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OPHTHALMOLOGY

Newer Techniques for Corneal Transplantation Expand Patient Options

Advances in corneal transplantation are improving outcomes and expanding indications for what is already the most common and most successful type of human-transplant surgery. Corneal transplantation, also known as keratoplasty, replaces a patient’s cornea, damaged by disease or infection, with donor corneal tissue. Four types of advanced procedures performed at UCLA are making a difference for these patients.

Descemet’s Stripping Endothelial Keratoplasty (DSEK) allows for fewer intraoperative and postoperative complications, more rapid visual recovery and a more predictable prescription result following surgery than the traditional approach, says Anthony Aldave, MD, director of Cornea Services at UCLA’s Jules Stein Eye Institute.
Chronic pancreatitis is an inflammatory disease that causes recurrent episodes of pain and increases the risk for developing pancreatic cancer. Gallstones and excess alcohol use are common causes of chronic pancreatitis among adults, while genetic disorders are most often associated with the condition in children. When drugs are no longer effective in managing the symptoms of chronic pancreatitis, partial or total removal of the pancreas (pancreatectomy) may become the last resort to alleviate patients’ debilitating pain.

“Surgery is very effective in eliminating pain and cancer risk in patients with chronic pancreatitis,” explains Howard A. Reber, MD, director of the UCLA Center for Pancreatic Diseases. “The problem is that patients lose the ability to produce insulin with the removal of all or part of their pancreas, and those patients will develop diabetes.”

In some patients, however, diabetes may be avoided by using a procedure called auto-islet transplantation. During the procedure, islets, which are clusters of pancreatic cells that sense blood-sugar levels and release insulin to maintain normal levels, are saved during pancreatectomy, isolated in the laboratory and then infused back into the patient’s body through a catheter inserted into the liver. Islet cells can then continue to produce insulin. Because islets are generated by the patient’s own pancreas, rejection does not occur and immunosuppressive drugs are not required. Surgery to remove all or part of the pancreas is common, but the final step is the key to preventing diabetes.

“We’re preserving islet cells that would normally be discarded and using them to potentially prevent future diabetes,” Dr. Reber says. At UCLA, patients who have undergone partial pancreatectomy followed by auto-islet transplantation have avoided both diabetes and insulin dependence. Those who have undergone total pancreatectomy followed by auto-islet transplantation have developed insulin dependence but avoided severe “brittle” diabetes, or unstable diabetes, characterized by dramatic and recurrent swings in glucose. All UCLA patients who have undergone auto-islet transplantation are now pain-free and living normal lives.

While other programs in Los Angeles and across the U.S. can surgically remove the pancreas, UCLA, in an innovative collaboration with a UC San Francisco lab that facilitates isolation of the islets, is one of only a few centers in the United States with the potential to prevent diabetes by performing auto-islet transplantation. Still, just a handful of auto-islet transplantations have been performed at UCLA to date.

“We have good evidence that auto-islet transplantation can free patients from relentless pain and may prevent future diabetes, but people don’t know about the procedure,” says Gerald Lipshutz, MD, surgical director of the Pancreas Transplant Program at UCLA. In addition to improving the prognosis for patients with chronic pancreatitis, the technique also holds the promise for helping patients with related conditions, according to Dr. Lipshutz.

“In part, we are learning how to perform procedures that will be necessary for stem-cell therapies five or 10 years in the future,” Dr. Lipshutz says. “Theoretically, we could biopsy the skin of diabetic patients, isolate and reprogram fibroblasts into stem cells and deliver them safely to the liver so that auto-generated islet cells can be used to produce insulin to overcome diabetes,” Dr. Lipshutz explains. Fibroblasts are cells commonly found in connective tissue that play an important role in healing wounds. Patients with inherited liver disorders (area cycle or other metabolic disorders) may also benefit from knowledge gained through auto-islet-transplantation procedures.

“Each time we perform auto-islet transplantations, we learn more about how many cells patients can tolerate, refine our transplantation techniques and improve how we monitor patients for current and future procedures related to preventing diabetes and related conditions,” Dr. Lipshutz says.
Artificial corneal transplantation is an option for patients who previously had no hope of seeing after experiencing repeat corneal-transplant failure. Patients who previously had no hope of seeing after experiencing repeat corneal-transplant failure now have a viable alternative (with artificial corneal transplantation) for reestablishing vision for a meaningful period of time.

