Off-label use of bevacizumab in age-related macular degeneration: protocol for a systematic review and meta-analysis

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Abstract

Background: Age-related macular degeneration (AMD) is recognized as the leading cause of vision loss in elderly people. Taking into account the phenomenon of aging worldwide, the prevalence of AMD is expected to increase gradually in the future. AMD can be divided into early, intermediate and late stages, where early and intermediate are mainly asymptomatic and, late-stage can be classified in non-vascular AMD and vascular AMD. Current pharmacological treatment in vascular AMD includes the administration of anti-VEGF agents, such as ranibizumab, pegaptanib, and aflibercept. Additionally, it has been reported that the off-label use of bevacizumab, through intravitreal administrations, demonstrates to be effective along with a lower cost in comparison to other agents used, which makes it a new possible pharmacological approach.

Objective: This review aims to evaluate the efficacy, safety, and efficiency of the use of bevacizumab in the treatment of neovascular AMD

Methods: To identify and select relevant articles present in current literature, it will be developed a highly sensitive search strategy. To develop this search, it will be used MEDLINE via the Pubmed platform. It will be only considered randomized controlled clinical trials, where it is compared the use of bevacizumab with another pharmacological agent, such as ranibizumab, or even a placebo, in patients aged 50 years and older, diagnosed with vascular AMD.

Results: This project has no funding and it has been done by a multidisciplinary research team of pharmacologists and orthoptists. The study was initiated in May 2021 with the lineation of the protocol, now the data are been extracted and analyzed, and it is expected to be released by the end of 2022.

Conclusions: This review will provide a synthesis of the current information and underlying evidence, about the influence of the off-label use of bevacizumab in this disease. Altogether, it will allow having a clearer vision of a new possible accepted pharmacological approach for the treatment of vascular AMD. Clinical Trial: The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the code CRD42021244931.

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Systematic Review and Meta-Analysis Protocol

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Off-label use of bevacizumab in age-related macular degeneration: protocol for a systematic review and meta-analysis

Abstract

Background: Age-related macular degeneration (AMD) is recognized as the leading cause of vision loss in elderly people. Considering the phenomenon of aging worldwide, the prevalence of AMD is expected to increase gradually in the future. AMD can be divided into early, intermediate and late stages, where early and intermediate are mainly asymptomatic and, late-stage can be classified in non-vascular AMD and vascular AMD. Current pharmacological treatment in vascular AMD includes the administration of anti-VEGF agents, such as ranibizumab, pegaptanib, and aflibercept. Additionally, it has been reported that the off-label use of bevacizumab, through intravitreal administrations, demonstrates to be effective along with a lower cost in comparison to other agents used, which makes it a new possible pharmacological approach. **Objective:** This review aims to evaluate the efficacy, safety, and efficiency of the use of bevacizumab in the treatment of neovascular AMD**. Methods:** To identify and select relevant articles present in current literature, it will be developed a highly sensitive search strategy. To develop this search, it will be used MEDLINE via the Pubmed platform. It will be only considered randomized controlled clinical trials, where it is compared the use of bevacizumab with another pharmacological agent, such as ranibizumab, or even a placebo, in patients aged 50 years and older, diagnosed with vascular AMD. **Results:** This project has no funding, and it has been done by a multidisciplinary research team of pharmacologists and orthoptists. The study was initiated in May 2021 with the lineation of the protocol, now the data are being extracted and analyzed, and it is expected to be released by the end of 2022. **Conclusions:** This review will provide a synthesis of the current information and underlying evidence, about the influence of the off-label use of bevacizumab in this disease. Altogether, it will allow having a clearer vision of a new possible accepted pharmacological approach for the treatment of vascular AMD. **Systematic review registration:** The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the code CRD42021244931.

Keywords: wet macular degeneration; age-related macular degeneration; bevacizumab; drug therapy.

