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INVITED COMMENTARY

Optimizing immunosuppression: who can do more with less?

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Clinical kidney transplantation has taken a remarkable journey over the last 60 years from concept, to high-risk endeavor for the few, to now a controlled and predictable activity [1,2]. Most of the risk has been taken by patients, many of them desperate, who are the heroes of this progression from a rare event to a common practice around the world. By example, small steps in surgical technique, histocompatibility testing, deceased donor organ recovery and preservation, living donor evaluation and safety, infectious disease isolation and treatment, diagnosing and treating allograft rejection, and the medical management of patients with renal failure both before and after transplant have been incrementally introduced to optimize the outcomes and promote patient safety. However, while we generally understand the role of both acute and chronic rejection in the fate of solid-organ transplants, we remain tentative regarding the use of immunosuppression to control the consequences of the alloimmune response. Although the state of drug-free tolerance may be the ultimate goal for patient care, contemporary clinical transplant practice remains a balance between not enough and too much immunosuppression. Not enough results in rejection, progressive graft injury, and perhaps recurrent disease; too much results in patient injury, primarily infection, and cancer (Fig. 1). The 10-year randomized trial from Thierry *et al.* [3] in this issue of Transplant International

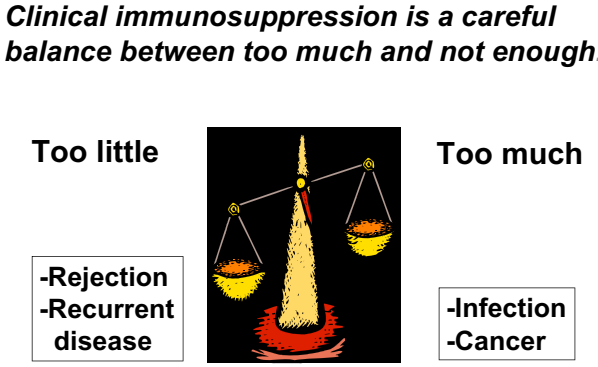

Figure 1 Clinical immunosuppression is a careful balance between too much and not enough.

adds some important observations from this journey of discovery on the best way to administer immunosuppression to kidney transplant patients. The message is one size may not fit all.

The authors report, with particularly well-done follow-up, that among 200 kidney recipients, comparable transplant outcomes can be achieved with cyclosporine (CsA) monotherapy, compared with CsA plus azathioprine (AZA) or CsA plus mycophenolate mofetil (MMF) after steroid withdrawal at 3–6 months. At 10 years, patient survival was 100%, 94.2%, and 95.8% ($P = 0.25$) and death censored graft survival was 94.9%, 94.7%, and 95.2% ($P = 0.34$) in AZA, MMF, and CsA monotherapy groups, respectively. Additional drug switching between groups was carried out for about 10% of patients. These findings are of significant interest when one considers that the transplants were all from deceased donors. However, before one considers these outcomes generalizable, there were very stringent criteria used for patient selection and continuation within the study that requires further in-depth analysis. *First*, all recipients were initially given a depleting antibody for induction; CsA–MMF–prednisone for 6 months; and at 11–24 months, "eligible" patients were randomized to one of the three study groups. *Second*, recipients had to survive 1–2 years with $\leq$1 steroid-responsive rejection episode, have an eGFR >50 cc/min/1.73 m2, and tolerate the CsA–MMF at established dosing. *Third*, the mean donor age was about 28 years and mean recipient age 46 years. *Fourth*, these were primary transplants among Caucasian-only recipients with low HLA sensitization <25% PRA. *Fifth*, only 4% of the recipients were diabetic. Each of these five sets of clinical characteristics are known to be drivers of long-term graft survival, which select for both low immunologic risk and patient compliance to the medical regimen [4]. With an international perspective, these criteria would be met by at most 20% of transplant recipients today and then only 2–3 years after transplant. Nevertheless, for those recipients who meet these criteria, monotherapy calcineurin inhibitor therapy may be particularly attractive. Clearly, there are some recipients who need less immunosuppression for their specific donor–recipient combinations than others. Just how we choose the best candidates for such limited drug therapy remains a work in progress.

A second-tier analysis in this trial relates to the reported frequencies of some of the known negative drivers of transplant outcome [4]. For the entire study group, low rates of subsequent biopsy confirmed acute rejection (4.9%), BK viremia (0), new onset diabetes (12%), and de novo solid-organ cancers (8%) are particularly notable. Whether these findings were more directly related to the younger, homogeneous, medically compliant, and noncomorbid recipients or to immunosuppressive drug minimization can be debated and remains a question. Clearly, these outcomes differ from registry reports that include a more heterogeneous population, in which immunosuppressive drug reductions after the first year were deleterious [5]. In addition, the 10-year renal function was also exemplary in this trial, with a mean estimated glomerular filtration rate of 70.4 ± 31.1, 60.1 ± 22.2, and 60.1 ± 19.0 ml/min/1.73 m^2, respectively ($P = 0.16$). Does this mean that continuous CNI treatment is safe without a negative impact on renal function? Again, the confounders of a mean donor age of 28 years, and eliminating all grafts with eGFR <50 cc/min. at 2 years, speak to the impact of selection. The 10-year histology may have provided a less salutary picture [6]. A final cautionary note was that the main cause of graft loss in this population was chronic antibody-mediated rejection.

In this immunologically privileged recipient population, de novo donor-specific antibodies were detected in 13% of AZA, 21% of MMF, and 14% of monotherapy CsA-treated patients (P=0.29), and the frequencies rose with time. Is this the yin–yang of low-dose immunosuppression? As emerging data that de novo DSA may be the leading cause of late graft loss [7,8], especially high-titer antibodies to HLA class II, and that early cellular rejections, even if reversed can lead to subsequent de novo DSA formation [9], give pause to the notion that extreme reductions in immunosuppression will uniformly result in better outcomes. In fact, uncontrolled reductions in immunosuppression manifest as nonadherence or drug holidays may be the single most significant reason for late development of de novo DSA causing subsequent transplant glomerulopathy and graft loss [10]. While these differing treatment strategies are perplexing, perhaps the key finding from the study by Thierry *et al.* is that there is no substitute for a well-followed transplant recipient. Close contact and excellent communication between the patient, treating physician, and nurse coordinator are essential to maintain grafts. In the future, a more patient-focused and selective way to deliver immunosuppression will be the seminal clinical challenge to continue the journey to optimize transplant outcomes.

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