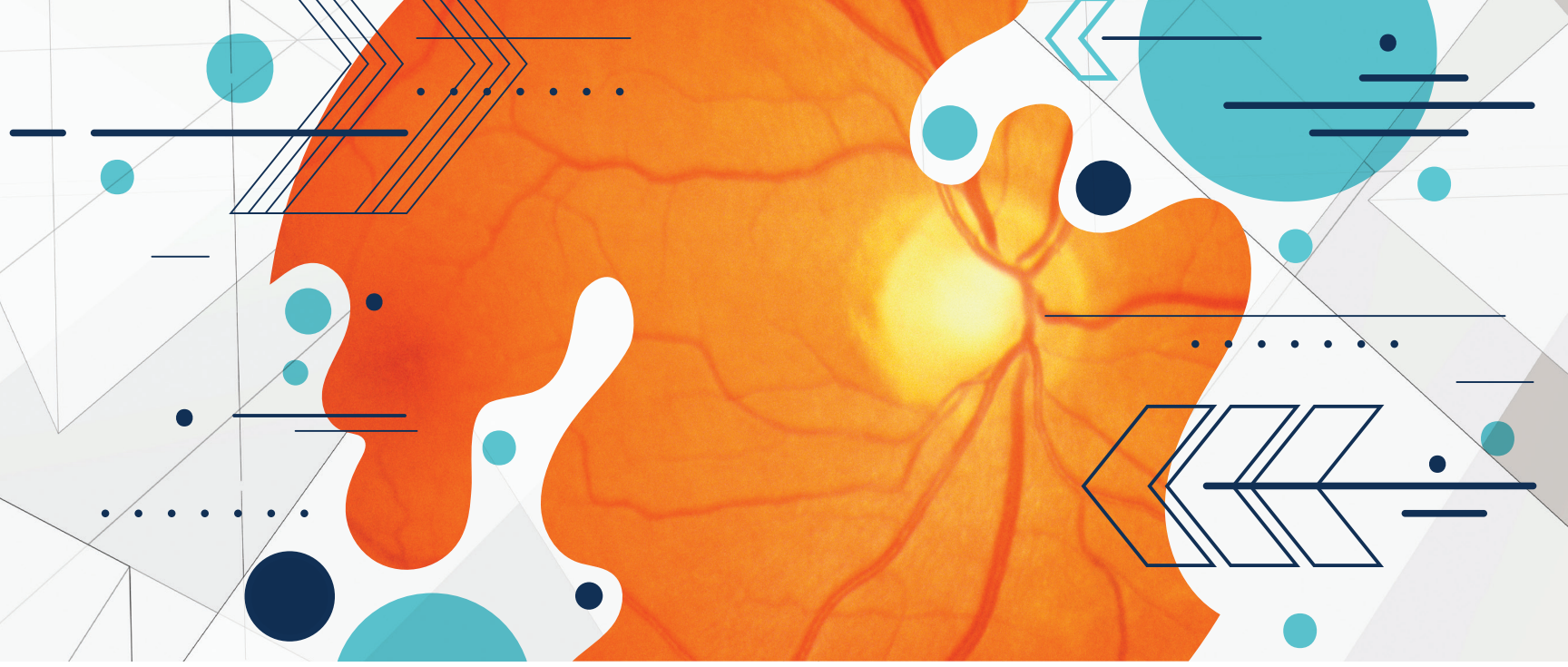

RETINA IN REVIEW

An overview of the latest developments and findings related to the treatment and management of diseases of the posterior segment.

BY CAROLYN MAJCHER, OD, FAAO, FORS, AND ETHAN WOHLGEMUTH, OD

The retina sector of our profession has been busy these past few years with new research and approvals, and it looks like there is no slowing down. In this article we discuss imaging techniques, emerging therapies, and referral considerations for geographic atrophy (GA), as well as therapies for neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME).

