

Study finds transplant patient thrives 2 years after stopping immunosuppressive drugs

January 24 2008

Luck smiled on Larry Kowalski when his brother agreed to donate a kidney Kowalski needed to live. He was even luckier that his brother's kidney was such a good match.

That last stroke of luck led Kowalski to connect with a team of researchers at the Stanford University School Medicine, whose efforts have enabled him for two years to live free of the heavy-duty drugs that transplant patients normally have to take for the rest of their lives.

The researchers describe Kowalski's case in a brief report to be published in the Jan. 24 issue of *The New England Journal of Medicine* on the technique they developed, based on 25 years of research by Samuel Strober, MD, professor of immunology and rheumatology. The journal issue also includes two reports from other research groups, describing their efforts to achieve organ transplantation without long-term immunosuppressive drugs.

Kowalski, now 50, was 3 years old when doctors discovered he had been born with only one kidney. His single kidney held out until he was 47. Then a blood test indicated that it was beginning to fail.

Kowalski's 49-year-old brother agreed to help, and that turned out to be crucial. His brother was a perfect fit of the six proteins most important in matching the immune systems of transplant donors with recipients.

Transplant recipients are matched as closely as possible with the donor

organs to minimize the body's normal response to reject the organs. The biggest danger with organ transplantation lies not in the surgery, but in the recipient's own body rejecting the organ as a foreign invader.

Without drugs to suppress that reaction, usually the recipient's immune system encounters unfamiliar proteins on the transplanted organ, attacks the organ and eventually destroys its function.

But unless the recipient has an identical twin, there will always be some minor differences between the organs, so even close matches require a lifetime of immunosuppressive drugs. Long-term use of these drugs can cause cancer, bothersome side effects and, most ironic for kidney transplant recipients, kidney damage.

The ultimate goal for transplant patients is to get their bodies to tolerate their donor organs without drugs. Transplant doctors have been trying to develop ways to do this for years, with little success.

The fact that Kowalski had such a good match with his brother's kidney made him an ideal candidate for the Stanford clinical study. The researchers were investigating whether a procedure that involved adjusting Kowalski's immune system, plus infusing blood cells from the brother who donated the kidney, could allow Kowalski's body to tolerate his brother's kidney.

The therapy was first developed in mice by Strober, the senior author of the study. In the last few years, Strober worked with Robert Lowsky, MD, associate professor of blood and marrow transplantation, to adapt this strategy from mice for human lymphoma and leukemia patients. The procedure combines localized blasts of irradiation and antibody treatments to tweak the recipient's immune cells. Then the recipient gets an infusion of blood cells from the donor. The procedure boosts levels of a type of immune cell called regulatory T cells. These cells function as the immune system's "peacekeepers" and can

avert the attack that causes rejection.

When the Stanford transplant team approached Kowalski with the offer, he jumped at the chance that might allow him to forego a lifetime of immunosuppressive drugs.

In February 2005, Kowalski received his brother's kidney at Stanford Hospital. He was started on an immunosuppressive drug with the intention that it would be temporary. His only notable complication came about a month after his transplant, when Kowalski had to be hospitalized briefly for a fever. He returned to work as a restaurant owner three months after the transplant.

Doctors began to taper the use of the immunosuppressive drug and, after six months, Kowalski was drug-free.

"Essentially, my immune system contains half my brother's immune cells and half of my own," said Kowalski. "It's enough that my body thinks my brother's kidney is mine."

After all the mouse studies leading up to testing in patients, Kowalski's case is rewarding for Strober. "It's been a long, long road that ends up with clinical trials that could lead to somebody's benefit," he said. "Tolerance has been the goal for decades, and we are just now beginning to see the fruits of all that labor."

Kowalski could be called the poster child of the procedure so far, but others in the same research study haven't fared as well. Six other patients treated before him haven't been able to go off of their drugs, but their kidneys came from donors not as perfectly matched as Kowalski's was.

He was the first patient in a new iteration of the technique that is being tried only in perfectly matched donors and recipients. So far, one patient

that followed Kowalski is showing promising results but is not yet off the drugs, said lead author John Scandling, MD, professor of nephrology and Kowalski's kidney transplant specialist.

The research team found Kowalski "remains in good health" 34 months after he stopped taking the immunosuppressive drugs. An interview with Kowalski shows this to be an understatement. Not only does he run four restaurants in California, but he bikes, snowboards, scuba dives, goes to the gym regularly and, most taxing of all, is the father of a 3-year-old. By anyone's definition, he is in great health.

"The idea of getting off drugs holds tremendous appeal for patients," said Scandling. "So far, there is hope, but we still have a long way to go."

Source: Stanford University Medical Center

Citation: Study finds transplant patient thrives 2 years after stopping immunosuppressive drugs (2008, January 24) retrieved 25 April 2024 from

<https://medicalxpress.com/news/2008-01-transplant-patient-years-immunosuppressive-drugs.html>

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