Debates in Nephrology

Should Protocol Kidney Biopsies Be a Part of Routine Post-Transplant Care? Commentary

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The incidence of acute rejection has continuously declined from a rate exceedingly over 50% during the 1970s to 10%–20% in the current era.[1] With this, early graft failure due to acute rejection is also in decline. Between 2000 and 2010 in Australia and New Zealand, <3% of all kidney graft failures were directly attributed to acute rejection in the first post-transplant year.[2] However, among late graft failure, acute rejection and mainly antibody-mediated rejection are the most common causes.[3]

At present, serum creatinine is the standard of care clinical surveillance test for detecting functional injury within the kidney graft. However, various studies have demonstrated serum creatinine is an unreliable, nonspecific, and delayed marker of graft injuries. By the time there is a significant rise in serum creatinine, there could be various acute and chronic changes in the kidney graft suggestive of rejection or various other changes including calcineurin inhibitor toxicity, BK polyomavirus nephropathy, and many more. Proteinuria is another easily available and routinely performed marker to assess for graft injury. However, in a study among kidney transplant recipients with stable serum creatinine and isolated proteinuria who underwent biopsy exclusively due to proteinuria, only 29% had acute rejection, 20% had GN, and the remaining had various other pathologies.[4] This highlights proteinuria alone is insufficient in signaling any specific types of pathological findings in the graft. In addition, the detection of anti-HLA *de novo* donor-specific antibodies (DSAs) with stable graft function (stable serum creatinine and proteinuria) is only 50% predictive in identifying subclinical rejection.[5] Recently, donor-derived cellfree DNA (dd-cfDNA) has gained widespread utility as a biomarker in the transplant community for early detection of active rejection based on surveillance. However, it is still far from the ultimate test to detect rejection. The results suggest that a negative dd-cfDNA test in a stable patient can exclude a rejection; however, a positive test may result in an unnecessary biopsy. Given all these, neither serum creatinine nor proteinuria nor HLA DSA or dd-cfDNA can replace kidney graft biopsies. Kidney graft biopsy remains the gold standard for the identification of underlying pathological processes.

This raises two important questions about kidney graft biopsy—(*1*) the timing of the biopsy and (*2*) the outcomes of the subclinical rejection with stable serum creatinine. In experienced hand, although kidney graft biopsy is a relatively safe procedure with a rate of complications needing intervention is <1%; however, it is still an invasive procedure that imposes a significant burden on the recipients, is labor-intensive, and requires a multidisciplinary team approach. With this, practically it is not possible to obtain a kidney graft biopsy regularly, like the aforementioned non-invasive tests. In addition, one randomized study did not show significant benefit in graft function and survival with frequent protocol biopsies within 6 months post-transplant, among recipients on standardized immunosuppressive medication with tacrolimus and mycophenolic acid.[6] Regarding the outcomes of subclinical rejection, we have reported that outcomes of subclinical antibody-mediated rejection defined as stable serum creatinine and those who underwent HLA DSA–guided protocol kidney graft biopsy have significant favorable outcomes compared with those with clinical rejection, as defined by those who underwent graft biopsy guided by high serum creatinine.[7]

In this current issue of *Kideny360*, titled "Should Protocol Kidney Biopsies be a Part of Routine Post-Transplant Care?" both the PRO and CON authors took a balanced view of the utility of the protocol kidney graft biopsy for routine post-transplant care.[8,9] Both the PRO and CON authors carefully outlined the advantages and disadvantages of protocol biopsies. Neither of the authors in these

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See related debates, "Should Protocol Kidney Biopsies be a Part of Routine Post-Transplant Care? PRO" and "Should Protocol Kidney Biopsies be a Part of Routine Post-Transplant Care? CON," on pages 501–503 and 504–506, respectively.

two groups was totally against or for protocol biopsies. Rather both groups came to the common ground of the utility of protocol biopsies with a high pretest probability of treatment-altering results. It is not unreasonable to obtain a protocol graft biopsy among high immunological risk recipients with a risk of rejection or recurrence, including recipients with pretransplant DSA, those who developed HLA-*de novo* DSAs, those with previous graft failure due to recurrence or *de novo* glomerular disease, those on calcineurin inhibitor-free regimen, or those on suboptimal immunosuppressive agents and prolonged delayed graft function. However, in those with stable graft function and overall lower immunological risk recipients, the utility of protocol biopsy is weak.

In summary, most of the studies about the utility of protocol biopsies are within an early post-transplant interval, mainly within the first 6 months to a few years post-transplant. In the current era of standardized calcineurin inhibitor-based immunosuppressive utilization, the risk of early graft failure due to rejection is low. Still, there is a role of early protocol biopsy in selected high immunological risk recipients. However, chronic rejection, particularly chronic active antibody-mediated rejection, is the leading cause of late kidney graft failure.[10] Also, it is still unknown the utility of protocol biopsy in these recipients who are more than 5 or 10 years post-transplant, mainly with the need for frequency of protocol biopsy, incidence and prevalence of chronic rejection, and management outcomes with ultimate graft outcomes. This will need a prolonged, multicenter study with larger sample sizes. Hopefully, in the future, new biomarkers-guided protocol biopsy for early detection of chronic rejection may be of value for monitoring and maintaining prolonged graft function and survival.

Disclosures

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