each of these analyses is discussed in the following subsections.

2.1 Modelling approaches

The cost-effectiveness estimates calculated for the base case in each model are provided in Table 2.

Table 2 Base-case cost-effectiveness estimates for each model

Leeds model	**Comparison for infliximab**	**Incremental cost**	**Incremental QALY**	**ICER**
	Episodic vs standard care	–£1392	0.0827	Dominant
	Maintenance vs standard care	£5720	0.0841	£68,014
	Maintenance vs episodic	£7112	0.0014	£5,024,522
	Comparison for adalimumab	**Incremental cost**	**Incremental QALY**	**ICER**
	Episodic vs standard Care	–£6381	0.0828	Dominant
	Maintenance vs standard care	£624	0.0842	£7411
	Maintenance vs episodic	£7005	0.0014	£4,949,900
SP model	**Comparison for infliximab**	**Incremental cost**	**Incremental QALY**	**ICER**
	Episodic vs standard care	-£708	0.1744	Dominant
	Maintenance vs standard care	£4831	0.186	£25,903
	Maintenance vs episodic	£5539	0.0121	£457,769
Abbott model	**Comparison for adalimumab**	**Incremental cost**	**Incremental QALY**	**ICER**
	Maintenance vs standard care	£1290	0.1177	£10,959

QALY, quality-adjusted life year
ICER, incremental cost-effectiveness ratio

While it is evident there was some consistency in the results among the three models, the DSU noted that the models were substantially different in terms of their inputs, structures and outputs (incremental cost-effectiveness ratios [ICERs], mean costs, effects and Markov traces).

A key difference between the sponsors' models and the Leeds model was the source of the data used to estimate the distribution of patients between various health states. While both sponsors primarily used data from pivotal clinical trials for adalimumab and infliximab, the Leeds model relied almost exclusively on data from a cohort of patients diagnosed with Crohn's disease between 1970 and 1993 in Olmsted County, Minnesota, USA (Silverstein et al. 1999). These patients may have been substantially different from those for whom anti-TNF therapy is indicated.

The DSU expressed concern about the methods used to allocate treatment costs to patients in the SP model, as it appeared their approach did not specifically link drug costs with the course of the disease.

2.2 Relapse rate

A key cause of differences in the cost-effectiveness estimates among the three models was the relapse rate.

Patient transitions in the Leeds model were governed by probabilities derived from the Olmsted county cohort (Silverstein et al. 1999). The Assessment Group assumed the probability of a patient moving from remission to relapse was 0.0059 for each 4 week cycle, every cycle. This low probability means that patients who are in remission are unlikely to relapse and episodic treatment would therefore be needed infrequently. As a result, episodic care was a much lower cost strategy compared with maintenance treatment, despite only generating a slightly lower benefit. Consultation raised numerous concerns about the use of the Olmsted county cohort as the basis for modelling the cost-effectiveness of infliximab and adalimumab.

The DSU noted that the ICER was highly sensitive to the relapse rate, with maintenance treatment falling below £30,000 per quality-adjusted life year (QALY) gained when the probability was assumed to be ≥ 0.33. Furthermore, analyses presented by Abbott from their clinical trial (CHARM study) suggested this probability could be as high as 0.42. Given the importance of this parameter, the DSU carried out a comprehensive systematic review to identify literature which specified the standard care relapse rate for patients with moderate to severe Crohn's disease who were already in remission.

Four studies were identified in the review, three of which were carried out in patients with moderate to severe Crohn's disease. These studies calculated 4-week probabilities of relapse of 0.072 (Rutgeerts et al. 1999), 0.136 (Hanauer et al. 2002) and 0.048 (Feagan et al. 2000). The fourth study (Sands et al. 2004) was carried out in patients with fistulising active Crohn's disease, and

estimated a 4-week transition probability of 0.180. Across the studies, the median time to relapse was 0.5 years. This was noted to differ from the average relapse time of 9 years assumed in the Leeds model.

Although the evidence base was limited, the identified studies suggested that 4-week probabilities of relapse ranging from 7–14% for moderate to severe Crohn's disease may be typical. This was notably different from the 0.59% estimate derived from the Olmsted country cohort of patients in the Leeds model (base case). However, the DSU noted that even if the different estimates of relapse were used in the Leeds model, the conclusions about cost-effectiveness may remain unchanged.

