International Journal of Health Science

ISSN 2764-0159 vol. 5, n. 34, 2025

ARTICLE 2

Acceptance date: 21/11/2025

COMPLEMENT INHIBITORS FOR THE TREATMENT OF GEOGRAPHIC ATROPHY CAUSED BY AGE-RELATED MACULAR DEGENERATION: FOCUS ON PEGOL AND PEGCETACOPLAN

Giulia Ferreira Tonon
Estudante - Universidade Positivo
Escola de Ciências da Saúde - Curso de Medicina - Curitiba -
ORCID 0009-0003-6472-2328

Pedro Henrique Pereira Corradini
Estudante - Universidade Positivo - Escola de Ciências da Saúde - Curso de Medicina - Curitiba
ORCID 0009-0008-4131-8644

Isabella Machado Barby
Estudante - Universidade Positivo - Escola de Ciências da Saúde - Curso de Medicina - Curitiba
ORCID 0009-0000-5184-7760

Gianna Cattoni Araldi
Estudante - Universidade Positivo - Escola de Ciências da Saúde - Curso de Medicina - Curitiba
ORCID 0009-0007-1021-5581

Alexandre Serafim
Estudante - Universidade Positivo - Escola de Ciências da Saúde - Curso de Medicina - Curitiba
ORCID 0009-0000-8969-2629

Lara de Oliveira Petry
Estudante - Universidade Positivo - Escola de Ciências da Saúde - Curso de Medicina - Curitiba
ORCID 0009-0002-1329-950X

Giovana Pomin Barros Sachetim
Estudante - Universidade Positivo - Escola de Ciências da Saúde - Curso de Medicina - Curitiba
ORCID 0000-0003-4048-2625

Julia Agibert Rohnelt
Estudante - Universidade Positivo - Escola de Ciências da Saúde - Curso de Medicina - Curitiba -
ORCID 0009-0007-7863-4950

Abstract: Introduction: Age-related macular degeneration is characterized by lesions in the medial region of the retina, compromising central visual acuity. Its epidemiology is on the rise due to increased life expectancy, but one of its classifications, the dry form, still lacks treatments that can modify the prognosis of patients. In this context, complement system inhibitors have emerged as protagonists that aim to block the main pathophysiogenesis of the disease. **Methodology:** Literature review, in English and Portuguese, in the PubMed database, with the descriptors: "complement inhibitors" AND ("geographic atrophy") AND "dry age-related macular degeneration," searching for results from treatment with Pegcetacoplan and Pegol. **Results:** The studies analyzed showed positive aspects involving a reduction in the degenerative process of geographic atrophy. However, they do not yet meet the ideal therapeutic criteria for universal adoption. **Conclusion:** Combined with the scarcity of articles on the subject, there is an undoubted need for further clinical trials, based on the complement system, to improve therapeutic techniques aimed at achieving a balance between noticeable visual improvement and low associated side effects.

Keywords: Age-related macular degeneration; Complement inhibitors; Geographic atrophy; Pegcetacoplan; Avacincaptad pegol

Introduction

Age-related macular degeneration (AMD) is directly associated with loss of visual acuity, accounting for 8.7% of all total anopsia cases worldwide. Given the increase in population longevity, triggered by new technological advances in medicine, AMD

is expected to affect 288 million patients by the end of 2040 (Girgis, S., & Lee, L. R., 2023).

As its name suggests, this pathology involves a breakdown and deposition of waste in the macula, the central region of the retina, which attracts immune cells from the complement system, causing a major inflammatory cascade. (Toomey, C. B., Landowski, M., Klingeborn, M., Kelly, U., Deans, J., Dong, H., Harrabi, O., Van Blarcom, T., Yeung, Y. A., Grishanin, R., Lin, J. C., Saban, D. R., & Bowes Rickman, C. 2018).

The complement system is an active part of the innate immune system, whose functions include supporting the fight against foreign antigens and eliminating waste from cells that have undergone apoptosis. In an attempt to combat these metabolic residues in the retina, it causes the formation of drusen—an authenti y mark that corresponds to the initial stage of AMD (Cruz-Pimentel, M., & Wu, L. 2023).

