Published in final edited form as:

Br J Ophthalmol. 2023 March ; 107(3): 299–301. doi:10.1136/bjo-2022-321488.

Subretinal Deposits in Young Patients Treated with Voretigene Neparvovec-rzyl for RPE65-mediated Retinal Dystrophy

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Abstract

We report a series of three young patients (ages: 22 months, 2 years, and 5 years) who developed subretinal deposits at post-operative week 1 following subretinal voretigene neparvovec-rzyl treatment for RPE65-mediated retinal dystrophy. In the 5-year-old, subretinal deposits were also observed in the inferior periphery of both eyes. All three patients experienced improved visual function with treatment, and both the macular and inferior subretinal deposits have improved or resolved over the follow-up period. These findings may inform the delivery parameters and safety profile of AAV-based gene therapy as the number of retinal gene therapy trials continues to grow.

Keywords

voretigene neparvovec-rzyl; Luxturna; retinal gene therapy

INTRODUCTION

Since its approval by the Food and Drug Administration in 2017, voretigene neparvovec-rzyl (VN; Spark Therapeutics, Philadelphia, PA) has been used to treat RPE65-mediated retinal dystrophy at gene therapy centers across the world.[1] Post-approval safety and efficacy studies are ongoing to determine how its use in the real world compares to Phase 3 clinical trials,[1–3] especially in light of a recent study describing progressive perifoveal chorioretinal atrophy.[4] Furthermore, because the Phase 3 trials were limited to subjects ages 4 years and older, less is known about VN safety in very young patients. Here we describe subretinal deposits in three young children treated with VN.

METHODS

The study was approved by the Institutional Review Board at Children's Hospital Los Angeles. Imaging included fundus photography (Optos California, Optos, Dunferline,

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Disclosures: JL: None; MSB: None; TCL: None; AN: Consultant for Biogen, REGENXBIO, Novartis, and Allergan Retina.

Scotland; RetCam 3, Clarity Medical Systems, Pleasanton, CA; Zeiss RESCAN 700 Carl Zeiss Meditec AG, Jena, Germany), fundus autofluorescence (Optos California), fluorescein angiography (RetCam 3), and optical coherence tomography (OCT, Heidelberg Spectralis, Heidelberg, Germany; InVivoVue, Bioptigen, Morrisville, NC, USA). Perioperative 1 mg/kg oral liquid prednisolone was given as described with a 10-day taper.[1] A total of 0.3 ml VN was delivered via one or two blebs using intraoperative OCT guidance without evidence of reflux followed by full air-fluid exchange.

RESULTS

Three patients ages 22 months, 2 years, and 5 years at the time of treatment were identified as having subretinal deposits following VN. Time from treatment to last follow-up was 2 years, 4 months, and 6 months, respectively.

Case descriptions:

Case 1 is a 22-month-old female with homozygous c.1067dup (p.Asn356Lysfs*9) *RPE65* variants. At baseline, she could fix and follow a 4-inch toy at 1 foot in each eye with a refraction of −1.50+1.00×090 OD and −5.50+1.50×090 OS. She was treated in her left eye and then her right eye 10 days later. A single subretinal bleb in the left eye encompassed most of the macula including the fovea (Fig. 1A). At post-operative week 1, she was noted to have mild vitreous opacities and curvilinear yellow subretinal deposits in the inferior mid-periphery (Fig.1B). By post-operative year 2, the subretinal deposits had resolved, leaving behind subtle pigment mottling (Fig. 1C). Her best corrected visual acuity (BCVA) was 20/150 OD and 20/200 OS but limited by poor compliance with amblyopia therapy.

Case 2 is a 2-year-old female with biallelic pathogenic variants c.370C>T (p.Arg124*) and c.858+1G>A (splice donor) in *RPE65*. Prior to treatment, she could fix and follow a 3-inch toy at 1 foot and had a baseline refraction of −0.50+2.00×90 in each eye. She was treated with VN in her left eye then her right eye one week later. In the left eye, two blebs were created, one superior and one inferior to the macula without foveal detachment (Fig. 2A). On post-operative week 1 of her left eye, she was noted to have arcs of subretinal deposits in the inferior mid-periphery and just below the fovea (Fig. 2B). OCT at baseline (Fig. 2C) and postoperative week 1 (Fig. 2D) revealed the presence of outer retinal folds versus subretinal deposits at this location. By post-operative month 4, these subretinal deposits were resolving and her visual function had improved.

