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GENE THERAPY: AN EMERGING FRONTIER IN THE TREATMENT OF NEOVASCULAR DISEASES

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable discussion.

ACTIVITY DESCRIPTION

There is potential for gene therapy to effectively treat neovascular diseases and eliminate the significant treatment burden. This roundtable discussion includes a review of the latest data, potential utility, and remaining questions surrounding this novel approach for management of neovascular age-related macular degeneration (nAMD).

TARGET AUDIENCE

This certified CME activity is designed for retina specialists and eye care professionals involved in the medical management of patients with retina disorders.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Describe** the current treatment options for nAMD.
- **Identify** the unmet needs with the currently available AMD treatments.
- **Categorize and critique** based on early clinical trial data the surgical and nonsurgical sustained-delivery AMD treatment options currently under investigation.
- **Categorize and critique** based on early clinical trial data the various types of gene therapy currently under investigation for the treatment of nAMD.
- **Interpret** the available literature and compare a subretinal surgical delivery with an intravitreal approach.

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1. Please rate your confidence in your ability to apply updates in gene therapy for the treatment of age-related macular disease (AMD) in the clinic (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Please rate how often you intend to apply updates in gene therapy for the treatment of AMD to “real-world” patient management (based on a scale of 1 to 5, with 1 being never and 5 being always).

a. 1
b. 2
c. 3
d. 4
e. 5

3. What is the biggest unmet need in the treatment of AMD?

a. Agents with different mechanisms of action
b. Treatment burden
c. Drug durability
d. Remote monitoring of fluid levels

4. The first-generation gene therapy trials in retina failed because ________

a. Efficacy was limited
b. A patient died
c. They resulted in serious inflammation
d. Delivery to the subretinal space was too great a barrier

5. How many rescue injections were needed in OPTIC cohort 1?

a. 0
b. 2
c. 4
d. 6

6. What percentage of patients in RGX-314 cohort 5 needed rescue injections?

a. 10%
b. 25%
c. 50%
d. 75%

7. What may be considered barriers to the adoption of gene therapies in clinic? Select all that apply.

a. Age and comorbidities of AMD patients
b. Limited widespread use of intraoperative OCT
c. Inflammation
d. Subretinal surgery

8. What are the potential complications from RGX-314? Select all that apply.

a. Endophthalmitis
b. Retinitis
c. Peripheral retinal break
d. Chorioretinitis

9. Patients in ADVM-022 cohort 1 experienced all but which of the following safety issues:

a. Floaters
b. Choroiditis
c. Blurry vision
d. Vision loss

10. Neutralizing antibody exposure and cellular immunity is not as significant ______________

a. When gene therapy is delivered intravitreally.
b. When limited areas of transfection are recognized.
c. As shown in preclinical, non-human primate models that found subretinal delivery results in the highest immune response.
d. When gene therapy is delivered with subretinal delivery.

Gene Therapy: An Emerging Frontier in the Treatment of Neovascular Diseases

The goal of gene therapy is to regulate, repair, add, or delete a genetic sequence for the treatment of an inherited or acquired disease by placing copies of genes into cells to produce proteins.[1] Although the study of gene therapy is not new—the earliest study in 1999 resulted in one death[2]—it took until 2017 for gene therapies to be approved by the US FDA.[3-5] Only one gene therapy has been approved in the ophthalmic space thus far,[3,6] and interest in the development of additional therapies is robust. There's potential for gene therapy to treat neovascular diseases by chronically expressing anti-VEGF proteins, thereby eliminating the significant treatment burden these patients currently experience with monthly injections and removing the potential for undertreatment with our current treat-and-extend approaches.[7] Numerous studies are ongoing, and, although early, the initial data are encouraging. In the following roundtable discussion summary, ophthalmic thought leaders in gene therapy review the data, potential utility, and remaining questions surrounding this novel approach for neovascular age-related macular disease (nAMD) management.

—Arshad Khanani, MD, MA, Moderator

CURRENT TREATMENT LANDSCAPE FOR NEOVASCULAR AMD

Q | ARSHAD KHANANI, MD, MA: It's a pleasure to have our expert faculty together to discuss gene therapy for the treatment of neovascular diseases. Our goal is to evaluate the future of gene therapy and other biologics of sustained delivery for nAMD. What do you see as the current biggest unmet needs in treating patients with nAMD, and how is that correlated with real-world outcomes?

NANCY HOLEKAMP, MD: The biggest unmet need in the AMD treatment landscape is durability of the anti-VEGF agents. It has been well documented that anti-VEGF intravitreal injections improve vision in patients with AMD.[8-12] We've been trying to alter dosing paradigms in order to space out appointments, so that we're not overburdening our patients but we're still maintaining vision and giving them appropriate care. We went from monthly injections, to bimonthly injections, to *pro re nata* (PRN) injections. Today most retina specialists in the United States use a treat-and-extend regimen.[13]

Although long-term data from treat-and-extend studies look good, recent analysis of treat-and-extend paradigms have shown that 30% of patients continue to receive very frequent anti-VEGF injections.[14-19] Further, less frequent dosing may result in suboptimal responses in some patients, and other patients do not benefit even with monthly treatments.[20-23]

When we look at real-world outcomes and what's really happening in our clinics, patients are getting five injections on average in the first year of treatment, but five isn't enough for most patients with nAMD to maintain vision.[24] For example, the SEVEN-UP study assessed long-term outcomes in 65 patients from three trials: ANCHOR, MARINA, and HORIZON.[25,26] Patients in those studies had a mean loss of 8 letters when you pool the populations together. The vision loss was primarily due to undertreatment. Patients in SEVEN-UP had an average of 6.8 ranibizumab injections, but patients who received 11 or more injections gained more letters than those who had fewer injections. This gets back to the issue that more durable anti-VEGF agents is the unmet need in our current treatment landscape.

DAVID BOYER, MD: Dr. Holekamp is correct. As physicians, we have been trying to reduce the frequency of injections to minimize the treatment burden on patients and their caregivers, but without compromising the visual acuity (VA). The AURA study clearly showed a decline in vision if less injections were administered.[27] New phase 3 clinical trials for both brolucizumab and abicipar were designed to show longer duration of these drugs compared to the current standard anti-VEGFs.

NEW TRIALS IN SUSTAINED DELIVERY

Q | DR. KHANANI: How is the sustained-delivery research landscape looking today compared with 10 years ago?

ALLEN HO, MD: I believe we're on the verge of some major advances for addressing the durability problem with nAMD. First, anti-VEGF compounds themselves are evolving. The injectables are focused on longer durability, whether it's by the molecules themselves or by getting more molar equivalents into an injection.[28] Brolucizumab was recently approved by the US FDA[29] and seems to be more effective at drying than aflibercept after three loading doses and 8- to 12-week dosing.[30,31]

A port delivery system for ranibizumab is currently in phase 3 clinical trials. It's a surgical procedure where a small, reusable, permanent port delivery system is implanted in the pars plana through a 3.5-mm scleral incision. The LADDER study showed impressive durability with the device, with many patients going well beyond 6 months before needing a refill.[32-34] Using a sustained-release device to address the durability problem in AMD makes sense. Long-term safety and efficacy data are pending in the ARCHWAY trial (NCT03677934), but that study looks promising as well.

