Kidney-transplant patients celebrate unprecedented freedom from immunosuppressant drugs

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Daniel Bitner, with his 2-year-old daughter, Madeline, at a March 4 event honoring a new therapy that has changed his and other kidney-transplant recipients' lives. Credit: Norbert von der Groeben

(Medical Xpress) -- In the year 2000, just as Daniel Bitner was starting dental school at the University of Louisville in Kentucky, he got a kick in the teeth. A routine physical turned up elevated blood pressure and creatinine levels, which taken together can mean kidney malfunction. He soon learned that his kidneys were beginning to fail, a complication of multi-surgical interventions during childhood to correct structural

problems within his urinary tract.

Boning up on his condition in the school's medical library, he began to realize the consequences of what was to come: ultimately, a kidney transplant operation, followed by what he expected to be a lifetime on immune-system-suppressing drugs to prevent rejection of the organ. A youthful 37 years old now, Bitner was only 25 then. The medical literature told him the drugs themselves carried numerous risks of side effects — risks that only accumulate over time. He also read reports about early experimental attempts to prevent organ rejection without the use of immune-suppressing medication. "Wouldn't it be nice," he remembers thinking, "if something like this could be made to work with kidney transplants?"

In February 2008, Bitner read a study in the Jan. 24 issue of the *New England Journal of Medicine* chronicling such a trial then under way at the Stanford School of Medicine, which had produced promising results in a handful of patients. This set into motion a chain of actions that have allowed him to live in robust health, entirely free of anti-rejection medications, for three-and-a-half years since his kidney-transplant operation at Stanford Hospital & Clinics.

Bitner recapped his story on March 4, during a "reunion" of 13 kidney-transplant recipients who participated in a clinical trial of a protocol developed by immunologist Samuel Strober, MD, a professor of medicine, and executed by a School of Medicine team including transplant surgeon and associate professor of surgery Stephan Busque, MD, and John Scandling, MD, attending nephrologist for the patients in the Stanford study. The three doctors joined the lunchtime gathering of about 60 people that also included patients' families and others on the medical team in the lobby of the medical School's Li Ka Shing Center for Learning and Knowledge. Bitner had driven down from his home in Eugene, Ore., with his wife and four children ages 11, 9, 8 and 2 to

attend the event.

For patients with kidney failure, kidney transplantation holds out the prospect of returning to a normal lifestyle, without dialysis (mechanical filtration of the blood). Dialysis, while life-extending, is far from a perfect solution. Patients typically must spend several hours immobilized in special centers three times a week for the rest of their lives or, less commonly, receive more frequent dialysis in home rigs. Moreover, life expectancy for patients on dialysis is significantly lower than for those who successfully receive new kidneys. Dialysis is also expensive, costing close to $70,000 per patient per year.

“On average, transplant recipients have twice the life expectancy of people on chronic dialysis,” said Scandling, a professor of medicine who is medical director of Stanford’s adult kidney and pancreas transplantation program. But unless the kidney donor is an identical twin, the patient’s immune system invariably perceives the transplanted organ as the foreign body that it in fact is. Thus, the new recipient anticipates a lifetime on immune-suppressing drugs. In their absence, the immune system will relentlessly attack the new organ, destroying it.

But the drugs themselves put patients at heightened risk for infection, cancer, diabetes and high blood pressure. Plus, they can themselves be toxic to the kidney. And sometimes they just don’t work. Even in the case of the best immunological recipient/donor match-ups, a new kidney lasts 25 to 30 years on average.

Strober’s protocol involves a precise mixing of blood-forming stem cells from recipients and donors, in combination with radiation treatments and infusions of antibodies over a 10-day period, to dial down the immune response until, when it eventually returns, it incorporates features of the donor’s as well as the recipient’s immune systems. When the protocol is successful, the typical fierce immune response to the new

organ no longer ensues.

Mounting evidence

The Stanford team published a second round of results late last year in the New England Journal of Medicine, indicating that eight of 12 enrolled patients had been successfully weaned off immune-suppressing drugs, for a least one year and in some cases more than three years, without any apparent damage to their new kidney. This is unheard-of in patients undergoing standard transplantation procedures.

