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Steroid Avoidance in Low-Immunologic Risk Kidney Transplant Recipients: The New Normal?

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From the beginning of kidney transplantation history, corticosteroids have been used to prevent acute rejection, to treat it, and to "define" antibody-mediated rejection when rejection was resistant to corticosteroids.

In addition, from the beginning of kidney transplantation history, the many toxicities of corticosteroids were precisely reported, either acute (psychiatric, high blood pressure, diabetes mellitus, healing delay, osteonecrosis, etc.), or more chronic (such as skin frailty, bone fractures, susceptibility to infections, etc.).[1]

It therefore became logical to try to get rid of these drugs. The various approaches were the following: dose reduction, early or late withdrawal, and avoidance.

Combination with other immunosuppressive drugs lead to a progressive dose reduction of corticosteroids (<10 mg/d around 3–6 months after transplantation) leading to a decreased rate of complications, mainly the acute ones, but not so obviously in the long-term.

The current dilemma about corticosteroid use in kidney transplantation is therefore the following: the incidence and severity of side effects have been significantly reduced through dose reduction, but side effects are still present, so that complete withdrawal and avoidance are interesting options that need to be studied. Diabetes mellitus has been considered as a reliable marker of overall corticosteroid toxicity, whereas rejection was a good marker of acute rejection risk due to corticosteroid withdrawal.[1]

Early and late withdrawal of corticosteroids has been extensively studied, and the main conclusion is that it leads to an increased incidence of rejection. Indeed, in a Cochrane database analysis in 2016, Haller *et al.*[2] concluded that compared with corticosteroid maintenance, withdrawal led to a 58% increased risk incidence of acute rejection, while it was 77% in case of avoidance.[2,3] The risk of graft loss and mortality was not increased. Interestingly the risk of post-transplant diabetes mellitus was decreased but with a rather low quality of evidence. Similar results were reported by Pascual *et al.*[1] and by Woodle *et al.*[4] In the landmark paper from Woodle *et al*,[4] the incidence of diabetes was similar with a 5-year follow-up comparing low dose maintenance versus withdrawal at day 7 after transplantation, while insulin requirement was barely significantly increased in the maintenance group (3.7% vs. 11.6%, $P = 0.049$).[2–4]

In the current issue of *KI Reports*, Ekberg *et al.*[5] report on a randomized controlled trial on safety of steroid avoidance in low-immunologic risk kidney transplant recipients. It was a 2-year multicenter open-label trial in which 222 patients were randomized to receive either anti-thymocyte globulin (ATG) induction + steroid avoidance + tacrolimus + mycophenolate mofetil ($n = 113$) or basiliximab induction + maintenance steroids + tacrolimus + mycophenolate mofetil ($n = 109$). Precisely, the authors compared ATG without steroids with basiliximab with steroid maintenance. The incidence of post-transplant diabetes mellitus was the primary end point.

At 1 year, these 2 immunosuppressive regimens did not differ regarding incidence of post-transplant diabetes mellitus but also biopsy-proven rejection. At 2 years, no difference was noted regarding the composite end point (freedom from rejection, graft loss, and death), while kidney function and adverse events were similar in the 2 groups.

This study is interesting and leads to the conclusion that steroid avoidance on the cover of ATG is comparable to steroid maintenance with basiliximab. One drawback is that there are 2 changes in the

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immunosuppressive regimens, so that the conclusion about steroid avoidance is limited by the need for a "stronger" induction in low-immunologic risk patients.[6,7] Similar conclusions were reached when alemtuzumab induction was compared with basiliximab in the 3C study.[7]

Overall, the increased risk of rejection due to steroid avoidance is compensated by the ATG induction. The other important message is that there is no difference in the incidence of diabetes, whatever steroid maintenance or avoidance. It may well be that diabetes is no longer a reliable marker, particularly in patients receiving tacrolimus.

It is therefore possible to conclude from this study and the literature that avoiding steroids (with ATG) does not convey an increased risk of post-transplant diabetes, while the risk of rejection is not increased. Low risk but low benefit.

DISCLOSURE

The author declared no competing interests.

REFERENCES

1. Pascual J, Royuela A, Gaelano C, Crespo M, Zamora J. Very early steroid withdrawak pr complete avoidance for kidney transplant recipients: a systematic reviews. *Nephrol Dial Transplant*. 2011;27:825–832. https://doi.org/10.1093/ndt/gfr374
2. Haller MC, Royuela A, Nagler EV, et al. Steroid avoidance or withdrawal in kidney transplant recipients. *Cochrane Database Syst Rev*. 2016;2016: CD005632. https://doi.org/10.1002/14651858.CD005632.pub3
3. Mudge DW. Avoiding or stopping steroids in kidney transplant recipients: sounds good but does it work? *Cochrane Database Syst Rev*. 2016;8:ED000114. https://doi.org/10.1002/14651858.ED000114
4. Woodle ES, First MR, Pirsch J, et al. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 days) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. *Ann Surg*. 2008;248:564–577. https://doi.org/10.1097/SLA.0b013e318187d1da
5. Ekberg J, Baid-Agrawal S, Jespersen B, et al. A randomized controlled trial on safety of steroid avoidance in immunologically low-risk kidney transplant recipients. *Kidney Int Rep*. 2022;7:259–269. https://doi.org/10.1016/j.ekir.2021.11.028
6. Naesens M, Berger S, Biancone L, et al. Lymphocyte-depleting induction and steroid minimization after kidney transplantation: a review. *Nephrologia*. 2016;36:469–480. https://doi.org/10.1016/j.nefro.2016.03.019
7. 3C Study Collaborative Group, Haynes R, Harden P, et al. Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation. *Lancet*. 2014;384:1684–1690. https://doi.org/10.1016/S0140-6736(14)61095-3