Allen C. Ho, MD: Gene therapy has gone from science fiction to science fact. Although many retina specialists don’t use gene therapy right now, there is an approved therapy, Spark Therapeutics’ voretigene neparvovec (Luxturna), for Leber congenital amaurosis biallelic RPE65 mutation.

Gene therapy has evolved from gene replacement for an inherited retinal degeneration to gene therapy to create a potential ocular biofactory for more common retinal conditions—for example, anti-VEGF therapy for AMD or diabetic retinopathy. We have significant history here and failed trials. For example, Avalanche for exudative AMD did not work, but there are multiple learnings from Avalanche and other first-generation gene therapy trials that have improved our next-generation clinical trials.

DR. HO: WHERE ARE WE TODAY WITH NEXT-GENERATION CLINICAL TRIALS AND THERAPIES?

Charles Wykoff, MD, PhD: There are currently two therapeutics in human clinical trials evaluating treatment for exudative retinal diseases. They work by establishing an intraocular biofactory that produces an anti-VEGF protein. ADVM-022 (Averum Biotechnologies) produces aflibercept following an intravitreal injection, and RGX-314 (Regenxbio) produces ranibizumab following either subretinal or suprachoroidal delivery.

Both gene therapies are being actively studied in wet AMD, and studies have enrolled patients who are anti-VEGF responsive and have, on average, received years of repeated intravitreal anti-VEGF injections prior to gene therapy treatment. ADVM-022 is in a phase 1 trial involving 30 patients, and RGX-314 is in a phase 1/2a trial involving 42 patients.

So far, we’ve seen strong efficacy signals in both of these programs and identified important safety signals, some of which were unexpected. Both programs appear to be moving forward in wet AMD, and both are investigating other exudative retinal diseases including diabetic retinopathy and diabetic macular edema (DME).

DR. HO: WHY DO THESE TRIALS SEEM TO BE DOING BETTER THAN THE FIRST-GENERATION TRIALS FOR WET AMD?

Jeffrey S. Heier, MD: We’ve learned a lot from the earlier trials. They initially looked at gene therapy in terms of the product loads. We saw certain levels of efficacy and issues such as lower expression and less-than-ideal delivery. For instance, Genzyme had a study that looked at a soluble sFLT1 with an AAV2 vector, and we didn’t get the level of efficacy that we wanted. In addition, Avalanche didn’t have quite the desired efficacy, likely due to issues with the delivery method.

We’ve taken the lessons from each of those and developed better vectors and standardized approaches to gene therapy delivery. That has enabled us to achieve greater efficacy and improved delivery of the gene therapy product.
**PIECING TOGETHER THE AMD PUZZLE**

**DR. HO: AAV2 IS THE FDA APPROVED VIRAL VECTOR FOR SUBRETINAL DELIVERY OF VORETIGENE NEPARVOVEC. WHAT DO WE KNOW ABOUT AAV2 AND ITS TRANSECTON AND TRANSDUCTION EFFICIENCY?**

Peter Campochiaro, MD, PhD: Viruses are good at getting into cells and getting into the nucleus. The viral capsid binds to certain molecules to enter a cell, and different serotypes of AAV bind to different molecules on the surface.

AAV2 binds to heparan-sulfate proteoglycan, which is abundant in the subretinal space. As a result, AAV2 injected into the subretinal space easily enters photoreceptors and retinal pigmented epithelium cells. But when you inject AAV2 into the suprachoroidal space, there’s as much heparan-sulfate proteoglycan on the basal surface of retinal pigmented epithelium cells compared with the apical surface, and it doesn’t enter very well. In the vitreous cavity, the problem is the internal limiting membrane; AAV2 binds to it, which prevents AAV2 from easily entering the retina to transduce cells.

**DR. HO: WHAT IS THE CURRENT STATUS OF ADVERUM’S PROGRAM?**

Szilárd Kiss, MD: Viral vectors currently being used in patients come in two broad forms. There are the naturally occurring vectors, either human serotypes such as AAV2, AAV8, and AAV9 or primate serotypes such as rhesus isolate 10. Then there are vectors that do not occur in nature but have been engineered for specific routes of administration or cellular tropism.

Adverum has overcome the challenges of retinal transduction posed by intravitreal injections with a novel vector, AAV7m8. This vector was engineered from AAV2 through directed evolution specifically for its ability for retinal transduction following intravitreal injection. Insertion of a peptide sequence in the viral capsid of AAV2 changes the binding properties of the vector, allowing intravitreal delivery.

