HANDLING COMPLICATIONS OF COMPLEMENT INHIBITION

The new therapies for geographic atrophy come with unique patient education and risk management considerations.

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AMD, projected to affect 400 million people by 2040, is characterized by both wet AMD and geographic atrophy (GA), which are nonexclusive.[1] Complement activation and chronic inflammation have been implicated in the pathogenesis of GA.[2,3] Unsurprisingly, the first FDA-approved drugs to treat GA, pegcetacoplan (Syfovre, Apellis) and avacincaptad pegol (Izervay, Iveric Bio/Astellas), target the complement system.[4] Pegcetacoplan inhibits C3 and C3b, while avacincaptad pegol inhibits C5.[5,6] These new therapies, although a welcome addition, come with unique complications and patient education considerations.

WATCH FOR COMPLICATIONS

In the 24-month combined results of the OAKS and DERBY trials of pegcetacoplan, 12.2% and 6.7% of eyes developed wet AMD in the every-month (EM) and every-other-month (EOM) group, respectively, compared with 3.1% of the sham group.[7] Ad-hoc analysis revealed that, in some cases, choroidal neovascularization (CNV) development could have been detected on an earlier visit with careful OCT examination. Intraocular inflammation (IOI) was present in 4% and 2% of eyes in the EM and EOM groups, respectively, compared with < 1% in the sham group. There were 1.7% and 0.2% of eyes that developed ischemic optic neuropathy (ION) in the EM and EOM groups, respectively, compared with 0% in the sham group. Other adverse reactions included endophthalmitis, ocular discomfort, vitreous floaters, subconjunctival hemorrhage,

AT A GLANCE

- The first FDA-approved therapies to treat geographic atrophy target the complement system.
- Clinical trials have identified possible complications of complement inhibition such as conversion to wet AMD, intraocular inflammation, endophthalmitis, and ischemic optic neuropathy.
- The authors' study revealed a 0.5% and 0.02% per patient risk of intraocular inflammation and occlusive retinal vasculitis, respectively, with the use of pegcetacoplan (Syfovre, Apellis).

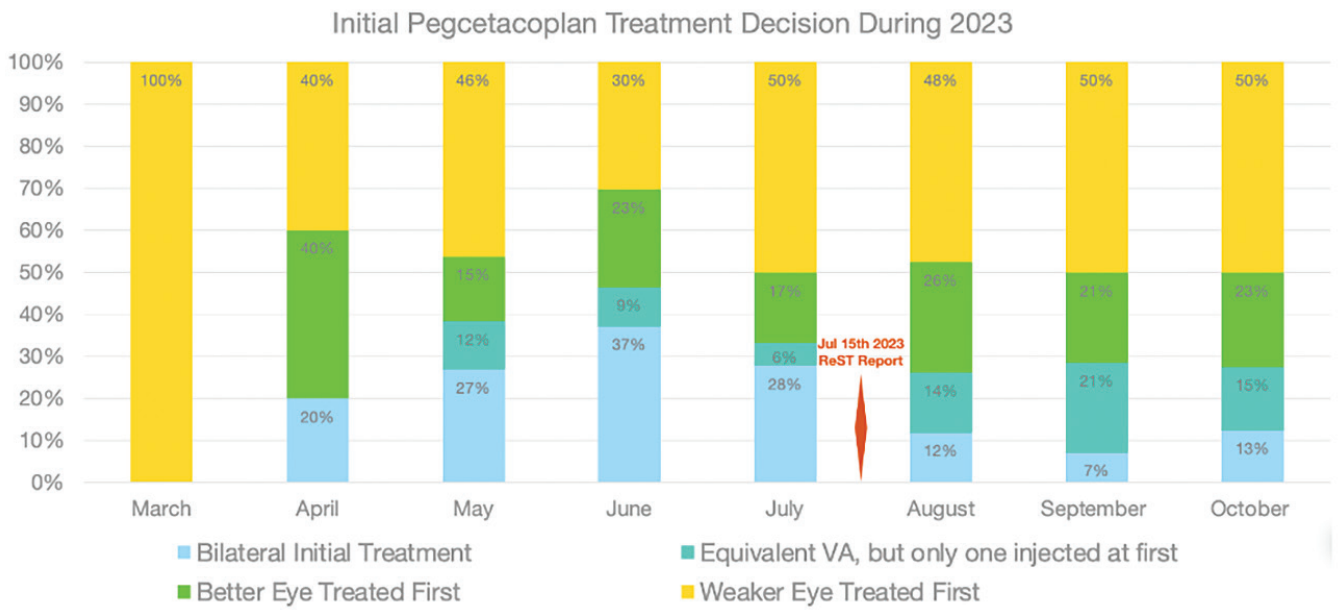

Figure. This stacked bar graph shows the relative proportion of each treatment decision for pegcetacoplan between March 2023 and October 2023.[12] After the ReST Committee released its report on July 15, 2023, there was a relative decrease in bilateral initial treatment with the predominant treatment decision shifting toward treating the weaker eye first.

posterior vitreous detachment, retinal hemorrhage, punctate keratitis, and increased IOP.

The GATHER1 and GATHER2 studies for avacincaptad pegol demonstrated similar adverse reactions. For wet AMD, 11.9% of treated eyes versus 2.7% of sham eyes developed CNV in GATHER1 over 18 months, and 11.6% of treated eyes versus 9% of sham eyes developed CNV in GATHER2 over 2 years. There were increased rates of wet AMD in the trials, particularly with macular neovascularization (MNV). Those with MNV during the trials were dropped from the study due to concern that the fundus autofluorescence measurements of GA would be confounded. In GATHER1, 1.5% of treated eyes each developed IOI, transient vascular occlusion, or ION compared with no eyes in the sham group. In GATHER2, which included EM and EOM dosing, 0.4% of eyes developed IOI compared with none in the sham group, and there were no cases of vascular occlusion or ION.[8,9] Other adverse reactions were similar to those mentioned for pegcetacoplan.

