Systematic review and meta-analysis: anti-tumor necrosis factor alpha therapy and cardiovascular events in rheumatoid arthritis

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CRD summary
The review concluded that anti-TNFα therapy was associated with a reduced risk of all cardiovascular events, myocardial infarction and cerebrovascular accident in observational cohorts and randomised controlled trials indicated a trend towards decreased risk in patients with rheumatoid arthritis. Given the limitations in the cohort studies, the authors' conclusions should be considered with caution.

Authors' objectives
To compare the effects of anti-tumour necrosis factor α (anti-TNFα) therapy with disease-modifying antirheumatic drugs (DMARDs) on risk of cardiovascular events in patients with rheumatoid arthritis.

Searching
PubMed (from 1950) and EMBASE (from 1980) were searched up to November 2009 for relevant studies. There were no language restrictions. Search terms were reported. Reference lists of retrieved studies and reviews were searched. Conference abstracts from 2007 to 2009 were checked and experts in the field were contacted for additional unpublished studies.

Study selection
Observational cohorts or randomised controlled trials (RCTs) of patients with rheumatoid arthritis who received anti-TNFα therapy compared to patients who received DMARDs were eligible for inclusion. Studies needed to report cardiovascular events (all events, myocardial infarction, congestive heart failure and cerebrovascular accident). Studies that reported surrogate markers of atherosclerosis and those with a duration less than 26 weeks were excluded.

In the included studies, reported disease duration ranged from 0.8 to 15 years. Anti-TNFα therapy was either unspecified or specified as infliximab, etanercept or adalimumab. Anti-TNFα therapy was compared with either methotrexate, leflunomide, DMARDs or placebo (with previous DMARD). Some cohort studies adjusted for potential confounders in the analysis.

Two reviewers independently selected studies for inclusion in the review. Discrepancies were resolved by discussion or with input from a third reviewer.

Assessment of study quality
Study quality was assessed by quality assessment checklists for observational cohorts and RCTs suggested by Egger 2001.

Two reviewers independently assessed studies for quality.

Data extraction
Data were extracted on cardiovascular events and relative risks (RRs) and hazard ratios (HRs) were calculated, together with 95% confidence intervals (CIs). Where incidence was reported, the number of events in both groups and patient-years of follow-up were extracted to calculate an incidence density ratio together with its variance. In studies where covariate adjustment was made in regression analysis, the most adjusted relative risk equivalent was extracted. Where anti-TNFα was compared to a general rheumatoid arthritis population with unspecified treatment, it was assumed that patients received DMARD therapy.

Two reviewers independently extracted data.

Methods of synthesis
Where possible, studies were pooled in meta-analyses and summary effect relative risks and 95% CIs were calculated.
Hazard ratios and incidence density ratios were considered relative risks. Results presented as odds ratios (ORs) in the studies were transformed into relative risks. Separate analyses were performed for cohort studies and RCTs. A random-effects model was used for assessment of all cardiovascular events in observational cohort studies; otherwise a fixed-effect model was used for all other outcomes in the cohort studies and all RCT analyses. Cumulative meta-analysis was performed for all cohort studies that reported myocardial infarction as an outcome. Heterogeneity was assessed with the $X^2$ test and $I^2$ value. Publication bias was assessed by visual inspection of the funnel plot and Begg's test.

**Results of the review**

Three RCTs (2,216 participants) and 13 cohort studies (106,202 participants) were included in the review. All three RCTs and eight of the cohort studies had data sufficient for meta-analyses. All three RCTs were considered high quality with the key elements of blinding, concealment of allocation and transparent reporting of patient flow. Two cohort studies were considered of high quality and 11 were considered of medium quality. Some of the limitations of the cohort studies were lack of information on representativeness and time point in the disease course and lack of adjustment at baseline. Most did not standardise or randomise treatment after entry. Follow-up ranged from 26 weeks to five years, where reported.

**RCTs:** There was no evidence of a statistical difference in cardiovascular event rates between anti-TNFα and DMARD treated patients (RR 0.85, 95% CI 0.28 to 2.59; three RCTs). No heterogeneity was identified in this analysis ($I^2=0\%$).

**Cohort studies:** Compared to DMARD therapy, anti-TNFα was associated with a significantly reduced risk for all cardiovascular events (adjusted RR 0.46, 95% CI 0.28 to 0.77; five studies, significant heterogeneity, $I^2=89\%$), myocardial infarction (adjusted RR 0.81, 95% CI 0.68 to 0.96; six studies, no significant heterogeneity, $I^2=39\%$) and cerebrovascular accident (adjusted RR 0.69, 95% CI 0.53 to 0.89; four studies, no significant heterogeneity, $I^2=39\%$). There was evidence of publication bias for all cardiovascular events, but not for myocardial infarction or cerebrovascular accident. Meta-analysis for the assessment of congestive heart failure was not appropriate; findings in six cohorts were inconsistent and ranged from a small reduction to increased risk in patients treated with anti-TNFα.

**Authors’ conclusions**

Anti-TNFα therapy was associated with a reduced risk of all cardiovascular events, myocardial infarction and cerebrovascular accident in observational cohorts. RCTs indicated a trend towards decreased risk.

**CRD commentary**

The review addressed a clear research question. Inclusion criteria appeared appropriate. Relevant sources were searched to identify published and unpublished studies. There were no language restrictions. Appropriate methods were used for the selection of studies, quality assessment and data extraction, which reduced the risk of reviewer error and bias. Studies were assessed for quality appropriately, but criteria were not reported. RCTs were considered to be of high quality. Cohort studies had several limitations and were considered to be of medium quality. Where possible, studies were synthesised appropriately in meta-analyses; otherwise, results were discussed in narrative format. Heterogeneity was appropriately assessed. There was evidence of substantial heterogeneity in one analysis, which the authors suggested was partly explained by the large sample size overpowering the heterogeneity test. There were too few studies for the results of the test for publication bias to be considered definitive and there was a suggestion in one analysis that publication bias was a possibility. The authors considered that the analysis of RCTs was underpowered, as the confidence interval around the summary estimate was wide. The authors suggested that inconsistency between the results of cohort studies and RCTs was explained by the fact that participants in the RCTs were highly selected and possibly at lower risk of cardiovascular events.

Given the limitations in the cohort studies that found a benefit for anti-TNFα therapy and the lack of evidence of an effect in RCTs, the authors’ conclusions should be considered with caution.

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

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

**Research:** The authors stated that further research (both cohorts and RCTs) with longer follow-up and more detailed information on confounders was required to adequately assess the effects of anti-TNFα therapy.
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