Aflibercept compared with dexamethasone in diabetic macular edema

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Abstract

Introduction

Diabetic macular edema is a frequent pathology that causes gradual deterioration of visual acuity, which does not have a standardized treatment. The anti-vascular endothelial growth factor (anti-VEGF) drugs and corticosteroids are widely used, especially aflibercept and dexamethasone, respectively, but it is unclear which one is best.

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

No evidence that compared the interventions directly in the population of interest was found, so systematic reviews that provide an estimate of the effect indirectly using network meta-analysis were selected. We identified two systematic reviews that together included four primary studies, all randomized trials.

We concluded that we are uncertain whether aflibercept compared to dexamethasone improves visual acuity or is safer, as the certainty of the evidence has been assessed as very low.

Problem

Diabetic macular edema is a manifestation of diabetic retinopathy, one of the most frequent eye diseases worldwide. The usual presentation of this condition is gradual deterioration of visual acuity, which without treatment is usually associated with a poor prognosis. For many years, laser therapy was used to reduce symptoms, but its results and multiple complications increased the urge to find alternative therapies. Nowadays, the most commonly used treatment by specialists is periodic intravitreal injection of anti-vascular endothelial growth factor drugs (anti-VEGF), among which aflibercept stands out, mainly due to its longer half-life, and corticosteroids, more specifically dexamethasone. Despite the above, there is no clear superiority between them, so it is important to summarize the evidence that allows us to compare both treatments.

Key messages

- No direct evidence that compares aflibercept versus dexamethasone in diabetic macular edema was found.
- We are uncertain whether aflibercept compared to dexamethasone improves visual acuity or reduces adverse events as 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	No evidence that compares the interventions directly in the population of interest was found, so systematic reviews that provide an estimate of the effect indirectly using network meta-analysis were selected. We found two systematic reviews [1], [2], which included four primary studies [3], [4], [5], [6], all randomized trials. This summary is based on the latter, since they evaluate the intervention in the population of interest, but against a different comparison.
What types of patients were included*	All trials included patients with the diagnosis of diabetic macular edema. None of the reviews reported if all the included patients had central involvement.
What types of interventions were included*	Two trials evaluated aflibercept [5], [6]: one compared it against other medications [4] and the other trial compared it against placebo [6]. Two trials evaluated dexamethasone [3], [5]: one evaluated the addition of dexamethasone to laser treatment [3] and the other compared it against another drug [5].
What types of outcomes were measured	The trials reported multiple outcomes, which were grouped by systematic reviews as follows: • Change in visual acuity in terms of mean change in best corrected visual acuity and gain of ten or more letters, which were measured using the Early Treatment Diabetic Retinopathy Study scale, at 12 months of follow-up. • Adverse events occurred during the 12 months of follow-up. The average follow-up of the trials was nine months with a range between six and 12 months.

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.

* Information about primary studies is not extracted directly from primary studies but from identified systematic reviews, unless otherwise stated.

Summary of findings

No direct evidence that compares aflibercept with dexamethasone in diabetic macular edema was found. Information of the effects of aflibercept compared to dexamethasone in diabetic macular edema is based on two systematic reviews that performed an indirect comparison using network meta-analyses [1], [2].

Since no studies were identified evaluating the question directly, the results in the summary of findings table are based on punctual estimators from each of the systematic reviews. All reviews [1], [2] assessed visual acuity outcomes and adverse events.

The summary of findings is the following:

- We are uncertain whether aflibercept compared to dexamethasone improves visual acuity as the certainty of the evidence has been assessed as very low.
- We are uncertain whether aflibercept compared to dexamethasone reduces adverse events as the certainty of the evidence has been assessed as very low.

Aflibercept versus dexamethasone in diabetic macular edema

Patients Patients with diabetic macular edema
Intervention Aflibercept
Comparison Dexamethasone

