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# Anti-vascular endothelial growth factor combined with intravitreal



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## [Intervention Review]

## Anti-vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema

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#### **ABSTRACT**

#### **Background**

The combination of steroid and anti-vascular endothelial growth factor (VEGF) intravitreal therapeutic agents could potentially have synergistic effects for treating diabetic macular oedema (DMO). On the one hand, if combined treatment is more effective than monotherapy, there would be significant implications for improving patient outcomes. Conversely, if there is no added benefit of combination therapy, then people could be potentially exposed to unnecessary local or systemic side effects.

## Objectives

To assess the effects of intravitreal agents that block vascular endothelial growth factor activity (anti-VEGF agents) plus intravitreal steroids versus monotherapy with macular laser, intravitreal steroids or intravitreal anti-VEGF agents for managing DMO.

## Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2018, Issue 1); Ovid MEDLINE; Ovid Embase; LILACS; the ISRCTN registry; ClinicalTrials.gov and the ICTRP. The date of the search was 21 February 2018.

## **Selection criteria**

We included randomised controlled trials (RCTs) of intravitreal anti-VEGF combined with intravitreal steroids versus intravitreal anti-VEGF alone, intravitreal steroids alone or macular laser alone for managing DMO. We included people with DMO of all ages and both sexes. We also included trials where both eyes from one participant received different treatments.

## **Data collection and analysis**

We used standard methodological procedures recommended by Cochrane. Two authors independently reviewed all the titles and abstracts identified from the electronic and manual searches against the inclusion criteria. Our primary outcome was change in best corrected visual acuity (BCVA) between baseline and one year. Secondary outcomes included change in central macular thickness (CMT), economic data and quality of life. We considered adverse effects including intraocular inflammation, raised intraocular pressure (IOP) and development of cataract.

## Main results

There were eight RCTs (703 participants, 817 eyes) that met our inclusion criteria with only three studies reporting outcomes at one year. The studies took place in Iran (3), USA (2), Brazil (1), Czech Republic (1) and South Korea (1). Seven studies used the unlicensed



anti-VEGF agent bevacizumab and one study used licensed ranibizumab. The study that used licensed ranibizumab had a unique design compared with the other studies in that included eyes had persisting DMO after anti-VEGF monotherapy and received three monthly doses of ranibizumab prior to allocation. The anti-VEGF agent was combined with intravitreal triamcinolone in six studies and with an intravitreal dexamethasone implant in two studies. The comparator group was anti-VEGF alone in all studies; two studies had an additional steroid monotherapy arm, another study had an additional macular laser photocoagulation arm. Whilst we judged these studies to be at low risk of bias for most domains, at least one domain was at unclear risk in all studies.

When comparing anti-VEGF/steroid with anti-VEGF monotherapy as primary therapy for DMO, we found no meaningful clinical difference in change in BCVA (mean difference (MD) -2.29 visual acuity (VA) letters, 95% confidence interval (CI) -6.03 to 1.45; 3 RCTs; 188 eyes; low-certainty evidence) or change in CMT (MD  $0.20~\mu m$ , 95% CI -37.14 to 37.53; 3 RCTs; 188 eyes; low-certainty evidence) at one year. There was very low-certainty evidence on intraocular inflammation from 8 studies, with one event in the anti-VEGF/steroid group (313 eyes) and two events in the anti-VEGF group (322 eyes). There was a greater risk of raised IOP (Peto odds ratio (OR) 8.13, 95% CI 4.67 to 14.16; 635 eyes; 8 RCTs; moderate-certainty evidence) and development of cataract (Peto OR 7.49, 95% CI 2.87 to 19.60; 635 eyes; 8 RCTs; moderate-certainty evidence) in eyes receiving anti-VEGF/steroid compared with anti-VEGF monotherapy. There was low-certainty evidence from one study of an increased risk of systemic adverse events in the anti-VEGF/steroid group compared with the anti-VEGF alone group (Peto OR 1.32, 95% CI 0.61 to 2.86; 103 eyes).