NEW THERAPEUTIC TREATMENTS FOR GA

The recent emergence of complement inhibition therapies for GA secondary to AMD is perhaps the most exciting pharmaceutical development in the retina landscape since the approval of the first anti-vascular endothelial growth factor (VEGF) agent pegaptanib (Macugen, Eyetech/Pfizer; no longer available) in 2004. Before 2023, eye care providers felt helpless when managing patients with GA because Age-Related Eye Disease Study (AREDS) supplements did little to slow the disease's relentless progression, which ultimately results in irreversible central vision loss.[1,2] GA is present in approximately 20% of all AMD cases, and the median time from GA diagnosis to foveal involvement in the AREDS study was 2.5 years.[3]

Complement Inhibition

Two new therapies for GA secondary to AMD became available this year: pegcetacoplan (Syfovre, Apellis), which is an inhibitor of complement C3, and avacincaptad pegol 2 mg (Izervay, Iveric Bio), a

AT A GLANCE

- Understanding and using imaging to detect early geographic atrophy (GA) lesions and high-risk biomarkers that predispose patients to future GA development and progression is critically important.
- New terminology is gaining popularity to describe various OCT stages of GA development.
- In primary care settings, artificial intelligence programs have the potential to enhance telemedicine screenings for diabetic retinopathy by assisting medical decision-making and addressing barriers in accessing eye care.

Image courtesy of Apellis Pharmaceuticals.

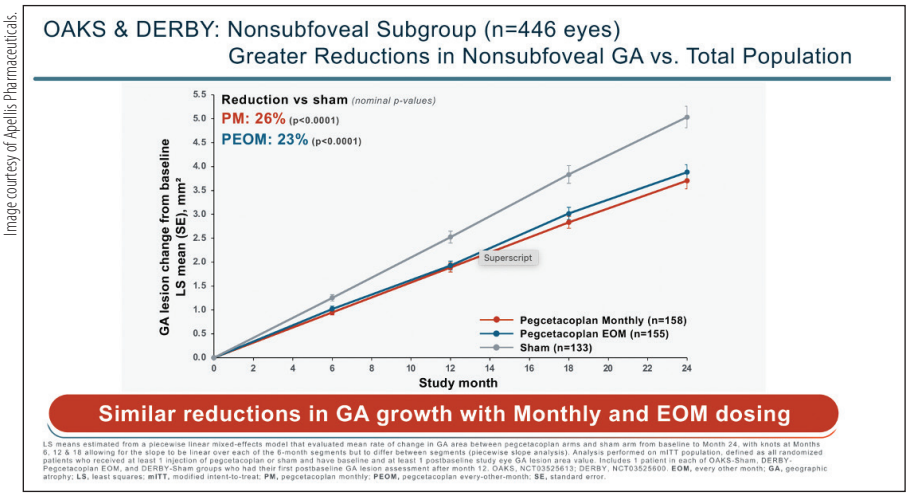

Figure 1. Subgroup analysis of OAKS and DERBY phase 3 clinical trials.

complement C5 inhibitor. Both are administered via intravitreal injection either monthly or every other month. Combined data from the OAKS and DERBY phase 3 clinical trials evaluating the safety and efficacy of pegcetacoplan show that monthly dosing reduced GA growth from baseline by 20% compared with sham with increased efficacy over time.[4] Subgroup analysis showed greater reduction in GA lesion growth in eyes *without* subfoveal involvement (lesions ≥ 250 µm away from the foveal center) compared with those *with* subfoveal involvement (26% vs 19% with monthly dosing, Figure 1).[4] With regard to functional benefits, post-hoc analysis showed that among eyes *without* subfoveal involvement, treatment preserved 5.6 letters of visual acuity compared with sham at 24 months.[5]

Data from the phase 3 clinical trials evaluating the safety and efficiency of avacincaptad pegol show that monthly dosing reduced mean GA growth rate from baseline to month 12 by 35.4% and 17.7% compared with sham in GATHER 1 and GATHER 2, respectively (Figure 2).[6,7] These studies included only eyes with GA that did not involve the foveal center, but was in part within 1,500 µm from the foveal center. Post-hoc time-to-event analysis on combined GATHER 1 and 2 data demonstrated a 56% risk reduction in persistent vision loss at 12 months (loss of ≥ 15 letters from baseline measured at two consecutive visits) in treated eyes compared with sham (Figure 3).[8]

Adverse Effects

Important adverse effects to be aware of include increased rates of macular neovascularization (nAMD) and ischemic optic neuropathy.[5,7,9] However, eyes that develop exudative nAMD can be concurrently treated with anti-VEGF therapies, which are well-evidenced and highly effective. In addition, several rare cases of real-world severe intraocular inflammation have recently been reported with Syfovre.[10]

IMAGING

Understanding and using imaging to detect early GA lesions and high-risk biomarkers that predispose patients to future GA development and progression is critically important. The gold standard for GA detection is OCT. On cross-sectional OCT, GA features include loss or attenuation of photoreceptors (external limiting membrane, outer nuclear layer, ellipsoid zone, interdigitation zone) and retinal pigment epithelium (RPE), along with corresponding choroidal hyper-transmission (Figure 4).[11]

Images courtesy of Iveric Bio.

