Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis


CRD summary
The review found that tumour necrosis factor blockers were effective for rheumatoid arthritis and were of comparable safety and efficacy to methotrexate. No individual tumour necrosis factor blocker was more effective than others, but etanercept may be the safest. Due to limitations in the review, including potential publication bias and use of indirect comparisons, these conclusions may require cautious interpretation.

Authors' objectives
To evaluate and compare the safety and efficacy of all currently-available tumour necrosis factor blockers (with or without concomitant methotrexate) for treating rheumatoid arthritis.

Searching
MEDLINE (to February 2010), The Cochrane Library, SCOPUS, Web of Knowledge, ClinicalTrials.gov and several other databases were searched for studies in any language for which the full text could be retrieved. Search terms were reported.

Study selection
Eligible studies were double-blinded randomised controlled trials (RCTs) of tumour necrosis factor blockers (infliximab, etanercept, adalimumab, certolizumab and golimumab) for treating rheumatoid arthritis. Blockers were given at recommended doses and compared to placebo, or to methotrexate plus placebo, given by the same route. Participants had to be aged over 16 years and diagnosed using American College of Rheumatology (ACR) 1987 criteria. Studies had to report ACR improvement (20%, 50% or 70%). The primary outcome efficacy outcome of the review was ACR 50% improvement at six months. All studies were required to report both efficacy and safety.

Participants in the included studies had from 11 to 25 swollen joints and from 14 to 37 tender joints, their mean time since diagnosis ranged from 0.6 to 13 years and most had a prior history of methotrexate use. Most studies excluded participants who had used tumour necrosis factor blocker before. All the studies evaluated a single type of tumour necrosis factor blocker and some had multiple intervention arms receiving different doses. For the primary outcome, all doses of tumour necrosis factor blocker were compared with any control, which in most studies was placebo with or without methotrexate in both arms. The review reported a wide range of outcomes, including combined drugs versus monotherapy and comparisons of high versus normal doses. Study duration ranged from 12 weeks to two years.

Two reviewers independently selected the studies, with disagreements resolved by a third reviewer.

Assessment of study quality
The Cochrane risk of bias tool was used to assess sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting and other risk of bias.

Two reviewers independently assessed study quality.

Data extraction
Risk ratios (RRs) and 95% confidence intervals (CIs) were extracted or calculated for all outcomes, using intention-to-treat principles. For some analyses outcomes at differing time-points were combined.

Two reviewers independently extracted the data.

Methods of synthesis
Studies were combined using a random-effects model to calculate pooled risk ratios and 95% confidence intervals. Findings were subgrouped by type of tumour necrosis factor blocker. Heterogeneity was assessed using X² and I².
Subgroup and sensitivity analyses were used to assess the impact of study quality, drug type, disease duration and prior use of methotrexate.

**Results of the review**

Twenty-six RCTs were included (9,862 patients). The number of RCTs rated as free of bias was: eight for sequence generation; 10 for allocation concealment; 21 for completeness of outcome data; 19 for other potential bias and all 26 for blinding and selective reporting.

When all tumour necrosis factor blockers with or without methotrexate were compared with controls (placebo or placebo plus methotrexate), there was a significantly higher rate of 50% improvement at six months in the tumour necrosis factor blocker group (RR 4.07, 95% CI 2.70 to 6.13; 14 RCTs; $I^2=84\%$). In subgroup analysis for this outcome, etanercept (two RCTs), adalimumab (five RCTs), and certolizumab (three RCTs) showed significant benefit, while infliximab (two RCTs) and golimumab (two RCTs) did not differ significantly from controls. Tumour necrosis factor blockers plus methotrexate were associated with a significantly higher rate of 20%, 50% or 70% improvement than methotrexate alone at all time-points (seven to 14 studies). There was no significant difference for any efficacy outcomes between tumour necrosis factor blocker monotherapy and methotrexate.

When all tumour necrosis factor blockers were compared with all controls, there was no significant difference in the risk of discontinuation due to adverse effects (RR 1.26, 95% CI 0.93 to 1.71; 25 RCTs; $I^2=45\%$). In subgroup analysis for this outcome, infliximab (four RCTs), adalimumab (eight RCTs), and certolizumab (three RCTs) were associated with significantly higher risk than controls, while etanercept was associated with a significantly lower risk. Findings for golimumab were not significant.

Sensitivity analyses did not substantially affect the main findings. Other findings were reported in the review.

**Authors’ conclusions**

Tumour necrosis factor blockers were effective for rheumatoid arthritis and were of comparable safety and efficacy to methotrexate. No individual tumour necrosis factor blocker was more effective than others, but etanercept may be the safest.

**CRD commentary**

The review question and inclusion criteria were clear in most respects but it was not clearly stated that the main comparison included tumour necrosis factor-blockers given with methotrexate. Relevant sources were searched for studies in any language. However, the exclusion of 12 studies unavailable in full-text meant that the review was at risk of publication bias. The potential for this bias was not addressed.

Steps were taken to minimise the risk of reviewer bias and error in the processes of study selection, data extraction and quality assessment and basic details were reported about the characteristics of included studies. Relevant methods were used to combine the studies and to assess and explore heterogeneity. The conclusions regarding differences between individual tumour necrosis factor blockers were of questionable validity because they were apparently based on indirect comparisons, without clear description of the statistical methods used. As the authors noted, there was some clinical heterogeneity between the studies, length of exposure was not taken into account in safety analyses and efficacy results were not reported at all time points. Due to limitations in the review, including potential publication bias and use of indirect comparisons, the authors’ conclusions require cautious interpretation.

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

**Practice:** The authors stated that etanercept may have been the safest choice of tumour necrosis factor blocker. Increasing the dose appeared to be safe but may not have improved efficacy.

**Research:** The authors stated that more post-marketing information was needed about certolizumab and golimumab and that the efficacy and safety of all biological treatments for rheumatoid arthritis should be studied in a large systematic review and meta-analysis.

**Funding**

ORTON Orthopaedic Hospital (ORTON Foundation); the National PhD Graduate School in Musculoskeletal Diseases
and Biomaterials.

**Bibliographic details**

**DOI**
10.1371/journal.pone.0030275

**Original Paper URL**
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0030275

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Humans; Tumor Necrosis Factor-alpha /antagonists and inhibitors; Arthritis, Rheumatoid /drug therapy

**AccessionNumber**
12012007482

**Date bibliographic record published**
24/03/2012

**Date abstract record published**
15/08/2012

**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.