

Editorial

Trials and Tribulations of Steroid Withdrawal After Kidney Transplantation

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The wide spectrum of morbidity associated with steroids has generated great enthusiasm in considering how they might be eliminated from immunosuppression regimens. Historically attempts to slowly wean steroids have yielded high rates of acute rejection (1,2), raising concerns for a potential increased risk of graft loss. Subsequent studies have focused on early steroid withdrawal or steroid avoidance. While many of the reports have been single center and nonrandomized, these studies have often been of large size and suggest that steroid minimization may be safe in the short term and in the correct setting (3–6). While these reports are encouraging, the issue of early steroid avoidance has not been tested with the same rigor the FDA would evaluate a new agent or new immunosuppressive regimen.

In the current issue of AJT, Vincenti and his collaborators from the 'FREEDOM' Study take an important step in this direction. This group reports a well designed prospective randomized trial to evaluate whether total steroid avoidance or early steroid withdrawal has a more favorable risk-benefit ratio compared to a standard maintenance steroid regimen, in recipients receiving basiliximab induction and maintenance cyclosporine in the microemulsion formulation and mycophenolate sodium (7). The study is relatively unique in that it allows evaluation of both steroid avoidance and early steroid withdrawal across a common protocol. Other strengths of the trial include a thorough evaluation of comorbidities associated with steroid therapy.

Both experimental arms of steroid avoidance and early withdrawal failed to meet the primary noninferiority endpoint for renal function compared to steroid maintenance.

This study was designed with a noninferiority primary endpoint powered to demonstrate noninferiority of either early steroid withdrawal or avoidance regarding calculated glomerular filtration rate (GFR) at 12 months, with a fairly wide noninferiority margin set at a difference of 7 mL/min/1.73 m² at 1 year posttransplant. Despite of this rather large margin to define inferior renal function the noninferiority condition was not met by either experimental arm in primary the intent-to-treat analysis. Only in a reduced sample of patients described as 'observed case analysis', the noninferiority hypothesis was met but after excluding 25% of patients in each arm. It is also worthy to note that the steroid-free group had more living donors, which would tend to bias this group toward better outcomes.

In strictest terms according to its own design, the trial did not prove efficacy and safety of either investigational arm for the primary study endpoint. Stated another way, the trial did not prove that steroid avoidance or steroid withdrawal were not inferior to maintenance steroid therapy. Consequently it is not possible to draw a sound conclusion regarding the relative risk-benefit ratio of either steroid withdrawal or steroid avoidance in this study.

An advantage of utilizing a noninferiority design is that it often allows for a smaller sample size in terms of the primary endpoint (8). However, this also means that subanalyses and secondary endpoints are potentially under-powered. In addition population subanalyses can introduce significant selection biases by altering the makeup of the original study population by typically looking at lower risk patients. The potential impact of sub sampling on sample size like in the 'per protocol analysis' in the FREEDOM trial is highlighted by the observation that at 12 months, only 59% of the patients randomized to the steroid avoidance arm and 71% of the patients in the steroid withdrawal group were free of steroids. Furthermore, 12% of the patients in the steroid maintenance arm had actually had steroids withdrawn, at odds with the protocol. Renal function as a primary endpoint has a potential bias already built in as it can be measured only in patients with a functioning graft. Unless graft losses are counted as a low GFR value in the analysis, differential graft loss between the analysis groups can introduce a significant bias.

The potential loss of power by subanalyses is also nicely illustrated in the 'FREEDOM' trial looking at the acute

rejection data. In the intent-to-treat analysis, the incidence of biopsy-proven acute rejection was statistically higher in both the steroid avoidance (31.5%) and the steroid withdrawal (26.1%) arms compared to maintenance steroid group (14.7%). When the investigators evaluated subgroups, including only recipients without delayed graft function or major protocol deviations, many of the differences became less apparent. In fact, the study was probably not powered to detect differences in the smaller sample size associated with these analyses. These offprotocol patients also affect the interpretation of other endpoints, specifically those related to the benefits of freedom from steroids.

Because the current trial was open label, it is possible that investigators were more likely to biopsy the recipients not receiving maintenance steroids, potentially leading to a higher rate of detection of rejection. A double blind study design would help address this bias. The only double blind randomized trial of early steroid withdrawal to date is the trial being conducted by the Astellas Steroid Withdrawal Group. Woodle et al., in the recent update of this trial reported that the steroid withdrawal group, treated with induction therapy and maintenance tacrolimus and mycophenolate mofetil has had more clinical acute rejection episodes and had a statistically significantly higher incidence of chronic allograft nephropathy at 4 years compared to the steroid maintenance group (9). It is important to note that comparability between these two trials and others is limited by the differences in induction and maintenance immunosuppression employed. To date most studies of early steroid withdrawal have been designed based on the currently most widely used immunosuppressive maintenance regimen of tacrolimus combined with mycophenolate mofetil and variable induction therapy. The results of the current trial by Vincenti et al. have to be interpreted within the setting of cyclosporin microemulsion and mycophenolate sodium maintenance immunosuppression with concurrent basiliximab induction.

Whether any potential decreases in toxicities are worth an increased risk of acute rejection and worse renal function, would have to be addressed by studies with longer follow-up and hard endpoints like graft and patient survival. Further studies based on rigorous study design and analyses are needed to define the risk-benefit ratio of steroid

avoidance strategies and assess the clinical safety of this rapidly proliferating strategy.

The study by Vincenti et al. is a considerable step forward in the understanding of the risks and benefits associated with steroid avoidance. It helps highlight that in addition to the widely advertised benefits of steroid avoidance strategies, there are potential risks of more acute rejection and worse renal function.

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