Inherited Retinal Diseases for the Retina Specialist: Where to Start

What can a clinician who is not an inherited retinal disease expert do for patients with these conditions? Start here.

BY DANIEL L. CHAO, MD, PHD

The maturation of gene therapy has changed the paradigm of inherited retinal diseases (IRDs) from a diagnostic field to one in which promising therapies may be able to prevent blindness in patients with IRDs in the future. It is important for every retina specialist to educate himself or herself about these diseases and about what new treatments or diagnostics might be available for these patients. This article presents several things retina specialists should know about IRDs.

A DIFFERENT APPROACH

Patients with IRDs require a different approach and workflow compared with patients with more typical diseases such as age-related macular degeneration and diabetic retinopathy. Careful history-taking is important, and counseling the patient about the diagnosis is a key part of the visit. This requires significant chair time as these patients have likely been told previously by other providers that they will go blind and that there are no treatments available.

Addressing patients' psychological concerns about the diagnosis is as important as any medical treatment. You can try to schedule these patients at the end of clinic or on another day that is conducive to longer visits, or you can refer such patients to a clinic that specializes in IRDs.

Gene-based classification of IRDs is becoming the norm, replacing the previous nomenclature based on fundus findings. Lower costs have made DNA sequencing more accessible to the general public, and genetic testing is becoming the standard of care for patients with IRDs. This can include single-gene testing if there is strong suspicion for a particular disease (eg, a mutation of *RPE65* leading to Leber congenital amaurosis), but it is common to order a panel of approximately 270 genes that have been implicated in retinal degenerations in which a genetic cause of the disease is found in about 50% of patients.[1] This type of testing can give patients a definitive diagnosis, which can be a great relief, and can also help physicians identify patients for potential enrollment in clinical trials.

There are a number of ways to arrange for genetic testing. One is through the Foundation Fighting Blindness My Retina Tracker portal (see sidebar *Foundation Fighting Blindness: Funding IRD Therapy Research*). Through this portal, patients are entered into a registry that alerts

AT A GLANCE

- In addition to the one approved gene therapy, there are more than 30 ongoing middle- and late-stage clinical trials using gene therapy or other molecular therapies for IRDs.
- Specialized IRD clinics can serve as one-stop shops for the needs of patients with IRDs.
- Support groups and online patient communities sometimes have as great an impact on a patient's quality of life as any medical treatment.

them to clinical trials for which they may qualify and can receive free commercial genetic testing with counseling.

Alternatively, commercial CLIA-certified laboratories such as Blueprint Genetics and GeneDx now offer relatively affordable genetic testing for retinal diseases. In general, insurance only partially covers the costs of these tests; out-of-pocket expense may range from $500 to $2,000.

GENETIC COUNSELING

Although technology now allows us to perform sequencing rapidly, the interpretation of these tests to identify a causative mutation is not always straightforward. Many times, there are mutations in multiple genes that are predicted to cause changes in a protein, but these mutations have not been determined to cause a deleterious effect responsible for the disease. These mutations are termed *variants of unknown significance*. Additionally, the phenotype may be caused by a *compound heterozygous mutation*, meaning heterozygous mutations in two separate genes.

Because of this complexity, it can be extremely helpful for genetic counselors to discuss findings with patients. Genetic counselors who have specialized training in interpreting these tests can explain the findings to patients, freeing up the retina specialist for other aspects of patient care.

Retina specialists who do not have easy access to a genetic counselor can consider using third-party genetic counseling groups such as InformedDNA.

FINDING TRIALS

The US FDA approval of the first gene therapy has ushered in a new era in the treatment of IRDs. In addition to voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics), there are more than 30 middle- and late-stage clinical trials ongoing using gene therapy or other molecular therapies for IRDs, some with encouraging results.

Resources such as clinicaltrials.gov can be useful when searching for clinical trials for specific IRDs, but clinical trials for IRDs are dynamic and constantly changing. The best way to find an appropriate trial is to directly contact retina specialists at centers that are participating in many of these clinical trials to learn the latest updates.

