NOTES FROM THE 47TH ANNUAL ARDS MEETING

Each year, the Aspen Retinal Detachment Society (ARDS) gathers in Snowmass, Colorado, for a 5-day conference unlike any other in retina. During the day, skiers shred the slopes and enjoy each other's company. Around 4 PM each day, when the ski jackets are exchanged for sweaters, the real fun begins. An all-star cast of speakers takes the stage for long-form lectures and panels. Meeting attendees ask questions, interrupt, and even challenge the speakers' assessments—all in the spirit of learning and camaraderie.

The conversations and presentations from the ARDS annual meeting are valuable to retina specialists at each point of their career. First-year fellows may gather one thing from a lecture, and an academic department chair may gather something else entirely. We strive to summarize the content from the meeting and put it in the pages of Retina Today *as a service our retina specialist community.*

In this issue, second-year retina fellow Nimesh A. Patel, MD, summarizes two major presentations. The first one, the ARDS Founders Lecture, was delivered by Allen C. Ho, MD, and it addresses the ever-changing world of gene therapy in retina. Like most ARDS lecturers, Dr. Ho placed his talk within the context of the continuum of a particular therapy—that is, he recognized that his lecture captured a moment in time of a story that has both a history and a future.

The second lecture Dr. Patel addresses was delivered by Mark W. Johnson, MD. Dr. Johnson describes the consequences of inadvertent treatment interruptions in patients undergoing anti-VEGF therapy for diabetic retinopathy. Dr. Johnson's research reminds us of the significant risks of treatment lapses in this patient population that is vulnerable to losses to follow-up, a factor that should be included in our decision algorithm when deciding a course of action for patients.

These two talks, and their associated discussions, truly embody the spirit of the ARDS. We look forward to seeing you at the 2020 meeting of the ARDS, which will occur February 29 to March 4 in Snowmass, Colorado. Visit MedConfs.com to register.

—Timothy G. Murray, MD, MBA

GENE THERAPY FOR NEOVASCULAR AMD 2019: PITFALLS AND PROMISE

A phase 1/2a trial of a gene therapy is showing promise in this space.

Presentation by Allen C. Ho, MD
Summarized by Nimesh A. Patel, MD

Allen C. Ho, MD, delivered the Founders Lecture, titled "Gene Therapy for Neovascular AMD 2019: Pitfalls and Promise." This article presents a summary of portions of his talk, including background on retinal gene therapy, advances in surgical techniques for subretinal delivery of gene therapy, and interim results of one early-phase gene therapy trial that is showing promise for the treatment of neovascular age-related macular degeneration (AMD).

Since the US FDA approval of voretigene neparvovec-rzyl intraocular suspension for subretinal injection (Luxterna, Spark Therapeutics) for the treatment of the biallelic *RPE65* mutation in Leber congenital amaurosis, the development of gene therapy has continued in ophthalmology, as in other fields of medicine.[1] The underlying concept of most of the ocular gene therapies in development is gene augmentation, whereby new genes are introduced into cells to replace defective ones. This goal is achieved using certain carriers, such as the adeno-associated virus serotype 2 (AAV2) viral vector.

The use of gene editing with the technology known as clustered regularly interspaced short palindromic repeats, or *CRISPR*, with CRISPR-associated protein 9 (Cas9) is also being investigated. In this approach, a target RNA is used with Cas9 enzyme to splice a somatic mutation.[1]

ALTERNATIVE APPROACHES

Several clinical trials examining gene therapy with vectors for the treatment of wet AMD are under way, and investigators have sought to avoid the pitfalls of previous unsuccessful studies. Gene therapy for neovascular AMD has not been successful in three recent phase 1 or phase 2a trials.[2-4] This was largely due to inadequate production of VEGF, not to safety concerns.

It has been postulated that the AAV2 vector may not be able to deliver enough DNA to manufacture a level of anti-VEGF protein that is therapeutic in wet AMD. Recently, experimentation with an alternative vector, AAV8, suggests that enhanced transfer of genetic material to the retinal pigment epithelium (RPE) can be achieved with this vector in comparison with AAV2.[5]

There is debate regarding which drug delivery method (ie, intravitreal injection or subretinal injection) is preferable for future trials. Several studies have demonstrated safety

with subretinal delivery.[4,6-12] The subretinal approach may be more invasive than intravitreal injection, but it has been shown to lead to greater yield of target protein expression.[13] Preexisting vitreous neutralizing antibodies, or *NAbs*, to vectors AAV8 or AAV2, prevalent in 20% to 50% and 70% of the population, respectively, may diminish the effective dose of therapies given intravitreally.[2,14,15] The subretinal space likely is more immune-privileged than the vitreous cavity, and NAbs do not appear to block transduction there.

SURGICAL TECHNIQUE

Advances have been made in the surgical technique for subretinal gene therapy in order to promote standardization and consistent dosing. Silicone treatment of the injection apparatus has decreased virus adherence, leading to improved efficiency of delivery. Additionally, intraoperative OCT is now employed as an adjunct to help calculate the volume of the subretinal bleb.

