A Systematic Review of Intravitreal Bevacizumab for the Treatment of Diabetic Macular Edema


**Introduction**

Diabetic retinopathy (DR) and diabetic macular edema (DME) are microvascular complications of diabetes that are a leading cause of blindness in the diabetic population. DME — which is swelling of the retina due to leakage of fluid from blood vessels within the macula, the central portion of the retina — may occur at any time during the progression of DR. The goal of treatment is to preserve current visual acuity and reduce the chances of progression to visual loss.

Available treatments for DME include laser photocoagulation therapy to cauterize leaking blood vessels, injection into the eye with a corticosteroid, and injection into the eye with anti-vascular endothelial growth factors (anti-VEGF) to prevent blood vessel growth. Successful laser treatment reduces moderate visual loss but has limited effects on improving visual acuity. Intravitreal injection of corticosteroids, such as triamcinolone, may moderately improve visual acuity, but it generally offers only short-term improvements in acuity in cases of DME refractory to laser treatment. Moreover, triamcinolone is not licensed by Health Canada for this indication.

Ranibizumab, an anti-VEGF, is the only drug therapy licensed by Health Canada for the treatment of DME. Bevacizumab, another anti-VEGF, is available as an anti-cancer agent and is being used to treat DME without an indication for this use. This systematic review was undertaken to compare the therapeutic effects of intravitreal bevacizumab with standard therapies for DME.

**Objective**

The objective of the report was to answer the following research question:

In randomized controlled trials (RCTs), does intravitreal injection of bevacizumab provide a therapeutic advantage in the effects on visual acuity, morbidity, and/or mortality, in comparison with other standard therapy (intravitreal injection of triamcinolone, pegaptanib, or ranibizumab, or other drug therapies; and laser photocoagulation), sham treatment, or placebo in the treatment of DME?

**Methods**

An information specialist conducted a literature search using a peer-reviewed search strategy, searching the following bibliographic databases: Ovid MEDLINE with In-Process records and daily updates through Ovid (1948 to present), Embase through Ovid (1980 to present), and The Cochrane Library through Wiley. Grey literature (literature that is not commercially published) was identified by a focused Google search. No filters were applied to limit the retrieval by study type. Regular alerts were established to update the search until May 1, 2012. Where possible, retrieval was limited to the human population.

A supplemental review based on a non-systematic literature search was conducted to further identify evidence regarding the safety of intravitreal bevacizumab use in ocular conditions. This search also considered observational studies and post-marketing surveillance safety data.
Only RCTs (open-label, single-masked, or double-masked) comparing intravitreal bevacizumab with placebo/sham or other treatments in patients with DME were included in this systematic review.

We analyzed outcomes in order of clinical importance, placing the greatest weight on all-cause mortality and serious adverse events (SAEs), validated visual acuity measures, activities of daily living, and quality of life. Meta-analysis was carried out whenever possible. We assessed risk of bias according to standardized criteria, which helped inform our conclusions.

**Results**

**Bevacizumab Versus Sham**

One trial\(^5\) (n = 78 eyes) compared bevacizumab with sham treatment in patients with DME refractory to laser therapy. Improvement in best-corrected visual acuity (BCVA) was not seen with bevacizumab at week 6, but differed significantly from sham at weeks 12 to 24. The logarithm of the minimum angle of resolution (logMAR) difference was 0.21 ± 0.7 (P = 0.01) at 24 weeks; this equates to an improvement of approximately 11 Early Treatment Diabetic Retinopathy Study (ETDRS) letters with bevacizumab compared with sham. Central macular thickness was decreased compared with sham at 6 and 24 weeks, but results were not significant at 12 and 18 weeks. No withdrawals due to adverse events (WDAE), increased intraocular pressure, or infections were reported in either group. Few adverse events (AE) were reported: eight eyes with mild anterior chamber reactions and one eye progressing to fibrous proliferation were reported in the bevacizumab group. Leakage on fluorescein angiography was not reported.\(^5\)

**Bevacizumab Versus Laser**

Five trials compared bevacizumab with laser photocoagulation.\(^6\)\(^-\)\(^8\) Three RCTs measured 15-letter (three-line) gain in BCVA ETDRS at 6, 12 to 16, \(^6\)\(^7\) and 36 to 52 weeks.\(^7\)\(^8\) Bevacizumab outperformed laser: absolute benefit increase was 12%, 16%, and 12% at 6, 12 to 16, and 36 to 52 weeks, respectively.\(^6\)\(^-\)\(^8\)