AMD can be classified as dry or wet (neovascular). In the dry form, the consumption of photoreceptors and retinal epithelial cells, in the face of exacerbated inflammation, causes thinning of the retina. The thinning of the structure and cell death contribute to the progression to the late stage of the disease, called geographic atrophy (GA). This stage results from the activation of the complement system and chronic local inflammation. Its effects are the growth of lesions that lead to irreversible blindness (Liao, D. S., Metlapally, R., & Joshi, P. 2022).

In order to halt the progression of retinal lesions and mitigate unfavorable outcomes, complement system inhibitors were introduced, represented, among others, by the drugs Pegcetacoplan and Pegol. These drugs are mainly based on blocking the C3 and C5 subtypes, respectively, as these markers symbolize the convergence of the three pathways of the complement system—classical, alternative, and lectin (Desai, D., & Dugel, P. U. 2022).

Method

A bibliographic search was conducted in the PubMed database using the following descriptors: "complement inhibitors" AND ("geographic atrophy") AND "dry age-related macular degeneration." Based on this search, a systematic review of the literature was conducted to select relevant studies from 2014 to 2024, in English and Portuguese, with 11 articles being manually included for detailed study.

Discussion

The pathophysiology of AMD is extremely complex, and several factors contribute to its onset: oxidative, environmental, inflammatory, and ischemic (Cabral de Guimaraes, T. A., Daich Varela, M., Georgiou, M., & Michaelides, M. 2022). In this scenario, the complement system plays an essential role, as it forms protein and lipid deposits that attach between the retinal pigment epithelium (RPE) and Bruch's membrane (BM), causing damage to the retina and compromising vision (Toomey, C. B., Landowski, M., Klingeborn, M., Kelly, U., Deans, J., Dong, H., Harrabi, O., Van Blarcom, T., Yeung, Y. A., Grishanin, R., Lin, J. C., Saban, D. R., & Bowes Rickman, C. 2018).

Initially, in dry AMD, drusen appear, which are extracellular deposits of regulatory proteins, activators, and complement system factors—which cause impaired dark adaptation and pigmentary changes in the RPE. Geographic atrophy only appears in the late stages of the disease, sparing the fovea and mainly affecting the perifoveal area at a variable rate of growth (Cruz-Pimentel, M., & Wu, L. 2023).

Considering the recent past, the strictly clinical management offered to people with dry AMD, containing only techniques for early recognition of visual problems and lifestyle changes, there was a considerable need to emphasize studies on the pathogenesis of this disease, with special emphasis on the complement system. (Cabral de Guimaraes, T. A., Daich Varela, M., Georgiou, M., & Michaelides, M. 2022)

The suggested complement system inhibitors, Pegol and Pegcetacoplan, are intended to interrupt the inflammatory cascade, recruited from the recognition of an unknown factor. This immunological sequence, in genetically predisposed individuals, has a high probability of dysregulation, followed by exacerbated reactivity to the antigen. The goal of these medications is to prevent the formation of the final byproducts, referred to as C3 and C5, as they trigger a complex attack on the cell membrane, which consequently causes apoptosis of retinal cells. (Girgis, S., & Lee, L. R. 2023)

This class joins other methodologies that are being proposed to revolutionize therapeutic models, including drugs with antioxidant characteristics, neuroprotective agents, genetic interventions, and the use of stem cells. Among them, complement blockers have shown greater efficiency and applicability, and their use in the treatment of geographic atrophy (GA) has been approved by the U.S. Food and Drug Administration (USFDA). (Cabral de Guimaraes, T. A., Daich Varela, M., Georgiou, M., & Michaelides, M. 2022)

To assess their effectiveness, methods were used to compute the progress of this complication of AMD, including fundus autofluorescence (FAF) and optical coherence tomography (OCT). In addition, parameters such as visual acuity in low-light areas and monocular reading speed were used as comparative pillars to verify whether there was clinical improvement with the treatment used. (Girgis, S., & Lee, L. R. 2023)

Research has shown a reduction in the progression of geographic atrophy after consecutive intravitreal injections of Pegcetacoplan and Avacincaptad Pegol. Histological analysis showed a reduction in photoreceptor destruction compared to placebo injections, minimizing retinal thinning. Although they slow down the degenerative process, the drugs did not improve visual acuity, a factor that hinders treatment adherence, since patients do not perceive changes in their quality of life and need to be exposed to several applications of the drug. (Girgis, S., & Lee, L. R. 2023)

