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The Need for Tolerance in Pediatric Organ Transplantation

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Transplantation is the preferred therapy for pediatric end stage diseases of a variety of solid organs. Unfortunately, however, transplantation does not restore patients to a normal life, because they are left on lifelong immunosuppression with its associated complications. In addition, even when immunosuppression is properly administered, there is progressive loss of allograft function through a process called “chronic allograft dysfunction” that leads to loss of ~4% of transplanted organs per year. Exciting new findings in adult transplant patients now offer the hope that both the need for chronic immunosuppression and the loss of organs to chronic rejection may be avoided by the induction of transplantation tolerance—the specific elimination of the rejection response through modification of the immune system. Below, we will outline the history of immunosuppression and its problems and provide some insights into how we believe that the induction of tolerance will be of special benefit to children.

Since the first kidney transplantation occurred in 1954, transplant physicians and surgeons have been faced with the challenge of properly balancing immunosuppression. Early on, the biggest hurdle was preventing acute rejection, which occurred almost universally. In 1954, Joseph Murray transplanted a kidney between 2 identical twins without immunosuppression and achieved normal kidney function¹ until the allograft was lost to recurrence of the original disease in the following decade. With the development of immunosuppressive agents such as azathioprine and later potent calcineurin inhibitors such as cyclosporine and tacrolimus, reductions in acute rejection rates were seen with improvements in short-term allograft function. However, despite initial enthusiasm, the lower rates of acute rejection in the first year have not resulted in a significant improvement in long-term survival after allograft.² Thus, even in grafts that display good function in the early years after transplantation, progressive tissue damage often develops, leading to gradual organ dysfunction, also referred to as chronic

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allograft dysfunction. Chronic allograft dysfunction can affect all transplanted organs and is the most common cause of graft loss more than 1 year after transplantation. Immunologic factors of this late graft loss consist of development of chronic rejection, inadequate immunosuppression, and noncompliance.

The advent of potent immunosuppressive therapy also led to the rise of new complications. Posttransplant lymphomas attributed to Epstein-Barr virus (EBV) infection, later known as posttransplant lymphoproliferative disorder (PTLD), became a more common and disturbing complication.^{3–5} The risk of PTLD was found to be further exaggerated in children as a result of higher rates of EBV seronegativity before transplant.^{6,7} Newer, more potent agents have further exacerbated this predicament because of the successful impairment of cell-mediated immunity, which leaves the immunocompromised transplant patient unable to mount an effective response to EBV and, thus, promotes the development of PTLD.⁸ Other infectious complications are also a consequence of effective and potential overimmunosuppression, such as cytomegalovirus, BK virus nephropathy,^{9,10} and *Pneumocystis carinii* pneumonia, among others, with infection now leading rejection as the leading cause of hospitalization of children after kidney transplantation.¹¹ Thus, although the current rates of acute rejection have decreased significantly, the price of this success has been novel infections and their complications.¹²

Opportunistic infections are among myriad posttransplant complications that plague patients and their clinicians, many of which are related to the immunosuppressive medications themselves. Calcineurin inhibitors (cyclosporine and tacrolimus) remain the backbone of immunosuppression regimens, although newer protocols have attempted to minimize or replace these agents because of the long-term risk of renal scarring associated with their use.¹³ This phenomenon is not unique to renal transplantation and had led to chronic kidney disease and end-stage renal disease as unfortunate consequences of nonrenal transplantation.¹⁴ Corticosteroids are also used widely with pediatric transplantation, and steroid avoidance or withdrawal has been used as a modality to minimize steroid-related toxicities, including but not limited to impairment of linear growth, bone disease, and cosmetic changes.^{15,16} Unfortunately, steroid withdrawal may increase the incidence of late rejection episodes.¹⁷ In addition, cyclosporine and steroids both negatively impact cardiovascular risk factors such as hypertension, hyperlipidemia, and the development of chronic kidney disease associated with long-term cyclosporine use.^{18,19} This is notably germane, because cardiovascular disease is a leading cause of morbidity in adolescents and young adults with kidney disease.²⁰ The price of success in transplantation has come at the consequence of toxicities related to immunosuppression.

Exciting new findings offer hope that some of these burdens may be alleviated by achieving long-term tolerance. Immune tolerance refers to an acquired modification of the host immune system, achieved without chronic drug therapy, with which the specific response to the graft is suppressed but the immune system is otherwise fully competent. Operationally, this would result in long-term acceptance of a foreign graft without the need for long-term immunosuppression. This state has been achieved in a variety of rodent models²¹ but only recently has been achieved in large animals and, finally, humans. On the basis of extensive animal studies^{22–25} and the experience in patients with myeloma,^{26–28} Kawai et al²⁹ at Massachusetts General Hospital recently reported on 5 adults who received combined kidney and bone marrow transplants from HLA-mismatched donors after receiving a nonmyeloablative conditioning regimen. All 5 patients developed transient mixed chimerism, and 4 of them were successfully weaned off all immunosuppression with stable kidney function 2 to 5.3 years after transplantation. It is particularly poignant to note that the first patient who participated in this study had received her first kidney transplant as a teenager but developed infectious complications that necessitated reduction of immunosuppression, followed by

rejection and eventually allograft loss. This seminal work provides the first evidence that acquired tolerance can be purposely induced in human transplant recipients and has profound implications for pediatric recipients.

What is the potential impact of these studies for clinical transplantation in children? First, inducing tolerance through mixed chimerism eliminates all of the long-term complications related to the immunosuppressed state and the toxicities of the drugs themselves. Second, it addresses one of the most pressing problems in the care of adolescents with any chronic disease, namely, compliance. Adolescents have the worst outcomes of all patients groups with regards to graft function, which is blamed primarily on the difficulties of adherence to the complex medication regimen and the inherent conflict between the developmental processes of adolescence and the burden of chronic disease.^{30–33} Third, younger patients may be advantaged in this particular protocol, because they have larger thymi, which in preclinical studies correlates with a more robust state of tolerance.³⁴ Finally, pediatric transplant recipients, as a group, have a greater demand for prolonged graft survival and, therefore, are more susceptible to graft vasculopathy and chronic rejection.

It is clear that we must consider extending this study protocol to adolescents and, eventually, younger patients. Given their already compromised outcomes, the adolescent and pediatric transplant population would experience even greater potential benefits from tolerance induction than adults. Ethicists have already stated that, “[o]nce promising protocols aimed at inducing tolerance...have proven successful in preclinical large animal models, it would be ethically sound to test them in human adult and pediatric heart transplant recipients in attempts to induce tolerance and thereby prevent chronic rejection and reduce or eliminate life-long immunosuppression.”³⁵

It has been more than 50 years since Medawar and co-workers²¹ first described immune tolerance. We are finally poised to use tolerance to its fullest and widest potential in human transplantation.

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Abbreviations

EBV	Epstein-Barr virus
PTLD	posttransplant lymphoproliferative disorder