Introduction

Age-related macular degeneration (AMD) is intimately associated with visual impairment, considered the leading cause of vision loss in elderly people.[1-3] Indeed, it is reported that 9% of all cases of blindness are related to the progression of this disease.[4] AMD frequency accompanies the advancing age and is known to be a progressive and degenerative disease in the macula.[1,5] It is estimated that around 200 million people are affected with AMD, and with the phenomenon of aging worldwide, the prevalence of this disease may increase in a near future.[3-6] Allied with the increased life expectancy, there are other risk factors identified such as environmental factors, obesity, atherosclerosis, smoking, genetic background, metabolic and functional factors.[2,7]

AMD can be divided into early, intermediate, and late stages. The early and intermediate stages are mainly asymptomatic and represent about 90% of cases.[6-8] Late AMD is classified into two main types, which are non-vascular or dry (atrophic) AMD and neovascular (wet or exudative) AMD, and is the main cause of AMD visual impairment.[2,4,5,8] AMD diagnosis and grading are based on color fundus examination in people ages 50 years and older.[9] There are some differences to be aware of between both main types of AMD, where non-advanced AMD is characterized by typical focal drusen with a whitish-yellow localized between retinal pigment epithelium and bruch membrane (BrMb). On the other hand, wet AMD is known to present neovascularization within the macula.[10]

AMD pathogenesis is not fully understood yet but some studies are starting to elucidate the underlying process behind the appearance of this disease.[8,10,11] Both non-vascular and neovascular AMD are related to a dysfunction and/or death of all constituents of the photoreceptor/retinal pigment epithelium (RPE)/BrMb/choriocapillaris (CC) complex, as they are working in combination. The development of each type of AMD seems to be associated with the location where initiating events start to disenroll.[11] Non-vascular AMD development is characterized, in the beginning, by a formation of large confluent drusen and hyperpigmentation, which can be underlined by RPE dysfunction, carrying a risk for the appearance of geographic atrophy.[11,12] On the other hand, neovascular AMD is associated with an initial loss of choroidal vasculature, which will affect the photoreceptor/RPE/BrMb/CC complex and, appears to be underlined by a reduction in blood supply, induced by stenosis of large vessels. An inflammatory environment establishes with an accumulation of proinflammatory cytokines, promoting the progression of AMD.[11,13] RPE remains intact however, due to the stenosis observed in large vessels, it becomes hypoxic and starts to release angiogenic substances, including vascular endothelial growth factor (VEGF), stimulating the formation of new vessels from CC, denominated as choroidal neovascularization.[11]

Taking into account the underlying process behind the development of neovascular AMD, its current pharmacological treatment is characterized by intravitreal administrations of molecules specifically targeted to VEGF.[4,14] Additionally, the drugs currently accepted by the regulatory authorities, for the treatment of this condition are, for example, pegaptanib, ranibizumab, aflibercept, and brolucizumab.[4,8] Also, it has been reported the off-label use of bevacizumab in the treatment of neovascular AMD, which is a drug commonly used in oncology, and more specifically, in the treatment of metastatic colorectal cancer, breast and lung cancers.[2,4,14] Indeed, some authors have shown a positive influence of intravitreal administrations of bevacizumab in cases of neovascular AMD, allied with a lower cost for the community in comparison with other drugs currently used, for example, ranibizumab.[2,14,15] Therefore, given the rise in bevacizumab use in neovascular AMD, it would be interesting to evaluate, more specifically, its long-term influence on the development and progression of this disease. In this sense, this study aims to evaluate the use of bevacizumab in the treatment of neovascular AMD, through the analysis of its efficacy, safety, and efficiency profiles from data present in clinical studies made, with special emphasis on long-term results.

Methods

The research group has followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) for the elaboration of this protocol in

Supplementary Material 1.[16] This study pretends to answer the following research question "When, how and what are the criteria to the treatment with bevacizumab in adults over 50 years old diagnosed with wet macular degeneration?".

