Brief Communication

Prospective Nonrandomized Study with Early Steroid Withdrawal (Day 5) Postrenal Transplant in Low Immunological Risk Patients: A Single-Center Experience at Prince Sultan Military Medical City Riyadh

Nawaz Zahir, Dujana Mousa, Alawi Al Taweel, Attia Ashraf, Akhtar Fahim, Khan Taqi, Rafat Zahid, Naveed Aslam

Department of Nephrology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia

ABSTRACT. Steroids remain an essential part of immunosuppressive therapy for renal transplant patients since the start of transplant era. Different immunosuppressive regimens are prescribed so as to minimize the side effects. The purpose of our study is to compare the outcome of early steroid withdrawal with steroid maintenance protocol. It is a prospective nonrandomized study. All patients that received renal transplants from January 2011 to December 2013 were included in the study. Early steroid withdrawal at day 5 was done in low immunological risk patients, and the results were compared with the steroid maintenance group, at one-year, posttransplant. Outcome measures included acute rejection (AR), slow graft function and delayed graft function (SGF and DGF), patient and graft survival, and new-onset diabetes after transplant (NODAT), dyslipidemia, hypertension, and obesity. A total of 249 patients were divided into two groups – 105 patients had early steroid withdrawal and 144 patients were maintained on steroid therapy. Outcome measures were compared one-year posttransplant. There was no significant difference in AR, patient and graft survival, creatinine level, and weight gain. However, a significant difference in systolic and diastolic blood pressure, lipid profile, NODAT, SGF, and DGF was found in the steroid group. Our study shows that early steroid withdrawal is a safe standard of care in low immunological risk patients.

Introduction

Steroids have remained an essential part of posttransplant maintenance therapy since the beginning of the renal transplant era. With the passage of time, it became evident that long-term steroid use was responsible for a great deal of morbidity, causing weight gain, hypertension, hyperlipidemia, diabetes mellitus (DM), infection, growth retardation, a number of skeletal effects, and so on. For this reason, transplant physicians started to reduce the dose of steroids as maintenance therapy, even before the introduction of cyclosporine. A study conducted in 1999 showed that these...
adverse effects cost US $5300 per patient per year. Later, with the introduction of new immunosuppressive drugs such as tacrolimus (FK), mycophenolate mofetil (MMF), sirolimus, and antibodies as induction therapy, the scenario changed. Transplant physicians got a number of new immunosuppressive therapy options. This led to both the physicians and the patients, opting for steroid-free regimens in organ transplant cases. However, previous reviews showed that steroid avoidance protocols led to increased incidence of complications, i.e., acute graft rejection and decreased graft survival at five years. Majority of the steroid-free regimens prescribed nowadays include either steroid avoidance or early withdrawal within five to seven days posttransplant.

**Methods**

*Study design*

It is a prospective nonrandomized study. All patients that received renal transplant at our center from January 2011 to December 2013 were included in the study. Patients were followed up for one-year posttransplant. No protocol biopsy was taken.

*Eligibility criteria*

All patients aged 14 years and above, who received either live related (LR), live nonrelated (LNR), or deceased donor (DD) kidney was included and was divided into an early steroid withdrawal (at day 5) group and a steroid maintenance group. Patients with low immunological risk and patients with diabetes or a strong family history of DM were selected for early steroid withdrawal regimen.

*Immunosuppression*

Almost all our patients received antithymocyte-globulin (ATG) (except a few) as induction therapy along with pulse steroids. Dose for ATG was 1.5 mg/kg/dose (maximum aggregate dose up to 6 mg/kg); adjusted as per white blood cell, platelet and lymphocyte count. Steroids were withdrawn on day 5 posttransplant in patients in the early steroid withdrawal group. Both groups remained on FK/MMF. FK levels were kept the same in both groups.

*Primary and secondary endpoints*

Our primary endpoints were acute rejection (AR), patient, and graft survival. Graft survival was also taken as a secondary endpoint. Dyslipidemia, new-onset diabetes after transplant (NODAT), weight gain, and changes in blood pressure were taken as safety endpoints.