There are some new scientific and biologic approaches to durability, and that speaks to specifically gene therapy. Gene therapy was first described in the 1960s and 1970s by Rogers and Pfuderer, who suggested good DNA could be used to replace defective DNA in

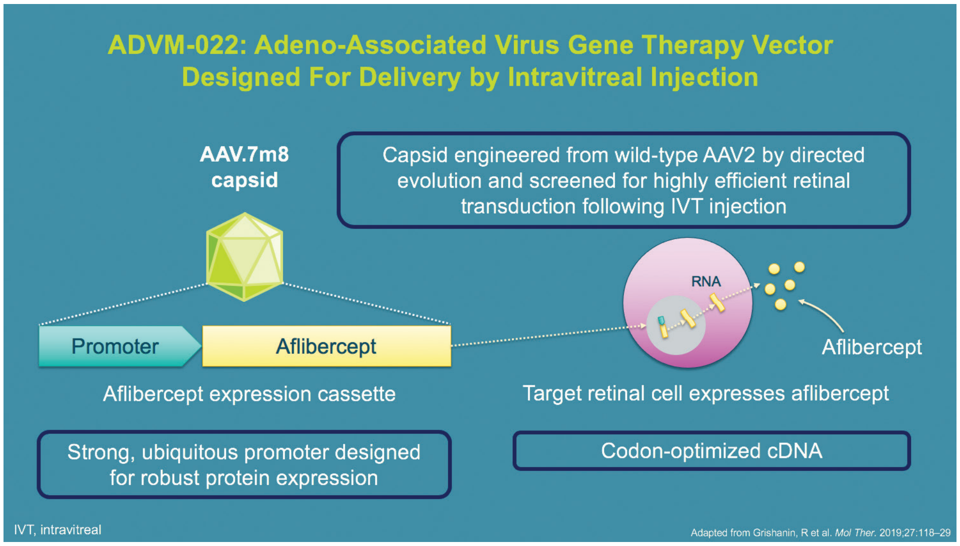

Figure 1. ADVM-022 is a gene therapy vector designed for long-term aflibercept expression following a single intravitreal injection.

people with genetic disorders.[35] In 2017, the FDA approved three novel gene therapy treatments for the first time; two for cancer and one for biallelic RPE65 mutation-associated retinal dystrophy.[3,36]

There have been a few attempts at gene therapy for nAMD, but those first-generation nAMD gene therapy studies did not show durability or significant efficacy. These trials included a phase I trial of AAV2-sFLT01, delivered intravitreally. Although it appeared safe and the study showed some response, that response was inconsistent.[37,38] The phase 1 GEM study delivered a lentiviral vector for endostatin and angiostatin subretinally.[39] Like AAV2-sFLT01, delivery was safe but there was no efficacy response. Finally, the phase 1/2a Avalanche trial delivered AAV2 sFlt subretinally. This trial had a similar story to the others; subretinal delivery was safe, but efficacy was limited.[40]

Despite these failures, there are now two new gene therapy options that look promising: ADVM-022 (Adverum) and RGX-314 (RegenxBio). ADVM-022 is currently being investigated through the OPTIC trial using a transgene encoding for aflibercept delivered intravitreally (Figure 1); RGX-314 is delivered to the subretinal space with vitrectomy and produces a ranibizumab-like anti-VEGF molecule.[41-44]

For OPTIC, clinical data are available for cohort 1, which includes six subjects with previously treated nAMD. Adverum reported positive 24-week clinical data; patients maintained vision and had improvements in retinal anatomy, with no anti-VEGF rescue injections required, after a single intravitreal injection of ADVM-022.[43,44] Intraocular inflammation was observed in some subjects but has been controlled with topical therapy. The company plans to release 52-week data from the first cohort and 24-week data from the second cohort in the first half of 2020. Dosing for cohort 3 and enrollment of cohort 4 are expected to begin soon.

For the phase 1/2a trial of RGX-314, 42 patients with previously treated nAMD have been enrolled across five dose cohorts, ranging from 3x109 to 2.5x1011 GC/eye. RegenxBio has reported interim data for cohorts 4 and 5, which included 12 patients each, at doses of 1.6x1011 and 2.5x1011 GC/eye, respectively. All 12 patients in cohort 4 had the full 6 months of follow-up. All but one patient in cohort 5 reached 5 to 6 months of follow-up. Patients in both cohorts had a meaningful reduction in their anti-VEGF treatment burden. A total of 42% and 75% of patients in cohort 4 and 5, respectively, had no injections during the 6-month follow-up period. Patients in cohort 5 had improved visual acuity and decreased retinal thickness, with a mean best corrected VA (BCVA) increase of 4 letters. The nine patients who did not receive additional anti-VEGF injections after RGX-314 administration had a mean BCVA increase of 5 letters. Patients in cohort 4 also had an increase in BCVA, but it wasn't quite as robust as cohort 5, with only a 2-letter increase.[42]

The data are early, but promising. I like the science, and I like the idea of turning the eye itself into an ocular biofactory.

DR. BOYER: Dr. Ho did an excellent job of reviewing the status of gene therapy today. In addition to gene therapy, other companies are aimed at increasing the duration of action, including Kodiak Sciences and Graybug Vision. Aerie Pharmaceuticals is looking at nanoparticles and tyrosine kinase inhibitors for extending the duration of drugs.

SZILÁRD KISS, MD: Perhaps the greatest change in the sustained-delivery landscape has been the clinical realization of the true potential for gene therapy as a treatment approach. After a 25-year preclinical journey, regulatory agency approval in the United States and in Europe of voretigene neparvovec-rzyl (Spark Therapeutics) marked the transition of ocular gene therapy from the bench to bedside.[45] The clinical success of voretigene neparvovec-rzyl gives confidence that gene therapy may serve as a drug-delivery platform for the long-term treatment of noninherited ocular disorders beyond inherited retinal diseases (IRDs) such as nAMD, diabetic retinopathy (DR), and diabetic macular edema (DME). In these more common disorders, a gene therapy platform may be used to deliver an anti-VEGF molecule to obviate the need for repeated intravitreal injections.[46] This offers at least the theoretical potential for a "one-and-done" treatment of VEGF upregulation.

GENE THERAPY OVERVIEW

Q | **DR. KHANANI:** Dr. Kiss, you've been involved with gene therapy for many years. Can you give us an overview of the components of gene therapy and how it works in nAMD versus inherited retinal diseases?

DR. KISS: Broadly speaking, gene therapy involves the interplay of four interrelated components[45]: (1) vector; (2) route of delivery; (3) specific transgene; and (4) manufacturing. These four components, of course, need to be all taken in the context of the side-effect profile of the gene therapy itself. In the early 1990s, replication-defective retroviruses were used as the first gene delivery vectors. However, inflammatory response to retroviruses, as well as direct toxicity from the virus itself, promptly restricted their clinical practicality. A decade later, adeno-associated virus (AAV) vectors derived from nonpathogenic replication-deficient parvovirus

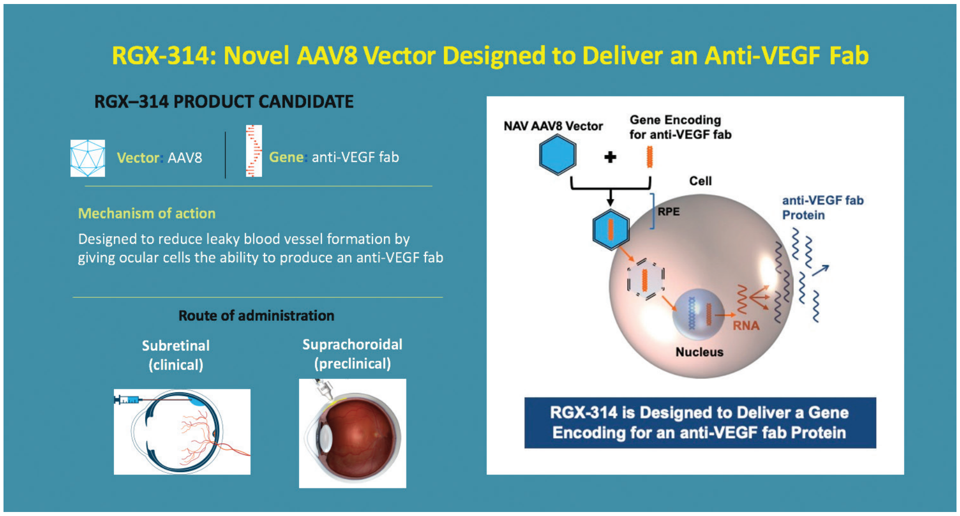

Figure 2. RGX-314 is designed to reduce leaky blood vessel formation by giving ocular cells the ability to produce an anti-VEGF fab.