Adverum’s OPTIC and INFINITY programs use the vector construct ADVM-022, which uses AAV7m8 with a transgene encoding aflibercept. The concept here is to allow AAV7m8 to be administered via an in-office intravitreal injection to transduce the retinal cells to make sufficient quantities of aflibercept to control disease activity in patients with VEGF-mediated retinal disorders such as wet AMD and DME.

The OPTIC trial enrolled wet AMD patients in four cohorts at two vector doses. These patients required frequent anti-VEGF injections to maintain visual acuity and control disease activity. Recent top-line data from OPTIC indicate that ADVM-022 provides durable and sustained efficacy at both doses. Patients maintained or gained vision and had stable or improved retinal anatomy seen on OCT. In patients who consented to anterior chamber taps, aflibercept protein expression was within the targeted therapeutic range and was stable out to 104 weeks following a single ADVM-022 injection.

Following ADVM-022 injection, there was an 85% to 96% reduction in annualized injection frequency. Following ADVM-022 injection, there was an 85% to 96% reduction in annualized injection frequency.

**AT A GLANCE**

- Regenxbio’s phase 1/2a trial for RGX-314 has up to 3 years of data for patients in cohort 3 with sustained visual gain and stable anatomy over time and sustained protein results at 2 years. At 1.5 years after RGX-314 treatment, patients in cohort 4 saw stable vision and improved anatomy with a 58.3% reduction in anti-VEGF treatment burden; patients in cohort 5 saw a reduction of 81.2%.

- Long-term data from Adverum’s OPTIC clinical trial for ADVM-022 showed durable expression of aflibercept following a single intravitreal injection of ADVM-022 for both doses; at 1 year, 60% of patients were injection-free following treatment with the low dose with an 85% reduction in annualized injection frequency.

- In the 12 to 48 weeks after administration of GT005 (Gyroscope) in the phase 1/2 open-label FOCUS trial, nine of 10 patients treated with GT005 had increases in vitreous complement factor I levels, with an average increase of 146% compared with baseline.

Patients in OPTIC did require steroid treatment to control what appeared to be dose-dependent intraocular inflammation following administration. Patients in the low dose cohort responded well to a topical steroid regimen, whereas the higher dose patients required longer duration therapy.

Adverum’s other ongoing clinical trial, INFINITY, enrolled patients with visually significant DME, and the company recently announced the occurrence of a suspected unexpected serious adverse reaction (SUSAR) 30 weeks after a patient received the high dose. Other than vision loss and hypotony, the specifics surrounding this SUSAR are still being evaluated. Fortunately, it does not appear that any patients enrolled in OPTIC experienced similar adverse events. Nonetheless, the occurrence of just one such event should make us take pause to ensure the safety of all clinical trial patients.

**DR. HO: WHAT ARE THE HIGHLIGHTS OF THE REGENXBIO PROGRAM?**

Robert L. Avery, MD: Regenxbio evaluated five dosing cohorts of RGX-314, all without significant inflammation. In the three highest dose cohorts, there was a significant reduction in anti-VEGF treatment burden, with reduction by more than 80% in cohort 5. Cohort 3 has 3 years of follow up, and there is retinal stability with a mean increase of 12 letters of Vision改善了。
visual acuity. Aqueous taps demonstrated a dose-dependent expression of ranibizumab-like protein levels across all cohorts at 1 year, with stability out to 2 years in cohort 3. One significant side effect noted was pigmentary changes in the inferior periphery, mostly in the higher doses.

Subretinal injection offers both advantages and disadvantages. Although you have to take the patient to the OR, the subretinal space is more immune-privileged, and we haven’t seen any significant inflammation thus far. The disadvantage is the need to perform vitrectomy, but suprachoroidal delivery is being evaluated and could obviate this need if it is efficacious. This would be beneficial not only for the elderly patient who doesn’t want to have an operation, but also for young diabetic patients who, were they to have surgery, might develop cataracts earlier in life.

