Subretinal Injection of Voretigene Neparvovec-rzyl in a Patient With RPE65-Associated Leber’s Congenital Amaurosis

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Gene therapy offers a novel approach to treating inherited retinal dystrophies. In this video, Dr. Berrocal’s group has showcased their excellent technique for treating RPE65-associated Leber congenital amaurosis using voretigene neparvovec-rzyl.

One of the most challenging aspects of this surgery is inducing a posterior vitreous detachment in a young eye. Removing the cortical vitreous from the vicinity of the injection site is critical to avoid plugging the injection cannula and postoperative vitreous contraction over the treatment area. Intraocular triamcinolone can be used to highlight residual hyaloid that will need to be meticulously removed, as shown in the video.

Although wide-angle non-contact viewing platforms for vitrectomy have significantly improved our speed and safety, I recommend a fundus contact lens during portions of the case involving the macula, as the authors did. These lenses offer enhanced depth perception and greater resolution, which are key. Many surgeons prefer to trim the 38-gauge subretinal cannula into a beveled tip. I have successfully created large blebs using the standard cannula, and there have been preliminary reports suggesting a link between a beveled cannula with higher rates of capillary bleeding at the injection site. The authors were astute to lower the intraocular pressure to around 10 mm Hg prior to the injection, as this softens the eye and allows for an easier delivery of the vector volume subretinally.

Finally, the postoperative transient ocular hypertensive response experienced by this patient is likely due to the sub-Tenon’s triamcinolone injection performed at the end of surgery. To avoid this while still minimizing postoperative inflammation, I initially perform a retrobulbar injection of 40 mg of triamcinolone mixed with a 1:1 mixture of 2% lidocaine and 0.5% bupivacaine. The anesthetic provides prolonged postoperative analgesia and helps stabilize the globe intraoperatively. Placement within the retrobulbar space prevents anterior migration of the steroid past the equator and may reduce ocular hypertensive side effects.

As this therapy becomes more mainstream, it will hopefully lead to the development of further treatments for numerous inherited eye diseases.

ABSTRACT: Leber’s congenital amaurosis (LCA) is a rare inherited retinal degeneration (IRD) that causes severe vision loss, nystagopia, and nystagmus within the first few years of life. RPE65 gene mutations cause approximately 6% of LCA cases and have become the target for therapy since voretigene neparvovec-rzyl became the first U.S. Food and Drug Administration-approved gene therapy product for IRDs in 2017. The surgery involves pars plana vitrectomy with subretinal injection of a viral vector that carries a functional copy of the RPE65 gene. Intraoperative optical coherence tomography is a useful adjunctive tool to confirm the injection has reached the subretinal space.

Leber’s congenital amaurosis (LCA) is a severe form of autosomal recessively inherited retinal degeneration (IRD) with a prevalence of approximately 1:80,000 spread across 19 disease variants, each caused by a unique genetic mutation.1 Biallelic mutations in the RPE65 gene account for approximately 6% of LCA cases and 2% of overall recessive early onset retinitis pigmentosa.2,3 The gene
encodes a 65 kDa enzyme responsible for isomerizing all-trans retinaldehyde to the 11-cis form within the eye to regenerate visual pigment required for photoreceptor function.\(^3,4\)

In December 2017, the U.S. Food and Drug Administration approved the first gene therapy product, voretigene neparvovec-rzyl (Luxturna; Spark Therapeutics, Philadelphia, PA), for IRDs, an adeno-associated virus type 2 vector designed to deliver a normal copy of the gene for treating patients ages 12 months and older with confirmed biallelic \(RPE65\)-mediated LCA.\(^5\)

Our patient is a 5-year-old girl with LCA that was referred to our clinic for consideration of gene therapy. She was diagnosed at age 2 after her parents noted nystagmus, nystagmus, and poor visual acuity (VA). Genetic testing confirmed biallelic mutations in the \(RPE65\) gene. One week prior to surgery, her best-corrected VA (BCVA) was 20/100 and 20/80 as measured by Snellen in the right and left eyes, respectively. She was treated with 1 mg/kg daily of oral prednisone for 3 days prior to surgery to minimize postoperative inflammation. The two eyes were treated 1 week apart.

The surgery consisted of 25-gauge pars plana vitrectomy with the NGENUITY “Heads-Up” 3-D Visualization System (Alcon, Fort Worth, TX). After the hyaloid was lifted and a core vitrectomy performed, dilute triamcinolone was injected to ensure no residual vitreous adherence. The periphery was shaved with the assistance of scleral depression. Prefilled 1 ml BD syringes (Franklin Lakes, NJ) with the therapeutic product were inspected and mounted on MedOne #3243 high-pressure 6” extension tubing with a MedOne #3219 PolyTip 25-gauge/38-gauge subretinal injection cannula (MedOne Surgical, Sarasota, FL). The tip of the cannula was trimmed to be beveled to facilitate subretinal penetration. The treatment syringe was reprimed to remove air bubbles.
and handed to the primary surgeon. The intraocular pressure was reduced to 10 mm Hg, and the tip of the needle was then placed into the vitreous cavity.

Using a flat contact high-magnification lens (Advanced Visual Instruments, New York, NY), an injection site was chosen in the superior macula along the superior vascular arcade at least 2 mm distal to the center of the fovea. The site was free of intraretinal pigment migration or dense atrophy. The needle tip was placed in contact with the retinal surface, and the primary surgeon instructed the assistant surgeon to initiate manual infusion. Any contact with the retinal vasculature was avoided. A second bleb was created inferiorly to allow a more diffuse subretinal injection and to avoid creating a macular hole by overstretching the superior bleb. The inferior bleb elevated the fovea.

The subretinal injection was confirmed with intraoperative optical coherence tomography imaging. The plunger remained depressed for 5 seconds after the syringe was empty, and then the needle was withdrawn. The central macula was included in the area of retinal elevation. A total volume of 0.3 ml of the therapeutic agent was administered.

Fluid-air exchange was performed with an infusion pressure of 30 mm Hg. Each of the sclerotomies was sutured with 7-0 vicryl. The eye was noted to be normotensive. Peribulbar anesthesia with a mixture of lidocaine and ropivacaine was administered followed by a sub-Tenon’s injection of triamcinolone. Subconjunctival injections of cefazolin and dexamethasone were performed, followed by topical neomycin/polymyxin B/dexamethasone ointment and atropine drops. The entire procedure was completed within 4 hours of preparation of the therapeutic agent.

The postoperative course was uneventful, and the retina flattened by the following day. Our patient had transient ocular hypertension, which was controlled with topical netarsudil (Rhopressa; Aerie Pharmaceuticals, Durham, NC). At the 4-month follow-up visit, her BCVA was measured to be 20/70 in each eye. The patient and her parents reported remarkable improvement in visual function and low light conditions.

REFERENCES


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