The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
The review concluded that there was a small increased risk of overall infections with short-term use of tumour necrosis factor antagonists for psoriasis and no difference in serious infections or malignancies. The review was generally well conducted and the authors’ conclusions seem reliable. The authors noted that results were limited by the rarity of events and short follow-up.

Authors’ objectives
To examine the risks of infection and malignancy with use of tumour necrosis factor (TNF) antagonists in patients with psoriatic disease.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were searched from inception to 30 July 2009 for articles published in English. Search terms were reported. Unpublished trials were searched for in Clinical Study Results Database and by contacting industry sponsors and authors of published trials.

Study selection
Randomised controlled trials (RCTs) of etanercept, adalimumab, infliximab, golimumab and certolizumab (as monotherapy) were eligible for inclusion if they compared these with placebo for the treatment of adult patients with moderate to severe plaque psoriasis and/or psoriatic arthritis. Trials had to have a follow-up of at least 12 weeks.

The included trials studied 25mg to 50mg etanercept, 40mg to 80mg adalimumab, 3mg to 5mg/kg infliximab, 50mg to 100mg golimumab and 200mg to 400mg certolizumab in patients with moderate to severe plaque psoriasis or psoriatic arthritis. All psoriatic arthritis trials allowed patients to use disease modifying anti-rheumatic drugs (DMARDs).

The authors did not state how many reviewers performed study selection.

Assessment of study quality
Validity assessment was undertaken using the Jadad criteria of randomisation, blinding and withdrawals and drop-outs to give a maximum score out of five. Trials that scored less than 3 on the Jadad scale were excluded.

Two reviewers independently performed validity assessment.

Data extraction
Data were extracted on infections and malignancies on an intention-to-treat basis and were used to calculate odds ratios and their 95% confidence intervals.

Two reviewers independently performed data extraction.

Methods of synthesis
A Mantel-Haenszel fixed-effect meta-analysis was used to calculate pooled odds ratios and their 95% confidence intervals. Incidence rate ratios were calculated. The number needed to harm (NNH) was estimated. Statistical heterogeneity was assessed using $I^2$. Publication bias was assessed using funnel plots and Egger’s test.

Subgroup analyses were performed by indication and drug. Sensitivity analysis used the random-effects model, excluded individual trials and used different continuity corrections.

Results of the review
Twenty RCTs (6,810 patients) were included in the review, comprising seven trials of etanercept, six trials of
adalimumab, five trials of infliximab, one trial of golimumab and one trial of certolizumab. Study sample sizes ranged from 60 to 1,212 patients.

Infections (20 trials): Compared with placebo, TNF antagonists were associated with a statistically significant greater risk of any infection (OR 1.18, 95% CI 1.05 to 1.33; I²=21.6%, NNH=29) and a significantly greater risk of non-serious infections (OR 1.20, 95% CI 1.07 to 1.35). Subgroup analysis indicated statistically significantly more infections with TNF antagonists in patients with psoriatic arthritis (OR 1.22, 95% CI 1.06 to 1.40), but no statistically significant difference in patients with plaque psoriasis (OR 1.09, 95% CI 0.87 to 1.37). Subgroup analysis by drug indicated that results were generally non-significant. There was no statistically significant difference in serious infections (OR 0.70, 95% CI 0.40 to 1.21). Results for incidence rate ratios were presented in the review.

Malignancies (10 trials): Compared with placebo, TNF antagonists were not associated with a statistically significant difference in malignancies (OR 1.48, 95% CI 0.71 to 3.09; I²=0%). Subgroup analysis by drug and indication were not significant. Results for incidence rate ratios were presented in the review.

Sensitivity analysis using the random-effects model did not alter the results. There was no evidence of publication bias.

Authors’ conclusions
There was a small increased risk of overall infections with short-term use of TNF antagonists for psoriasis and no difference in serious infections or malignancies.

CRD commentary
Inclusion criteria for the review were clearly defined. Several relevant data sources were searched. Only English language trials were included, so there was potential for language bias. Publication bias was assessed and not detected. Attempts were made to reduce reviewer error and bias during data extraction and quality assessment; the authors did not state whether the same methods were used for study selection.

Trial quality assessment was undertaken using a simple checklist; the authors did not report the results of this analysis, but all included trials scored at least 3. Trials were combined using appropriate statistical methods. Statistical heterogeneity was assessed. There was evidence of clinical heterogeneity, but this did not translate into statistical heterogeneity across trials.

This was a well-conducted review and the authors’ conclusions seem reliable. The authors noted that the results of the review were limited by the rarity of events and short duration of follow-up.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that larger long-term studies with appropriate control groups were needed to assess the risk of infections and malignancies.

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