Sirolimus: Defining Nephrotoxicity in the Renal Transplant Recipient

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The introduction of new immunosuppression drugs in the 1990s resulted in marked reduction in acute rejection but had no appreciable impact on long-term graft survival. A major impediment to the improvement of long-term outcome has been attributed to the inexorable and progressive nephrotoxicity associated with the use of calcineurin inhibitors (CNI).

With the introduction of sirolimus in transplantation, it was hoped that its lack of nephrotoxicity in animal models would be translated in humans to improve immunosuppression with minimal effect on renal function. However, the results of the US Multicenter Trial with cyclosporine and sirolimus revealed that sirolimus-treated patients had significantly higher serum creatinine values at 6 and 12 mo despite a significant reduction in acute rejection rates (1). Further investigations proposed a pharmacokinetic interaction between sirolimus and cyclosporine to enhance tissue concentration of cyclosporine, augmenting its inherent nephrotoxic potential rather than a direct nephrotoxic effect of sirolimus (2). This clinical finding led to trials of sirolimus with cyclosporine minimization or withdrawal to address this combination-induced toxicity (3).

Another twist in the story occurred when reports of sirolimus causing the prolonged recovery of delayed graft function after renal transplantation were published (4,5). The initial belief in the renal transplant community that sirolimus was not nephrotoxic led to its use in delayed graft function to bridge the gap of immunosuppression until a CNI could be safely introduced. Another report described an example of cast nephropathy developing in the setting of delayed graft function (6). An animal model revealed a specific renal injury resulting in protein overload nephropathy and intratubular cast formation (7). It has been proposed that sirolimus impairs tubular epithelial cell regeneration through its effect on mammalian target of rapamycin (mTOR) and possibly via cell cycle arrest and apoptosis, thereby leading to delayed recovery of renal function in some patients.

Again, with the primary belief that sirolimus lacked inherent nephrotoxicity, clinicians began to use sirolimus to withdraw or minimize CNI exposure in patients with chronic renal insufficiency due to CNI nephrotoxicity or chronic transplant nephropathy. In addition, reports in animal models suggested that sirolimus, through its antiproliferative and anti-VEGF effects, might cause certain types of tumors to regress, and reports of sirolimus introduction causing the remission of Kaposi’s sarcoma in transplant patients led to the use of sirolimus replacing CNI in patients with different tumor types (8). Unfortunately, recent papers have described an increase in proteinuria in some patients converted from CNI to sirolimus for these indications (9–12). These studies suggest that the proteinuria increases primarily in patients with preexisting proteinuria (baseline values ranging from 0.3 to >1.0 g/d) or in the presence of advanced glomerular lesions. However, some patients had minimal proteinuria at baseline and subsequently developed nephrotic range proteinuria. This increased proteinuria has been attributed to the loss of CNI-mediated vasoconstriction, increased glomerular permeability, and proximal tubular cell injury caused directly or indirectly by sirolimus binding to albumin. Some papers described incompletely characterized de novo glomerular lesions as well as, in some cases, de novo FSGS-like lesions (13,14).

A case report described 12 g of proteinuria within 10 d of transplantation that resolved after the withdrawal of sirolimus (15). The renal biopsy did not reveal a glomerular lesion and the authors proposed a tubular injury leading to a decrease in tubular protein absorption as an explanation for the proteinuria. Another paper described proteinuria developing in patients on sirolimus and low-dose tacrolimus after islet cell transplantation (16). The patients may have had diabetic nephropathy (only one patient had a renal biopsy) predisposing them to progressive proteinuria. However, the proteinuria resolved after discontinuation of sirolimus, which suggests a direct effect of the drug.

Transplant immunosuppressive medications have been frequently utilized off-label in many types of both primary and secondary forms of glomerulonephritis. An animal model of the accelerated experimental model of membranous nephropathy demonstrated beneficial effects of sirolimus on tubulointerstitial inflammation, interstitial fibrosis, and compensatory renal hypertrophy (17). However, Fervenza et al. reported that six of 11 patients developed acute renal failure after the introduction of sirolimus for various types of glomerulonephritis (18). Unlike mycophenolate mofetil, sirolimus has not yet been embraced by the nephrology community for the treatment of immune-mediated glomerular diseases.

These accumulated clinical and scientific data suggest that sirolimus has inherent nephrotoxicity in certain circumstances. The cause of this nephrotoxicity is completely different from the mechanism of CNI-induced nephrotoxicity. In this issue of CJASN, Letavernier et al. have characterized the FSGS lesion developing in...
patients receiving sirolimus de novo or after conversion from CNI (19). This paper is the first to characterize both the histopathological as well as the immunohistochemical changes in patients developing proteinuria after exposure to sirolimus. The investigators provide convincing data to directly implicate sirolimus in podocyte dysregulation, thereby leading to the classic lesion of de novo FSGS. Sirolimus may mediate this process via a decrease in vascular endothelial growth factor or through its effect on mTOR to decrease cell survival. The development of nephrotic-range proteinuria was relatively uncommon, and the patients affected were exposed to relatively high levels of sirolimus. It is not clear that these patients had higher levels than the other 255 patients receiving sirolimus who did not develop the FSGS lesion. There were no apparent distinguishing features in the affected patients to predict who might be at risk for developing this infrequent complication. It is encouraging that the proteinuria resolved after sirolimus withdrawal. However, none of the patients had repeat biopsies to determine whether changes in podocytes were reversed. This report should alert clinicians to monitor urinary protein in patients on sirolimus on a regular basis and consider discontinuation if the proteinuria is substantial and progressive.

Sirolimus has been a drug looking for a dominant role in immunosuppression regimens. Up to this point its long-term use has been limited by its profound effect on hematopoeisis as well as lipid metabolism in some patients. We must now add proteinuria to the list of complications that clinicians must consider when either using sirolimus de novo or for conversion in patients with CNI nephrotoxicity.

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References


See the related article, “High Sirolimus Levels May Induce Focal Segmental Glomerulosclerosis De Novo,” on pages 326–333.