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Cascades

APRIL 2008 NEWSLETTER TO PHYSICIANS — SPECIAL ANNOUNCEMENT



More Than Five Years (and Several Marathons) Later, the First Patient in Immune Tolerance Trial is Still Faring Well



Massachusetts librarian Jennifer Searl, 28, knows first-hand about the downsides of maintenance immunosuppression and the delights of being free from it.

Jennifer Searl with Tatsuo Kawai, MD, PhD

Following her first renal transplant from

her father at age 12 for end-stage renal disease secondary to Alport's syndrome, Searl developed cataracts and osteopenia, memory loss, facial swelling and an overgrowth of body hair, while taking about 20 pills a day.

Even worse were the disabling, disseminated warts caused by HPV infections that covered her entire right foot, causing crippling pain. "The warts were debilitating," says Searl. "I couldn't walk, and had to have handicapped license plates in college." When her physicians reduced her immunosuppressive therapy in an attempt to deal with the warts, which had eluded all attempts at treatment, her graft was rejected.

In the fall of 2002, at 22, Searl courageously chose to become the first patient in Massachusetts General Hospital's tolerance induction protocol, receiving a simultaneous kidney and bone marrow transplant from her mother. She has been completely off immunosuppressant drugs since March 2003 and, more than five and a-half years later, has had continuously stable renal function. She has a full-time job, works out six days a week, and has even run several marathons. "For the first time in my life," says Searl, "I have a healthy body. I feel great.

"I've done transplants both ways," she adds. "The way I see it, the first was a treatment in which you're exchanging one disease for another; the second is a cure."

Major Breakthrough in Tolerance Induction for Organ Transplantation

Innovative Protocol in Adults to be Evaluated in Adolescents at MGHfC

In 1954, the first successful human organ transplantation took place in Boston, ushering in an exciting new era in which patients with end-stage organ failure no longer faced certain death. In the five-plus decades since that historic achievement, organ transplantation has evolved to become a viable option for many adults and children, saving thousands of lives each year.

Despite dramatic breakthroughs in organ transplantation, many of which were pioneered at Massachusetts General Hospital, significant challenges have remained. Among the most formidable of these are complications from immunosuppression, which include an increased risk of infection and cancer, as well as serious metabolic and physiologic changes, such as hypertension, hyperlipidemia, and chronic kidney disease. Another is chronic rejection, which accounts for the overall 4-5% annual attrition rate of organ transplantation.

Unique risks in children

These challenges are especially problematic in the pediatric population, largely because a child's allograft must remain functional for much longer — often decades longer — than an adult's, putting pediatric organ recipients at risk of immune-mediated events for a significantly greater period of time.

On top of all the complications of immunosuppression that adults face, pediatric patients have unique risks, such as osteopenia and retarded growth, to cite just a few. Adolescents, in particular, confront distinct hurdles — indeed, adolescents consistently have the worst outcomes in long-term renal allograft survival of all age groups.

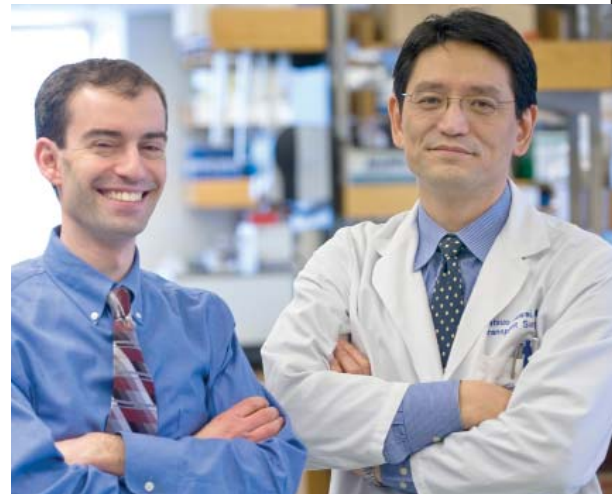
It is widely believed that this phenomenon is due to poor medication compliance rather than distinct immunologic differences between adolescents and other age groups. Considering the strict medication regimen for maintenance immunosuppression and its cosmetically disfiguring side effects — which can include weight gain, facial swelling, and hair and/or gum overgrowth — poor compliance is perhaps not surprising among individuals at a developmental stage in which issues like conforming with the group and physical appearance are paramount, not to mention youthful feelings of rebellion and immortality.

Immune tolerance achieved in adults

In January, the *New England Journal of Medicine* (358:353-61) published a paper by members of the Massachusetts General Hospital Transplantation Unit and the Transplantation Biology Research Center (see enclosed reprint) that reports on a major breakthrough in immune tolerance induction. This achievement, which received widespread national media attention, has the potential to dramatically extend and improve the lives of both adult and pediatric transplantation patients, with the greatest potential benefit to the latter.

In brief, this landmark paper describes a pivotal trial that included five Massachusetts General Hospital patients with end-stage renal disease. Each received a nonmyeloablative preparative regimen and a

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The principal and co-principal investigators of the MassGeneral Hospital for Children Transplant Center's proposed pediatric clinical trial in tolerance induction are, respectively, Tatsuo Kawai, MD, PhD (right), and Avram Traum, MD.

simultaneous bone marrow transplant (BMT) and kidney transplant from an HLA single-haplotype mismatched living, related donor. The protocol, the culmination of decades of basic, preclinical, and clinical research at Mass General, is based on the process of mixed chimerism, in which the donor's and recipient's immune system are blended in a manner that both prevents rejection and suppresses graft-versus-host disease.

