The use of TNF-α inhibitors, adalimumab and infliximab, for Crohn's disease

A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-α) inhibitors, adalimumab and infliximab, for Crohn's disease

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Executive summary

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Executive summary

Background

Crohn's disease (CD) is a severe, lifelong disease characterised by inflammation of the gastrointestinal mucosa. Main symptoms include chronic diarrhoea, abdominal pain, rectal bleeding and weight loss, and growth failure in children. Common complications are strictures (narrowing of the bowel), fistulas (creation of abnormal passageways between the bowel and other structures) and perianal disease (comprised of fissures, fistulas and abscesses). The disease is characterised by recurring flares of variable duration alternating with periods of remission of variable duration. There is no cure and most patients will need to take medication for large periods of their life and many will require surgery. CD manifests itself mainly during late adolescence or early adulthood; prevalence estimates range from 50 to 375 per 100,000. The impact on patients and society is high as ill health can be lifelong and can negatively affect education and employment as well as patients' quality of life. Costs to the NHS are high, particularly for patients needing hospitalisation.

Conventional treatment pathways are complex and include a wide range of drugs (corticosteroids, aminosalicylates, immunosuppressants, antibiotics), nutritional therapy and surgery. More recently, a group of drugs called tumour necrosis factor (TNF) inhibitors (anti-TNF-α agents) have been evaluated for their effectiveness in CD. One of these, infliximab, is currently recommended by the National Institute for Health and Clinical Excellence (NICE; 2002) for patients with severe, active CD where patients are refractory to or intolerant of conventional treatment.

Objectives

The objectives of this Technology Assessment Report (TAR) were:

- To update a previous TAR on the effectiveness and cost-effectiveness of infliximab in adults with moderate-to-severe CD or fistulising CD who are refractory to or intolerant of conventional treatment.
- To review the evidence on the clinical effectiveness and cost-effectiveness of infliximab in children with moderate-to-severe CD who are refractory to or intolerant of conventional treatment.
- To review the evidence on the clinical effectiveness and cost-effectiveness of a further anti-TNF-α antibody, adalimumab, in adults with moderate-to-severe CD who are refractory to or intolerant of conventional treatment.
- To investigate whether there is evidence for greater clinical effectiveness or cost-effectiveness for either adalimumab or infliximab.

Methods

Data sources

Data for the review were sought from the Cochrane Library (Cochrane Central Register of Controlled Trials), MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and EMBASE up to June 2007. The European Medicines Agency, the US Food and Drug Administration and other relevant websites were also searched.

Clinical effectiveness

Standard systematic review methods were used for study identification and selection, data extraction and quality assessment. Only randomised controlled trials (RCTs) comparing adalimumab or infliximab with standard treatment (placebo), RCTs comparing adalimumab with infliximab, or RCTs comparing different dosing regimens of either adalimumab or infliximab in adults and children with moderate-to-severe active CD intolerant or resistant to conventional treatment were eligible for inclusion. Outcomes reported in the trials were based mainly around changes in the Crohn's Disease Activity Index (CDAI), a questionnaire measuring various parameters associated with CD. Results were presented in forest plots, but not pooled because of the existence of either a single trial or clinical heterogeneity where there were two trials that potentially could have been pooled. Formal indirect comparisons were not undertaken owing to clinical heterogeneity of trials. Results are reported for those trial arms where dosing regimens were consistent with the respective licence indications.

Cost-effectiveness

A systematic review of published studies on the cost and cost-effectiveness of adalimumab and infliximab was undertaken. The economic models of cost-effectiveness submitted by the manufacturers of both drugs were critically appraised and, where appropriate, rerun using parameter inputs based on the evidence identified by the authors of the TAR. A de novo Markov state transition model was constructed to calculate the incremental cost-effectiveness ratio (ICER) for adalimumab and infliximab therapy respectively compared with standard care.

Results

Clinical effectiveness review

Based on 11 trials, there was evidence from both induction and maintenance trials that both adalimumab and infliximab therapy were beneficial compared with placebo (standard care) for adults with moderate-to-severe CD and, for infliximab, for adults with fistulising CD; results were statistically significant for some time points. These results were based on changes to the CDAI and, for fistulising disease, on rates of fistula closure. Results from maintenance trials were almost exclusively based on subgroups of 'responders'. Between 6% and 24% (adalimumab) and 21% and 44% (infliximab) more patients achieved remission with anti-TNF-α antibodies than with placebo in the induction trials. Between 24% and 29% (adalimumab) and 14% and 24% (infliximab) more patients achieved remission with anti-TNF-α antibodies in the two large maintenance trials at reported follow-up. In fistulising CD, between 29% and 42% (induction trial) and 23% (maintenance trial) more patients achieved a > 50% reduction in fistulas with infliximab than with placebo at reported follow-up.

There was no direct evidence to show that 'responders' were more likely to benefit from treatment than 'non-responders' in the longer term. The maintenance trials, in the main, did not inform on persistence of the response (remission) state as point prevalence only was reported. There was likely to be a benefit of infliximab therapy for children, but these results were uncertain as the trials had no placebo (standard care) arm; rates of spontaneous improvement could therefore not be quantified. There was no valid evidence regarding the relative effectiveness of 'episodic' and 'scheduled' infliximab treatment regimens. Few differences were found between treatment and standard care arms for selected adverse events, though high proportions of scheduled crossovers resulted in a lack of a true placebo group in most of the maintenance trials.

Cost-effectiveness review

No published studies on the cost-effectiveness of adalimumab were identified. The four independently funded studies identified for infliximab suggested high cost-effectiveness ratios

[all above £50,000/quality-adjusted life-year (QALY) for non-fistulising disease and all above £100,000/QALY for fistulising disease].

