Begin at the Beginning to Prevent the End

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In recent years, epidemiologic studies have provided a clearer picture of the pathways associated with kidney allograft failure.1–4 Apart from recurrent disease, the common observation is that alloimmunity precedes death—censored graft loss in the majority of patients and that calcineurin inhibitor (CNI) toxicity plays a relatively minor role. In this issue of JASN, two papers provide additional support for the dominant role for antibody-mediated rejection (ABMR) as the mechanism leading to allograft injury and loss of function and furthermore, make the argument that T cells are playing a minor role in the process leading to graft loss.5,6

In the study by Loupy et al.,5 subclinical ABMR was associated with accelerated graft loss compared with subclinical T cell–mediated rejection (TCMR) or normal histology in the 1-year surveillance biopsy. In the study by Halloran et al.,6 for-cause biopsies that exhibited ABMR or mixed rejection had worse graft survival compared with those with TCMR or no rejection. The study by Halloran et al.6 showed that TCMR and ABMR molecular classifiers were largely concordant with the histologic diagnosis but in some patients, suggested a reclassification that better correlated with outcomes. Finally, Halloran et al.6 noted that late TCMR was nonexistent beyond 10.2 years post-transplant by both histologic and molecular criteria, leading to the hypothesis that adaptive tolerance in the recipient’s T cell compartment was present late post-transplant, whereas alloreactivity in the B cell compartment largely persisted.

What should we conclude from these studies? What do they suggest regarding clinical practice and future research directions? Do we declare victory over the T cell and instead, focus on B cells?

In the paper by Loupy et al.,5 approximately 80% of the patients with subclinical ABMR at 1 year had preexisting donor-specific antibodies (DSAs) at transplant. As Loupy et al.5 advocate, the obvious solution to mitigate most of the poor outcomes is to modify allocation policies to avoid these antibodies. Indeed, with routine use of solid-phase assays, development of kidney paired donation programs, and national priority sharing for highly sensitized patients, the need to cross DSAs is greatly diminished—strategies that are currently operational in many countries (e.g., the United States, France, Canada, and Eurotransplant).

What of the relative lack of effect of subclinical TCMR on allograft survival? In prior studies where subclinical TCMR did predict poor allograft survival, it was in the absence of treatment.7 In the paper by Loupy et al.,5 subclinical TCMR was, in fact, treated, and Loupy et al.5 suggest that this may be why a deleterious effect of subclinical TCMR was not seen—the conclusion of the randomized trial by Rush et al.8 in 1998. Additionally, Loupy et al.5 link subclinical TCMR with the subsequent risk for the development of de novo DSAs and ABMR, further supporting the observations that have already been reported by a number of groups.4,9,10 Our group hypothesizes that TCMR–associated IFN-γ expression upregulates class II HLAs in the microcirculation that can be shed and lead to B cell activation in the lymph node compartment.4 Therefore, we advocate strategies to optimize the prevention, detection, and treatment of subclinical TCMR.

As reported in the FK-008 Study, prevention of subclinical TCMR to date is most effectively achieved with tacrolimus- and mycophenolate mofetil-based regimens.11 Furthermore, it is important to consider not just the immunosuppressive combination but also, the adequacy—the FKC-008 Study targeted tacrolimus C0 of 12 ng/ml in weeks 1 and 2, 10 ng/ml from 3 weeks to 3 months, 8 ng/ml from 4 to 6 months, and 6 ng/ml for 2 years and beyond. Eventually, optimal monitoring for subclinical TCMR will not be through surveillance biopsies but will be made with noninvasive diagnostics. At present, the only non-invasive tool shown to consistently detect subclinical TCMR has been the urine protein measurements of the IFN-γ-induced chemokines CXCL-9 or CXCL-10.12,13 What is currently lacking is a prospective study showing that a treatment strategy on the basis of urine chemokine measurements can affect outcomes—a key requirement before adopting urine chemokine measurement into routine clinical practice.