CLINICAL CARE FOR PATIENTS WITH IRDS

There is no consensus on nutritional supplementation for IRDs, although a healthy balanced diet is recommended. Vitamin A should be avoided by patients with Best disease or the cone-rod dystrophy Stargardt disease, as vitamin A may exacerbate these diseases due to increased toxicity through the visual cycle.

A number of studies have investigated whether nutritional supplements such as high-dose vitamin A, docosahexaenoic acid, lutein, and beta carotene can prevent progression of vision loss in patients with IRDs.[2] A combination of high-dose vitamin A (15,000 IU) and carotenoids has shown a modest effect with decreased vision loss in patients with retinitis pigmentosa, but the combination is currently not recommended given equivocal efficacy, hepatotoxicity, and other side effects.

How should a clinician who is not an IRD expert work up a patient with an IRD? Currently, the standard

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RETINA TODAY ON THE ROAD

This article is adapted from a lecture the author presented in April at the Annual Vit-Buckle Society Meeting. The next meeting will be held March 26-28, 2020, in Miami. Visit VitBuckleSociety.org and MedConfs.com for details.

FOUNDATION FIGHTING BLINDNESS: FUNDING IRD THERAPY RESEARCH

The Foundation Fighting Blindness, the world's leading private funding source for inherited retinal disease (IRD) research, has raised more than $750 million toward its mission. The nonprofit's portfolio currently consists of 75 projects, including emerging gene, stem-cell, and small-molecule therapies. Through its global My Retina Tracker patient registry, the Foundation is conducting a no-cost genetic testing study. Approximately 5,000 patients with IRDs have participated in the program.

In 2018, the Foundation established its Retinal Degeneration (RD) Fund, a venture philanthropy fund for emerging IRD therapies in the translational stage or undergoing evaluation in early clinical trials. With more than $70 million under management, the RD Fund's publicly disclosed projects include:

- **Nacuity:** A Dallas-based startup developing n-acetylcysteine amide, a small molecule targeting oxidative stress in patients with retinitis pigmentosa and potentially other IRDs.
- **SparingVision:** A Paris-based company developing rod-derived cone viability factor, a neuroprotective gene therapy for IRDs including retinitis pigmentosa.
- **ProQR:** An RNA therapeutics biotech developing antisense oligonucleotides for a broad range of IRD genes including *USH2A* (exon 13 mutations) and Leber congenital amaurosis 10 caused by a *CEP290* mutation.

Visit FightingBlindness.org and RetinalDegenerationFund.com to learn more.

One Year in: Perspectives on Voretigene

Looking back at the first year of the first ocular gene therapy.

BY AARON NAGIEL, MD, PHD

For novel therapeutic agents, the first few years of use in the real world can occasionally raise concerns that did not come to light during tightly controlled clinical trials.[1] How has voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) fared in the 15 months since treatment centers began administering it to patients with Leber congenital amaurosis (LCA) caused by biallelic mutations in *RPE65*?

To be fair, its current use is not exactly "real world" in the sense that any physician with the appropriate training can provide the treatment. Rather, since voretigene received approval by the US FDA, nine treatment centers have been designated across the United States, and each site has only a few (most have one or two) surgeons cleared to provide the treatment. All treating physicians were required to undergo wet laboratory training and to review in detail the surgical manual put forth by the manufacturer of this ocular gene therapy, which is the first to be approved by the FDA.

Formal analysis on 1-year outcomes of voretigene in the postapproval period are eagerly awaited. In this article, I review in general terms our center's experience with the treatment and highlight two areas in which our approach has evolved: patient selection and surgical delivery.

PATIENT SELECTION

At Children's Hospital Los Angeles, we have treated nine children and five adults bilaterally (28 eyes), and I believe the greatest benefits will be observed with early treatment in childhood.

Although it is not surprising that patients treated earlier in the course of disease would fare better, young children benefit dramatically through enrichment of their social, motor, and cognitive development. Improvements in eye contact, confidence in locomotion, and ability to read, play, and eat in normal or dim lighting have enormous lifelong consequences and should not be underestimated. This highlights the importance of early genetic testing and treatment, perhaps in patients as young as 1 year old.