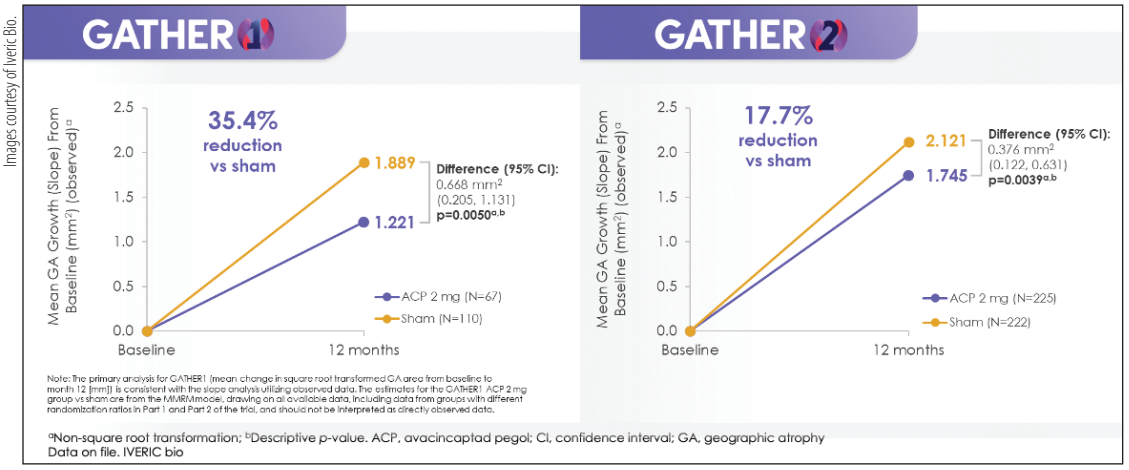

Figure 2. Monthly dosing of avacincaptad pegol reduced mean GA growth rate from baseline to month 12 by 35.4% and 17.7% compared with sham, respectively.

WORDS MATTER

New terminology developed by the Classification of Atrophy Meeting (CAM) Group is gaining popularity to describe various OCT stages of GA development.[11] The CAM Group defined complete RPE and outer retinal atrophy as a ≥ 250 µm diameter zone of

Image courtesy of Iveric Bio.

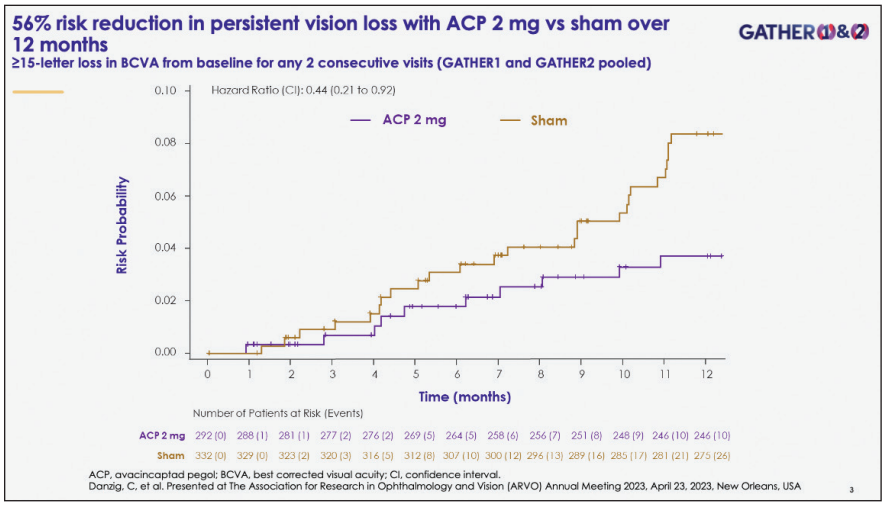

Figure 3. Post-hoc time-to-event analysis on combined GATHER 1 and 2 data demonstrated a 56% risk reduction in persistent vision loss at 12 months in treated eyes compared with sham.

