Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and meta-analysis of randomised placebo-controlled trials
Fouque-Aubert A, Jette-Paulin L, Combescure C, Basch A, Tebib J, Gossec L

CRD summary
This review concluded that the risk of serious infection was very low in patients with ankylosing spondylitis not exposed to immunosuppressive drugs and that this risk was not increased by treatment with tumour necrosis factor blockers; further research is needed. The authors' conclusions reflect the limited data available and appear likely to be reliable.

Authors' objectives
To assess rates and types of serious infections in patients with ankylosing spondylitis both exposed to and not exposed to tumour necrosis factor blockers.

Searching
PubMed, EMBASE (from 1995 to 2008) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies published in French or English; search terms were reported. Manufacturers of three tumour necrosis factor blockers were contacted for additional data.

Study selection
Eligible studies were randomised controlled trials (RCTs) of adults with ankylosing spondylitis (definition reported) treated with non-steroidal anti-inflammatory drugs or tumour necrosis factor blockers. Eligible trials had to monitor and report infections events.

Included trial durations ranged from 12 to 30 weeks. The mean age of participants was 41 years (standard deviation three years); 74% were men. Treatments included non-steroidal anti-inflammatory drugs, infliximab, etanercept and adalimumab; some regimen details were reported. Control groups were mostly placebo.

One reviewer selected articles for inclusion in the review.

Assessment of study quality
The Jadad scale was used to assess the methodological quality of included trials.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
The reviewers extracted data required to calculate serious infections, which was defined as the percentage of patients with at least one infection; confidence intervals (CIs) were estimated using the Clopper-Pearson method. Trial authors were contacted if missing data was required.

Two reviewers independently extracted data required for the review using a standardised form; disagreements between reviewers were resolved by consensus with a third reviewer.

Methods of synthesis
Pooled risk differences (RDs) with 95% confidence intervals were calculated using a fixed-effect model. Heterogeneity was assessed using the Cochran test. Numbers needed to treat (NNT) were also calculated.

Sensitivity analyses were performed by calculating pooled odds ratios (ORs) and risk ratios (RRs) using the Mantel-Haenszel method with two types of continuity correction, by assessing the impact of individual trials on the pooled results, and by stratifying trials by duration (over 16 weeks versus 16 weeks or less).
Publication bias was assessed using funnel plots.

**Results of the review**

Fourteen trials (n=3,445 patients; range 42 to 611) were included in the review, of which 12 were placebo controlled. The mean Jadad score was 3.6 out of 5 points. Duration of follow-up ranged from six weeks to 58 weeks (mean 20 weeks; standard deviation 14 weeks).

Based on nine trials, the authors estimated that there was no statistically significant risk difference for serious infections between placebo and tumour necrosis factor blockers (two events out of 2,202 patients not exposed to tumour necrosis factor blockers; 14 events out of 1,243 patients exposed to tumour necrosis factor blockers). No statistically significant heterogeneity was detected ($I^2=0\%$).

The risk of infection in groups not using tumour necrosis factor blockers ranged from 0 to 0.9%. Only two trials reported serious infections in the placebo groups. From one of these trials, the risk was estimated as 0.4 serious infections per 100 patient-years; in the other trial, a serious infection was reported in the placebo group, but not in the treatment group.

The risk of serious infections with tumour necrosis factor blockers ranged from 0 to 2.9%; the risk was estimated as 2.2 serious infections per 100 patient-years.

Sensitivity analyses produced similar results to the main results.

**Authors’ conclusions**

The risk of serious infection was very low in patients with ankylosing spondylitis included in trials and not exposed to immunosuppressive drugs, and was not increased by treatment with tumour necrosis factor blockers. Further adequately powered studies are needed.

**CRD commentary**

The study selection was defined in terms of population, study design, intervention and outcome. More than one database was searched; search terms were reported, which improved review transparency. The search was limited to published studies and two languages, so some relevant studies may have been missed. Only one author performed the study selection, and the number of reviewers who performed the quality assessment was not reported, so the risk of reviewer error and bias was increased.

A standard and appropriate instrument for RCTs was used to assess trial quality. Average trial quality was assessed was moderate, but results for individual trials were not reported. Basic primary trial details were reported. Data extraction and synthesis appeared appropriate. The reporting of the results was adequate.

The authors’ conclusions reflect the limited data available and appear likely to be reliable.

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

**Practice:** The authors stated that physicians should be aware of infections when prescribing tumour necrosis factor blockers.

**Research:** The authors stated that longitudinal prospective studies are required to confirm the results of the review.

**Funding**

Not stated.

**Bibliographic details**

Fouque-Aubert A, Jette-Paulin L, Combescure C, Basch A, Tebib J, Gossec L. Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and meta-analysis of randomised placebo...

PubMedID
19640854

DOI
10.1136/ard.2008.098822

Original Paper URL
http://ard.bmj.com/content/69/10/1756.abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Antirheumatic Agents /adverse effects; Humans; Opportunistic Infections /complications /epidemiology; Randomized Controlled Trials as Topic; Risk Assessment /methods; Spondylitis, Ankylosing /complications /drug therapy /epidemiology; Tumor Necrosis Factor-alpha /antagonists & inhibitors

AccessionNumber
12010007169

Date bibliographic record published
09/03/2011

Date abstract record published
06/07/2011

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.