“Complement-ary” Therapies for Age-Related Macular Degeneration
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Although anti-VEGF agents have transformed our ability to treat patients with advanced exudative age-related macular degeneration (AMD), there are currently no approved treatments to slow photoreceptor and retinal pigment epithelium degeneration, termed “geographic atrophy” (GA), in patients with advanced nonexudative AMD. Based on preclinical and human studies suggesting that complement dysregulation may contribute to AMD pathogenesis, significant efforts have been directed toward using complement modulation to slow GA. One such strategy has been to enhance the function of complement factor H (CFH), a regulatory protein in the complement cascade, because the CFH Y402H polymorphism has been shown to be strongly associated with AMD.

In this issue of Ophthalmology Science, Khanani et al (XOPS 100154) report timely results from an industry-sponsored Phase 1 study examining the safety of intravitreal (IVT) GEM103, recombinant human CFH, in patients with GA. In their open-label, single ascending dose trial of 12 participants, IVT GEM103 was found to be tolerable up to the maximum tested dose of 500 µg. Although 1 patient in the 50 µg dose group developed “mild retinal hemorrhage” at study day 15, this finding was not thought to be related to GEM103 or the injection procedure and improved without treatment. Other adverse effects, including ocular hyperemia and mild eye pain, were reported but were thought to be related to the injection process rather than GEM103 itself. Best-corrected visual acuity and GA lesion size remained largely stable over the 8-week follow-up period in patients who received IVT GEM103.

The investigators also collected aqueous humor from participants and measured CFH, C3a, and Ba at various time points after IVT GEM103 administration. Some data were missing because of inadequate sample volumes and sample mishandling. Nonetheless, IVT GEM103 increased local ocular CFH levels in all participants and caused modest reductions in aqueous humor C3a and Ba, markers of complement activation, in some but not all participants. Statistical analyses were not possible because of small sample sizes.

Taken together, this study provides initial evidence that GEM103 is well tolerated as an IVT injection. Although confirmatory studies are necessary, this study also provides preliminary evidence that IVT GEM103 may be able to alter complement regulation in the eye and might reduce pathologic complement activation. This study provides a foundation for future clinical studies investigating whether IVT GEM103 may slow GA lesion growth in patients with advanced nonexudative AMD.

Prior studies have evaluated complement modulation for treating advanced nonexudative AMD. Despite promising preclinical evidence for this strategy, some agents have failed to show efficacy in human studies. The anti-complement factor 5 antibodies eculizumab and LFG316 both failed to slow GA growth despite showing a positive signal in initial safety and tolerability trials. Although the anti-complement factor D antibody lampalizumab showed promise in the Phase 2 MAHALO trial, the Phase 3 SPECTRI and CHROMA trials showed no effect of lampalizumab on GA growth rate.

In contrast to these failures, the complement factor 3 inhibitor pegcetacoplan (APL-2; Apellis) and anti-complement factor 5 aptamer avacincaptad pegol (Zimura, IVERIC) remain under active investigation based on promising results from Phase 2 and Phase 2/3 trials showing that they may slow GA lesion growth rate. Nonetheless, patients randomized to these agents were also 3 to 17 times more likely to develop exudative AMD compared with those randomized to sham injections. This unanticipated consequence of complement inhibition in these trials may limit widespread use. Khanani et al speculate that GEM103 may be less prone to cause this unintended consequence because GEM103 is not pegylated like other complement modulators are and because preclinical evidence suggests that CFH protects against neovascularization. Future clinical studies are needed to corroborate this hypothesis.

Although conversion to exudative AMD may be considered an acceptable alternative given the availability of anti-VEGF therapies to manage this condition, further research is necessary to determine whether complement modulation is the optimal treatment strategy and whether there may be other consequences of complement modulation. These questions must be answered before complement-based therapies, including GEM103, can become widely adopted for AMD.

Footnotes and Disclosures

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