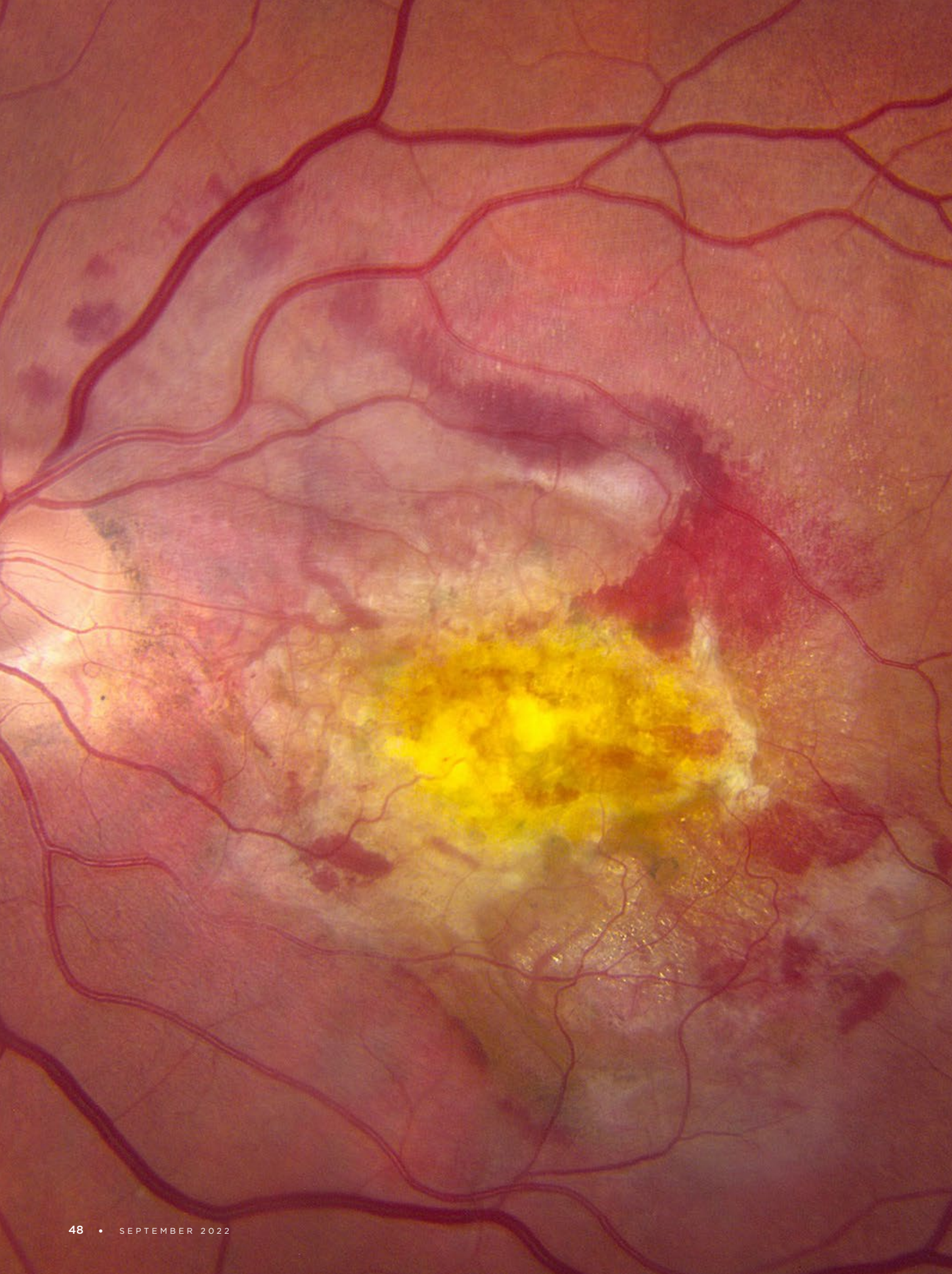


Gene Therapy for AMD

By Rebecca Taylor, Contributing Writer

Researchers are coaxing the eye to become a biofactory to make its own anti-VEGF medications. An overview of the leading AAV-based contenders.

A NEW GENERATION of gene therapies is poised to reshape the treatment of age-related macular degeneration (AMD). Instead of replacing a faulty protein, as with other approaches, these therapies prompt the eye to make a novel therapeutic protein. In essence, they teach the eye to make its own anti-VEGF drugs.

Moreover, for neovascular AMD, this approach raises the potential that a single injection will protect patients for a lifetime.[1] This new way of delivering medication truly is revolutionary, said Szilárd Kiss, MD, at Weill Cornell Medical College in New York City. "You may not have to inject therapeutics every month; you can have cells within the eye make it. No other field in medicine has been able to do this."

