Gene Therapy Approach Demonstrated Safety With Durable Effect in Interim Wet AMD Trial Results

A dose-dependent increase in protein expression was noted in interim results, with lasting effect in higher doses.

BY JEFFREY S. HEIER, MD; ALLEN C. HO, MD; AND ROBERT L. AVERY, MD

There is no doubt that anti-VEGF therapy has revolutionized care for individuals with exudative age-related macular degeneration (AMD). Frequent intravitreal injections of an anti-VEGF agent can control edema and preserve vision for many patients with this potentially blinding disease. However, as we all know from real-world retina practice, a regimen of frequent injections places burdens on patients, practices, and health care systems, and over time adherence and efficacy suffer.[1]

In recent years, gene therapy has shown promise for the treatment of inherited retinal disorders, and the first US FDA approval of a gene therapy was granted for a treatment for Leber congenital amaurosis.[2]

Now, researchers have taken a novel tack with a different kind of genetic therapy for AMD. At this year's AAO Annual Meeting, interim data from an ongoing phase 1/2a clinical trial of that novel therapy, RGX-314 (RegenxBio) was presented.[3] This article recaps some of what we have learned so far about this new approach to treatment of wet-AMD.

THE PROMISE OF RGX-314

RGX-314 is an investigational one-time treatment for AMD and for diabetic retinopathy. This article concentrates only on investigation for AMD. RGX-314 consists of a novel adeno-associated viral vector carrying a gene that encodes for a monoclonal antibody fragment (fab). The protein expressed is designed to neutralize VEGF activity that leads to neovascularization.

Today, anti-VEGF therapy requires frequent injections of a fab that binds to VEGF and suppress its activity. The innovation of RGX-314 is that it is designed to insert a gene into

AT A GLANCE

- RGX-314 is a novel adeno-associated viral vector carrying a gene that encodes a monoclonal antibody fragment designed to neutralize VEGF.
- In a phase 1/2a study, patients who were given the highest concentrations of RGX-314 showed the highest rates of protein expression and efficacy.
- RGX-314 may one day be an option for patients who have demonstrated a need for frequent anti-VEGF therapy.

