Debates in Nephrology

Early Steroid Withdrawal in Kidney Transplant Recipients: CON

Fahad Aziz and *Sandesh Parajuli*

Kidney360 6: 187–190, 2025. doi: https://doi.org/10.34067/KID.0000000000000323

Introduction

The use of steroids for kidney transplantation changed the world of kidney care and is an integral part of the immunosuppression regimens in the current era. The long-term use of steroids may cause hyperlipidemia, obesity, new-onset diabetes after transplant, cataracts, and avascular necrosis.[1] Given these side effects, in the past two decades, several studies advocated that steroid-free regimens should be adopted.[2,3] However, the proper selection for steroid withdrawal is controversial. This review will discuss the possible adverse outcomes associated with steroid withdrawal among kidney transplant recipients.

Steroid Withdrawal and Risk of Allograft Rejection

a. Effect of early steroid withdrawal (ESW) on allograft:

Several studies have reported that steroid withdrawal increases the risk of kidney allograft rejection and subsequent allograft failure. A systemic review of 48 randomized trials with close to 8000 recipients compared steroid avoidance and steroid withdrawal regimens with steroid maintenance regimens and found that the risk of kidney allograft rejection significantly increased among recipients where steroids were withdrawn within 14 days of the transplantation.[4] Dharnidharka *et al.* looked at the effect of immunosuppression regimens within the first 90 days of transplant. ESW was associated with reduced risk of pneumonia (adjusted hazard ratio [aHR]=0.89, 95% confidence interval [CI], 0.83 to 0.96, $P = 0.002$), sepsis (aHR=0.80, 95% CI, 0.74 to 0.87, $P < 0.001$), and diabetes (aHR=0.77, 95% CI, 0.70 to 0.85, $P < 0.001$), but significantly higher risk of allograft failure (aHR=1.35, 95% CI, 1.17 to 1.57, $P < 0.001$).[5] In another recent study, Bae *et al.* evaluated ESW and its association among high immunological risk recipients with high panel-reactive antibodies and reported ESW among recipients with panel-reactive antibodies >60 was associated with a substantial increase in allograft rejection ($P < 0.001$) and subsequent allograft failure ($P = 0.02$).[6]

In another study, Bae *et al.* evaluated the effect of ESW among recipients with delayed graft function. Using the Scientific Registry of Transplant Recipients, 110,019 kidney transplant recipients were assessed between 2005 and 2017. ESW was associated with an increased risk of allograft rejection (adjusted odds ratio=1.12, 95% CI, 1.02 to 1.23) and a significant increase in allograft failure (adjusted odds ratio=1.16, 95% CI, 1.08 to 1.26).[7]

These studies indicate that ESW was associated with an increased risk of kidney allograft rejection with a subsequent increased risk of kidney allograft failure.

a. Effect of late steroid withdrawal on allograft:

Several studies showed that even late steroid withdrawal could be associated with an increased risk of allograft rejection and subsequent graft failure. A meta-analysis of 20 steroid withdrawal studies showed that steroid withdrawal was associated with a higher risk of allograft rejection and subsequent allograft failure. Interestingly, these adverse results were worse than cyclosporine withdrawal.[8] Vanrenterghem *et al.* conducted a study in 47 European transplant centers to investigate the discontinuation of steroids after 3 months post-transplant. Triple immunosuppression, including tacrolimus, steroids, and mycophenolate, was used for 3 months. From day 92, recipients continued triple therapy or discontinued steroids or discontinued mycophenolate. Between 3 and 6 months, the incidence of biopsy-proven rejection was higher in the

Division of Nephrology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

Correspondence: Dr. Sandesh Parajuli, email: sparajuli@medicine.wisc.edu

See related debate, ''Early Steroid Withdrawal in Kidney Transplant Recipients: PRO,'' and commentary, ''Early Steroid Withdrawal in Kidney Transplant Recipients: COMMENTARY,'' on pages 191–193 and 194–196, respectively.