Two contenders in pivotal human trials—the nonintegrating vectors RGX-314 (Regenxbio) and ADVM-022 (Adverum Biotechnologies)—are showing promise for wet AMD, while a third, GT-005 (Gyroscope Therapeutics), is emerging as a candidate for dry AMD (see "What About Dry AMD?"). Research with all three is continuing to build on lessons learned from the first gene therapy trial in 1990,[2] with the goal of improving delivery methods and outcomes.

An Inside Look

In gene therapy, a viral vector acts as the envelope that carries an encoded genetic message, often based on an AAV (adeno-associated virus) vector.

Nonintegrating vectors. Gene therapy researchers have always had to field questions about the potential of changes to a host cell's DNA. But "the subtypes of AAV vectors being used in these [RGX-314 and ADVM-022] programs are nonintegrating, so the genetic material they inject into the target cell doesn't affect the native cellular DNA," said Dr. Kiss.

Enhancers, promoters, and ITRs. Dr. Kiss, who helped design both RGX-314 and ADVM-022, explained the building blocks of these therapies. "The vector itself is like the carrier pigeon for the protein-coding genetic sequence," he said. Equally critical are the promoters, enhancers, and what are called ITRs, or internal terminal repeats. The latter are "sequences that allow the genetic material to hijack the cellular machinery of the target cell that's being transduced to make the protein of choice," Dr. Kiss said.

The vector, aka the capsid, is the shell of a virus with everything stripped out. It binds to receptors on the target cell and then injects its genetic payload, Dr. Kiss said. "With RGX-314 and ADVM-022, that genetic material is coding DNA, called cDNA, which reads like a book. The first and last chapters are the ITRs, which allow the cell to read the book. The second and third chapters are the 'enhancers' and 'promoters,' which rev up the engine of the cell that's being targeted," he said. "The remaining chapters are the transgene, the protein itself, that you are trying to make." In the case of RGX-314 and ADVM-022, these are anti-VEGF proteins.

RGX-314 for Wet AMD

This gene therapy candidate uses AAV8 to deliver genetic code that expresses a protein similar to ranibizumab.[2]

Jason S. Calhoun, COA

AAVIATE trial: key takeaways. The ongoing phase 1/2a AAVIATE trial has found RGX-314 to be generally well tolerated in patients previously responsive to anti-VEGF medications.[2]

With subretinal delivery, "Regenxbio has shown that it can achieve reasonably good efficacy [and safety] and decrease the number of injections significantly from standard treatment," said Jeffrey S. Heier, MD, at Ophthalmic Consultants of Boston.

The AAVVIATE study started with five cohorts at progressive dosing, with cohort 5 receiving the highest dose.[3] "The amount of anti-VEGF protein [produced within the eye] increased in a dose-responsive fashion," said Robert L. Avery, MD, at California Retina Consultants in Santa Barbara.

Dr. Avery noted that in cohorts 3, 4, and 5, there seemed to be enough protein produced to reduce the treatment burden, with cohort 5 demonstrating about an 85% reduction in treatment burden in year 1 and a 79% reduction in year 2. With regard to VA outcomes, in long-term follow-up of those in cohort 3, RGX-314 also resulted in a mean VA improvement of 14 letters at year 2 and 12 letters at year 3, he said.

The trial found some pigmentary changes in the far inferior periphery with the higher doses, said Dr. Avery. "This was possibly due to inferior migration of the bleb where we injected the gene therapy, as patients sat up after the procedure," he said. "With inferiorly placed blebs and patient positioning postoperatively, we expect to keep these pigment changes far from the macula."

Delivery methods. Researchers continue to focus on delivery methods that limit inflammation from the gene therapy product itself. "We can now give it subretinally or suprachoroidally and limit the inflammatory response, [as well as] limiting systemic blood concentrations," said Gregg T. Kokame, MD, at the University of Hawaii in Honolulu.

Suprachoroidal approach. RGX-314 can be given via an in-office injection that delivers the product behind the retina into the suprachoroidal space. "The suprachoroidal approach is more investigative right now," said Dr. Kokame, "but it's promising because if it works, we avoid the risks of surgical complications from vitrectomy."

"Initial impressions from the first few cohorts appear to indicate that suprachoroidal delivery of RGX-314 is relatively safe and well tolerated," said Dr. Kiss. But because this approach is still in its infancy, more patients with longer term follow-up will be needed to determine its ultimate viability, he added.

