EDITORIAL

Avoiding or stopping steroids in kidney transplant recipients: sounds good but does it work?

David W Mudge

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Receiving a kidney transplant is so transformative for a patient who is on dialysis that recipients prioritize keeping the transplanted kidney functioning above all other outcomes, even cancer and death.[1] Dialysis typically means being attached to a machine for 15 hours or more a week, and it causes extreme tiredness and has a major impact on family life. Transplantation means a major operation, short-term and long-term monitoring, and multiple drugs to prevent rejection of the new organ, but the promise of a more normal life. Chalk and cheese.

We have seen enormous changes in the immune-suppressing medications used to prevent rejection soon after transplantation, with the hope that this might translate into improvements in long-term graft survival. However, improvements in acute rejection rates seen in the last two decades have not led to similar improvement in long-term outcomes[2], which has been disappointing. In part, perversely, this has been due to the complications of the drugs themselves – cardiovascular disease, cancer, and infection.[3] Reducing exposure to these drugs may be one way to improve long-term outcomes.

Corticosteroids have been one of the mainstays for preventing rejection since the inception of solid organ transplantation. They dampen down the immune system response to the introduction of a new organ, reducing the likelihood of rejection, but also causing post-transplant diabetes, high-risk lipid profiles, infections, and probably a dose-related effect on mortality.[4] Steroid use after kidney transplantation is a classic example of a trade-off between benefits and harms. Reducing the risk of rejection with steroids needs to be carefully balanced against the harms. Many researchers have tried to either avoid (not use at all) or minimise steroids (use a lower dose or stop after a certain period has elapsed after transplantation) to reduce these risks and improve short- and long-term outcomes. To date, very limited data on long-term outcomes and from properly conducted trials of have been available.

An updated Cochrane Review by Haller and co-authors has provided substantially more information on this important topic.[5] Data from 20 new trials have been added to the data from 28 trials included in the 2009 review. We now have evidence from over 7800 kidney transplant recipients. The updated review strengthens the evidence that steroid avoidance and withdrawal both substantially increase rates of acute rejection (by 58% and 77%, respectively) but that the effect on long-term mortality, diabetes, and infections remains uncertain. An important finding is the similar rate of post-transplant diabetes in the steroid avoidance arms of the trials. This is important because reducing the incidence of diabetes after transplantation is one of the major arguments for steroid avoidance or withdrawal. The findings of the Cochrane Review suggest that the incidence of post-transplant diabetes is not as steroid-dependent as the proponents of steroid avoidance or withdrawal would have us believe, and it is perhaps more associated with the more widespread use of tacrolimus, now the major calcineurin inhibitor used in kidney transplantation.[6]

Most of the studies included in the review only provided follow-up data from one to three years after transplantation, with five years the maximum. This is a major limitation for integrating this review into clinical practice. Most people receiving a kidney transplant now would be expected to survive more than 10 years.[7]

In various subgroup analyses, the reviewers examined the effects of different immunosuppressive regimens and the effects within different subpopulations. Firstly, there was no evidence of a difference across the subgroups in mortality, graft loss, or biopsy-proven acute rejection when stratified for calcineurin inhibitor type (cyclosporine versus tacrolimus), antimetabolite used (azathioprine versus mycophenolate), or induction treatment. The increase in acute rejection rate was greater in the cyclosporine subgroup, suggesting that tacrolimus might be more protective if steroids are avoided. Only two studies compared steroid avoidance with maintenance in children, and event rates were very small, as expected, so these studies were relatively uninformative.

How confident can we be in the review's findings? The risk of bias in the included studies is a key limitation of the available evidence, with methods of allocation poorly reported and lack of blinding affecting the reliability of the treatment effects observed for some of the key outcomes. Reporting of outcome data was also suboptimal: less than half (23 out of 48) actually reported acute rejection rates, and 70% (34 out of 48) reported mortality. Outcomes were relatively short and endpoints often sparse. For harms, more than half of the studies did not report the outcomes

of infection, particularly cytomegalovirus (CMV), or the other important outcomes of cardiovascular events and malignancy.

What should transplant clinicians and patients think about the use of steroids at the time of transplantation? Despite half the studies in this review under-reporting important outcomes such as acute rejection, a very significant increase in acute rejection was seen with both steroid avoidance and withdrawal. Until evidence from well-conducted trials with adequate follow-up demonstrates equivalent patient-level outcomes for steroid avoidance or withdrawal, steroids should remain in the mix for patients other than in the small group of recipients in whom there is a specific reason not to use them.

Author Information

David W Mudge[1,2]

[1]University of Queensland at Princess Alexandra Hospital, Brisbane, Australia. [2]Cochrane Renal and Transplant

Declarations of interest

The author has completed the ICMJE form for disclosure of potential conflicts of interest (form available upon request).

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