Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials

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CRD summary
High-dose tocilizumab in combination with methotrexate as a treatment for rheumatoid arthritis was associated with a small but significant increase in adverse events and infection compared to controls; the effect was unclear for tocilizumab monotherapy. Limitations in study numbers and the review process mean that the results should be treated with caution.

Authors' objectives
To evaluate the risk of adverse events with tocilizumab monotherapy and combined methotrexate and tocilizumab in patients with rheumatoid arthritis.

Searching
PubMed, EMBASE and The Cochrane Library were searched to September 2009 for peer-reviewed publications; search terms were reported.

Study selection
Randomised controlled trials (RCTs), limited to late phase II or III trials of monotherapy with 8mg/kg tocilizumab and combination therapy with 4mg/kg and 8mg/kg tocilizumab with methotrexate in patients with rheumatoid arthritis were eligible for inclusion. Eligible trial participants had to be adults (≥18 years) with a diagnosis of rheumatoid arthritis (American College of Rheumatology 1987 criteria). The primary outcomes were adverse events including serious infections. One study was excluded due to insufficient patient details.

Half of the studies were of combination therapy; one combined tocilizumab with one of six disease-modifying anti-rheumatic drugs (DMARDs) of which methotrexate was the most common. Tocilizumab was administered every four weeks and methotrexate weekly, where reported. Two studies were of tocilizumab monotherapy. One study included both combination and monotherapy. The controls for most studies were placebo tocilizumab with methotrexate (and folate in one study); one study used methotrexate alone and another study used placebo tocilizumab plus one or more DMARDs. All of the studies were of active rheumatoid arthritis methotrexate-naïve patients; one study was of patients refractory to conventional DMARDs or anti-tumour necrosis factor treatment. Mean age ranged from 49.3 to 54.0 years. Seventy-three to 90.2% of participants in the treatment groups were female. The adverse events most consistently reported and evaluated were: one or more adverse events, serious adverse events, infection and serious infection. Individual definitions were not available and it was assumed that adverse event definitions were consistent. Inconsistently reported adverse events that were not included in the meta-analyses were neutropenia, abnormal liver function tests and altered lipid profile.

The authors did not report how many reviewers performed the study selection.

Assessment of study quality
Quality criteria were selection, performance, attrition and detection biases, and analyses performed.

The authors did not report clearly how many reviewers performed the quality assessment.

Data extraction
Numbers of events were used to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Monotherapy group comparisons were made between the 8mg/kg tocilizumab group and controls. Combination therapy group comparisons were made between 4mg/kg and controls, 8mg/kg and controls and 8mg/kg versus 4mg/kg. Low-dose therapy was 4mg/kg tocilizumab. High-dose therapy was 8mg/kg tocilizumab.
Data was extracted in duplicate. Any discrepancies were resolved by checking data and through discussion with other reviewers.

**Methods of synthesis**
Odds ratios were pooled using fixed-effects models. $X^2$ and $I^2$ were used to test for heterogeneity ($p<0.1$ was considered to be significant heterogeneity). Studies with zero total event were excluded from meta-analyses. Where contingency tables contained zero values, a continuity correction was applied to the relevant tables. Forest plots were produced. Publication bias was estimated using funnel plots. A sensitivity analysis was performed by removing the smallest study.

**Results of the review**
Six RCTs were identified (3,501 participants, range 127 to 1,220). Most were phase III trials and one was a late phase II trial. All the studies were double-blind RCTs; one was a double-dummy parallel group RCT. The authors concluded that all the studies were of adequate quality as each had accounted for the sources of error that were considered important. Follow-up ranged from 20 to 24 weeks. Loss to follow-up ranged from 0.1% to 31.5%.

**Combined therapy with tocilizumab and methotrexate:** Risk of at least one adverse event was significantly higher for high-dose tocilizumab than for controls (OR 1.53, 95% CI 1.26 to 1.86; four studies) but not for low-dose versus controls (three studies, $I^2=30\%$) and high-doses versus low-dose tocilizumab (three studies, $I^2=35\%$). For at least one serious adverse event, there was no significant difference in risk for high-dose versus low-dose tocilizumab (three studies, $I^2=46\%$) and for low-dose versus controls (three studies). Results for high-dose versus controls (four studies) was not reported due to high heterogeneity ($I^2=59\%$).

For at least one infection, there was a significant increase in risk for high-dose tocilizumab versus controls (OR 1.30, 95% CI 1.07 to 1.58; three studies). There was no significant increase in risk for low-dose versus controls (two studies) and high-dose versus low-dose tocilizumab (two studies). There was no significant increase in risk of at least one serious infection for high-dose versus controls (four studies), low-dose versus controls (two studies) and high-dose versus low-dose tocilizumab (three studies).

**Monotherapy with 8mg/kg tocilizumab (high dose):** There was no significant increase in risk for 8mg/kg tocilizumab versus controls for at least one serious adverse event (three studies), at least one infection (two studies) and for at least one serious infection (two studies). No results were reported for high-dose monotherapy versus controls for at least one adverse event (three studies) due to high heterogeneity ($I^2=64\%$).

The main adverse events reported were nasopharyngitis, respiratory tract disorder, skin and soft tissue pathology, and gastrointestinal side effects. The main infections reported were skin, subcutaneous and respiratory tract infections. Except where stated otherwise, heterogeneity was very low ($I^2<1\%$). Results of the sensitivity analysis were reported. The authors considered that the funnel plots showed no evidence of publication bias.

**Authors’ conclusions**
High-dose tocilizumab in combination with methotrexate as a treatment for rheumatoid arthritis was associated with a small but significant increase in adverse events and infection. Vigilance was needed for patients treated with these immunosuppressive agents.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions and relevant outcomes. No comparison was made between tocilizumab monotherapy versus combined tocilizumab and methotrexate therapy; this was not made clear in the study design description. The search for unpublished studies was not extensive, only peer-reviewed publications were included and no handsearching was recorded, so some relevant studies may have been missed. Study quality was assessed using relevant criteria but little relevant data was provided to enable the reader to assess study quality. Efforts were made to reduce error and bias in data extraction, but the authors did not report whether this applied to other aspects of the review process. Some relevant study details were reported. The authors reported patient details; there was one clear transcription error in the mean duration of rheumatoid arthritis.

The basic method of synthesis seemed appropriate. It would have been better for the reader if the forest plots displayed...
meta-analysis results and heterogeneity. The authors did not report two meta-analyses results due to the presence of high heterogeneity, which cast doubt on the validity of the conclusions as the reader was unable to evaluate these results. Random-effects models were not used where there was evidence for significant heterogeneity. Other results were reported in the abstract for risk of malignancy, tuberculosis reactivation and hepatitis, but no evidence was presented for these.

In view of limitations in the number of studies identified and the review process, the authors’ conclusions should be treated with caution.

Implications of the review for practice and research
Practice: The risk of an increase in adverse events with high-dose tocilizumab was comparable to that of other biological agents, although the risk of a serious infection may be lower than that for tumour necrosis factor antagonists.

Research: The authors suggested that further research was required to investigate the effect of tocilizumab on plasma lipids and its related effect on cardiovascular risk.

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