

Editorial

One Kidney for Life

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Human clinical tolerance to renal allografts is now a reality. Protocols for achieving it vary but all involve withdrawing immunosuppression after transplanting a kidney along with donor bone marrow–derived cells. The benefits of eliminating immunosuppression are self-evident. Improvements in posttransplant quality of life without the need for constant compliance with a complex multi-drug regimen cannot be underestimated. Although unproven, the elimination of prophylactic immunosuppression may well be associated with a reduction in chronic diseases that continue to limit life expectancy after transplantation including hypertension, diabetes, ischemic heart disease, hyperlipidemia, metabolic bone disease, cancer and infectious diseases. The payoff of trading dialysis for a transplant will rise sharply for the segment of the transplant population that will be eligible for these protocols. For these patients, the cost to the health-care system will be limited to the transplant event and not continue on indefinitely.

All of these benefits will change the face of transplantation forever but the most far-reaching effect of attaining durable allograft tolerance is the elimination of the need for retransplantation—one kidney for life. Without the systemic side effects of immunosuppression and the inevitable return to dialysis, a young person could achieve a normal life expectancy. Without the renal toxicity caused by calcineurin inhibitors and allo-reactivity manifesting as acute and chronic rejection, the half-life of the allograft could approach that of a native kidney. Reducing the accumulation of patients awaiting retransplantation will ease the organ supply crisis.

The younger the patient the more profound the expected benefit of allograft longevity. Noncompliance, especially during the teen years, often means that a pediatric patient's first kidney has a truncated survival. When a pediatric patient returns to dialysis after losing an allograft they will have a >30% waitlist mortality over the next 15 years,

some will never reach adulthood (Figure 1). The fate of highly sensitized patients who have lost a kidney is also dire. Over the ensuing 15 years their mortality rate on dialysis will be greater than 60%, worse than that of many types of cancer (Figure 1). It is these two groups, children and sensitized patients, which may benefit the most from tolerance. It is also these two groups for which societal and immunologic barriers may be the most difficult to surmount. There certainly will be ethical challenges to exposing children to tolerance conditioning regimens but children should not be deprived of the opportunity of benefiting from them. Once tolerance protocols are proven with acceptable toxicities in the healthiest patients we must rapidly move them into the pediatric population. Clinical trials will need to be carefully designed to limit toxicities and provide long-term follow-up. Likewise, attention should remain focused on the plight of the sensitized patient and their dismal survival on dialysis. Rapid loss of chimerism due to either donor-specific antibodies or donor-directed T cells thus far has thwarted attempts to induce tolerance in sensitized patients.

Current tolerance protocols fall into two broad categories: those in which the goal is transient chimerism and those meant to achieve full donor chimerism (1–3). Transient chimerism is vulnerable to the loss of tolerance and rejection, whereas, full donor chimerism is irreversible and carries with it the risk of graft versus host disease (GVHD), which can be fatal. GVHD can be minimized by manipulating the dose of certain cellular phenotypes in processed donor bone marrow–derived preparations or by using high dose, posttransplant cyclophosphamide (3,4). Nonmyeloablative protocols designed to produce full donor chimerism include chemotherapeutic agents and total body irradiation that results in prolonged neutropenia and an increased risk of serious infections. The tradeoff is that once full donor chimerism is established it is thought that tolerance will be permanent. Both of these strategies need to be further evolved and the essential components of each must be elucidated in order to reduce to a minimum the toxicities and long-term adverse side effects.

The field of human clinical tolerance is young and the protocols will undergo many iterations before they are perfected. One would not expect that every transplant patient would benefit from immunosuppression withdrawal. For example, patients whose renal failure is associated with autoimmunity may require immunosuppression regimens similar to those in current use. Some patients may be

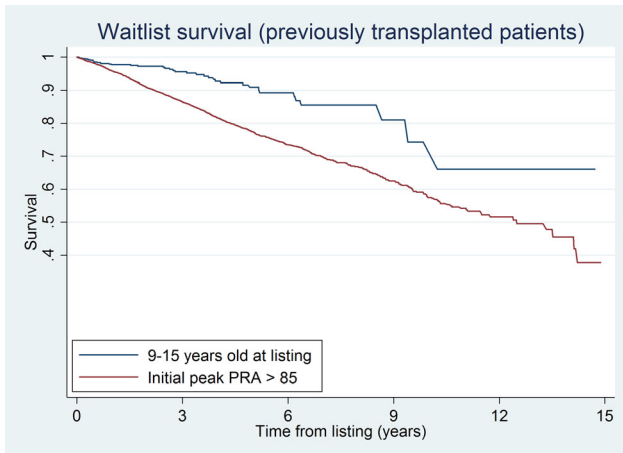


Figure 1: Waitlist survival for selected deceased donor registrants 1999–2013 with at least one prior transplant. The blue line depicts waitlist survival for registrants age 9–15 at listing; the red line depicts waitlist survival for registrants with peak panel-reactive antibody (PRA) at listing of 86 or higher.

conditioned for immunosuppression reduction or monotherapy, while others may achieve complete withdrawal. It seems likely that a wider spectrum of maintenance immunosuppression strategies will comprise the future face of transplantation.

As in any new innovation in solid organ transplantation long-term follow-up will be required to prove efficacy and surrogates for long-term outcomes will need to be identified and verified to hasten progress. It will require a sea change to reverse the drift that has occurred away from

the early, inspired observations of Medawar but imagine a future in which the gift of life will be for life (5).

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Disclosure

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