**DR. HO: HAVE WE SEEN RETINAL VASCULITIS OR INFLAMMATION IN THE ADVERUM PROGRAM?**

**Dr. Kiss:** A limited anterior and vitreous inflammatory response has been noted with ADVM-022 administration. From the available data, this seems to be dose-dependent, with the higher vector doses leading to a more prolonged inflammation that requires more steroid and a longer duration of treatment. I am not aware of any instances of retinal vasculitis, retinal vascular occlusion, or retinitis/choroiditis in any of the patients treated with ADVM-022. The major caveat, of course, is that we don’t have the full analysis of the recently reported SUSAR in one patient in the INFINITY trial.

**DR. HO: IF A GENE THERAPY WERE TO BECOME AVAILABLE, WHERE DO YOU THINK THIS WOULD FIT IN YOUR PATIENT POPULATION?**

**Dr. Wykoff:** The more tools in our toolbox, the better. We’re moving in a direction where individualized therapy is going to become more important than ever as the number of approved pharmaceuticals and devices increases.

In the context of gene therapy for wet AMD, we are still looking at early stage data for both ADVM-022 and RGX-314. Long-term efficacy and safety outcomes will be critical. The broader field of medical science has been överpromising gene therapies for too long. I’m a little hesitant to do that now. These are complicated therapies, and the way they are changing the intraocular environment is still incompletely understood. We’re looking at promising phase 1/2a data, and we have a tremendous amount still to learn before the commercialization of gene therapy for wet AMD.

**DR. HO: WHAT IS THE LATEST STRATEGY TO IMPROVE GENE THERAPY DELIVERY TO THE SUBRETINAL SPACE WITHOUT A RETINOTOMY?**

**Dr. Heier:** For this technique, a scleral incision allows entry to the suprachoroidal space. A thin, well-designed, flexible cannula is guided posteriorly until it gets close to the arcades. When it is in the desired position, a curved needle enters the subretinal space and the gene therapy product is injected without exposure to the intraocular space. This took several years to design and to make it safe and reproducible. The elegance of this approach is that you don’t enter the intraocular cavity. You’re not running the risk of inducing cataracts, you’re not allowing the therapy into the vitreous cavity to cause untoward effects, and you’re delivering into the space that you believe will allow the best expression.

Again, the more weapons we have in our arsenal—the more delivery methods we have—the greater the likelihood of achieving success in the long run.

**DR. HO: I’VE TOLD MY PATIENTS, “I HAVE NO WEAPON TO FIX AGING IN YOUR EYE. EVEN IF YOU HAVE WET MACULAR DEGENERATION, I MIGHT BE ABLE TO CONTROL THE LEAKAGE, BUT NOT THE ATROPHY.” NOW WE HAVE A GENE THERAPY THAT’S EXPLORING THIS. WHAT ARE YOUR INSIGHTS ON THIS?**

**Dr. Wykoff:** It makes a lot of sense to use gene therapy to manage geographic atrophy (GA), and I can see this eventually being more clinically applicable than gene therapy for wet AMD. Anti-VEGF pharmacotherapies have changed the epidemiology of blindness in many countries, and GA has emerged as a tremendous unmet need.

The Gyroscope approach is to deliver a vector designed to overexpress complement factor I, which is a natural downregulator of complement activity. The team is using a unique subretinal delivery approach via the suprachoroidal space. The goal in this case is not to completely shut down the complement cascade by inhibiting C3 or C5, which are both being studied in global phase 3 programs; rather, the goal is to limit overactivation of the complement cascade while allowing some natural physiologic activity. It’s an elegant, targeted approach in early stage clinical trials, whose future likely partially depends on the results of the ongoing phase 3 trials studying C3 and C5 inhibition; if those do not work, it seems unlikely that upregulation of complement factor I would work to slow GA progression.

**DR. HO: IT’S INTERESTING THAT APELLIS AND IVERIC ARE SHOWING AN INCREASED RISK OF CHOROIDAL NEOVASCULARIZATION AS A POTENTIAL SIDE EFFECT OF TREATMENT. IT TELLS ME THAT SOMETHING MAY BE WORKING. IS THAT TRUE?**

**Dr. Campochiaro:** It suggests that choroidal neovascularization may be adaptive. There’s dropout of the choriocapillaris that causes ischemia of the outer retina. If severe, that results in GA. If less severe, you get hypoxia of the outer retina, which stimulates increased VEGF and choroidal neovascularization. In these programs where you’re inhibiting or slowing GA, you may be allowing that tissue to be less ischemic. As a result, you get more upregulation of VEGF and more choroidal neovascularization.

