Use of antivascular endothelial growth factor for diabetic macular edema

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CRD summary
This review concluded that, in patients with diabetic macular oedema, anti-vascular endothelial growth factor treatment improved visual acuity and central macular thickness at least in the short-term. The authors’ conclusions may be too strong considering the small number of trials included and queries over trial quality.

Authors' objectives
To evaluate the effectiveness of intravitreal anti-vascular endothelial growth factor for the treatment of diabetic macular oedema.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE databases were searched up to October 2008; search terms were reported. Reference lists of included studies and review articles were searched. The Australian National Health and Medical Research Council guidelines for diabetic retinopathy reference list was examined for additional eligible studies. The Archives of Ophthalmology, Ophthalmology, Retina and the New England Journal of Medicine were searched for clinical trials and reviews. The clinical trials repository held by the National Institute of Health, Current Controlled Trials and the National Research Register were searched for unpublished studies. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) of any form that compared intravitreal anti-vascular endothelial growth factor (anti-VEGF) with another treatment, placebo or no treatment for any type of diabetic macular oedema (focal or diffuse) were eligible for inclusion. Any dose or duration of anti-VEGF was considered. Trials of participants with diabetic retinopathy with no mention of diabetic macular oedema were excluded, as were trials of participants with macular oedema due to causes other than diabetic macular oedema.

The primary outcomes were change in best-corrected visual acuity and change in central macular thickness measured by ocular coherence tomography. Secondary outcomes were reduction of macular oedema, presence of oedema via direct fundoscopy and fluorescein leakage.

In included trials, anti-VEGF treatments were intravitreal bevacizumab or pegaptanib. Trial participants either had clinically significant macular oedema or diabetic macular oedema. Some trials included only patients unresponsive to laser treatment, while others excluded patients with previous laser eye treatment. Definitions of visual acuity varied between trials. In some trials only participants with visual acuity over 20/40 were included; in others, visual acuity was between 20/32 and 20/40 or 20/50 and 20/320. The mean age of included participants ranged from 59.7 years to 67.08 years. Duration of diabetes and baseline intra-ocular pressure were not reported. Trial durations ranged from 12 to 36 weeks.

One author assessed articles for inclusion.

Assessment of study quality
Quality was assessed using methods described in the Cochrane Handbook (version 6.7, 2007). Parameters assessed included the randomisation process, allocation concealment, and blinding of participants and investigators.

One author assessed articles for methodological quality.

Data extraction
The primary outcomes were expressed as continuous variables. For each study, the mean difference in the primary outcomes was calculated. Standard deviations were calculated using actual P-values obtained from t-tests quoted in the
Cochrane Handbook. Authors of unpublished closed trials were contacted for initial results.

One author carried out data extraction of included studies.

**Methods of synthesis**

Data were pooled using a fixed-effect model due to the small number of included trials. Heterogeneity was estimated using Cochran’s Q statistics and $I^2$, and was examined using forest plots.

Subgroup analysis was not performed due to the small number of trials identified.

**Results of the review**

Five trials (n=525 eyes) meeting the inclusion criteria were identified; data from three trials (n=232 eyes) were included in the meta-analysis. Trial quality was graded either B or C in all trials; no definition of grades was provided but trial quality was discussed narratively. The process of randomisation was described in one trial and allocation concealment was not described in any trial. Outcome assessment was adequately blinded in three trials and partially blinded in two. The review authors described quality as adequate.

Anti-vascular endothelial growth factor (anti-VEGF) treatment resulted in an improvement in visual acuity of -0.17 (95% CI -0.23 to -0.10; n=234 eyes) and in central macular thickness of -84.69μm (95% CI -117.09 to -52.30).

One trial assessed three doses of pegaptanib (0.3mg, 1mg and 3mg); similar effects on visual acuity and central macular thickness were observed regardless of which pegaptanib arm was included in the meta-analysis.

Two trials of patients treated with anti-VEGF in combination with intravitreal triamcinolone (n=140 eyes) showed slightly larger improvements in visual acuity and central macular thickness. No significant increases in complications were reported from anti-VEGF treatment.

Substantial heterogeneity was observed between trials both for the assessment of visual acuity ($I^2$ 65% to 81% depending on pegaptanib arm included) and for central macular thickness ($I^2$ 49% to 73%). Forest plots suggested the treatment effects were largely consistent, so the results were pooled regardless of heterogeneity.

**Authors’ conclusions**

Anti-vascular endothelial growth factor (alone or in combination with triamcinolone) was effective for the treatment of diabetic macular oedema with improvements in visual acuity and central macular thickness (at least in the short-term).

**CRD commentary**

The aim and inclusion criteria for this review were clear and appropriate. The literature search appeared thorough, covering several databases as well as hand searches of pertinent journals. Attempts were made to identify grey literature, which limited the potential for publication bias. No language restrictions were used, which suggested that language bias should not be an issue. Only one author carried out each of the main stages of the review, which left some potential for reviewer bias.

Quality assessment was performed with reference to the Cochrane Handbook. However, the lack of a definition of the quality ‘grades’ assigned, along with the fact that several areas of bias were unclear, implied that trial results may not be fully reliable. The statistical synthesis of included trials was likely to be appropriate despite the heterogeneity observed.

Given the small number of trials included and questions over trial quality, the authors’ conclusions may be overly strong considering the evidence presented.

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

**Practice**: The authors did not state any implications for practice.
Research: The authors stated that future research could examine whether anti-vascular endothelial growth factor treatment could be initiated during earlier stages of diabetic macula edema rather than being reserved for those with chronic or refractory disease. Longer term follow-up studies are needed that consider adverse effects as well as economic and quality of life data. No trials comparing different types of anti-vascular endothelial growth factor were found.

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