# Aflibercept versus dexamethasone for macular edema secondary to central retinal vein occlusion

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## Abstract

### Introduction

Macular edema is a frequent complication of central retinal vein occlusion that might lead to deterioration of visual acuity. The most commonly used treatments are dexamethasone implant and anti-vascular endothelial growth factor drugs, being aflibercept one of the most commonly used them. However, there is no consensus about which treatment constitute the best alternative.

### Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

### Results and conclusions

We identified two systematic reviews that included four primary studies overall, all randomized trials. We concluded that it is not possible to establish whether aflibercept is superior to dexamethasone in terms of improvement of visual acuity and safety, because the certainty of the existing evidence has been evaluated as very low.

## Problem

Macular edema is a frequent complication of central retinal vein occlusion. It is characterized by the accumulation of fluid in the macula, which translates into a deterioration of visual acuity. The most common mechanism is the obstruction of the central vein of the retina by a thrombus, a situation that leads to the formation of new blood vessels and blood extravasation due to local inflammation, which in turn causes macular edema. Corticosteroid implants were mostly used to treat this pathology in the past due to the presence of inflammation, with slight improvements in symptoms. Over time, it has been observed that endothelial vascular growth factors have an important role in the formation of edema, since they are potent inducers of vessel formation, in

addition to promoting their permeability. Currently, the most common treatment for this condition is the injection of drugs against vascular endothelial growth factor (anti-VEGF). However, it is not clear that anti-VEGF is superior than dexamethasone.

## Key messages

- We are uncertain whether aflibercept compared to dexamethasone leads to a greater level of improvement in visual acuity, because the certainty of the evidence has been assessed as very low.
- We are uncertain whether aflibercept compared to dexamethasone is safer, either due to adverse events or loss of visual acuity, because the certainty of the evidence has been assessed as very low.

## About the body of evidence for this question

| | |
|---|---|
| What is the evidence. See evidence matrix in Epistemonikos later | We found two systematic reviews[1,2] that included four primary studies[3,4,7,9], reported in eight references[3-10]. All corresponded to randomized trials.<br><br>No studies were found comparing interventions directly, so all analyses come from indirect comparisons obtained through network meta-analysis technique. |
| What types of patients were included* | All selected trials included patients with a diagnosis of macular edema secondary to occlusion of the central vein of the retina. One trial[4] also considered patients with occlusion of branches of the central vein of the retina, but these were analyzed separately, so they are not part of the results of this summary. Two trials [7,9] specified that patients should not have been older than 9 months since the diagnosis of the mentioned condition.<br><br>No exclusion criteria were specified. |
| What types of interventions were included* | Two trials [7,9] evaluated injections of aflibercept compared to placebo. Another trial[4] considered a dexamethasone implant against placebo. The fourth trial compared dexamethasone versus ranibizumab[3].<br><br>As mentioned earlier, the selected systematic reviews performed a network meta-analysis to indirectly compare these two treatments. |
| What types of outcomes were measured | The trials reported multiple outcomes, which were grouped by systematic reviews as follows:<br><br>• Visual acuity measured as proportion of patients who gained 3 lines or more on the Early Treatment Diabetic Retinopathy Study scale at 6 and 12 months, and as an average change of the best corrected visual acuity in 6 months using the same scale.<br>• Proportion of patients who lost 3 lines or more on the Early Treatment Diabetic Retinopathy Study scale at 6 months.<br>• Adverse events in each treatment.<br><br>The average follow-up of the trials was nine months, with a range from six to twelve months. |

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

## Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

## Summary of findings

The information on the effects of aflibercept versus dexamethasone in patients with central retinal vein occlusion is based on four randomized trials[3,4,7,9], from which two systematic reviews performed an indirect comparison using the network meta-analysis technique [1,2].

Two trials (361 patients)[7,9], compared aflibercept versus placebo, one trial (287 patients)[4] compared dexamethasone versus placebo, and one trial (243 patients)[3] compared dexamethasone versus ranibizumab.

It was not possible to reanalyze the information presented by the systematic reviews, so the results obtained directly from these are presented, instead of a reanalysis of the data.

The summary of findings is as follows:

- We are uncertain whether aflibercept compared to dexamethasone leads to a greater level of improvement in visual acuity, because the certainty of the evidence has been assessed as very low.
- We are uncertain whether dexamethasone compared to aflibercept leads to a greater loss of visual acuity, because the certainty of the evidence has been assessed as very low.
- We are uncertain whether aflibercept compared to dexamethasone leads to less adverse effects at 12 months of follow-up, because the certainty of the evidence has been assessed as very low.

**Aflibercept vs dexamethasone in macular edema secondary to central retinal vein occlusion**

**Patients** Macular edema secondary to central retinal vein occlusion
**Intervention** Aflibercept
**Comparison** Dexamethasone

