ASRS 2024: LOOKING BEYOND COMPLEMENT INHIBITION

Could the next generation of geographic atrophy therapies be born of these novel strategies?

BY SCOTT KRZYWONOS

Drugs treating geographic atrophy (GA) secondary to AMD through complement inhibition have struggled to captivate retina specialists the way some forecasters expected. Myriad explanations abound: cost, efficacy, safety, hiccups in integrating yet another therapy that requires refrigerator space, you name it. Whatever the reason, researchers continue to look beyond the complement pathway for the treatment of GA.

This year's American Society of Retina Specialists (ASRS) Annual Meeting showcased several talks covering investigative GA treatments that ignore the complement pathway altogether or include it as only part of the therapeutic approach. Here, I summarize four of those talks.

FAS INHIBITION

Fas, a member of the TNF family of receptors that regulates cell death and inflammation, acts upstream of the complement pathway. When cell-surface Fas receptors experience upregulation and activation, an inflammatory cascade accelerates cell death and tissue damage. Administration of a Fas inhibitor could be an effective means of preserving retinal cells and reducing activation of the inflammatory cascade.[1]

Durga S. Borkar, MD, MMCi, presented first-time results of the phase 1b study of ONL1204 (ONL Therapeutics), a Fas inhibitor, for the treatment of GA associated with AMD. The primary endpoint was safety, and secondary endpoints concerned efficacy. This study had two components.

The first component was an open-label, dose-escalation study in which patients with GA received a single intravitreal injection of ONL1204 and were observed for 6 months. Doses included 50 µg, 100 µg, and 200 µg. Patients (n = 6) with GA and BCVA in the study eye of 20/100 to counting fingers were eligible for this part of the study.

The second component of the study monitored patients for 6 months to assess their natural rates of GA growth. At month 6, patients were randomly assigned to 50 µg or 200 µg ONL1204 or sham. They were dosed at months 6 and 9 and were followed to month 12. Sixteen patients with bilateral GA, no evidence of choroidal neovascularization (CNV), and BCVA 20/400 or better in each eye were enrolled.

Researchers found that ONL1204 was well tolerated with four serious adverse events observed, none of which were linked with the study drug. Two treatment-emergent adverse events, a moderate increase in IOP and a moderate increase in vitreous floaters, were observed in the second part of the study, both of which occurred in the higher-dose arm. No cases of CNV in the study eye, dose-limiting toxicity, or intraocular inflammation were observed.

Signs of efficacy were also observed. In the first component, a 42% reduction in lesion growth rate was observed in study eyes compared with fellow eyes at week 24. In the second component, lesion growth rates were 24% lower and 50% lower in the 50 µg and 200 µg treatment arms, respectively, compared with sham at 24 weeks.

The first patient in the phase 2 study is expected to be dosed by the end of this year.

GENE THERAPY

Although much of the attention regarding gene therapy for AMD has focused on wet AMD, researchers have been gathering data about potential gene therapies for GA. The most recent study results regarding JNJ-1887 (Janssen/Johnson & Johnson) add another dataset to the discourse.

Christine N. Kay, MD, shared the pooled safety analysis and immunogenicity of this gene therapy at ASRS 2024. JNJ-1887 is a single intravitreal gene therapy injection that expresses

ASRS MEETING COVERAGE

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soluble CD59. An open-label, single-center phase 1 study assessing the safety of JNJ-1887 in patients (n = 17) with GA over a 24-month period did not include corticosteroid prophylaxis. Baseline and post-treatment serum AAV2-neutralizing antibodies and anti-sCD49 antibodies were measured to assess the immunogenicity of JNJ-1887.

No dose-limiting toxicities, serious adverse events, or systemic adverse events were observed in treated patients. Inflammation was manageable, with 29% of patients experiencing mild ocular inflammation. A single case of vitritis was observed but went unresolved due to an unrelated fatal adverse event. No patients demonstrated anti-sCD59 antibodies. All patients were positive for AAV2-neutralizing antibodies at baseline, and 53% of patients developed at least a 4x increase of AAV2-neutralizing antibodies after dosing.