**Statistical Analysis**

Independent sample t-test was done for continuous variable and Chi-square/Fisher’s exact test for categorical variables to assess the baseline difference between the two groups. The log-rank test was used for assessing survival differences between the two groups. The graphical and statistical tests did not indicate the violation of proportional hazard assumption. Statistical significance was set to 0.05, and Statistical Package for the Social Sciences version 20.0 (IBM Corp., Armonk, NY, USA) was used for analysis.

**Results**

From January 2011 to December 2013, 249 patients aged 14 and above (age range 14–80 years, of which 50% recipients were between 31–50 years of age) received renal transplants, from male/female live LR, LNR and DDs at Prince Sultan Military Medical City, Riyadh, (Figure 1). Of these 249 patients, 105 patients (42%) were considered for early withdrawal protocol, while 144 patients (58%) were kept on steroid maintenance therapy. All of the patients received ATG and pulse steroid as induction therapy and were maintained on FK/MMF.

Male to female ratio was 79:21 in the early steroid withdrawal group, whereas in steroid maintenance group, the ratio was 63:37. In steroid withdrawal group 82% received LR, 9.5% received LNR and 8.5% received DDs, whereas in the other group 40% received LR, 28% received LNR, and 32% received DDs. (Figure 2). Of 144 patients in the early steroid
withdrawal group, 4 patients were lost to follow-up. In the early steroid maintenance group, 10 patients lost to follow-up within one year and one patient died of pulmonary tuberculosis eight months’ posttransplant. There was no significant difference in acute graft rejection and graft survival in patients of both groups at one year follow-up. In both groups, AR rate was the same (10%). Those patients, in early steroid withdrawal group, who had graft rejection within three months posttransplant were shifted to steroid maintenance therapy. At one year follow-up, no differences in serum creatinine levels and weight gain were seen among patients of both groups. However, statistically significant rise in systolic blood pressure (SBP) (6.33 vs. 22.13 mm Hg) and diastolic blood pressure (DBP) (mean 3.11 mm Hg vs. 9.46 mm Hg) was found. Moreover, a significant increase in lipid profile was noticed in patients on steroid maintenance therapy. The incidence of NODAT was higher in steroid-dependent group (6.6% vs. 11.5%). Slow graft function and delayed graft function (SGF and DGF) was found more in steroid-dependent group (Table 1 and Figure 3). DSA positivity at one year was higher in steroid-dependent group in both cadaveric and living (Figure 4). Mismatch more than four was also
Table 1. Demographics.

| Variables                        | Early steroid withdrawal | Steroid maintenance | Standard deviation | P    |
|----------------------------------|--------------------------|---------------------|--------------------|------|
| Age                              | 42.14                    | 39.56               | 16.032             | 0.051|
| Creatinine (umol/L) at 1 year    | 97.42                    | 104.75              | 36.789             | 0.542|
| Systolic BP rise (mm Hg)         | 6.33                     | 22.13               | 17.673             | **0.004**|
| Diastolic BP rise (mm Hg)        | 3.11                     | 9.46                | 10.844             | **0.001**|
| Weight gain (kg)                 | 9.20                     | 10.26               | 8.257              | 0.653|
| Cholesterol rise (mmol/L)        | 0.28                     | 1.04                | 1.055              | **0.032**|

Figure 3. Impact of steroid withdrawal.
DGF: Delayed graft function, ACR: Acute cellular rejection, NODAT: New-onset diabetes after transplant.

Figure 4. Impact of steroid withdrawal on the development of donor-specific antibodies.
DSA: Donor-specific antibodies
higher in steroid-dependent group (Figure 5). New-onset proteinuria found to be slightly higher in steroid-dependent cadaveric recipients, although majority of patients had no follow-up proteinuria (Figure 6) graft survival rate at one year was the same in both groups (Figure 7).

**Discussion**

Steroid maintenance therapy is still used extensively in majority of kidney transplant centers across the world. Although now, a shift toward either steroid avoidance or early withdrawal at day 5–day 7 posttransplant is gathering momentum; the reason being the adverse effects caused by prolonged use of low dose steroids (<7.5 mg/d) such as weight gain, dyslipidemia, acne, bruises, gastritis, and so on. A meta-analysis by Pascual et al has confirmed that steroid avoidance or withdrawal is possible in low immunological risk transplant recipients.

