Stem Cells Hold Vision for the Future

AS AN OPHTHALMOLOGIC surgeon, Edward J. Holland, MD, tries to offer hope to hopeless eyes. One of his beneficiaries is 77-year-old Donald Smolley. The men met several years ago at the University of Minnesota Hospitals and Clinics in Minneapolis, where Holland directs the Corneal and External Disease Service. After a burning backsplash of drain-clearing liquid in 1968, Smolley was left legally blind in his right eye and with little vision in the left.

A corneal transplant in Smolley’s right eye shortly after the injury failed outright. Some sight returned to his left eye, and Smolley continued working as building superintendent at the Minneapolis public library. But eventually the left eye began to fail. Smolley took early retirement, and he and his wife moved to the small western Minnesota town of Montevideo.

“I couldn’t see to go across the street; I couldn’t see what was on my plate at dinner,” Smolley recalled. So when he was referred to Holland in the early 1990s, “I couldn’t see anything, so I was willing to try anything,” Smolley said. “Dr Holland said it wasn’t guaranteed, but the surgery was better for the type of chemical burn I had than for disease. I was a good candidate.”

Importance of Ocular Surface

Holland performed a keratolimbal allograft on Smolley’s right eye as a prelude to a subsequent penetrating keratoplasty. The procedure Holland used has evolved from a finding in the mid 1980s that at the junction of the cornea and sclera are limbal stem cells that give rise to the corneal epithelium (J Cell Biol. 1986;103:49-62).

Since then, ophthalmologists have realized that, in some patients, keratoplasty doesn’t fail because of tissue rejection but because the stem cells have been destroyed and the transplanted cornea can’t thrive without a healthy ocular surface. Therefore, the mission for some ophthalmologic surgeons in recent years has been to develop techniques to transplant stem cell-containing tissue capable of replenishing the ocular surface, helping to ensure more successful keratoplasties and restoration of sight.

During a recent Research to Prevent Blindness science writers seminar in Universal City, Calif, Holland discussed refinements in epithelial transplantation that have enabled some patients with profound visual loss to regain sufficient sight to drive a car or see a loved one’s face. Or in Smolley’s case, surprise his friends and neighbors by reading the breakfast menu at a local cafe.

Epithelial transplantation is a term that includes several different types of procedures. Holland has proposed a system to classify the procedures based on the source of tissue for transplantation and the type of tissue used as the stem cell carrier (Cornea. 1996;15:549-556). For example, tissue can be taken from a patient’s healthy eye in cases of unilateral ocular surface disease. In patients with bilateral disease, successful operations have been performed using tissue from cadaveric and living related donors. Depending on patient characteristics, grafts of conjunctiva, limbus and conjunctiva, or limbus and cornea may be used to re-establish a healthy ocular surface.

Treating Bilateral Blindness

Even though the concept of ocular surface transplantation has been around for 20 years (Arch Ophthalmol. 1977;95:1425-1427) and has produced several techniques, Holland has focused his attention specifically on the keratolimbal allograft. The procedure is intended for patients who are blind in both eyes as a result of chemical or thermal injuries, stem cell failure from multiple surgical procedures, aniridia, or Stevens-Johnson syndrome. “A lot of these patients have fallen out of the system because there was nothing to offer them,” Holland said. “Now we’re trying to get them back in because this is a new opportunity for them.”

The procedure consists of harvesting a rim of corneoscleral tissue that contains stem cells from a cadaveric or living related donor and transplanting it into the diseased or injured eye. “In standard corneal transplantation, we punch the central two thirds of the cornea and...
that is the tissue we transplant,” Holland said. “In this operation, we don’t want that tissue, we want the peripheral tissue where the cornea meets the sclera. The base of this epithelium is where the stem cells are located.” The rims of tissue are cut into pieces and placed around the limbus of the diseased cornea to form a 360-degree circle of stem cells.

The Minnesota Lions Eye Bank in Minneapolis works closely with Holland to provide tissue for the transplants. About 10 patients currently are waiting for keratolimbal allograft surgery. “But the list seems to be growing,” said Jackie Malling, RN, technical director of the eye bank.

Malling said preparation and storage procedures differ for tissues used in keratolimbal allograft from those used in corneal transplant. “To preserve stem cells and prevent damage to them, the conjunctiva around the limbus of the cornea is kept in place,” Malling said. Normally, the conjunctiva is removed to prevent possible bacteria growth. More sclera is kept in place, Malling added, and the tissue has to be used within 72 hours, as opposed to the 7 to 14 days for a standard corneal transplant. And for keratolimbal surgery, she noted, the epithelial layer of the graft has to be “almost perfect.”

