Treat and extend compared to *pro re nata* regimen in neovascular age-related macular degeneration

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Abstract

Introduction

Age-related macular degeneration is the leading cause of blindness in older people in the world. One of the most effective treatments consists of injection intravitreal of anti-endothelial vascular growth factor (anti-VEGF) drugs. However, there is no consensus on their frequency of administration, being the treat and extend and the *pro re nata* the most commonly used regimens, but there is still controversy regarding their effectiveness.

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 together included two primary studies, both observational studies.

We concluded that we are uncertain whether the treat and extend regimen is superior in terms of visual gain, decrease in retinal thickness, number of injections and serious adverse effects at 12 months in comparison with the *pro re nata* regimen, because the certainty of the existing evidence has been assessed as very low.

Problem

Age-related macular degeneration is the leading cause of blindness in people over 50 years of age[1] and its global projection is estimated to reach 288 million cases in 2040[2]. The disease is a result of the excessive accumulation of drusen, a residual material that can be found in the macula or peripheral retina, which produces the histological changes leading to macular degeneration[1].

Currently, one of the most effective treatments for neovascular age-related macular degeneration of injection of drugs against endothelial vascular growth factor[3] (anti-VEGF), but there is no consensus in the literature on the frequency of administrations, or under which specific criteria the injections should be applied.

Among its application protocols, we can find the fixed regimes that generally consist of monthly injections, the *pro re nata* consisting of monthly visits and administration of medication only if there are certain findings on the ophthalmological examination, and thirdly the treat and extend regimen, in which the drug is supplied independent of what is observed by the specialist, but the visit intervals are defined according to the examination, which can range from four to twelve weeks[4].

In this summary, we aimed to evaluate the effectiveness and safety of the treat and extend regimen in comparison with the *pro re nata* regimen, whose use is still controversial.

Key messages

- We are uncertain whether the treat and extend regimen is superior in terms of visual gain, decrease in retinal thickness, number of injections at 12 months and serious adverse effects in comparison with the *pro re nata* regimen, as the certainty of the existing 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 identified two systematic reviews[5,6] that included two observational studies[7,8].
What types of patients were included*	Both studies included patients with the diagnosis of neovascular age-related macular degeneration, regardless of stage. One study included patients treated between 2007 and 2008[7], and one between 2010 and 2014[8]. One study included only Caucasians with visual acuity over 0.5 (Snellen) [8].
What types of interventions were included*	The two studies evaluated treatment with anti-VEGF drugs, comparing treat and extend versus *pro re nata* regimens[7,8]. In both studies ranibizumab was used as the anti-VEGF drug in doses of 0.5 milligrams per injection[7,8].
What types of outcomes were measured	The studies reported multiple outcomes, which were grouped by the systematic reviews as follows: • Gain in visual acuity at 12 months using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. • Central thickness of the retina at 12 months. • Number of injections in 12 months. • Serious adverse effects in 12 months. Follow-up of the trials was at least 12 months, without specifying the maximum time in each work.

* 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 presented on the effects of the use of treat and extend versus *pro re nata* is based on two observational studies that included 230 patients[5,6].

The two observational studies measured visual acuity gain at 12 months, serious adverse effects in 12 months and the number of injections in 12 months in each regimen[7,8] [230 patients]. One study also measured the central thickness of the retina at 12 months[7] (140 patients).

However, no systematic review allowed data extraction of central thickness of the retina, number of injections and serious adverse effects in a way that they could be incorporated into a meta-analysis, so the information of these outcomes is presented as a narrative synthesis of the only review that identified both studies[5].

The summary of findings is the following:

- We are uncertain whether the treat and extend regimen leads to a greater visual acuity gain at 12 months in comparison with the *pro re nata* regimen, as the certainty of the existing evidence has been assessed as very low.
- We are uncertain whether the treat and extend regimen leads to a greater decrease of the central thickness of the retina at 12 months in comparison with the *pro re nata* regimen, as the certainty of the existing evidence has been assessed as very low.
- We are uncertain whether the treat and extend regimen is associated with a greater number of injections in 12 months in comparison with the *pro re nata* regimen, as the certainty of the existing evidence has been assessed as very low.
- We are uncertain whether the treat and extend regimen is associated with fewer serious adverse effects in 12 months in comparison with the *pro re nata* regimen, as the certainty of the existing evidence has been assessed as very low.