2.3 Reconciliation between sponsor and Leeds models

Changes to the Leeds model were made in a stepwise fashion to reconcile the different modelling approaches. This approach was undertaken specifically to address differences in model results because of:

- cost, utility and discount parameter differences
- structural issues such as time horizon and the patient pathway
- transition probabilities that could be quantified
- residual probabilities that could not be quantified

After reconciling the Leeds and SP models, the DSU noted that the changes made did align the models to some extent, but substantial differences in the model outputs remained. Furthermore, while changes to the models made the relapse and remission rates for the episodic and maintenance arms much closer, the standard care remission rate in the revised Leeds model remained higher than the predicted rate in the SP model. It was noted that unless the health states and transition probabilities used in the Leeds model were changed, and in effect the SP model was rebuilt, it was not possible to reconcile every element of the Markov process. The DSU concluded that the

SP model did replicate the relevant clinical trials, to the best of their knowledge. However, because the Leeds model used transition probabilities derived from a different source, the results produced by the SP model differed from those generated by the Leeds model.

The revised Leeds model was also run after each change with the adalimumab drug costs. The final results were consistent with the outcomes in the Abbott model, in that maintenance treatment generated a relatively low ICER.

When the utility values and health state costs from the Abbott model were substituted into the Leeds model, maintenance treatment with adalimumab dominated standard care. The DSU noted that these results provided further support for the finding that the sources of the patient transitions (that is Silverstein-based transitions compared with those from the clinical trial based analyses) were the drivers of differences in the model outcomes.

2.4 Conclusions

Adapting the Leeds model to more closely reflect the sponsors' analyses suggested that episodic treatment with adalimumab dominated standard care, while maintenance treatment with adalimumab was cost effective compared with episodic treatment (£7445 per QALY gained).

When cost and utility values from the Leeds model were substituted into the Abbott model (which estimated an ICER of £11,998 per QALY gained for maintenance treatment in the base case), maintenance treatment dominated standard care.

The SP model estimated that episodic treatment with infliximab dominated standard care in the base-case analysis and that maintenance treatment generated an ICER of £457,769 per QALY gained when compared with episodic care. The Leeds base-case model was in broad agreement with

these findings, despite the fact that the drug costs estimated in the SP model were substantially lower.

When the Leeds model was adapted to more closely reflect the SP model, high ICERs for episodic treatment with infliximab resulted for all scenarios considered. For maintenance versus standard care, the ICERs ranged from approximately £29,000 to £69,000 depending on assumptions about drug costs.

3 Cost effectiveness of adalimumab and infliximab: Publication by Bodger et al. 2009

A paper was recently published on the cost effectiveness of adalimumab and infliximab (Bodger et al. 2009) and is summarised below. Secondary analyses conducted in this study over a short time horizon, in line with the time period used in the Leeds model, produced findings consistent with those reported by the Assessment Group and the DSU.

3.1 Study overview

A Markov model was used to estimate the cost effectiveness of infliximab and adalimumab compared with standard care. The drugs were administered according to their licensed regimens to adult patients with moderate to severely active Crohn's disease. Health states were defined according to Crohn's Disease Activity Index (CDAI) scores and were 'full response' (CDAI < 150), 'partial response' (CDAI 150–220), 'non-response' (CDAI 220–600), 'surgery' and 'death'. The natural course of Crohn's disease for patients receiving standard care was based on the Olmsted County cohort study (Silverstein et al. 1999), while clinical effectiveness for the drugs was determined from clinical trial information on maintenance regimens (the ACCENT I study for infliximab and the CHARM study for adalimumab) identified after a systematic literature review.

In the base case, the life-time costs and health outcomes (measured as QALYs) for infliximab, adalimumab and standard care were calculated using UK average treatment costs for each health state, and EQ-5D utility values, which were calculated from CDAI scores using a previously published algorithm (Buxton et al. 2007).

3.2. Results

Maintenance treatment for 1 year for initial responders to infliximab or adalimumab produced ICERs of £19,050 and £7190 per QALY gained respectively, compared with standard care. Similarly, for a treatment period of 2 years with either infliximab or adalimumab compared with standard care, ICERs of £21,300 and £10,310 per QALY gained were estimated respectively.

After 4 years of continuous treatment, infliximab was no longer considered to be cost effective if a threshold of £30,000 per QALY gained was assumed. Results suggested that adalimumab may be cost effective when used long-term. Outcomes in this study were sensitive to the time horizon chosen for the analysis. When the time horizon of the analysis was shortened to match the base-case treatment duration, neither agent was cost effective. The authors noted that a short-term horizon was adopted by the Assessment Group (Leeds model) for the ongoing Crohn's technology appraisal, producing similar results and conclusions. The authors stated that the selection of shorter time horizons for analysis was likely to bias the cost-effectiveness estimates, and their choice of a lifetime horizon in the analysis was because of the chronic nature of the disease, the reduced survival of patients with Crohn's disease compared with the general population, and the differential effect of treatment on mortality.