Subretinal approach. When RGX-314 is delivered via standard surgical vitrectomy, "We take out the vitreous gel and raise a bleb by injecting the gene product in saline underneath the retina, peripheral to the central retina," said Dr. Avery. "We're taking over cells, transducing them to make a diffusible anti-VEGF agent, with protein production starting within a few weeks from the procedure."

"Transduced" cells are native cells that are overwritten by a new genetic code. The delivery of RGX-314 directly into the subretinal space transduces retinal pigment epithelial and retinal cells, prompting them to produce their own anti-VEGF protein, "right where the choroidal neovascularization is located," said Dr. Kokame. This surgical approach is similar to the approach used with Luxturna (Novartis), the FDA-approved gene therapy for inherited retinal disease, he said.

Considerations. "The principal benefit to the suprachoroidal approach is that you don't have to take someone to the OR, while the main drawback is that it's not yet a proven method of delivering gene therapy," said Dr. Kiss. And although the preclinical and early patient data look promising, long-term safety and efficacy data are limited, he emphasized.

As for the subretinal approach, one of its benefits is that "with vitrectomy and subretinal injection, we see almost no inflammation and minimal side effects," said Dr. Kokame. He confirmed the finding of potential pigmentary changes: "It can cause a little pigmentary change where we inject the vector, which we've minimized by only injecting inferiorly, so the subretinal material doesn't migrate into the macula."

So far, durability appears promising: RGX-314 has been shown to produce the desired therapeutic protein more than two years after injection, said Dr. Kokame, and "central foveal thickness remained stable, even up to two years after the initial surgery."

A phase 3 study, which will compare RGX-314 to the standard of care with ranibizumab, is currently enrolling, said Dr. Avery.

ADVM-022 for Wet AMD

OPTIC is the first human trial of ADVM-022, which encodes for an aflibercept-like molecule using a novel engineered capsid called AAV.7m8. The vector is delivered via an in-office intravitreal injection.[2]

OPTIC trial: key takeaways. The phase 1 OPTIC trial looked at safety, efficacy, and dose-finding for a single injection of ADVM-022.

"The OPTIC study demonstrated strong efficacy in many patients who were hard to treat [due to] persistent fluid or recurrent fluid any time we deviated from a certain regimen," said Dr. Heier. He added, "ADVM-022 was highly effective at getting

rid of the fluid with a durable response, though the concern is the ability to control inflammation."

The efficacy shown by the OPTIC trial "is impressive," Dr. Kiss agreed, "with a majority of patients not needing rescue for two-plus years after injection, after [previously] needing injections every month for years."

Dr. Kiss added that "ADVM-022 was generally well tolerated, and topical steroids worked well to control inflammation, especially in the lower dose cohort." With regard to safety, he noted that "the safety events noted in the diabetic [macular edema] trial of ADVM-022 were not seen in the AMD population." (Adverum paused its INFINITY trial of ADVM-022 for diabetic macular edema after finding hypotony and severe inflammation.[2])

Patients in the four OPTIC cohorts were evaluated at two different doses and steroid regimens. All told, 78% had mild adverse events while 22% had moderate adverse events, typically inflammation. Early data showed BCVA changes of –2.5 to +0.2 letters, with more than 80% of participants free from additional anti-VEGF injections

What About Dry AMD?

The early trials of gene therapy for wet AMD have set the stage for new treatments for the dry version of the disease, said Dr. Kiss.

One leading contender, GT-005, uses the adeno-associated virus vector AAV2 to encode for a protein that downregulates the complement cascade believed to contribute to dry AMD.[1] "We're in the midst of potentially exciting times for dry AMD," said Allen C. Ho, MD, at Wills Eye Hospital in Philadelphia. "Complement factor I [CFI] is a natural brake in the complement system that targets the C3 amplification loop that leads to progressive atrophy, and GT-005 encodes for CFI."

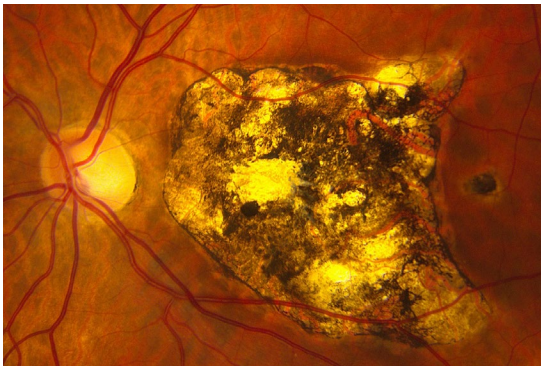
Dr. Ho added, "Multiple clinical trials are telling us that by modulating an immune system gone awry in the back of the eye—specifically within the choroid, retinal pigment epithelium, and at the level of the neurosensory macula—we can impact the growth of geographic atrophy [GA]."

