KIM-1 expression in kidney allograft biopsies: Improving the gold standard

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Long-term outcomes of kidney allografts have shown only marginal improvement over the last three decades, despite the remarkable improvement in acute rejection and one-year graft survival. Novel biomarkers of tubular injury may prevent irreversible damage to the tubulointerstitial compartment and improve allograft survival.


In kidney transplantation, the diagnosis of acute kidney injury (AKI) has depended on morphologic evaluation of the allograft biopsy as the gold standard. Unfortunately, histologic findings of tubular injury do not differentiate among its possible etiologies, nor do they correlate with severity of the injury or its prognosis. Even protocol biopsies have not succeeded in correlating histologic changes with allograft outcome. Interest in improving the diagnostic tools for the early detection, treatment, and prognosis of immune injury to the graft has resulted in several advances in recent years. Specifically, markers of immune activation in the peripheral blood such as soluble CD30 and urinary markers of immune injury such as perforin and granzyme B were found to correlate with acute rejection. Tissue expression of CD20 or FOXP3 in allograft biopsies which appear histologically similar was found to correlate with response to treatment. If confirmed in longitudinal and less selective kidney transplant populations, these markers may result in better management of the transplant patients.

A particular problem in kidney transplantation is the need for biomarkers of immune and nonimmune injury at different time periods after transplantation (Figure 1). In the immediate perioperative period, days 0–30, there is a desperate need for a biomarker with the following characteristics: (1) predicts the development of delayed graft function and its severity and prognosis at the donor stage; (2) indicates the course of the transplant after implantation in order to assist in the choice of induction and length of time when calcineurin inhibitors need to be avoided; (3) allows early detection of immune injury in order to guide the timing of the biopsy; (4) adds to the morphologic diagnosis by guiding type and length of immunosuppressive therapy; (5) allows early detection of drug toxicity and indication of its course after reduction or withdrawal. In the second time period, days 31–180, stabilization of graft function and gradual reduction of immunosuppression are expected. The characteristics of the desired biomarker at this stage include many of those outlined previously, with major emphasis on the early detection of immune activation and drug toxicity and the guiding of biopsy and therapy. The third time period includes long-term follow-up after day 180. In addition to the previously mentioned characteristics, a biomarker that can detect early development of tubulointerstitial fibrosis and its extent and progression is needed in the diagnosis, management, and development of newer therapies for chronic allograft nephropathy.

Evaluation of biomarkers of acute allograft dysfunction of nonimmune etiology has not fared as well as markers of immune activation and injury. Kidney injury molecule-1 (KIM-1) is a recently discovered transmembrane type 1 epithelial cell protein with an extracellular domain that includes immunoglobulin and mucin domains.1 It is not detected in normal kidneys but is upregulated in renal proximal tubules after injury. If cleaved by metalloproteinases, its ectodomain can be measured in urine after acute tubular injury. Published studies on the utility of KIM-1 as a biomarker of acute tubular injury in kidney transplantation are limited. In a rat model, increased mRNA expression of KIM-1 correlated with nephrotoxicity induced by the combination of cyclosporine and sirolimus.2 In another rat model, KIM-1 mRNA and urinary KIM-1 correlated with cyclosporine toxicity and improved with intervention.3 A small human cross-sectional study of KIM-1 mRNA expression and urinary KIM-1 protein measurement has recently been reported.4 KIM-1 mRNA expression was increased to a larger extent in acute than in chronic rejection, and urinary KIM-1 correlated with immunohistochemical staining of the biopsies. Thus the transplantation community welcomes the study by Zhang et al.5 (this issue) showing promising data on KIM-1 expression in kidney allograft biopsies. An important strength of this study is the availability of follow-up data 18 months after the biopsy. As was observed by the same group in ischemia/reperfusion and nephrotoxic AKI, KIM-1 staining correlated with the severity of the injury as measured by the deterioration in allograft function. KIM-1 staining also predicted prognosis in some transplant biopsies, as heavy staining correlated with improved kidney function at 18 months. Previous assumptions of the role of KIM-1 in regeneration and differentiation of proximal tubular cells after injury were not borne out in biopsies with acute rejection, as no improvement in outcome was found to correlate with KIM-1 staining. As KIM-1 is not detectable in normal kidneys, its demonstration in 28% of protocol biopsies without histologic evidence of acute or chronic tubular injury could be interpreted as an improvement on the sensitivity of the allograft biopsy. In this group of protocol biopsies, there was no change in allograft
function or outcome at 18 months. Without the use of cutoff values, this overlap in KIM-1 staining is likely to be problematic and may result in unnecessary biopsies if the test is the sole marker. The retrospective nature of this study, especially when the etiology of acute tubular injury is missing, does not allow scrutiny of the utility of the test in identifying drug-induced toxicity and its further management. Similarly, lack of information on the interventions undertaken after the biopsies further undermines confidence in the test's ability to predict prognosis. Further evidence for the utility of this biomarker will need to come from a prospective study to test its validity in an unselected transplant population.

To date, there are few published studies of markers of acute tubular injury in kidney transplantation. Neutrophil gelatinase-associated lipocalin (NGAL) has been tested as a biomarker for delayed graft function. Staining for NGAL in biopsies obtained from deceased-donor kidneys correlated with the development of delayed graft function. Also, urinary NGAL and interleukin-18 predicted the development of delayed graft function with excellent sensitivity. Experimental proteomic analysis of urinary protein profiles has shown promise. Peaks in three different regions accurately identified patients with acute rejection and were not shared by transplant recipients suffering from acute tubular necrosis. Proteomic analysis could not discriminate between stable allografts with normal protocol biopsies and those with subclinical rejection.

In summary, it should be obvious that no single biomarker has been identified to fulfill all the needs of a single stage in the course of kidney transplantation. Histologic evaluation of allograft biopsies remains the gold standard for the diagnosis of acute and chronic allograft dysfunction. At the same time, reliance on serum creatinine to time the biopsy, failure to detect subtle but consequential signs of injury, and inability to predict prognosis and guide therapy have resulted in missed opportunities to affect long-term graft survival. There are now several available biomarkers with acceptable predictive values in animal studies and limited cross-sectional human studies of kidney allografts. Advances in identifying biomarkers of AKI in the intensive care unit and after cardiac surgery have been significant. Only a few of these studies have included kidney transplant recipients, an ideal field to test biomarkers of ischemia/reperfusion, drug-induced nephrotoxicity, and other causes of AKI. Now is the time to validate the utility of these markers in large prospective trials that would study the performance of each biomarker alone and as part of a panel of markers for immune and nonimmune, acute and chronic injury. The close monitoring of kidney transplant recipients with frequent urinary and blood testing lends itself to testing of these biomarkers. In addition, the relative ease and lack of significant complications have encouraged physicians to include protocol biopsies as part of patient management. These biomarkers are prime testing sites for novel molecular targets.

**REFERENCES**


