The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events

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CRD summary
The review evaluated anti-tumour necrosis factor treatment for rheumatoid arthritis and found that recommended doses did not increase the risk of death, serious adverse events, serious infection or malignancy. High dose anti-TNF therapy was associated with a twofold increase in the risk of serious infections. The review was well-conducted and the authors’ conclusions are likely to be reliable.

Authors' objectives
To evaluate the safety of anti-tumour necrosis factor treatment for rheumatoid arthritis.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched to 31 December 2007 for publications in English. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that evaluated anti-tumour necrosis factor alpha (anti-TNF) compared to a control group of a non-biological disease-modifying antirheumatic drug (DMARD) or placebo were eligible for inclusion if the study was for at least 10 weeks, included at least 30 patients with rheumatoid arthritis and attracted a Jadad score of 2 or greater. Treatment arms of combination biological therapies were excluded (more than one anti-TNF drug). The anti-TNF drugs used in the included studies were adalimumab, etanercept and infliximab. Details of the dosage and frequency of the drugs are provided in the review. Dose categories in the intervention groups were divided into low, recommended or high; low-dose treatment arms were excluded. There were combination treatment arms in many of the included RCTs; these additionally used methotrexate or (for a small number of studies) combination therapy with sulfasalazine or a DMARD. Most of the control groups in the included studies used methotrexate or placebo; a few studies used sulfasalazine or a DMARD. The mean disease duration in patients in the included studies ranged from 0.7 to 13 years. Overall, the anti-TNF patients had longer follow-up than the controls: 307 days versus 285 days (p=0.001). No details were provided of the age or sex of the included patients. Eligible outcomes were death, serious adverse events, serious infections and malignancy.

Two independent researchers were involved in the literature search and study selection; disagreements were resolved by consensus.

Assessment of study quality
Methodological quality was assessed using the method developed by Jadad and Schulz. Studies were excluded if their Jadad score was lower than 2 and if randomisation did not occur. No further quality details were provided.

The authors stated neither how many reviewers performed the validity assessment nor how the Jadad scores were assessed.

Data extraction
The number of events for each outcome was extracted in order to calculate rate ratio (RR), odds ratio (OR) and 95% confidence intervals (95% CI). Malignancies were allocated into three classes: lymphomas; non-melanoma skin cancers; and the composite endpoint of non-cutaneous cancers and melanomas. If subjects presented with two types of cancer, these were allocated as a single event in the following order of priority: lymphoma; non-cutaneous cancer/melanoma; and non-melanoma skin cancer. If the number of events was reported instead of the number of subjects who experienced an event, an assumption of one event per subject was made.
Two authors performed the data extraction. Any disagreements were resolved by consensus. The authors made efforts to obtain missing information.

Methods of synthesis
Two types of meta-analysis were performed for events that occurred during the controlled portion of the trials: pooled OR and 95% CI; and pooled RR and 95% CI unadjusted and adjusted for unequal follow-up times. Where exposure was not reported, it was estimated by assuming a linear dropout between time points at which subject disposition was reported.

A fixed-effects model was used initially. Between-study heterogeneity was determined using Χ² (Q-statistic, where a p value of 0.10 rather than 0.05 was used to determine the presence of heterogeneity) and I² tests (values over 50% were considered to indicate heterogeneity). If heterogeneity was found, a random-effects model was used.

The Mantel-Haenszel method with Robins variance estimation was used for the meta-analysis. The reciprocal of the opposite treatment arm size was used as the base case continuity correction factor. Sensitivity analysis was undertaken using different methods to estimate risk and different continuity corrections.

Further details of the methods used and the reasoning behind them were provided. The primary analysis was the effect of each anti-TNF agent alone and anti-TNF agents together. The secondary analysis was investigated the effect of high doses of anti-TNF agents.

Results of the review
Eighteen relevant RCTs (n=8,808) were identified and over 7,846 years of follow-up were included in the analysis. There was no evidence for increased mortality, serious adverse effects, serious infections, lymphomas, non-cutaneous cancer/melanoma or non-melanoma skin cancer with any anti-TNF used at recommended doses compared to controls.

Higher than recommended doses were given to 15% of patients who received adalimumab, 54% of patients who received infliximab and none of the patients who received etanercept. The unadjusted meta-analyses identified an increased risk of serious infection with high dose anti-TNF therapy, OR 2.07 (95% CI 1.31 to 3.26) and RR 1.83 (95% CI 1.18 to 2.85). Adjustment for exposure found evidence of heterogeneity and a random-effects analysis was no longer significant, RR 1.99 (95% CI 0.90 to 4.37).

Risk of death, serious adverse effects, all malignancies, lymphomas and non-melanoma skin cancer did not increase with high dose anti-TNF therapy; however, risk of non-cutaneous cancer/melanoma combined showed a trend towards significance in the unadjusted meta-analyses, which was not significant after adjustment for exposure.

The duration of the individual trials did not affect the OR for death, serious adverse effects, non-cutaneous cancer/melanoma or non-melanoma skin cancer. The OR for serious infection decreased as the length of trials increased, from 2.08 after 12 weeks duration to 0.97 for trials of 104 weeks duration. A meta-regression showed the risk of serious infection with anti-TNF therapy decreased with increasing trial duration (p=0.04). The effect of time on lymphoma risk could not be determined due to the low levels of lymphoma.

Details of the previous treatment for arthritis and concomitant treatment with methotrexate in the patients were provided.

The results of sensitivity analyses were reported.

Authors’ conclusions
Meta-analytic and exposure-adjusted pooled analyses in more than 8,800 rheumatoid arthritis subjects in trials of anti-tumour necrosis factor treatment over an average of 0.8 years did not identify an increased risk of death, serious adverse events, serious infection, lymphoma, non-cutaneous cancer/melanoma or non-melanoma skin cancers with recommended doses. High dose anti-TNF therapy was associated with a twofold increase in the risk of serious infections.
CRD commentary
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched, but it appeared that only studies published in English were considered and unpublished studies were not considered; therefore, some relevant studies may have been missed. The start date for the search was not given, but since anti-TNF agents are relatively recent it was unlikely that any older studies were missed. Publication bias was not assessed. Study quality was assessed using suitable criteria, but few quality details were given and no details of the process were provided. The literature search, study selection and data extraction included efforts to reduce error and bias. Relevant study details were reported, but no details of the sex or age of the patients were given. Statistical heterogeneity was assessed; there was evidence for heterogeneity with some outcomes. The statistical methods used for the meta-analysis of the RCTs seemed appropriate. Sensitivity analyses were performed. The review was well conducted and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the trials in this review that commenced with higher than recommended doses of anti-TNF agents did not mimic common practice (use of recommended doses initially, increased over time when deemed necessary). The authors aimed to provide a tool in this review for practising rheumatologists to review quantitative data from clinical trials.

Research: The authors stated that the duration of clinical trials must be considered when evaluating the risk of serious infection.

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