FOCUS trial: key takeaways. Preliminary data from the phase 1 FOCUS trial indicate that GT-005 is safe, Dr. Ho said, "and months later, CFI is elevated compared to baseline." In addition, he said, there is evidence that C3 and its byproducts are reduced over time.[1]

"GT-005 has shown over a 100% increase in CFI," said Dr. Avery, "with a reduction in downstream products of complement activation—C3, C3b—which we think are activated in the complement attack that could induce GA."

Two phase 2 studies of GT-005 (EXPLORE and HORIZON) are currently recruiting patients. In addition, two other companies, Apellis and Iveric Bio, are researching complement inhibitors, Dr. Avery said, "so we may be doing a lot more injections for GA in the years to come."

Delivery method. GT-005 is administered via either subretinal injection or a newer, FDA-approved subretinal delivery system called the Orbit SDS (Gyroscope Therapeutics), which Dr. Ho helped develop. The first approach requires a vitrectomy with retinotomy, while the second entails a suprachoroidal-to-subretinal surgical approach.



Jason S. Calhoun, COA

Why the Orbit SDS was developed. After traditional vitrectomy with retinotomy and subretinal injection, researchers learned from cell therapy trials that "investigational-agent cells were escaping the retinotomy and creating membranes on the retina and even traction retinal detachments, so we needed a way to get to the subretinal space without creating a hole in the retina," Dr. Ho said.

Using the Orbit SDS involves starting with a sclerotomy; the surgeon then stabilizes a 3-mm flexible microcatheter inserted through the sclerotomy into the suprachoroidal space. "Under direct surgical visualization, you pass the microcatheter into the suprachoroidal space and along the curvature of the globe to the target area," Dr. Ho said. A retractable microneedle then delivers the gene therapy of choice.

This approach allows for precise, consistent dosing of the gene therapy without leakage through a hole in the retina, Dr. Ho said.

1 Khanani AM et al. *Eye*. 2022;36(2):303-311.

through 92 weeks of follow-up.[4]

Dr. Avery noted that the efficacy results included a "97% reduction in treatment burden in [those who received] the higher dose" of ADVM-022.

Considerations. The fact that ADVM-022 can be given via a standard intravitreal injection in the clinic is a benefit, Dr. Kokame noted.

With regard to side effects, "This is a vector engineered to penetrate through the internal limiting membrane and then into the subretinal space," said Dr. Kokame. "The most significant problem has been dose-dependent inflammation." Dr. Avery added, "The gene product diffuses in the vitreous to other parts of the eye, such as the ciliary epithelium. That might be part of why we see hypotony as a potential problem in the higher doses." To date, steroids appear effective in controlling most instances of dose-dependent intraocular inflammation.[4]

Looking Ahead: One and Done?

Might these new gene therapies really become a future "one and done" treatment for wet AMD, thus replacing a lifetime of injections?

"With gene therapy, we have a continuous release of medicine," said Dr. Kokame. "We cannot predict if it's going to last five, 10, or 15 years down the line—but at least up to three years, it can still produce the protein at the therapeutic levels needed. Some people will require additional therapy, but the reduction in frequency of injections is significant."

Dr. Heier noted that real-world outcomes with traditional anti-VEGF drugs rarely match those achieved in clinical trials, partly due to the treatment burden posed by frequent injections. "On average, patients receive far fewer injections in the real world than they get in studies; similarly, their visual gains are usually less" than those reported by investigators. Gene therapy may be able to overcome both gaps, he said.

The Race to the Clinic

When might ophthalmologists see gene therapy for AMD in the clinic? Phase 3 trials are already in planning or recruiting stages, said Dr. Kokame, and "if one of these studies shows similar results to the phase 1/2 trials, it could be approved and in physicians' offices in three to four years. Ophthalmology really is leading the entire field of medicine in terms of gene therapy."

"It's going to come down to the risk-benefit ratio, with the unknowns of efficacy and safety with the suprachoroidal approach versus the unknowns of safety management with the intravitreal approach," Dr. Kiss noted.

And Dr. Heier concluded, "If we can safely deliver a gene therapy product to the eye"—and that product proves to be efficacious and safe over the long term—"the potential benefits are huge. The [future] need for drug delivery cannot be overstated, and the ability to do it with gene therapy is an elegant solution."

1 Hussain RM et al. *Drug Des Devel Ther.* 2021;15:2653-2665.

2 Khanani AM et al. *Eye.* 2022;36(2):303-311.

3 https://clinicaltrials.gov/ct2/show/NCT03066258.

4 Busbee B et al. *Invest Ophthalmol Vis Sci.* 2021;62(8):352.

Meet the Experts

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