RPE attenuation or disruption with overlying evidence of photoreceptor degeneration and underlying choroidal hyper-transmission (Figure 4). En-face OCT using a sub-RPE slab can be valuable for quantitatively tracking GA progression over time (Figure 5). Fundus autofluorescence may also be used to detect GA lesions, which appear dark or hypoautofluorescent, and the degree of surrounding hyperautofluorescence can be used as a predictor for future expansion.[11,12]

When considering referral, target patients who are at greatest risk of rapid progression (ie, those who have GA lesions that are multifocal, extrafoveal, and/or bilateral).[13] Patients with extrafoveal GA in one eye and central GA in the fellow eye are often highly motivated to treat the eye with extrafoveal involvement. Patients should be educated on and must be willing to undergo chronic therapy including intravitreal injections, and have realistic expectations that therapy will not restore vision, but rather slow visual decline.

EXTENDED-DURATION THERAPIES FOR NAMD AND DME

Exciting developments to decrease the burden of often frequent and long-term intravitreal injection therapies for nAMD and DME include aflibercept injection 8 mg (Eylea HD, Regeneron Pharmaceuticals), faricimab-svoa injection 6 mg (Vabysmo, Genentech), and the anticipated arrival of the Notal Home OCT (Notal Vision) for remote disease activity monitoring.[14]

High-Dose Aflibercept

PULSAR was a phase 3 randomized, controlled clinical trial that included 1,009 patients with treatment-naïve nAMD and compared the following treatment options: 1) Eylea HD every 12 weeks following three initial monthly injections, 2) Eylea HD every 16 weeks following three initial monthly injections, and 3) Eylea (aflibercept 2 mg) every 8 weeks following three initial monthly injections.[15] During the first year of the study, patients in the Eylea HD groups could have their assigned dosing intervals shortened if they met the prespecified study criteria for dose regimen modification; intervals could only be shortened, and the minimum dosing interval was every 8 weeks.[15] Through 48 weeks, 79% of patients among the Eylea HD every 12-week group maintained 12-week dosing, and 77% of patients in the Eylea HD every 16-week group maintained 16-week dosing (Figure 6).[16] Clinically equivalent vision gains were achieved in the Eylea HD groups compared with the Eylea group; the mean visual acuity gains at 48 weeks were +7.6 letters in the Eylea group, +6.7 letters in the Eylea HD every 12-week group, and +6.2 letters in the Eylea HD every 16-week group.[17] No new safety signals with Eylea HD were identified.[18,19]

PHOTON was a phase 3 randomized, controlled clinical trial that included 658 patients with center-involved DME (CI-DME) and compared the following treatment options: 1) Eylea HD every 12 weeks following three initial monthly injections, 2) Eylea HD every 16 weeks following three initial monthly injections, and 3) Eylea every 8 weeks following five initial monthly injections.[15] During the first year of the study, patients in the Eylea HD groups could have their assigned dosing intervals shortened if they met the prespecified study criteria for dose regimen modification; intervals could only be shortened, and the minimum dosing interval was every 8 weeks.[15] Through 48 weeks, 91% of patients among the Eylea HD every 12-week group maintained 12-week dosing, and 89% of patients in the Eylea HD every 16-week group maintained 16-week dosing.[20] Clinically equivalent vision gains were achieved in the Eylea HD groups compared with the Eylea group; the mean visual acuity gains at 48 weeks were +9.2 letters in the Eylea group, +8.8 letters in the Eylea HD every 12-week group, and +7.9 letters in the Eylea HD every 16-week group.[17] No new safety signals with Eylea HD were identified.[19,21]

Faricimab

Faricimab is a new generation bispecific anti-VEGF agent that received FDA approval for the management of nAMD and DME