Appraisal of industry submissions

For adalimumab there was a lack of clarity over the source and interpretation of data used in the industry model, and key elements of the model could not be verified. Corrected results for both severe CD and moderate and severe (combined) CD were substantially higher than in the industry submitted model; in the severe subgroup of patients the corrected ICER approached cost-effectiveness (at a threshold of £30,000). For infliximab, errors were identified in the industry model (active CD), some of which could not be corrected. The authors' revision of the model (active CD) suggested that infliximab was cost-effective for episodic (clinician discretion) treatment, although an exact description of this intervention was lacking. The revised model indicated that scheduled maintenance treatment with infliximab was unlikely to be cost-effective. The revised industry model for fistulising CD also suggested that infliximab was unlikely to be cost-effective. The model provided for paediatric CD was non-functional.

De novo economic model

A Markov model was developed from an NHS/Personal Social Services perspective to estimate the incremental cost per QALY for both drugs compared with standard care in (a) induction/episodic therapy (as it was defined for the de novo economic model) for moderate and severe disease; and (b) maintenance therapy for moderate and severe disease. The model had a 1-year time horizon and was constructed and analysed in TREEAGE PRO 2008 (TreeAge Software Inc., Williamstown, MA, USA). The findings were that for induction, both adalimumab and infliximab were cost-effective (dominant relative to standard care) in the management of severe CD and that adalimumab was cost-effective (dominant relative to standard care) for moderate CD, according to limits usually accepted by NICE. Induction therapy with infliximab was not cost-effective for moderate CD (ICER of £94,321). Neither drug was cost-effective as maintenance therapy for moderate or severe disease by these criteria (ICER around £5M for severe disease for both drugs, and around £14M for moderate disease for both drugs). Additional work on severe CD suggested that relapse rates were one important factor in determining cost-effectiveness.

A budget impact assessment suggested that the total cost to the NHS in England and Wales for induction in severe disease only could range between £17M and £92M and for maintenance for 1 year between £140M and £200M. These totals would be less if treatment was directed towards only those CD patients whose condition was refractory to other treatment or who were intolerant or experienced toxicity from these treatments and for whom surgery was inappropriate. It is unclear how many people would be in this category so the precise budget impact if the current NICE guidance is maintained was unclear.

Discussion

Regarding clinical effectiveness, there were concerns about the trial design and lack of clarity, particularly regarding the maintenance trials, which may have affected interpretation of results. These related to the division of patients into subgroups (responders and non-responders) at different time points; the high proportions of scheduled crossovers resulting in a lack of a true placebo group; and uncertainties regarding the handling of missing binary and continuous data. Overall, the trials showed a benefit of both adalimumab and infliximab therapy over standard care, as measured by CDAI-related outcome measures (or fistula closure for patients with fistulising CD). Uncertainties remain over the size of the effect for both drugs, the duration of effect (after 1 year), the best type of treatment regimen (e.g. scheduled or as required) and the type of patient who would benefit most (e.g. in terms of disease severity or being an early

'responder'). There are also uncertainties over whether the CDAI-derived measures were adequate for capturing clinically meaningful changes in disease severity. While trial populations overall may appear homogenous based on similar CDAI scores, individual patients are likely to vary in their disease manifestations and severity. All of the trials were in patients with 'moderate-to-severe' CD (or fistulising CD) and therefore none matched exactly the licence indications or NICE guidance, which specify the use of these drugs in patients with 'severe' disease. All trials were multicentre and applicability to UK populations, particularly in terms of standard care being provided and in terms of patients having failed or having become intolerant to conventional treatment, was uncertain.

The uncertainties in the clinical data (as outlined above) complicated the economic analyses. The published economic models relied heavily on little information and data from small samples. In such cases, the interpretation of economic models within the published papers was difficult. Assessments of the industry-submitted models were hampered by inconsistent use of data and lack of clarity about the source and interpretation of data. Both manufacturers submitted Monte Carlo simulation Markov models, but unfortunately some of the models had serious errors. Also, Markov models assume zero memory; how long a patient has been in a health state and how they got there may impact on resources and could be important in a CD patient group. Both the published cost-effectiveness studies and the industry submission models lacked input of long-term clinical data.

Conclusions

Anti-TNF therapy with adalimumab or infliximab may have a beneficial effect compared with standard care on CDAI-related outcome measures for induction and maintenance. Formal comparisons between the two drugs were not possible owing to clinical heterogeneity between trials. Uncertainty remains regarding the size and duration of the effect of the two drugs and over the type of patient that is likely to benefit more or less from treatment. The findings were that for induction, both adalimumab and infliximab are cost-effective (dominant relative to standard care) in the management of severe CD, and adalimumab (but not infliximab) is cost-effective for moderate CD, according to limits generally accepted by NICE. On the basis of the analysis presented here, neither drug is likely to be cost-effective as maintenance therapy for moderate or severe disease. Perhaps, most importantly, the analysis reflected the fact that a substantial number of patients would achieve remission under standard care and that the incidence of relapse among those in remission was such that maintenance therapy would have to show greater effectiveness than at present and/or be much less costly than it currently is in order to reach the levels of generally accepted cost-effectiveness.

Any future trials need to be designed to meet the particular challenges of measuring and quantifying benefit in this patient group. For example, trials should be conducted in the whole eligible CD population and not be limited to 'responders', for whom no particular benefit has been shown. 'Scheduled crossovers' should be avoided as these result in a lack of a true placebo arm, and results become difficult to interpret. The length of trials should also be sufficient to account for natural periods or remission and relapse. Finally, different treatment strategies (e.g. episodic vs scheduled) need to be evaluated in appropriately designed trials.

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Publication

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