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Commentary

Durable Safety and Efficacy of Voretigene Neparvovec-Rzyl in Postapproval Studies in the USA: CRAning for Perfection

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Voretigene neparvovec-rzyl (VN; Luxturna) was approved by the US Food and Drug Administration nearly 9 years ago as the first gene therapy product to treat an inherited disease. Now, VN is approved by the European Medicines Agency and a total of 29 countries. Interim postapproval results from 10 centers in the VN postauthorization safety study group in the United States reported by Nagiel et al[1] (p. 1420) are consistent with those previously reported from other centers and the clinical trials themselves. Most patients show rapid, significant, and sustained improvements in light sensitivity and other measures. Voretigene neparvovec-rzyl also continues to have a favorable safety profile. The one postapproval safety finding that has garnered attention is chorioretinal atrophy (CRA), which, except for the expected cannula touch-down scars, was rarely detected in the clinical trials using the then-available imaging tools. Nagiel et al[1] used widefield scanning laser ophthalmoscopy and spectral-domain OCT to anatomically classify CRA as follows: (1) touch-down site (i.e., the expected retinotomy scar), (2) nummular (peripheral coin-shaped), and (3) macular (perifoveal) lesions. The investigators compared the prevalence of each type with other details (genotype, patient age, anatomic features, surgical device, steroid prophylaxis, etc.). Interestingly, they found that CRA correlated with an enhanced therapeutic effect in a subset of patients.

Nonretinotomy site CRA occurred in 66% of eyes, with 26.7% being perifoveal and 60% showing complex patterns (combinations of nummular and perifoveal). Some of the findings could be explained by surgical complications. Of the remainder, statistical analyses revealed the following 2 primary risk factors: (1) history of myopia (previously identified as a risk factor in the clinical trials[2]); and (2) use of an automated foot pedal. Interestingly, a higher proportion of eyes with CRAs after automated injection system use was also reported in a multicenter prospective postapproval study of VN in Europe and the United Kingdom.[3] The clinical trials had used manual injection as described in the Food and Drug Administration prescribing guidelines.[4] Although automated injection is now considered state-of-the-art, increased CRA-identified postapproval could be related to the need to transfer the material from the Spark Therapeutics—validated syringe to a second syringe required for the automated device. Although this may seem trivial, there may be differences in binding properties and biocompatibility with the second syringe. Also, the use of the automatic system may alter mechanical conditions (such as injection pressure, speed, or other variables).

Most subretinal injection experience derives from experimental gene-based therapies. Although VN is the only approved retinal gene therapy product, thousands of eyes have received subretinal injections of other adeno-associated viruses, many using foot pedal injection techniques. Chorioretinal atrophy of the type described by Nagiel et al has not been reported in gene therapy trials for diseases caused by mutations in genes other than that which encodes the retinal pigment epithelium-specific 65 kDa protein (*RPE65*), including choroideremia, neovascular age-related macular degeneration, X-linked retinitis pigmentosa, and Leber congenital amaurosis because of mutations in genes that encode lebercilin (*LCA5*), retinal guanylyl cyclase 1 (*GUCY2D*), or centrosomal protein of 290 kDa (*CEP290*). What features of the *RPE65* disease might predispose to CRA? Perhaps there is increased sensitivity of photoreceptors and retinal pigment epithelial cells to focal pressure. Perhaps the relative anatomic preservation in the *RPE65* disease simply enhances the ability to detect CRA changes after injection. It may also be more difficult to identify treatment-induced CRA when this phenomenon occurs in eyes with extensive, advanced degeneration (as in adults with choroideremia).

What is clear is that, in most cases, VN improves visual function in patients with *RPE65* disease. Continued tabulation of details of the VN injection procedure, vision outcomes, and identification and characterization over time of different subtypes of CRA as done by Nagiel et al[1] will help optimize treatment parameters for *RPE65* deficiency and ultimately also other diseases in the gene therapy pipeline.

Footnotes and Disclosures

Disclosure(s):

The author has completed and submitted the ICMJE disclosures form.

The author has made the following disclosures:

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