Table 1. Steroid withdrawal and allograft rejection

Studies	Number of Patients	Data Source	Time of Steroid Withdrawal	Allograft Rejection	Graft Outcomes
Early steroid withdrawal					
Bae *et al.* 2022[6]	121,699	SRTR	Within 30 d of the transplant	Increased risk of allograft rejection among recipients with PRA >60% ($P < 0.001$)	Increased risk of allograft failure among recipients with PRA >60% ($P < 0.002$)
Bea *et al.* 2020[7]	110,019	SRTR	Steroid withdrawal at the time of discharge after transplant	Increased risk of allograft rejection (aOR=1.12, 95% CI, 1.02 to 1.23)	Increased risk of allograft failure (aOR=1.16, 95% CI, 1.08 to 1.26)
Dharnidharka *et al.* 2016[5]	45,164	USRDS	Within 90 d of the transplant		Increased risk of graft failure (aHR=1.35, 95% CI, 1.17 to 1.57, $P < 0.001$)
Late steroid withdrawal					
Vanrenterghem *et al.* 2005[9]	833	47 European centers	Steroid withdrawal after 3 mo	Biopsy-proven rejection was higher in steroid stop group (5.9%) than the mycophenolate group (1.8%, $P = 0.044$) or the control group (0.9%, $P = 0.004$)	Graft survival at 6 mo was similar with 94.2% (control), 92.8% (steroid stop), and 92.4% (MMF stop) ($P = 0.669$)
Smak Gregoor *et al.* 2002[11]	212	Single-center study	Steroid withdrawal at 6 mo post-transplant	Biopsy-proven chronic rejection incidence was higher in the steroid withdrawal group than in the control group (21% versus 11%)	

aOR, adjusted odds ratio; CI, confidence interval; MMF, mycophenolate; PRA, panel-reactive antibodies; SRTR, Scientific Registry of Transplant Recipients; USRDS, United States Renal Data System.

Table 2. Steroid withdrawal and risk of GN recurrence

Studies	Number of Patients	Data Source	Recurrence of GN	Graft Outcomes
Von Visger *et al.* 2014[13]	124 patients	Single-center study	Higher incidence of GN recurrence in the steroid withdrawal group (HR=8.59, 95% CI, 3.03 to 24.38, $P < 0.001$)	At 60 mo, graft survival was 72% in patients on steroids versus 44% in patients who were steroid-free ($P = 0.03$)
Kukla *et al.* 2011[12]	2164	Single-center study	Higher incidence of GN recurrence in the steroid withdrawal group (HR=4.86, 95% CI, 2.34 to 10.07, $P < 0.0001$)	No difference in graft outcomes
Clayton *et al.* 2011[14]	1521	ANZDATA registry	Steroid use was strongly associated with a reduced risk of IgA recurrence by 50% (HR=0.50, 95% CI, 0.30 to 0.84)	Steroids were only associated with less graft failure from recurrence in those with IgAN (P for interaction = 0.0002)

ANZDATA, Australia & New Zealand Dialysis and Transplant Registry; CI, confidence interval; HR, hazard ratio.

steroid discontinuation group (5.9%) than the mycophenolate discontinuation group (1.8%, $P = 0.044$) or the control group (0.9%, $P = 0.004$). However, the graft survival at 6 months was similar with 94.2% (control), 92.8% (steroid discontinuation group), and 92.4% (mycophenolate discontinuation group) ($P = 0.669$).[9] Similar results were reported by a meta-analysis, where steroid withdrawal between 3 and 6 months post-transplant was associated with significantly higher kidney allograft rejection.[10] Smak Gregoor *et al.* evaluated 212 kidney transplant recipients who were maintained on triple immunosuppression considering mycophenolate mofetil, cyclosporine, and steroids. Recipients were randomly assigned to steroid withdrawal, cyclosporine withdrawal, or continued triple immunosuppression regimen at 6 months post-transplant. At the 2-year follow-up, biopsy-proven chronic rejection incidence was higher in the steroid withdrawal group than in the control group (21% versus 11%). However, the cyclosporine withdrawal group had a substantially higher incidence of chronic rejections as compared with the control group (14% versus 1.3%, $P = 0.006$).[11]

These studies suggest that even a late withdrawal of steroids from the immunosuppression regimen can increase kidney allograft rejection, which is summarized in Table 1.

