Infliximab for Crohn's disease

Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease

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Executive summary

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Executive summary

Background

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract of unknown aetiology. It can occur at any age, but most commonly presents in those aged 15–25 years. Approximately 31,000 people in England and 1800 in Wales are estimated to have the disease, with about 2650 new cases being diagnosed each year.

Patients with Crohn's disease suffer recurrent attacks with acute flares of the disease interspersed with periods of spontaneous remission. The disease can be complicated by the development of obstructions, perianal disease and fistulae (seen to develop in about one-third of patients).

Crohn's disease is currently neither medically nor surgically curable. Treatment is aimed at reducing symptoms and maintaining/improving quality of life while minimising toxicity. Corticosteroids and immunomodulators (chiefly azathioprine or 6-mercaptopurine) form the mainstay of treatment for active Crohn's disease. Treatment is less clear in fistulising Crohn's disease. When fistulae result from mechanical strictures, surgery will return patients to good health. Fistulae that develop in the absence of an obstruction respond poorly to drug therapy. Simple perianal fistulae show an excellent response to surgery. When medical treatment is required, azathioprine and 6-mercaptopurine are currently considered the most effective, although randomised controlled trial (RCT) data are limited. Overall, surgery will be required by 50–80% of patients with Crohn's disease at some stage. Main indications are strictures causing obstructive symptoms, failure to respond to medical therapy and complications, such as fistulae.

Infliximab is the first tumour necrosis factor inhibitor to be licensed for the treatment of Crohn's disease. Infliximab is indicated for use in adults with chronic active or fistulising Crohn's disease who have not responded to an adequate course of conventional treatment. The drug is given by intravenous infusion. Treatment can be repeated up to 14 weeks from the last infusion in patients where signs and symptoms of the disease recur. Re-administration after this time is not recommended because of the risk of delayed hypersensitivity.

Objectives

The objectives of the review were to address the following questions.

- How effective is infliximab as a second- or third-line treatment for severe active Crohn's disease in adults who have not responded to conventional treatment?
- How effective is infliximab at reducing the number of draining fistulae in adult patients with fistulising Crohn's disease who have not responded to conventional treatment?
- What is the frequency and severity of adverse effects associated with the use of infliximab?
- What adverse events are associated with repeated treatment with infliximab?
- How cost-effective is infliximab for the above indications compared with standard practice?

Methods

A systematic review of RCTs addressing the above questions was undertaken. The economic evaluation submitted by Schering-Plough Ltd was critiqued and the cost/quality-adjusted life-year (QALY) re-estimated by adjusting the assumptions.

Results

Number and quality of studies

Four RCTs were included in the review: three completed and one ongoing, with preliminary data available to 30 weeks. All trials appeared to be of good methodological quality but this could not be confirmed in the case of the ongoing study.

Clinical effectiveness

The use of infliximab in chronic active Crohn's disease resistant to conventional treatment was evaluated in three trials involving 754 patients. Only the two smaller trials (n = 181) had been completed. The larger ACCENT I trial (n = 573) has yet to be fully reported. A single dose of

infliximab was associated with significant treatment benefit at week 4 (number needed to treat (NNT) = 3 for response defined as a ≥ 70-point reduction in Crohn's Disease Activity Index), with approximately 30% of patients achieving remission of their symptoms at this time (NNT = 4). Benefit was, however, short-lived with the majority of patients relapsing beyond week 12. Data on repeated treatment were less clear. The evidence suggested that a positive treatment effect was seen, but current data were too limited to confirm this. The full results from the ACCENT I trial will address this.

Only one trial evaluated the use of infliximab in fistulising Crohn's disease. A three-dose treatment course resulted in complete healing of perianal/abdominal fistulae for more than 21 days in 46% of patients treated with infliximab versus 13% treated with placebo (NNT = 4). Again, treatment benefit was short-lived, with a median duration of 3 months. Data on repeated treatment are not currently available but will be provided by the ACCENT II trial.

Cost-effectiveness

Costs

For a 70 kg patient, the cost of one dose of infliximab, 5 mg/kg, is approximately £1800, with a three-dose course costing about £5400.

Cost/QALY

Using the Schering-Plough Ltd model, the cost/QALY in the treatment of chronic active Crohn's disease was calculated as £6700 with a single-dose treatment, £10,400 with episodic re-treatment and £84,400 with maintenance treatment. It is considered that these overestimate the benefits of infliximab owing to assumptions that the drug influences the natural history of the disease (see below).

In fistulising Crohn's disease, the cost/QALY values were high, £102,000–123,000 for initial treatment and £82,000–96,000 with the most favourable re-treatment assumptions on closure rates.

Sensitivity analyses

The chronic active model was highly sensitive to rate of 'flare' for episodic treatment. The flare rate chosen was 10%, which seemed reasonable based on clinical opinion. If more frequent flare was seen, then costs increased substantially: the incremental cost/QALY was £55,000 with a 50% likelihood of flare. The fistulising model was relatively insensitive to costs offset (owing to surgery averted), even when 100% offset was assumed.

Limitations of the assumptions made

In developing the model for chronic active Crohn's disease, the manufacturer made the implausible assumption that treatment with infliximab would alter the natural course of the disease. There were no observational data available but the RCT data suggest that patients return to their pre-treatment disease state with time.

Conclusion

Implications for practice

Infliximab is a specialised treatment requiring intravenous administration. Patients being considered for infliximab treatment need to be fully assessed by specialists experienced in the management of severe Crohn's disease. These patients will have disease that is not amenable to conventional medical and surgical management. Use of infliximab is, therefore, likely to be limited to a small group of patients, in whom benefits over existing treatment can be expected.

Recommendations for research

Considerable further research is required in this rapidly developing therapeutic field. In particular, research needs to clarify optimal dosage and dosage frequency for infliximab, the characteristics of poorly responding patients, and its optimal place in therapy amongst the other available treatment options, including surgery.

Publication

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