Because keratolimbal allograft outcomes are best with tissue from young donors, Malling said tissue taken from any donor aged 40 years or younger is automatically prepared for a possible keratolimbal procedure. Because of the briefer viability of the tissue, Malling said, coordinating the surgeon, patient, and a suitable graft to carry out the procedure “is very much a timing issue.” The procedure also can be done with tissue from a living related donor. “If the donor has a healthy eye, we can take 50% of the stem cells and not see any problem in the donor eye,” Holland said. But not every patient has a relative able and willing to become a donor, he noted.

Evaluating Outcomes

Holland said he has performed keratolimbal allografts on about 40 patients. In a recent evaluation of 25 eyes of 21 of those patients, Holland said 72% developed a stable ocular surface and 60% demonstrated significant improvement in visual acuity. In 46% of 13 eyes, subsequent keratoplasty was successful (Trans Am Ophthalmol Soc. 1996;94:677-743). Stabilization of the ocular surface generally takes about 3 months and frequently is associated with reduced sensitivity to pain and light.

Holland said keratolimbal allograft can restore sight to some of ophthalmology’s most challenging patients desperate to see even a small slice of life. “Tens of thousands are bilaterally blind in the United States alone,” he said. For Don Smolley, the surgery and subsequent keratoplasty in both eyes has meant restoring vision in his left eye to 20/25 and the renewed independence that comes with being able to drive a car. “Sometimes I can see better than my wife,” he quipped.

But Holland conceded that the surgery won’t help every patient with ocular surface disease, and because the procedure is relatively new, with data on fairly short follow-up times of 1 to 2 years, many questions about the procedure remain unanswered. For example, he said, patients with no aqueous tear production or preoperative conjunctival keratinization have a poor prognosis. And even though all patients receive systemic immunosuppression, Holland said the possibility of rejection can’t be overlooked. “About 1 or 2 years after the surgery, we see some failure of the stem cells,” he noted. “It’s also possible that the stem cells may just give out. The trauma from surgery and the trauma from postoperative drugs may injure the stem cells.”

Advances on the Horizon

Whether it’s rejection or stem cell burn-out, the success rate generally seems to fall from between 70% and 80% of patients who initially benefit from the surgery to about 50% who retain those benefits for longer than 2 to 3 years. “There is gradual attrition in the success rate,” said Scheffer Tseng, MD, PhD, associate professor of ophthalmology at the University of Miami Bascom Palmer Eye Institute in Miami, Fla. Tseng and Kenneth Kenyon, MD, of the Massachusetts Eye and Ear Infirmary of Harvard Medical School in Boston, Mass, were the first to report that stem cells could successfully be transplanted from one eye to the other (Ophthalmology. 1989;96:709-722).

Now Tseng is working to reduce the allograft attrition rate with an advance based on knowledge of scarless fetal wound healing. “One thing we have known for decades is that if a wound occurs in the fetus, after birth there is no scar.” So Tseng and his colleagues have performed allografts in which amniotic membrane is sutured in along with the tissue carrying the stem cells. They hope the amniotic tissue will result in the same scarless wound healing in the eye and reduce complications.

To date, Tseng said he has performed the procedure using amniotic membrane in about 200 patients with stem cell deficiency. In 31 eyes he has evaluated, about 80% have had improvements in vision. The data have not been published yet, he said, but adding the amniotic membrane appears to have improved surgical outcomes.

A new technique from researchers in Italy holds great promise for patients with unilateral disease, noted Ernest Kornmehl, MD, an ophthalmologic surgeon at the Massachusetts Eye and Ear Infirmary. The Italian researchers took 1 mm2 of limbal tissue from the healthy eye in each of 2 patients with unilateral stem cell deficiency. They then cultured sheets of corneal epithelium from those biopsy specimens and used the cultured epithelium in autografts in the diseased eyes. The grafts restored the patients’ corneal epithelium, which remained stable for 2 years after surgery (Lancet. 1997;349:990-993).

Patients with unilateral disease or injury “are very wary of physicians taking tissue from the healthy eye, and justifiably so,” Kornmehl said. Therefore, the culturing technique could offer patients greater peace of mind because it uses far less tissue than a standard autograft. In the future, the technique may also be adapted for patients with bilateral disease, the Italian researchers wrote.

In the meantime, Tseng said, there is room for improvement and refinement in keratolimbal allograft surgery in the use of immunosuppression, surgical techniques, and determination of which patients are optimal candidates for the procedure. “Every bit of sight that we can save is very, very worth it,” he said.

—by Rebecca Voelker