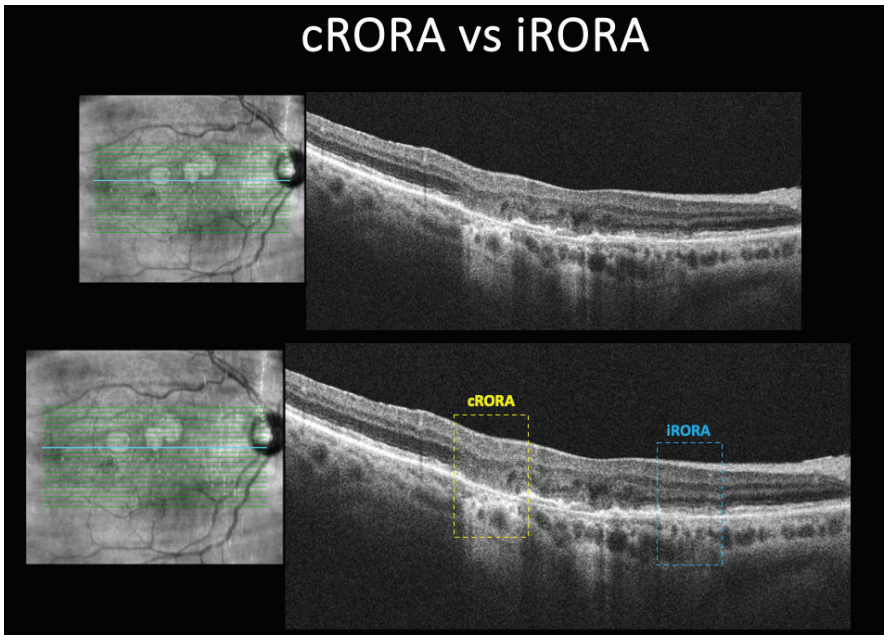

Figure 4. Cross-sectional OCT shows GA features such as loss or attenuation of RPE and corresponding choroidal hyper-transmission.

Abbreviations: cRORA, complete RPE and outer retinal atrophy (≥ 250 µm diameter zone of RPE attenuation or disruption with overlying evidence of photoreceptor degeneration and underlying choroidal hyper-transmission); iRORA, incomplete RPE and outer retinal atrophy (RPE and ellipsoid zone attenuation/discontinuity along with nonuniform choroidal hyper-transmission)

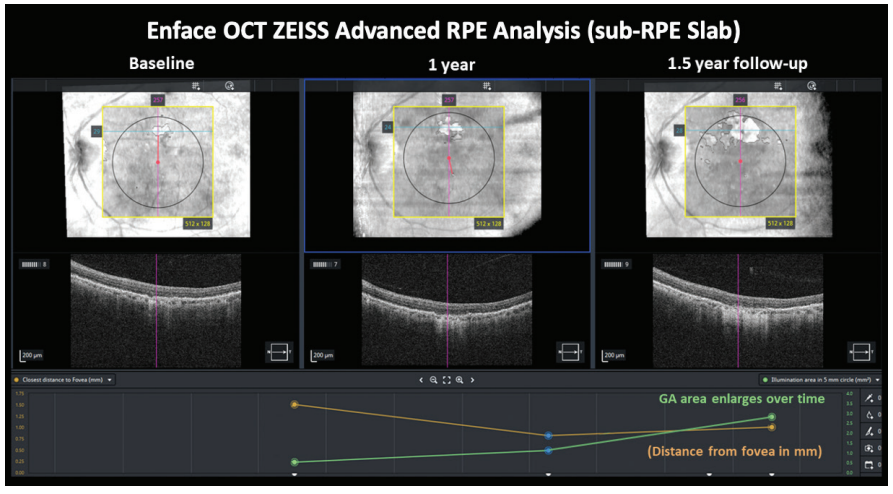

Figure 5. En-face OCT analysis can help track GA progression.

in January 2022. Retinal vascular disease and neovascularization are mediated synergistically by both VEGF and the angiopoietin/Tie pathway.[22,23] Angiopoietin-2 (Ang-2) is a proinflammatory and pro-angiogenic cytokine that is upregulated in disease conditions including diabetic retinopathy (DR) and AMD.[22,23] Ang-2 negatively regulates the Ang-Tie pathway, contributing to reduced vessel stability, increased vascular leakage, and angiogenesis.[22,23] Additionally, Ang-2 potentiates VEGF-A's role in vascular hyperpermeability and neovascularization.[22,23] Faricimab's dual action inhibits both VEGF-A and Ang-2 to address the multifactorial pathophysiology of retinal vascular disease and nAMD, which may promote improved outcomes compared with anti-VEGF monotherapy.[24,25]

Two global phase 3 clinical trials comparing faricimab with aflibercept 2 mg, YOSEMITE and RHINE, demonstrated the efficacy of faricimab for treating CI-DME.[25] Faricimab and aflibercept 2 mg demonstrated similar BCVA improvements, and this was maintained through 2 years.[25,26] Superior anatomic outcomes were seen with faricimab, with greater reduction in macular thickness and a greater proportion of participants achieving absence of DME and intraretinal fluid.[25] Compared with aflibercept 2 mg, resolution of DME and intraretinal fluid was achieved 16 and 36 weeks earlier, respectively, with fewer injections with faricimab.[26] The majority of participants in the faricimab treat-and-extend group (70%) achieved treatment intervals greater to or equal to every 12 weeks.[24]

