Systematic review: infliximab therapy in ulcerative colitis

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CRD summary
This review evaluated the efficacy and safety of infliximab in patients with ulcerative colitis (UC). The authors concluded that in patients with moderate-to-severe UC, infliximab is more effective than placebo at approximately 9 months’ follow-up; further studies are needed to address long-term effects. These conclusions appear reliable.

Authors' objectives
To assess the efficacy and tolerability of infliximab administration in patients with ulcerative colitis (UC).

Searching
The Cochrane Library (Issue 4, 2005), MEDLINE, EMBASE and CINAHL were searched up to January 2006; the search terms were reported. No language restrictions were applied. In addition, ISI Web of Knowledge, bibliographies of retrieved trial reports and reviews, and the conference abstracts from the American Digestive Disease Week and United European Gastroenterology Week congresses (from 2000 to 2005) were checked to identify additional studies.

Study selection
Study designs of evaluations included in the review
Randomised clinical trials (RCTs) were eligible.

Specific interventions included in the review
Studies evaluating infliximab for the treatment of UC were eligible for inclusion in the review. For the meta-analysis, studies had to compare infliximab with placebo or steroids. Infliximab reinfusions were permitted; they were provided at the physician's discretion, with no uniform schedule. Immunosuppressive therapy before or after starting infliximab infusion was provided in some of the included studies. Infliximab was mainly prescribed at a dose of 5mg/kg.

Participants included in the review
Studies of patients with UC were eligible. Trials of patients with UC or Crohn's disease were eligible if the data could be extracted for the group with UC. UC was moderate to severe in most of the patients in the included studies, and mild in a minority. About half of the patients were classified as steroid-refractory where this characteristic was assessed.

Outcomes assessed in the review
Studies had to report responses or remission rates for each therapy group to be eligible. This encompassed partial or complete symptomatic response and complete symptomatic response. Adverse events were also reported.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study quality was assessed on the basis of randomisation, double-blinding, withdrawals and drop-outs using the Jadad scale. Each study was allocated a score from 0 (lowest) to 5 (highest). Two reviewers independently assessed the quality of the studies, with any discrepancies resolved by consensus.

Data extraction
The data extraction was performed using standardised forms. The authors did not state how many reviewers performed the data extraction. The first control performed in the study was extracted as a short-term outcome, whereas the last control performed in the study was extracted as a long-term outcome. In the case of duplicate data, only the most recent
published results were used.

**Methods of synthesis**

How were the studies combined?

Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a fixed-effect model (Peto method) in the case of statistical heterogeneity, or with a random-effects model (DerSimonian and Laird) otherwise. The number-needed-to-treat (NNT) and the number-needed-to-harm for adverse events were also calculated.

How were differences between studies investigated?

Statistical heterogeneity was assessed by the chi-squared test and the I-squared statistic. A priori-specified sensitivity analyses were performed for patient age (children or adults), indication for infliximab (steroid-refractory or steroid-dependent UC), dose of infliximab (5 or 10 mg/kg), infliximab reinfusions during follow-up, and the type of control group (placebo or steroids).

**Results of the review**

Thirty-four studies (n=896) were included in the review.

Overall, short-term response and remission with infliximab therapy were 68% (95% CI: 65, 71) and 40% (95% CI: 36, 44), respectively. The corresponding estimates in the long-term follow-up were 53% (95% CI: 49, 56) and 39% (95% CI: 35, 42).

Infliximab versus placebo (5 studies).

All studies comparing infliximab and placebo were high-quality double-blinded RCTs. Compared with placebo, treatment with infliximab achieved more often a short-term response (OR 3.6, 95% CI: 2.67, 4.95, p<0.001; 4 datasets) and a short-term remission (OR 4.56, 95% CI: 1.98, 10.5, p<0.001; 2 datasets). The NNTs were 3 (95% CI: 3, 4) and 4 (95% CI: 3, 6), respectively. There was statistical heterogeneity for the outcome short-term remission (p=0.09; I-squared 66%). In the long-term follow-up, infliximab was associated with higher response rates (OR 3.4, 95% CI: 2.52, 4.59; p<0.001; 2 datasets) and remission rates (OR 2.72, 95% CI: 1.92, 3.83, p<0.001; 2 datasets), without significant heterogeneity. The NNTs were 3 (95% CI: 3, 4) and 5 (95% CI: 4, 7), respectively.

Infliximab versus steroids (2 studies).

Two open-label RCTs with quality scores of 2 and 3, respectively, compared infliximab versus steroids and showed similar short-term and long-term responses for both treatments. Short-term remission was also comparable in one of the studies, while the second trial found remission rates of 70% and 80% among patients treated with infliximab and steroids, respectively.

Adverse events.

The frequency of adverse events was higher with infliximab (OR 1.52, 95% CI: 1.03, 2.24, p=0.04).

**Authors’ conclusions**

In patients with moderate-to-severe UC, infliximab is more effective than placebo at approximately 9 months’ follow-up; long-term effects need to be addressed in further studies.

**CRD commentary**

This review addressed a well-defined question in terms of the participants, intervention, outcomes and study design. Several relevant databases were searched and efforts were made to identify unpublished studies; this reduces the potential for publication bias, which was not evaluated in the review. No language restrictions were applied, thereby reducing the risk of language bias being introduced in the review. It was not reported whether the study selection and data extraction stages were carried out in duplicate, which might have introduced error and bias into the review process.
Statistical heterogeneity was assessed and further explored, and the decision to pool the data in a meta-analysis seems appropriate. The authors' conclusions appear appropriate, although the reporting limitations and the fact that the review is based on a small number of studies with few participants should be noted.

**Implications of the review for practice and research**

**Practice:** The authors stated that infliximab may be considered for patients who are being evaluated for cyclosporine therapy or colectomy, and in those with acute steroid-refractory disease who are reluctant to undergo colectomy and in whom cyclosporine is contraindicated. A dose of 5 mg/kg, rather than 10 mg/kg, may be the preferred initial dose of infliximab.

**Research:** The authors stated that further studies are needed to evaluate the long-term efficacy and the cost-effectiveness of infliximab versus cyclosporine.

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