emerged as a safe and effective tool for gene delivery. The current upsurge of clinical gene therapy in the eye and elsewhere is based primarily on this AAV technology. The differences among various serotypes of novel AAV vectors enables improved efficiency in targeting a broad range of retinal disorders via the intravitreal, subretinal, and suprachoroidal routes.[46]

More than a dozen different naturally occurring AAV serotypes have been identified in primates with more than 100 variants.[47] The naturally occurring serotypes AAV2, AAV5, and AAV8 have been most widely studied for use as ocular gene therapy vectors. These three vectors work most efficiently via a subretinal delivery route. Voretigene neparvovec-rzyl, for example, uses AAV2 vector while RGX-314 is an AAV8 capsid (Figure 2). Transfection of retinal cells following intravitreal injection of these viral vectors is limited by the barrier imposed by the internal limiting membrane. In addition, preexisting neutralizing antibodies can limit naturally occurring AAV transfection of retinal cells. For example, depending on geographic region, 30 to 60% of humans have neutralizing antibodies (nAbs) to AAV2[48]; in addition to causing a severe secondary inflammatory reaction, these nAbs have the potential to severely limit cellular transduction and transgene protein production in the target tissues.

To overcome these limitations, the range of AAV vectors for ocular gene therapy has been expanded beyond naturally occurring serotypes to second- and third-generation vectors; these new vectors have been designed or isolated explicitly to have greater transduction efficiency, altered tropism, and/or improved immunogenicity profile when compared to their naturally occurring counterparts.[45] Two different approaches have been used to generate these novel vectors: rational design and directed evolution.

An example of a second-generation vector developed through directed evolution that is showing great promise in nAMD patients is AAV.7m8, which is a unique AAV2 capsid variant that is capable of efficient and robust gene delivery to all retina layers in both mice and primates following a single intravitreal injection.[49] AAV.7m8 overcomes the internal limiting membrane (ILM) barrier as it was explicitly designed, through a process of in vivo directed evolution, to enhance retinal penetration and transfection from the vitreous, in an effort to optimize intravitreal AAV delivery. ADVM-022 gene therapy that is currently in clinical trials uses AAV.7m8 as the gene therapy vector.

The most obvious difference between gene therapy for an IRD compared to that for a noninherited disorder such as nAMD lies in the transgene, which is the specific payload that the viral vector is delivering to the target cells. With IRDs, the transgene corresponds to the specific genetic abnormality that resulted in the retinal degeneration. For example, the target IRD population with voretigene neparvovec-rzyl are those patients with a nonfunctional RPE65 protein; as such, the genetic sequence for a functional RPE65 is packaged inside the AAV2 viral vector. With a non-IRD disorder like nAMD, the payload is actually the genetic sequence for an anti-VEGF molecule. The goal here is not to replace an abnormal anti-VEGF gene, but rather to have the eye itself become a bio-factory to produce an anti-VEGF molecule without the need for repeated intravitreal injections. In the case of RGX-314, the transgene produces a molecule that is equivalent to ranibizumab; for ADVM-022, the payload genetic material results in aflibercept production.

DR. KHANANI: Dr. Ho, you've been involved in many subretinal trials with different devices and procedures. What are your thoughts on the surgical complexity of subretinal gene therapy? Is that something that can be translated easily in terms of the skills of the procedure for the average retinal specialist?

DR. HO: I'd say I'm cautiously optimistic. There's excitement about the science, but we have to remember that fewer than 200 patients have received gene therapy for nAMD. Although the first-generation trials failed, RGX-314 and ADVM-022 are showing significant promise, and the safety profiles to date are acceptable.

In terms of the treatment complexity, ADVM-022 is an intravitreal injection. This is a major delivery advantage because it's an office-based procedure, and we're accustomed to doing them. The researchers have seen some inflammation in the early cohort of subjects, but it was addressed with topical steroids. We need more experience. Inflammation is not surprising, and time will tell if it's a real barrier to adoption or will result in significant safety issues.

I'm confident that, should gene therapy prove to be worthwhile for patients with nAMD, most retinal surgeons will be trained on OR-based subretinal injections Many of us already treat large submacular hemorrhages with vitrectomy and a microcatheter into the subretinal space. The operating room is a barrier, but I don't think it's an insurmountable one.

DR. BOYER: All retinal surgeons are capable of subretinal delivery of drugs. Even with intraoperative OCT (iOCT), there are risks of bleeding and injecting in the wrong space. Vitrectomy surgery carries with it certain risks such as an increase in cataract formation, epiretinal membrane formation, bleeding, infection, and retinal detachment. These risks have led to the development of equipment that allows subretinal delivery without a vitrectomy. ORBIT has developed a suprachoroidal probe with a small needle that allows the delivery of subretinal gene therapy from the choroidal side without making a hole in the retina. This therapy is currently being used to deliver stem cells into the subretinal space.

DR. KHANANI: We all agree that RGX-314 and ADVM-022 are showing promise. I think we need to look at the risk and benefits of each approach and see how the patients will fit. I think most patients will feel comfortable with gene therapy, but the operating room and comorbidities are likely barriers. In general, it's exciting to see that things are moving forward.

Let's discuss the immune response. Why is the immune response different in the subretinal versus intravitreal versus suprachoroidal space?

DR. KISS: The subretinal and intravitreal spaces are immunologically different.[50,51] One of the advantages of going into the subretinal space is it's a more immune-privileged site. We're taught in medical school and residency that the eye itself is immune privileged and able to tolerate the introduction of antigens without causing an inflammatory immune response, but we forget that it's a relatively immune-privileged site.[52,53] When you go into the eye intravitreally, you're exposing the immune system to viral particles. Our bodies have been exposed to these viruses before, and as far as we know they don't cause disease in humans.[54] Once we are exposed, we develop neutralizing antibodies, meaning the immune system is trained to stop the transduction of these viruses.

When you inject into the intravitreal space, you expose more of those viral particles to the immune system, and potentially the neutralizing antibodies can prevent the transfection of those viral particles. In the subretinal space, the neutralizing antibody issue is not as great. It probably is not relevant at all because you're going into a potential space where the virus is able to transfect the cell through the retinal pigment epithelium (RPE) or the photoreceptors without being exposed to the neutralizing antibodies and neutralization. That's the first aspect of the immune response.

The next aspect is a secondary T-cell inflammation. When you're infected with a virus, your body mounts an immune response. The immune system sees a viral particle that's foreign, and you get a secondary T-cell infiltration. There, too, is a slight advantage to the subretinal space. Not only is the neutralizing antibody exposure not as great but the exposure to the cellular immunity is not as great either. In the intravitreal space, there is a greater exposure to the cellular immunity as these viral particles try to transfect cells. As the viral particles are hanging out inside the eye, they can be picked up by the immune system.