Three RCTs measured BCVA logMAR at 6 weeks and found that bevacizumab provided a significant improvement versus laser.\(^7\)\(^8\)\(^10\) This difference is approximately equivalent to nine ETDRS letters. The difference was not statistically significant at weeks 12, 16, or 24.\(^7\)\(^8\)\(^10\)

One trial reported visual acuity at 12 months: a median gain of eight letters in the bevacizumab group versus a median loss of 0.5 letters in the laser group.\(^8\)

Over all five trials, four eyes had increased intraocular pressure in the bevacizumab group versus none in the laser group. One eye developed endophthalmitis in the bevacizumab group. In total, 22% of AEs were reported in the bevacizumab group versus 12% in the laser group.\(^7\)\(^8\)

Mean change in central macular thickness did not differ significantly between bevacizumab and laser at week 6. At week 24, laser performed better than bevacizumab. This outcome was measured in two trials, but results mainly reflect one trial, with 84% of the weight.\(^10\) Median change in central macular thickness was reported in two trials, and did not differ between bevacizumab and laser.\(^8\)\(^11\) One trial reported on macular leakage, with a 62% decrease in macular leakage in the bevacizumab group versus a 53% decrease in the laser group.\(^10\)
**Bevacizumab Versus Triamcinolone**

Four RCTs compared bevacizumab with triamcinolone.\(^{11-14}\) One RCT reported a two-line or greater improvement (ETDRS); this occurred in 58% of eyes on triamcinolone versus none treated with bevacizumab.\(^{12}\) It also reported deterioration of one or more lines in three bevacizumab-treated eyes and in none of the triamcinolone-treated eyes. This trial had inadequate masking and allocation concealment, resulting in a high risk of bias.\(^{12}\)

Two trials reported that BCVA logMAR was significantly better on triamcinolone than bevacizumab at weeks 6, 12, and 24; in other words, approximate mean differences of eight, six, and five ETDRS letters, respectively.\(^{13,14}\)

Both trials had either inadequate allocation concealment and masking, or inadequate reporting on methods. The one-line ETDRS gain (five letters, 0.1 logMAR) for triamcinolone at week 24 is of questionable clinical significance, as the minimum clinically important difference cited in the literature is generally two lines or greater.\(^{15-18}\)

Increased intraocular pressure occurred in 8/50 (16%) eyes on triamcinolone versus zero on bevacizumab in two trials.\(^{12,19}\) Two other trials compared the mean change in intraocular pressure.\(^{13,14}\) Results favoured bevacizumab, with a −1.67 mmHg change in intraocular pressure on bevacizumab at week 6 versus triamcinolone, and no significant differences at week 12.\(^{13,14}\) No infections were reported. One anterior chamber reaction was reported as an AE in the triamcinolone group. Leakage on fluorescein angiography was not reported in any of the trials.

**Critical Appraisal**

Of the 10 included RCTs, three trials comparing bevacizumab with laser had low risk of bias.\(^{6-8}\) These three trials measured ETDRS line improvement and consistently found a benefit for bevacizumab over laser, both for greater improvement and less deterioration. The two other trials that compared bevacizumab with laser had a high risk of bias due to problems with research methods and reporting.\(^{9,10}\) One of these trials did not adequately report on randomization, allocation concealment, or masking.\(^{10}\) This trial was also responsible for heterogeneity at six weeks for both the BCVA logMAR and central macular thickness measurements. All trials comparing bevacizumab versus triamcinolone either had inadequate masking and concealment of treatment allocation or inadequate reporting of these aspects of trial methods. Six trials (one comparing bevacizumab with sham,\(^{5}\) two of five comparing bevacizumab with laser,\(^{9,10}\) and three of four comparing bevacizumab with triamcinolone\(^{12-14}\)) failed to report on early withdrawals and loss to follow-up, and only selectively reported common and SAEs. It is unclear whether reported results for these trials reflected the full patient population or only those who completed all assessments.