One study compared anti-VEGF/steroid versus macular laser therapy. At one year investigators did not report a meaningful difference between the groups in change in BCVA (MD 4.00 VA letters 95% CI -2.70 to 10.70; 80 eyes; low-certainty evidence) or change in CMT (MD  $-16.00 \, \mu m$ , 95% CI -68.93 to 36.93; 80 eyes; low-certainty evidence). There was very low-certainty evidence suggesting an increased risk of cataract in the anti-VEGF/steroid group compared with the macular laser group (Peto OR 4.58, 95% 0.99 to 21.10, 100 eyes) and an increased risk of elevated IOP in the anti-VEGF/steroid group compared with the macular laser group (Peto OR 9.49, 95% CI 2.86 to 31.51; 100 eyes).

One study provided very low-certainty evidence comparing anti-VEGF/steroid versus steroid monotherapy at one year. There was no evidence of a meaningful difference in BCVA between treatments at one year (MD 0 VA letters, 95% CI -6.1 to 6.1, low-certainty evidence). Likewise, there was no meaningful difference in the mean CMT at one year (MD - 9  $\mu$ m, 95% CI -39.87 $\mu$ m to 21.87 $\mu$ m between the anti-VEGF/steroid group and the steroid group. There was very low-certainty evidence on raised IOP at one year comparing the anti-VEGF/steroid versus steroid groups (Peto OR 0.75, 95% CI 0.16 to 3.55).

No included study reported impact of treatment on patients' quality of life or economic data. None of the studies reported any cases of endophthalmitis.

#### **Authors' conclusions**

Combination of intravitreal anti-VEGF plus intravitreal steroids does not appear to offer additional visual benefit compared with monotherapy for DMO; at present the evidence for this is of low-certainty. There was an increased rate of cataract development and raised intraocular pressure in eyes treated with anti-VEGF plus steroid versus anti-VEGF alone. Patients were exposed to potential side effects of both these agents without reported additional benefit. The majority of the evidence comes from studies of bevacizumab and triamcinolone used as primary therapy for DMO. There is limited evidence from studies using licensed intravitreal anti-VEGF agents plus licensed intravitreal steroid implants with at least one year follow-up. It is not known whether treatment response is different in eyes that are phakic and pseudophakic at baseline.

## PLAIN LANGUAGE SUMMARY

## Anti-vascular endothelial growth factor (anti-VEGF) plus intravitreal steroids for diabetic macular oedema

#### What is the aim of this review?

The aim of this Cochrane Review was to find out whether injecting two drugs in combination (inhibitors of VEGF and steroids) into the vitreous jelly of eyes with macular oedema (swelling at the centre of the retina) due to diabetes works better than treatment with one drug alone.

#### **Key messages**

There is insufficient evidence to suggest that the two drugs in combination are better than treatment with one drug alone.

#### What was studied in the review?

Diabetic macular oedema is swelling at the back of the eye (retina) in people with diabetes. It is the most common cause of aquired visual loss in the mainly working-age population.

Both steroids and anti-VEGF agents, injected into the vitreous jelly of the eye (intravitreal), improve vision and reduce the amount of fluid accumulating in the central retina. The drugs have different mechanisms of action and may work well in combination, with significant implications for improving patient outcomes. However, if there is no added benefit of combination therapy, then people could be potentially exposed to unnecessary side effects such as cataract, glaucoma, stroke and heart attack.

## What are the main results of the review?



The Cochrane Review authors found eight relevant studies. Three studies were from Iran, two from USA and one each from Brazil, Czech Republic and South Korea. These studies compared an anti-VEGF (in most studies an unlicensed version called bevacizumab) plus intravitreal steroid agents versus anti-VEGF alone, an intravitreal steroid alone or macular laser alone.

We found insufficient evidence to suggest that the two drugs classes in combination are better than treatment with one drug class alone as the initial treatment for diabetic macula oedema. Moreover, there was a greater risk of raised intraocular pressure and cataract in people receiving anti-VEGF plus steroids compared with anti-VEGF alone.

## How up-to-date is this review?

Cochrane Review authors searched for studies that had been published up to 21 February 2018.