New Geographic Atrophy Drugs: The Good, the Bad, and the Unknown

Early last year, the FDA approved pegcetacoplan (Syfovre) as the first treatment for geographic atrophy (GA) from age-related macular degeneration (AMD). Retina specialists could finally offer these patients treatment. In August 2023, another GA treatment, avacincaptad pegol (Izervay) gained approval.

However, concerns about whether these two complement inhibitors help patients enough to warrant the risks and burdens of treatment have left some ophthalmologists reluctant to use them. "This is a big controversy in our field," said Jason Miller, MD, PhD, adding that opinions on the matter run sufficiently strong that discussions can grow heated. Dr. Miller is the James Grosfield Endowed Professor and Assistant Professor of Ophthalmology and Visual Sciences at the University of Michigan in Ann Arbor.

A Mixed Reception

"It really was a breakthrough once the FDA approval of pegcetacoplan occurred," said Margaret Chang, MD, MS, a senior partner at Retinal Consultants in Sacramento, California. She offers it to patients with clearly worsening GA, after telling them that it may slow, but does not stop, GA progression.

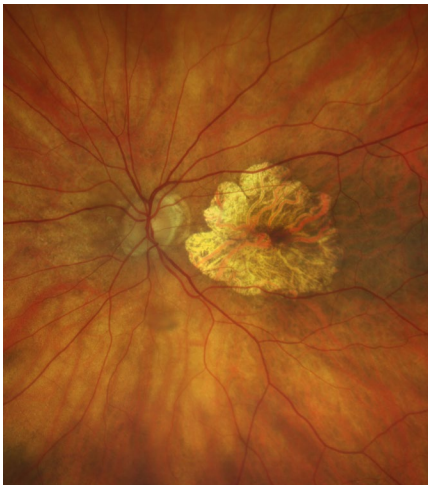
In contrast, Stephen Jae Kim, MD, said, "I honestly was shocked that the FDA approved it." When patients ask about the new drugs, he tells them, "I don't feel the drugs are safe or effective at this time." Dr. Kim is the Phyllis G. and William B. Snyder, MD, Endowed Chair in Ophthalmology and Visual Sciences, Professor of Ophthalmology, and Chief of the Retina Division at Vanderbilt Eye Institute in Nashville, Tennessee.

The enthusiasm for pegcetacoplan exceeds the clinical evidence of its efficacy, said Dr. Miller. Yet, he is willing to consider it for the few patients who still want it after he describes its modest effects on lesion growth, its lack of vision benefits after two years of treatment, and its risks. He plans to use the same approach with avacincaptad pegol, a recent addition to the formulary at the University of Michigan.

Complement Inhibition

Dr. Miller said interest in complement inhibition to treat GA arose out of genome-wide association studies, particularly those tying complement factor H to AMD. The complement system thwarts pathogens and removes dead cells, but it may go into overdrive in genetically susceptible people. That dysregulation promotes drusen deposits and inflammation. It may also push the membrane attack complex to destroy cells in the retinal pigment epithelium, photoreceptors, and choriocapillaris.

Pegcetacoplan inhibits complement factor 3, which sits at the nexus of three complement pathways. Avacincaptad pegol inhibits complement factor 5.



GA. *Color fundus photo of geographic atrophy.*

Pegcetacoplan

Much of the evidence for the two drugs comes from clinical trials funded by the drugmakers. That includes OAKS and DERBY,[1] the phase 3 trials for pegcetacoplan, which together enrolled more than 1,200 patients aged 60 and older with GA from AMD. Participants were randomly assigned to receive either pegcetacoplan, administered by intravitreal injection, monthly or every other month, or sham injections on the same schedule. The main endpoint was growth in total lesion area, assessed by fundus autofluorescence, from baseline to 12 months.

Some progress on progression. In DERBY, one year of pegcetacoplan treatment failed to significantly impact lesion growth. The drug did better in OAKS, where it curbed GA progression

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by 21% when administered monthly and by 16% when given every other month, compared with the combined sham-injection groups.

Despite the mixed results at 12 months, both studies showed efficacy after two years of treatment. By then, pegcetacoplan had reduced progression by 16% to 22%. Those numbers, while statistically different from the sham-treated group, fall way short of what Dr. Kim says he expects from a new drug.

Post-hoc analyses hinted of growing efficacy with continued pegcetacoplan treatment,[1] a finding that requires confirmation. Also, the GALE trial treated patients for an additional year, and while results of the open-label study are trickling out, they have yet to be published in a peer-reviewed journal.

A poor showing on vision tests. Slowing GA progression should, in theory, slow vision loss, but neither DERBY nor OAKS bore this out. Two years of pegcetacoplan injections failed to postpone the loss of best-corrected visual acuity, reading ability, patient-reported visual functioning, or, in OAKS, threshold sensitivity measured by mesopic microperimetry. "That's not surprising because the onset of vision benefit may happen three, four, five years down the road," said Dr. Kim.

Avacincaptad Pegol

The clinical trials for avacincaptad pegol include GATHER1 and GATHER2, which tested the drug's efficacy and safety in participants age 50 and older with GA.[2,3] Patients were randomly assigned to receive either sham injections or intravitreal avacincaptad pegol injections each month. The main efficacy endpoint was change in GA lesion area, measured by fundus autofluorescence, from baseline to six months and to 12 months.

