

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

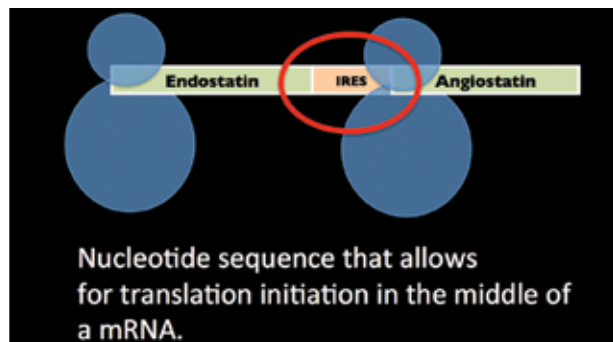


Figure 1. The gene transfer agent RetinoStat uses a viral vector to deliver a package of 2 anti-angiogenic genes, endostatin and angiostatin, separated by an internal ribosome entry site (IRES). An IRES is a nucleotide sequence that allows translation to be initiated in the middle of a messenger RNA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

USHER TRIAL

Another phase 1/2a trial, also sponsored by Oxford BioMedica, using a gene transfer agent called UshStat (Oxford BioMedica), also based on the ElAV vector, is currently recruiting patients with retinitis pigmentosa (RP) associated with Usher syndrome type 1b.⁴

Usher syndrome is a recessively inherited disorder associated with both congenital deafness and progressive blindness from RP. It is caused by a defect in the gene encoding the myosin motor protein (MYO7A). This gene is important in the movement of melanosomes and phagosomes in the retinal pigment epithelium, and it is also involved in transport of opsin through the ciliary plasma membrane.

This trial, enrolling patients at Casey Eye Institute, will evaluate the safety of subretinally injected UshStat. The primary outcome measure will be the incidence of adverse events. Secondary outcome measures will include determination of any delay in degeneration; changes in function relative to the fellow untreated eye will be evaluated with retinal analytical techniques. An estimated 18 patients will be enrolled, 18 years of age or older, and each will receive a single dose in 3 escalating doses.⁴

Patients currently being enrolled have very significant visual field constriction, with pronounced degeneration in the outer retina. We are deliberately not placing the vector underneath the macula, but rather putting it in nasally.

AMD TRIAL

Finally, a phase 1 clinical trial in patients with neovascular AMD, again sponsored by Oxford BioMedica and using a similar gene delivery technology developed by the company, is enrolling patients at Casey Eye Institute and Johns Hopkins University Hospital.⁵

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 ElAV vector to deliver a package of 2 anti-angiogenic genes, endostatin and angiostatin, 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. ■

Andreas K. Lauer, MD, is Vice Chair of Education, Associate Professor of Ophthalmology, Chief of the Vitreoretinal Division, and Director of the Residency Program at the Casey Eye Institute at Oregon Health & Science University. Dr. Lauer states that his employer, Oregon Health & Science University, receives funding from the National Eye Institute, GlaxoSmithKline, Acucela, Oxford BioMedica, and Applied Genetic Technologies Corporation for investigator participation in clinical trials. He can be reached at +1 503 494 8093; fax: +1 503 494 7233; or at lauera@ohsu.edu.



1. Stone EM. Leber congenital amaurosis - a model for efficient genetic testing of heterogeneous disorders: LXIV Edward Jackson Memorial Lecture. *Am J Ophthalmol.* 2007;144(6):791-811.

2. Phase 1/2 Safety and Efficacy Study of AAV-RPE65 Vector to Treat Leber Congenital Amaurosis. <http://clinicaltrials.gov/ct2/show/NCT00749957>. Accessed May 22, 2013.

3. Phase I/IIa Study of StarGen in Patients With Stargardt Macular Degeneration. <http://clinicaltrials.gov/ct2/show/NCT01367444?term=stargen&rank=2> Accessed May 22, 2013.

4. Study of UshStat in Patients With Retinitis Pigmentosa Associated With Usher Syndrome Type 1B. <http://clinicaltrials.gov/ct2/show/NCT01505062?term=ushstat&rank=1>. Accessed May 22, 2013.

5. Phase I Dose Escalation Safety Study of RetinoStat in Advanced Age-Related Macular Degeneration (AMD) (GEM). <http://clinicaltrials.gov/ct2/show/NCT01301443?term=retinostat&rank=2>. Accessed May 22, 2013.