GEOGRAPHIC ATROPHY: TARGETING THE COMPLEMENT PATHWAY

This form of AMD is creating a lot of buzz with novel therapeutics under investigation.

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To date, no treatments are approved to reverse, prevent, or reduce the rate of geographic atrophy (GA) progression—an area of urgent unmet medical need as the population ages. A leading contributor to the pathogenesis of GA is complement system–mediated inflammation and retinal cell degeneration.[1] Genome-wide association studies identified polymorphisms in a number of complement proteins among patients with AMD.[2] In addition, patients with GA had alterations in complement cascade components both systemically and within the eye.[1,3] Active research is underway to find a treatment for GA, and most studies focus on the complement cascade.

This article discusses several therapies on the horizon and the latest research findings (Table).

C3 INHIBITION

Pegcetacoplan (Apellis Pharmaceuticals) is a pegylated inhibitor of complement C3. In the phase 2 FILLY study, 15-mg monthly and every-other-month intravitreal injections were found to reduce the growth rate of GA lesions by 29% (P = .008) and 20% (P = .067), respectively, compared with sham therapy at 12 months.[4]

The results of the confirmatory phase 3 OAKS study of 637 patients demonstrated that monthly injections of 15 mg/0.1 mL pegcetacoplan led to a 22% (P = .0003) reduction in GA lesion growth compared with sham therapy at 12 months; every-other-month treatment resulted in a 16% (P = .0052) reduction.[5]

The results of the second confirmatory phase 3 study, DERBY (621 patients), did not meet the primary endpoint.

In the combined analyses of the phase 3 trials, pegcetacoplan demonstrated a greater effect on eyes with extrafoveal lesions at baseline; GA lesion growth decreased by 26% (P < .0001) and 23% (P = .0002) with monthly and every-other-month injections, respectively.[5]

Pegcetacoplan was well tolerated in both phase 3 trials.[6] Combined results reported three cases of confirmed

15TH ANNIVERSARY ISSUE

HOW IT STARTED

In *Retina Today*'s first issue in 2006, the Age-Related Eye Disease Study II (AREDS II) wasn't even recruiting patients yet—that didn't happen until October of that year.[1] Still, some studies were focused on geographic atrophy, also known as *atrophic macular degeneration* back then.

An implant containing encapsulated human NTC-201 cells releasing ciliary neurotrophic factor was in a phase 2 trial for participants with vision loss due atrophic macular degeneration.[1]

Another study involving patients with GA and/or choroidal neovascularization with drusen was evaluating whether certain genetic polymorphisms predisposed individuals to develop AMD.[1]

A September 2006 article shared information on complement factor H and noted that the complement factor H gene *Y402H* polymorphism appeared to account for a substantial proportion of AMD.[2]

Complement factors 3 and 5 hit the scene in 2008, with preliminary research showing a new association between complement system variations and AMD—setting the stage for where we are today with promising therapeutics targeting C3 and C5.[3]

1. Clinical trial update: macular diseases. *Retina Today*. 2006;1(1).
2. de Jong PTVM. CFH polymorphism may cause more than half of all AMD cases. *Retina Today*. 2006;1(3).
3. Seddon JM. Complement factor 3 variation is associated with AMD risk. *Retina Today*. 2008;3(1):37-39.

or suspected infectious endophthalmitis (0.047% risk per injection), 13 cases of intraocular inflammation (0.21% risk per injection), and no retinal vasculitis or vascular occlusion. Pooled phase 3 data also provided further evidence that pegcetacoplan was associated with a dose-dependent increased incidence of new-onset wet AMD with rates of 6.0% in the monthly cohort, 4.1% in the every-other-month cohort, and 2.4% in the sham group.[6]

Based on these findings, the company plans to submit a New Drug Application for pegcetacoplan for GA. Both studies will continue masked injections for a total of 24 months.