Outcome	Effect	Certainty of evidence (GRADE)
Visual acuity improvement (at 12 months)	No studies were found that directly evaluated the comparison of interest, but indirect evidence was identified: Two systematic reviews that conducted a network meta-analysis reported that the use of aflibercept improves visual acuity compared with dexamethasone [1], [2]. One review evaluated it through the gain of 10 or more letters (RR 2.1; 95% CI 1.29 to 3.4) [1] and the other through the ETDRS* scale (MD -7.07; 95% CI -13.77 to -0.27) [2].	⨁◯◯◯[1,2,3] Very low
Adverse events (at 12 months)	No studies were found that directly evaluated the comparison of interest, but indirect evidence was identified: Two systematic reviews that performed a network meta-analysis reported that the use of aflibercept decreases the incidence of adverse events [1], [2]. A systematic review [1] reported that the use of aflibercept compared with dexamethasone is associated with a lower risk of increased intraocular pressure (RR 0.08; 95% CI 0.02 - 0.42), vitreous hemorrhage (RR 0.3; 95% CI 0.07 - 1.39), eye pain (RR 0.8; 95% CI 0.29 - 2.21), decrease in visual acuity in treatment (RR 0.64; 95% CI 0.24 - 1.67) and cataracts (RR 0.42; 95% CI 0.13 - 1.39). The second systematic review [2] reported that in the aflibercept group there were a lower risk of increased intraocular pressure and progression to cataracts, without reporting statistical results.	⨁◯◯◯[1,2,3] Very low

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*Visual acuity improvement was assessed through the *Early Treatment Diabetic Retinopathy Study* (ETDRS) scale.

[1] The certainty of evidence was downgraded in two levels due to indirectness, since the results come from studies that evaluated a different comparison.
[2] The certainty of evidence was downgraded in one level due to serious risk of bias, because the trials were not blind.
[3] The certainty of evidence was downgraded in one level due to imprecision in the results, since each limit of the confidence interval leads to different decisions.

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

The evidence presented applies to patients with diagnosis of diabetic macular edema, regardless of the stage, central involvement and previously used treatments.

About the outcomes included in this summary

The outcomes included in this summary of the evidence are those considered critical for decision-making in the opinion of the authors and generally coincide with those reported by the identified systematic reviews, since they have clinical repercussions on the patient, both favorable, as is the gain in visual acuity, and unfavorable, referring to the complications during therapy.

Balance between benefits and risks, and certainty of the evidence

Both treatments are widely used, however, there are no studies that directly compare both drugs.

Indirect evidence facing both treatments shows a possible benefit of the use of aflibercept in improving visual acuity and reducing complications, but the uncertainty associated with these results is very high.

Therefore, it is not possible to make an adequate balance between risks and benefits between the evaluated interventions.

Resource considerations

The systematic reviews presented did not analyze the cost-effectiveness of the aforementioned treatments.

Although an aflibercept injection is considered to be less expensive than the dexamethasone implant, the price of both treatments would be similar considering the total number of injections used.

In the absence of a proven benefit, it is not possible to establish whether the use of aflibercept compared with dexamethasone is a cost-effective intervention.

What would patients and their doctors think about this intervention

In clinical practice, the most widely used treatment worldwide by specialists are anti-VEGF drugs, among which aflibercept stands out due to its long half-life. On the other hand, patients in general do not have preferences for one treatment over another.

Faced with the available evidence, it is likely that this same trend will continue, although the decision making will ultimately depend on the clinical history, characteristics and individualized preferences of the patients.

Differences between this summary and other sources

The conclusions of this summary are in agreement with those of one systematic review [1], which states that although aflibercept would be superior to dexamethasone in terms of visual acuity gain and safety, there is not enough evidence to conclude it with certainty, requiring new and better studies.

The second systematic review [2] concludes that aflibercept is superior to dexamethasone in gaining visual acuity. However, these differences may be due to the fact that this review does not take into consideration the certainty of the evidence.

The American Academy of Ophthalmology [7] and the *Sociedad Española de Retina y Vítreo* [8] suggests anti-vascular endothelial growth factor drugs as the first line for this condition, without a clear preference for one medication over another.

Could this evidence change in the future?

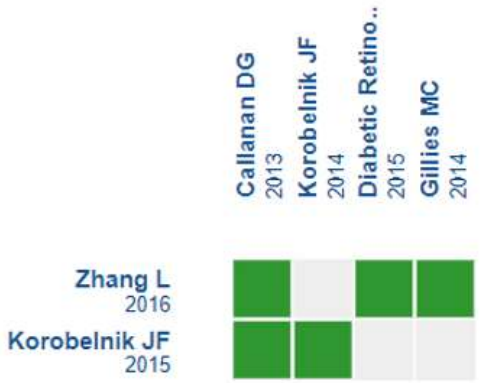
It is very probable that the information presented in this summary of the evidence will change in the future, because of the very low certainty of the available evidence.

We did not identify ongoing trials in the International Clinical Trials Registry Platform of the World Health Organization that answer the question investigated.

There is one systematic review in progress [9] registered in PROSPERO that compares anti vascular endothelial growth factor drugs versus dexamethasone, so that it could eventually include some direct analysis between aflibercept and dexamethasone.

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 diabetic macular edema.

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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