There are two different types of immune responses that we think about. I'm going to address the first one in terms of neutralizing antibodies. The dogma has always been that neutralizing antibodies are bad.[55] Recent data, however, indicates that neutralizing antibodies may not be as big a barrier to delivery as we thought.[56]

We're injecting billions of viral particles into the eye. Although the transfection rate may be decreased because you do have some neutralizing antibodies, it's likely the neutralizing antibodies can be overcome. In the ADVM-022 trial, more than 90% of those who were screened actually met a cutoff threshold. The only patients who were screened who did not meet the cutoff threshold were those who had the highest levels of neutralizing antibodies. There was no difference in terms of the efficacy or inflammatory response when it comes to the neutralizing antibody story. The T-cell response remains. This is a shifting landscape in favor of intravitreal.

The cellular response remains an issue and much more so with an intravitreal injection in humans. I think that's what you're seeing in the ADVM-022 trial, and it's something that's been seen in the GenSight RESCUE phase 3 clinical trial of GS01057 (NCT03406104)[57] and the Applied Genetic Technologies Corporation phase 1/2 trial evaluating the safety and efficacy of subretinal rAAV2tYF-PR1.7-hCNGA3 for the treatment of achromatopsia (NCT02935517).[58]

We need to figure out how to control the inflammation. The learnings from the first dozen patients in the OPTIC trial indicate that you may not need systemic corticosteroids, but there are a number of remaining questions. How and when do we control that inflammation? Can we use drops? If so, how many drops and for how long? Do we even need to go to subtenon triamcinolone? This is an evolving landscape. Too few patients have been treated to give us a good indication of how to best control the inflammation.

DR. KHANANI: To summarize, initially there was a worry about the neutralizing antibodies causing decreased efficacy and increasing the risk of inflammation. In terms of safety, we are seeing more inflammation with the intravitreal approach versus the subretinal approach, potentially caused by nAbs. But the majority of patients in the Adverum trial were eligible after the nAb criteria were relaxed, which resulted in 95% of patients qualifying for the study, and nAbs really don't seem to have any correlation with inflammation. Drs. Boyer and Holekamp, please share your comments about this issue.

DR. BOYER: Many people have been exposed to AAV viruses and carry neutralizing antibodies. In animals, it doesn't appear that all neutralizing antibodies reduce gene transfer and subsequent protein production. With the modified AAV viruses, we are trying to find how much this affects transfection. This obviously is more important with the intravitreal injection than with subretinal delivery of gene therapy.

DR. HOLEKAMP: The concept of neutralizing antibodies is fascinating, and I think we can glean insights from the recent FDA approval of brolucizumab. The FDA label includes, for the first time, information on preexisting neutralizing antibodies to brolucizumab.[29] Almost 50% of patients who had never been exposed to this drug previously had preexisting antibodies. What they found is that the inflammation rate in this subgroup of patients was slightly higher at 6%, whereas for the overall group, including those patients with antibodies, it was 4%.[30]

Therefore, we may see slightly more inflammation, but nothing that raised concerns from the FDA. Secondly, there was no indication that the treatment efficacy was less robust in patients with these preexisting antibodies.

DR. KHANANI: That's an excellent observation. As long as safety can be managed appropriately, intravitreal gene therapy can be a great option for patients.

SUBRETINAL SURGICAL DELIVERY VS AN INTRAVITREAL APPROACH

Q | DR. KHANANI: How is gene therapy in the suprachoroidal space different from the intravitreal and subretinal space?

DR. KISS: Gene therapy in the suprachoroidal space is emerging. There are some encouraging signs that the suprachoroidal space can and may offer the advantage of doing gene therapy in the office, while mitigating the inflammation risk. I put a big asterisk there. There was a very nice study from Campochiaro et al in which they looked at transfection using an AAV8 vector and a reporter gene GFP in nonhuman primates.[59] They achieved excellent transfection, although it may require multiple injections into the suprachoroidal space.

On the other hand, data presented by Glenn Yiu, MD, PhD, from UC Davis Eye Center during the 2019 Retina Society Meeting in London may tell a slightly different story.[60] Dr. Yiu and his colleagues studied different routes of administration of the AAV8 vector, the same one that's being used in the RGX-314 study, in a nonhuman primate model. Suprachoroidal delivery resulted in protein expression that was diffuse, punctate, and confined to the periphery. Subretinal AAV8 produced focal expression near the injection site, and intravitreal AAV8 showed very limited peripapillary expression. Protein expression after suprachoroidal delivery of AAV8 was detectable at 1 week, increased to maximal expression at 1 month, but decreased by 3 months after injection. Histological analysis of the suprachoroidal delivery showed that suprachoroidal AAV8 transduced RPE, but triggered a robust inflammatory cellular infiltration. Subretinal AAV8 provided robust protein expression in the outer nuclear layer and RPE as well as some retinal ganglion neurons and axons.

It's still not clear to me how to exactly explain this inflammatory response to the suprachoroidal injection noted in this NHP work. One potential explanation for the results seen by Yiu and colleagues may be related to the fact that his group did not test clinical grade vector and that his construct used a CMV promoter, a known cause of inflammation within the gene therapy field.

DR. KHANANI: There's obviously exposure to the immune system with suprachoroidal delivery. Are you worried about the vectors entering the systemic circulation and producing or making a factory somewhere else outside the eye?

DR. HO: I'm always cautiously optimistic about new investigational delivery pathways and interventions. The science is remarkable. Although I'm concerned about safety, I'm also keenly interested in the possibilities. If suprachoroidal delivery takes gene therapy into an office-based setting, not only can we have something that has less of an obstacle to deliver but also avoids potential vitrectomy. For those reasons, we need to do the careful clinical science to determine whether this is a viable route of delivery of gene therapy in terms of safety and efficacy, both locally in the eye and for the body in general.

DR. BOYER: We know drugs can be safely injected into the suprachoroidal space. We have to determine if there can be adequate transfection in this space. This is being evaluated by Clearside Biomedical and could make gene therapy an office procedure.

DR. KHANANI: Clearside Biomedical has introduced a novel injector[61] and triamcinolone acetonide suprachoroidal injectable suspension, which target the suprachoroidal space. This was explored in the recently published phase 3 PEACHTREE trial, a randomized, masked, sham-controlled trial that enrolled 160 patients with macular edema-associated noninfectious uveitis, comparing 12-week triamcinolone acetonide suprachoroidal injectable suspension to sham control (NCT02595398).[62] Dr. Holekamp, how comfortable are you with suprachoroidal delivery? How will community retina specialists respond to this treatment delivery method? How about surgical subretinal delivery versus intravitreal approach?

DR. HOLEKAMP: We're all very comfortable with intravitreal injections, but as soon as we modify that straightforward intravitreal injection we get barriers to treatment. I don't think medical retinal specialists will be initially comfortable with the Clearside injection technique and needle, if science proves it to be a viable approach.[61] It's important to note that the Clearside needle is undergoing modification and evolution. They have adjusted the needle length because there is more variability in the thickness of sclera and where exactly the suprachoroidal space lies. I think the needle will undergo additional evolution.

The operating room will be a barrier for the AMD population. I think almost every patient would opt for an office-based procedure over a surgical procedure if efficacy was equal. The safety profile would be likely more favorable in the office than the operating room. Although still needing to be proven in large clinical trials, I'm cautiously optimistic about intravitreal injections as a means of delivering gene therapy to this patient group.