| Outcome | Effect | Certainty of evidence (GRADE) |
|---|---|---|
| Visual acuity improvement | One review[1] showed that aflibercept was associated to a greater improvement in visual acuity* at 6 months (RR 2.65, 95% CI 1.48 to 4.95), consistent with the second review[2] (RR of 5.67; 95% CI 0.73 to 13.87).<br>The follow-up of this outcome at 12 months was reported by a review[2], also favoring aflibercept (RR 2.22; 95% CI 0.34 to 13.46).<br>One review[2] also reports the average change in the best corrected visual acuity at 6 months**, concluding that aflibercept would be better than dexamethasone (DM 21.6 95% CI -0.36 to 44.17). | ⨁◯◯◯[1,2,3] Very low |
| Loss of visual acuity*** | One review[2] reports that patients treated with dexamethasone had more loss of visual acuity* (RR 8.34; 95% CI 0.14 to 746.86). The other review[1] did not report it. | ⨁◯◯◯[1,2,3] Very low |
| Adverse effects in 12 months | The main adverse effects reported by one systematic review[2] associated with dexamethasone were: increased intraocular pressure (78 of 252 patients); eye pain (15 of 119); cataract (13 of 263); conjunctival hemorrhage (13 of 119); neovascularization of the iris (9 of 119); and retinal ischemia (6 of 119). In aflibercept were: eye pain (12 of 114); increased intraocular pressure (10 of 104); conjunctival hemorrhage (9 of 104); eye irritation (3 of 104); endophthalmitis (1 of 114); and retinal ischemia (1 of 104). | ⨁◯◯◯[1,3] Very low |

**GRADE:** Evidence grades of the GRADE Working Group (see later).

* Improvement and loss of visual acuity were evaluated through the ETDRS scale, as the proportion of patients who gained or lost 3 lines or more, respectively.
** Evaluated with ETDRS scale.
*** It is presented as a different outcome to improvement of visual acuity, since it is usually due to complications, so it would be more related to the safety of the treatment.

[1] The certainty of the evidence was downgraded in one level due to serious risk of bias, because the studies were not blinded.
[2] The certainty of the evidence was downgraded in one level for imprecision in the results, since they have a very wide confidence interval.
[3] The certainty of the evidence was downgraded in two levels due to indirectness, because the results come from an indirect analysis through network meta-analysis.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

## About the certainty of the evidence GRADE)*

⊕⊕⊕⊕
**High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
**Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
**Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
**Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

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* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

## Other considerations for decision-making

### To whom this evidence does and does not apply

This evidence applies to patients diagnosed with macular edema secondary to occlusion of the central vein of the retina.

### About the outcomes included in this summary

The selected outcomes are the most relevant for decision-making according to the opinion of experts in the subject, since they are those that directly affect the patient's quality of life, either due to the improvement in their visual acuity or to the avoidance of complications during treatment.

### Balance between benefits and risks, and certainty of the evidence

Both treatments, aflibercept and dexamethasone, have proven effectiveness regarding the gain of visual acuity in patients with macular edema secondary to occlusion of the central vein of the retina, however there are no direct comparisons.

Regarding safety, there is also no direct evidence comparing both treatments.

Therefore, the certainty of the evidence is very low, so it is not adequate to estimate the balance between risks and benefits of one treatment over another.

### Resource considerations

Systematic reviews did not evaluate the economic impact of each treatment. The individual cost of each aflibercept injection is less expensive than dexamethasone implant, but since the injection must be repeated several times unlike the corticosteroid implant that lasts approximately six months, the direct costs of anti-VEGF drugs could end up being higher than that of corticosteroids.

Considering the very low certainty of the evidence, it is not possible to make an adequate balance between benefits and costs.

### What would patients and their doctors think about this intervention

The most used treatment worldwide for this condition by ophthalmologists experts in the field, is the injection of anti-VEGF drugs, and within these, lately there is a tendency to use aflibercept for its longer half-life, although there is no proven evidence of superiority with respect to dexamethasone, which is another common therapy with proven efficacy.

Additionally, patients might also be in favor of anti-VEGF medications, since they are associated with lower incidence of undesirable outcomes such as cataract or increased intraocular pressure, which might frequently lead to loss of visual acuity.

With the evidence presented, it is unlikely to expect a modification in current behaviors, since according to expert's opinion, anti-VEGF would have better clinical outcomes.

### Differences between this summary and other sources

The conclusions of this summary coincide with those of one of the systematic reviews identified[1], since it establishes there is no clear superiority of one treatment over the other, considering the very low certainty of the evidence. However, the second review[2] concluded that aflibercept would be superior and safer than dexamethasone as a treatment of macular edema secondary to occlusion of the central vein of the retina. These conclusions could be explained in part because this review did not conduct an analysis of the certainty of the evidence, but simply limited its conclusions to the results of the statistical analysis.

The guideline of The Royal College of Ophthalmologists of the United Kingdom[11] concluded, like this summary, that aflibercept or other anti-VEGF would not be superior to dexamethasone. In contrast, the guideline of the American Academy of Ophthalmology of the United States[12] recommends anti-VEGF drugs over corticosteroids, with no clear superiority of aflibercept or another specific one.

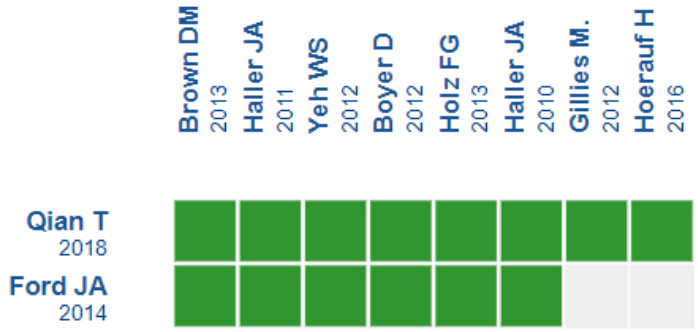
### Could this evidence change in the future?

It is very likely that the information provided in this summary will change with future research, because the certainty of the available evidence is very low.

We searched PROSPERO database and the International Clinical Trials Registry Platform of the World Health Organization, without finding ongoing reviews or trials that answer the question of interest.

## How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.




An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Aflibercept versus dexamethasone in macular edema secondary to central vein occlusion

## Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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