Gene therapy has long been imagined as a potential treatment approach for wet age-related macular degeneration (AMD).\textsuperscript{1,2} A viral vector such as an adeno-associated virus (AAV) can be used as a long-term drug delivery platform to deliver genetic material encoding an anti-VEGF molecule directly to the retinal layers. The resulting endogenous production of a therapeutic molecule (such as aflibercept [Eylea, Regeneron]) within the eye itself would thus eliminate the need for repeated injections.

This approach has the potential to significantly reduce the treatment burden associated with frequent, repeated intravitreal injections in patients with wet AMD.\textsuperscript{2} Because, in a real-world setting, receiving fewer anti-VEGF injections is associated with decreased VA,\textsuperscript{3,4} there is also a potential that anti-VEGF gene therapy, by avoiding undertreatment, could improve visual outcomes seen with current real-world anti-VEGF injection protocols.

**ADVM-022**

ADVM-022 (Adverum Biotechnologies) is an investigational gene therapy that uses a novel AAV2 viral capsid (AAV2.7m8) to deliver a transgene encoding aflibercept directly to retinal cells following a single intravitreal injection.\textsuperscript{5,6} AAV2.7m8 was designed through a process of directed evolution to enhance retinal cell transduction in order to optimize intravitreal AAV gene therapy.

Directed evolution is a high-throughput molecular engineering technique that simulates natural evolution, although at a much accelerated pace.\textsuperscript{7} With directed evolution, AAV capsid proteins are altered on a large scale; those AAVs with specific desirable capsid variants (eg, those capsids capable of retinal cell transfection following intravitreal injection) are then isolated and further characterized.

The development of innovative vectors such as AAV2.7m8 via directed evolution is a significant advance in the field, as intravitreal administration of naturally occurring AAV vectors (eg, AAV2) have traditionally been plagued by particularly low efficiency of retinal cell transduction. The internal limiting membrane is but one of several recognized and notorious barriers to intravitreally delivered gene therapy.\textsuperscript{8} Intravitreally administered AAV2 based gene therapy programs, for example, have not yielded positive clinical results due to their lack of retinal penetration and thus lack of sufficient protein production. This may be, in part, why previous attempts at anti-VEGF gene therapy for wet AMD have failed.\textsuperscript{9}

On the other hand, AAV2.7m8 has been shown to yield robust, widespread, panretinal cellular transduction of multiple retinal layers following a single intravitreal injection in rodent and nonhuman primate (NHP) preclinical models.\textsuperscript{5,6}

The genetic material carried within AAV2.7m8 includes a strong expression cassette encoding a codon-optimized aflibercept gene that is under the control of a ubiquitous promoter;
in addition, numerous regulatory elements are included to enhance aflibercept protein expression. Following a single intravitreal injection of ADVM-022, the AAV2.7m8 vector transfects the retinal cells, inserting its genetic payload, which is then transcribed in the target cells to make the aflibercept protein. The aflibercept that is produced and secreted by cells transfected with ADVM-022 is functionally equivalent to the aflibercept routinely injected in clinical practice for the treatment of wet AMD. Given that aflibercept is a secreted protein, the specific cells within the eye that are transfected (e.g., tropism of ADMV-022) matters less in the context of anti-VEGF wet AMD therapy than the level of aflibercept being produced to inhibit choroidal neovascular activity.

PRECLINICAL STUDIES

Numerous NHP preclinical studies demonstrate the clinical potential for long-term safety and effectiveness of ADVM-022 in controlling VEGF-driven disease activity with a single in-office intravitreal injection in patients with active wet AMD. A single intravitreal injection of ADVM-022 produced aflibercept levels in NHPs within the therapeutic window for standard-of-care aflibercept. Levels of vector-derived aflibercept measured in the vitreous 56 days after ADVM-022 injection matched levels of aflibercept recombinant protein 3 to 4 weeks after a bolus protein injection. These measured levels are well within the duration of action of aflibercept seen in clinical practice. Notably absent were any detectable systemic levels of aflibercept with the gene therapy.

In one long-term protein expression study, ADVM-022 resulted in aflibercept protein production for at least 30 months within the therapeutic range for single-dose intravitreal aflibercept injection. In contrast, a bolus of aflibercept protein is typically undetectable by around 50 days after intravitreal injection in an NHP. This potential durability of ADVM-022 may considerably reduce or even eliminate the need for repeated bolus intravitreal aflibercept injections in individuals with wet AMD.

In this same NHP study, no obvious retinal nor choroidal toxicity or safety issues were noted when the animals were assessed with serial clinical dilated ocular exams, fluorescein angiography (FA), optical coherence tomography (OCT), full field and multifocal electroretinography (ERG), and histologic evaluation.

THE OPTIC TRIAL

OPTIC is an ongoing 2-year phase 1 multicenter prospective open-label dose-escalation safety and tolerability study of a single in-office intravitreal injection of ADVM-022 in patients with wet AMD who have been previously treated. The primary endpoint of OPTIC is safety and tolerability, but key secondary outcome measures include the effect of ADVM-022 on BCVA, the effect of ADVM-022 on anatomic outcomes as measured by spectral-domain OCT (SD-OCT), and the need for rescue aflibercept injections. Patients under active anti-VEGF treatment are given ADVM-022 (at a dose of 6 x 10^11 in cohorts 1 and 4, and 2 x 10^11 in cohorts 2 and 3) 7 to 14 days after a screening aflibercept injection. Because ADVM-022 produces aflibercept, the screening injection is used to ensure that the enrolled patients respond adequately as measured by an improvement in OCT parameters.

