Use of Viral Vectors in the Treatment of Retinal Disease

Early-phase clinical trials of several gene therapy entities are under way.

BY ANDREAS K. LAUER, MD

The rapidly emerging field of ophthalmic gene therapy promises to provide unique opportunities for the treatment of retinal diseases that were previously considered untreatable. Gene transfer approaches using safe viral vector delivery systems offer the possibility of promoting sustained gene expression with therapeutic efficacy.

The Casey Eye Institute at Oregon Health & Science University is currently participating in several gene therapy clinical trials, for diagnoses including Leber congenital amaurosis (LCA), Stargardt disease, Usher syndrome type 1b, and neovascular age-related macular degeneration (AMD). This article presents an overview of the status of these early-stage clinical trials.

**LCA TRIAL**

LCA is a rare inherited eye disease that appears within a few months of birth.1 A phase 1/2 study evaluating the safety and efficacy of an adeno-associated virus (AAV)-based vector expressing RPE65 in patients with LCA caused by mutations in the RPE65 gene is ongoing but no longer enrolling patients.2 The trial, sponsored by Applied Genetic Technologies Corporation, enrolled patients at Casey Eye Institute and the University of Massachusetts in Worcester.

The biologic, called rAAV2-CB-hRPE65, consists of a nonreplicating recombinant AAV vector that contains cDNA encoding the human retinal pigment epithelium (RPE)-specific protein hRPE65. The treatment is administered via transvitreal subretinal injection at the time of vitrectomy surgery.

In this nonrandomized, open-label study, 12 patients with LCA caused by mutations in the RPE65 gene received 1 subretinal injection of rAAV2-CB-hRPE65. The study included 2 cohorts of 6 patients each, receiving 2 concentrations of the vector. In the 12 patients, all of whom were older than 6 years, no drug-related adverse events, vision loss, serologic abnormalities, or inflammatory sequelae were seen.

The patients were injected using a 41-gauge dual-bore cannula, and blebs were created in a number of locations, including 1 that involved the macula. Although I am not at liberty to discuss detailed results, gains in letters of vision were seen in treated eyes, whereas in untreated fellow eyes the vision remained relatively unchanged.

**STARGARDT TRIAL**

Stargardt disease is the most common form of inherited juvenile macular degeneration, with typical age of onset from 7 to 12 years. It is caused by mutation in the ABCA4 gene on Chr1p22 that codes for an ATP-binding cassette transporter that is present in the photoreceptor outer disc. Because it is virtually impossible to increase the activity of a defective transport protein using any other molecule, delivery and expression of a functional version of the ABCA4 gene is potentially an ideal use of gene therapy. Even a modest restoration of the gene’s activity should lead to delayed degeneration.

A phase 1/2a clinical trial, sponsored by Oxford BioMedica, using a lentiviral vector developed by that company, is currently recruiting patients at the Casey Eye Institute and the Hôpital Nationale des Quinze-Vingt in Paris. The purpose of the study is to examine the safety of an experimental gene transfer agent, called StarGen (Oxford BioMedica), in which the vector is based on the equine infectious anemia virus (EIAV). A dose-escalation phase of the study will evaluate 3 doses of StarGen, with 8 patients at the first dose level and 4 at each of the next 2 levels. A dose-confirmation phase will follow, in which the highest dose that is safe and well-tolerated will be evaluated in up to 12 patients. All patients will be older than 18 years and will have the ABCA4 mutation.3
The study design is similar to the other trials described above, with 3 cohorts receiving escalating doses of gene therapy in a single subretinal injection, followed by a dose-confirmation phase in which 12 patients will receive the maximum tolerated dose. The primary outcome measure will be the incidence of adverse events, and secondary outcome measures will include change from baseline in the amount of subretinal and intraretinal fluid as measured by optical coherence tomography. A total of 21 patients age 50 years or older, with a clinical diagnosis of AMD, best corrected visual acuity of 20/200 or worse in the study eye, and clinical evidence of choroidal neovascularization will be recruited.5

The gene transfer agent, in this case called RetinoStat (Oxford BioMedica), uses the EIAV vector to deliver a package of 2 anti-angiogenic genes, endostatin and angiotatin, separated by an internal ribosome entry site (IRES). An IRES is a nucleotide sequence that allows translation to be initiated in the middle of a messenger RNA (mRNA)—in other words, essentially allowing translation of both proteins at once (Figure 1).

CONCLUSION

These phase 1 and phase 1/2 studies, which will report safety data and preliminary efficacy data, are projected to conclude this year or in 2014. This is an exciting time for ophthalmologists, as we can look forward to learning more about the prospects for the use of gene therapy approaches in a variety of posterior segment disorders. The first announcements of results may come as soon as later this year.

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