Case 3 is a 5-year-old female with homozygous pathogenic c.65T>C (p.Leu22Pro) *RPE65* variants. Her BCVA was 20/150 in each eye with a baseline refraction of −1.50+3.00 × 85 in both eyes. She was treated with VN in her left eye then her right eye one week later. In both eyes the blebs were placed along the superior arcade with extension into the macula without foveal detachment (Fig. 3A–B). On post-operative week 1 of the left eye, she was noted to have curvilinear subretinal deposits in the macula, mild vitreous opacities, and a large area of subretinal whitening inferiorly (Fig. 3C). Fluorescein angiography performed at this time was notable for the absence of leakage (Fig. 3D). Post-operative week 1 images of the right showed similar findings along with subretinal deposits in the nasal periphery (Fig. 3G). These findings were gradually resolving in both eyes by month 3 (Fig. 3E, F, and

H). Compared to baseline (Fig. 3I), her OCT at post-operative week 1 revealed a subretinal deposit in the nasal macula (Fig. 3J), which resolved by month 3 (Fig 3K). The BCVA had improved to 20/70 in each eye with significant improvements in dim-light function.

DISCUSSION

This series describes 3 young patients who developed subretinal deposits following VN treatment. The findings are notable for: 1) the young age of the patients, two of which would not have met the age cutoff for the Phase 3 clinical trial; 2) the acute onset of these deposits with gradual resolution; and 3) the presence of these deposits distant from the original bleb location.

In each case, subretinal deposits were noted inferior to the original bleb position, and in Case 3 there was a larger area of subretinal deposits inferiorly (Fig. 3). Given the postulated risks of active foveal detachment during VN delivery,[5–8] these findings may suggest that a significantly larger (and more inferior) area may be exposed to vector in a passive fashion, especially with poor compliance with supine positioning.

The presence of visible subretinal material immediately following treatment may be the result of a transient immune response to the AAV vector in these young patients. Supporting this hypothesis were the presence of self-resolving vitreous opacities in Cases 1 and 3, but the absence of fluorescein leakage at post-operative week 1 in Case 3 (Fig. 3D) argues against a persistent disruption of the blood-retina barrier.

In summary, we present three young patients who developed subretinal deposits following subretinal VN treatment. This has potential implications on the safety profile and delivery approaches for retinal gene therapy in young patients.

ACKNOWLEDGEMENTS

The authors would like to acknowledge study coordinators Margaret Havunjian, Hillary Schwartz, and Dilshad Contractor.

Financial Support:

This study was supported in part by an unrestricted grant to the Department of Ophthalmology at the USC Keck School of Medicine from Research to Prevent Blindness (MSB, TCL, AN), the Las Madrinas Endowment in Experimental Therapeutics for Ophthalmology (TCL, AN), NIH/NEI Career Development Award K08EY030924 (AN), and a Research To Prevent Blindness Career Development Award (AN).

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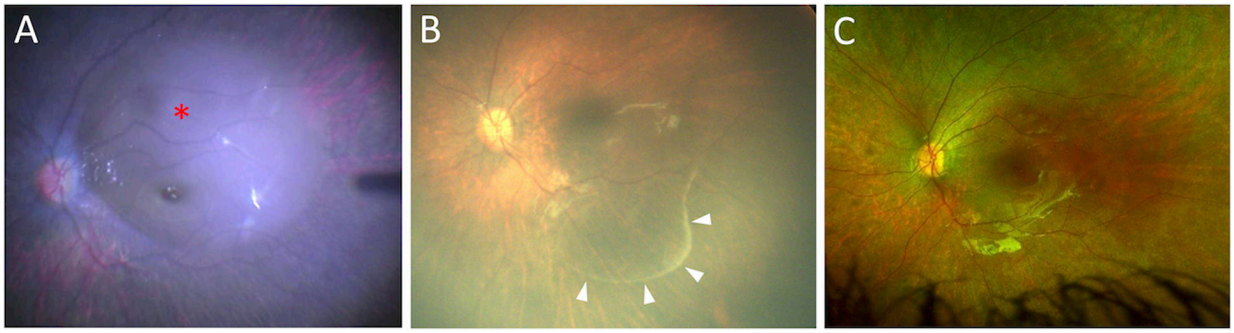

Figure 1.