The phase 2b trial (NCT05811351) enrolled 305 patients with GA. This therapy has been granted Fast Track designation by the FDA and Advanced Therapy Medicinal Product designation by the European Medicines Agency.[2]

MODULATING MACROPHAGE ACTIVITY

Rishi P. Singh, MD, presented results from the phase 2a SIGLEC trial assessing AVD-104 (Aviceda Therapeutics) for GA. AVD-104 is a sialic acid-coated nanoparticle that targets sialic acid-binding immunoglobulin-type lectin (siglec) receptors on the surface of activated macrophages. When AVD-104 binds to siglec receptors, macrophages are repolarized to a healing state. AVD-104 also binds to complement factor H to downregulate complement amplification.

The safety and efficacy of a single dose of AVD-104 was assessed in the phase 2 SIGLEC study, a single-dose, dose-escalation study in which patients with GA were assigned to one of four AVD-104 doses. Patients were followed for 3 months, at which point the primary endpoints of safety and dose-limited toxicity were assessed. At 3 months, researchers found that AVD-104 was well tolerated with no dose-limiting toxicity. There were no instances of ischemic optic neuropathy, retinal detachment, endophthalmitis, retinal vasculitis, conversion to CNV, or elevated IOP. One instance of asymptomatic intraocular inflammation was observed on day 1 and resolved spontaneously by day 15.

At month 3, patients in the 0.1 mg, 0.5 mg, 1.0 mg, and 3.0 mg arms experienced changes in VA from baseline of -0.7, +0.1, +4.8, and +6.5 letters, respectively. At the primary endpoint, 40% of patients gained at least 5 letters from baseline; 84% of patients in the two highest-dose cohorts experienced no change in vision or a gain of at least 1 letter. Patients who received a single dose of 1.0 mg or 3.0 mg AVD-104 experienced a mean change of 5.2 letters at month 3 in study eyes compared with 1.7 letters in untreated fellow eyes.

In a phase 2b/3 head-to-head superiority study, 300 patients with GA lesions of 2.5 mm^2 to 15.5 mm^2 were randomly assigned to 1.0 mg or 2.0 mg AVD-104 or avacincaptad pegol (Izervay, Astellas). The primary endpoint will be the rate of change from baseline in GA lesion area at month 12, with data expected in 2025.

PHOTOBIOMODULATION

Photobiomodulation (PBM) is a light-based therapy that uses LEDs to deliver near-infrared spectrum light to retinal tissue, which induces a cellular photochemical reaction. Although the specific mechanism of action is not fully understood, the literature suggests that PBM may lead to improved mitochondrial function in photoreceptor cells, a means of counteracting inflammation and enhanced functioning of supporting cells.[3] The Valeda Light Delivery System (LumiThera), a platform that delivers PBM, has the CE mark in Europe and gained FDA clearance in November.[4]

Eleonora M. Lad, MD, PhD, presented safety and efficacy data from LIGHTSITE III, a prospective, double-masked, randomized, sham-controlled, parallel group, multicenter study evaluating PBM for intermediate dry AMD. Researchers enrolled 100 patients (148 eyes) who were randomly assigned to PBM or sham. Every 4 months, patients received treatment or sham three times per week for 3 to 5 weeks, and data were analyzed at 24 months.

Researchers found sustained BCVA improvement at 24 months with PBM treatment. At 24 months, approximately 58% of patients in the PBM arm gained at least 5 letters, 19% gained at least 10 letters, and 6% gained at least 15 letters. Patients who received sham treatment lost vision at 24 months compared with baseline: 18% of sham-treated patients lost more than 5 letters at 24 months, and 24% showed signs of conversion to GA. The hazard ratios of losing more than 5 letters (0.47) and converting to GA (0.27) were both statistically significant ($P < .05$). Researchers concluded that PBM resulted in a 53% reduced risk of losing more than 5 letters and a 73% reduced risk of progression to new GA at 24 months.

LumiThera announced the assignment of a new Category III CPT code, "Photobiomodulation therapy of retina, single session," that becomes effective January 1, 2025.[5] ■

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2. Janssen to highlight latest advances in retina portfolio at the European Society of Retina Specialists (EURETINA) 2023 annual meeting [press release]. Johnson & Johnson. October 3, 2023. Accessed September 4, 2024. bit.ly/3Zd0Ka9
3. Muste JC, Russell MW, Singh RP. Photobiomodulation therapy for age-related macular degeneration and diabetic retinopathy: a review. *Clin Ophthalmol*. 2021;15:3709-3720.
4. LumiThera obtains FDA authorization of Valeda treatment for dry AMD patients to improve vision [press release]. Lumithera. November 4, 2024. Accessed November 15, 2024. bit.ly/4fsnIzy
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