**Supplemental Safety Evaluation**

Given the relative paucity of high-quality safety evidence reported in the trials included in the systematic review, we conducted a supplemental search of the literature to further evaluate the evidence for the safety of intravitreal bevacizumab among patients with DME and other ocular conditions. This supplemental (non-systematic) safety review included two systematic reviews,\(^{20,21}\) one head-to-head RCT comparing bevacizumab with ranibizumab in treating age-related macular degeneration (AMD),\(^{22,23}\) two retrospective cohort analyses,\(^{24,26}\) and a multicentre case series.\(^{27}\)

In the two systematic reviews of intravitreal bevacizumab, safety, study designs, and the number of patients in reviewed studies were generally insufficient to detect rare AEs such as endophthalmitis due to bevacizumab. A systematic review comparing ocular and systemic AEs associated with bevacizumab and ranibizumab used in patients with AMD did not
show important differences in the frequency of events between the drugs. However, the results of the review were compromised by relatively lower quality evidence for bevacizumab compared with that for ranibizumab. A head-to-head, randomized, non-inferiority trial between bevacizumab and ranibizumab in patients with AMD reported similar rates of AEs between the treatments, including total SAEs after one year: 28.3% on bevacizumab versus 23.9% on ranibizumab; total cumulative SAEs have not been reported for the full two-year study period. In a secondary analysis, the authors note more serious systemic AEs (39.9% on bevacizumab versus 31.7% on ranibizumab). The authors noted the excess systemic events were largely those not previously associated with systemic therapy with anti-VEGF agents. It was unclear whether this imbalance in serious systemic events arose from factors unaccounted for in the trial design and analysis, by chance, or truly reflects an important safety signal for bevacizumab versus ranibizumab. Additionally, the rate of endophthalmitis for bevacizumab was almost twice that of ranibizumab (1.2% on bevacizumab versus 0.7% on ranibizumab) at two years; however, the difference was not statistically significant and may have occurred by chance.

One large retrospective analysis of insurance claims data failed to show a difference between bevacizumab and ranibizumab in the rate of serious systemic events in the treatment of AMD. Similarly, a case series involving greater than 12,000 and 14,000 injections of intravitreal bevacizumab and ranibizumab, respectively, reported no difference in the crude incidence proportions of endophthalmitis between these anti-VEGFs in the treatment of DME and AMD. These systemic AEs and ocular infection data are in contrast to a manufacturer-supported analysis that reported a higher risk of overall mortality, hemorrhagic cerebrovascular accident, ocular inflammation, and cataract surgery following AMD treatment with bevacizumab versus ranibizumab. However, the latter analysis may have been confounded by a lack of sufficient adjustment for important confounding factors, such as socioeconomic status and health factors (smoking, lipid, and blood pressure levels).

Limitations

As can be seen from the main outcomes in the bevacizumab versus laser trials, effects of bevacizumab regarding BCVA logMAR and central macular thickness diminish over time after each treatment. This is consistent with reports that the effective period following bevacizumab treatment is between 6 and 12 weeks following a single injection. In most included trials, patients had one injection only, making longer-term effects difficult to ascertain.

Regarding the bevacizumab versus triamcinolone trials, only one of the included trials mentions a sample size calculation to ascertain study power. However, it does not state the degree of difference in the primary outcomes measure that the study is powered to detect. In our meta-analysis, BCVA logMAR showed a significant difference in favour of triamcinolone to week 24. However, in the largest included trial, the difference favouring triamcinolone disappeared after 12 weeks, and final measurements of visual acuity (BCVA logMAR) and central macular thickness at 24 weeks did not differ between groups. In our meta-analysis of this outcome, results for another trial influenced the statistically significant finding at 24 weeks. This is despite the trial’s small sample size, with only 13 eyes in each treatment group. In general, however, this trial had fewer methodological shortcomings in relation to randomization, allocation concealment, and masking than the other bevacizumab versus triamcinolone trials.

As was highlighted in the descriptions of the included studies, patient inclusion and exclusion criteria were quite variable across studies; for example, some studies included only patients...
with diffuse DME, while others included patients with focal disease, and still others included patients with mixed disease. Studies were also variable regarding previous treatment, with some including patients who were treatment-naive versus others that included patients with DME refractory to laser. Despite this variability, there were few analyses with significant statistical heterogeneity in our meta-analysis, although a handful of the analyses did show substantial heterogeneity ($I^2 > 75\%$) and tended to be associated with mean changes in central macular thickness. In addition, there were few instances of inconsistency in the direction of effects, further suggesting the extent of heterogeneity was within acceptable limits.