22-month-old female (Case 1). A, Intraoperative photograph of the left eye demonstrating the bleb with a red asterisk at the retinotomy site. B, Retcam image of the left eye at post-operative day 10 showing inferior curvilinear subretinal deposits (arrowheads). C, Optos image at post-operative year 2 showing resolution of deposits.

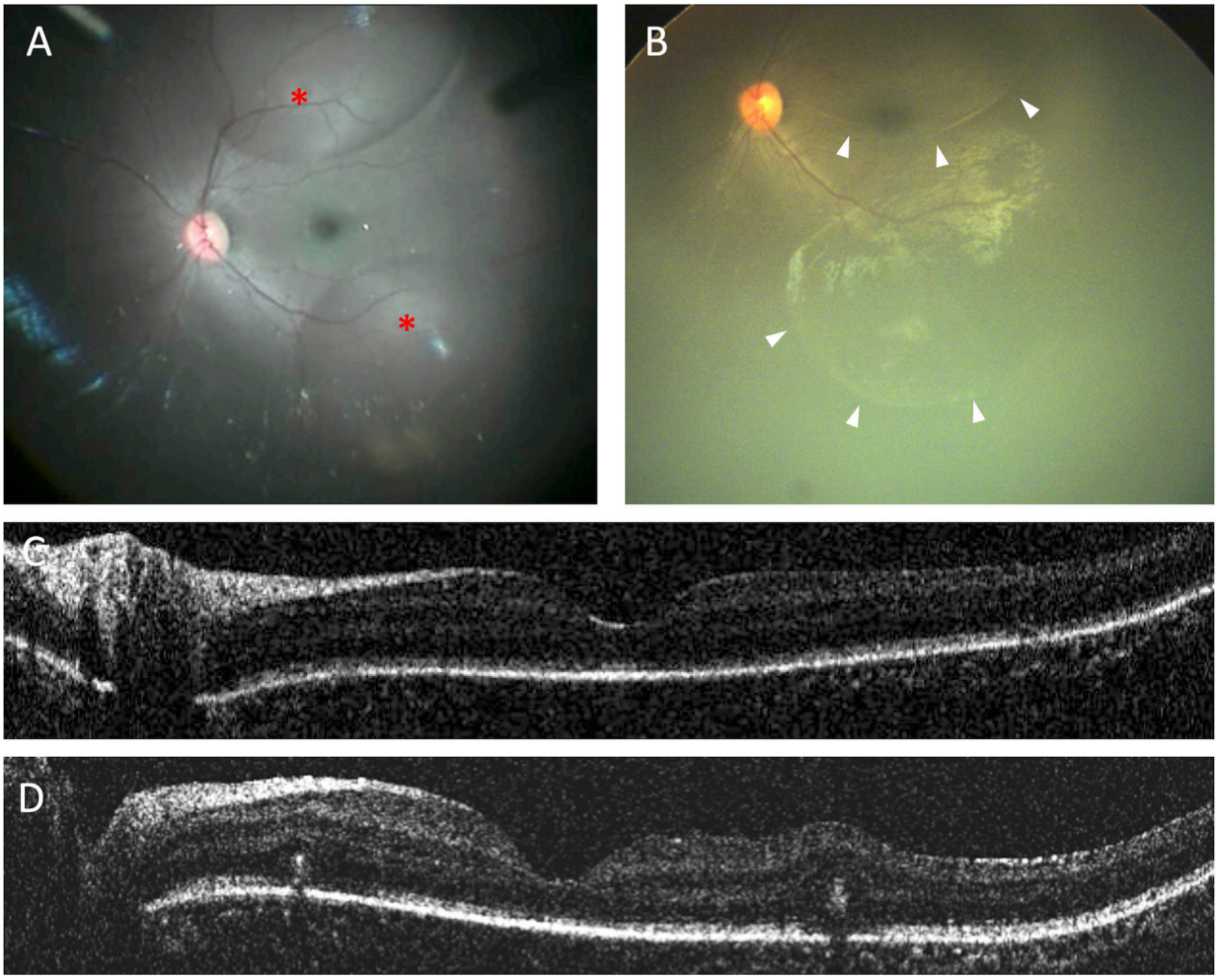

Figure 2.

