The AMD Pipeline: A Look At The Latest Results

Myriad therapeutics are making their way through clinical trials. Here’s a look at recent data.

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AMD is the leading cause of permanent impairment of central vision in individuals 65 years of age and older, affecting more than 1.8 million Americans 40 years of age and older. No cure exists for the condition, but myriad therapeutics and drug delivery systems are moving through the development pipeline.

This article provides a brief overview of some of the novel therapies under investigation for the treatment of dry and wet AMD.

DRY AMD

OpRegen (Lineage Cell Therapeutics) is being evaluated in a phase 1/2a study. In the trial, a single injection of human retinal pigment epithelium (RPE) cells, derived from an established pluripotent cell line, is transplanted in suspension and delivered subretinally in patients with advanced dry AMD with geographic atrophy (GA).

The company announced completion of patient enrollment in November, and interim results were presented at the 2020 Virtual ARVO Meeting. The open-label, dose-escalation safety and efficacy trial includes four cohorts of patients with advanced dry AMD and GA. Patients in cohorts 1–3 have worse baseline VA (< 20/200); cohort 4, which includes patients with an average VA of 20/125 and smaller areas of atrophy, is still recruiting. Eyes with the poorest vision were implanted with 50,000 to 200,000 OpRegen cells. The trial’s primary objective is to assess the therapy’s safety and tolerability. A secondary objective is evaluating the cells’ survival and possible effects of OpRegen treatment by assessing changes in retinal structure and visual function.

At the interim analysis, patients in cohorts 1–3 had no marked, sustained reductions in visual acuity. The five patients in cohort 4 demonstrated improved vision with up to 1 year of follow-up. One patient experienced a 10-letter gain that was sustained for 15 months. There were no reports of acute or delayed inflammation, but all patients reported at least one adverse event.

Apellis Pharmaceuticals announced positive 18-month data from its phase 1b study of pegcetacoplan (APL-2), a pegylated cyclic peptide inhibitor of complement C3, in patients with advanced GA secondary to AMD. Subsequently, Apellis announced the results of its FILLY phase 2 study. In this 246-patient, multicenter, randomized, single-masked, sham-controlled trial, pegcetacoplan was administered as an intravitreal injection monthly (n = 86) or every other month (EOM, n = 79) for 12 months, followed by 6 months of monitoring post-treatment. The primary efficacy endpoint was the change in mean GA lesion area from baseline to month 12 in patients treated with pegcetacoplan compared with those treated with sham.

AT A GLANCE

- A number of new pharmaceuticals are making their way through the pipeline for the treatment of both dry and wet AMD.
- Novel approaches include the use of human retinal pigment epithelium cells, pegylated cyclic peptides, recombinant human anti-VEGF and anti-complement bispecific fusion proteins, gene therapy, biosimilars, a port delivery system, humanized single-chain antibody fragments, and bispecific antibodies that binds to and inactivate Ang-2 and VEGF-A.
The results of FILLY showed a 29% reduction in lesion growth in the monthly treatment group and 20% reduction in those treated EOM compared with sham. Overall, pegcetacoplan was well tolerated; however, new onset exudation appeared to be higher in the treatment groups (20.9% in the monthly group, 8.9% in the EOM group, and 1.2% in the sham group). Notably, the incidence was higher in those with wet AMD in the fellow eye. Patients with exudation were treated with anti-VEGF therapy, and no negative impact on visual acuity was observed. The phase 3 DERBY and OAKS trials of pegcetacoplan for GA were fully enrolled as of July 2020, with results expected in Q3 2021.

Investigators recently published results from the multicenter, randomized, double-masked GATHER1 phase 2/3 clinical trial evaluating avacincaptad pegol (Zimura, Iveric bio) in patients with GA secondary to AMD.\(^6\) Avacincaptad, a novel complement C5 inhibitor, met the trial’s primary efficacy endpoint at 12 months. The reduction in the mean rate of GA growth over 12 months for the 2 mg avacincaptad group compared with the corresponding sham control group was 27.4% (\(P = .0072\)), and for the 4 mg avacincaptad group compared with the corresponding sham control group the reduction was 27.8% (\(P = .0051\)).\(^7\) Avacincaptad was generally well tolerated in the GATHER1 clinical trial, and there was no avacincaptad-related inflammation. At 18 months, new onset exudation was noted in 15.7%, 11.9%, and 2.7% of the 4 mg, 2 mg, and sham groups, respectively.\(^8\) In a second phase 3 clinical trial (GATHER2), an estimated 400 patients will be randomly assigned to receive either monthly administration of 2 mg avacincaptad or sham for 12 months.

Collectively, these results for pegcetacoplan and avacincaptad suggest that both agents have the potential to slow the progression of GA secondary to AMD by modulating complement inhibition. However, the exact mechanisms of action for each drug differ, as do study methodologies, making comparisons across clinical trials inadvisable.