LEARNING FROM THE PAST: FAILED FIRST-GENERATION TRIALS INFORM CURRENT PARADIGMS

Q | DR. KHANANI: When people think about gene therapy, the failed trials by Avalanche and Sanofi-Genzyme often come to mind.[37,38,40] What were those two programs, and why were they unsuccessful in moving forward and attaining the efficacy we were expecting?

DR. KISS: I was involved in both those two previous programs. Yes, they failed, but you don't have a chance of success if you don't try.

I'll start with the Sanofi-Genzyme program. This program was first conceived about 20 years ago, and it used AAV2 viral vector administered through an intravitreal injection. In the decades since, we've learned that AAV2 is not a viable vector that results in sufficient protein production through an intravitreal injection (due to the ILM and nAbs, as outlined earlier).

Second, Sanofi-Genzyme used a proprietary form of the VEGF soluble receptor, sFLT01, as the anti-VEGF molecule. Unfortunately, sFLT01 was not an ideal therapeutic anti-VEGF protein. We now know that the novelty of aflibercept comes from the fact that the native sFLT, which served as the backbone of the Sanofi-Genzyme sFLT01 transgene, is extremely sticky and gets cleared from the vitreous very quickly. Moreover, unlike aflibercept or ranibizumab, sFLT01 is not able to diffuse as well throughout the vitreous and the retina to mop up the pathogenic VEGF we know is present in wAMD. Although there may have been a small efficacy signal in Sanofi-Genzyme trial, overall, the patients really did not show significant reduction in their treatment burden. Nonetheless, this trial was extremely valuable in showing the favorable side-effect profile of intravitreal gene therapy and proving that a gene therapy platform may play a role in addressing unmet needs in more common, non-IRD disorders.

The other failed program from Avalanche also used AAV2 as the viral vector. However, this program built on the learnings from the Sanofi-Genzyme trial by going into the subretinal space rather than through an intravitreal injection. AAV2 does not work as well as AAV8 (the vector being used by Regenxbio in RGX-314) in the subretinal space, but it does work, as evidenced by the voretigene neparvovec-rzyl trials and the FDA approval of voretigene neparvovec.[6,36] Here, the viral vector was being placed in the right location—the subretinal space—but the transgene was another form of sFLT. We now know that there was just no possibility that sFLT would have enough anti-VEGF activity to provide sufficient clinical benefit to substantially reduce the treatment burden in our high-need anti-VEGF nAMD patients. Nonetheless, the great takeaway from this failed trial was that subretinal surgery was safe in the setting of nAMD and is scalable as a potential treatment paradigm even for non-IRD, more common retinal disorders.

The two ongoing clinical trials for nAMD have built on the learnings of these past failures. The RGX-314 program is using an optimized viral vector that works well through a subretinal injection (AAV8); inside AAV8 is the genetic material for a well-tested and proven anti-VEGF molecule, ranibizumab. These two factors are likely why we are seeing the favorable clinical outcomes with the RegenxBio program in previously treated wAMD patients.

With the ADVM-022 program (OPTIC trial), the Schaffer Research Group from the University of California, Berkeley, developed novel viral capsids such as AAV.7m8.[49] Unlike AAV2 or other previously tried capsids, AAV.7m8 works exquisitely well when you inject it into the intravitreal space. For specific reasons that are not well understood, AAV.7m8 is able to overcome the ILM barrier and transfect the retinal cells at sufficient levels to show efficacy. That's one significant way the ADVM-022 program differs from the Sanofi-Genzyme trial (which used AAV2 that is blocked by the ILM and is not useful through an intravitreal route of delivery). Equally important to the viral capsid, the anti-VEGF genetic material that is delivered in the OPTIC trial with the ADVM-022 product encodes aflibercept, which has proven successful in treating wAMD, among other retinal disorders.

We've learned from previous failures to use the right payload (a proven anti-VEGF molecule), in the appropriate delivery vehicle (AAV8 in the subretinal space and AAV.7m8 via an intravitreal injection), and that's likely why we're seeing some significant preliminary success in both the ongoing nAMD clinical trials.

DR. KHANANI: We know that ranibizumab and aflibercept work well in our patients with neovascular AMD. It makes sense for us to get those proteins secreted. Dr. Ho, how does the Avalanche subretinal delivery compare to RGX-314?

DR. HO: The procedures are essentially the same as vitrectomy, then retinotomy with a 41-gauge internal diameter microcatheter with delivery into the subretinal space. Avalanche and the GenSight cell therapy trials taught us that you have to be careful in the subretinal space, and sometimes you can be in the choroidal space.

Secondly, our surgical techniques have become easier over time as the hardware and technology has improved. We now have other ways to deliver in the subretinal space, which is a huge benefit. For example, MedOne has developed a subretinal delivery kit that includes a 1 mL, microcalibrated syringe that hooks up to the viscous fluid injection systems of all the major vitrectomy on manufacturers. With this, you don't have to worry about having as assistant manually inject—you can do it. The surgeon controls the foot pedal response like a gas pedal accelerator, allowing the surgeon to initiate and titrate the subretinal delivery of gene therapy.

Although the procedures between the first-generation Avalanche trial and subretinal delivery for RGX-314 are essentially the same, we've benefited from surgical experiences in previous subretinal gene therapy trials and from the new surgical hardware and technology available to us now.

DR. HOLEKAMP: Technologic improvements can assist in the translation of these surgical techniques to the community of retina specialists. Dr. Ho, do you see a role for iOCT to verify that people are in the subretinal space?

DR. HO: Although iOCT is not widespread, it could make the procedure safer and the delivery more consistent as the technology evolves.[63] iOCT provides heads-up visualization and microscope integration. It can measure volume over time and tell you where you are within the eye in real time. Not only do you have a two-dimensional cross-sectional view, but you have a 3D heads-up display to determine whether or not you've delivered a volume that's appropriate for that particular patient.

DR. BOYER: I agree with comments from Drs. Ho and Holekamp. As the technology continues to improve, iOCT will make the subretinal approach safer and more consistent. The surgical technique, however, can certainly be done without it.

DR. KHANANI: These innovations have made surgery safer and have decreased the risk of adverse events. Will all practicing retina specialists have access to these technologies and use subretinal gene therapy once it's approved, or will it be limited to bigger centers because of the necessary access to iOCT?

DR. HOLEKAMP: If science validates gene therapy as a successful platform for treating our patients with wAMD, I think it will be adopted. If subretinal surgery is required for gene therapy, technology will help shorten the learning curve and allow surgeons to come up to speed in just a few cases. Subretinal surgery has been around since the 1990s. Many of us have worked in the subretinal space.

I think gene therapy is very encouraging, whether it's a surgical procedure with viral vector delivery to the subretinal space or an office injection into the vitreous or suprachoroidal space. Retina specialists are capable of adopting new techniques. I remain optimistic that if this is the future, we will be able to deliver this care.

DR. KHANANI: I have performed the RGX-314 surgery, and I thought it was relatively straightforward. How hard will it be to take an 85-year-old patient with nAMD into the operating room? What are the potential hurdles for subretinal surgery compared to intravitreal or suprachoroidal delivery?

DR. HOLEKAMP: Our patients in their 80s have a lot of comorbidities. We know that significant cardiovascular disease comigrates with AMD,[64-67] and that the underlying etiology to both of these disease states may involve complement dysregulation. That said, the proposed surgery for surgical subretinal delivery can be performed on an outpatient basis in an ambulatory surgical center under local anesthesia with monitoring by an anesthesiologist or a certified registered nurse anesthetist. If the surgical approach is the best course of action, we will find a way to take appropriate patients to surgery. The good news is some of our nAMD patients are a bit younger, in their 60s and 70s, and perhaps a bit healthier.