Early effect on progression. In GATHER1, avacincaptad pegol showed efficacy after six months of treatment. By the one-year mark, treated patients showed about 27% less progression than sham-treated patients. Since both the 2-mg and 4-mg doses showed similar efficacy, GATHER2 focused on the lower dose to minimize adverse effects. This time, avacincaptad pegol delayed progression by just 14% after a year of treatment—still a statistically significant effect.

No definitive vision effect. What patients care about is how well they see, not some anatomic outcome, said Dr. Miller. To that point, the evidence from GATHER1 and GATHER2 suggests that a year of avacincaptad pegol failed to delay vision loss, as reflected in best-corrected visual acuity in normal or low light.

Descriptive analyses of GATHER1 data hinted that longer treatment—specifically, 18 months—might slow visual decline,[4] but Dr. Miller said such analyses are tentative and prone to artifact. He cautioned that post-hoc analyses "are not something that we as clinicians should hang our hat on as the truth."

The Risks of Treatment

Dr. Kim noted that given the complement system's role in keeping eyes healthy, drugs that block it might produce off-target effects. In fact, the biggest controversy regarding these drugs concerns their safety, said Dr. Chang.

Vasculitis. She noted that the American Society of Retina Specialists has received reports of vasculitis in at least 14 eyes of 13 patients after a first pegcetacoplan injection.[5] "In some cases, it has led to severe, irreversible vision loss," she warned.

Ischemic optic neuropathy. In addition, three clinical trial participants developed ischemic optic neuropathy within 24 months of starting pegcetacoplan.[1] All had received monthly injections.

Neovascular AMD. More commonly, Dr. Miller noted, patients on pegcetacoplan or avacincaptad pegol may develop neovascular AMD. At 12 months in the OAKS and DERBY studies, 5% and 7% of patients, respectively, who received pegcetacoplan monthly were found to have new-onset exudative AMD.[1] And in the GATHER2 study, 5% of patients who received avacincaptad pegol monthly developed exudative macular neovascularization after one year.[3] As to which drug makes that more likely, he said they cannot be compared because the trials used different criteria to select patients. Some trials excluded people who had neovascular AMD in the fellow eye, while others did not. "We know that people who have wet macular degeneration in one eye are more prone to getting it in the other eye," he said.

Infection. No matter what the syringe holds, any injection into the eye carries a small risk of endophthalmitis. According to Dr. Miller, that risk goes from minuscule to meaningful when GA patients receive shots every four to eight weeks, often in both eyes, for the rest of their lives. Whereas the risks of injections for neovascular AMD are outweighed by their efficacy, the lesser benefits of GA therapies may make their risks harder to accept, he said.

In the Clinic

"The challenge is the leap from phase 3 results into real-world practice and whether the risk-benefit ratio is right for patients in real life to receive treatment," said Dr. Chang. In day-to-day practice, results rarely live up to those seen in trials performed under ideal conditions in select patients, Dr. Kim

Tips for Drug Use

Patient selection. According to Dr. Miller, one way to minimize harm is to reserve complement blockers for patients who show fast progression over six to 12 months. His thinking is that slow progressors might never reach the point of losing vision from their GA.

Administration. Dr. Chang said some retina specialists administer pegcetacoplan every other month rather than monthly. She added that some treat the worse eye first, to see how the patient reacts to the drug, before treating the better eye.

Report issues. She urged ophthalmologists to report any problems encountered with either drug "to make sure that we know exactly what's happening in the real world so we can continue to make the best choices for our patients."

To report, go to www.accessdata.fda.gov/scripts/medwatch/.

said. He questioned whether patients will keep returning for more injections if they see no benefit. He also expressed concern that avacincaptad pegol might cause unforeseen side effects given the relatively little experience ophthalmologists have with it.

Dr. Miller said patients go to their appointments expecting the treatment to suddenly improve their eyesight or at least keep it the same. To temper expectations, he asks them, "Is the burden of an injection every one or two months, with its side effects, worth the as-yet unproven theoretical vision benefit?" Out of all his GA patients, fewer than 5% have decided to proceed with treatment after this discussion.

Reimbursement. As for the financial aspects of treatment, Dr. Chang said insurance generally covers pegcetacoplan. And as of April 1, avacincaptad pegol was approved for HCPCS code J2782 *Injection, avacincaptad, pegol, 0.1 mg,* which you would report with 20 units.

Unfolding evidence. "Treatment should have a clear, definable benefit that exceeds the risk and burden and cost of treatment," Dr. Kim said. He has seen many drugs hit the market with considerable fanfare, only to disappoint. Time will tell where pegcetacoplan and avacincaptad pegol will land; meanwhile, he will wait for more data and see what it shows.

1 Heier J et al. *Lancet*. 2023;402(10411):1434-1448.
2 Jaffe GJ et al. *Ophthalmology*. 2021;128(4):576-586.
3 Khanani AM et al. *Lancet*. 2023;402(10411):1449-1458.
4 Patel SS et al. *Eye* (Lond). 2023;37(17):3551-3557.
5 Witkin AJ et al. *J Vitreoretin Dis*. 2024;8(1):9-20.

Dr. Chang is a senior partner at Retinal Consultants in Sacramento, Calif. *Relevant financial disclosures: Iveric Bio: C; Genentech: C; NGM: I; Alexion: I.*

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