Intravitreal bevacizumab (Avastin) vs ranibizumab (Lucentis) for the treatment of age-related macular degeneration: a systematic review
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CRD summary
The review concluded that compared to photodynamic therapy, bevacizumab showed a relative improvement in visual acuity similar to that of ranibizumab with photodynamic therapy; however, this was based on one small RCT with short-term follow-up. Limited evidence and poor reporting of results mean that the authors' conclusions should be interpreted with some caution.

Authors' objectives
To determine the efficacy and safety of intravitreal bevacizumab compared with ranibizumab in neovascular age-related macular degeneration.

Searching
MEDLINE, EMBASE, the Cochrane Library, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform were searched to August 2009; search terms were reported. The pharmaceutical manufacturers of ranibizumab and bevacizumab were contacted. References of relevant studies and reviews were checked by hand.

Study selection
Randomised clinical trials (RCTs) that evaluated intravitreal bevacizumab or ranibizumab as monotherapy compared with any other treatment in patients with exudative age-related macular degeneration were eligible. Case series were included if they enrolled a minimum of 10 participants and met predefined quality standards (adequate information regarding patient selection or consecutive selection of patients). Studies that included patients with other indications than exudative age-related macular degeneration, patients previously treated with vascular endothelial growth factor inhibitors and patients who received systemic treatment were excluded.

RCTs that evaluated ranibizumab (0.3/0.5mg monthly) versus photodynamic therapy, sham or usual care and bevacizumab (1.0 to 2.5mg single injection monthly or as required) versus triamcinolone were included. The mean number of injections received ranged from one to 24. A number of case series that examined bevacizumab were included in the review; patients received between one and four intravitreal bevacizumab injections (dosage ranged from 1.0mg to 2.5mg). In the RCTs, the number of participants treated with anti-vascular endothelial growth factor ranged from 10 to 478 and follow-up ranged from three to 24 months. Three of the ranibizumab trials were pharmaceutical industry sponsored. All the RCTs that evaluated bevacizumab were single-centre trials. Two studies reported that no pharmaceutical sponsorship was involved.

Two reviewers independently selected studies for inclusion in the review. Any disagreement was resolved by discussion and consensus.

Assessment of study quality
Two reviewers independently assessed study quality using a modified tool taken from Centre for Reviews and Dissemination guidelines which considered the number of participants, follow-up times, masking of outcome assessor, ascertainment of exposure and outcome measures and transparency of patient flow. Any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted data from the primary studies. Any disagreements were resolved by consensus.

Methods of synthesis
Studies were combined in a narrative synthesis grouped by treatment and outcome of interest.

Results of the review
Eight RCTs (1,679 patients) and 25 case series (2,519 patients, range 12 to 165) were included. Four RCTs examined ranibizumab and four RCTs examined bevacizumab. All the case series (13 prospective and 12 retrospective) examined bevacizumab.

The authors stated that in contrast to the ranibizumab trials none of the RCTs that evaluated bevacizumab met the quality requirements of phase III trials: validity was limited by small sample size, inadequate masking, lack of standardised vision measurements, missing intention-to-treat analyses and lack of longer-term data.

Ranibizumab:

At 24 months, approximately 90% of patients treated with monthly ranibizumab injections showed stable acuity compared with the control arms, which showed 66% for photodynamic therapy and 53% for sham (two RCTs). Between 34% and 40% of patients treated with 0.5mg ranibizumab gained 15 or more letters of visual acuity compared with 5% of patients who received sham or photodynamic therapy treatment (one RCT). Greater improvement in near activities, distance activities and vision specific dependency activities was found in patients treated with ranibizumab compared with sham treatments at 24 months (two RCTs).

Compared with photodynamic therapy (with or without intravitreal triamcinolone), bevacizumab showed a relative improvement in visual acuity similar in size to the comparison of ranibizumab with photodynamic therapy (30% to 35% improvement) after six and 12 months (two RCTs). None of the case series reported a significant decrease in visual acuity.

Adverse events:

Intravitreal ranibizumab was associated with endophthalmitis (≤2.1%, four trials), uveitis (≤1.3%, four trials), retinal detachment (≤1.5%, four trials), retinal tear (≤1.9%, four trials), vitreous haemorrhage (≤8.0%, four trials), traumatic lens damage (≤0.4%, three trials) and transient increase in intraocular pressure (proportion of patients not reported; four trials). No statistically significant between-group differences were found in the four RCTs for serious non-ocular adverse events.

Intravitreal bevacizumab was associated with an increased rate of pigment epithelial tears (5.5% versus 0.0%; one RCT), posterior vitreous detachment (14.6% versus 0.0%; one RCT) and cataaract progression (7.3% versus 0.0%; one RCT). No transient increase in intraocular pressure after injection was reported. Safety outcomes for the case series reported an increased rate of endophthalmitis (0.2% to 0.9%; four studies), retinal pigment epithelial tears (0.9% to 7.5%; six studies), vitreous detachment (9.8%; one study), submacular haemorrhage (1.5% to 7.5%; three studies), uveitis (0.3%; one study), retinal detachment (0.6%; one study) and vitreous haemorrhage (0.08%; one study). Seven case series reported minor ocular adverse events. Non-ocular events were reported in one retrospective case series.

Authors' conclusions

Compared to photodynamic therapy, bevacizumab showed a relative improvement in visual acuity that was of a similar size as in the comparison of ranibizumab with photodynamic therapy. However, this was based on one small RCT with short-term (12 months) follow-up. Given the lack of controlled data, the widespread off-label use of bevacizumab was not justified in clinical practice.

CRD commentary

The review question was supported by clear if somewhat broad inclusion criteria. Several relevant databases were searched and some attempt was made to locate unpublished studies, which minimised the possibility of publication bias. It was unclear whether the literature search was restricted by language. Appropriate steps were taken to minimise the likelihood of error or bias in study selection, data extraction and validity assessment.

Some appropriate criteria were used to evaluate trial quality, but important criteria (randomisation and allocation concealment) were lacking. Individual trial results were not reported. Given the differences between the included trials a narrative synthesis seemed suitable, but the results were not clearly presented; it seemed that effectiveness results were not reported for at least two of the RCTs. The authors acknowledged that no direct head-to-head RCTs that compared ranibizumab with bevacizumab existed and as a result of the large differences in trial quality no reliable indirect comparison could be performed; this limited assessment between the two treatments.
Limited evidence and poor reporting of results mean that the authors’ conclusions should be interpreted with some caution.

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

**Practice:** The authors stated that widespread off-label use of bevacizumab was not justified in clinical practice. Doctors and patients should be aware of the insufficient safety data regarding intravitreal bevacizumab.

**Research:** The authors stated a need for head-to-head studies that compared both vascular endothelial growth factor antibodies, or at least well-controlled randomised trials that evaluated intravitreal bevacizumab.

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