The procedure used in recent studies includes subretinal injection with 250 µL of the therapy outside of the macula, in conjunction with fluid-air exchange. A footpedal-controlled 41-gauge cannula is used with a MicroDose Injection Kit (MedOne) injector. This allows the surgeon to be independent during this portion of the procedure and decreases the risk of inadvertent mistiming of injection.

There is potential to achieve subretinal delivery of gene therapy without creation of a retinotomy. One disadvantage of retinotomy formation is the unknown amount of leakage of the therapy from the subretinal space into the vitreous cavity. A novel surgical technique, in which ab externo access to the suprachoroidal space is achieved without vitrectomy, has been described. This experimental device and procedure has FDA 510K approval based on a favorable safety profile in an atrophic AMD study and is currently employed in other AMD trials.

A PROMISING TRIAL

The subretinal AAV8–anti-VEGF compound being developed by Regenxbio for the treatment of wet AMD (RGX-314) is showing promise in phase 1/2a clinical trials. The therapy transports a gene encoding for anti-VEGF expression. The antibody produced is comparable in structure to ranibizumab (Lucentis, Genentech). Preliminary protein expression experiments using aqueous paracentesis in nonhuman primates exhibited improvements, on the order of log units, when compared with previous gene therapies for AMD.

The ongoing clinical trial is enrolling pseudophakic, nontreatment-naïve patients who have exhibited a treatment response to anti-VEGF therapy as documented on OCT. VA range for inclusion is 20/63 to 20/400. The trial design groups participants into cohorts of six patients each, with the dose increased from cohort 1 to cohort 5.

The primary outcome is safety. Secondary outcomes include BCVA, central retinal thickness, and protein production, as measured by taking aqueous samples from the anterior chamber. Rescue criteria included choroidal neovascularization–related subretinal or intraretinal fluid, loss of 5 letters of BCVA or more with accumulation of fluid, subretinal hemorrhage, and investigator-determined need for rescue.

An interim report included data on patients in cohorts 1 to 3. On average, patients had 35 anti-VEGF injections before inclusion in the study. At 6 months, there was a dose-dependent increase in anterior chamber protein production across the cohorts. BCVA and central retinal thickness were stable for the duration of treatment.

The average number of rescue injections was 4.7, 3.8, and 1.3, respectively, in the ascending dose cohorts. This finding suggests that a higher initial dose of RGX-314 may decrease the need for future anti-VEGF treatment. At month 6 in the highest dose cohort, there was sustained protein production, and 50% of patients did not require rescue injection.

Eyetube: Dr. Ho Recaps His Talk

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The therapy and the procedure used in the trial were generally well tolerated. There was one peripheral retinal detachment that was treated without sequelae. There was one cancer recurrence and one death from a preexisting cause.

SUMMARY

The future of gene therapy for AMD shows promise. Early studies demonstrated acceptable safety, albeit with inadequate protein production. The pitfalls observed in previous trials have led to improvements in the delivery of medication and the consistency of dosing. The RGX-314 phase 1/2a trial, with its limited sample size, has, to date, demonstrated a potential dose-related decrease in need for rescue injections over 6 months.

There are multiple choices on the horizon for the treatment of patients who need frequent anti-VEGF injections, including port delivery and longer-acting medications. The role that surgical options will play in the AMD treatment paradigm of the future is unknown. Rather than as a monotherapy for treatment-naïve patients, it is possible that subretinal gene therapy could be used as an adjunct to decrease the burden of intravitreal injections in patients refractory to injected therapies.

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ANTI-VEGF TREATMENT FOR DIABETIC RETINOPATHY: CONSEQUENCES OF INADVERTENT TREATMENT INTERRUPTIONS

The treatment effect of PRP is more durable, a factor that should be considered in treatment decisions.

Presentation by Mark W. Johnson, MD
Summarized by Nimesh A. Patel, MD

Mark W. Johnson, MD, delivered a presentation titled "Anti-VEGF Treatment for Diabetic Retinopathy: Consequences of Inadvertent Treatment Interruptions." This article presents a summary of portions of his presentation.

PERPETUAL TREATMENT

Diabetic retinopathy (DR) is a progressive disease that requires close attention to prevent vision loss. Unless permanent regression is achieved or temporary regression is maintained with ongoing treatment, DR can lead to severe neovascular complications, most notably tractional retinal detachment (TRD) and neovascular glaucoma (NVG).[1] With the availability of anti-VEGF drugs for intravitreal injection, there has been an increase in the use of these agents as monotherapy for patients with proliferative DR (PDR). With this approach, given its requirement for continuous dosing, there are potential severe consequences due to interruptions in treatment.