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Deep Anterior Lamellar Keratoplasty

A complement to DSEK is deep anterior lamellar keratoplasty (DALK), a selective transplant procedure for patients with a corneal scar or keratoconus, but who have normal corneal endothelial cells. Rather than replacing the entire cornea, DALK replaces only the diseased portion. Like DSEK, DALK involves the injection of air, in this case to separate the corneal stroma from the underlying Descemet’s membrane and endothelial cells. By enabling the surgeon to preserve the inner layer of the cornea, DALK has several advantages over penetrating keratoplasty, explains Dr. Aldave. Because the inner layer of the cornea remains intact, the eye is not entered, and thus there is no risk of damaging the intracorneal tissue such as the lens and the iris, and there is less chance of intraocular infection. In addition, because the healthy endothelial cells are not replaced, there is no risk of rejection and failure of the endothelial cells that are critical to keeping the cornea clear. Moreover, the requirements of the donor tissue are much less stringent than with the penetrating keratoplasty.

Penetrating and Deep Anterior Lamellar Keratoplasty with a Femtosecond Laser

The third, and newest, approach to corneal transplantation at UCLA is lamellar and penetrating keratoplasty with a femtosecond laser. The laser replaces the trephine by using ultra-fast energy pulses to make incisions in the cornea. This enables the surgeon to create precisely shaped incisions so that the transplanted tissue fits into the cornea like a interlocking puzzle piece, resulting in faster visual rehabilitation and less astigmatism.

The procedure is most appropriate for patients who have not had a prior corneal transplant or incisional corneal surgery and don’t have dense corneal scarring, says Dr. Aldave. It is ideal for patients with keratoconus, in whom the cornea is clear but misshapen, affecting their vision. As with DSEK, the femtosecond laser offers the promise of a decrease in astigmatism because of the precision of the laser, as well as a stronger wound that is more resistant to traumatic opening.

Artificial Corneal Transplantation

Artificial corneal transplantation is an option for patients who are not candidates for traditional corneal transplantation or who have experienced corneal-transplant failure.
Face transplantation offers the potential to restore humanity to persons who have suffered the devastating loss of their face.

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Face-Transplant Program Will Help to Restore Devastated Lives

UCLA Health is the first center in the western United States to offer facial transplantation to qualified patients who cannot be adequately treated using conventional reconstructive techniques. The UCLA Face Transplant Program is one of only a handful in the nation to offer this still-experimental innovative treatment. Facial transplantation is a complex procedure that is part of the emerging transplant field called vascularized composite allotransplantation (VCA). This is the transplantation of skin, blood vessels, nerves, bone, muscle and other supportive structures from a donor to a candidate. To accomplish this, the UCLA program has assembled an outstanding team of specialists, including those in plastic and reconstructive surgery, head and neck surgery, microvascular surgery, occlusal plastic surgery, neurosurgery, oral surgery, dentistry, psychiatry and transplantation medicine. Kodi Azari, MD, FACS, chief of reconstructive transplantation, talks about the program.

How did this program evolve?

UCLA has been involved over the past several years with the U.S. military through Operation Mend, providing reconstructive surgery to service members wounded in Iraq and Afghanistan. Our face-transplant program grew from our desire to do more for our wounded service members. The face is the most exposed body part and is integral to our sense of self. So you can only imagine what it’s like to not have a face. Face transplantation offers the potential to restore the sense of self to persons who have suffered the devastating loss of their face. People with massive facial injuries often have trouble breathing, speaking and eating, as well as depression and social isolation. Early surgeries have demonstrated very promising results in improving both appearance and function. While the program is an outgrowth of our relationship with the military, it will accept both civilians and veterans as candidates.

What are the criteria to become an eligible candidate for face transplantation?

The first requirement is that the patient’s facial disfigurement cannot be the result of cancer and, in spite of repeated attempts, cannot adequately be reconstructed by conventional means. We can do amazing things through reconstructive plastic surgery, but there are injuries from trauma or from burns that are just beyond our capabilities to restore. Facial transplantation offers us that capability. Appropriate candidates must be between 18 and 60 years of age, have no serious infections, including hepatitis B or C or HIV, and be in otherwise generally good health. In addition, candidates must commit to extensive rehabilitation, adhere to an immunosuppression medication regimen, and participate in all appointments at the transplant center.

Patients needing an organ transplant can spend years on the waiting list before an appropriate donor is found. What are the challenges of matching an appropriate donor and recipient for this procedure?

Finding the right donor is a challenge, and this is such a new field that there is no streamlined way for finding donors. We would like to push for a national database, like what exists for organ transplantation, to identify and match potential donors and patients. It would be a very important part of accelerating the pace of these procedures. That said, the donor’s tissue must match that of the recipient in terms of blood group, sex, age, skin color and size. Potential donor families are approached with sensitivity to the emotional and ethical issues of donation. Our program also works with James Kelly, DDS, an expert in maxillofacial prosthetics to provide the donor family a facial reconstructive mask to recreate the donor’s visage and allow for an open-casket funeral if that is desired. Identifying the right candidate for the surgery also is a significant challenge. Because this is a life-altering procedure rather than a life-saving one, an appropriate candidate must not only meet the medical criteria, but must also be psychologically ready for this surgery, and for what it means afterward. While there might be some resemblance, recipients will neither look like themselves nor like the donor. It can be a lot for someone to grasp, even for a patient who up to this point has been living with a badly disfigured face. That is why candidates are screened for psychological issues, including depression and post-traumatic stress disorder, which would interfere with their ability to accept and recover from the transplant. The program also provides psychiatric care around the time of the procedure as well as long-term follow-up with psychiatric therapy.