How should we approach de novo DSA-associated ABMR, which is predominately associated with class II HLA? In the 2010 Food and Drug Administration workshop on ABMR, it was noted that randomized, controlled trials are needed to define effective treatment for late ABMR.14 Indeed, Walsh et al.15 have shown that late ABMR (>6 months) is much less responsive to existing therapies than early ABMR. Thus, given the lack of effective therapy, our principal strategy
must be one of prevention. In this regard, the major risk factors for de novo DSA are class II HLA mismatching, early subclinical and clinical TCMR, and medication nonadherence.16

Medication nonadherence is underappreciated as a cause of alloimmune activation. Nevins et al.17 used electronic pill bottle monitoring and documented that 22.4% of patients had decreased dose adherence by 7% or more by month 2 post-transplant, and this level of subclinical nonadherence was associated with increased rates of acute rejection and graft loss. Two groups independently reported that late ABMR is associated with 50% nonadherence.4,18 Therefore, research to derive effective interventions to improve adherence early is urgently needed as a major strategy to improve graft outcomes.

In an effort to avoid CNI nephrotoxicity and metabolic side effects, physician-guided immunosuppressive minimization has been at the forefront for the last decade. Unfortunately, just like nonadherence, minimization also comes at a cost. Indeed, Liefeld et al.19 reported that mammalian target of rapamycin substitution for CNI between 3.0 and 4.5 months post-transplant was associated with a significantly increased rate of de novo DSAs and ABMR. At present, we do not have validated risk assessment profiles as to who can and who cannot safely undergo minimization.

What of the lack of TCMR late post-transplant and the hypothesis by Halloran et al.6 of adaptive T cell tolerance (involving exhaustion) and preserved B cell activation? What alternative explanations exist? Halloran et al.6 discount that time leads to a selection bias in favor of adherent patients and that immunosuppression differentially controls T and B cell alloactivation. What have not been discussed are the different pathways of allorecognition that might be operational late versus early post-transplant.20 The direct pathway involves recipient CD4 and CD8 T cells directly binding intact donor HLA proteins on the surface of donor–derived antigen-presenting cells (APCs) that accompany the transplant. The indirect pathway involves recipient CD4 T cells that recognize soluble donor HLA proteins, which have been taken up and processed to allopeptides by recipient APCs in association with self-HLA. These CD4 T cells can differentiate into T follicular helper cells that localize to germinal centers to bind allopeptide expressed by self-HLA on allo–specific B cells. This indirect CD4 T cell help is required for B cells to class switch and differentiate into plasma cells secreting de novo DSAs. The semidirect pathway results from recipient APCs migrating through the graft and acquiring intact donor HLAs by membrane transfer from donor cells (e.g., endothelium). These APCs express both intact donor HLAs and donor HLA allopeptide in association with self-HLA, allowing for direct allo–specific CD8 T cells to receive linked indirect allo–specific CD4 T cell help from the same recipient APCs. The degree to which this pathway is operational in humans is unclear.

A key point is the durability of these pathways over time. Although the direct pathway can lead to a robust and high-frequency response early post-transplant, it cannot be sustained, because there is no renewable source of donor APC. Beyond the early post-transplant period, only the semidirect and indirect pathways remain intact, by which indirect allo–specific CD4 T cells can provide long-term help signals to direct allo–specific CD8 cytotoxic T lymphocyte and indirect allo–specific B cells, respectively. Thus, it is not unexpected that ABMR is a dominant pathway leading to late graft loss given that the indirect pathway is always operational because of the endless supply of recipient APCs. However, the emphasis, given the ever-present potential for allorecognition by CD4 T cells, must be on adequate immunosuppression of the T cell to prevent the development of de novo DSAs.

In summary, we suggest that the most effective strategy to improve graft outcomes is to begin at the beginning: (1) avoid transplanting patients with preexisting DSAs, (2) limit allorecognition through class II HLA matching and adequate immunosuppression long term, (3) screen for medication nonadherence and intervene, (4) screen for and treat subclinical TCMR, (5) avoid drug minimization in those patients at risk for de novo DSAs (class II HLA mismatched or early TCMR), and (6) when deemed acceptable or necessary, use allograft monitoring to minimize immunosuppression, (e.g., urine chemokines and serum DSAs). Clearly, research is still needed to optimize each one of these strategies. Finally, given the smoldering nature of de novo DSA-associated ABMR, it should be detected early (before graft dysfunction), and these patients should be enrolled into randomized, controlled trials to determine how best to treat it before it results in irreversible injury.

DISCLOSURES

P.W.N. and D.N.R. are consultants for Astellas Pharma Canada.

REFERENCES