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Moving Beyond Minimization Trials in Kidney Transplantation

Arthur J. Matas* and Robert S. Gaston†
*Department of Surgery, University of Minnesota, Minneapolis, Minnesota  †Comprehensive Transplant Institute, University of Alabama at Birmingham, Birmingham, Alabama


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Correspondence: Arthur J. Matas, M.D., University of Minnesota, 420 Delaware Street S.E., MMC 195, Minneapolis, MN 55455. Email: matas001@umn.edu

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It was nearly a decade between the first identical twin living donor kidney transplant and successful allotransplantation. That interval saw the development of azathioprine and the recognition that steroids could both prevent and treat transplant rejection. Almost immediately, two clinical pictures became apparent: (1) at equivalent doses of immunosuppression, some kidney transplant recipients did well, others poorly, and (2) immunosuppression was associated with a myriad of side effects. In the ensuing half-century, these observations have driven clinical research to identify new drugs and/or protocols that would prevent rejection (maximize efficacy) while reducing or eliminating adverse events (minimize toxicity). Clinical approaches have varied from dose reduction for an entire population to individualized immunosuppression (identifying the proper drug and dose for each individual) to protocols targeting immunologic tolerance and making long-term immunosuppression unnecessary. However, even with the progress of the last five decades (notably the development of more powerful immunosuppressants and better antiviral drugs, better HLA characterization, more sensitive cross-match techniques, better diagnostic tools, as well as the introduction of genomics, proteomics, microarrays, and other technologies) effective minimization, individualization, and tolerance remain elusive.

Early approaches attempted to minimize immunosuppressive drug dosing (or its correlate, blood levels) in an entire kidney transplant recipient population, or a subgroup selected by characteristics at the time of transplant (e.g., first transplants; low percent reactive antibody [PRA]). Initially, when only prednisone and azathioprine were available, these studies focused on limiting prednisone dosing in an attempt to minimize steroid-related side effects. Although some recipients did well with this approach, most had early and frequent acute rejection episodes leading to short- and long-term graft failure. With the development of cyclosporine and mycophenolate mofetil (MMF), reliance on large doses of steroids diminished, leading to new trials of steroid elimination, including large prospective randomized trials in both Europe and the United States in “low immunologic risk recipients.” Both trials demonstrated that steroid elimination at 3 months posttransplant was associated with increased acute rejection rates. More recently, however, protocols discontinuing steroids within the first posttransplant week (under cover of depletional induction and full dosing of other immunosuppressives) have had better success—slightly more acute rejection, but no decrement in 5-year patient and graft survival, with fewer steroid-related side effects.

The introduction of calcineurin inhibitors (CNIs) resulted in less acute rejection, but concerns regarding long-term nephrotoxicity and other CNI-specific side effects led quickly to trials of CNI minimization. Similar to the previous approaches with corticosteroids, CNI-minimization and avoidance trials enrolled cohorts either from the entire transplant population or preselected subgroups thought to be at low immunologic risk. Some but not all trials demonstrated better renal function (eGFR) with CNI minimization, perhaps slight improvement in some CNI-specific adverse events, but none showed improved patient or graft survival. It seems increasingly evident that many of these trials were based on a false premise: that CNIs were the principal cause of chronic graft dysfunction. As our understanding of late graft dysfunction evolved to recognize a critical role for antibody-mediated injury, it is ironic that evidence of the importance of antibody emerged in part from studying the impact of CNI withdrawal or avoidance.

Without a doubt, “individualization” of immunosuppression is more appealing than adjustments in an entire cohort. Application of clinical criteria alone, with more intense immunosuppression for some recipients (e.g., highly sensitized, retransplant), less intense for others (0% PRA, first transplant), is widely practiced but without strong supportive evidence or standardization. There has been great interest in defining biomarkers predictive of risk, to enable individualization at the time of transplant or with subsequent monitoring. Despite some progress in identifying associations and mechanisms, successfully using known biomarkers to tailor immunosuppression has yet to happen. Finally, personalized medicine and genomic studies (other than single nucleotide polymorphisms that affect tacrolimus levels) have not resulted in validated observations.

In this issue of the journal, Hricik and colleagues report a multicenter trial, performed under the auspices of the National Institute of Allergy and Infectious Diseases, in which a combination of approaches was applied to define a subgroup of kidney recipients at low risk for rejection and potentially amenable to CNI withdrawal. All recipients were maintained on tacrolimus, MMF, and prednisone. Randomization (at 6 months posttransplant) required both favorable pretransplant demographics (first transplant, living donor, peak PRA<30%, no donor-specific antibody [DSA], negative cross-match) and a benign early posttransplant course (no acute rejection, de novo DSA, or evidence of rejection on 6-month surveillance biopsy, and tolerance of ≥1500 mg of MMF daily). Subjects meeting these criteria were randomized to maintenance tacrolimus versus withdrawal, with planned enrollment of 300 patients. The study was stopped by its data safety monitoring board after 52 patients were enrolled (47 transplanted; of these, 21 randomized), based on predetermined stopping rules (increased rates of acute rejection or DSA in the withdrawal group).