Aims

This study aims to undertake a systematic review and meta-analysis of the evidence about the off-label use profile of bevacizumab in the treatment of neovascular AMD, through the identification and critical appraisal of clinical studies. In this sense, the specific objective is to summarize and analyze the current evidence on the clinical outcomes related to the efficacy, safety, and efficiency resulting from the use of bevacizumab in neovascular AMD.

Types of studies

The study will only include randomized controlled clinical trials for further analysis. In this sense, all the non-randomized clinical studies, with an experimental or observational design, will be excluded.

Exclusion criteria

As exclusion criteria, it was established: studies using participants with less than 50 years old, preclinical studies including in vitro and in vivo studies, and studies with participants diagnosed with polypoidal choroidal vasculopathy (PCV) or retinal angiomatous proliferation (RAP).

Participants

According to the natural history of AMD considered by the American Academy of Ophthalmology Preferred Practice Pattern [17], the study will only include participants diagnosed with neovascular AMD aged 50 years and older.

Intervention and comparison

Patients diagnosed with neovascular AMD treated with bevacizumab, administered intravitreally, in comparison to other accepted treatments, such as another anti-VEGF drug, such as ranibizumab or a placebo.

Outcomes

To evaluate the influence of intravitreal administration of bevacizumab in neovascular AMD, there are several outcomes to be analyzed in terms of comparison with other established treatments or placebos, such as:
- Outcomes of efficacy - visual acuity, presence of neovascularization, and retinal thickness;
- Outcomes of safety – presence of macular atrophy, endophthalmitis, leakage, and increased intraocular pressure;
- Outcomes of efficiency - administrated dose, number of administrations, frequency of administration, duration of treatment, and cost vs beneficial effect of the treatments compared with ranibizumab or placebo.

Database and search strategy

We will use MEDLINE via the Pubmed platform to develop our search, utilizing a highly sensitive search strategy to identify and select relevant and eligible studies. Supplementary Material 2 presents the search strategy developed for the MEDLINE database. This search will be directed to studies

indexed from 2010 until 2021.

Data extraction and management

The retrieved studies from the Medline database will be exported and analyzed through a Systematic Reviews Web Application (Rayyan QCRI), which will be utilized throughout the review for study screening and overall management.

Study selection

Titles and abstracts of retrieved studies will be screened, and full text of potentially eligible articles assessed by two independent reviewers. In case of discrepancies, a third reviewer will be included to make a final decision. Inclusion and exclusion criteria will be used throughout this process to decide whether a study is included or excluded. Relevant data will be extracted from eligible studies and inserted in a customized data extraction document, by the two independent reviewers. As inclusion criteria, only studies using a comparator (ranibizumab or placebo) will be of interest. Additionally, in terms of language, it will be only accepted articles written in English and published starting from 2010.

Quality assessment

All the selected studies will be assessed to evaluate their quality and potential for risk of bias by two independent reviewers. In cases of discrepancies between these two reviewers, a third element will arbitrate to make a final decision. To evaluate the quality and risk for bias in experimental studies, the Critical Appraisal Skills Programme (CASP) Randomised Controlled Trials Checklist, CASP Cohort Study Checklist, and CASP Case-Control Study Checklist will be used. Additionally, it will be used the Effective Public Health Practice Project tool, with the same objective previously referred to, but for cross-sectional and observational studies. We will derive domain-specific and overall quality grading for each study as follows: A—low risk of bias; B—moderate risk of bias; C—high risk of bias. We will evaluate the potential for publication bias by using funnel plots and Begg and Egger tests and the Trim and Fill approach to explore the possible influence of publication bias on the results.

