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[Intervention Review]

Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis

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ABSTRACT

Background

Diabetic macular oedema (DMO) is a common complication of diabetic retinopathy. Antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) modalities can reduce oedema and thereby improve vision and prevent further visual loss. These drugs have replaced laser photocoagulation as the standard of care for people with DMO.

Objectives

The 2014 update of this review found high-quality evidence of benefit with antiangiogenic therapy with anti-VEGF modalities, compared to laser photocoagulation, for the treatment of DMO.The objective of this updated review is to compare the effectiveness and safety of the different anti-VEGF drugs in preserving and improving vision and quality of life using network meta-analysis methods.

Search methods

We searched various electronic databases on 26 April 2017.

Selection criteria

We included randomised controlled trials (RCTs) that compared any anti-angiogenic drug with an anti-VEGF mechanism of action versus another anti-VEGF drug, another treatment, sham or no treatment in people with DMO.

Data collection and analysis

We used standard Cochrane methods for pair-wise meta-analysis and we augmented this evidence using network meta-analysis methods. We focused on the relative efficacy and safety of the three most commonly used drugs as interventions of direct interest for practice: aflibercept and ranibizumab, used on-label; and off-label bevacizumab.

We collected data on three efficacy outcomes (gain of 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters; mean change in best-corrected visual acuity (BCVA); mean change in central retinal thickness (CRT)), three safety outcomes (all severe systemic adverse events (SSAEs); all-cause death; arterial thromboembolic events) and quality of life.

We used Stata '*network*' meta-analysis package for all analyses. We investigated the risk of bias of mixed comparisons based on the variance contribution of each study, having assigned an overall risk of bias to each study.

Main results

Twenty-four studies included 6007 participants with DMO and moderate vision loss, of which two studies randomised 265 eyes of 230 participants and one was a cross-over study on 56 participants (62 eyes) that was treated as a parallel-arm trial. Data were collected on drugs of direct interest from three studies on aflibercept (975 eyes), eight studies on bevacizumab (515 eyes), and 14 studies on ranibizumab (1518 eyes). As treatments of indirect interest or legacy treatment we included three studies on pegaptanib (541 eyes), five studies on ranibizumab plus prompt laser (557 eyes), one study on ranibizumab plus deferred laser (188 eyes), 13 studies on laser photocoagulation (936 eyes) and six studies on sham treatment (793 eyes).

Aflibercept, bevacizumab and ranibizumab were all more effective than laser for improving vision by 3 or more lines after one year (high-certainty evidence). Approximately one in 10 people improve vision with laser, and about three in 10 people improve with anti-VEGF treatment: risk ratio (RR) versus laser 3.66 (95% confidence interval (CI) 2.79 to 4.79) for aflibercept; RR 2.47 (95% CI 1.81 to 3.37) for bevacizumab; RR 2.76 (95% CI 2.12 to 3.59) for ranibizumab. On average there was no change in visual acuity (VA) with laser after one year, compared with a gain of 1 or 2 lines with anti-VEGF treatment: laser versus aflibercept mean difference (MD) −0.20 (95% CI −0.22 to −0.17) logMAR; versus bevacizumab MD −0.12 (95% CI −0.15 to −0.09) logMAR; versus ranibizumab MD −0.12 (95% CI −0.14 to −0.10) logMAR. The certainty of the evidence was high for the comparison of aflibercept and ranibizumab with laser and moderate for bevacizumab comparison with laser due to inconsistency between the indirect and direct evidence.

People receiving ranibizumab were less likely to gain 3 or more lines of VA at one year compared with aflibercept: RR 0.75 (95% CI 0.60 to 0.94), moderate-certainty evidence. For every 1000 people treated with aflibercept, 92 fewer would gain 3 or more lines of VA at one year if treated with ranibizumab (22 to 148 fewer). On average people receiving ranibizumab had worse VA at one year (MD 0.08 logMAR units, 95% CI 0.05 to 0.11), moderate-certainty evidence; and higher CRT (MD 39 µm, 95% CI 2 µm to 76 µm; low-certainty evidence). Ranibizumab and bevacizumab were comparable with respect to aflibercept and did not differ in terms of VA: RR of gain of 3 or more lines of VA at one year 1.11 (95% CI 0.87 to 1.43), moderate-certainty evidence, and difference in change in VA was 0.00 (95% CI −0.02 to 0.03) logMAR, moderate-certainty evidence. CRT reduction favoured ranibizumab by −29 µm (95% CI −58 µm to −1 µm, low-certainty evidence). There was no evidence of overall statistical inconsistency in our analyses.