In addition, in patients who are treated with anti-VEGF agents, those who develop macular atrophy frequently develop it in areas where choroidal neovascularization has regressed. This suggests that choroidal neovascularization was...
providing some benefit to that tissue. We should keep an open mind about that. I would be fine trading a treatable component of the disease for a previously untreated component.

**DR. HO: HOW IS THE SYSTEM GOING TO PAY FOR THIS?**

**Dr. Avery:** We don’t know for sure. Currently approved gene therapies are very expensive but are for rare conditions. For common diseases, the price will have to be less. Billions are spent on anti-VEGF agents each year, and some justification for pricing could come from a reduction in these costs. A reduction in patient visits and overall treatment burden would be attractive, as would less concern about compliance. Theoretically, constant delivery could yield better outcomes, but this remains to be seen. Regardless, whether this becomes cost-effective compared with injections depends upon pricing, which will likely be contentious. But these therapies could potentially provide a huge benefit for patients.

**Dr. Ho:** The demand for improved therapies for common diseases such as AMD and diabetic retinopathy is infusing resources into our retina clinical ecosystem. We have companies such as Adverum, Regenxbio, and Gyroscope, among others, but also major pharmaceutical companies that are just beginning to look at the major retinal diseases. AbbVie/Allergan, Roche/Genentech/Spark, and Johnson & Johnson/Janssen, to name a few, have entered the arena, so we will have even greater opportunity to innovate and improve treatments for patients. Vision matters, and we have demographic trends such as an aging population and a global diabetes pandemic driving the need for better treatments. Many gene therapy industry leaders are not focused only on the science; they believe the science will work. They’re challenged by the reimbursement and payment structure. There are hurdles in science, clinical trials, potential commercial execution, and in rewarding those who bring these to market—but ultimately the patients tell us that these therapies are very important because vision is so integral to quality of life.

**DR. HO: ANY SUMMARY THOUGHTS FOR OUR READERS?**

**Dr. Heier:** If ever there was a role for gene therapy, it would be for dry AMD. We treat wet AMD, but many of us recognize that the treatment burden leads to undertreatment. Fortunately, we have biomarkers (i.e., OCT and retinal fluid) that can guide us, hopefully minimizing the extent of undertreatment. There is no possibility for doing that in dry AMD. If the study says you have to treat monthly, you have to treat monthly forever. So gene therapy could be ideal for the long-term treatment of dry AMD.

**Dr. Kiss:** We’ve entered a new realm of gene therapy as a drug delivery platform. We are not taking an abnormal gene and trying to fix it; we’re using gene therapy as a therapeutic platform to deliver drugs to the eye.

It’s exciting, but it’s early. The Regenxbio and Adverum programs are now entering pivotal trials, which might be the first time that has happened for gene therapy as a drug delivery platform in any field of medicine.

**Dr. Campochiaro:** In trials testing gene therapy for wet AMD, we’re learning things that are going to help in other areas. For instance, most of the gene therapies in the eye are with transgenes that aren’t soluble, so it’s difficult to know how much transgene is being expressed and for how long. With Leber congenital amaurosis, we must rely on how a patient responds with regard to mobility and measures of visual function to assess whether expression is occurring. But with these wet AMD programs we can measure the transgene. We’re learning for the first time if this going to be a one and done treatment or if efficacy is going to wane.

**Dr. Wykoff:** It is worth noting that, as far as I know, there have been no nonocular adverse events attributable to these ocular gene therapies, which is important. From a systemic perspective, there are no concerning signals so far, which is very encouraging.

**Dr. Avery:** The eye is an excellent organ for advancing gene therapy. It’s a self-contained organ with a nice window through it, allowing our great tools to evaluate it. We’ve had a lion’s share of advances, and I think we’ll continue to see more because the eye is such a good model for developing gene therapy.

**Dr. Ho:** It’s a real privilege to have these partners, colleagues, and friends on this journey. Our goal here has been to provide an overview of why and how gene therapies may become relevant tools. Sometimes this road has unexpected turns and hazards, but early data from phase 1/2 programs are showing promise. We must continue to do the work of evolving viral vectors, understanding immune responses, improving delivery methods, and more. Because vision is so highly valued in quality of life evaluations, improved therapies for common conditions such as AMD and diabetic retinopathy will find their place in our toolbox. For those of you who aren’t up to date on gene therapy, we hope this discussion has piqued your interest to look for papers, presentations, and podcasts on this topic. Stay on course, as the story will continue to unfold.

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