Anti-TNF-alpha drugs for refractory inflammatory bowel disease: clinical- and cost-effectiveness analyses

CRD summary
The review concluded that infliximab and adalimumab showed consistent superiority to placebo in the induction and maintenance of clinical remission and reduction in rates of surgery and hospitalisation in refractory Crohn's disease. The authors' conclusions reflect the evidence, but this does not answer the review question; no head-to-head trials or comparisons with conventional therapy were found.

Authors' objectives
To compare the effectiveness of anti-TNF-α drugs with each other, and with conventional therapy, in patients with Crohn's disease or ulcerative colitis with an inadequate response to conventional therapy.

Searching
PubMed, EMBASE, The Cochrane Library and BIOSIS Previews were searched from 1995 to 2008 without language restrictions; search terms were reported. Bibliographies of key papers were also searched. Relevant websites and trial registers were searched to identify unpublished studies.

Study selection
Studies (randomised, non-randomised, before-after, or observational) of the efficacy and adverse effects of infliximab, adalimumab, or etanercept in adults (≥18 years) with luminal or fistulising Crohn's disease or ulcerative colitis, who were not responding to conventional treatment were eligible. Placebo, infliximab, adalimumab, etanercept, conventional therapy (defined in report) and surgical treatment were the eligible comparators. Outcomes of interest included clinical response, hospitalisations, surgery, clinical remission, death, need for increased dose, and adverse events.

Nearly all trials were placebo-controlled and most were of infliximab or adalimumab; some trials used single doses and some used multiple doses. Most trials allowed the use of a number of other medications. Most trials studied patients with Crohn's disease. All treatment was given for the purpose of induction and/or maintenance of remission. Most study sites were located in North America or Europe. Observational study characteristics were also tabulated in the report.

Two reviewers independently selected studies for inclusion, with disagreements resolved by discussion.

Assessment of study quality
Study quality was assessed using the Jadad (randomised trials) and Newcastle-Ottawa (observational studies) scales. Randomisation procedure details were also provided.

One reviewer assessed study quality, with the results being checked by a second reviewer.

Data extraction
One reviewer extracted data, to calculate risk ratios (RR) and 95% confidence intervals (CIs), which were then checked by a second reviewer. Disagreements were resolved by discussion.

Methods of synthesis
Meta-analyses were performed to calculate pooled risk ratios and 95% confidence intervals, using a fixed-effect model. Heterogeneity was assessed using $I^2$. A narrative synthesis was performed when meta-analysis was not possible.

Results of the review
Twenty randomised controlled trials (including around 3,500 patients, range 11 to 499) and 17 observational and single-arm trials (including around 1,600 patients, range 10 to 614) were included. Jadad scores ranged from 1 to 5; fifteen trials scored 4 or 5 (out of 5). Follow-up periods ranged between two and 56 weeks.
**Crohn's Disease:**

Infliximab showed superiority to placebo for maintenance response (5mg/kg: RR 2.75, 95% CI 1.72 to 4.40, I²=21%, two trials; 10mg/kg: RR 2.59, 95% CI 1.85 to 3.62, two trials, I²=41%) and clinical remission after maintenance therapy (10mg/kg: RR 2.80, 95% CI 1.83 to 4.30, I²=0%, two trials). There was no evidence of a clinically important effect with etanercept (one trial) for response or remission at eight weeks. The results from three studies indicated that earlier timing of treatment initiation was better for improving the rate of remission.

Adalimumab showed superiority to placebo for response to induction therapy (160/80mg: RR 1.60, 95% CI 1.29 to 1.98, I²=0%, two trials) and remission (160/80mg: RR 2.94, 95% CI 1.86 to 4.66, I²=0%, two trials).

No head-to-head trials that compared the effectiveness of infliximab with adalimumab or with etanercept were found nor were studies that directly compared infliximab, adalimumab or etanercept with conventional therapy.

**Ulcerative colitis:**

Infliximab led to higher remission rates compared with placebo (5mg/kg: RR 2.93, 95% CI 2.06 to 4.15, I²=66%, four trials). Significant results were also seen for clinical response using 5 and 10mg/kg (RRs between 1.97 and 2.12) and remission using 5 and 10mg/kg (RRs between 2.23 and 2.93).

No trials of adalimumab or etanercept were found.

Further results were reported.

**Cost information**

**Crohn’s Disease:** The incremental cost-utility ratio (ICUR) of adalimumab therapy compared with usual care was estimated to be $193,305 per quality-adjusted life-year (QALY). The ICUR of infliximab therapy compared with adalimumab therapy was estimated to be $451,165. The cost per QALY of infliximab therapy compared with usual care was estimated to be $222,955. The adalimumab strategy had the highest probability of being cost-effective at willingness-to-pay values greater than or equal to $208,000.

**Ulcerative colitis:** The cost-utility of a strategy that consisted of first-line 5 mg infliximab treatment followed by second-line adalimumab treatment was $358,088 per QALY compared with usual care. The same strategy based on an assumption of 10 mg/kg led to less favourable cost-utility results. Compared to a strategy involving 5mg/kg of infliximab and adalimumab, usual care was likely to be the most cost-effective strategy unless society was willing to pay more than $370,000 per QALY.

**Authors' conclusions**

Infliximab and adalimumab have shown a consistent superiority to placebo in the induction and maintenance of clinical remission and in reducing the rates of surgery and hospitalisation in refractory Crohn's disease. Infliximab also leads to higher response and remission rates in patients with ulcerative colitis, compared with placebo.

**CRD commentary**

The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify all relevant studies in any language were undertaken. Suitable methods were employed to reduce the risks of reviewer error and bias throughout the review.

Most RCTs appeared likely to be of reliable quality, but the reporting of just overall Jadad scores precludes the reader from making an evaluation of trial reliability. Quality results for the observational studies were not reported. Study details were provided and meta-analyses were used to synthesise some data. It was unclear whether there was double counting of participants. Studies which could not be pooled by meta-analyses were presented narratively, although this was largely based on presenting individual study results without then describing an overall evaluation. Sources of statistical heterogeneity were not explored. The authors noted that the reporting was limited for some studies, or there was a lack of usable data on clinical outcomes.

The authors' conclusions reflected the evidence presented. However, the evidence does not answer the review question.
since no head-to-head trials nor comparisons with conventional therapy were found.

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

**Practice:** The authors stated that given the limited number of long-term trials on the effectiveness and safety and cost-effectiveness of the studied drugs, it was appropriate to weigh the potential risks and benefits when deciding whether patients with inflammatory bowel disease should use the drugs. The authors added that the results may not be generalisable to paediatrics or newly diagnosed patients.

**Research:** The authors made a number of recommendations including a need for more head-to-head trials with long-term follow-up, in patients with inflammatory bowel disease.

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.