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Over the next few decades, many new-
er and more potent immunosuppressive agents were developed, leading to remark-
able declines in early acute rejection (AR) rates and some improvements, to a lesser degree, in graft survival. With these results, many investigators justifiably questioned the time-honored belief that steroids were still needed. Initial studies focused on ster-
oid “withdrawal,” i.e., the phased removal of steroids at some point after transplant, in a select group of patients who were con-
sidered “low-risk” (usually those without prior AR episodes). Many of these studies showed an unacceptably high rate of AR postwithdrawal (1, 2), leading to the belief that patients developed an immunological dependency on steroids once they began receiving this class of drugs.

Are steroids necessary with modern immunosuppressants?

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efits included less hypertension and less hyperlipidemia, two major cardiovascular risk factors.

In order to get around the “dependen-
cy” phenomenon, regimens were devised that eliminated steroids completely (avoid-
ance) or exposed patients to steroids only for a brief period posttransplant, in most cases less than a week (minimization). Prospective limited center studies with his-
torical controls suggested no detriment in terms of AR increase or worse graft surviv-
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ter compliance with medications.

Yet the gold standard for evidence-
based medicine remains the randomized controlled trial. Initial results were prom-
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aminal outcomes (12). The study was open-
label. In the intent-to-treat analysis, the incidence of biopsy-proven acute rejection was statistically higher in both the steroid avoidance (31.5 percent) and the steroid withdrawal (26.1 percent) arms compared with the steroid maintenance group (14.7 percent).

Hricik has provided further insight into this study’s results (13). The graft survival rates were similar among the three groups, but the study was not powered to detect differences in graft survival. The metabolic benefits observed were modest (fewer anti-
hyperglycemic medications in the steroid-
free group and less frequent lipid-lowering agents in the steroid withdrawal group), but actual incidences of diabetes mellitus were the same in all groups. Lipid levels were not measured. Less weight gain was seen only in the steroid withdrawal group, not in the avoidance group.

The groups did not remain as they were initially assigned: 12 percent of steroid maintenance subjects were not on steroids at 12 months, and a substantial minority of steroid-sparing subjects started steroids through the course of the study. The patient population was set up to be standard im-
cent with early withdrawal and 3.6 percent with maintenance. Cockrall-Gault GFR was 58.6 mL/min in the early withdrawal group and 59.8 mL/min in the mainte-
nance group. Once again, metabolic ben-
efits were modest. Serum triglycerides were better with steroid early withdrawal at ear-
lier time points, but no different between groups at the study end point of five years. Newly onset diabetes requiring treatment was also no different (early withdrawal, 20.5 percent; long-term steroid mainte-
nance, 20.9 percent), although the per-
centage of patients who needed insulin was less in the early steroid withdrawal group.

Steroids in children

The NIH-funded SNS01 prospective rand-
omized controlled trial of steroid avoidance versus maintained steroids in children is nearing completion. Analysis of 12-month clinical end points was presented by Min-
nie Sarwal, MD, PhD, at the American Transplant Congress in 2008. The inci-
dence of AR and graft loss were identical in both groups, as were the improvements in linear height and incidence of hyper-
tension. Thus, the primary end point, a

Glucoctcorticoids (more commonly re-
ferred to as steroids) have been a key component of posttransplant immuno-
suppression and rejection treatment since the 1960s, the very early days of solid or-
gan transplantation. At the time, steroids, in combination with azathioprine (AzA) or other mercaptopurine analogs, were the most common oral maintenance immu-
nosuppressive agents used. Graft survival was not great, but in the absence of ster-
oids, graft rejection and loss were almost assured.

While steroid avoidance might be a suitable strategy for a select group of patients, a significant number will not qualify.
Not for All

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cal significance, but the likelihood that the steroid withdrawal group was worse is extremely remote.

Another highly rated form of evidence-based medicine is the Cochrane review system. Pascual et al. recently published a systematic review of steroid avoidance or withdrawal, evaluating 30 studies containing 5945 patients (16). Patients on any steroid-sparing strategy showed a higher risk of graft loss (excluding deaths) than those with conventional steroid use (relative risk (RR), 1.23; 95 percent confidence interval (CI), 1.00 to 1.52). Acute rejection was also more frequent (RR, 1.27; 95 percent CI, 1.14 to 1.40).

Sarwal will argue that steroid avoidance is not inferior and may remove one drug from a long list of medications that transplant patients need to take daily. Although steroid avoidance certainly may be feasible for some recipients, the following groups may not be candidates for steroid avoidance: patients with high CRA levels or the need for steroids for primary renal disease (such as lupus nephritis) and those with delayed graft function (DGF). DGF, as defined by need for dialysis in the first week posttransplant, currently occurs in 24 percent of all deceased donor kidney transplants in the United States. Milder degrees of kidney injury, called slow graft function by some, are much more frequent.

Steroid avoidance and acute rejection

What about those patients on steroid avoidance in whom an AR occurs? Are these patients at risk for worse outcomes if they stay steroid-free? There are no rigorous data at present. However, Humar et al. provided some indication of possible outcomes in a retrospective uncontrolled analysis (17). They looked at 842 adult kidney transplant recipients on a steroid minimization protocol. Of these, 17.7 percent, or 149, had at least one AR episode. Thirty-four percent of these patients restarted maintenance steroids; the other 66 percent remained steroid-free. The choice was not randomized; physician preference and concomitant diabetes played a significant role. Not restarting steroids after the first AR resulted in a borderline increase in risk for a second AR episode (RR = 2.1; P = 0.07). The study suggested that some patients might be worse off if steroids were not restarted, although graft survival was not different between the two retrospective groups.

An analysis of the Scientific Registry of Transplant Recipients (SRTR), to be presented by Santos et al. at the American Transplant Congress this month, supports this view. This study looked at all solitary kidney transplants performed between 2002 and 2006. By 12 months posttransplant, 34 percent of recipients who were reported as steroid-free at initial discharge were now on steroids. The patients who restarted were predictable: African Americans, retransplants, those with high PRAs, and those who received expanded criteria kidneys. Patients newly started on steroids had a 20 percent increased risk of graft loss compared to those maintained on steroids from the start.

In summary, while steroid avoidance might be a suitable strategy for a select group of patients, a significant number will not qualify. Patients with high PRAs or a prior transplant constitute an ever-increasing proportion of the transplant population. Furthermore, published studies did not enroll African Americans to a significant extent, yet this group is known to be at higher immunologic risk. DGF occurs in a quarter of all deceased donor transplant recipients. A significant minority of such recipients will have a greater propensity to immunologic events requiring steroid use pretransplant.

Potential side benefits of steroid avoidance or minimization have been much more modest in the recently reported randomized controlled trials than in prior series. Whether steroid minimization is better than avoidance when DGF is present is unknown. Furthermore, late steroid withdrawal may not be as bad as previously thought, with the switch from CsA-Aza to tacrolimus-myocophenolate mofetil-based maintenance immunosuppression.

References


References