Centre for Eye Health

# ATLAS LITERATURE REVIEW

Issue 10• Summer 2023-24

**Welcome to the tenth issue of Centre for Eye Health's ATLAS Literature Review. Each quarter we'll be bringing you reviews from our pick of the latest literature as part of your ATLAS subscription.**

## Efficacy and safety of Avacincaptad Pegol in patients with geographic atrophy

*Prepared by Meri Galoyan*

Clinical applications: After the FDA approval of pegcetacoplan, another complement inhibitor, avacincaptad pegol (ACP), came under the spotlight and received FDA approval in August 2023. ACP targets the C5 protein, a component further down in the complement cascade. In theory, this could offer more targeted inhibition and potentially reduce the risk of adverse effects compared to a C3 inhibitor like pegcetacoplan. This paper aims to explore the efficacy and safety profile of ACP

Summary: This randomized, double-masked, and sham-controlled 24-month phase 3 trial was conducted across 205 clinics worldwide and included 448 eligible patients. The trial randomly assigned avacincaptad pegol or sham treatment to two groups. The key outcome was to assess any statistically significant difference in geographic atrophy lesion growth at 12 months using fundus autofluorescence (FAF) imaging in the treatment group compared to the sham group.

Key findings: Treatment with avacincaptad pegol 2 mg demonstrated a significantly slower mean rate of geographic atrophy growth, reduced by 14.3% compared to the sham group. The safety profile was reassuring, with no reported events of intraocular inflammation, endophthalmitis, ischemic optic neuropathy, or occlusive vasculitis in the study eye. However, there were reports of exudative macular neovascularization occurring in 11 patients (5%) in the avacincaptad pegol 2 mg group and seven patients (3%) in the sham group.

Reference: Khanani, A. M., Patel, S. S., Staurenghi, G., et al. GATHER2 trial investigators (2023). Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial. Lancet (London, England), 402(10411), 1449–1458.

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## Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration

*Prepared by Meri Galoyan*

Clinical applications: Geographic atrophy stands as the leading cause of progressive, irreversible vision loss and, for decades, had no available treatments. In February 2023, the US Food and Drug Administration (FDA) approved pegcetacoplan, a complement C3 inhibitor, as the first treatment for geographic atrophy secondary to Age-related Macular Degeneration (AMD). This paper summarizes the key findings from two large phase 3 trials that led to the approval of this groundbreaking drug.

Geographic atrophy stands as the leading cause of progressive, irreversible vision loss and, for decades, had no available treatments. In February 2023, the US Food and Drug Administration (FDA) approved pegcetacoplan, a complement C3 inhibitor, as the first treatment for geographic atrophy secondary to Age-related Macular Degeneration (AMD). This paper summarizes the key findings from two large phase 3 trials that led to the approval of this groundbreaking drug.

Summary: Two multi-center and randomized phase 3 trials, OAKS and DERBY, aimed to assess the efficacy and safety of intravitreal pegcetacoplan compared to sham treatment in patients with geographic atrophy. A total of 1,258 patients were enrolled across more than 220 worldwide sites. In both studies, patients were randomly assigned to four groups: group 1 received a 15 mg per 0·1 mL intravitreal injection of pegcetacoplan monthly, group 2 received the same treatment every other month, group 3 underwent a monthly sham injection, and group 4 received a sham injection every other month for 24 months. The key primary outcome was to assess a statistically significant difference in geographic atrophy lesion growth at 12 months using fundus autofluorescence (FAF) imaging. Additionally, secondary functional outcomes included best-corrected vision, maximum reading speed, functional reading independence index, and microperimetry.

Key findings: At 24 months, both trials, OAKS and DERBY, demonstrated similar treatment effects, revealing significant reductions in geographic atrophy growth ranging from 16% to 18% with every-other-month pegcetacoplan dosing and 19% to 22% with monthly dosing. However, functional outcomes did not show significant improvements in best-corrected vision, maximum reading speed, functional reading independence index, and microperimetry in the treatment group compared to controls.

The safety profile, including ocular inflammation, was comparable to other intravitreally administered drugs (e.g., anti-VEGF). Notably, there was a potential increased risk of Exudative AMD with Macular Neovascularization development in treated eyes, with exudation rates of 11.9% in the monthly dosing group, 6.7% in the every-other-month dosing group, and 3.1% in the sham group at 24 months.

