Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease

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CRD summary
The review concluded that certolizumab was effective and safe for treatment of Crohn's disease, but that more studies were required to fully assess the safety profile. The authors' conclusions reflected the evidence base and were appropriate but given the small number of studies for each outcome and shortcomings in the review process their reliability is unclear.

Authors' objectives
To assess the efficacy and safety of certolizumab in patients with Crohn's disease.

Searching
PubMed (1966 to October 2008), EMBASE (1980 to October 2008), The Cochrane Library (Issue 4, 2008) and Science Citation Index (1975 to August 2008) were searched; search terms were reported. Reference lists of retrieved studies and the 2006 to 2008 proceedings of American Gastroenterological Digestive Week and United European Gastroenterology Week were searched.

Study selection
Studies were eligible if they provided data on efficacy and safety of certolizumab in Crohn's disease. No more specific inclusion criteria were reported.

Included studies were either phase II or III randomised double-blind placebo-controlled trials in patients with mostly moderate to severe Crohn's disease. For some outcomes, participants were non-responders or were intolerant to infliximab. Doses of certolizumab ranged from a single intravenous dose of 1.25mg/kg to 20mg/kg or subcutaneous doses of 100mg to 400mg administered at different time points. Outcomes included: clinical response (defined as a decrease of ≥100 points from baseline in Crohn's disease activity index (CDAI) or reduction in Harvey-Bradshaw Index (HBI) score of ≥3 points), remission (defined as a CDAI score of ≤150 points or HBI score ≤4 points), health-related quality of life (measured by the Inflammatory Bowel Disease Questionnaire) and adverse events (both treatment-emergent common events and common events).

The authors did not state how study selection was undertaken.

Assessment of study quality
The quality of the included studies was assessed with the Jadad composite five-point scale of randomisation, double blinding, withdrawals and dropouts. A low-quality study was defined as Jadad score 2 or less and a high-quality study as Jadad score 3 or more.

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

Data extraction
Data were extracted on short-term (<26 weeks) and long-term (>26 weeks) clinical response and remission. For the assessment of short term efficacy (at four weeks), relative risks (RR) together with 95% confidence intervals (CI) were calculated for each included study.

The authors did not state how data extraction was performed.

Methods of synthesis
For the assessment of short term efficacy, studies were pooled in a meta-analysis using a fixed-effects model. Heterogeneity was assessed with the $\chi^2$ test and the $I^2$ value. Studies were synthesized in a narrative format for the assessment of all other outcomes.
Results of the review
Eight studies were included in the review. Three of these (n=1,043) assessed short-term efficacy; all were multicentre randomised double-blind placebo-controlled trials with the maximum Jadad score of 5. For all other outcomes, variable numbers of studies were included and patient numbers and quality were not always reported. Five of the eight included studies were randomised controlled trials (RCTs), two were open label extensions of previous RCTs, one was a case series and one synthesized the results of six studies for the assessment of safety.

At week four, certolizumab therapy significantly improved response rates (RR 1.36, 95% CI 1.1, 1.68; three studies) and remission rates (RR 1.95, 95% CI 1.41, 2.7; three studies). Statistical heterogeneity for clinical response was 39.6% and for remission was 0%. Certolizumab was also an effective long term maintenance therapy for patients who had responded to certolizumab induction therapy (two trials) (no pooled estimate available). Re-induction with certolizumab in patients who flared on maintenance therapy was effective in one uncontrolled trial. Certolizumab was also effective in non-responders or patients intolerant to infliximab, but response was more effective in infliximab naive than in infliximab exposed patients. No significant association was found between the efficacy of certolizumab and baseline C-reactive protein level. Certolizumab 400mg was also effective in improving health-related quality of life in two trials. An indirect comparison of three anti-TNF agents (infliximab, adalimumab and certolizumab) from three separate trials, suggested that efficacy of all three treatments appeared to be roughly similar. One study that synthesized the results from six included studies confirmed that there was no increased short-term risk of serious or common adverse events with certolizumab, but infections were more common.

Authors' conclusions
The authors concluded that certolizumab was effective and safe for treatment of Crohn's disease, but that more studies were required to fully assess the safety profile.

CRD commentary
The review addressed a clear research question. Inclusion criteria were appropriate, although broad and non specific. A number of electronic databases and reference lists of retrieved studies were searched. Attempts were made to find unpublished studies by searching conference proceedings of two journals. The likelihood of publication bias was not formally assessed. It was unclear whether a language restriction was applied and so language bias could not be excluded. The authors did not report how study selection, data extraction and validity assessment were undertaken, so reviewer error and bias in the review process could not be excluded. Multiple outcomes were assessed, with the inclusion of only a few studies for each outcome. Given the small number of studies with variable outcomes, the methods of synthesis were appropriate. Heterogeneity for clinical response was in the mild to moderate range for clinical response, but minimal for remission and did not require the use of the random-effects model. Multiple outcomes were assessed with only a few studies included for each outcome.

The authors’ conclusions reflected the evidence base and were appropriate. Given the small number of studies for each outcome and shortcomings in the review process, the reliability of the conclusions is unclear.

Implications of the review for practice and research
Practice: The authors stated that certolizumab might be an additional treatment option in patients who had lost response to or were intolerant to infliximab.

Research: The authors stated that more placebo-controlled RCTs were required to confirm the efficacy of certolizumab in patients who had lost response or who were intolerant to infliximab. They also stated that further studies were required to clarify the relationship between efficacy of certolizumab and baseline C-reactive protein levels in Crohn's disease patients and that studies with longer duration (≥12 months) and a larger number of patients were required to fully assess the safety profile of certolizumab.

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