2-year-old female (Case 2). A, Intraoperative photograph of the left eye demonstrating two blebs with red asterisks at the retinotomies. B, Retcam image of the left eye at post-operative week 1 showing the arcuate subretinal deposits (arrowheads). Hand-held OCT of the left macula pre-operatively (C) and at post-operative week 1 (D) showing the subretinal deposits.

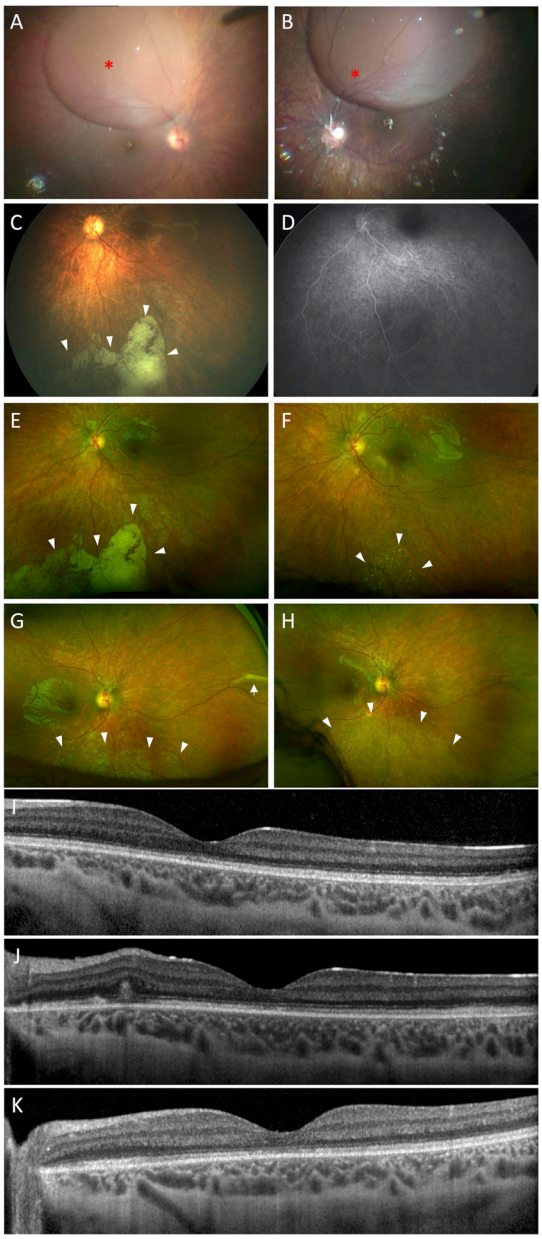

Figure 3.

5-year-old female (Case 3). Intraoperative photographs of the right (A) and left (B) eyes showing the bleb positions, with retinotomies denoted by red asterisks. C, Fundus photograph of the left eye at post-operative week 1 showing a subtle line in the nasal macula and an inferior area of subretinal whitening (arrowheads). D, Fluorescein angiography showed blockage over the subretinal whitening without evidence of leakage. Fundus photographs of the left eye at post-operative week 2 (E) and month 3 (F). G, Post-operative week 1 photo of the right eye showing an inferior area of subretinal whitening (arrowheads), a white deposit nasally (arrow), and a subtle strip in the nasal macula. At post-operative month 3 (H), the subretinal deposits in this eye are resolving. OCT of the left macula

showing EZ attenuation at baseline (I), subretinal deposits nasally at post-operative week 2 (J), and resolution at month 3 (K).