Approximately 80% of individuals receiving dosing every 16 weeks at 1 year maintained this interval through the second year.[26] These trials support the use of faricimab in the management of CI-DME given equivocal visual outcomes and superior anatomic results compared with conventional anti-VEGF monotherapy, and highlight faricimab's durability and potential for increased treatment intervals.[25]

Faricimab's role in the management of nAMD is supported by two phase 3 clinical trials, LUCERNE and TENAYA, which compared the efficacy of faricimab and aflibercept 2 mg in anti-VEGF–naive individuals with nAMD.[24] BCVA improvements and the proportion of patients achieving Snellen VA of 20/40 or better were similar for faricimab and aflibercept 2 mg at 1 year.[23] Anatomic outcomes were consistent with functional outcomes in both trials; improvements in macular thickness, choroidal neovascular lesion size, and extent

Image courtesy of Regeneron.

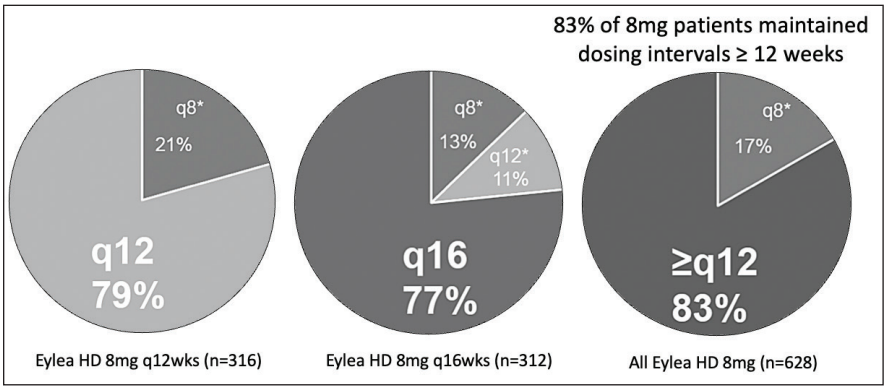

Figure 6. This is the proportion of patients taking aflibercept 8 mg who maintained 12- and 16-week intervals through week 48 in the PULSAR clinical trial.

Image courtesy of Regeneron.

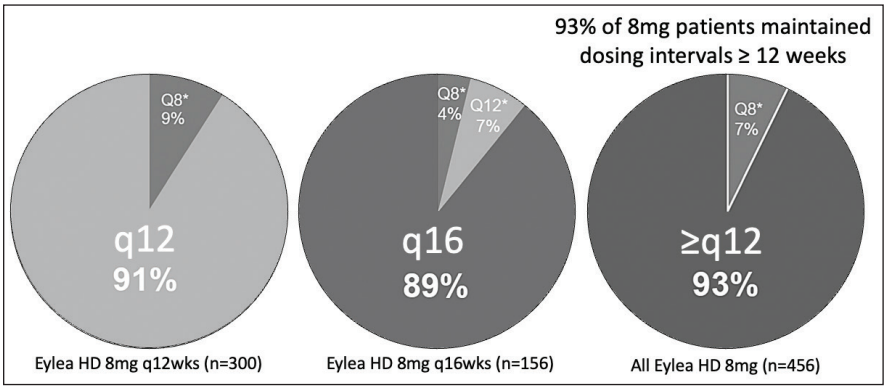

Figure 7. This is the proportion of patients taking aflibercept 8 mg who maintained 12- and 16-week intervals through week 48 in the PHOTON clinical trial.

of macular leakage were comparable between faricimab and aflibercept 2 mg.[24] Absence of intraretinal and subretinal fluid was achieved more rapidly and with fewer injections with faricimab (8 weeks) compared with aflibercept 2 mg (12 weeks).[27] Approximately 80% of individuals receiving faricimab achieved 12- or 16-week dosing intervals.[24] These clinical trials support the efficacy of faricimab in managing nAMD, and demonstrate potential for extended treatment intervals; this may reduce treatment burdens and address barriers to effective nAMD management.[24]