How is the surgery performed?

Once an appropriate donor is identified, two teams begin work in concert. One team travels to the donor hospital and procures the tissue to be transplanted, taking only the tissue that the recipient will need. A second team prepares the patient, removing damaged tissue and scab tissue down to the healthy, underlying structures. The reconstruction begins by anchoring bone in place and attaching muscle to the facial skeleton. Blood vessels, nerves, ducts and glands are attached to corresponding structures, and then skin is closed. It is a laborious, lengthy procedure than can take more than 20 hours, depending on the case.

Patients will remain in the hospital for the first month following surgery, and will start speech and occupational therapy, which will continue for a year to 18 months. After they are discharged from the hospital, they will spend another two months at nearby UCLA housing, and then they will be seen monthly for the next year, and then with decreasing frequency.

The surgery is very complex and involves many different specialties. How is it being funded?

As one might imagine, this kind of procedure is very expensive — around $600,000. Right now our funding is coming from UCLA Health and private sources. But we are hopeful that the U.S. military may become involved in supporting our program as we move forward. The Pentagon has been very interested in research into such programs as facial transplantation and regenerative medicine to treat wounded veterans, and it has given several million dollars to Brigham and Women’s Hospital in Boston, which has done the majority of face transplants in the U.S.

In March 2012, Richard Lee Norris, who was injured in a gas accident, received a full-face transplant at the University of Maryland Medical Center. He is pictured in the second photograph a year and a half after the procedure.

Photo. Courtesy of University of Maryland Medical Center.

Kodi Azari, MD, FACS, chief of reconstructive transplantation, talks about the program.
Kidney-Transplant Chains Help to Keep Patients and Hope Alive

Demand for donor kidneys is far greater than the supply, and some patients must wait as long as a decade for a suitable donor. While a loved one or friend may be motivated to donate, about one-third of the time they are unable to do so because they are not immunologically compatible.

But an innovative program that exchanges the kidney from an incompatible family or friend for a compatible kidney from a stranger is giving UCLA patients hope of being freed from the constraints of dialysis. “It’s a winning situation for everyone,” says Jeffrey Veale, MD, assistant professor of urology and director of the UCLA Kidney Exchange Program. “Instead of waiting years for a deceased-donor kidney, patients can quickly receive a living-donor kidney — which in general lasts twice as long. Additionally, once these patients receive their living-donor kidney they are removed from the deceased-donor waiting list, reducing the competition for cadaveric organs.”

“However, none of this would be possible without the generosity of altruistic donors to trigger the chains,” says Dr. Veale. “There are no obvious benefits for altruistic donors, and they are putting themselves at risk for a total stranger. I don’t think our society has adequately recognized the heroism of altruistic donors.”

A transplant chain begins when an altruistic donor gives his or her kidney to a recipient who already has a willing donor but that donor’s organ is incompatible.

UCLA has one of the world’s highest-volume kidney-transplantation programs and is the most active chain-transplantation center in the United States, performing 90 chain transplantations to date. “Besides getting people transplanted rapidly with the highest-quality organs, there’s a real humanitarian component to this program,” says Dr. Veale. “It’s beautiful to see people giving and receiving kidneys from complete strangers. The recipient usually doesn’t meet the donor until after the transplantation, and I feel extremely fortunate to often be the one who gets to make that initial introduction.”

Dr. Veale was senior author on a recent article that reported the results of 272 chain transplantations (the largest study to date). Approximately 50 percent of the chain recipients were female and 46 percent were ethnic minorities — two groups that have historically had a difficult time finding matches due to their naturally elevated antibody levels.

One of the factors driving the growth of chains is that donor surgery now is being performed laparoscopically. In the past, donating a kidney meant being hospitalized for up to a week; most of today’s donors leave the hospital the next day. Similarly, the amount of time donors would miss work in the past was two to three months, now it is typically only four to six weeks. With shorter recovery times for kidney donors, the relationship to the recipient has become more elastic. Originally, it was just family members who were able to donate, but over the years it has become acceptable for spouses, friends and now complete strangers to donate a kidney for transplantation.

In 2011, a chain intertwined the lives of 60 strangers and involved the donation of 30 kidneys across the country; UCLA handled 16 of the patients, the largest number of any participating hospital. “The chain-transplantation program is truly remarkable, as it enables us to take the gift from a single altruistic donor and amplify it dozens of times,” Dr. Veale says.