In the big picture, the market will move toward an in-office injection over surgery if it's safe and effective. Neovascular AMD could become a disease we manage with a single injection and eyedrops. That is far better than the current standard of care, which is multiple injections over a long period of time. I'm enthusiastic about gene therapy for these reasons.

DR. HO: We are all experienced in administering intravitreal injections; these can be done quickly in the office. A suprachoroidal injection is a bit different and more nuanced.The injection experience is longer for the patient, and it can hurt more than an intravitreal injection. The choroid is sensitive. An intravitreal injection has some sensitivity, but less than a suprachoroidal injection. Therefore, we must also consider that our patients will have treatment preferences.

RGX-314 TRIAL: WHAT'S KNOWN

Q | DR. KHANANI: How does the vector in RGX-314 work? What postoperative care is required?

DR. HO: The first thing to know is that both the Adverum and RegenxBio trials have enrolled previously treated and frequently treated nAMD patients. These are patients who have had many, many injections over time, yet remain wet. RegenxBio has enrolled 42 patients over five cohorts. On average, these patients have had 30 to 40 previous injections; they've been treated for years (Figure 3).

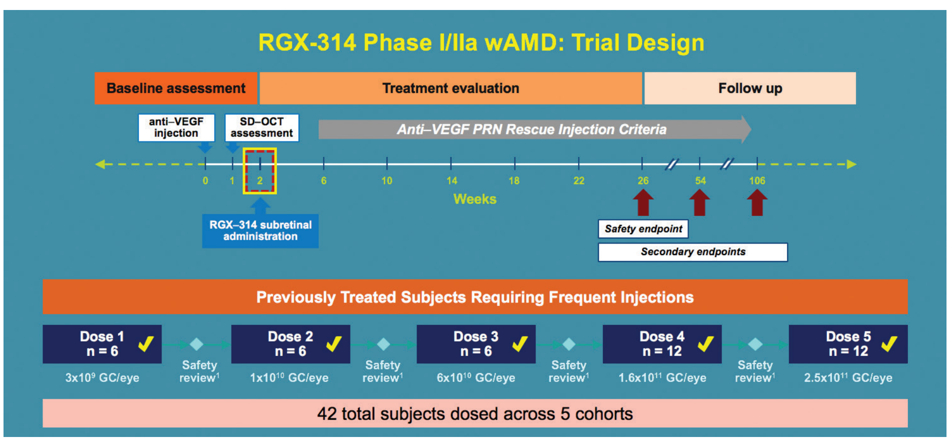

Figure 3. RGX-314 trial design.

Patients in the RegenxBio trial had a test injection of ranibizumab to make sure that they had an anatomic response to the investigational agent. If they did, they were eligible to enroll and have subretinal gene therapy with vitrectomy. At the time of surgery, patients received another ranibizumab injection because it takes time for gene therapy transfection and translation to work to produce anti-VEGF protein. It turns out that they start producing protein, most of them within a month.

When you look at the efficacy data, you might not expect a previously treated patient to have improvements in VA or changes in their anatomy like a treatment-naive patient. Yet that's what's happening for some subjects in cohorts 3 through 5. We also have to look at the number of rescue injections, as that's a key outcome of the trial. We'd love to see an improvement of 5 to 10 letters, but we're really trying to achieve durable treatment above all else. Therefore, retreatment criteria are important.

The criteria were a little stricter in RegenxBio than in the Adverum trial. In general, nAMD trials with durable devices like the port delivery system are going toward more liberal retreatment criteria. In RegenxBio, researchers are tolerating a loss of greater than 5 letters. According to the safety data, this particular intervention is incredibly safe. I was concerned about inflammation and about a variety of potential effects from injecting this type of volume into an eye and into the subretinal space. But eyes were quiet. We only used topical steroids and antibiotics postoperatively.

The protein production story is interesting. We're seeing dose-dependent increases in protein production that were obtained from aqueous samples at 1 month, 6 months, and 1 year. This was exciting, as there were few rescue injections during this time period. In the first couple cohorts, everyone was requiring rescue injections on a monthly basis. In other words, we weren't at the right dose. But starting in cohort 3, 50% of the six patients required no rescue injections after a year. Think about that. These were patients who received injections every 4 weeks, and suddenly no rescue injections were needed for a year or longer. We're now seeing this type of result in cohorts 4 and 5 as well.

This is the promise of RGX-314. The company is going to enroll more patients in these nAMD trials and expand to DR.

DR. KHANANI: It seems like there's dose-dependent protein production, OCT improvements, VA improvements, and a decrease in rescue injections. Clearly, patients in RegenxBio cohort 5 with higher gene copies are doing better than patients in cohort 1. Have you seen any surgical-related complications or retinal changes in these patients?

DR. HO: Yes, we have. After 42 surgeries, there was one patient with a retinal detachment from a peripheral retinal tear, not related to the posterior retinotomy that's done when the surgeon delivered RGX-314 to the subretinal space.[42,68] The retinal detachment was repaired, and the patient is now doing well within the program. There was one patient who had a peripheral retinal break, which we would expect with surgery. That patient was also repaired. We had one patient who developed an endophthalmitis after an anterior chamber tap, and this patient has recovered as well.

These are some of the complications of invasive procedures. This particular program is not immune to that. Overall though, the data show that RGX-314 is very safe.

DR. KHANANI: The rescue criteria for RGX-314 is liberal compared to the LADDER, ARCHWAY, and OPTIC studies.[32,43,44] When looking at the data, how does the retreatment criteria effect the results? I've also noticed that the protein production data is variable across patients in the same RGX-314 cohort. What are your thoughts?

DR. KISS: This is a great time for gene therapy for AMD as both RGX-314 and ADVM-022 appear to deliver an anti-VEGF therapy that significantly decreased, and even eliminates, the need for intravitreal rescue injections in so-called VEGF addicts. There is clearly an efficacy signal, and it looks very safe overall. As for the retreatment criteria, the devil is in the details, especially as we move into these sustained-delivery technologies. Yes, there are different retreatment criteria between these and other trials. But I think the bottom line is that, when you look at the OCTs at all the time points in any of those trials, no matter which retreatment criteria you choose, none of the patients in OPTIC would have received a rescue treatment.

It is very important to look at the retreatment criteria and make sure it passes the "smell test." What do I mean by that? The first question is, "Would I inject this patient with anti-VEGF therapy if they were not in the clinical trial?" If that answer is yes, then you do it even if it violates the retreatment criteria of any preassigned retreatment for sustained-delivery technology. Although there are some differences in the trials, the differences are not clinically meaningful. The OCTs and the vision in terms of activity of nAMD speak for themselves. The patients in the first cohort of OPTIC did not need any rescues no matter which retreatment criteria was used.

Regarding the protein levels, I don't think we should hang our hat on these. The best indication for the efficacy of the gene therapy in these early trials is the OCT–the OCT is an exquisite "VEGF meter" and a very sensitive measure of nAMD disease activity. If a patient who required frequent intravitreal injections to control nAMD CNV activity is treated with gene therapy and subsequently they do not require any further rescue treatments, it means that the anti-VEGF protein being produced with the vector is sufficient, regardless of what specific level you may measure.

RGX-314 works because only 25% of the patients in cohort 5 needed rescues, meaning gene therapy was making sufficient anti-VEGF protein in 75% of patients to suppress exudation from CNV. To me, that's proof more than any protein level would be in terms of the potential for gene therapy in this space. The same is true for ADVM-022: zero rescue injections required in the first cohort through a mean of 40+ weeks of follow-up is really the best indication of the efficacy of this product.

