Comparison of certolizumab pegol with other anticytokine agents for treatment of rheumatoid arthritis: a multiple-treatment bayesian metaanalysis

CRD summary
This review reported that certolizumab pegol was at least as efficacious as pre-existing antirheumatic anti-cytokine biotherapies for the treatment of rheumatoid arthritis. Review data appeared to support the authors' conclusions, but the risk of missing data and the clinical differences between the included studies suggest that the findings may not be reliable.

Authors' objectives
To determine whether certolizumab pegol is not inferior to alternative anti-cytokine agents in combination with conventional disease modifying anti-rheumatic drugs (DMARD) for treatment of rheumatoid arthritis in patients with inappropriate or no response to conventional DMARD treatment including methotrexate.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched up to June 2009 for studies published in English. Search terms were reported. Proceedings of American College of Rheumatology and European League Against Rheumatism congresses since 2004 were screened for further studies.

Study selection
Double-blind randomised controlled trials (RCTs) that compared anti-cytokine biotherapies (anti-tumour necrosis factor alpha and anti-interleukin 1 or 6) for rheumatoid arthritis with placebo in combination with conventional DMARD for treatment of adult patients with rheumatoid arthritis were eligible for inclusion. Eligible patients had shown an inappropriate response or no response to previous conventional DMARD treatment including methotrexate. Therapies had to be used in accordance with their Summary of Product characteristics. Clinical efficacy had to be assessed at 24 weeks (± eight weeks) using American College of Rheumatology (ACR) response criteria, which included ACR 20 (primary efficacy outcome) and ACR 50 and ACR 70 (secondary efficacy outcomes) response rates.

Around three-quarters of the included studies assessed one of five anti-tumour necrosis factors (infliximab, etanercept, adalimumab, golimumab and certolizumab pegol). The other studies assessed anti-interleukin agents (anakinra and tocilizumab). In most studies the combined DMARD treatment was methotrexate. Other studies used sulphasalazine. Where reported and with the exception of two studies, included participants were generally positive for rheumatoid factor (usually more than 70% of participants per study). Duration of rheumatoid arthritis positivity varied between studies (median eight years, range five to 13 years); in general the duration was longer (at least 10 years) in studies before 2005 and shorter (seven years or less) in more recent studies (2008 to 2009). Mean age of participants ranged from 35 to 57 years. Where reported, mean C-reactive protein ranged from 0.8 to 3.3mg/dL and mean Health Assessment Questionnaire score ranged from 1.3 to 1.8.

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

Assessment of study quality
Methodological quality of the included studies was assessed using Jadad criteria of randomisation, blinding and numbers of withdrawals/dropouts. Each study was awarded a score up to a maximum of 5 points.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Number and percentage response rates were reported. Odds ratios with 95% confidence intervals (CIs) were calculated for direct comparisons with placebo.
Two reviewers independently extracted study data. Discrepancies were resolved by a third reviewer.

**Methods of synthesis**

Direct comparisons between trials were made using conventional frequentist methods to calculate pooled direct odds ratios with 95% CIs. Indirect comparisons were carried out using a multiple treatment Bayesian random-effects meta-analysis (mixed-treatment comparison). A normal (mean 0, precision 0.00001) prior distribution was used for all population means and a non-informative uniform (0, 10) prior for all variances. The pooled mean and credible interval (CRI) were reported. The absolute probability of success of each treatment was estimated using the mean of responses in all studies.

For each pairwise comparison, assessment of certolizumab pegol non-inferiority (defined a priori as an absolute difference margin of 5% in all response rate criteria) was assessed and the log-OR absolute efficacy calculated using the Markov chain Monte Carlo method. The non-inferiority was inferred at a posterior probability of at least 0.975 (corresponding to a conventional one-sided probability of 0.025 or less). The probability of non-inferiority was calculated using random-effects and fixed-effect models.

**Results of the review**

Nineteen placebo-controlled RCTs (7,158 participants) were included in the review. Sample sizes ranged from 70 to 1,216. All of the studies scored at least 3 points on the Jadad quality scale.

The efficacy of certolizumab pegol was superior to infliximab, adalimumab and anakinra with respect to ACR 20 response and superior or equivalent to etanercept, golimumab and tocilizumab (individual effect sizes reported in the review). Pooled effect sizes for ACR 50 and ACR 70 showed the odds ratio for certolizumab pegol compared to placebo was not significantly higher than other anti-cytokine biotherapies.

The mixed treatment comparison (random-effects model) showed a statistically significant difference in favour of the intervention group (compared with placebo) with respect to ACR 20 response rate for the drugs infliximab (OR 3.31, 95% CrI 2.05 to 5.03), etanercept (OR 8.07, 95% CrI 3.34 to 16.75), adalimumab (OR 3.73, 95% CrI 2.35 to 5.93), golimumab (OR 3.62, 95% CrI 1.62 to 6.97), certolizumab pegol (OR 11.82, 95% CrI 5.98 to 21.71) and tocilizumab (OR 4.13, 95% CrI 2.64 to 6.19). There was no significant difference between anakinra and placebo.

Similar findings were reported for ACR 50 response rate and ACR 70, although there were insufficient numbers of patients to assess ACR 70 response rate for etanercept, golimumab and anakinra. When the analyses were repeated using a fixed-effect model all of the effect sizes were significantly in favour of the intervention group in comparison with placebo.

The results of the non-inferiority analysis showed that for ACR 20, the probability of certolizumab pegol being not inferior to the mean of all treatments and each individual intervention was significantly high (probability over 99% versus all other interventions for the random-effects model and 100% in the fixed-effect model). The only exception was certolizumab pegol versus etanercept, where the probability of being not inferior was greater than 90% for the random-effects model and greater than 95% for the fixed-effect model.

Results were reported for ACR 50 and ACR 70 responses.

**Authors' conclusions**

Certolizumab pegol was at least as efficacious as pre-existing antirheumatic anti-cytokine biotherapies.

**CRD commentary**

This review answered a clearly defined research question. Several databases were searched for relevant studies. There was a risk of missing data leading to publication and language bias as only studies published in English were included in the review. The authors did not assess the risk of publication bias. Steps were taken to reduce the risk of bias during data extraction. It was unclear whether similar precautions were taken during study selection and quality assessment, so the risk of reviewer error and bias was unclear.
Study quality was assessed using relevant criteria and all of the studies appeared to be good quality, although individual study data were not presented. There were differences between the studies, particularly with respect to study populations; in some cases the potential effects of these differences were discussed by the authors. Although indirect comparisons are helpful when assessing interventions where a direct comparison is lacking, they are at risk of bias. In some instances the reliability of the pooled effect sizes (both direct and indirect) was questionable due to the presence of clinical heterogeneity between the studies.

Overall, the data appear to support the authors' conclusions. However, the risk of missing data and the clinical differences between the studies suggest that the findings may not 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 studies under real-life conditions were required, such as pragmatic assays to compare certolizumab pegol with alternative anti-cytokine agents for treatment of rheumatoid arthritis.

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