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STEM CELL THERAPY: A RIGHT WAY AND A WRONG WAY

Many mainstream news outlets recently carried the story of three elderly women in Florida blinded by an unapproved so-called stem cell treatment at a for-profit clinic there.[1] Overlooked by many of those media reports, however, was the parallel story of the first use of an experimental autologous stem cell treatment for age-related macular degeneration (AMD).[2]

The contrast could not be more stark between the two stories. On the one hand, the unapproved use of autologous adipose tissue at the Florida clinic, reportedly taken from the abdomens of the three women and injected bilaterally, directly into their eyes.[3] On the other, the meticulous and carefully designed technique employed by Japanese researchers, treating one eye of a carefully selected patient with polypoidal choroidal vasculopathy.

Both episodes were documented side by side in the March 16 issue of the *New England Journal of Medicine*, along with a scathing editorial by George Q. Daley, MD, PhD, noting the "polar extremes" demonstrated in the conduct of the Japanese researchers compared with the practitioners at the for-profit Florida clinic.[4]

The good news: Mandai et al reported that they successfully generated induced pluripotent stem cells (iPSCs) from fibroblasts from the patient's skin and cultured them into a monolayer sheet of retinal pigment epithelium (RPE) cells. After extensive characterization of the iPSC-RPE cell line, including whole-genome sequencing and expression analyses, the sheet was implanted in the patient's eye. In this procedure, surgeons first removed the neovascular membrane and then implanted the sheet under the fovea. Postoperatively, the patient experienced elevated intraocular pressure (IOP) that was controlled by medication, and her vision stabilized at 20/200 without further deterioration. Her scores on a questionnaire indicated improvements in visual function and general health.

The not-so-good-news: As has been widely reported, three women are now blind after receiving a so-called stem-cell treatment at a clinic called Bioheart, Inc., since renamed US Stem Cell. Ophthalmologists at Bascom Palmer Eye Institute who later treated the women described their efforts in the *New England Journal* article. Sequelae of the treatments included ocular hypertension, hemorrhagic retinopathy, vitreous hemorrhage, combined traction and rhegmatogenous retinal detachment, and lens dislocation. At 1 year follow-up, the patients' visual acuity ranged from 20/200 to no light perception.

1. McGinley L. Three women blinded by unapproved stem-cell 'treatment' at South Florida clinic. *Washington Post*. March 15, 2017. www.washingtonpost.com/news/to-your-health/wp/2017/03/15/three-women-blinded-by-unapproved-stem-cell-treatment-at-south-florida-clinic/?utm_term=.9fe9a9c3f0a0. Accessed April 7, 2017.
2. Mandai M, Watanabe A, Kurimoto Y, et al. Autologous induced stem-cell-derived retinal cells for macular degeneration. *N Engl J Med*. 2017;376(11):1038-1046.
3. Kuriyan AE, Albini TA, Townsend JH, et al. Vision loss after intravitreal injection of autologous "stem cells" for AMD. *N Engl J Med*. 2017;376(11):1047-1053.
4. Daley GQ. Polar Extremes in the Clinical Use of Stem Cells. *N Engl J Med*. 2017;376(11):1075-1077.

Vision Gains Maintained in Aflibercept Extension Study

Improvements in visual acuity achieved with treatment by an anti-VEGF agent in a randomized clinical trial were then maintained out to 4 years in an extension study using aflibercept (Eylea, Regeneron), according to the published results of the study.[1]

The prospective, multicenter, open-label, 2-year VIEW 1 extension study included 323 patients who had been randomly assigned to one of several fixed dosing regimens of anti-VEGF therapy in the VIEW 1 trial. In the extension study, they received 2 mg aflibercept on a modified quarterly dosing schedule followed by dosing at least every 2 weeks. Total time from baseline of VIEW 1 to the end of the extension study was 212 weeks.

Patients enrolled in the extension study had gained a mean 10.2 letters from VIEW 1 baseline to the end of that study at week 96. These patients then largely maintained those vision gains during the extension study, with a mean gain of 7.1 letters from VIEW 1 baseline to week 212. There was an average loss of 2.7 letters (range, -0.02 to -3.0) between VIEW 1 week 96 and the end of the VIEW 1 extension study at week 212.

Anti-VEGF injections were well tolerated, including up to 4 years of 2 mg aflibercept injections in those randomized to that treatment arm in VIEW 1, with no new safety signals seen during the extension.