ANALYZING EARLY OPTIC DATA

Q | DR. KHANANI: Dr. Kiss, you presented the OPTIC trial data during the American Academy of Ophthalmology 2019 Annual Meeting in San Francisco[43,44] How does ADVM-022 work? What kind of efficacy and safety are we seeing, and how are we managing inflammation?

DR. KISS: OPTIC is very similar to the RegenxBio trial in terms of inclusion criteria. These are frequent flyers, the patients in our clinics who require a lot of injections: the so-called VEGF addicts. In OPTIC, patients had an average 35 previous injections and were diagnosed more than 3 years prior. One patient had more than 100 injections, and aflibercept was injected. You don't want to give a patient gene therapy before you make sure they respond to that gene therapy product. In the RGX-314 trial, it was a ranibizumab challenge, and in OPTIC it is an aflibercept challenge. Once patients were deemed to be receptive or responsive to aflibercept, they were given ADVM-022 and followed accordingly.

There's much more robust evidence from the RGX-314 trial: 42 patients and significantly longer follow-up. OPTIC is still a small trial with only one cohort of six patients reporting and an 8-month follow-up, on average. However, there were no rescue injections given in that timeframe, which is extremely impressive, especially with an in-office intravitreal injection (Figure 4).

In terms of the safety profile, there was inflammation noted in those patients who received ADVM-022. Patients were given oral steroids for a total of 13 days, and the patients were started on the oral steroid before ADVM-022 was injected. The investigators were specifically asked to look for inflammation. Inflammation occurred in all six patients in the first cohort, but not all the inflammation was symptomatic. Patients with symptomatic inflammation complained of floaters and blurry vision. The inflammation that required treatment occurred after the oral steroids, so it wasn't a breakthrough on the oral steroids. When the investigators treated those patients with topical drops very aggressively, the inflammation was controlled (Figure 5).

What's becoming evident in the intravitreal route is that inflammation is something that is a class act, meaning a class of intravitreal gene therapies, and needs to be mitigated and controlled. Let me get to the mitigation issue. In the second cohort, an unusual step

OPTIC

Cohort 1

As of December 1, 2019 (Median of 44 Weeks; Range 40–52 Weeks)

Outcomes Through December 1, 2019 (Median 44 Weeks Follow-up)*	Value
Mean BCVA change from baseline, ETDRS letters	–1.0
BCVA change from baseline (min, max), ETDRS letters	–7, +7
Mean CST change from baseline, µm	–25.5
CST change from baseline (min, max), µm	–117, +32
Total number of rescue injections	0

*BCVA and CST for patient 4 with retinal detachment (unrelated to study treatment) use last observations prior to detachment (week 36)
BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study

Figure 4. OPTIC cohort 1 additonal data through Dec. 1, 2019. These data were first presented at the Macula 2020 meeting in January.

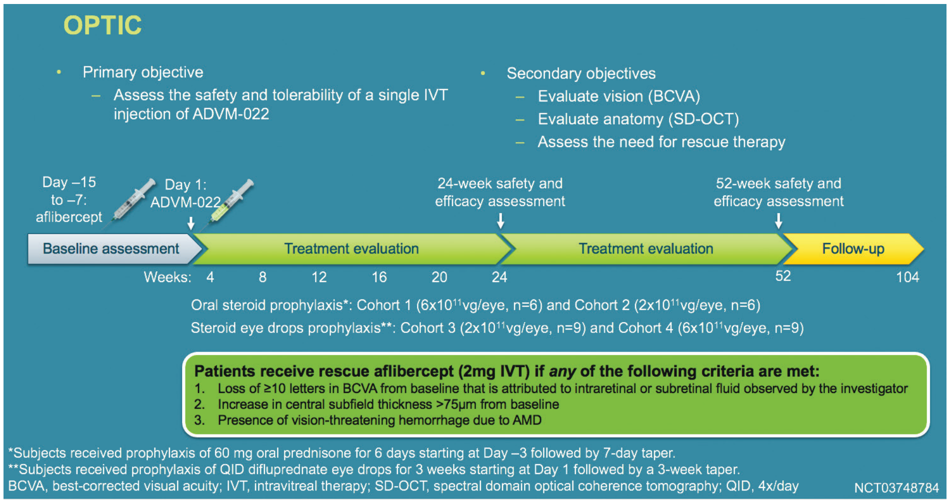

Figure 5. OPTIC is a phase 1, 2-year, multicenter, open-label study of ADVM-022 in nAMD.

was taken by Adverum to dose down. The question was, are there any other safety issues that may have caused that down dosing? The answer was no. The inflammation was not a retinitis, choroiditis, or chorioretinitis. Those are the types of inflammatory events that keep us up at night, and those were not seen.

There is a difference in the retreatment criteria between OPTIC and the RGX-314 trial. However, even under the RGX-314 retreatment criteria, none of the patients in OPTIC would have required rescue injection. OPTIC is only a phase 1 trial with fewer patients and shorter follow-up compared to RGX-314, so we don't want too many conclusions, but the data thus far appears to be extremely promising.

DR. KHANANI: The anatomic response that we're seeing in these patients speaks for itself. We obviously need to address safety and inflammation. I know retina specialists talk a lot about the VA that was presented at week 24, minus 2 letters. Why is the vision down while we are seeing great efficacy in terms of anatomic outcomes?

DR. KISS: When we look at VA in a small phase 1 trial, we obviously don't want patients losing vision because of lack of control or some toxicity from the product being tested. I can say with confidence that at this point, after 8 months of follow-up, there are no signs of undertreatment and/or toxicity. I think a decrease in 2 medium letters is flat and means that patients are maintaining vision. The goal of this particular trial, as is with all sustained-delivery trials and treatment-naive patients, is to maintain vision and decrease the treatment burden.

DR. KHANANI: Dr. Ho, what are your thoughts on the OPTIC data overall and the inflammation seen?

DR. HO: Yes, the trial is small, with only six patients reporting, but there is a positive signal with respect to OCT anatomic changes and potential efficacy. Inflammation, patient safety, and vision loss are real issues. We've seen inflammation with nongene therapy products as well. We've seen that with all anti-VEGF therapies, both on-label and off-label. I believe the current mitigations make sense for OPTIC and I look forward to more efficacy and safety data.

DR. BOYER: I was fortunate enough to be involved in the clinical trial. The degree of inflammation was mild and was easily controlled with topical therapy. I did not observe any long-term negative effects. I was also not surprised by its presence.

DR. HOLEKAMP: The OPTIC data, although very early with a limited number of patients, is very encouraging. The in-office injection approach to delivering gene therapy is a major advance as long as the inflammatory sequelae can be managed. I am encouraged to learn that future cohorts of patients will not receive oral steroids, only topical steroids. I am also encouraged to learn that the inflammation was mild-to-moderate and responsive to local therapy in all patients. Moving forward, these are all favorable developments.

MOVING GENE THERAPY FROM THE BENCH INTO PRACTICE

Q | DR. KHANANI: Is gene therapy real? Do you think we'll be able to help our patients with this approach?

DR. BOYER: I think that gene therapy for wAMD will become a reality mainly because the levels of VEGF necessary to control the disease are low, and I believe that adequate levels of drug will be able to be transfected. This treatment probably will be very effective for the long-term treatment of proliferative diabetic disease, as the amount of anti-VEGF needed to control the proliferative disease is very low. For retinal vascular occlusion or DME, we may need more anti-VEGF than currently can be transfected.

