A systematic review on the effect of bevacizumab in exudative age-related macular degeneration

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CRD summary
The results of this review suggested that patients with age-related macular degeneration experienced improvements in visual acuity and central retinal thickness after treatment with bevacizumab. The low quality of the very limited evidence made the reliability of the authors’ conclusions unclear.

Authors’ objectives
To assess the effects on bevacizumab on visual acuity and central retinal thickness in patients with exudative age-related macular degeneration.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched to March 2008 for relevant studies in English, German, French or Dutch; search terms were reported. Reference lists of included articles and personal files of the authors were searched.

Study selection
Published studies of patients with exudative age-related macular degeneration (AMD) treated with bevacizumab and in which visual acuity was the primary outcome were eligible for inclusion. Studies of systemic or intravitreal therapy were eligible. Exclusion criteria were those in which visual acuity was not the primary outcome, where included patients did not have AMD and studies in which the primary objective was the study of differences between subgroups. Studies were also excluded if they were case series; basic science or experimental studies; cost studies; or only used follow-up with optical coherence tomography.

The included study design types were randomised controlled trials (RCTs), non-randomised controlled trials and before-and-after studies with more than one patient. In the RCTs, bevacizumab treatment was compared to photodynamic therapy with or without triamcinolone and a combination of bevacizumab and photodynamic therapy. Bevacizumab was administered by intravitreal injections of 1.25mg in most studies. There was a range of strategies for additional injections; these were principally either monthly injections irrespective of the results or injections on recurrence of vision loss or recurrence of macular fluid diagnosed by optical coherence tomography. Visual acuity was specified as the a priori primary outcome and was measured using the Snellen test or the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.

Two reviewers independently selected the studies from the search lists. Study selection was determined by discussion between the reviewers.

Assessment of study quality
The methodological quality of the included RCTs was assessed using the Delphi list supplemented by criteria from the Dutch Cochrane Centre. Eleven items were appraised to provide a score from 0 to 11, including: randomisation; allocation concealment; use of eligibility criteria; assessor and care-provider blinding; follow-up, use of point estimates and variability; and use of intention-to-treat-analyses. Quality characteristics of all the uncontrolled studies were tabulated with six items that related to prospective study, use of consecutive cases, losses to follow-up, blind assessment, use of standardised assessments and whether more than 50% of the included patients had received previous treatment for AMD.

One reviewer assessed methodological quality. It was unclear whether quality was checked by any other reviewer.

Data extraction
Data were collected on baseline values of visual acuity (using the ETDRS) and central retinal thickness, changes in these values at follow-up and adverse events. In studies where the ETDRS scores were not assessed directly, visual acuity scores were converted using 0.1 logMAR (one Snellen test line) to five ETDRS letters.

Two reviewers retrieved the data. Differences between these two reviewers and a third reviewer (who only assessed quality and scored differences between baseline and follow-up values for the primary outcomes) were resolved by discussion.

**Methods of synthesis**
The results of the studies were summarised in a narrative review with accompanying tables.

**Results of the review**
Twenty six studies (n=1,420) were included in the review: three RCTs and 23 uncontrolled studies. Sample sizes ranged between nine and 156 participants. Follow-up times ranged from four to 48 weeks. Quality scores of the three RCTs ranged between 5 to 8 out of 11, which indicated poor- to reasonable-quality trials. The methodological quality of the remaining studies was middling, with consecutive cases being enrolled in 10 studies, no blinded assessment of primary outcomes and 15 studies that used standardised methods of assessment of outcomes.

Three RCTs (n=248) showed greater effectiveness of bevacizumab compared to photodynamic therapy with and without triamcinolone in improved visual acuity (range of weighted mean changes with bevacizumab on the ETDRS across the trials: 8.6 to 12 letters) and decreased central retinal thickness (range of weighted mean changes with bevacizumab in central retinal thickness across the trials: -55μm to -113μm).

One small RCT (n=52) found benefits of a combined treatment of bevacizumab and photodynamic therapy in improvements in visual acuity (weighted mean change on the ETDRS: 12.3 letters compared to 8.6 letters for bevacizumab and 2.5 letters for photodynamic therapy) and decreased central retinal thickness (weighted mean change: -65μm).

Adverse events reported included mild inflammatory responses, mild vitritis, pigment epithelial ruptures, cataract progression, endophthalmitis and transient corneal epitheliopathy. Eighteen studies reported no adverse ocular or systemic adverse events.

**Authors’ conclusions**
Improvements in visual acuity and central retinal thickness had been reported after treatment with bevacizumab in patients with exudative age-related macular degeneration. The effect of bevacizumab was likely to be at least equivalent to that of ranibizumab. The incidence of adverse events was low and serious adverse events were rare in the short term.

**CRD commentary**
The review addressed a clear question and inclusion criteria were stipulated. The literature search was confined to published studies and studies in certain languages only; relevant studies may have been missed and publication and language biases could not be ruled out. Steps were taken to minimise errors and bias for most parts of the review process. The reviewers’ conclusions about the evidence of benefits of bevacizumab treatment were based on the results of three small RCTs and non-randomised studies. No statistical test results were provided for the results from the included RCTs. The authors made some tentative conclusions about the effectiveness of bevacizumab in relation to ranibizumab without any supporting data. Although the results of the studies showed some benefits of bevacizumab treatment, the poor conduct of most studies made it difficult to draw firm conclusions about the effectiveness of these interventions. The findings from non-randomised studies were associated with a number of potential biases. Patients with a wide range of visual and other comorbidities were excluded in the studies, which meant that the results of the review may only be applicable to a limited range of patients with AMD. The low quality of the very limited evidence and the possibility of missing studies means that the authors’ conclusions should be interpreted with some caution.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.
Research: The authors did not state any implications for research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.