Reference: Heier, J. S., Lad, E. M., Holz, F. G., Rosenfeld, P. J., Guymer, R. H., Boyer, D., Grossi, F., Baumal, C. R., Korobelnik, J. F., Slakter, J. S., Waheed, N. K., Metlapally, R., Pearce, I., Steinle, N., Francone, A. A., Hu, A., Lally, D. R., Deschatelets, P., Francois, C., Bliss, C. OAKS and DERBY study investigators (2023). Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials. Lancet (London, England), 402(10411), 1434–1448. https://doi.org/10.1016/S0140-6736(23)01520-9

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## The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration

*Prepared by Meri Galoyan*

Clinical applications: Geographic atrophy (GA), indicative of late age-related macular degeneration (AMD), results in the progressive and irreversible loss of visual function. Initially, these lesions manifest in the perifoveal macula, sparing the foveal center. Over time, they expand and coalesce, eventually encompassing the fovea. Although progression rates vary significantly among individual patients, an increasing body of evidence suggests that specific characteristics may play a crucial role in predicting disease progression and outcomes. This article aims to synthesize the current understanding of relevant factors for predicting lesion enlargement in both affected eyes and fellow eyes.

Summary: This review article conducted a PubMed literature search using key terms such as geographic atrophy, atrophy, macular degeneration, progression, enlargement, and growth. The search identified several high-quality studies reporting on the rate of lesion enlargement and analyzing characteristics predictive of progression. These characteristics included baseline lesion size, location, lesion configuration and Fundus Autofluorescence (FAF) patterns as well as status of the fellow eye.

Key findings: Notable baseline characteristics associated with faster progression included larger lesion size (greater than 1 disc diameter), extrafoveal location, multifocal configuration, and banded or diffuse FAF patterns around the lesion (please refer to the figure shown). Progression is positively associated with the extent of hyper-autofluorescence surrounding the lesion, defined as the convex hull (a convex polygon of increased FAF surrounding the lesion).

The most rapidly progressive lesions were associated with a diffuse trickling FAF pattern, described as a grey (rather than markedly decreased) FAF signal in areas of atrophy, as well as a coalescent lobular configuration of atrophic patches. The presence of geographic atrophy in the fellow eye also indicated a faster progressive lesion.

Reference: Fleckenstein, M., Mitchell, P., Freund, K. B., Sadda, S., Holz, F. G., Brittain, C., Henry, E. C., & Ferrara, D. (2018). The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration. Ophthalmology, 125(3), 369–390. https://doi.org/10.1016/j.ophtha.2017.08.038

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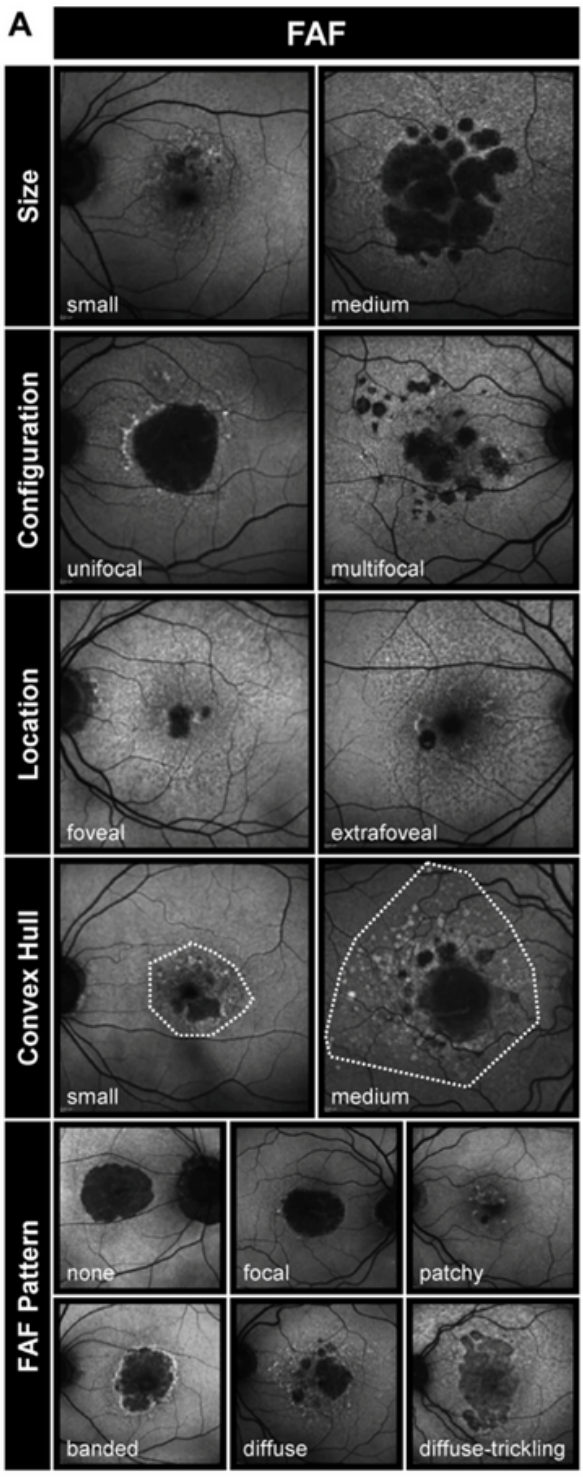
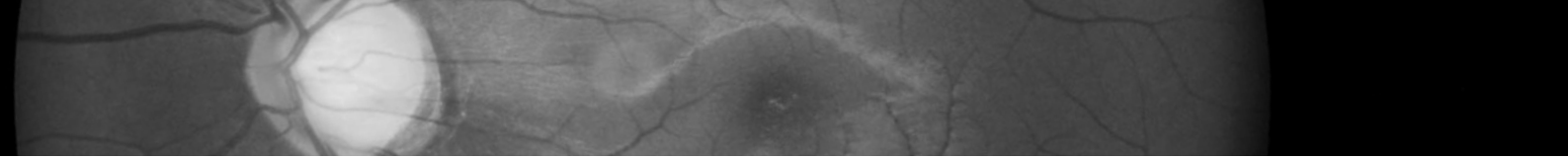



