Are Maintenance Corticosteroids No Longer Necessary after Kidney Transplantation?

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Ask any group of transplant physicians or surgeons to discuss the benefits and risks of withdrawing corticosteroids after kidney transplant transplantation and you will likely hear "pro" and "con" arguments more vehement than those elicited during a discussion of politics or religion. In this issue of *CJASN*, Rizzari *et al.* (1) present yet another sequel in their amazing experience with early withdrawal of steroids from primary kidney transplant recipients at the University of Minnesota. Patients participating in this protocol all received induction therapy with rabbit antithymocyte globulin and maintenance immunosuppression with a calcineurin inhibitor and either mycophenolate mofetil or sirolimus. Each patient was subjected to rapid withdrawal of prednisone, generally by the sixth postoperative day. In a careful analysis of patient outcomes, the authors speak favorably about the safety and benefits of early steroid withdrawal with strong arguments that even the most loyal proponents of steroid-based immunosuppression may find difficult to refute.

Steroid withdrawal naysayers, arguing against steroid-free immunosuppression, will often start by citing the Canadian Multicenter Study, one of the first large randomized controlled trials of steroid withdrawal after kidney transplantation. Results of that trial indicated inferior graft survival after 5 years in patients initially randomized to steroid withdrawal (2). Although the concomitant immunosuppressive drugs used in the Canadian trial are irrelevant in the modern era, the study is still widely quoted as one that demonstrated the need for large numbers of patients followed for long periods of time to unmask the risks of steroid-free immunosuppression. Rizzari *et al.* impressively describe the outcomes of 1241 patients followed for up to 10 years! That should be big enough and long enough for most critics. Multicenter randomized trials performed in the modern era (3,4) indicate higher rates of acute rejection in patients randomized to early steroid withdrawal, raising the concern that patients experiencing rejection will have inferior long-term graft survival rates. In the Minnesota experience, rejection-free survival rates were no different than those observed in a historical control group. More importantly, 10-year patient and graft survival rates among patients experiencing acute rejection after early discontinuation of steroids were no different than those who never experienced rejection. There has been a concern that overt or subclinical rejection after steroid withdrawal will have a negative impact on long-term allograft function. However, Rizzari *et al.* reported no significant deterioration in the estimated GFRs between 5 and 10 years of follow-up in their large cohort of patients. The outcomes of this cohort of patients are truly outstanding!

Recent analyses of data accumulated by the Scientific Registry for Transplant Recipients indicate that as many as 35% of kidney transplant recipients are now discharged home from the hospital without corticosteroids (5), presumably receiving immunosuppressive regimens similar to those used at the University of Minnesota. However, considering the superb results reported by Rizzari *et al.*, it is reasonable to question why a substantial majority of patients continue to be treated with maintenance corticosteroids in the modern era. Why haven't all transplant centers adopted an early steroid withdrawal protocol based in the remarkably positive results at the University of Minnesota?

First, many transplant centers are conservative and remain reluctant to prescribe "off-label" protocols. While there is general agreement that the best outcomes of early steroid withdrawal occur in patients who receive induction therapy with polyclonal antibodies (3), it remains true that rabbit antithymocyte globulin—the agent used in all patients described by Rizzari *et al.*—has never been approved for use as an induction antibody in transplant recipients. Moreover, prescribing information for the other commonly used maintenance drugs (*i.e.*, calcineurin inhibitors, mycophenolate mofetil, and sirolimus) most often recommends use of these agents with other immunosuppressants, including corticosteroids. The Food and Drug Administration (FDA) is efficient in studying the efficacy and safety of new drugs, but has no well-defined role in commenting on the efficacy or safety of drug withdrawal. Conservative clinicians may be reluctant to follow a protocol that is not officially approved by the FDA.