Four of the patients, who ranged in age from 22 to 46, have been successfully off immunosuppression, with stable renal function, for periods ranging from 2.0 to more than 5.3 years. One patient experienced irreversible rejection and underwent another transplant, after which the protocol was modified.

This is the first time that immune tolerance has been achieved intentionally in a series of mismatched human organ transplant recipients, and Mass General is the first — and only — hospital in the world where this has been done.

MGHfC pediatric trial

With the generous support of Massachusetts General Hospital's recently established Transplant Center (see sidebar, right), beginning this summer MassGeneral Hospital for Children (MGHfC) proposes to conduct a trial involving up to three adolescents, ages 13-17 years, who are candidates for renal transplantation (on dialysis or eligible for a preemptive transplant). The protocol, which was evaluated by medical ethicists, will soon be under review by the hospital's Institutional Review Board.

To be led by principal investigator and Mass General transplant surgeon Tatsuo Kawai, MD, PhD, and co-principal investigator Avram Traum, MD, a MGHfC pediatric nephrologist, the protocol to be used in this study is identical to the modified version used successfully in the adult trial.

Adolescents were chosen for the first pediatric trial because they have comparatively poorer outcomes and, thus, stand to benefit the most from being off immunosuppression. They are also physiologically close to adults; in fact, the first patient in the adult trial, Jennifer Searl (see sidebar, front), was just 22 years old when she received her simultaneous kidney/BMT transplant.

Other replacement organs

According to the Organ Procurement Transplantation Network, in the United States an average of approximately 800 renal transplants and 563 liver transplants were performed annually in patients ages <1 to 17 years in the period between 2003-2007. Currently all of these children, as well as pediatric recipients of hearts, lungs, and other donor organs, face a lifetime of immunosuppression and its myriad and serious complications, as well as the ever-present threat of chronic rejection, eventual organ loss and, in some cases, death.

If the proposed MGHfC protocol is as successful in adolescents as it was in adults, subsequent trials will evaluate it in younger renal transplant patients (whose less mature immune systems may predispose them to even faster induction of tolerance) and, eventually, in children and adolescents needing other replacement organs, including livers and, potentially, all organs.

Achieving immune tolerance has long been the Holy Grail of organ transplantation, particularly for pediatric patients, who have so much to gain from such a revolutionary advance. Based on the results of the proposed clinical trial at MGHfC, it may well be that the Holy Grail has, at last, been found, which would be very welcome news to pediatric patients, their parents, and physicians alike. ■

Writing: Bennett Medical Communications

Massachusetts General Hospital Transplant Center Integrates Hospital's Strengths in Organ Transplantation

Under the leadership of director Joren C. Madsen, MD, DPhil, and associate director Jay A. Fishman, MD, the Massachusetts General Hospital Transplant Center was recently established to integrate the hospital's longstanding, extraordinary strengths in organ transplantation, transplantation biology research, education and training into a single, multidisciplinary center.

As the largest transplant center in New England, the Massachusetts General Hospital Transplant Center offers patients and their family members enormous depth and breadth of experience in all aspects of transplantation, from evaluation and treatment through lifelong follow-up care of organ recipients, as well as donor monitoring. In collaboration with the Massachusetts General Hospital Transplant Center, the MassGeneral Hospital for Children (MGHfC) Transplant Center currently provides pediatric transplantation (kidney, liver, and small bowel), offering, when appropriate, minimally invasive surgical techniques and novel approaches to immunosuppression.

The MGHfC Transplant Center's highly experienced, multidisciplinary team of pediatric physicians, nurses, social workers, case managers, transplant coordinators, and other transplant specialists work closely together to ensure that children and adolescents receive the comprehensive, seamless care and specialized services they require. Young patients and their parents benefit from the many specialized pediatric services and family-centered facilities of MGHfC, as well as the clinical innovations first evaluated in adults.

The MGHfC Transplant Center also facilitates ongoing programs in basic and clinical transplantation research, all of which are aimed at rapidly bringing discoveries into the clinical setting for the benefit of pediatric patients. The pediatric tolerance induction trial described in this issue of *Cascades* is an example of the center's commitment to improving outcomes through bench-to-bedside research.

The multidisciplinary physician team involved in the proposed pediatric tolerance induction clinical trial at MGHfC includes:

- A. Benedict Cosimi, MD**, chief, Transplantation Unit
- Tatsuo Kawai, MD, PhD** transplant surgery; principal investigator
- Dicken Ko, MD**, surgical director, Renal Transplantation
- James Markmann, MD, PhD**, clinical director, Abdominal Transplant Program
- David H. Sachs, MD**, director, Transplantation Biology Research Center
- Thomas R. Spitzer, MD**, director, Bone Marrow Transplantation Program
- Avram Traum, MD**, pediatric nephrology; co-principal investigator

FOR MORE INFORMATION

For more information about the proposed pediatric tolerance induction protocol at MGHfC or to refer a patient, please contact Avram Traum, MD, co-principal investigator, at **617-726-2908** or atraum@partners.org.