Steroid Withdrawal and Risk of Disease Recurrence

Steroid avoidance or withdrawal may increase the risk of recurrence of GN in the transplanted kidney. Kukla *et al.* reported that the rapid discontinuation of steroids after the kidney transplant was significantly associated with an increased risk of recurrence of GN at 1-, 5-, and 7-year recurrence rates of GN at 6.7%, 13.7%, and 19.2%, respectively, among rapid steroid discontinuation groups compared with the recipients on maintenance steroids, the recurrence rate at 2.4%, 3.8%, and 5.3%, respectively ($P < 0.0001$). Overall, the discontinuation of steroids was associated with a significantly higher recurrence of GN (hazard ratio [HR]=4.86, 95% CI, 2.34 to 10.07, $P < 0.0001$).[12] Von Visger *et al.* reported their observation in 124 recipients with IgA nephropathy as their primary kidney disease. In total, 60.5% of these patients received steroid-based immunosuppression, while 39.5% had either late steroid withdrawal or ESW. IgA nephropathy recurrence was significantly higher in patients managed with steroid-free (HR=8.59, 95% CI, 3.03 to 24.38, $P < 0.001$) and sirolimus-based (HR=3, 95% CI, 1.16 to 7.75, $P < 0.024$) immunosuppression regimens.[13] Using the Australia & New Zealand Dialysis and Transplant Registry, Clayton *et al.* evaluated the effect of steroid use on kidney allograft failure due to the recurrence of IgA nephropathy. Prevalence of steroid use was 92% at the baseline, 84% at 1 year, and 64% at 5 years. After adjusting for age, sex, HLA-mismatch, dialysis duration, and transplant era, steroid use was strongly associated with a reduced risk of IgA recurrence by 50% (HR=0.50, 95% CI, 0.30 to 0.84). Furthermore, the overall 10-year cumulative incidence of allograft failure from recurrent IgA nephropathy was 4.3%. The study concluded that the risk of allograft failure from recurrent disease should be considered while tailoring immunosuppression for patients with IgA nephropathy.[14] These studies are summarized in Table 2.

Advantages of Low-Dose Steroid Continuation

There may be several advantages to continuing low doses of steroids after kidney transplantation.

a. Reduced risk of rejection: As discussed above, the continuation of low-dose steroids reduces the risk of kidney allograft rejection.[2]
b. Modulation of calcineurin inhibitors (CNI): The maintenance of low doses of steroids may provide an opportunity to lower the CNI dose, which may have beneficial long-term effects, such as decreased rates of nephrotoxicity, neurotoxicity, or diabetes. Woodle *et al.* compared three induction regimens: alemtuzumab/belatacept, antithymocyte globulin, or antithymocyte globulin/tacrolimus. All recipients underwent ESW. A significant difference was observed in biopsy-proven acute T-cell–mediated rejection among the three

(10.3% versus 18.3% versus 1.9%, respectively, $P < 0.0001$). This shows that simultaneous withdrawal of CNIs and steroids is associated with a higher risk of rejection.[3]

c. Reduced risk of cytopenia: Several maintenance and induction immunosuppressive medications, such as mycophenolate or azathioprine, have bone marrow suppressive effects, leading to anemia and leukopenia.[15] Low-dose steroids lessen the risk of cytopenia.[16] Furthermore, if the dose of mycophenolate or azathioprine needs to be reduced for cytopenia or any other comorbidities (*e.g.*, infections, diarrhea), a low dose of steroids may prevent rejections.

Steroid withdrawal in kidney transplant recipients remains controversial. Although withdrawal of steroids may have several metabolic advantages, it may be associated with the increased risk of allograft rejection and recurrence of primary GN, which subsequently is related to poor kidney allograft outcomes. Low-dose continuation of steroids may have less metabolic effects with reduced risk of allograft rejection and recurrence of GN. After carefully assessing the immunological risk, a decision should be made about steroid withdrawal. Large interventional mechanistic clinical trials are needed to better understand the group of kidney transplant recipients who may benefit from steroid withdrawal. Until then, we support low-dose steroid continuation.

Disclosures

S. Parajuli reports the following: Research Funding: Veloxis; and Advisory or Leadership Role: CareDx; Eurofin; Horizon Pharmaceuticals. The remaining author has nothing to disclose.

Funding

None.

Acknowledgments

The content of this article reflects the personal experience and views of the authors and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or *Kidney360*. Responsibility for the information and views expressed herein lies entirely with the authors.

Author Contributions

Conceptualization: Fahad Aziz, Sandesh Parajuli.
Data curation: Fahad Aziz.
Supervision: Sandesh Parajuli.
Validation: Sandesh Parajuli.
Writing – review & editing: Sandesh Parajuli.