No cases of retinal vasculitis or retinal vascular occlusion were reported in the OAKS and DERBY trials, but since the commercialization of pegcetacoplan on February 17, 2023, through October 12, 2023, there have been 14 eyes of 13 patients diagnosed with retinal vasculitis.[10] The ASRS Research and Safety in Therapeutics (ReST) Committee recently published an update regarding their analysis of these cases.[10] All cases occurred after the patient's first pegcetacoplan injection, the vasculitis involved retinal veins (100%) more than arteries (73%), and 86% of patients experienced retinal hemorrhages. The median VA was 20/60 at baseline, 20/300 at vasculitis presentation, and 20/200 at last follow-up. The company recommended only using its 18-gauage kits (the 19-gauage kits had structural variation), but there has been no clear link between the kits and the vasculitis cases[11]; in fact, several reported cases used the 18-gauge needle.[10] There is currently no confirmed etiology for these cases. The ReST Committee also documented one case of occlusive retinal vasculitis after avacincaptad pegol in a patient treated for Stargardt disease who had previously received pegcetacoplan and developed occlusive vasculitis in the fellow eye.[10] Note that FDA approval of avacincaptad pegol was on August 4, 2023; thus, fewer patients have been treated with avacincaptad pegol than with pegcetacoplan.

Although no definitive treatment for suspected retinal vasculitis exists, the ReST Committee has provided the following suggestions[10]:

- Wait 1 month after treating the first eye with anti-complement before initiating therapy in the fellow eye.
- Initiate appropriate antibiotic treatment if infectious endophthalmitis is suspected.
- Closely follow inflammation after complement inhibition. Corticosteroid treatments may reduce inflammation, but the visual impact is unknown.
- Patients with peripheral ischemia may benefit from anti-VEGF injections or panretinal photocoagulation to prevent neovascular complications.
- Given the vasculitis severity, care should be taken when considering initiating treatment in a monocular patient or when bilateral injections are being considered.

To investigate these concerns, we initiated a retrospective study of real-world practice patterns and adverse events as a collaboration between Retina Consultants of America and Mid-Atlantic Retina.[12] Initial data, presented at the Angiogenesis, Exudation, and Degeneration 2024 meeting,

included 5,925 eyes that had received 16,398 injections of pegcetacoplan across 4,524 patients by November 29, 2023.

After the initial ReST Committee reports, there was a decrease in bilateral initial treatment, while treating the eye with the weakest visual acuity became the most common initial treatment (Figure).[12] The rates of IOI and occlusive vasculitis were 0.5% and 0.02% per patient, respectively. The most typical form of IOI was an intermediate uveitis that resolved with topical steroid drops. A retrospective real-world analysis of avacincaptad pegol is ongoing.

PATIENT MANAGEMENT CONSIDERATIONS

When considering a complement inhibitor, clinicians should first identify patients who may benefit from these therapies. Based on the clinical trials, these are patients with AMD who have developed GA between 1 and 7 disc diameters in size. Eyes with less involvement of the central macula would have the potential to maintain better vision for a longer period of time. Older patients (eg, 95 or older) would likely have less appreciable benefit within their life expectancy. Patients should understand that therapy involves intravitreal injections at a 1- to 2-month interval, indefinitely.

When we discuss complement inhibition with patients, we highlight four potential complications: endophthalmitis (similar for any eye receiving intravitreal injection), conversion to wet AMD, IOI, and ION.

Eyes with advanced glaucoma, a history of uveitis, or a history of CNV in the fellow eye should be considered higher risk. Eyes with concurrent wet AMD may benefit from GA therapy, although such eyes were not included in the clinical trials; thus, the true treatment effect is currently unknown, and studies are ongoing to assess benefit in such eyes. Although the etiology is yet to be determined in cases of ION, care should be taken when considering these medications in patients with a disc at risk (cup-to-disc ratio ≤ 0.25), vascular risk factors, or both.

For detection of new CNV due to wet AMD, we recommend a careful examination of all OCT images covering the area of GA because new fluid due to CNV usually appears at the edge of the GA lesion. Denser scans (ie, 97 cut scans when using the Heidelberg Spectralis) would increase the chance of detecting subtle new intraretinal or subretinal fluid. We also recommend slit-lamp biomicroscopy for the detection of subtle retinal hemorrhage, which might indicate new CNV.

The complement inhibition injection and an anti-VEGF injection can be administered in the same visit if wet AMD develops. However, clinicians should consider strategies to prevent an IOP spike, such as waiting between injections or pre-injection ocular decompression by cotton swab, IOP-lowering drops, or anterior chamber paracentesis.

For detection of IOI, clinicians should carefully examine the anterior chamber and vitreous for inflammation on follow-up visits, particularly after the first or second injection. The peripheral retina should be examined for retinal hemorrhage, vascular sheathing, or other evidence of vascular occlusion and/or vasculitis.

For detection of ION, clinicians should examine the optic nerve head for edema, hemorrhage, or pallor on follow-up examinations. Routine nerve fiber layer analysis might aid in identifying active or previous ION.

BE VIGILANT

Complement inhibition holds significant promise to reduce the progression of GA in certain patients. If clinicians are ready to start using these treatments, they must be ready to educate patients carefully and remain vigilant with follow-up examinations. ■

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