For more information and to watch a video about the UCLA Kidney Exchange Program, go to: transplant.ucla.edu/kidneyexchange

Paired Donor Exchange Transplantation:

If a donor and a recipient have a different blood type, they can exchange their kidneys with another donor and recipient pair in a similar situation. This can also be done among three pairs.

Chain Transplantation:

A donor chain creates opportunities for endless recipient-donor pairings. It starts with an altruistic donor — someone who wants to donate a kidney out of the goodness of his or her heart. That kidney is transplanted into a recipient who had a donor willing to give a kidney, but was not a match. To keep the chain going, the incompatible donor gives a kidney to a patient unknown to him or her who has been identified as a match. A specialized computer program matches donors and recipients across the country.
Bone Marrow

Hematopoietic-Stem-Cell Transplantation
Among Oldest Forms of Cancer Immunotherapy

Targeted therapies that mobilize the body’s immune system to attack cancer cells continue to emerge as promising weapons in the arsenal of cancer treatment options. But the idea behind cancer immunotherapy is not a new one. More commonly known as bone marrow transplantation (BMT), hematopoietic-stem-cell transplantation (HSCT) has been performed in the United States for more than 40 years to support patients undergoing treatment for cancers such as acute myeloid leukemia (AML), multiple myeloma or lymphoma.

“Few immune therapies have the track record and demonstrated efficacy that we observe with HSCT,” says Gary Schiller, MD, director of the Hematologic Malignancies/Stem Cell Transplant Unit at UCLA. “It is the most common immune therapy done in the world for cancer and is the immune therapy for which there is the greatest experience.”

In fact, more than 60,000 HSCTs are performed internationally each year, according to Dr. Schiller. Approximately half of transplanted hematopoietic stem cells (those capable of reconstituting bone marrow and blood) are autologous, in which the recipient acts as his or her own donor. The other half are allogeneic, in which stem cells are donated from related (usually a sibling with closely matched human leukocyte antigen) or unrelated adults or from the umbilical-cord blood of a newborn. Both procedures are done to replace bone marrow and blood. Autologous HSCTs, however, also serve another purpose.

“Allogeneic HSCTs deliver an immunoreactive organ, which is more likely to favorably impact the disease,” Dr. Schiller explains. “When using autologous stem cells, the chemo and radiation therapies do not necessarily need to completely kill every last malignant cell because some of the heavy lifting will be done by the donor’s immune system.”

The procedure carries major risks. Infection and graft-versus-host disease, an inflammatory condition in which the immune cells of the donor attack the recipient’s tissues, are major complications of allogeneic HSCT. Newer strategies, however, have led to fewer complications and improved outcomes.

“Few ‘immune therapies’ have the track record and demonstrated efficacy that we observe with HSCT. It is the most common immune therapy done in the world for cancer.”

“We have become better at identifying and matching potential donors; we have begun to reduce the chemo and radiation therapy we use to treat malignancies because we are more skilled in harnessing the immune effect of donor cells; and we have more effective antibiotics that we use to prevent infections,” Dr. Schiller says. These developments have enabled physicians to expand allogeneic HSCTs to broader populations of patients for whom the risks of transplantation might have previously been too great. For example, “mini-transplant” procedures have been developed that require smaller doses of chemo and radiation therapies. This enables HSCT to be conducted in the elderly, patients with co-morbid conditions and those who would otherwise be considered too weak to undergo a conventional treatment regimen. Use of “mini-transplant” strategies has so far produced mixed results.

“Early results suggest that a greater number of patients relapse using this approach,” Dr. Schiller says. “We do not yet fully understand the reason for this, however, which could be that older people have different kinds of cancer. They certainly have more resistant leukemia, in general, than younger people.”

Patients with severe organ dysfunction, those on dialysis and people for whom no donor can be identified are still not appropriate candidates for allogeneic HSCT. In addition, HSCT has not demonstrated efficacy in the treatment of many solid tumors (breast, lung or colon cancer, for example). Despite its current limitations, HSCT will continue to expand beyond the cancer care continuum, including the treatment of autoimmune and other diseases.

“As one of the oldest and largest transplant centers in the region, we have seen very favorable outcomes using HSCT,” Dr. Schiller says. “We will use our broad experience and lessons learned as we continue to build the evidence base for this and related techniques, but we need more available donors so that we can help more patients.”

This image illustrates in detail the characteristic morphologic features of the myeloid response following G-CSF stem cell mobilization.

STORY HIGHLIGHTS

Hematopoietic-stem-cell transplantation has been performed in the United States for more than 40 years to support patients undergoing treatment for cancers such as acute myeloid leukemia, multiple myeloma or lymphoma.

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continued on p. 4