Artificial Intelligence in DR

Telemedicine DR screenings have shown promise in improving detection and referral rates of DR to eye care providers.[28,29] In primary care settings, artificial intelligence (AI) programs have the potential to enhance telemedicine screenings for DR by assisting medical decision-making and addressing barriers in accessing eye care, particularly in remote areas.[30-32] There are several FDA-approved fundus photography-based AI DR screening programs, including IDx-DR (LumineticsCore; formerly Digital Diagnostics), EyeArt AI Eye Screening System (Eyenuk), and most recently AEYE Diagnostic Screening (AEYE-DS; AEYE Health), which received FDA approval in 2022. AI DR screenings have shown good diagnostic accuracy, and a recent meta-analysis reported a positive post-test probability of 93%.[32] Overall, sensitivity and specificity are high and within acceptable ranges.[30,33-35] The first FDA-approved program, IDx-DR, had a sensitivity of 87.2% for detecting more than mild DR, and 92.2% for vision-threatening DR in clinical trials.[33]

A number of challenges exist for incorporating AI DR screenings into clinical practice, including biases from nonrepresentative databases, which affect outcomes for marginalized populations.[31] Infrastructure costs, such as internet availability and technology literacy, are further barriers, and may be greater in target populations of AI screening programs; this may exacerbate already existing health disparities if AI is not implemented appropriately.[31] Further, these programs are not designed to detect other ocular pathologies that may be elucidated in a standard optometric eye exam, and may confound AI analysis.[33,35] Finally, medico-legal responsibilities are yet to be fully outlined for AI DR screenings.[35]

KEEP UP TO STAY AHEAD

Management of conditions such as GA, AMD, and DME has come a long way in recent years, but still has further to go. Keep up with the latest advancements to give your patients the best chance of quality care and successful outcomes. ■

1. Keenan TD, Agrón E, Domalpally A, et al; AREDS Research Group. Progression of geographic atrophy in age-related macular degeneration: AREDS2 Report Number 16. *Ophthalmology*. 2018;125(12):1913-1928.
2. Keenan TDL. Geographic atrophy in age-related macular degeneration: a tale of two stages. *Ophthalmol Sci*. 2023;3(3):100306.
3 Lindblad AS, Lloyd PC, Clemons TE, et al; Age-Related Eye Disease Study Research Group. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. *Arch Ophthalmol*. 2009;127(9):1168-1174.
4. Chiang A, Bliss C, Ribeiro R, et al. Assessment of geographic atrophy (GA) lesion progression in the phase 3 OAKS and DERBY trials. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; April 23-27, 2023; New Orleans, LA.
5. Apellis presents phase 3 functional analyses of SYFOVRE (pegcetacoplan injection) for geographic atrophy. Apellis. April 23, 2023. Accessed October 23, 2023. https://investors.apellis.com/news-releases/news-release-details/apellis-presents-phase-3-functional-analyses-syfovretm
6. Khanani AM, Patel SS, Staurenghi G, et al. The efficacy of avacincaptad pegol in geographic atrophy: GATHER 1 and GATHER 2 results. Paper presented at The Retina Society 55th Annual Scientific Meeting; November 2-5, 2023; Pasadena, CA.
7. Jaffe GJ, Westby K, Csaky KG, et al. C5 Inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal phase 2/3 trial. *Ophthalmology*. 2021;128(4):576-586.
8. Danzig CJ, Kaiser PK, Lally DR, et al. Intravitreal avacincaptad pegol in geographic atrphy: post-hoc analysis of vision loss from the GATHER clinical program. Paper presented at: the Association for Research in Vision and Ophthalmology annual meeting; April 23-27, 2023. New Orleans, LA.
9. Patel SS, Lally DR, Hsu, et al. Avacincaptad pegol for geography atrophy secondary to age-related macular degeneration: 18-month findings from the

