Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials

Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF

CRD summary
This review assessed the safety and efficacy of tumour necrosis factor antagonists for Crohn's disease. The authors concluded that infliximab, adalimumab and certolizumab were effective and safe in luminal Crohn's disease. This was a generally well-conducted review and the authors' conclusions appear to be supported by the data.

Authors' objectives
To assess the safety and efficacy of tumour necrosis factor (TNF) antagonists for Crohn's disease.

Searching
MEDLINE (PubMed) (1966 to December 2006), The Cochrane Library (Issue 4, 2006) and EMBASE (1980 to December 2006) were searched without language restrictions. Search terms were reported. Additional articles were identified through handsearches of two relevant journals between 2004 and 2006, and references of reviews, meta-analyses and RCTs. Authors of identified studies and pharmaceutical companies were contacted to retrieve unpublished studies.

Study selection
Placebo controlled trials of adults with Crohn's disease that evaluated an anti-TNF agent (infliximab, certolizumab pegol, adalimumab, etanercept, onccept or CDP571) were eligible for inclusion. Clinical remission had to be defined and remission in patients who received placebo described. The outcomes eligible for inclusion were clinical remission at week four, weeks 20 to 30 and weeks 48 to 52 and steroid free remission at weeks 48 to 52 (where available) for luminal Crohn's disease. For fistulising Crohn's disease the endpoints evaluated were closure of at least 50% of draining fistulas and complete closure of fistulas at two or more consecutive visits. The studies included in the review used various doses of anti-TNF agent and ranged from four to 52 weeks in duration. Deaths, malignancies and serious infections (defined as needing antimicrobial therapy or hospitalisation) were investigated in the safety review.

The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed using the Jadad criteria (aspects such as randomisation, blinding, allocation concealment and withdrawals and dropouts) to obtain a quality score out of 5. This was performed independently by two reviewers. Disagreements were resolved by consensus.

Data extraction
Difference in effect (treatment minus placebo) and corresponding 95% confidence intervals (CIs) for each study was calculated for each outcome using an intention-to-treat analysis. The number of patients with clinical remission was extrapolated when the clinical remission rate was reported as a percentage. Authors and pharmaceutical companies were contacted for missing data or to obtain exact data. Two authors extracted data using a standardised form. Discrepancies were resolved through discussion or consultation with two other reviewers.

Methods of synthesis
For efficacy, mean differences for continuous outcomes and risk differences for dichotomous outcomes were pooled to calculate mean difference (MD) and 95% CIs. Short-term induction trials, long-term maintenance trials and long-term induction trials were pooled separately. Subgroup analysis by anti-TNF agent was performed for each efficacy endpoint. For safety analysis all RCTs were analysed, then subgroup analysis according to study design was performed. In dose-ranging studies anti-TNF groups were pooled. DerSimonian and Laird random-effects meta-analyses were performed. Weighting was inversely proportional to variance in observed effects. Statistical heterogeneity was assessed using Cochran Q test.
Results of the review

Fourteen RCTs were included in the review of efficacy (n=3,955). Twenty-one RCTs were included in the review of safety (n=5356). All 21 trials had a Jadad score greater than 3.

**Luminal Crohn’s disease:** Anti-TNF therapy was associated with greater rates of induction of remission at week four compared with placebo (MD 11%, 95% CI 6% to 16%, p<0.001; 10 RCTs). In open label induction trials anti-TNF therapy was also associated with greater maintenance of remission compared with placebo (four RCTs) at weeks 20 to 30 (MD 23%, 95% CI 18% to 28%, p<0.001) and weeks 48 to 52 (MD 23%, 95% CI 18% to 29%, p<0.001). In both long- and short-term trials in which patients were randomised before induction (three RCTs) anti-TNF therapy was associated with more effective maintenance of remission (MD 8%, 95% CI 3% to 12%, p<0.001). Anti-TNF therapy was also significantly more effective in maintaining steroid-free remission at weeks 48 to 52 than placebo (MD 15%, 95% CI 5% to 25%, p<0.0046; two RCTs).

**Fistulising Crohn’s disease:** No significant differences were detected between anti-TNF agent and placebo for at least 50% or complete fistula closure in the short-term trials, or in short- and long-term trials overall. In the maintenance trials (three RCTs) anti-TNF therapy was significantly more effective than placebo for complete fistula closure (MD 16%, 95% CI 8% to 25%, p<0.001).

There was no evidence of statistical heterogeneity or publication bias in these analyses.

There was no evidence of differences in the frequency of deaths, malignancies and serious infections between anti-TNF therapy and placebo.

**Authors’ conclusions**

Infliximab, adalimumab and certolizumab were effective and safe in luminal Crohn’s disease.

**CRD commentary**

The review question was clear and supported by inclusion criteria for participants, intervention, outcomes and study design. Relevant databases were searched in all languages, which reduced the possibility of language bias. Authors were contacted for unpublished studies, which reduced the risk of publication bias. Assessment of validity of the primary studies and data extraction were performed by two reviewers, which reduced the risk of reviewer error and bias; the authors did not report whether similar steps were taken during study selection. Statistical heterogeneity was assessed and sensitivity analyses performed; pooling appeared to be appropriate from this standpoint. Few participant details were reported, so their clinical similarity at baseline could not be assessed. This was a generally well-conducted review and the authors’ conclusions appear to be supported by the data.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that studies with longer duration of follow-up and larger sample sizes were required to better assess the safety of TNF antagonists in Crohn’s disease. Additional investigations were required to assess the efficacy of anti-TNF agents other than infliximab for treating fistulising Crohn’s disease.

**Funding**

Not stated. One author had received research support from Centocor, Abbott Laboratories, UCB Pharma, Immunex and Serono International.

**Bibliographic details**

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.