There was also variability across the included trials regarding the number of eyes randomized to treatment, with studies using either a paired-eye design, single-eye design, or (most frequently) a two-eye design in which some or all subjects contributed both eyes. This has implications for study sample size requirements, statistical methodologies, and the denominator used to calculate event rates in the included trials. This is particularly important for the safety analyses for systemic AEs, as using eyes as the denominator may underestimate the incidence of these events.

A major limitation of the reviewed evidence is the lack of a head-to-head comparison between bevacizumab and ranibizumab for treating DME, although this is the most closely related treatment and ranibizumab has received Health Canada Notice of Compliance for DME.

Additionally, the dearth of evidence for patient-centred outcomes — such as mortality, serious morbidity, and impact on patients’ ability to perform activities of daily living and quality of life — are concerning. Such outcomes require greater consideration in future research.

Conclusions

There is insufficient evidence to draw conclusions on the effects of bevacizumab on mortality, serious morbidity, activities of daily living, and quality of life. Bevacizumab has been shown to improve visual acuity in patients with DME refractory to laser therapy. A clinically significant mean difference was observed in visual acuity of $0.21 \pm 0.7$ compared with sham treatment, which is the equivalent of a two-line (10-letter) gain on the ETDRS scale. In patients who have not yet undergone laser therapy, bevacizumab significantly improved visual acuity versus laser therapy in trials lasting up to one year. The absolute benefit increase ranged from 15\% to 19\% over 6 to 52 weeks. However, patients experienced more AEs on bevacizumab than laser.

There is insufficient evidence that bevacizumab improves visual acuity to an equal or greater extent than triamcinolone. The trials that compared bevacizumab to triamcinolone had a high risk of bias, as measured both by design features such as lack of masking of patients or those providing treatment or of those assessing outcomes, and inadequate reporting.

There is also a lack of robust evidence as to the long-term safety profile of intravitreal bevacizumab, particularly due to sparse AE reporting and short study follow-up periods. The single head-to-head randomized trial between bevacizumab and ranibizumab (for the treatment of AMD) suggested an excess risk of non-specific serious systemic AEs for bevacizumab-treated patients over the two-year period of the trial. However, the importance of this difference remains unclear. There is conflicting evidence from large health claim database analyses, with one study failing to find a difference in AEs between bevacizumab and ranibizumab, and a manufacturer-sponsored analysis finding greater harm with bevacizumab than ranibizumab. As well, the lack of post-marketing surveillance compounds the situation.
The results of this systematic review align with those of another recently published health technology assessment performed for the United States Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), which assessed the effects of anti-VEGFs for treating DME. In that review, pairwise indirect comparisons between anti-VEGF agents suggested bevacizumab is not significantly different from ranibizumab for improving visual acuity in patients with DME. Compared with this review, differences in study inclusion criteria and use of indirect comparisons methodology may, in part, explain the more definitive conclusion of the MEDCAC health technology assessment that intravitreal bevacizumab has benefit in the treatment of DME. However, both reviews echo the relative paucity of evidence available for bevacizumab versus ranibizumab, especially regarding safety profiles.

Large, well-conducted RCTs of sufficient duration are needed to provide better evidence of the effects of intravitreal bevacizumab compared with other treatments used for DME. As well, such studies would better define the optimal dose, timing, and duration of treatment with intravitreal bevacizumab for DME.

References


This report was commissioned by the NIHR HTA programme as project number 10/21.


24. Avastin (bevacizumab for injection) 100 and 400 mg vials (25 mg/mL solution for injection) [product monograph]. Mississauga (ON): Hoffmann-La Roche; 2011 Sep 2.
25. Gower EW, Cassard S, Chu L. Adverse event rates following intravitreal injection of Avastin or Lucentis for treating age-related macular degeneration [Internet]. Abstract presented at: The Association of Research in Vision and Ophthalmology; 2011 May 1-5; Fort Lauderdale. [cited 2011 Dec 6]. Available from: http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=3a667d20-f42d-421e-a859-e1b680de80ed&cKey=4e534aee-b678-4b9d-91dc-20a9d6ae0c56&mKey=6f224a2d-af6a-4533-8bbb-6a8d7b26ed83