In this study, we did not find any difference in AR rate in both groups at one-year follow-up. A similar result was shown in DOMINOS study, though the comparison was between...
steroid-free and steroid withdrawal regimens. On the contrary, Vincenti et al showed that there was a higher incidence of AR in both steroid-free and steroid withdrawal regimens as compared to steroid-dependent regimens ($P = 0.004$) at one-year follow-up. However, graft survival was the same in both groups at one year. Other trials by Vítko et al and another multicenter prospective trial showed a higher rate of acute rejection in steroid-free and steroid withdrawal group, respectively. However, the results of multiple studies show no difference in AR when calcineurin inhibitor (CNI) was used in combination with MMF and antibody induction.

Rostaing et al compared Dacluzimab/Tacrolimus (TAC)/MMF with TAC/MMF/Steroid and found AR rate at six months to be same (16.5%) in both groups. Although in the study, the steroid maintenance group did not receive antibody and was given a higher TAC dosage. Sureshkumar et al have showed in OPTN/UNOS database that, the use of ATG as an induction agent was associated with better graft survival and AR rate was less with CNI/MMF/steroid-free regimen compared with induction with interleukin-2 receptor antagonist.

In our study, we used ATG and pulse steroid as induction therapy, followed by steroid withdrawal at day 5 posttransplant. Among full house match patients, 14 patients were given steroid only while seven others were given basiliximab along with steroids. Our rejection rate in both groups was 10% over one year, irrespective of varying induction therapies with similar TAC levels in both groups. (ATG/TAC/MMF/Steroid vs. ATG/TAC/MMF).

No difference was found in graft and patient survival at one year. Our findings are same as those published by Woodle and Fuysane Steroid withdrawal study group. In that study, a total of 396 patients were enrolled and randomly assigned to TAC/MMF/Steroid or TAC/MMF/steroid withdrawal at day 7; although, in this study, the AR was different from ours (6% vs. 12% steroid-dependent and steroid withdrawal groups). The results of our study are also substantiated by other studies.

Serum creatinine levels were better in steroid withdrawal group at three and six months follow-up, although at one-year follow-up no significant difference was found in both groups. This was assumed to be due to selection criteria (low immunological risk patient, low number of cadaveric transplants, and low number of extended criteria donor in steroid withdrawal group). A recent meta-analysis of steroid-free kidney transplant patients found that this regimen was associated with higher risk of AR and rise in creatinine level but the same risk of death or graft failure in both groups.
This study showed a significant rise in both systolic and DBPs, lipid profile, and NODAT in steroid maintenance group. The same group showed a higher occurrence of SGF/DGF (1% vs. 9% and 3% vs. 12%, respectively). The reason for which could be a higher percentage of the group receiving DD kidneys, where factors such as increased cold ischemia time may have contributed to the slow or delayed graft function. TAC levels were kept at the same range in both groups, and no difference in CNI toxicity was observed.

Another observation of this study, which is also corroborated by many other previous studies is that majority of kidney transplant recipients were males. It might be due to unsuitability of the female recipients because of multiparity or unwilling of females to accept donation from close relatives. AR was more common in cadaveric group 22% versus 9%. AR, DGF, SGF, and NODAT all was common in female recipients. We are unable to explain this.

In literature, posttransplant new-onset proteinuria varies between 15% and 45%. In our study, we found similar results with no significant difference between two groups. Although we had high percentage of patients with no follow-up proteinuria as it was not included in primary or secondary outcome.

More than four HLA mismatch was higher in steroid-dependent group, both in cadaveric and living related.

We could not find any significant difference in DSA at one-year follow-up in two groups, although the percentage was slightly higher in steroid-dependent group.

There was no cytomegalovirus (CMV) and polyomavirus (BK) infection in steroid-free group whereas five cases of CMV viremia and one case of BK viremia and one case of BK nephropathy in steroid-dependent group. All patients receive CMV prophylaxis for three to six months.