1. Kaiser PK, Singer M, Tolentino M, et al. Long-term safety and visual outcome of intravitreal aflibercept in neovascular age-related macular degeneration: VIEW 1 Extension Study [published online ahead of print March 18, 2017]. *Ophthalmology Retina*.

First Gene Therapy Trial for XLRP Begun

A phase 1/2 clinical trial to treat patients with X-linked retinitis pigmentosa (XLRP) using gene therapy has begun enrolling and treating patients, according to a press release from the developer of the therapy, NightstaRx.

XLRP, one of the most common causes of blindness in

young people, is a congenital degenerative disease of the rod and cone photoreceptors for which there is no treatment. This is the first clinical trial of gene therapy in XLRP, according to the company.

In this treatment approach, an adeno-associated viral vector (AAVV) will be used to deliver a codon-optimized copy of the retinitis pigmentosa GTPase regulator (*RPGR*) gene into cells in the retina.

"Based on previous findings in preclinical in vivo disease models, which have shown significant rescue of photoreceptors, we believe this approach has great potential to restore or maintain sight in patients. The unique codon-optimization strategy overcomes the inherent instability problems of *RPGR* that confounded earlier attempts at gene replacement," said Robert E. MacLaren, FRCOphth, FRCS, VR, a professor of ophthalmology at the University of Oxford and a principal investigator in the trial.

The multicenter open-label dose-escalation study will enroll at least 24 male patients who will receive a single subretinal injection of AAV-XLRPGR gene therapy, according to the company. The primary goal of the study is to assess safety and tolerability of AAV-XLRPGR over a 12-month period.

Intravitreal Injections Associated With Increased Risk for Glaucoma Surgery

Patients receiving more than seven intravitreal injections of the anti-VEGF agent bevacizumab (Avastin, Genentech) per year had a higher risk of undergoing glaucoma surgery than control patients, according to a study published in *JAMA Ophthalmology*.[1]

It is known that sustained IOP elevation occurs after intravitreal anti-VEGF injections, but the longer-term effects of these IOP rises have not been explored. Investigators in British Columbia, Canada, analyzed data from large, population-based health databases to determine the risk of glaucoma surgery after repeated injections of bevacizumab. In this nested case-control study they included all patients who had received intravitreal injections of bevacizumab for AMD over a 5-year period. They then identified all patients who had undergone glaucoma surgery using surgical codes for glaucoma procedures.

In 74 glaucoma surgery patients and 740 controls, the investigators compared the number of intravitreal injections per year, adjusting for comorbidities and other factors. They found that the rate ratio for glaucoma surgery was higher in those who had received seven or more injections per year; there was a 10% higher number of injections among cases compared with controls. There was also a higher rate ratio for those who had received four to six injections, but this difference was not statistically significant.

1. Eadie BD, Etminan M, Carleton BC, Maberley DA, Mikelberg FS. Association of repeated intravitreous bevacizumab injections with risk for glaucoma surgery [published online ahead of print March 16, 2017]. *JAMA Ophthalmol*.

Allergan Has Option to License Genome Editing Programs

Allergan Pharmaceuticals and Editas Medicine have entered into an agreement through which Allergan will have the option to license up to five of Editas Medicine's genome-editing ocular programs, according to a joint press release from the companies. The agreement will include Editas Medicine's lead program for a form of Leber congenital amaurosis (LCA10), which is now in the preclinical development stage.

Editas' is one of the companies and academic centers developing clustered regularly interspaced short palindromic repeats (CRISPR) gene editing technology, which allows editing of DNA at specified locations in the human genome. According to Editas, CRISPR genome editing has the potential to treat a broad range of genetically defined and genetically treatable diseases.

"The CRISPR genome editing platform holds the potential to transform the treatment of many genetic and non-genetically derived diseases, including diseases and conditions of the eye," said David Nicholson, chief research and development officer at Allergan, in the press release.

Under the agreement, Editas will receive an upfront payment of $90 million for the development of five candidate programs, with the potential to earn additional payments on achievement of milestones related to LCA10. Allergan can option up to five programs and can develop and commercialize those products. Editas will have the option to codevelop and copromote up to two of those programs in the United States and will be eligible to receive royalty payments. ■

ERRATUM

The January/February Innovations in Retina column incorrectly referred to the ongoing clinical trials of RG7716 as the RUBY study (for patients with center-involving diabetic macular edema) and the ONYX study (for patients with wet AMD). The correct study names are BOULEVARD and AVENUE, respectively. *Retina Today* regrets the errors.