Second, many transplant centers remain skeptical about results from uncontrolled trials no matter how large or how long the duration of the study. For example, the similarity in acute rejection rates that Rizzari *et al.* report when comparing their steroid-free cohort to historical, steroid-treated controls is incongruous with the consistent observation of higher rejection rates after early steroid withdrawal in prospective trials using concurrent randomized controls. It is possible that clinicians at the

University of Minnesota are more meticulous than those from other centers in managing their steroid-free patients. They may be more proficient at assuring optimal doses of the other drugs. They may be better at recognizing acute rejection early and treating it completely to eliminate any detrimental long-term effects. Because most industry-sponsored trials are meticulous in specifying target drug doses and criteria for the diagnosis and treatment of rejection, this explanation seems unlikely. Other explanations include biases in patient selection and data interpretation that are inherent to all uncontrolled trials and/or unique characteristics of the University of Minnesota's patient population that may differ from the broader US population. Regarding the latter, the authors freely acknowledged this limitation of their experience. Their patients are predominantly recipients of living donor kidneys, nonsensitized, and non-African American. Their results may be difficult to duplicate at centers that care for larger proportions of patients traditionally regarded to be at higher risk for immune injury, with or without steroids.

Third, it has been argued that maintenance doses of corticosteroids in the modern era are much lower than they were historically and that the side effects of such low doses (typically $\leq$5 mg/d of prednisone) are minimal even compared with no steroids at all (6). Rizzari *et al.* describe significantly lower rates of cytomegalovirus infection, cataracts, new-onset diabetes mellitus, and aseptic necrosis in their steroid-free cohort compared with control patients receiving 5 mg of prednisone daily. These are relatively unique and important findings that warrant further study in trials powered to examine these end points. They are findings that have not been demonstrated consistently in randomized trials, perhaps because of the relatively short duration of follow-up in most of those studies. The entire steroid withdrawal movement in kidney transplantation was probably motivated more by the concern that corticosteroids enhance the risk of cardiovascular disease by promoting hypertension, hyperlipidemia, and hyperglycemia. Rizzari *et al.* do not comment on cardiovascular death rates in their patient population, but overall 10-year patient mortality was no different in steroid-free patients than in those treated with steroids. Previous uncontrolled studies and registry analyses suggesting better long-term survival in patients subjected to steroid withdrawal have been overtly flawed by biases in patient selection (7,8). Overall, it has been difficult to prove any cardiovascular benefit of steroid-free immunosuppression compared with low-dose steroid therapy. Finally, it must be noted that corticosteroids remain very effective in treating acute cellular rejection and that most centers, including our own and the University of Minnesota (9), believe that steroids should be renewed in patients who experience even a single rejection episode.

With these comments in mind, we must acknowledge that we represent a transplant center that has routinely used an early steroid withdrawal protocol in nonsensitized primary transplant recipients since 2003, irrespective of the recipient's ethnicity. We also use rabbit antithymocyte for induction therapy in most of these patients and treat most patients with tacrolimus and mycophenolate mofetil. Our African-American patients have higher rates of acute rejection than our Caucasian patients (10). However, this may be true with any immunosuppression regimen. We continue to use maintenance prednisone in most nonprimary transplant recipients, in those who are highly sensitized, and in those with prolonged delayed graft function. Based on our own experience, we agree that a large majority of patients can safely undergo early steroid withdrawal in the modern era. We congratulate Rizzari and colleagues on amassing what is probably the largest single center experience with early steroid withdrawal after kidney transplantation and for serving as champions of this strategy. However, we would argue that corticosteroids still play an important role as immunosuppressants in selected patients. A blanket policy of withdrawing steroids from all kidney transplant recipients is probably no wiser than a policy of maintaining all patients on these agents. The latest summary of the University of Minnesota's outstanding experience will not likely put to rest the traditional arguments about steroid-free immunosuppression, but should certainly impress even the staunchest of clinicians who support the use of maintenance corticosteroids in all kidney transplant recipients.

Disclosures

None.

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See related article, "Ten-Year Outcome after Rapid Discontinuation of Prednisone in Adult Primary Kidney Transplantation," on pages 494–503.