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GATHER1 trial [published online ahead of print March 24, 2023]. *Eye (London)*.
10. Apellis provides update on review of rare safety events with SYFOVRE (pegcetacoplan injection) for geographic atrophy. Apellis. July 29, 2023. Accessed October 23, 2023. https://investors.apellis.com/news-releases/news-release-details/apellis-provides-update-review-rare-safety-events-syfovrer
11. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of Atrophy Report 3. *Ophthalmology*. 2018;125(4):537-548.
12. Biarnés M, Arias L, et al. Increased fundus autofluorescence and progression of geographic atrophy secondary to age-reWlated macular degeneration: the GAIN Study. *Am J Ophthalmol*. 2015;160(2):345–353.e5.
13. Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125(3):369-390.
14. Notal Home OCT. Notal Vision. Accessed October 24, 2023. https://notalvision.com/technology/home-oct
15. Afibercept 8 mg meets primary endpoints in two global pivotal trials for DME and wAMD, with a vast majority of patients maintained on 12- and 16- week dosing intervals. Regeneron Pharmaceuticals. Accessed October 24, 2023. https://investor.regeneron.com/news-releases/news-release-details/aflibercept-8-mg-meets-primary-endpoints-two-global-pivotal
15. Wet AMD: extended dosing. Regeneron Pharmaceuticals. Accessed October 24, 2023. https://eyleahcp.us/s/eyleahd/wet-amd-extended-dosing
16. Wet AMD: vision outcomes. Regeneron Pharmaceuticals. Accessed October 24, 2023. https://eyleahcp.us/s/eyleahd/wet-amd-vision-outcomes
17. Wet AMD: safety data. Regeneron Pharmaceuticals. Accessed October 24, 2023. https://eyleahcp.us/s/eyleahd/wet-amd-safety-data
18. Matei V, Majcher C. Intravitreal Anti-VEGF Injections (chapter in The Ophthalmic Office Procedures Handbook). Lippincott Williams & Wilkins. Publication date February 2024.
19. DME: extended dosing. Regeneron Pharmaceuticals. Accessed October 24, 2023. https://eyleahcp.us/s/eyleahd/dme-extended-dosing
20. DME: vision outcomes. Regeneron Pharmaceuticals. Accessed October 24, 2023. https://eyleahcp.us/s/eyleahd/dme-vision-outcomes
21. Heier JS, Singh R P, Wykoff CC, et al. The angiopoietin/tie pathway in retinal vascular diseases: a review. *Retina*. 2021;41(1):1-19.
22. Wang R, Yang M, Jiang L, Huang, M. Role of angiopoietin-tie axis in vascular and lymphatic systems and therapeutic interventions. *Pharmacol Res*. 2022;182:106331.
23. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): Two randomised, double-masked, phase 3, non-inferiority trials. *Lancet*. 2022;399(10326):729-740.
24. Wykoff CC, Abreu F, Adamis AP, et al. YOSEMITE and RHINE Investigators. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. *Lancet*. 2022;399(10326):741-755.
25. Pollreisz A, Camino A, Gibson K, et al. Faster time to retinal fluid control with faricimab versus aflibercept in patients with DME in the phase 3 YOSEMITE/RHINE trials. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; April 23-27, 2023; New Orleans, LA.
26. Querques G, London N, Kotecha A, et al. Faricimab rapidly improves fluid parameters in patients with nAMD. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; April 23-27, 2023; New Orleans, LA.
27. Dhediya R, Chadha M, Bhattacharya AD, Godbole S, Godbole S. Role of telemedicine in diabetes management. *J Diabetes Sci Technol*. 2023;17(3):775-781.
28. ElSayed NA, Aleppo G, Aroda VR, et al; on behalf of the American Diabetes Association. 12. Retinopathy, neuropathy, and foot care: standards of care in diabetes—2023. *Diabetes Care*. 2022;46(Suppl 1:S203-S215.
29. He J, Cao T, Xu F, et al. Artificial intelligence-based screening for diabetic retinopathy at community hospital. Eye (Lond). 2020;34(3):572-576.
30. Nakayama LF, Zago Ribeiro L, Novaes F, et al. Artificial intelligence for telemedicine diabetic retinopathy screening: a review. *Ann Med*. 2023;55(2):2258149.
30. Wang Z, Li Z, Li K, et al. Performance of artificial intelligence in diabetic retinopathy screening: A systematic review and meta-analysis of prospective studies. *Front Endocrinol (Lausanne)*. 2023;14:1197783.
31. Abràmoff MD, Lavin PT, Birch M, et al. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *NPJ Digit Med*. 2018;1:39.
32. Bhaskaranand M, Ramachandra C, Bhat S, et al. The value of automated diabetic retinopathy screening with the EyeArt System: a study of more than 100,000 consecutive encounters from people with diabetes. *Diabetes Technol Ther*. 2019;21(11):635-643.
35. Scheetz J, Koca D, McGuinness M, et al. Real-world artificial intelligence-based opportunistic screening for diabetic retinopathy in endocrinology and indigenous healthcare settings in Australia. *Sci Rep*. 2021;11(1):15808.

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