Avoiding Steroids can be Successful Strategy After Kidney Transplantation...

By Joshua Augustine

Acceptance of steroid avoidance in kidney transplantation has grown appropriately in recent years as a result of a lower rate of acute rejection and increased potency of immunosuppressive therapy. Until recently, steroid withdrawal was associated with a greater negative impact on allograft function and survival. Data on steroid avoidance from uncontrolled single center studies (1–4), nonrandomized multicenter trials (5), and registry analyses (6) have suggested excellent outcomes with relatively low rates of acute rejection, stable renal function over long periods of time, and patient and graft survival rates comparable to those of nonrandomized control groups. More recent data from randomized trials have shed further light on the benefits and risks of steroid withdrawal.

The Astellas Steroid Withdrawal Study was a randomized, double-blind, placebo-controlled study in which patients treated with induction antibody therapy (either antithymocyte globulin or an anti-IL-2 receptor antibody), tacrolimus (TAC) and mycophenolate mofetil (MMF) were randomized to either early withdrawal of steroids (day 7) or to maintenance prednisone therapy (7). Of the 386 patients enrolled, 43 percent were deceased donor recipients, and 20 percent were African Americans. TAC target trough levels were 10–20 ng/ml in the first 90 days post-transplant, and MMF dosage was initially 2 g/day. Importantly, patients randomized to maintenance steroid therapy were receiving only 5 mg of prednisone daily by six months posttransplant.

After five years of follow-up, the cumulative incidence of biopsy-proven acute rejection was 17.8 percent in patients in the steroid withdrawal group versus 10.8 percent in the group maintained on steroids (P = 0.04, by Kaplan Meier analysis) (7). However, the composite primary endpoint of death, graft loss, or moderate to severe acute rejection (defined as Banff stage 2A or higher or requiring treatment with an antibody) was similar between groups, occurring in 15.7 percent of patients withdrawn from steroids versus 14.4 percent of patients maintained on steroids (P > ns). This trial demonstrated that steroids could be withdrawn safely in the majority of patients with acceptable acute rejection rates using induction therapy and TAC/MMF maintenance immunosuppression.

Compared with previous transplant eras, the rates of rejection have dropped dramatically in steroid withdrawal patients. A meta analysis of seven clinical trials from the 1980s and early 1990s reported rejection rates of 48 percent in steroid withdrawal patients (8). Death censored graft loss was 19 percent at five years in the steroid withdrawal group from the original Canadian Multicentre Transplant Study Group (9), compared with 6.3 percent in the Astellas trial.

Complications of immunosuppressive therapy

With improved early outcomes and lower rejection rates in transplant recipients, more attention has been given to long-term complications related to immunosuppressive therapy, including infection, malignancy, cardiovascular disease, and metabolic abnormalities. Infection remains a prominent cause of morbidity and the second highest cause of mortality in transplant patients (10).

In the Astellas trial, rates of specific infections were not significantly different between groups, but the overall adverse event rate for infection reported in the trial was 16.4 percent for the steroid maintenance group versus 9.4 percent for the steroid withdrawal group (P = 0.04). A recent meta analysis of 30 randomized controlled trials in kidney transplantation also found a lower rate of infection in steroid withdrawal patients (11).

Metabolic benefits related to the severity of diabetes after transplantation have been demonstrated in recent clinical trials. In the Astellas trial, the number of patients requiring treatment with insulin was lower in the steroid withdrawal group than in the steroid-maintained group (3.7 percent versus 11.6 percent, P = 0.05) (7). These data were consistent with the CARMEN study, which examined outcomes in 260 European kidney recipients randomized to daclizumab, TAC, and MMF with one-day steroid exposure and compared to a group of 278 patients treated with TAC/MMF and maintenance steroids (12).

Bone complications, including avascular necrosis and pathologic fractures, can be devastating late complications in patients with long-term transplant survival. Avascular necrosis is a painful condition resulting from ischemic injury to bone. Most commonly affecting the proximal femur, it typically requires surgical intervention, and has been linked to early steroid dosage in kidney transplantation (13).

Bone fractures are surprisingly common in kidney transplantation after long-term follow-up (14). In the Astellas trial, posthoc analysis found that the combined rate of bone fracture and avascular necrosis was higher in the steroid maintenance group (11.3 percent) compared with the steroid withdrawal group (5.2 percent, P = 0.04). This finding was likely observed due to the prolonged five-year follow-up of this trial and illustrates the significance of bone complications that manifest after years of steroid therapy.

Given the current clinical data, it is feasible to argue for steroid avoidance in kidney transplantation. The majority of patients will enjoy stable renal function with no overt rejection in the absence of steroid therapy. The challenge is to identify the small minority of high-risk patients for whom steroid withdrawal will lead to detrimental outcomes.

Identifying patients at risk for complications from steroid withdrawal

Patients with moderate to high levels of antibody sensitization were not included in recent randomized trials, and the Astellas trial excluded patients with delayed graft function, a known correlate of acute rejection (15). It may therefore be prudent to continue steroids in these higher risk subgroups. New immune monitoring techniques should ultimately allow for more precise identification of high-risk patients. For example, patients with donor reactive cellular immunity at the time of transplant may particularly benefit from maintenance steroid therapy (16).

In the meantime, all patients must be counseled on the small increased risk of acute rejection with steroid withdrawal. Close monitoring of renal function is mandatory, and protocol biopsies may be useful in identifying subclinical rejection after steroid elimination. Early steroid withdrawal may be favorable to a late steroid taper because most transplant centers obtain frequent bloodwork early post-transplantation, and patients may be reluctant to follow as closely with increased time from transplantation. The prognosis for early rejection is superior to that for late rejection, likely due to increased monitoring and patient compliance (17). After rejection, it is prudent to reintroduce maintenance steroid therapy, based on a recent report of a high rate of recurrent rejection in the absence of steroid therapy (18).

Induction therapy important in early steroid withdrawal

Induction therapy appears critical to the success of early steroid withdrawal. In the ATLAS study, 151 European renal transplant recipients received TAC and MMF with no induction therapy and steroid elimination after a single 500-mg dose of cyclosporin (19). At six months, the incidence of biopsy-proven acute rejection in this cohort was 30.5 percent and three times the rate in a cohort on maintenance steroids. Renal function was also inferior in the steroid elimination cohort at six months posttransplantation.

Rejection rates were much lower in the Astellas trial, and polyclonal antibody therapy appeared to offer a further advantage over anti-IL-2 receptor antibody therapy. Acute rejection at five years occurred in 24.2 percent of steroid-free patients who received an anti-IL-2 receptor antibody and in 14.4 percent of patients who received rabbit-antithymocyte globulin (ATG) (P = 0.09), despite a greater percentage of deceased donors in the ATG group (7).

Continued on page 24
Avoiding Steroids

Most transplant centers in the United States are using induction therapy along with calcineurin inhibitors and MMF. In this setting, steroid withdrawal has already become an accepted practice in the transplant community.

Data from the most recent report of the Scientific Registry for Transplant Recipients indicate that as of 2006, more than 30 percent of patients receiving kidney transplants in the United States are discharged from their initial hospitalization without maintenance steroid therapy.

The push for steroid elimination has been driven by patient preference and patient demand. In our center’s experience, patients remain eager to avoid steroids, despite the increased risk of acute rejection. We routinely encounter patients who refuse to initiate oral steroids or who independently taper prednisone after transplantation. Use of corticosteroid therapy will likely diminish further over time as immunosuppressive regimens are further optimized.

References