Addition of photodynamic therapy to anti-vascular endothelial growth factor drugs compared to anti-vascular endothelial growth factor monotherapy for polypoidal choroidal vasculopathy

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Abstract

Introduction

Polypoidal choroidal vasculopathy is characterized by multiple and recurrent serosanguineous detachments of the retinal pigment epithelium and aneurysmal protrusions in the choroidal vessels. Different therapeutic options have been proposed, including anti-vascular endothelial growth factor drugs and photodynamic therapy. Controversy exists as to whether combination therapy is superior to anti-vascular endothelial factor drugs alone.

Methods

We searched Epistemonikos, the largest database of systematic reviews in health, maintained by screening multiple sources of information, including MEDLINE/PubMed, EMBASE, and Cochrane. We extracted data from the identified reviews, analyzed the data from the primary studies, performed a meta-analysis, and prepared a summary table of the results using *the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.*

Results

We identified three systematic reviews that together included twelve primary studies. Of these, two were randomized trials, and only one of them was included in the analysis.

Conclusions

The addition of photodynamic therapy may result in little or no difference in the incidence of retinal hemorrhage and visual acuity gain at six months (low certainty of evidence). On the other hand, the combination of photodynamic therapy and anti-vascular endothelial growth factor drugs compared to anti-vascular endothelial growth factor alone is likely to increase polyp regression at three and six months and reduce central retinal thickness at six months.

Problem

Polypoidal choroidal vasculopathy is considered to be a possible variation of age-related macular degeneration. This pathology is characterized by multiple and recurrent serosanguineous detachments of the retinal pigment epithelium and aneurysmal protrusions in the choroidal vessels.

Although there is no universally accepted definition for polypoidal choroidal vasculopathy, its prevalence is estimated to be 0.3% in the general population and up to 60% among patients with neovascular macular degeneration[1]. This disease typically presents in the late fifth to the sixth decade of life, with unilateral deterioration of visual acuity.

Although a small proportion of patients progress favorably with observation alone, different types of treatments are available. These include focal laser, photodynamic therapy, and anti-vascular endothelial growth factor injections. There is no consensus on whether to use anti-vascular endothelial growth factor monotherapy – which has shown favorable results in final visual acuity – or a combined strategy with photodynamic therapy – which could improve polyp regression. Therefore, a summary of the present evidence is essential to compare both treatments.

Main messages

- The addition of photodynamic therapy to anti-vascular endothelial growth factor drugs compared to anti-vascular endothelial growth factor monotherapy may result in little or no difference in the risk of retinal hemorrhage and visual acuity gain (low certainty of evidence).
- The addition of photodynamic therapy to anti-VEGF compared to anti-VEGF monotherapy may make little or no difference to the risk of retinal hemorrhage and to visual acuity improvement at 6 months (low certainty of the evidence).

About the body of evidence for this question

What is the evidence **See the evidence matrix in Epistemonikos below.**	We found three systematic reviews[2-4] that included 12 primary studies[5-16]. Of these, two are randomized trials[8-14]. One trial[14] includes patients with another diagnosis, so it was not incorporated in the analysis. This table, and the summary in general, is based on a randomized trial[8], as information from observational studies does not increase the certainty of the evidence or add additional relevant information.
What type of patients did the studies include?*	The trial[8] included 40 eyes of 40 patients diagnosed with previously untreated polypoidal choroidal vasculopathy. Of these, 39 completed the study. No exclusion criteria were reported.
What type of interventions did the studies include?*	The trial[8] compared combination therapy with ranibizumab and photodynamic therapy versus ranibizumab therapy as monotherapy. There is also a third group comparing photodynamic therapy in monotherapy in this study, but this was not included in the analysis. The doses used in that work were photodynamic therapy (6 milligrams per square meter) and 0.5 milligrams of intravitreal ranibizumab, versus 0.5 milligrams of intravitreal ranibizumab as monotherapy.
What type of outcomes did they measure	The trials reported multiple outcomes, which were grouped by the systematic reviews as follows: • Retinal hemorrhage. • Polyp regression. • Gain in visual acuity, as measured by best corrected visual acuity at six months. • Reduction in central retinal thickness at six months. Patients were followed six months for the included trial[8].

Methods

We searched Epistemonikos, the largest database of systematic reviews in health, maintained by searching multiple sources of information, including MEDLINE/PubMed, EMBASE, and Cochrane. We extracted data from the identified reviews and analyzed primary studies. We generated a structured summary called FRISBEE (*Friendly Summaries of Body of Evidence using Epistemonikos*), following a pre-established format with this information. This format includes: main messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), a meta-analysis of the total studies when possible, a summary table of results using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) method, and a section on other decision-making considerations.

*Information on primary studies is extracted from the identified systematic reviews, not directly from the studies unless otherwise specified.

