Bevacizumab for ocular neovascular diseases: a systematic review
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CRD summary
This review concluded that bevacizumab alone or combined with other treatments was more effective than other options (including photodynamic therapy, focal photocoagulation and triamcinolone) for patients with eye neovascular diseases. Given the small number of varied trials included, and the potential for publication or language bias, the authors' conclusions should be interpreted with caution.

Authors' objectives
To evaluate the effectiveness and safety of bevacizumab for treating patients diagnosed with ocular neovascular diseases.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and LILACS were searched from inception to June 2008, search terms were reported.

Study selection
Quasi-randomised or fully randomised controlled trials (RCTs) that compared bevacizumab with another intervention in patients with a diagnosis of ocular disease or ocular conditions, or ocular conditions with the same underlying pathophysiological mechanism of increased local levels of vascular endothelial growth factor, were eligible for inclusion. Trials where eyes of individual patients were independently allocated for treatment were excluded, due to potential of adverse events affecting both eyes.

Outcomes of interest were visual acuity measured by any validated instrument and adverse events.

In included trials, patients were diagnosed with: diabetic macular oedema; clinically significant macular oedema that had not responded to previous treatment; age-related macular degeneration; subfoveal choroidal neovascularisation; and proliferative diabetic retinopathy. Included trials were two, three and four armed, comparing bevacizumab alone with; bevacizumab plus triamcinolone; sham injections; photodynamic therapy alone or with triamcinolone; focal photocoagulation; macular laser photocoagulation; or panretinal photocoagulation. Interventions were delivered once, or repeated after three or six weeks. Trials were conducted in Brazil, Iran, Lebanon, USA, Austria, Croatia and Germany. Participant and outcome measure details were not reported.

It was unclear how many reviewers conducted the study selection.

Assessment of study quality
Methodological quality was assessed by two independent reviewers on the following criteria: selection bias, performance bias, detection bias and attrition bias. Each criterion was rated in terms of risk of bias as low, moderate or high.

Data extraction
Dichotomous data were extracted as risk ratios (RR) with 95% confidence intervals (CI) and continuous outcomes as mean differences and standard deviations.

It was unclear how many reviewers performed the data extraction.

Methods of synthesis
A random-effects model was used to pool primary trials and calculate risk ratios and 95% confidence intervals, and weighted mean differences (WMD) with 95% confidence intervals, where appropriate. The number-needed-to-treat (NNT) was also calculated. Heterogeneity was assessed using $I^2$. Trials were grouped according to outcomes and
comparators.

**Results of the review**

Nine trials were included in the review (n=667 eyes). Four trials were judged to be at low risk of selection bias; the rest were rated as moderate risk. Three trials used sham interventions which accounted for performance bias; five trials used blinded outcome assessors; three trials were judged to be at high risk of detection bias. All trials were rated as low risk of attrition bias.

**Best corrected visual acuity:** One trial demonstrated significant mean differences in visual acuity in favour of bevacizumab versus sham treatment (WMD -0.18, 95% CI -0.28 to -0.08), and bevacizumab plus triamcinolone versus sham treatment (WMD -0.15, 95% CI -0.26 to -0.04). One trial also reported significant benefits for the bevacizumab alone versus photodynamic therapy (WMD -0.09, 95% CI -0.13 to -0.06), bevacizumab plus photodynamic therapy versus bevacizumab alone (WMD -0.14, 95% CI -0.18 to -0.11) and bevacizumab plus photodynamic therapy versus bevacizumab alone (WMD -0.24, 95% CI -0.27 to -0.20). There were no other statistically significant differences for the other comparisons.

**Improvements in best corrected visual acuity** (all definitions): Patients receiving bevacizumab were significantly more likely to present improved visual acuity than those receiving photodynamic therapy alone or with triamcinolone (RR 0.49, 95% CI 0.31 to 0.78; NNT=4, 95% CI 1 to 4).

**Adverse events:** The most common adverse events associated with bevacizumab were moderate anterior chamber reaction, transient anterior chamber reaction, iris neovascularisation, subconjunctival haemorrhage, posterior vitreous detachment, and foreign body sensation. Further details were listed in the paper.

**Cost information**

In order to improve visual acuity in one patient, 3.45 patients would have to be treated with bevacizumab at a cost of 113.85 US dollars ($) and 8.25 patients with photodynamic therapy at a cost of $56,925.

**Authors’ conclusions**

Bevacizumab alone or combined with other treatments was more effective than other options (including photodynamic therapy, focal photocoagulation and triamcinolone) for patients with ocular neovascular diseases. The use of bevacizumab instead of photodynamic therapy could significantly reduce treatment costs.

**CRD commentary**

This review addressed a clear question with appropriate inclusion criteria. A small number of relevant databases were searched. However, EMBASE (a major European medical database) was omitted from the search and grey literature was unlikely to have been assessed. It was unclear if language restrictions were applied to the searches or included studies. The review processes were not clearly described, except for quality assessment, which made it difficult to rule out reviewer error or bias.

Relatively little information on the primary trials was reported; the extent to which they were clinically similar was unclear. The quality assessment and analyses appear to have been appropriate.

Given the small number of heterogeneous trials and potential for publication or language bias, the conclusions should be interpreted with caution.

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

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

**Research:** The authors recommended that specialists should come to a consensus on relevant outcomes and how best to analyse them, and that future research should provide more information on comparison treatments and co-interventions, such as photodynamic therapy, laser photocoagulation, triamcinolone and vitrectomy.
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