CLINICAL VIGNETTE

Balancing the Efficacy and Toxicity of Maintenance Immunosuppression in a Kidney Transplant Recipient: A Case Report

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A retired engineer who originally had ESRD ascribed to hypertension underwent kidney transplantation from an 8-year-old deceased donor in 1999. His initial post-transplant course was uncomplicated, and there was immediate function of the allograft. His induction immunosuppression consisted of basiliximab, methylprednisolone, and cyclosporine, though the cyclosporine dose was half of the usual dose as part of a clinical trial. His baseline creatinine was initially 1.2. Almost exactly 12 months post-transplant, an increase in creatinine to 1.4 prompted an allograft biopsy, which showed acute tubular injury and no signs of acute cellular rejection. Another biopsy, performed 12 months later (2y post-transplant) due to increasing proteinuria, showed Focal Segmental Glomerulosclerosis (FSGS), IgA deposition, and no rejection; extensive foot process effacement suggested primary FSGS. The proteinuria was treated with an angiotensin receptor blocker and remained subnephrotic. Other complications included post-transplant diabetes (about 1-2y post-transplant with poor control), hypertension (requiring multiple agents), atrial fibrillation (6y post-transplant, on warfarin), legionella pneumonia complicated by non-ST-elevation myocardial infarction and acute kidney injury (about 7y post-transplant), and Parkinson disease (15y post-transplant).

About 2-3 years after the transplant, the maintenance prednisone was stopped (perhaps due to post-transplant diabetes), and mycophenolic acid was added. The creatinine remained about 1.2-1.3 at baseline until about 15 years post-transplant when it started to trend up along with increasing proteinuria. Over the past 2 years, he had worsening edema, and it became increasingly difficult to control hypertension. Now 18 years post-transplant, the creatinine has been around 2.0, and proteinuria has increased to the nephrotic range. Donor-specific antibodies have developed though the time of onset is unclear. He has been advised that his kidney transplant allograft is unlikely to last for more than 12-24 months and that preparation for dialysis access should begin.

Kidney transplantation offers the best quality of life, longest survival, and lowest cost compared to the other forms of renal replacement therapy for end stage renal disease (ESRD).[1] Maximizing allograft survival is critical: 10-12% of transplants each year are retransplants,[2] and many patients waitlisted for kidney transplant do not survive to receive one due to increasingly long waiting times.[3] Indeed, this patient's age, comorbidities, and long waitlist times make him very unlikely to receive another kidney transplant.

Allograft longevity made great leaps forward with introduction of prednisone and azathioprine in the 1960s[4] and cyclosporine in the early 1980s.[5,6] More modest improvements have been seen with mycophenolate in 1998[7,8] and belatacept in 2010.[9] The estimated crude and death-censored half lives for recipients of deceased-donor kidney allografts are now 10 and 15 years, respectively.[2,7] Despite this progress in allograft longevity, the long-term attrition rates remain high and have improved little over time at about 5-7% per year after the first post-transplant year.[7] Antibody-mediated rejection (AMR) and recurrent primary glomerulonephritis are the two most common causes of chronic allograft loss as shown in a recent prospective study.[10] These conditions are treated with higher doses of immunosuppression, but this strategy and indeed all solid organ transplants are limited by the toxicity of chronic immunosuppression.

Kidney transplant patients frequently experience immune-mediated allograft injury and toxicity from immunosuppression at the same time. In this patient, the maintenance corticosteroids were stopped due to the development of new onset diabetes after transplant (NODAT). Though perhaps less feared than opportunistic infections or cancer, NODAT is due in part to immunosuppressive medications and is associated with worse outcomes, including increased rates of cardiovascular events, graft failure, and death.[11] The incidence at 6 months post-transplant was 8.9-16.8% in a recent trial of kidney transplant recipients using modern triple-drug maintenance immunosuppression[12] in comparison to an annual incidence of about 6% for patients on the kidney transplant waitlist.[11] In addition to sharing traditional risk factors for type 2 diabetes, risk factors for NODAT also include glucocorticoids, tacrolimus, cyclosporine, sirolimus, chronic hepatitis C virus infection, HLA-mismatches, and HLA-DR mismatches.[13]

Though stopping the corticosteroids in this patient is a common response to NODAT,[13] this change might have led to formation of the donor-specific antibodies. A multicenter Canadian study comparing glucocorticoid + cyclosporine versus cyclosporine maintenance alone found higher rates of allograft loss in the steroid-free arm at five years.[14] However, a more recent trial using the more potent and widely-used maintenance immunosuppression of tacrolimus and mycophenolate found equivalent rates of patient and allograft survival but a higher rate of acute rejection at 5 years follow up.[15] The recurrent GN occurring in this patient's allograft could have also been worsened by stopping of the steroids.

Retrospective and prospective studies have shown increased rates of allograft loss and recurrent GN both for all types of GN and for IGA nephropathy in patients maintained on steroid-free regimens.[16-18]

Unfortunately, additional treatment options for this patient and the many patients who suffer from chronic allograft nephropathy are limited. There are little clinical trial data for the treatment of chronic AMR.[19] A common strategy is to maximize the dose of the antimetabolite as this usually does not substantially increase the side effects of immunosuppression, although the efficacy is unknown. Prednisone can be re-added to this patient's long list of medications, but this patient's diabetes and sodium retention would probably get worse. His recurrent GN would be unlikely to respond this late. Therefore, this patient's options are limited to increasing the mycophenolate dose and preparing for returning to dialysis.

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