In the first two cohorts of OPTIC, all patients received a 13-day course of oral prednisone, starting 3 days prior to ADVM-022 injection and continuing for 3 days after administration, with a short taper afterward. In light of the encouraging safety results from the first two cohorts, cohorts 3 and 4 do not require oral steroids, and patients were instead given topical steroid drops to control any inflammation secondary to ADVM-022.

All patients in the OPTIC study could receive aflibercept rescue injections based on prespecified criteria, which included (1) loss of 10 or more letters in BCVA from baseline, (2) increase in central subfield thickness of greater than 75 μm secondary to wet AMD activity as determined by SD-OCT; (2) increase in central subfield thickness of greater than 75 μm secondary to wet AMD activity from baseline as assessed by SD-OCT; and/or (3) presence of vision-threatening hemorrhage due to active wet AMD. These rescue criteria are in line with ongoing and recently completed clinical trials evaluating a variety of sustained delivery approaches.

Safety and efficacy assessments were prespecified at 26 and 52 weeks of follow-up, and all patients are being followed to at least 104 weeks after gene therapy with ADVM-022. Preliminary results from the first cohort of six patients enrolled in the OPTIC trial have been presented this year at several professional meetings. Before to enrollment, patients recruited to OPTIC required frequent anti-VEGF injections to maintain vision. The enrolled patients were diagnosed with wet AMD a mean of 3.3 years previous and had received a mean of 35.3 anti-VEGF injections since initial diagnosis (range, 7-109). The mean number anti-VEGF
injections in the 8 months prior to screening was 6.2, with an average annualized injection frequency of 9.3 injections per year. At baseline, mean BCVA in the study eye was 65.8 ETDRS letters (approximately 20/50 Snellen equivalent) with a mean central retinal thickness in the study eye of 369.2 μm as measured by SD-OCT.

Through week 24, in the six patients in cohort 1, ADVM-022 appeared to be safe and well tolerated. No serious adverse events (AEs) were noted; no AEs met criteria for dose-limiting toxicity; and no drug-related nonocular adverse events were seen. Nineteen ocular AEs related to ocular inflammation potentially associated with ADVM-022 administration were observed in this cohort: 14 were classified as mild AEs and five as moderate AEs. These inflammatory events included anterior chamber cell and flare, vitreous cells, intermediate uveitis, keratic precipitates, poor pupil dilation, ocular floaters, vitreous debris, and vitreous haze. No early clinically significant inflammation was observed after ADVM-022 administration, with no vasculitis, no retinitis, and no choroiditis seen in any treated patients at any time during follow-up. The inflammation noted in these patients responded well to topical steroid drops.

The 24-week data presented at the Retina Society annual meeting showed a maintenance of BCVA (with a mean change of -2 ETDRS letters) with an improvement of central retinal thickness (-52.7 μm) without any of the six patients.

steroid drops.

reduced treatment burden, improve retinal anatomy, and maintain visual function with a single in-office intravitreal injection in patients with wet AMD.

As with wet AMD, patients with diabetic retinopathy (DR), diabetic macular edema (DME), and macular edema associated with retinal vein occlusion also require long-term repeated intravitreal anti-VEGF injections for control of disease activity. In-office intravitreal administration of ADVM-022 may offer an ideal platform for treating these patients as well. Adverum plans to submit to the US FDA an investigational new drug application for ADVM-022 for the treatment of DR and DME in the first half of 2020.19

CONCLUSIONS

Approval in the United States and in Europe of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) marked the transition of ocular gene therapy from the realm of science fiction to that of clinical reality.20 The success of voretigene in RPE65-associated inherited retinal degenerations (IRDs) gives confidence that gene therapy may serve as a drug delivery platform beyond IRDs, for the long-term treatment of noninherited ocular disorders such as wet AMD, DR, DME, and retinal vein occlusion. The preliminary results from the OPTIC trial, as well as encouraging results with RGX-314 gene therapy (RegenxBio),21 indicate that anti-VEGF gene therapy may one day serve as the primary drug delivery platform for patients with wet AMD, and even perhaps DR and DME. This will, of course, depend on the outcomes of larger phase 2 and 3 prospective clinical trials that will be coming in the next few years. ■


THE PIPELINE

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5. Kiss S. Intravitreal gene therapy with ADVM-022 (AAV.7m8-aflibercept) for neovascular age-related macular degeneration. Paper presented at: Retina Subspecialty Day, AAO Annual Meeting; October 2018; Chicago.

6. Kiss S. 24-week cohort 1 data from the OPTIC trial – intravitreal gene therapy with ADVM-022 (AAV.7m8-aflibercept) for neovascular age-related macular degeneration. Paper presented at: European Society of Gene and Cellular Therapy Annual Meeting; October 2019; Barcelona, Spain.


8. Kiss S. Intravitreal gene therapy with ADVM-022 (AAV.7m8-aflibercept) for neovascular age-related macular degeneration. Paper presented at: European Society of Gene and Cellular Therapy Annual Meeting; October 2019; Barcelona, Spain.

9. Kiss S. 24-week cohort 1 data from the OPTIC trial – intravitreal gene therapy with ADVM-022 (AAV.7m8-aflibercept) for neovascular age-related macular degeneration. Paper presented at: AAO Annual Meeting; October 2019; San Francisco.


