# 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.

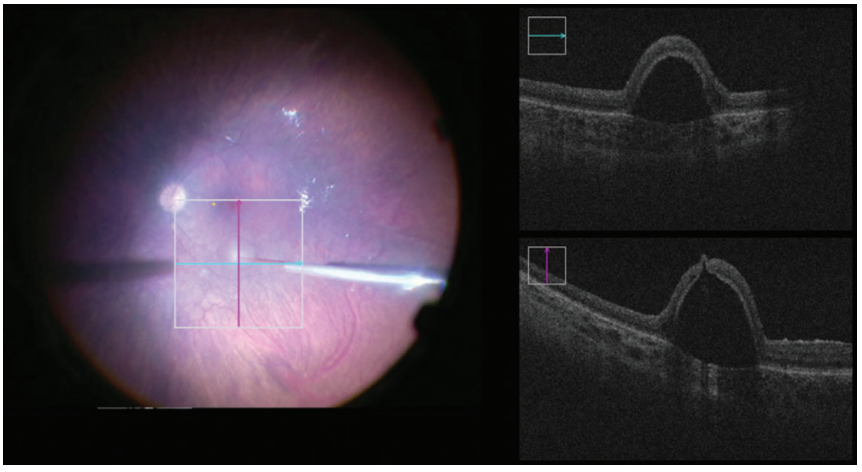

Figure. Intraoperative OCT-guided subretinal injection of voretigene neparvovec-rzyl in a pediatric patient.

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## 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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