Panretinal photocoagulation (PRP) induces regression of proliferative diabetic disease, as exhibited in the Diabetic Retinopathy Study.[1] The efficacy of PRP for regression of PDR and preservation of VA over a long-term follow-up period has been established in multiple studies.[2-5] Blankenship et al followed patients with PDR treated with PRP at the Bascom Palmer Eye Institute and found that after 15 years only 4% required additional laser treatment.[6] Vander et al verified this stability, reporting that after PRP-induced regression of PDR, visual outcomes did not vary with length of follow-up.[7] Occasionally, vitreous hemorrhage can occur despite PRP. However, this does not necessarily indicate a treatment failure, worsening ischemia, or new proliferative changes; it is typically due to vitreous-induced tractional forces leading to shearing of blood vessels.

In contrast to PRP, the durability of anti-VEGF therapy with ranibizumab (Lucentis, Genentech) and other agents is limited. The 5-year results of the DRCR Retina Network Protocol S study found no benefit in VA or visual field preservation for anti-VEGF therapy over PRP.[8] Notably, there was no decline in the number of intravitreal injections performed each year from years 2 to 5 in the anti-VEGF group. Moreover, 84% of patients treated with ranibizumab required reinjection after a period during which treatment was withheld.[8]

Retreatments are required because anti-VEGF medications do not permanently reverse the underlying retinal ischemia in PDR, which is the primary driving factor for VEGF production and neovascularization. Clinical features and severity scores may improve with anti-VEGF treatment in PDR, but the area of retinal nonperfusion remains the same or can increase.[9] This was seen in the RISE, RIDE, VISTA, and VIVID trials, in which, despite monthly anti-VEGF therapy, more than 15% of patients developed PDR. Thus, anti-VEGF therapy for PDR must be regarded as a long-term, perpetual treatment option.

MISSED APPOINTMENTS ARE COMMON

The need for continuous anti-VEGF therapy must be considered a limitation because people with diabetes have a high potential for missed clinic appointments and tend to underutilize eye care services. Unanticipated events can affect even the most reliable patients.

More than 10 million people with diabetes are evaluated in general emergency departments annually, and more than 6 million of them are hospitalized. Moreover, 46% of patients with diabetic macular edema have experienced a treatment lapse of greater than 100 days.[10-12] Even though clinical trials employ study coordinators to try to ensure adequacy of

Inadvertent interruptions of anti-VEGF monotherapy for PDR can lead to visually significant consequences, some of which may be irreversible.

ARDS Eyetube Meeting Coverage

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follow-up, difficulties in patient retention persist. In Protocol S, an alarming 33% of participants were lost to follow-up over a period of 5 years.[5] This rate would be expected to be higher in real-world practices that are not capable of maintaining a similar intensity of patient oversight. Therefore, the outcomes from Protocol S and other clinical trials may not be generalizable to all clinical settings.[10]

CONSEQUENCES

With the lack of durability of anti-VEGF therapy in PDR noted above, if inadvertent lapses occur with patients being treated solely with anti-VEGF therapy, there is a potential for marked progression of PDR and devastating visual complications.

A multicenter study reviewed results in 13 eyes of 12 patients with PDR being treated with anti-VEGF therapy who experienced unintentional treatment interruptions.[13] The mean A1C in these patients was 9.5, and all had type 2 diabetes mellitus. Prior to the treatment interruption, the mean number of injections during a mean treatment duration of 16.8 months was 7.1.

Patients' explanations for loss to follow-up included socioeconomic factors, such as change in insurance coverage, and comorbid medical conditions requiring hospitalization. Consequences included vitreous hemorrhage in 69% of eyes, NVG in 38%, and TRD in 31%. Regarding visual outcomes, 77% of eyes lost 3 or more lines of VA, 46% had hand motions or worse VA, and two eyes had no light perception at final follow-up. As might be expected, the longer the duration of treatment interruption, the worse the final VA.[13]

Notably, three patients in this study were receiving treatment for nonproliferative DR and diabetic macular edema before their treatment hiatus. Despite not having proliferative disease initially, two of the three developed NVG. In patients with nonproliferative PDR, it is appropriate to perform fluorescein angiography to assess degree of retinal ischemia, as this may correlate to the risk of progression.[13]

More evidence for the long-term benefit of PRP over anti-VEGF therapy for PDR can be seen in a study by Obeid et al.[11] They studied 76 eyes of 59 patients with PDR treated with PRP or anti-VEGF agents who experienced unplanned treatment disruptions.[11] The anti-VEGF group had a statistically significantly higher rate of VA decline, TRD, and iris neovascularization than the PRP group.

CONCLUSION

Despite the best efforts of health care providers, patients with diabetes are subject to treatment lapses due to unanticipated hospitalizations, financial hardships, and noncompliance. Inadvertent interruptions of anti-VEGF monotherapy for PDR can lead to visually significant consequences, some of which may be irreversible. Eyes with PDR treated solely with anti-VEGF therapy have worse anatomic and functional outcomes after unplanned breaks in treatment compared with eyes that received PRP. Clinicians must consider this difference carefully when making initial treatment decisions for patients with diabetic eye disease. ■

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NIMESH A. PATEL, MD
- Second-year Retina Fellow, Bascom Palmer Eye Institute, Miami
- nimeshpatel300@gmail.com
- Financial disclosure: None