Demonstrating these improvements in a rigorous fashion in young children remains a challenge,

AT A GLANCE

- At nine treatment centers across the United States, selected surgeons have been designated to provide treatment with voretigene neparvovec-rzyl.
- In the first year after this gene therapy's postapproval use, clinicians have refined their approaches to patient selection and surgical delivery.
- The greatest benefit may be seen with treatment in early childhood for *RPE65*-associated LCA.

however, because these patients may not cooperate with standard outcome measures such as light sensitivity testing or visual fields.

Another aspect that may be underappreciated is the complexity of molecular diagnostic testing. Although I have a scientific background, I do not have formal training in molecular pathology or bioinformatics. Our clinical training as ophthalmologists and retina specialists glosses over the intricacies of genetic testing as we come to associate names of genes with certain conditions. By now, it should be obvious that mutations in *RPE65* cause LCA.

If only it were that easy.

Many mutations, or *variants*, are benign, and they are predicted not to cause significant alteration in protein function. Some variants are predicted to be pathogenic, even if they are novel mutations. And still others are labeled *variants of uncertain significance*, or VUS, which means we are not sure of their effect.

As a treating surgeon, I have the ultimate responsibility to ensure the validity of genetic testing before subjecting a patient to bilateral vitrectomies. I am fortunate to have excellent bioinformaticists and molecular pathologists at my institution to aid me in this regard. Furthermore, I require that the parents of every voretigene candidate also undergo *RPE65* gene testing. This segregation analysis is especially crucial for compound heterozygous mutations to demonstrate that they are *in trans* (ie, on separate alleles).

Panel-based testing should be emphasized over single-gene testing to allow us to see the landscape of genetic alterations and prevent a "love at first sight" scenario, wherein we associate causation to the first and only gene we test, especially when the evidence for pathogenicity may be wanting.

Finally, when VUS arise, one should strongly consider in vitro mutagenesis with functional protein assays to definitively demonstrate mutational pathogenicity before proceeding with gene therapy surgery.

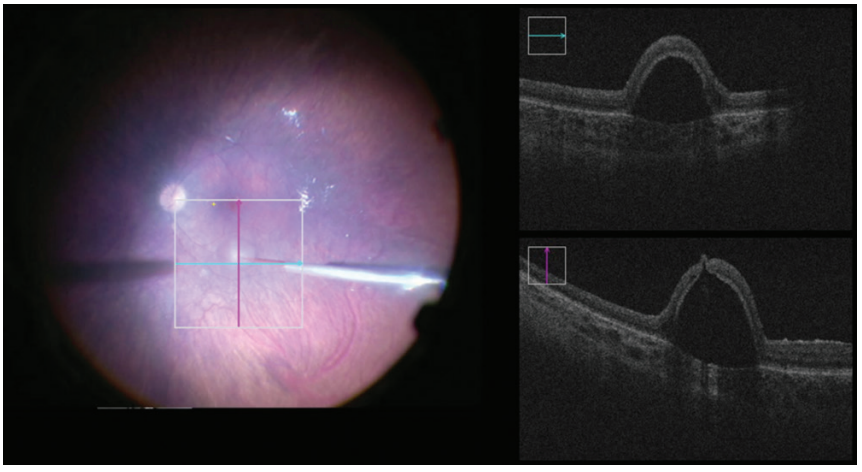

Figure. Intraoperative OCT-guided subretinal injection of voretigene neparvovec-rzyl in a pediatric patient.

AS WE AGGREGATE OUR DATA ACROSS TREATMENT CENTERS, IT MAY BE POSSIBLE TO IDENTIFY BEST PRACTICES OR DEMONSTRATE THE EQUIVALENCE OF VARIOUS TECHNIQUES, LEAVING THESE TO INVESTIGATOR DISCRETION.