This work is an important extension of the literature by demonstrating that, after decades of attempts, state-of-the-art clinical and laboratory observations were unable to predict which patients on standard immunosuppression would fare well with CNI withdrawal. Two substudies were also noteworthy. First, urine samples were collected at each study visit and tested for the chemokine CXCL9, shown in previous studies to correlate with acute rejection in patients with graft dysfunction. In the current study, CXCL9 assays in all randomized patients were negative...
at 3 and 6 months posttransplant, demonstrating that this assay would not be predictive in determining which recipients could be successfully withdrawn from tacrolimus. Beyond 6 months posttransplant, there were seven positive CXCL9 assays in six patients in the withdrawal arm, associated with either BK virus infection \((n = 2)\) or a rejection episode \((n = 5)\). In control subjects and those successfully withdrawn from tacrolimus, CXCL9 assays remained negative, indicating a potential role for monitoring CXCL9 after changes in immunosuppression. A second substudy confirmed previous findings that a high DQ epitope load was associated with a higher rate of development of de novo DSA.19

Another significant aspect of this study is its design: two surrogate endpoints—acute rejection and development of de novo DSA—effectively halted the trial after only 21 patients had been randomized. Not surprisingly, with the small number of enrollees, there was no difference between the two study arms in patient and graft survival. Twenty years ago, Hunsicker et al. noted that short-term transplant outcomes were sufficiently good that it would take a randomized study with enrollment in the hundreds to demonstrate significant improvement in patient and graft survival.20 Yet, with close follow-up of outcomes and the use of surrogate markers, this study was stopped after only one sixth of the planned enrollment. To our knowledge, this is the first National Institutes of Health–sponsored study to use a combination of these two surrogate endpoints, and it paves the way for use in future trials.

Where, then, do we stand regarding optimizing immunosuppression? Should we continue pursuing minimization? Certainly rapid discontinuation of steroids, at least in a select group of recipients, is now commonplace.21 Regardless of whether CNI nephrotoxicity is a major cause of graft failure, reducing drug-specific toxicity is a noble goal worthy of pursuit. However, this study demonstrates the difficulty of defining a broadly successful approach to minimization of CNIs with our limited monitoring capabilities. One factor that has not been addressed in these minimization trials is nonadherence. Recent data indicate that nonadherence, including “subclinical nonadherence” (detected by monitoring, pill count, or missing renewal of prescriptions), is associated with development of de novo DSA and increased rates of graft loss.12,13,22 It is likely that for each transplant recipient there is a critical threshold of immunosuppression below which, either by physician or patient dose reduction, an immunologic response will ensue. Is it possible that recipients assume that if one of their immunosuppressive drugs can be successfully minimized or withdrawn, other dose minimization is possible? And they undertake this dose minimization themselves?

The best alternative to minimization would likely be immunologic tolerance. There has been significant progress in moving this approach forward: three institutions, using different protocols, have demonstrated clinical success.23 Currently, however, none of these protocols are ready for widespread implementation, and challenges remain including limited success in poorly matched or presensitized recipients, and the requirement for pretransplant conditioning or preparation of donor cells for infusion (limiting the protocol to living donor transplants).24

In a sense, Hricik et al. have highlighted the boundaries of our progress in clinical immunosuppression. Using one of the most powerful combinations of anti-rejection therapy, and with well defined clinical and laboratory parameters, they were unable to select a subgroup not dependent on CNIs. What limits moving the field forward? There has been an explosion of knowledge in immunology, with new technologies waiting to be applied in our field (e.g., genomics, proteomics, microarrays). Yet with the realities of clinical care responsibilities, regulatory oversight, and limited research funding, there is a relatively small cadre of researchers engaged in translating these advances to clinical transplantation. In addition, neither the Food and Drug Administration approval process nor the 5-year limitation on federal research grants facilitates studies of long-term outcomes that are critically needed to advance the field. The findings of Hricik and colleagues challenge us to move the field forward in a different way: with a new paradigm, beyond minimization, based on relevant endpoints and able to define effective protocols for long-term success.

DISCLOSURES

The authors have no relevant financial interests to disclose.

REFERENCES

Glomerular Effects of Age and APOL1

Timothy W. Meyer and Colin R. Lenihan

Department of Medicine, Veterans Affairs Palo Alto Health Care System and Stanford University, Palo Alto, California

Two articles in this issue of JASN seek to identify structural weaknesses that render glomeruli liable to failure. Hodgin et al. examine glomerular loss with aging and propose that a gradual reduction in the number of podocytes per unit glomerular volume reaches a point where it triggers glomerular failure. As glomeruli are lost, compensatory hypertrophy of those that remain leads to additional reduction in podocyte density, because podocytes are terminally differentiated and cannot divide. The resultant self-perpetuating process of glomerular destruction causes age-related loss of renal function.

In advancing their podometric view, Hodgin et al. re-examine the problem of age-related loss of renal function at increased structural resolution. However, as noted in the introduction to the work by Hodgin et al. and recently reviewed by Glasscock and Rule, it has been remarkably hard to characterize even the most basic structural features of renal aging. This difficulty is exemplified by the two JASN papers that we are considering. Hodgin et al. report that glomerular volume increases markedly with age. Hoy et al. see little change in glomerular volume with age, except perhaps in African Americans with APOL1 risk alleles. Differences in tissue processing and clinical parameters, including body size, may account for some of the variation in these descriptions and others of renal aging. We suspect that differing morphometric methods are also a major source of variation. Hodgin et al. calculate average glomerular volume on the basis of the open glomerular profiles. Sclerosed glomeruli are not included in the calculation. Hoy et al. calculate average glomerular volume as the aggregate volume of glomeruli divided by the number of glomeruli. Inclusion of sclerosed glomeruli will tend to keep the average volume stable if some glomeruli enlarge while others are sclerosed. The magnitude of the difference will be increased by underrepresentation of shrunken glomeruli in small biopsy specimens as opposed to larger autopsy specimens unless mathematical corrections are made. Measurements may also be affected by inclusion of more superficial glomeruli in biopsy specimens.

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Correspondence: Dr. Timothy W. Meyer, Nephrology 111R, Palo Alto VAHCS, 3801 Miranda Avenue, Palo Alto, CA 94303. Email: twmeyer@stanford.edu

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