*Above: Figure 3 from Fleckenstein et al. Lesion features associated with geographic atrophy as seen on FAF imaging*



## Polygenic risk score improves prediction of glaucoma onset in patients with ocular hypertension

*Prepared by Henrietta Wang*

Clinical applications: Unlike juvenile-onset forms of glaucoma, primary open angle glaucoma (POAG) does not display a Mendelian inheritance pattern. This confounds the use of traditional methods of genetic testing to identify patients at risk of disease. A polygenic risk score (PRS) combines risk across multiple common genetic variants to give an aggregate measure of genetic burden which is useful in conditions with multiple genetic variants implicated. This study aimed to evaluate the usefulness of PRS in predicting the development of POAG in patients with ocular hypertension.

Summary: This study used data from the Ocular Hypertension Treatment Study (OHTS), which monitored patients with ocular hypertension from 1994 to 2020. Of the 1,636 patients from the OHTS, 1009 underwent polygenic risk score calculations. Survival regression analysis was utilised with the development of POAG as the analysis endpoint. At the 20-year mark, there was a significantly higher incidence of POAG-onset in patients with higher polygenic risk scores compared to those with lower polygenic risk scores. Despite this, the predictive performance of PRS in isolation remained inferior to other parameters currently used to stratify glaucoma risk such as the vertical cup-to-disc ratio and central corneal thickness. The addition of PRS to the current parameters used to predict POAG risk in patients with ocular hypertension showed a modest improvement in the mean area under the curve (AUC).

Key findings: These results suggest the addition of PRS to the risk factors identified by OHTS can help to improve prediction of POAG development in patients with ocular hypertension. However if used in isolation, the predictive ability of PRS remains inferior to structural risk factors such as central corneal thickness or vertical cup-to-disc ratio.

Reference: Singh RK, Zhao Y, Elze T, Fingert J, Gordon M, Kass MA, Luo Y, Pasquale LR, Scheetz T, Segrè AV, Wiggs JL, Zebardast N. Polygenic Risk Score Improves Prediction of Primary Open Angle Glaucoma Onset in the Ocular Hypertension Treatment Study. medRxiv [Preprint]. 2023 Aug 16:2023.08.15.23294141. doi: 10.1101/2023.08.15.23294141. PMID: 37645858; PMCID: PMC10462203

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## Preservative-free latanoprost treats the ocular surface better than preservative-free bimatoprost

*Prepared by Henrietta Wang*

Clinical applications: To improve compliance by reducing potential side effects related to ocular surface disease, there has been a shift in prescribing patterns towards using preservative-free (PF) options where possible. This study aimed to compare the impact of latanoprost and bimatoprost PF eye drops on ocular surface disease.

Summary: 44 eyes from 44 participants were included in this study: 11 were treated with Latanoprost PF, 9 eyes with Bimatoprost PF and 24 control eyes. Patients underwent evaluation using Schirmer' test, the tear break-up time (TBUT) test as well as the InflammaDry kit to assess levels of MMP-9, a molecule associated with ocular surface disease. The Schirmer's test and TBUT test results were lower in the bimatoprost group compared to the latanoprost group. There were also elevated levels of MMP-9 in the bimatoprost group compared to the latanoprost group.

Key findings: Although patient symptoms do not always directly correlate with objective tests such as TBUT or InflammaDry kit, clinicians may err towards prescribing latanoprost PF over bimatoprost PF for patients with ocular surface disease and concomitant glaucoma to reduce drop-related side effects.

Reference: Dimtsas, G. S., Tsiogka, A., & Moschos, M. M. (2023). Latanoprost PF vs. Bimatoprost PF: Which Treats the Ocular Surface Better?. Journal of clinical medicine, 12(21), 6732. https://doi.org/10.3390/jcm12216732

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The team at Centre for Eye Health would like to take this opportunity to thank you for your support of our education program this year.

We hope you have found these literature updates useful in keeping abreast of the ever-evolving knowledge base.

If you have any comments, feedback or questions, please email us at any time - education@cfeh.com.au

Finally, we would like to wish you and your family a relaxing and joyful break over the Christmas period, and we look forward to bringing you more exciting educational resources in 2024.

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