NGM621 (NGM Biopharmaceuticals) is a humanized IgG1 antibody that inhibits the enzymatic cleavage of complement C3. Unlike the other complement-targeting therapeutics for GA, NGM621 is not pegylated.[7]

In phase 1, the study agent was well tolerated with no drug-related adverse events.[7]

Currently, the phase 2 CATALINA trial is ongoing with approximately 320 patients enrolled.[8] The study is designed to randomly assign patients to receive intravitreal injections of 15 mg versus sham therapy (2:1 ratio), every 4 or 8 weeks, for a total of 52 weeks. The primary efficacy endpoint is the rate of change in GA lesion area measured by fundus autofluorescence (FAF) over the course of 52 weeks.

C5 INHIBITION

Avacincaptad pegol (Zimura, Iveric Bio), a pegylated RNA aptamer, inhibits the enzymatic cleavage of C5, thus inhibiting the downstream complement cascade and C5-mediated activities, such as those hypothesized to lead to retinal cell degeneration in GA.

The results of the pivotal phase 2/3 trial of 286 patients showed that monthly intravitreal injections of 2 mg or 4 mg avacincaptad pegol led to a reduction in the mean rate of GA growth by 27.4% (P = .0072) and 27.8% (P = .0051), respectively, over 12 months.[9] Treatment effect, measured by FAF, was observed as early as month 6 and was maintained at month 12. It was well tolerated with no drug-related adverse events and no cases of endophthalmitis. However, there was an increased risk of choroidal neovascularization or wet AMD in treated eyes, with rates of 9.0% in the 2-mg cohort and 9.6% in the 4-mg cohort compared with 3.5% in the fellow eyes and 2.7% in the sham group.[9]

A second phase 3 trial, GATHER2, completed enrollment of 448 patients.[10] Patients were randomly assigned in a 1:1 ratio to receive monthly intravitreal injections of 2 mg avacincaptad pegol or sham therapy, with a primary efficacy endpoint of the mean rate of change in GA area over 12 months.

C1Q INHIBITION

ANX007 (Annexon Biosciences) is the antigen-binding fragment of a humanized recombinant monoclonal antibody. ANX007 binds to the globular heads of C1q and blocks the downstream activation of the classical complement cascade.

Data from two phase 1 studies involving patients with primary open-angle glaucoma showed promising safety and efficacy.[11,12] The phase 2 ARCHER study is investigating the efficacy of intravitreal injections of ANX007 for patients with GA. The study is enrolling approximately 240 individuals randomly assigned to monthly or every-other-month intravitreal injections of 5 mg ANX007 or sham therapy over 12 months, followed by an off-treatment period of 6 months. The primary efficacy endpoint is the change in GA lesion area.[13]

GENE THERAPY

HMR59 (Hemera Biosciences) consists of a recombinant adeno-associated viral (AAV2) vector containing the *sCD59* gene. CD59 is a glycosylphosphatidylinositol-anchored membrane inhibitor of the membrane attack complex. It prevents the recruitment of complement C9.[14] Membrane attack complex is the terminal step of an activated complement cascade.

A completed phase 1 study of HMR59 investigated the dose-escalating safety and tolerability of a single intravitreal injection for GA with a total of 17 patients.[15] No systemic or severe adverse events were associated with HMR59 injections. Mild ocular inflammation occurred in three patients' treated eyes, including two eyes that developed vitreous inflammation that resolved after 6 weeks of observation and one eye that developed anterior chamber and vitreous inflammation that resolved with topical corticosteroids. None of the 17 patients converted to wet AMD during the 18-month follow-up period.