In addition to not restoring already compromised visual functions, complement system inhibitors can attenuate more rigid responses from the immune component, which are necessary to combat complicated pathogens. Therefore, theoretically, this suggests an increased risk for other infections, especially those involving the ophthalmic and genitourinary systems. Recently, the research committee composed of the American Society of Retina Specialists (ASRS) warned of the emergence of post-treatment occlusive vasculitis with Pegcetacoplan, en-

compassing 11 cases, 8 of which were confirmed. (Cruz-Pimentel, M., & Wu, L. 2023)

Furthermore, the drugs mentioned here cause concern due to the possibility of converting AMD to the wet form, also called neovascular, a characteristic that modifies the therapeutic approach used. Given this possibility, therapeutic management becomes more evident in view of the fact that the neovascular form has a well-established treatment, represented by Anti-VEGF. However, patients may experience additional vision loss and, above all, become exposed to a new and significant medication burden. (Cruz-Pimentel, M., & Wu, L. 2023)

Conclusion

Based on the analysis of the studies cited, it became evident that the complement inhibitors Pegol and Pegcetacoplan proved to be adequate as slowdown agents for macular inflammatory damage, reducing the diameter of GA lesions. Despite this significant advance compared to past treatments, the drug did not improve the visual acuity of those affected, which, combined with the heavy application burden and financial cost, makes adherence difficult. Regarding the monitoring of the evolution of this pathology, the refinement of tests such as FAF and OCT is crucial, since the visual acuity reported by the patient does not provide an accurate marker for assessing disease progression.

Clearly, given the high epidemiology of dry AMD, there is a need for further clinical trials aimed at finding optimized therapies—especially those involving the symbiosis between clinical and histological improvement. As an ally, a more robust understanding of the complement system and the improvement of the treatment methodologies used today could greatly contribute to the consolidation of a dominant treatment for this disease. Ideally, unifying: reduction in the size of geographic atrophy lesions and the regression of dry AMD.

References

CABRAL DE GUIMARAES, T. A. et al. Treatments for dry age-related macular degeneration: therapeutic avenues, clinical trials and future directions. The British Journal of Ophthalmology, v. 106, n. 3, p. 297–304, 1 mar. 2022.

CRUZ-PIMENTEL, M.; WU, L. Complement Inhibitors for Advanced Dry Age-Related Macular Degeneration (Geographic Atrophy): Some Light at the End of the Tunnel? Journal of Clinical Medicine, v. 12, n. 15, p. 5131, 1 jan. 2023.

DESAI, D.; DUGEL, P. U. Complement cascade inhibition in geographic atrophy: a review. Eye, v. 36, n. 2, p. 294–302, 9 jan. 2022.

DREISMANN, A. K. et al. Functional expression of complement factor I following AAV-mediated gene delivery in the retina of mice and human cells. Gene Therapy, v. 28, n. 5, p. 265–276, 10 mar. 2021.

GIRGIS, S.; LEE, L. R. Treatment of dry age-related macular degeneration: A review. Clinical and Experimental Ophthalmology, 22 set. 2023

KASSA, E. et al. Complement inhibition as a therapeutic strategy in retinal disorders. v. 19, n. 4, p. 335–342, 11 fev. 2019.

LEUNG, E.; LANDA, G. Update on current and future novel therapies for dry age-related macular degeneration. Expert Review of Clinical Pharmacology, v. 6, n. 5, p. 565–579, set. 2013.

LIAO, D. S.; METAPALLY, R.; JOSHI, P. Pegcetacoplan treatment for geographic atrophy due to age-related macular degeneration: a plain language summary of the FILLY study. Immunotherapy, 21 jul. 2022.

NEBBIOSO, M. et al. Therapeutic Approaches with Intravitreal Injections in Geographic Atrophy Secondary to Age-Related Macular Degeneration: Current Drugs and Potential Molecules. International Journal of Molecular Sciences, v. 20, n. 7, p. 1693, 4 abr. 2019.

QUERQUES, G. et al. Treatment of Dry Age--Related Macular Degeneration. Ophthalmic Research, v. 52, n. 3, p. 107–115, 2014.

TOOMEY, C. B. et al. Effect of Anti-C5a Therapy in a Murine Model of Early/Intermediate Dry Age-Related Macular Degeneration. Investigative Ophthalmology & Visual Science, v. 59, n. 2, p. 662–662, 1 fev. 2018.