DR. HOLEKAMP: I remain positive about gene therapy for AMD. The real watershed moment in this scientific area came from the gene therapy for RPE65, which is an inherited retinal degeneration.[50] It was proof of concept for treating retinal disease with gene therapy. Although that breakthrough was in the IRD space, I think the technology and "know how" has the potential to be readily translated to AMD.

Of course, everything boils down to science. As Dr. Kiss discussed, the challenges are getting the payload where it needs to be and having sufficient cells to produce the desired molecule to combat AMD, whether it's an analog of ranibizumab, aflibercept, or some other anti-VEGF agent. Right now, we find ourselves in an exciting period where we have early clinical trial information for both RGX-314 and ADVM-022 that look promising. But we must maintain healthy skepticism about extended durability and we must retain a sharp eye for safety, which will only come with long-term data from larger clinical trials. That said, I'm very excited about the current momentum and the work that's being done in this field.

DR. KHANANI: I agree. The efficacy we are seeing from both treatment programs seems to be real. It's early, but hopefully we can continue to progress and establish long-term efficacy and safety.

DR. KISS: I think we're seeing a paradigm shift in gene therapy. With RGX-314 and ADVM-022, gene therapy is a platform for drug delivery. It's not a therapy to fix an inborn error. Ophthalmology, and retina in particular, is leading the way in this revolution. The phase 1 trials from RegenxBio and Adverum look extremely promising. We are shifting the paradigm of drug delivery away from repeated injections, away from hardware in the eye, to actually turning the eyes into bio-factories to produce the anti-VEGF medications and control nAMD activity. I look forward to longer follow-up with more patients, not only in nAMD but also in diabetic eye disease, DME, and DR.

DR. HO: The first-generation gene-therapy trials that came before these allowed us to refine our approaches with viral vectors, transgene selection, and delivery. There are still many questions to answer, but it's exciting regardless. We owe a huge debt of gratitude to the persistence, intelligence, and scientific expertise of Jean Bennett, MD, PhD, and Albert M. Maguire, MD. Gene therapy was shelved in 1999 after a patient died because of gene therapy for a systemic liver problem.[2] Now, 20 years later, gene therapy has risen from the ashes to treat nAMD and maybe even DR in the future. I am excited for the future of gene therapy for these common and important retinal conditions.

DR. KHANANI: This is an exciting time for us as physicians. We have multiple options, whether it's intravitreal, suprachoroidal, or subretinal gene therapy. We'll see where the efficacy and safety of all these approaches lead us. The paradigm is shifting. Thank you all for your time and insights into the future of gene therapy for retinal diseases. ■

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GENE THERAPY: AN EMERGING FRONTIER IN THE TREATMENT OF NEOVASCULAR DISEASES

Release Date: March 2020
Expiration Date: March 2021

INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please visit https://evolvemeded.com/online-courses/1932-supplement. If you are experiencing problems with the online test, please email us at info@evolvemeded.com. Certificates are issued electronically; please be certain to provide your email address below.

Please type or print clearly, or we will be unable to issue your certificate.

Name _______________________________ ❏ MD/DO participant ❏ OD ❏ non-MD participant

Phone (required) ______________ ❏ Email (required) ______________________________

Address ____

City ______________________________ State ________ Zip ______________

License Number ______________________________

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DEMOGRAPHIC INFORMATION

Profession
- ___ MD/DO
- ___ OD
- ___ NP
- ___ Nurse/APN
- ___ PA
- ___ Other

Years in Practice
- ___ > 20
- ___ 11-20
- ___ 6-10
- ___ 1-5
- ___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
- ___ 0
- ___ 1-15
- ___ 16-30
- ___ 31-50
- ___ 50+

Region
- ___ Northeast
- ___ Northwest
- ___ Midwest
- ___ Southeast
- ___ Southwest

Setting
- ___ Solo Practice
- ___ Community Hospital
- ___ Government or VA
- ___ Group Practice
- ___ Other
- ___ I do not actively practice

Models of Care
- ___ Fee for Service
- ___ ACO
- ___ Patient-Centered Medical Home
- ___ Capitation
- ___ Bundled Payments
- ___ Other

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Describe the current treatment options for neovascular age-related macular degeneration (AMD).	_____	_____	_____
Identify the unmet needs with the currently available AMD treatments.	_____	_____	_____
Categorize and critique based on early clinical trial data the surgical and nonsurgical sustained-delivery AMD treatment options currently under investigation.	_____	_____	_____
Categorize and critique based on early clinical trial data the various types of gene therapy currently under investigation for the treatment of neovascular AMD.	_____	_____	_____
Interpret the available literature and compare a subretinal surgical delivery with an intravitreal approach.	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to apply updates in gene therapy for the treatment of age-related macular disease (AMD) in the clinic (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Based on this activity, please rate how often you intend to apply updates in gene therapy for the treatment of AMD to "real-world" patient management (based on a scale of 1 to 5, with 1 being never and 5 being always).

a. 1
b. 2
c. 3
d. 4
e. 5

3. What is the biggest unmet need in the treatment of AMD?

a. Agents with different mechanisms of action
b. Treatment burden
c. Drug durability
d. Remote monitoring of fluid levels

4. The first-generation gene therapy trials in retina failed because ________

a. Efficacy was limited
b. A patient died
c. They resulted in serious inflammation
d. Delivery to the subretinal space was too great a barrier

5. How many rescue injections were needed in OPTIC cohort 1?

a. 0
b. 2
c. 4
d. 6

6. What percentage of patients in RGX-314 cohort 5 needed rescue injections?

a. 10%
b. 25%
c. 50%
d. 75%

7. What may be considered barriers to the adoption of gene therapies in clinic? Select all that apply.

a. Age and comorbidities of AMD patients
b. Limited widespread use of intraoperative OCT
c. Inflammation
d. Subretinal surgery

8. What are the potential complications from RGX-314? Select all that apply.

a. Endophthalmitis
b. Retinitis
c. Peripheral retinal break
d. Chorioretinitis

9. Patients in ADVM-022 cohort 1 experienced all but which of the following safety issues:

a. Floaters
b. Choroiditis
c. Blurry vision
d. Vision loss

10. Neutralizing antibody exposure and cellular immunity is not as significant _______________

a. When gene therapy is delivered intravitreally.
b. When limited areas of transfection are recognized.
c. As shown in preclinical, non-human primate models that found subretinal delivery results in the highest immune response.
d. When gene therapy is delivered with subretinal delivery.

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low ___________
Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low ___________
This activity improved my competence in managing patients with this disease/condition/symptom. ____ Yes ____ No
Probability of changing practice behavior based on this activity: _____ High _____ Low ____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy ____
Change in diagnostic testing _____
Change in current practice for referral _____
My practice has been reinforced ______
Change in nonpharmaceutical therapy ____
Choice of treatment/management approach ____
Change in differential diagnosis ______
I do not plan to implement any new changes in practice ___

Please identify any barriers to change (check all that apply):

____ Cost
____ Lack of consensus or professional guidelines
____ Lack of administrative support
____ Lack of experience
____ Lack of time to assess/counsel patients
____ Lack of opportunity (patients)
____ Reimbursement/insurance issues
____ Lack of resources (equipment)
____ Patient compliance issues
____ No barriers

Other. Please specify: ______________________
____
____
____

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

____ Patient Care
____ Practice-Based Learning and Improvement
____ Professionalism
____ Medical Knowledge
____ Interpersonal and Communication Skills
____ System-Based Practice

Additional comments:

____

____ I certify that I have participated in this entire activity.

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

____