The previous version of this review found moderate-certainty evidence of good safety of antiangiogenic drugs versus control. This update used data at the longest available follow-up (one or two years) and found that aflibercept, ranibizumab and bevacizumab do not differ regarding systemic serious adverse events (SSAEs) (moderate- or high-certainty evidence). However, risk of bias was variable, loop inconsistency could be found and estimates were not precise enough on relative safety regarding less frequent events such as arterial thromboembolic events or death (low- or very low-certainty evidence).

Two-year data were available and reported in only four RCTs in this review. Most industry-sponsored studies were open-label after one year. One large publicly-funded study compared the three drugs at two years and found no difference.

Authors' conclusions

Anti-VEGF drugs are effective at improving vision in people with DMO with three to four in every 10 people likely to experience an improvement of 3 or more lines VA at one year. There is moderate-certainty evidence that aflibercept confers some advantage over ranibizumab and bevacizumab in people with DMO at one year in visual and anatomic terms. Relative effects among anti-VEGF drugs at two years are less well known, since most studies were short term. Evidence from RCTs may not apply to real-world practice, where people in need of antiangiogenic treatment are often under-treated and under-monitored.

We found no signals of differences in overall safety between the three antiangiogenic drugs that are currently available to treat DMO, but our estimates are imprecise for cardiovascular events and death.

PLAIN LANGUAGE SUMMARY

Anti-vascular endothelial growth factor (anti-VEGF) drugs for diabetic macular oedema

What is the aim of this review?
The aim of this Cochrane Review was to find out which is the best type of anti-VEGF drug for diabetic macular oedema (DMO). Cochrane researchers collected and analysed all relevant studies to answer this question and found 24 studies.

Key messages
Anti-VEGF drugs given by injection into the eye improve vision in people with diabetic macular oedema as compared to no average improvement with laser photocoagulation. One of these drugs, aflibercept, probably works slightly better after one year. There did not appear to be important harms from any of these drugs.

What was studied in the review?

The light-sensitive tissue at the back of the eye is known as the retina. The central area of the retina is called the macula. People with diabetes can develop problems in the retina, known as retinopathy. Some people with diabetic retinopathy can also develop oedema (swelling or thickening) at the macula. DMO is a common complication of diabetic retinopathy and can lead to visual loss.

One type of treatment for DMO is anti-VEGF. This drug is given by means of an injection into the eye. It can reduce the swelling at the back of the eye and prevent visual loss. There are three main types of anti-VEGF drugs in use: aflibercept (Eyelea™), bevacizumab (Avastin) and ranibizumab (Lucentis™). Only aflibercept and ranibizumab have received marketing authorisation for the treatment of DMO. All three drugs are used to prevent visual loss and improve vision. They do this by slowing down the growth of new blood vessels and thereby reducing the swelling at the back of the eye. They may have adverse effects, particularly related to effects on blood vessels in the rest of the body. These effects may include stroke and heart attack.

What are the main results of the review?
Cochrane researchers found 24 relevant studies. Fourteen of these studies were industry-sponsored studies from USA, Europe or Asia. Ten studies were independent of industry funding and were from USA, Europe, Middle East and South America.

These studies investigated ranibizumab, bevacizumab and aflibercept. These anti-VEGF drugs were compared with no treatment, placebo treatment, laser treatment, or each other. The drugs were given every month, every two months, as needed or 'treat and extend', which means that the time period between treatments is extended if the condition has stabilised. Decisions about re-treating were based on visual acuity or by looking at the back of the eye.

The review reveals the following results.

• All three anti-VEGF drugs prevent visual loss and improve vision in people with DMO (high-certainty evidence).

• People receiving ranibizumab were probably slightly less likely to improve vision compared with aflibercept at one year after the start of treatment (moderate-certainty evidence). Approximately three in 10 people improve vision by 3 or more lines with ranibizumab and one in 10 additional people can achieve this with aflibercept.

• People receiving ranibizumab and bevacizumab probably have a similar visual outcome at one year after the start of treatment (moderate-certainty evidence).

• Aflibercept, ranibizumab and bevacizumab are similar for common and serious systemic harms (such as any disease leading to hospitalisation, disability or death) (moderate- or high-certainty evidence) but is less certain for arterial thromboembolic events (mainly stroke, myocardial infarction and vascular death) and death of any cause (very low-certainty evidence).

How up to date is this review?
Cochrane researchers searched for studies that had been published up to 26 April 2017.