Indirect comparison of the effects of anti-TNF biological agents in patients with ankylosing spondylitis by means of a mixed treatment comparison performed on efficacy data from published randomised, controlled trials

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CRD summary
The authors concluded that there were no statistically significant differences between infliximab, adalimumab, and etanercept. Compared with placebo, infliximab was expected to provide the highest rate of positive response in patients with chronic arthritis of the spinal joints (ankylosing spondylitis). The paucity of evidence and poor review methods suggest that the findings are insufficient, so should not be considered reliable.

Authors' objectives
To indirectly compare the effects of anti-tumour necrosis factor biological agents in patients with chronic arthritis of the spinal joints (ankylosing spondylitis).

Searching
MEDLINE and EMBASE were searched; search terms were reported. No other search details were reported.

Study selection
Eligible for inclusion were double blind placebo-controlled randomised controlled trials (RCTs) with at least six month follow-up. Eligible trials had to assess the efficacy of anti-tumour necrosis factor inhibitors (etanercept, infliximab/remicade and adalimumab) in the treatment of ankylosing spondylitis. The primary outcome was Assessment in Ankylosing Spondylitis Response Criteria for a 20% clinical improvement (as defined in the review); the included domains were patient’s global assessment of disease activity, inflammation assessed as morning stiffness, function, and pain.

Included trials were of patients with similar mean age (40 to 43.4 years) and gender (73.8% to 87.2% were men). Trials had a similar percentage of patients with positive genetic marker HLA-B27 (78.4% to 88.5%). It was unclear whether mean Bath Ankylosing Spondylitis Disease Activity Index scores were similar across trials. Duration of disease ranged from 7.7 to 13.2 years. The proportion of patients showing response to response criteria ranged from 19% to 61.2%.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
The authors did not state whether they assessed study quality.

Data extraction
The number of patients in the intervention and placebo groups who were considered to respond to treatment or not (according to Ankylosing Spondylitis Response Criteria) was extracted at baseline and at six months. Odds ratios (ORs) and 95% credible intervals (CrIs) were calculated. Missing outcome data were assumed to be imputed using last observation carried forward.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
A fixed-effect Bayesian mixed-treatment model was used to pool odds ratios and 95% credible intervals to directly compare interventions versus placebo and indirectly compare the different tumour necrosis factor biological agents. The probability of the most effective treatment was also assessed and reported for each biological agent.

Results of the review
Three RCTs were included in the review. The number of included patients was unclear.
All three biological agents were statistically significantly more effective in gaining a positive response in Ankylosing Spondylitis Response Criteria than placebo; infliximab (OR 6.88, 95% CI 3.66 to 13.46), adalimumab (OR 4.48, 95% CI 2.63 to 9.16), and etanercept (OR 4.95, 95% CI 2.71 to 8.16).

Indirect comparison between the three biological agents showed no statistically significant differences in effectiveness. Inflliximab was reported to have 72% probability of being the best treatment in ankylosing spondylitis. Adalimumab showed a probability of 13% and etanercept showed a probability of 15%.

**Authors' conclusions**
No statistically significant differences were reported between infliximab, adalimumab, and etanercept. Compared with placebo, infliximab was expected to provide the highest rate of response in Ankylosing Spondylitis Response Criteria for ankylosing spondylitis.

**CRD commentary**
The review question and inclusion criteria were clear. The literature search was limited and included only two databases, so potentially relevant studies may have been missed. The authors did not state whether each stage of the review was performed in duplicate, which meant that reviewer error and bias could not be ruled out.

The quality of included trials was not assessed, so the reliability of the result was unclear. The authors acknowledged the small number of trials included, with one trial each comparing a different biological agent. Given the small number of trials included and the heterogeneity among trials, use of a fixed-effect Bayesian mixed-treatment approach may not have been appropriate.

The paucity of evidence and the poor review methods suggest that the findings are insufficient, so should not be considered reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that the results may be relevant for clinical decision-making, contributing to improving the rate of positive response to Ankylosing Spondylitis Response Criteria in patients with ankylosing spondylitis.

**Research:** The authors did not state any implications for further research.

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