Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials


**CRD summary**
This review concluded that while there was no statistically significant difference in malignancy risk between patients with rheumatoid arthritis treated with etanercept and those treated with control interventions, a clinically meaningful association could not be excluded. This conclusion reflected the results of the review and is likely to be reliable.

**Authors' objectives**
To assess the risk of malignancy associated with etanercept therapy for rheumatoid arthritis.

**Searching**
EMBASE, MEDLINE, The Cochrane Library and Web of Science were searched from inception to December 2006. Search terms were reported. The manufacturers of etanercept were contacted to identify additional trials, including unpublished studies.

**Study selection**
Randomised controlled trials (RCTs) with a duration of at least 12 weeks and that assessed etanercept in patients with a diagnosis of rheumatoid arthritis according to American College of Rheumatology criteria were eligible for inclusion. The primary review outcome was first incidence of cancer. Carcinoma in situ were excluded from the analyses.

Included trials had various inclusion criteria; most specified that patients must have had an inadequate response to methotrexate, sulphasalazine or disease-modifying drugs as a class. Doses of etanercept used ranged from 10mg per week to 50mg per week or from 0.50mg/m² per week to 16.0mg/m² per week. Control groups received placebo, placebo plus methotrexate or placebo plus sulfasalazine. Trial duration ranged from 12 to 180 weeks.

Two reviewers independently selected the studies for the review; the process included obtaining trial protocols from sponsors.

**Assessment of study quality**
Two reviewers independently assessed studies for validity using the criteria of randomisation, allocation concealment, blinding, use of intention-to-treat analysis, attrition and completeness of follow-up, and outcome assessment. Original study protocols as well as published reports were used in the assessment. Disagreements were resolved through consensus.

**Data extraction**
Three independent assessors who were blinded to treatment allocation adjudicated potential malignancies based on adverse event case narratives from the included studies. After completion of this process complete individual patient data was obtained from the sponsors for each patient who participated in an included study, including demographics, treatment information including duration of therapy and concomitant therapies, date of last follow-up and reasons for withdrawal. All patients who received at least one dose of the assigned treatment were included in the review. The risk window for malignancies was defined as the date of the first dose up to the date of last follow-up. Hazard ratios (HR) and odds ratios (OR) with 95% confidence intervals (CI) were calculated for each trial.

**Methods of synthesis**
A survival analysis of time-to-first-event was conducted using a fixed-effect Cox's proportional hazards model stratified by trial. A sensitivity analysis using a random effects analysis was conducted. A random effects meta-analysis of study-level hazard ratios was carried out. Sensitivity analyses were conducted to determine the effect of excluding malignancies diagnosed in the six weeks that followed trial entry and of omitting all non-melanoma skin cancers from the analysis. Separate analyses were conducted for the following time periods: less than six months; six to 12 months;
and more than 24 months. A fixed-effect stratified analysis was used to investigate the impact of etanercept dose (less than 50mg/week versus 50mg/week or more). As a secondary analysis the odds ratios from each study were pooled using a fixed-effect Mantel-Haenszel model with continuity correction; this was repeated using a random-effects DerSimonian and Laird model. Heterogeneity for these aggregate analyses was assessed using the I² statistic. A power calculation was used to assess the ability of the meta-analysis to detect a two-fold difference in risk of malignancy.

Results of the review

Nine RCTs (n=3,316) were included in the review (plus 80 individuals excluded from analysis). Data for analysis comprised 2,244 patients who received etanercept (2,484 person-years of follow-up) and 1,072 who received control therapies (1,051 person-years of follow-up).

Twenty six patients treated with etanercept developed malignancies (incidence rate of 10.47 per 1,000 person-years). Seven patients given control treatments developed malignancies (incidence rate of 6.66 per 1,000 person-years). The proportional hazards model found no statistically significant difference between the patient groups (HR 1.84, 95% CI 0.79 to 4.28). The aggregate analysis also did not show a statistically significant effect of treatment (OR 1.93, 95% CI 0.85 to 4.38). There was no evidence of statistically significant heterogeneity between studies (I²=0.0%); use of random effects models did not materially affect the results of the analysis.

None of the other sensitivity or stratified analyses revealed significant effects of the variables investigated. A power calculation showed that to detect a doubling of risk with 80% power and a 5% significance level a minimum of 9,305 patients would be required; the probability of the present meta-analysis detecting such a difference was 39%.

Authors’ conclusions

The point estimate for malignancy risk was higher in etanercept patients than in control patients, although this result was not statistically significant. Given the wide confidence interval, a clinically meaningful association could not be excluded.

CRD commentary

The review question and inclusion criteria were clear. The authors searched several relevant databases and made attempts to identify unpublished studies, thus reducing the risk of publication bias and omission of relevant studies. Methods to reduce reviewer error and bias were reported at all stages of the review process. The authors assessed validity using appropriate criteria for a review of aggregate data, but did not report double checking of individual patient data. The analysis used was appropriate and possible sources of heterogeneity at both study and patient level were explored. The authors’ conclusions reflected the results of the review and are likely to be reliable.

Implications of the review for practice and research

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

Research: The authors stated that a large comprehensive meta-analysis of all three anti-tumour necrosis factor treatments for a range of conditions was underway and would have greater statistical power to detect increases in risk associated with these treatments.

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