In summary, both infliximab and adalimumab were suggested to be a cost-effective use of healthcare resources when used continuously for limited periods, but not for a whole lifetime.

4 Issues for consideration

- Does the Committee feel that any valid issues about the reliability of the Leeds model have been omitted from the DSU assessment?
- What are the Committee's conclusions on the issues highlighted by the DSU?
- Does the Committee consider the methodology used to calculate QALYs is appropriate?
- What factors should be captured in estimating health-related quality of life?
- Does the Committee accept the DSU's conclusions after review of comments from consultees and commentators on the DSU report?

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Appendix A: Sources of evidence considered in the preparation of the overview

The report from the Decision Support Unit was prepared by Allan Wailoo, Jon Tosh, and Pippa Hemingway from the School of Health and Related Research, University of Sheffield (June 2009).

Additional references used:

Bodger K, Kikuchi T & Hughes D (2009). Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. *Aliment Pharmacol Ther*; 30(3): 265-74

Buxton MJ, Lacey LA, Feagan BG et al. (2007). Mapping from disease specific measures to utility: An analysis of the relationship between the inflammatory Bowel Disease Questionnaire and Crohn's Disease Activity Index in Crohn's Disease and measures of utility. *Value in Health*; 10(3): 214-20

Feagan BG, Fedorak RN, Irvine EJ et al. (2000). A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *New Engl J Med*; 342: 1627-32

Hanauer SB, Feagan BG, Lichtenstein GR et al. (2002). Study group maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*; 359: 1541-49

Rutgeerts P, D'Haens G, Targan S et al. (1999). Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology*; 117: 761-79

Sands BE, Anderson FH, Bernstein CN et al. (2004). Inflximab maintenance therapy for fistulising Crohn's disease. *New Engl J Med*; 350: 876-85

Silverstein MD, Loftus EV, Sandborn WJ et al. (1999). Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. *Gastroenterology*; 117: 49-57

Appendix B: Guidance on the use of infliximab for Crohn's disease (NICE technology appraisal guidance 40)

1.1. Infliximab is recommended for the treatment of patients with severe Crohn's disease who fulfil all three of the following criteria:

- Patients who have severe active Crohn's disease. These patients will already be in very poor general health with weight loss and sometimes fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. They may or may not be developing new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more and a Harvey-Bradshaw Index of 8/9 or above.

- Patients whose condition has proved to be refractory to treatment with immunomodulating drugs (e.g. azathioprine or 6-mercaptopurine, methotrexate) and corticosteroids, or who have been intolerant of, or experienced toxicity from, these treatments.

- Patients for whom surgery is inappropriate (e.g. because of diffuse disease and/or a risk of short bowel syndrome).

1.2. Treatment can be repeated for those patients who match the above criteria and have responded to the initial treatment course, but then relapsed. A decision about whether or not to re-administer infliximab after the first course or subsequently should be made only after discussion with the patient who has been fully informed of the potential risks and benefits of repeated therapy (episodic treatment).

1.3. Infliximab should be prescribed by a gastroenterologist experienced in the management of Crohn's disease.

1.4. Infliximab is not recommended for patients with fistulising Crohn's disease who do not have the other criteria for severe active Crohn's disease as detailed in section 1.1.

Appendix C: Appraisal Committee's preliminary recommendations – August 2008

1.1. Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active, non-fistulising Crohn's disease as episodic treatment; that is, they can be re-administered to those people whose disease has responded to the first treatment course but then severe symptoms have recurred.

1.2. For the purposes of this guidance, severe active Crohn's disease is defined as very poor general health with weight loss and sometimes fever, severe abdominal pain and usually frequent (3-4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally but not exclusively corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more.

1.3. The choice of either adalimumab or infliximab in the circumstances described in 1.1 should be determined by the healthcare professional in consultation with patients and carers. The decision should take into account preferences regarding the delivery of the drug and potential adverse effects and contraindications. If all other considerations are equal, the drug with the lowest acquisition and delivery cost should be used.

1.4. Infliximab is recommended as episodic treatment for people with fistulising Crohn's disease who fulfil the criteria in 1.2.

1.5. Infliximab within its licensed indications is recommended for the treatment of children and adolescents with severe Crohn's disease as detailed in section 1.2.

1.6. Infliximab and adalimumab are not recommended for regular maintenance treatment (treatment given continually at regular intervals) to prevent relapse of Crohn's disease.