Summary of results

Information on the effects of the addition of photodynamic therapy to anti-vascular endothelial growth factor for polypoidal choroidal vasculopathy is based on one trial involving 39 eyes[8]. This paper measured the outcome of retinal hemorrhage, polyp regression at three and six months, the gain of best-corrected visual acuity at 6 months, and reduction of central retinal thickness at six months. All outcomes in this trial included 39 eyes.

To summarize, the addition of photodynamic therapy to anti-vascular endothelial growth factor drugs compared to anti-vascular endothelial growth factor monotherapy:

- May result in little or no difference in the risk of retinal hemorrhage (low certainty of evidence).
- Is likely to increase polyp regression at three and six months.
- May result in little or no difference in visual acuity gain at six months (low certainty of evidence).
- Is likely to reduce central retinal thickness at six months.

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Patients	Patients with polypoid choroidal vasculopathy
Intervention	Addition of photodynamic therapy to anti-vascular endothelial growth factor
Comparison	Anti-vascular endothelial growth factor monotherapy

Outcomes	Absolute effect size*		Relative risk (95% CI)	Certainty in evidence (GRADE)
	WITHOUT Photodynamic therapy	**WITH Photodynamic therapy**		
	Difference: patients per 1000			
Retinal hemorrhage	5 per 1000	26 per 1000	RR 5.50 (0,28 to 107,78)	⊕⊕◯◯[2] Low
	MD: 21 (Margin of error: -3 to 508)			
Polyp regression at 3 months	333 per 1000	722 per 1000	RR 2.17 (1.11 to 4.23)	⊕⊕⊕◯[1] Moderate
	MD: 389 (Margin of error: 37 to 1000)			
Polyp regression at 6 months	286 per 1000	778 per 1000	RR 2.72 (1.33 to 5.59)	⊕⊕⊕◯[1] Moderate
	MD: 492 (Margin of error: 94 to 1000)			
Visual acuity gain at 6 months**	9.2 letters	10.9 letters	-	⊕⊕◯◯[2] Low
	MD: 1.7 letters (Margin of error: -5.61 to 9.01 letters)			
Change in central retinal thickness at 6 months***	-65.7µm	-145.6µm	-	⊕⊕⊕◯[1] Moderate
	MD: -79.9 µm (Margin of error: -153,47 to -6,33)			

Error margin: 95% confidence Interval (95% CI).
RR: Relative risk
MD: Mean difference.
GRADE: Levels of evidence from GRADE *Working Group* (see below).

*Risks/means **WITHOUT photodynamic therapy** are based on the average of the control group. The risks/means **WITH photodynamic therapy** (and its margin of error) are calculated from the relative effect/mean difference (and its error margin).

** The outcome "visual acuity gain" was measured using the *Early Treatment Diabetic Retinopathy Study* chart. This table consists of 14 rows with five letters each. A score is obtained according to the number of letters read correctly. The higher the score, the greater the visual acuity. The minimum clinically important difference is an increase from 10 to 15 letters in the reading of the projected chart.

*** The outcome "change in central retinal thickness" was measured using optical coherence tomography. In general, higher retinal thickness values are consistent with a retina more affected by the disease, with no established cut-off point for diagnosis. Nevertheless, the average value for central retinal thickness in healthy patients is approximately 250 microns, which varies according to population and type of instrument used for its measurement. Therefore, there is no absolute value to define response to therapy. However, a response will be interpreted as favorable if there is a reduction in retinal thickness prior to the start of treatment.

[1] One level of certainty of evidence was decreased for imprecision in the central retinal thickness and polyp regression at three and six months outcomes, as the confidence interval limits range from a value close to no effect to one that favors the use of combination therapy.
[2] One level of certainty of evidence was decreased for imprecision in the retinal hemorrhage and visual acuity gain at six months outcomes. In addition, two levels of certainty were decreased because the confidence interval limits are wider, favoring one therapy or the other at each confidence interval limit.

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

About the levels of evidence (GRADE)*

⊕⊕⊕⊕
High: the research provides a very good indication of the likely effect. The probability that the effect is substantially different† is low.

⊕⊕⊕◯
Moderate: the research provides a good indication of the likely effect. The probability that the effect is substantially different† is moderate.

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

⊕◯◯◯
Very low: the research does not provide a reliable estimate of the likely effect. The probability that the effect is substantially different† is very high.

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

†Substantially different means a difference large enough to affect a decision.

Other considerations for decision-making

To whom this evidence applies and to whom it does not apply

The presented evidence applies to patients diagnosed with polypoidal choroidal vasculopathy who have not received treatment.

About the outcomes included in this summary

According to the authors of this review, visual acuity gain and adverse events, evaluated as retinal hemorrhage, were included as they are the most important outcomes for patients and their treating physicians.

Polyp regression at three and six months and central retinal thickness were evaluated despite surrogate outcomes because they are associated with a good response to treatment and a better medium-term prognosis.

The outcomes included in this summary are those considered relevant by the authors for decision-making, which coincides with those reported by the included systematic reviews.