Analysis

The included studies will be descriptively analyzed and presented in a tabular form. Additionally, the studies excluded from a quantitative synthesis will be subjected to a qualitative analysis in order to withdraw all the important data available. In methodologically and statistically homogeneous studies, we will perform meta-analyses using random-effects models to quantify a pooled estimate of the effect of systemic adverse events (SAE) vs ocular adverse events (OAE). Meta-analyses will be undertaken separately for each specific study design. It will also be considered other subgroup analysis, for instance, age groups (50-70, ->70). We will quantify the heterogeneity between studies using the I2 statistic and Kendal’s Tau and if high values were found, to try to explain heterogeneity across studies, a meta-regression will be conducted. This technique can be performed if there is a suspected variable that may lead to differences in treatment effects across studies. For meta-analysis, it will be used the R (version 4.0.5) packages metafor and meta.

Grading of the overall strength of the evidence

To evaluate the quality and strength of the overall evidence, it will be used the approach Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[18] This procedure will be divided in two stages, as recommended by the GRADE system. Firstly, each outcome will be rated on a scale of 1-9, where: punctuation between 7-9 represents an outcome that is critical for clinical decision-making; a punctuation between 4-6 represents an outcome that is important but not critical for clinical decision-making and, punctuation between 1-4 represents an outcome that is not important for clinical decision-making and with lower importance to patients.[18] In the second stage, the quality of the overall evidence for each outcome will be reviewed and will be presented using the GRADE evidence profiling template.

Registration and reporting

The protocol for this review was submitted and registered in the PROSPERO 2021 CRD42021244931. The present protocol will be conducted by following the PRISMA-P guidelines for the development of systematic reviews and meta-analysis. In case of modifications in the protocol, it will be reported in the final document, including the rationale behind the origin of such amendments.

Results

The study has 15 randomized controlled clinical trials, which were already selected taking in account the inclusion and exclusion criteria and the information of interest is being thoroughly extracted. A multidisciplinary research team of pharmacologists and orthoptists are working in the review since May 2021 with the lineation of the protocol and it is expected that the data will be released until the end of 2022.

Discussion

Age-related macular degeneration is intimately associated with blindness and has a significant impact on social, health, and economic factors in society. Currently, this disease has no cure and pharmacological treatment aims to slow its rate of development and preventing the major consequence previously referred to, which is blindness. Considering the cost of current drug therapies that are accepted for the treatment of neovascular AMD, bevacizumab appears as a possible alternative treatment. The off-label use of bevacizumab in the treatment of neovascular AMD was first time reported in 2006, and since then, an increase in its use has been demonstrated as well.[2] Indeed, bevacizumab has been associated as a treatment option for this condition, taking into account the demonstration that its efficacy is non-inferior, in comparison to ranibizumab, a well-known drug used in this context.[19] In this sense, this review will allow a clearer vision of the influence of bevacizumab in the treatment of neovascular AMD, evaluating its efficacy, safety, and efficiency compared to another drug used or placebo. Additionally, this study presents as key strengths: synthesize the information available about the off-label use of bevacizumab in patients diagnosed with neovascular AMD; clarify the current evidence about the off-label use of bevacizumab in neovascular AMD context, taking into account its efficacy, safety, and efficiency and, the development of a comprehensive and highly sensitive search strategy, which will provide the identification of current literature and the underlying evidence existent. With the literature currently available, we are in a position to, objectively, evaluate the influence of bevacizumab in the treatment of this disease, in comparison to another drug accepted by the regulatory authorities.

Acknowledgements

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Conflicts of Interest

The authors declare that they have no competing interests.

Abbreviations

AMD - Age-related macular degeneration
BrMB - Bruch membrane
CC - Choriocapillaris
CASP - Critical appraisal skills programme
GRADE - Grading of recommendations assessment, development, and evaluation
PROSPERO - International prospective register of systematic reviews
OAE - Ocular adverse events
PCV - Polypoidal choroidal vasculopathy
PRISMA-P - Preferred reporting items for systematic reviews and meta-analysis protocols
RPE - Retinal pigment epithelium
RAP - Retinal angiomatous proliferation
SAE - Systemic adverse events
VEGF - Vascular endothelial growth factor

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