TABLE. NOVEL THERAPIES FOR GA THAT TARGET THE COMPLEMENT PATHWAY

Study Drug (Company)	Complement Target	Delivery Method	Current Trial Phase	Most Recent Trial(s)	Study Status
Pegcetacoplan (Apellis)	C3	IVI	3	OAKS, DERBY	Active, not recruiting
Avacincaptad pegol/ Zimura (Iveric Bio)	C5	IVI	3	GATHER2	Active, not recruiting
NGM621 (NGM)	C3	IVI	2	CATALINA	Active, not recruiting
ANX007 (Annexon)	C1q	IVI	2	ARCHER	Recruiting
HMR59 (Hemera)	C9	IVI	1	HMR-1001	Completed
GT005 (Gyroscope Therapeutics)	Complement factor I	Subretinal	1/2 and 2	FOCUS, EXPLORE, HORIZON	Recruiting

Abbreviations: GA, geographic atrophy; IVI, intravitreal injection.

GT005 (Gyroscope Therapeutics) is a recombinant AAV2 vector that contains a nucleotide sequence encoding complement factor I (CFI). The therapy, delivered via subretinal injection, is designed to enable cellular transduction and induce secretion of CFI. While low serum CFI levels have been associated with a much higher risk of AMD,[4] an increase in intraocular CFI level could dampen an overactivated alternative complement pathway and potentially reduce AMD progression.[16]

FOCUS is a phase 1/2 study evaluating the safety and tolerability of subretinal delivery of GT005 gene therapy in patients with GA. Dose escalation cohorts 1 to 3 have completed dosing via transvitreal delivery, and cohort 4, a dose expansion cohort, is still enrolling.[17] Cohorts 5 to 7 receive gene therapy via the Orbit Subretinal Delivery System (Gyroscope Therapeutics).[18]

Interim results from cohorts 1 to 4 showed that GT005 subretinal delivery was well tolerated.[18,19] There was an average increase of 146% in CFI levels compared with baseline. The first patient treated had a sustained CFI increase at 84 weeks. In addition, reductions in downstream complement biomarkers were detected, with an average decrease of 42% in C3 breakdown proteins and a 41% decrease in Ba levels compared with weeks 24 and 56.

Two phase 2 studies, EXPLORE and HORIZON, are actively enrolling patients.[20,21] Both studies are evaluating the safety and efficacy of two doses of GT005 administered as a single subretinal injection, with GA lesion growth measured by FAF at 48 weeks as the primary efficacy endpoint.

HTRA1 INHIBITION

An outlier to the complement pathway inhibitors, FHTR2163 (Genentech) is an antigen-binding fragment of a humanized monoclonal antibody against the high-temperature requirement A1 protein. A single nucleotide polymorphism associated with elevated expression levels of the high-temperature requirement A1 protein was estimated to confer a risk of 49.3%.[1]

FHTR2163 was well tolerated in phase 1, with no dose-limiting toxicities, ocular serious adverse events, or drug-related systemic adverse events reported.[2] The phase 2 GALLEGO study is ongoing. It is evaluating the efficacy of intravitreal injections of 20 mg FHTR2163 every 4 or 8 weeks over the course of 76 weeks.[3] The primary efficacy endpoint is the growth of GA lesion area measured on fundus autofluorescence imaging from baseline to 72 weeks.

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NEXT STEPS

These data are encouraging, and we are certainly getting closer to finding an effective treatment for GA, but we aren't there yet. We will continue to follow these trials closely to assess each therapy's safety and efficacy. ■

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- Financial disclosure: Consultant (4DMT, Adverum, Aerie, Aerpio, Aldeyra, Allegro, Alzheon, Annexon, Apellis, Aprea, Asclepix, Aviceda, BVT, Dark Horse, DTx, Eloxx, Galimedix, Genentech, Graybug, Gyroscope, Iveric Bio, jCyte, Kanghong, LensGen, NGM, Novartis, Ocular Therapeutix, OcuTerra, Oxurion, Palatin, Regeneron, Regenxbio, Stealth, Thea, Verseon, Vinci, Voyant); Research Grants (Apellis, Asclepix, Bayer, Genentech, Graybug, Gyroscope, Hemera, Iveric Bio, Kanghong, Kodiak, NGM, Notal Vision, Novartis, Regeneron, Regenxbio, Stealth)