Treat and extend compared to *pro re nata* in neovascular age-related macular degeneration			
Patients	Patients diagnosed with neovascular age-related macular degeneration		
Intervention	Treat and extend regimen		
Comparison	*Pro re nata* regimen		
Outcome	Absolute effect*		Certainty of evidence (GRADE)
	WITH *pro re nata*	WITH treat and extend	
Visual acuity gain at 12 months*,**	9.3 letters	15.58 letters	⊕◯◯◯[1,2] Very Low
	MD: 6.28 letters more (Margin of error: 3.48 more to 9.08 more)		
Central thickness of the retina at 12 months	One systematic review [5] reported that at 12 months of follow-up there was a greater reduction in central retinal thickness in the group that received the treat and extend regimen compared to *pro re nata* (MD -58 um; 95% CI -9.5 to -106.5).		⊕◯◯◯[1,2,3,4] Very Low
Number of injections in 12 months	One systematic review [5] reported that the treat and extend group used a greater number of injections compared to *pro re nata* group (MD 1.44; CI 95% 1.15 to 1.73).		⊕◯◯◯[1,2] Very Low
Serious adverse effects in 12 months	One systematic review [5] reported that the studies only informed serious adverse effects in the *pro re nata* group. One study [8] reported the case of one patient who had a recurrence that threatened his vision, and 23 patients who developed severe bleeding. The other study [7] reported the cases of two people who had severe subretinal hemorrhage. There were no serious adverse effects in the treat and extend group in the evaluated studies.		⊕◯◯◯[1,2] Very Low

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

* The average **WITH *pro re nata*** is based on the PRONTO study [9], which is a widely cited study by specialists. The average **WITH treat and extend** (and its margin of error) is calculated from the difference in means (and its margin of error).
** Measured as the number of letters gained using the Early Treatment Diabetic Retinopathy Study scale.

[1] Observational study.
[2] The certainty of evidence was downgraded in one level for risk of bias, since the studies were not blinded and also did not adjust for confounding factors such as the stage of the disease and other ophthalmological pathologies, among others.
[3] The certainty of evidence was downgraded in one level due to imprecision, since different decisions would be made at each end of the confidence interval.
[4] The certainty of evidence was downgraded in one level for indirect evidence, since the central thickness of the retina corresponds to a surrogate outcome.

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.

* 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 with a diagnosis of neovascular age-related degeneration who have not received treatment.

About the outcomes included in this summary

The outcomes of visual acuity gain, number of injections and serious adverse effects at 12 months were selected because they are the most relevant for decision making according to the authors of this summary.

The central thickness of the retina at 12 months was selected despite being a substitute outcome, since it correlates with a good response to treatment.

These outcomes generally coincide with those reported by the identified systematic reviews.

Balance between benefits and risks, and certainty of the evidence

Current evidence shows a possible benefit of using the treat and extend regimen compared to *pro re nata* in terms of visual acuity gain, reduction in central retinal thickness and serious adverse effects associated with treatment. However, it would be associated with a greater number of injections per year.

Despite the above, it is not possible to make an adequate balance in terms of benefits and risks comparing both regimens, because the certainty of the available evidence is very low.

Resource considerations

The systematic reviews evaluated the number of injections in a year due to its economic impact, concluding that more injections would be needed in the treat and extend group versus *pro re nata*. However this was achieved with fewer visits. The above was not analyzed in greater detail in any systematic review.

Additionally, since there is uncertainty about the benefits of the intervention, it is not possible to perform a cost-benefit analysis.

What would patients and their doctors think about this intervention

The most widely used regimen worldwide is the treat and extend regimen, since it allows patients to have wider control intervals, which would increase adherence and reduce discomfort, without noticeable variations between regimens.

Faced with the available evidence, it is likely that most patients and caregivers continue this trend, generally preferring the treat and extend regimen over the *pro re nata* regimen.

Differences between this summary and other sources

The conclusions of this study are consistent with those of the two systematic reviews identified, which stated that the evidence is not sufficient to prefer one regimen over another, even though results might favor the treat and extend regimen.

The clinical guidelines of the *Sociedad Española de Retina y Vítreo* [10] and The American Academy of Ophthalmology of the United States of America [11] also state that more evidence is needed to reach a consensus on the regimen of choice.

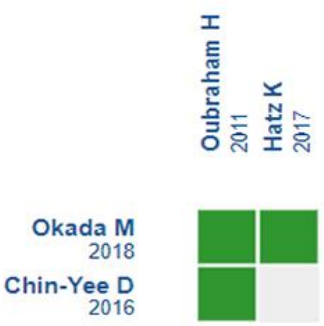
Could this evidence change in the future?

The probability that the conclusions of this summary will change in the future, with new evidence, is high due to the uncertainty of the existing evidence.

A search was carried out in PROSPERO and in the platform of international registries of the clinical trials of the World Health Organization, without finding reviews or ongoing trials that answer the question investigated.

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:** Treat and extend versus *pro re nata* in age-related macular degeneration.

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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