**WET AMD**

Results of Innoven Biologics’ phase 1 open-label, multicenter, dose-escalation clinical trial of IBI302, a first-in-class ophthalmic recombinant human anti-VEGF and anti-complement bispecific fusion protein, were presented during the 2020 AAO Virtual Annual meeting. The trial evaluated the safety and tolerability of a single intravitreal injection of IBI302 in patients with wet AMD.

A total of 31 patients were enrolled, and no serious adverse events or dose-limiting toxicity were reported. The study demonstrated good safety and tolerability. Researchers observed improved vision and a reduction of retinal edema 1 week after administration; after 28 days, BCVA in all patients had increased by an average of 6 letters from baseline. Additionally, average central retinal thickness decreased by 141.2 \(\mu m\) compared with baseline, and the effect lasted until 6 weeks after administration for some.\(^9\)

In October 2020, RegenxBio announced positive interim results from its phase 1/2a trial for RGX-314 for the treatment of wet AMD.\(^10\) This therapy involves subretinal delivery of the NAV adeno-associated virus (AAV8) vector that encodes an antibody fragment designed to inhibit VEGF. The study includes 42 patients with severe disease who require frequent anti-VEGF therapy. At 1 year, therapy was generally well tolerated across all five dosing cohorts—ranging from 3x10\(^8\) to 2.5x10\(^11\) GC/eye—with 77% of nonserious adverse events classified as mild. One possible drug-related adverse event of visual loss was reported in a patient with preexisting retinal pigmentary changes and extensive previous treatment who developed additional pigment changes. Patients across several cohorts had changes in retinal pigmentation, most of which were peripheral and inferior. There were no reports of clinically determined immune responses or drug-related inflammation beyond what is expected following routine vitrectomy.\(^10\)

Cohorts 4 and 5 (dosed at 1.6x10\(^{11}\) and 2.5x10\(^{11}\) GC/eye, respectively) showed 61% and 85% reduction of anti-VEGF injections at 1 year, respectively. Both cohorts also experienced stable vision (mean BCVA change of +4 letters and -2 letters from baseline, respectively) and decreased retinal thickness (mean change of -61 \(\mu m\) and -79 \(\mu m\), respectively). A dose-dependent increase in RGX-314 protein expression was observed across all five cohorts at 1 year, which was stable over 2 years in cohort 3, and over 1 year in cohorts 4 and 5. The reduction in injection burden in the higher dose cohorts correlated with higher protein measurements in these groups.

In September 2020, RegenxBio announced the initiation of its phase 2 trial, AAViATE, investigating the efficacy, safety, and tolerability of RGX-314 delivered with the in-office SCS suprachoroidal microinjector.\(^11\)

Adverum Biotechnologies announced positive interim data from cohorts 1–4 of its OPTIC phase 1 clinical trial of ADVM-022 intravitreal injection gene therapy in patients with wet AMD who require frequent anti-VEGF injections.\(^12\)

The data further demonstrate the potential for the drug to greatly reduce the injection burden for patients with AMD. The therapeutic maintained efficacy at both high and low doses (\(n = 30\)); durability out to 92 weeks with zero supplemental injections in cohort 1 (high dose); and elevated
TRIAL DATA ON THE HORIZON

Several other ongoing studies for dry and wet AMD therapies are worth keeping an eye on:

Gyroscope Therapeutics recently announced the initiation of its phase 2 HORIZON trial evaluating GT005 for patients with GA secondary to dry AMD. This single-dose AAV-based gene therapy is designed to increase production of the complement factor I (CFI) protein, thereby restoring balance to an overactive complement system. The GT005 program includes three clinical trials, all of which are in progress. The phase 1/2 FOCUS open-label clinical trial is evaluating the safety and dose response of three doses of GT005 in approximately 45 patients.1 HORIZON and EXPLORE are both phase 2, multicenter, randomized, controlled trials evaluating the safety and efficacy of a single subretinal injection of GT005 with a primary endpoint of progression of GA over 48 weeks.1 EXPLORE is evaluating the therapy in patients with GA who have rare variants in their CFI gene, while HORIZON has a broader patient base.

AXT07, Asclepix Therapeutic's investigational drug candidate that inhibits VEGF-A/-C and activates Tie2, is showing potential as a single intravitreal injection with yearly dosing to treat wet AMD. In 15-month animal studies, the unique intravitreal self-assembling gel depot formation was well tolerated and demonstrated superiority to and greater durability than aflibercept, according to the company. Asclepix has received new investigational new drug application for AXT07 in December 2020 and plans to begin a first-in-human clinical study in Q4 2020.2-5

Chengdu Kanghong Biotechnology recently announced successful completion of week-36 primary endpoint visits for its phase 3 clinical development program, PANDA, evaluating conbercept (Lumitin) for the treatment of wet AMD. Two masked, randomized, controlled trials are evaluating the efficacy, safety, and durability of 0.5 mg conbercept every 8 weeks and 1.0 mg conbercept every 12 weeks in comparison with 2.0 mg aflibercept every 8 weeks. The primary outcome measure is BCVA, and secondary outcomes include the mean change in central retinal thickness at 36 weeks, change in visual acuity up to 96 weeks, and adverse events up to 96 weeks. Already approved for use in China, the drug recently gained approval in Mongolia as well.6-8

