

Retinal Pigment Epithelium Atrophy After Subretinal Voretigene Neparvovec-rzyl for RPE65-Related Disease: A 6-Month Follow-Up

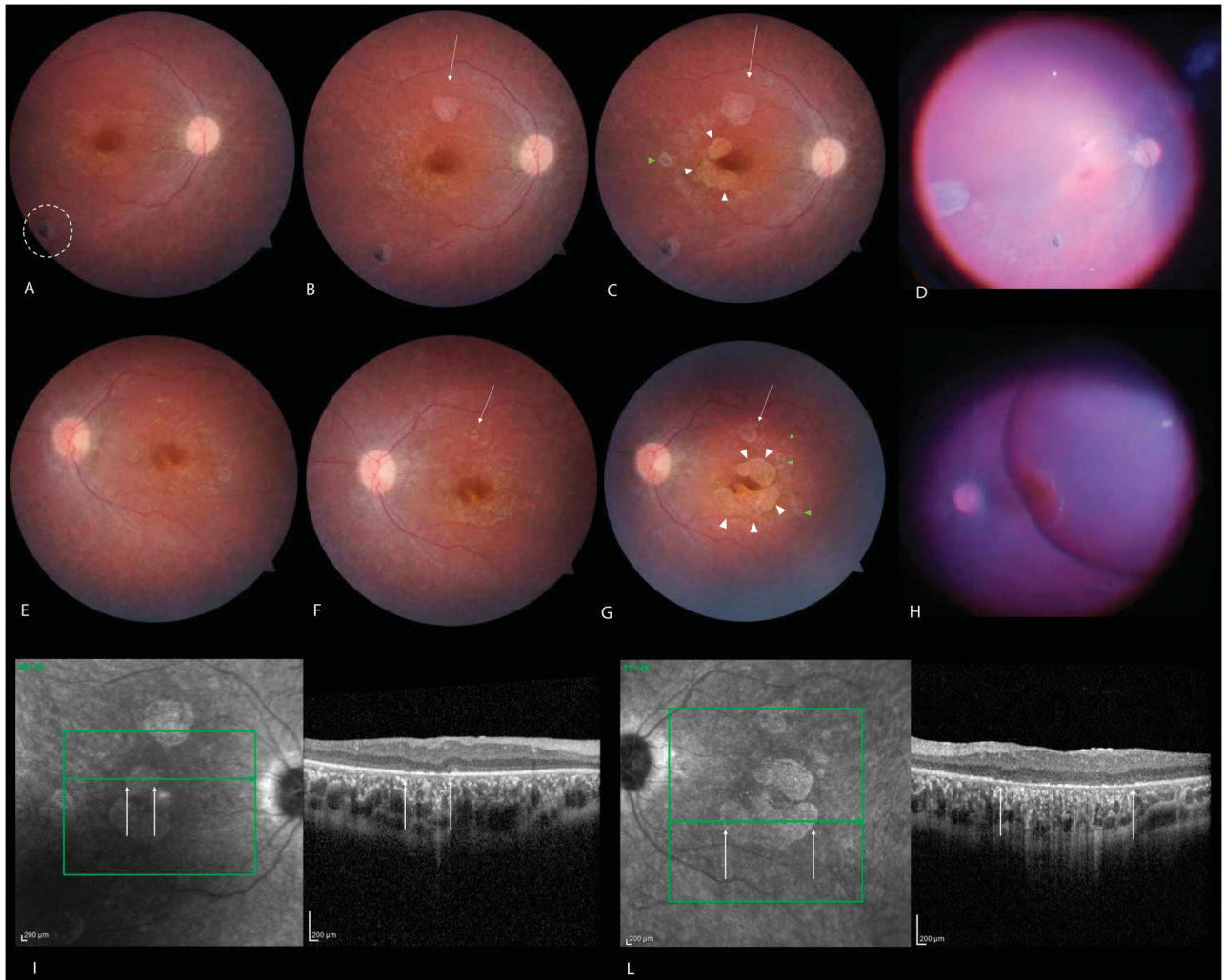


Fig. 1. Color fundus photographs of the right eye (A–C) and the left (E–G) eye of a 20-year-old male patient showing bilateral progressive RPE atrophy during a 6-month follow-up after VN gene therapy. Intraoperative images (D and H) demonstrating the extent of the subretinal bleb. Before the VN injection, a small atrophic area is present in the right eye (A) (white circle); 3 months after the VN injection, a small circular atrophic area appears at the posterior pole (B) (arrow) which corresponds to the touchdown site of the cannula for the subretinal injection; 6 months after the VN injection, 4 small RPE atrophic areas appear (arrowheads) (C): 3 small coalescent perifoveal areas (white arrowheads) and one small atrophic area at the boundaries of the vascular arcades (green arrowhead). In the left eye, image (F) showing a small RPE atrophic area 3 months later VN gene therapy (arrow) which corresponds to the touchdown site of the cannula, image (G) showing confluent perifoveal RPE atrophic areas (white arrowheads) and small circular atrophic RPE areas inside the vascular arcades (green arrowheads) 6 months later the VN gene therapy. Optical coherence tomography images (I, L) showing atrophic RPE areas (arrows) of the right and the left eyes, respectively.

Retinal disease caused by biallelic mutations in the *RPE65* gene is a sight-threatening disorder that eventually progresses to complete blindness.¹ Voreti-

gene neparvovec (VN) gene therapy (Luxturna, Spark Therapeutics, Philadelphia, PA) is the current treatment for patients affected by retinal dystrophy caused

by biallelic *RPE65* mutations.^{2,3} Some common adverse events were intraocular pressure elevations (18%), cataract (18%), retinal tears (8%), and ocular inflammation (8%).^{2,4} To date, there is only one report which described the occurrence of chorioretinal atrophy after VN gene therapy in 18 eyes of 10 patients.⁵

We have reported a 6-month follow-up of a 20-year-old patient who developed a progressive bilateral retinal pigment epithelium atrophy (RPE) after subretinal injection of VN (Figure 1). Our findings agree with the results of Gange et al⁵; more specifically, we showed that even the atrophic areas which correspond to the touchdown site of the cannula for the subretinal injection enlarged up to 6 months of follow-up (Figure 1). Although the pathogenesis of the chorioretinal atrophy is not known at this time, Gange et al⁵ hypothesized several potential factors which could be responsible of this phenomenon; moreover, Gange et al⁵ observed the progressive enlargement in all patients up to the last follow-up examination, in 1 case up to 18 months. Regarding our patient, the areas of atrophy occurred on areas already devoid of photoreceptors before the treatment, sparing the center of the fovea; for this reason, we attributed the main cause of the development of these atrophic areas to the atrophy of the RPE. Furthermore, in our patient, we did not observe a worsening of the visual acuity (0.60 logMAR in both eyes) and visual field (Goldmann visual field); however, we did not know how this phenomenon will change over a longer period of time.

Key words: gene therapy, RPE65, atrophy, inherited retinal disease.

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