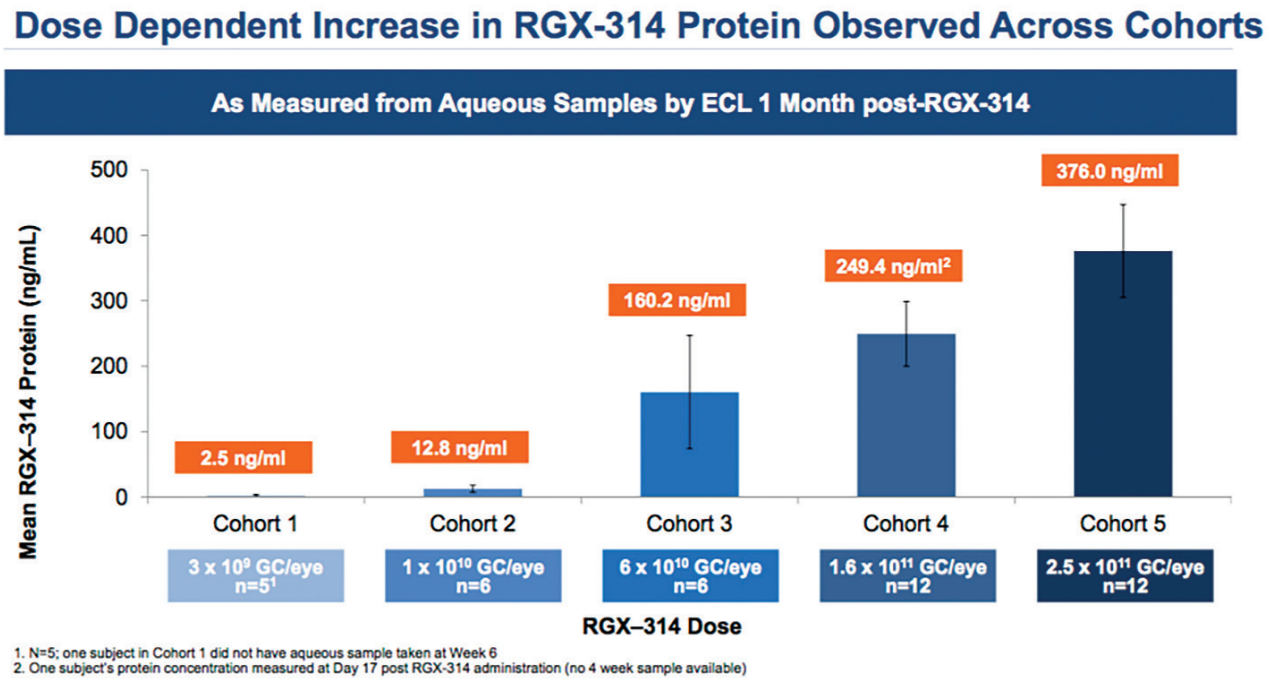

Figure credit: RegenxBio.

Figure 1. A dose-related increase in RGX-314 protein was noted in the phase 1/2a clinical trial, with patients in cohort 5 showing the highest protein expression.

retinal cells so that they can produce their own supply of anti-VEGF fab indefinitely, reducing or perhaps eliminating the need for intravitreal anti-VEGF injections.

The interim results of the phase 1/2a trial announced in October suggest that one-time administration of RGX-314 shows promise as a mechanism for sustained delivery of anti-VEGF fab protein in individuals with wet AMD.

INTERIM RESULTS

A phase 1/2a clinical trial has two goals. The first is to demonstrate the safety of the treatment, and the second is to look for signs of efficacy.

This trial was designed to include five cohorts receiving ascending doses of RGX-314, from 3 x 10^9 GC/eye in cohort 1 to 2.5 x 10^{11} GC/eye in cohort 5. Cohorts 1 to 3 included six patients each, and cohorts 4 and 5 included 12 patients each. At baseline, each patient received an anti-VEGF injection, with an OCT assessment 1 week later. If a positive anti-VEGF response was noted, RGX-314 was administered subretinally 1 week later. Patients were then examined every 4 weeks, with the safety endpoint at week 26 and secondary endpoints at the 2-year mark. Rescue anti-VEGF injection was permitted based on defined criteria.

Subretinal dosing has been completed in all 42 participants across the five cohorts, and at the time of the interim analysis there was 5- to 6-month follow-up for cohort 5, 6-month data for cohort 4, and 18-month data for cohorts 1 to 3.

The therapy was well-tolerated in all dose cohorts. No drug-related serious adverse events (SAEs) were seen in the trial. There were 15 SAEs in nine patients that were unrelated to treatment, including two deaths and two procedure-related SAEs.

Perhaps the most compelling finding of the interim analysis was that a dose-related increase in RGX-314 protein was noted across the cohorts (Figure 1). This showed that when we deliver more gene therapy, we get higher protein expression.

Likewise, as we look across the cohorts, we see what looks like an increase in efficacy. Patients in cohort 3 have continued to demonstrate good vision and anatomic outcomes over 1.5 years of follow-up. Those in cohort 4 have demonstrated a reduction in injection burden along with stable or improved anatomic and visual outcomes. And cohort 5 has shown the highest level of clinical response, with 75% of patients injection-free with stable to improved anatomic and visual outcomes.

NOT TREATMENT-NAÏVE

It is important to keep in mind that, unlike in registration trials for injected anti-VEGF therapies, participants in this trial have been previously treated with anti-VEGF agents. In fact, this is a group of patients who had demonstrated a high need for anti-VEGF therapy before enrollment, with many injections in some cases over a long history of treatment.

Cohort 5 illustrates trial patients' high need for anti-VEGF therapy. Some patients in that cohort received as many as 13 injections in the year before