While the Stanford trial is largely funded by the National Institutes of Health, in recent months the medical school's Institute for Immunity, Transplantation and Infection has supplied additional support. This has enabled the trial's continuation and expansion. On March 7, a more complete report in the American Journal of Transplantation noted that, of 16 patients enrolled in the since-expanded trial, 11 are now entirely off anti-rejection drugs (for an average time of 28 months) and a 12th is being weaned from them. There have been no serious adverse effects.

Bitner, an endodontist, was doing his residency in 2005 at University of Pennsylvania, in Philadelphia, when his kidney condition worsened. His physicians had told him he could go a few more years before a transplant would become necessary so he finished his residency and moved to Eugene, where he now lives, to begin practice. Not long after the move, he started to feel the classic symptoms of kidney failure. A grim routine — nausea every day, passing out on the couch at night — set in. "You get pretty sick," he said.

The 2008 New England Journal article chronicling the early progress of Stanford's clinical trial was electrifying for Bitner and his family. "My mom and brother called me that same night to make sure I'd seen it, which I had." He contacted the Stanford team immediately. "Dr.

Scandling said to come on down."

The operation at Stanford Hospital took place on April 28, 2008, Bitner's oldest son's birthday, with Bitner's brother as donor. Six months later, he was taken off immune-suppressing drugs, and he has remained off them for almost three-and-one-half years. "I haven't felt this good since I was in my 20s," before being diagnosed, he said. "I tell people I'm a walking miracle."

First, do no harm

Importantly, no significant adverse consequences have accrued even to the trial's "failures." John Evey is one of them, though "failure" is a relative term in this instance.

Evey, now 62, was diagnosed in 1976 with polycystic kidney disease, a genetic condition in which cysts slowly grow within the kidneys over time. This growth continues unrelentingly, eventually choking off kidney function. In April 2000, Evey, who was then a Stockton-based vice president at the University of the Pacific, had both kidneys removed in a 10-hour operation. By that time, the two organs — each of which, in the healthy state, is the size of a fist — together weighed 30 pounds.

Already on dialysis prior to the procedure, Evey remained on dialysis for six months afterward. Then he became the first patient enrolled in the trial of Strober's protocol. "They treated me like part of the team," he said. "It was a splendid opportunity for me."

On Oct. 30, 2000, he received a new kidney donated by his wife's sister. Steroids, a standard component of the multi-drug anti-rejection regimen, were phased out almost immediately, and his remaining immunosuppressant regimen continued to be scaled down through February 2001. At that point, his physicians detected a slight upward

creep in his measured creatinine levels (a sign of kidney stress), and he was put back on “exceedingly low doses” of immunosuppressants, a regimen he has maintained ever since: A total of only a couple of pills a day, far fewer than nearly all transplant recipients need. Tall, lanky and fit, Evey exhibits none of the bloat normally seen in people on steroids.

Also looking remarkably fit was Karen Burke, a 55-year-old Modesto resident and former teacher who home-schooled her two daughters, ages 17 and 19. She came by her diagnosis accidentally in the 1980s, when an ultrasound revealed that, like Evey, she had polycystic kidneys. “I lived in denial for a few years after that, because I didn’t have any symptoms,” she said.

In 2008, when fatigue and nausea were becoming far too familiar, her sister came across the celebrated New England Journal article. Burke got Scandling’s phone number and soon met with the medical team. Her health insurer, which contracted with a different hospital, had to be persuaded to allow the Stanford team to take over. One call from Scandling sliced through that red tape, Burke said.

Her surgery was scheduled for early December, but as the day approached, her donor, another sister, caught a cold, and the procedure had to be postponed. This was a problem: Burke’s husband’s employer would be switching to a new health insurer on Jan, 1, meaning starting from scratch. So the Stanford Hospital surgical team cut a hole in their holiday break in order to perform the transplantation on Dec. 29, before the year ended.

After one year on anti-rejection drugs, Burke has now been anti-rejection-drug-free for a little more than two years years.

“To me, it is a dream fulfilled to see the happy faces of patients who are doing so well in the aftermath of what used to be a fatal disease,” said

Strober to his fellow attendees. “I hope this becomes an annual reunion that, 10 years from now, will included hundreds of patients.”

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