SURGICAL DELIVERY

Our surgical approach to the delivery of voretigene has evolved since the first patient we treated in March 2018. Although Spark Therapeutics provided wet laboratory training and a surgical manual, there are no hard-and-fast procedural rules on the medication label. This has allowed each treatment center to evolve over time and adopt slightly different approaches. As we aggregate our data across treatment centers, it may be possible to identify best practices or demonstrate the equivalence of various techniques, leaving these to investigator discretion.

Some of the fine points include the following:

Use of Triamcinolone

Because the clinical trials of voretigene did not permit the routine use of triamcinolone intraoperatively, we avoided it during our first case. Since then, we have used it in all cases to aid in removal of vitreous. Because the vitreous tends to be syneretic in patients with *RPE65* mutations, triamcinolone is helpful for confirming the presence of a posterior vitreous detachment.

Bleb Creation

For the first few surgeries we adhered to the surgical manual's recommendation to have a trained assistant inject the vector manually as

the primary surgeon positioned the subretinal cannula. We moved on to using the MicroDose Injection Kit (MedOne Surgical) to allow autonomous control of the subretinal injection by the primary surgeon. This has been a fantastic improvement. We proceed directly with injection of the vector without first creating a saline "prebleb."

OCT Guidance

Although it is not essential, the use of OCT intraoperatively has been a great visual aid for determining the location of the bleb and status of the fovea. I deliver the vector with the two-line crosshair overlay on the ReScan microscope (Carl Zeiss Meditec; Figure). This has allowed me to better understand the importance of cannula positioning and to characterize some atypical bleb appearances (eg, schisis at the edge of the bleb).

Air-Fluid Exchange

We routinely perform a complete air-fluid exchange, as recommended in the surgical manual. The idea is to tamponade the retinotomy and limit extravasation of potentially inflammatory vector into the vitreous cavity, but I am not sure if this step is necessary.

SUMMARY

It is an extraordinary privilege to be able to deliver this unique treatment to our patients. I am hopeful that the collective outcomes from our nine centers will buttress the findings of the phase 3 trial[2] and support continued enthusiasm for voretigene in the treatment of this previously incurable form of blindness.

We all must recall the grit and dedication of individuals such as Michael Redmond, PhD; Jean Bennett, MD, PhD; Albert M. Maguire, MD; and many more, and the funding sources that made the investigation and approval of this novel gene therapy possible. Ideally, our early clinical real-world experience with voretigene will serve as a blueprint for future gene therapy approaches in the retina and beyond. ■

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workup to diagnose and follow patients includes a standard ophthalmic examination with fundus photos, fundus autofluorescence, and OCT imaging. Genetic testing can be considered. Additional workup that is not common in the retina clinic may include periodic kinetic perimetry (eg, Goldman or automated kinetic perimetry) and electroretinography, which may be done at a more specialized IRD clinic.

IRD centers can serve as one-stop shops for the needs of patients with IRDs. IRD specialists can provide specialized workups, an infrastructure for genetic testing and counseling, and access to the latest clinical trials and research.

NONCLINICAL RESOURCES

Patient communities and online groups are invaluable for patients with IRDs. As noted previously, many of these patients have been told that they will go blind and that there is no treatment available, which can have significant psychological and functional effects on patients. Patient advocacy groups and foundations provide excellent venues for patients to support each other, and such support can have a dramatic effect on patients' quality of life. The largest of these is the Foundation Fighting Blindness. The foundation has many local chapters across the United States. Additionally, online communities such as Facebook groups can be helpful. I recommend referring patients to these groups because, many times, this support can have as great of a significance on quality of life as any medical treatment.

HOPE FOR THE FUTURE

A multidisciplinary approach is important when treating patients with IRDs. Given the complicated nature of care for these patients, such a multidisciplinary team should include a retina specialist, preferably with some training in IRDs; a genetic counselor; a low-vision specialist; and social workers. All of these individuals play essential roles in making sure these patients are taken care of at all levels.

It is an exciting time in the care of patients with IRDs. Today, clinicians can provide treatments that can potentially prevent blindness for some patients with IRDs. As these patients present to retina clinics, I hope that the information presented here will be helpful and can serve as a framework to care for these patients. ■

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