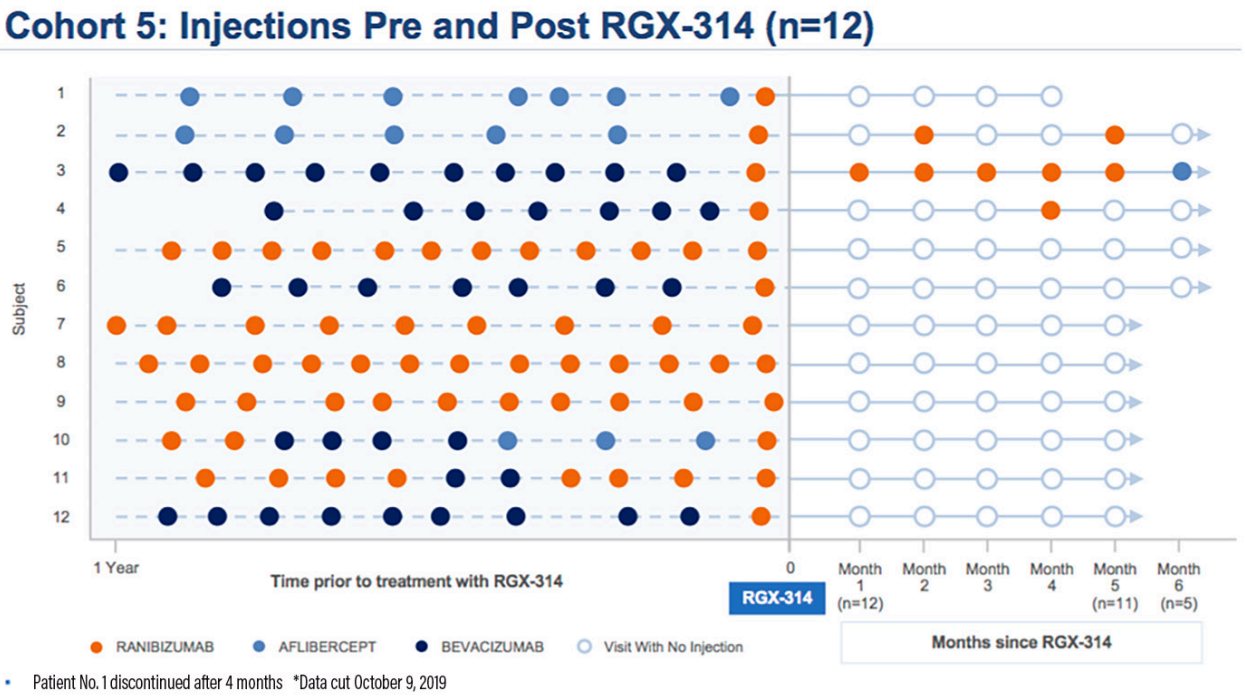

Figure credit: RegenxBio.

Figure 2. At 5 or 6 months after application of RGX-314, 75% of patients in cohort 5 did not require anti-VEGF therapy, and only one patient required monthly therapy.

enrollment; many of them switched anti-VEGF agents during that year.

At 5 or 6 months after RGX-314 treatment, 75% of patients (9 of 12) have required no rescue therapy (Figure 2); of the three patients who required rescue therapy, only one patient needed to continue monthly anti-VEGF injections.

NEXT STEPS

Delivery of RGX-314 in this trial required core vitrectomy to achieve subretinal placement. The gene therapy product was then administered subretinally using a subretinal PolyTip cannula (MedOne Surgical).

The designers of the trial made considerable effort to standardize the surgery to maximize delivery of therapy. We spent a great deal of time on understanding the dynamics of the automated delivery, standardizing the delivery so that all surgeons were approaching it in a similar manner, and making sure all the equipment used to deliver the gene therapy product subretinally had been thoroughly tested before being used in the clinical trial. Much of the success of the study is due to the work expended on planning ahead of time and standardizing procedures.

The safety profile of the surgeries performed in the trial was good. There was only one intraoperative complication, leading to a retinal detachment that was repaired with good outcome. Nonetheless, it would be desirable to move away from surgical delivery if possible. Therefore, investigators hope to use suprachoroidal delivery with the SCS Microinjector (Clearside Biomedical) in future trials and potentially in clinical use. If this mode of delivery is successful, it could allow in-office administration of this gene therapy product.

In the meantime, RGX-314 is moving into a phase 2b trial for wet AMD and a phase 2 clinical trial for diabetic retinopathy. Watch this space for future developments regarding this promising new approach to treatment of these potentially blinding retinal disorders. ■

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3. Heier J, Campochiaro P, Ho H, et al. Key takeaways from the RGX-314 phase I/IIa clinical trial for wet AMD (cohorts 1-5). Paper presented at: Retina Subspecialty Day, AAO 2019; November 11, 2019; San Francisco, CA.

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