Phase II trial

Neural cell transplant may improve vision for RP, AMD patients

Clinical evidence of improvement seen in seven of the first 10 patients

By Nancy Groves
Reviewed by Norman D. Radtke, MD

Louisville, KY—Implantation of sheets of immature neural retinal progenitor cells with their retinal pigment epithelium could benefit people with retinitis pigmentosa (RP) and age-related macular degeneration (AMD). The first results of a phase II trial, which corroborated findings from animal models, are promising, said Norman D. Radtke, MD, Retina Vitreous Resource Center, Louisville, KY.

"Fetal retinal sheets bypass the difficulty of stem cells that need complex molecular and external factors to grow into mature and functional retinal cells," he said.

"Transplantation with fetal retinal sheets avoids the current complexity of gene therapy. For example, at least 135 types of mutations so far have been identified in retinitis pigmentosa. The beneficial effects seen in several animal degeneration models and in patients indicate that retinal transplantation could be a viable therapy," he explained.

The rationale for this transplantation technique is that, even in advanced RP, despite near total loss of the photoreceptors, 80% of the inner nuclear layer and 30% of the retinal ganglion cell layer still remain. Preservation of the ganglion cells is even greater in patients with AMD.

Take-Home Message

Results so far in a phase II clinical trial indicate that a technique to implant sheets of immature neural retinal cells and retinal pigment epithelium together can improve vision of patients with retinitis pigmentosa or age-related macular degeneration. Clinical evidence of visual improvement was seen in seven of the first 10 patients of the phase II trial. (Ten additional patients were treated in the preceding phase I trial.)

"Our hypothesis is that cells damaged in retinitis pigmentosa or macular degeneration can be replaced with progenitor cells that will integrate with the still-functional inner retina and restore visual function," Dr. Radtke said.

First tests

He and his colleagues first tested their hypothesis in an animal model. They developed the transplant procedure, showed that the transplant improved visual function, and demonstrated that the transplant integrated with the neural circuitry.

In their preclinical studies, the researchers transplanted sheets of immature, donated human fetal neuroretinal tissue along with retinal pigment epithelium into albino immunodeficient rats, which do not reject foreign tissue. About 8 months later, they observed well-developed photoreceptors in contact with the transplanted epithelium monolayer, which indicated that the transplant was technically possible, Dr. Radtke said.

They demonstrated preserved or restored light sensitivity responses to flash stimuli in the eye in four mouse and rat degeneration models. Electrical recordings in an area of the superior colliculus that corresponds with the placement of the transplant in the retina showed that the transplant improved visual function.

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Visual response

Two to 6 months after the transplantation, the recordings confirmed a specific area of visual response. This response was verified by injecting a virus that migrated through the optic nerve to the transplant in the eye. On the basis of these and other studies, the investigators received an FDA investigational new drug number in May 1999 to undertake clinical trials.

Focal Point

The positive outcomes of seven patients encourages researchers to complete the phase II study with more patients and prepare for a phase III trial.

Before transplantation, the doctor, the patient, and the patient's family held extensive discussions to ensure realistic expectations. Preoperative and postoperative testing and surgery were conducted at no cost to the patient. The donor and recipient were unknown to one another.

A variety of tests was conducted pre- and postoperatively; ETDRS testing was performed by the study team and at an independent site. If results differed, the data from the independent site were recorded. Complete eye exams with fluorescein were done at each visit. Multifocal electroretinogram and scanning laser ophthalmoscope tests were conducted at independent sites. Patients were offered yearly follow-up exams, and one has been followed out to 5 years.

Both donors and recipients were typed. No immunosuppressive medications were used, and the recipients did not produce donor-specific antibodies.

"From this information, we conclude that the survival of the transplant was not due to donor-recipient matches," Dr. Radtke said.

Of 10 transplants on which 1-year follow-up data are available, seven patients have had visual improvement in one or both eyes, two have continued to experience deterioration of their vision, and one has demonstrated no change. The criterion for success was improvement on ETDRS testing, which was performed by an independent ophthalmologist in masked fashion.

Several patients expressed subjective improvement, including a patient whose vision had deteriorated according to ETDRS results and a patient whose vision was unchanged.

The most successful case has been a patient whose visual acuity improved from 20/800 preoperatively to 20/160 at 12 months postoperatively. Her vision remains 20/200 5 years postoperatively.

"We recognize that, although results are with a few patients, the positive outcomes of seven patients encourages us to complete the phase II study with more patients and prepare for a phase III trial," Dr. Radtke said. **OT**

FYI

Norman D. Radtke, MD
Phone: 502/636-2823
E-mail: radtke@prodigy.net
Dr. Radtke has a commercial relationship with Ocular Transplantation LLC.