HMR59 (AAVCAGsCD59, Hemera Biosciences, recently acquired by Janssen), a transgene product that is a soluble form of CD59 that blocks complement at the membrane attack complex, remains under investigation for both dry and wet AMD. HMR-1001, a phase 1, open-label, multicenter, dose-escalating safety and tolerability study, evaluated safety after a single injection of HMR59 in treatment naïve eyes with dry AMD with GA. Hemera is also beginning a phase 2 trial for HMR59 for dry AMD to evaluate intravitreal high- or low-dose HMR59 with a sham injection. HMR-1002 is an ongoing phase 1 proof-of-concept study evaluating 25 eyes with new-onset wet AMD treated with anti-VEGF followed by HMR59 7 days later.9-11

GB-102 (Sunitinib malate, Graybug Vision), a microparticle depot formulation, is showing promise for the use of tyrosine kinase inhibitors (TKIs) to treat wet AMD. In the ADAGIO phase 1/2a clinical trial, GB-102 met its safety endpoint and provided evidence of durable biological activity for up to 8 months from a single intravitreal injection. To read more about this therapy, see A Timely Debut for Extended-Release Polymer Technologies on page 30.12

Ocular Therapeutix reported interim phase 1 results for OTX-TKI, a bioresorbable, hydrogel fiber implant incorporating axitinib, delivered by intravitreal injection. The TKI implant was generally well tolerated, and a clinically meaningful decrease in subretinal and intraretinal fluid was seen in some patients. Find more about this therapy in A Timely Debut for Extended-Release Polymer Technologies on page 30.13

Clearside Biomedical is planning a study of suprachoroidal delivery of axitinib for wet AMD in the Oasis trial scheduled to begin in December 2020.14

Eyepoint Pharmaceuticals has announced plans for a phase 1 study of vorolanib, a TKI, released from the company’s intravitreally injected implant.15 This TKI has previously been tested orally in a phase 1/2a clinical trial evaluating 25 eyes with new-onset wet AMD treated with anti-VEGF followed by HMR59 7 days later.16

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aqueous anti-VEGF protein expression at 18 months in cohort 1 in the two patients reported. Most patients in the trial were free from supplemental anti-VEGF injection, and ADV VM-022 was generally well tolerated; inflammatory events were managed with topical steroids, although a minority of patients remained on these drops at 1 year after injection.

At the AAO meeting, investigators presented 1-year results from a randomized, double-masked, multicenter phase 3 study of SB11 (Samsung Bioepis), a proposed biosimilar to ranibizumab (Lucentis, Genentech), in patients with wet AMD. Of the 705 patients enrolled, 634 had completed the study up to week 52. Patients were randomly assigned to receive monthly injections of SB11 or 0.5 mg ranibizumab. The study met its primary endpoints, changes from baseline in BCVA at week 8 and central subfield thickness at week 4. Secondary endpoints included long-term efficacy, safety, pharmacokinetics, and immunogenicity, which were comparable between SB11 and ranibizumab.

Results from the phase 3 ARCHWAY study of the Port Delivery System (PDS, Roche) were presented at the ASRS and AAO 2020 meetings. Patients received either the PDS, a permanent refillable eye implant refilled every 6 months with a customized formulation of ranibizumab, or monthly 0.5 mg ranibizumab injections. Over 98% (n = 244/248) of patients in the PDS group were able to go 6 months between refill injections. In addition, patients in the PDS group maintained stable vision comparable to the monthly ranibizumab group. The PDS was generally well-tolerated, with a favorable benefit-risk profile. The most common complication reported was mild conjunctival bleb or leak (6.5%).

Roche and Genentech have also initiated two global phase 3 clinical trials in wet AMD investigating faricimab, a bispecific antibody that simultaneously binds to and inactivates angiopoietin-2 (Ang-2) and VEGF-A. Phase 2 clinical trial data revealed that faricimab dosed every 12 or 16 weeks resulted in visual acuity and central subfield thickness changes similar to monthly ranibizumab. The multicenter, randomized, double-masked, active-comparator-controlled phase 3 TENAYA and LUCERNE studies will evaluate the efficacy, safety, and durability of faricimab compared with aflibercept for wet AMD. Nearly 1,300 patients have been randomly assigned to receive either faricimab every 16 weeks (with an option to drop to every 12 or 8 weeks), or aflibercept every 8 weeks. The primary endpoint of each study is the change in BCVA at week 48 from baseline.

KSI-301 (Kodiak) is an anti-VEGF–biopolymer conjugate under investigation for the treatment of wet AMD. KSI-301 is designed to rapidly reduce VEGF burden and provide extended durability. Preliminary data from a phase 1b trial show that BCVA improved by 5.8 letters from baseline at 44 weeks in treated patients. The company’s phase 2b/3 DAZZLE study is evaluating KSI-301 once every 3, 4, or 5 months after 3 monthly doses compared with aflibercept every 2 months after 3 monthly doses.