References

1. Matas AJ, Kandaswamy R, Humar A, et al. Long-term immunosuppression, without maintenance prednisone, after kidney transplantation. *Ann Surg.* 2004;240(3):510–516; discussion 516–517. doi:10.1097/01.sla.0000137140.79206.d0
2. Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. *Ann Surg.* 2008;248(4):564–577. doi:10.1097/SLA.0b013e318187d1da
3. Woodle ES, Kaufman DB, Shields AR, et al. Belatacept-based immunosuppression with simultaneous calcineurin inhibitor avoidance and early corticosteroid withdrawal: a prospective, randomized multicenter trial. *Am J Transplant.* 2020;20(4):1039–1055. doi:10.1111/ajt.15688
4. Haller MC, Royuela A, Nagler EV, Pascual J, Webster AC. Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev.* 2016;2016(8):CD005632. doi:10.1002/14651858.CD005632.pub3
5. Dharnidharka VR, Schnitzler MA, Chen J, et al. Differential risks for adverse outcomes 3 years after kidney transplantation based on initial immunosuppression regimen: a national study. *Transpl Int.* 2016;29(11):1226–1236. doi:10.1111/tri.12850
6. Bae S, McAdams-DeMarco MA, Massie AB, Garonzik-Wang JM, Coresh J, Segev DL. Panel-reactive antibody and the association of early steroid withdrawal with kidney transplant outcomes. *Transplantation.* 2022;106(3):648–656. doi:10.1097/TP.0000000000003777
7. Bae S, Garonzik Wang JM, Massie AB, et al. Early steroid withdrawal in deceased-donor kidney transplant recipients with delayed graft function. *J Am Soc Nephrol.* 2020;31(1):175–185. doi:10.1681/ASN.2019040416
8. Kasiske BL, Chakkera HA, Louis TA, Ma JZ. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. *J Am Soc Nephrol.* 2000;11(10):1910–1917. doi:10.1681/ASN.V11101910
9. Vanrenterghem Y, van Hooff JP, Squifflet JP, et al. Minimization of immunosuppressive therapy after renal transplantation: results of a randomized controlled trial. *Am J Transplant.* 2005;5(1):87–95. doi:10.1111/j.1600-6143.2004.00638.x
10. Pascual J, Galeano C, Royuela A, Zamora J. A systematic review on steroid withdrawal between 3 and 6 months after kidney transplantation. *Transplantation.* 2010;90(4):343–349. doi:10.1097/TP.0b013e3181e58912
11. Smak Gregoor PJ, de Sévaux RGL, Ligtenberg G, et al. Withdrawal of cyclosporine or prednisone six months after kidney transplantation in patients on triple drug therapy: a randomized, prospective, multicenter study. *J Am Soc Nephrol.* 2002;13(5):1365–1373. doi:10.1097/01.ASN.0000013298.11876.bf
12. Kukla A, Chen E, Spong R, et al. Recurrent glomerulonephritis under rapid discontinuation of steroids. *Transplantation.* 2011;91(12):1386–1391. doi:10.1097/TP.0b013e31821bf157
13. Von Visger JR, Gunay Y, Andreoni KA, et al. The risk of recurrent IgA nephropathy in a steroid-free protocol and other modifying immunosuppression. *Clin Transplant.* 2014;28(8):845–854. doi:10.1111/ctr.12389
14. Clayton P, McDonald S, Chadban S. Steroids and recurrent IgA nephropathy after kidney transplantation. *Am J Transplant.* 2011;11(8):1645–1649. doi:10.1111/j.1600-6143.2011.03667.x
15. Khalil MAM, Khalil MAU, Khan TFT, Tan J. Drug-induced hematological cytopenia in kidney transplantation and the challenges it poses for kidney transplant physicians. *J Transplant.* 2018;2018:9429265. doi:10.1155/2018/9429265
16. Woodle ES, Peddi VR, Tomlanovich S, Mulgaonkar S, Kuo PC. A prospective, randomized, multicenter study evaluating early corticosteroid withdrawal with thymoglobulin in living-donor kidney transplantation. *Clin Transplant.* 2010;24(1):73–83. doi:10.1111/j.1399-0012.2009.01127.x