Harm/benefit balance and certainty in evidence

When comparing the benefits and risks between the two therapies, the combined treatment is likely to increase polyp regression at three and six months, in addition to increasing the reduction in central retinal thickness at six months (moderate certainty of evidence).

On the other hand, the combination of both therapies could result in little or no difference in the risk of central hemorrhage and visual acuity gain (low certainty of evidence).

However, it is not possible to perform a correct harm/benefit balance analysis regarding visual acuity gain and central retinal thickness given the uncertainty in the evidence, so other aspects should be considered for decision-making.

Costs

The included systematic reviews did not perform a cost-effectiveness analysis between the two treatments.

Combination therapy is associated with a higher cost for the patient compared with monotherapy, but in turn, could be associated with better medium-term visual outcomes.

A cost-effectiveness analysis between both therapies is needed.

What do patients and their caregivers think

Although many physicians favor combination therapy, uncertainty remains about its potential superiority over monotherapy with anti-vascular endothelial growth factor drugs. Moreover, the availability of photodynamic therapy worldwide is limited, so this is not a routine treatment for this pathology.

Regarding patients consideration, given the limited availability of photodynamic therapy and the uncertainty about its superiority when associated with anti-vascular endothelial growth factor drugs, they probably prefer to maintain monotherapy.

Differences between this summary and other sources

The conclusions of this summary differ from two included systematic reviews[2,3], where authors report the superiority of combination therapy over monotherapy. Despite these conclusions, it is not possible to establish treatment superiority given the current uncertainty in the evidence.

On the other hand, our results are in line with a third systematic review[4].

When comparing with international clinical guidelines, it is noted that both the *American Academy of Ophthalmology*[17] and the Spanish Retina and Vitreous Society[18] state that there is controversy about the superiority of combination therapy compared to monotherapy. Consequently, further studies are needed, which can be extrapolated to the results of this review.

Could this information change in the future?

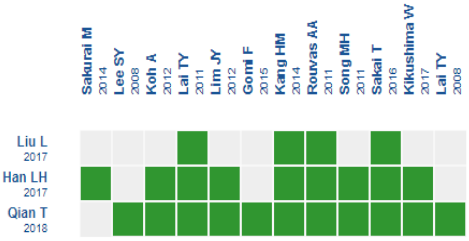
The likelihood that future evidence will change the conclusions of this summary is high due to the current uncertainty of evidence.

A systematic review protocol was identified on the International Prospective Register of Systematic Reviews platform, PROSPERO, comparing the use of combination therapy versus monotherapy with anti-vascular endothelial growth factor for polypoidal choroidal vasculopathy that could shed new light on the topic[19].

We also found a trial protocol on the World Health Organization's International Clinical Trials Registry Platform comparing the use of combination therapy versus monotherapy with anti-vascular endothelial growth factor for polypoidal choroidal vasculopathy. This study could shed new light on the subject once the analysis of the results is completed[20]. In addition, we found the preliminary results of a trial in the same database that could also provide new information on the subject addressed in this paper[21].

How we conducted this summary

We collected all the relevant evidence for this question and presented it in an evidence matrix using automated and collaborative methods.



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 to the **interactive version**: Anti-VEGF + photodynamic therapy versus anti-vascular endothelial growth factor monotherapy for polypoidal choroidal vasculopathy.

Contributor roles

FMY: methodology, validation, formal analysis, research, resources, data curation, draft writing, review and editing, visualization, fund acquisition. VMV: methodology, validation, formal analysis, research, resources, data curation, draft writing, review and editing, visualization, fund acquisition. RGC: conceptualization, methodology, validation, formal analysis, research, resources, data curation, draft writing, review and editing, visualization, supervision, project management, fund acquisition. AMQ: conceptualization, methodology, validation, resourcing, review and editing, visualization, supervision, project management, fund acquisition.

Competing interests

The authors declare that they have no conflicts of interest.

Funding

The authors declare that they had no external sources of funding for this study.

Ethics

The present study did not require evaluation by an ethics committee, given that it uses secondary data sources to summarize current evidence.

Language of submission

Spanish.

Notes

If new systematic reviews on this topic are published after this summary's publication, a "new evidence" notification will be displayed at the top of the matrix. While the project provides regular updates of these summaries, users are invited to comment on the Medwave website or contact the authors by e-mail if they believe evidence warrants an earlier update.

After creating an Epistemonikos account, you will receive automatic notifications whenever new evidence potentially answers this question by saving the matrices.

This article is part of the Epistemonikos evidence synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and an internal peer review process. Each of these articles corresponds to a summary, called FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence of a specific question in a friendly manner for physicians. The main resources are based on the Epistemonikos evidence matrix, and the result analysis is based on the GRADE methodology. Further details of this FRISBEE elaboration method are described here.

The Epistemonikos Foundation is an organization that seeks to bring information closer to health decision-makers through the use of technologies. Its main source is the Epistemonikos database.

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