Mean cold ischemia time in cadaveric transplant was 12.5 h with a range between 2 and 21 h and median of 10 h. It is not comparable between two groups, as the number of cadaveric transplant in steroid-free was less.

Various studies show that the risk of AR increases if antibodies are not used in induction therapy. In this study, contrarily, no increase in AR was seen using only steroid as induction therapy in full house match patients.

This study, nonetheless, has some limitations. It is a nonrandomized study; moreover, the follow-up duration is short. The study is being extended for up to 10 years’ follow-up, to see the outcome regarding chronic rejection ratio, and graft as well as patient survival.

**Conclusion**

The study suggests that in low immunological risk patients, ATG induction followed by TAC, MMF, and steroid withdrawal at day 5 posttransplant is a fairly safe regimen. This regimen gives better metabolic outcome and similar graft and patient survival, provided patient selection is made carefully. The study also shows that methylprednisolone induction alone is quite safe in well-selected full house match patients.

On account of these findings, we suggest that all cadaveric renal transplants should be placed on steroid-based maintenance regimen. In a patient on steroid-free regimen, a rejection within three months posttransplant warrants a shift to steroid maintenance therapy. On the other hand, if the rejection occurs after three months posttransplant, it can be treated with pulse steroids and the patient can be continued on steroid-free regimen.

This study also finds it safe to keep TAC level in the same range in both groups.

Finally, more long-term studies are needed to validate the safety of steroid-free or early steroid withdrawal regimens on a long-term basis.

**Acknowledgments**

The authors would like to thank Dr. Kamran Baig, MPH for his help in the data analysis.

**Conflict of interest:** None declared.
Early steroid withdrawal postrenal transplant

References

1. Veenstra DL, Best JH, Hornberger J, Sullivan SD, Hricik DE. Incidence and long-term cost of steroid-related side effects after renal transplantation. Am J Kidney Dis 1999;33: 829-39.
2. Siegels RR, Luke RG, Hellebusch AA. Reduction of toxicity of corticosteroid therapy after renal transplantation. Am J Med 1972;53: 159-69.
3. Buckels JA, Mackintosh P, Barnes AD. Controlled trial of low versus high dose oral steroid therapy in 100 cadaveric renal transplantation. Proc Eur Dial Transplant Assoc 1981; 18:394-9.
4. Hricik DE. Steroid-free immunosuppression in kidney transplantation: An editorial review. Am J Transplant 2002;2:19-24.
5. Moons P, De Geest S, Abraham I, Cleemput JV, Van Vanhaecke J. Symptom experience associated with maintenance immunosuppression after heart transplantation: Patients’ appraisal of side effects. Heart Lung 1998;27:315-25.
6. Prasad GV, Nash MM, McFarlane PA, Zaltzman JS. Renal transplant recipient attitudes toward steroid use and steroid withdrawal. Clin Transplant 2003;17:135-9.
7. Hricik DE. Use of corticosteroids in kidney transplantation. In: Sayegh MH, Remuzzi G, editors. Current and Future Immunosuppressive Therapies Following Transplantation. London: Kluwer Academic Publishers; 2001. p. 61-84.
8. Hricik DE, O’Toole MA, Schulak JA, Herson J. Steroid-free immunosuppression in cyclosporine-treated renal transplant recipients: A meta-analysis. J Am Soc Nephrol 1993;4: 1300-5.
9. Sinclair NR. Low-dose steroid therapy in cyclosporine-treated renal transplant recipients with well-functioning grafts. The Canadian multicentre transplant study group. CMAJ 1992;147:645-57.
10. Kasiske BL, Chakker HA, Louis TA, Ma JZ. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. J Am Soc Nephrol 2000;11:1910-7.
11. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007;357:2562-75.
12. Tedesco Silva H Jr., Cibrik D, Johnston T, et al. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. Am J Transplant 2010;10:1401-13.
13. Pascual J, Zamora J, Galeano C, Royuela A, Quereda C. Steroid avoidance or withdrawal for kidney transplant recipients. Cochrane Database Syst Rev 2009;(1):CD005632.
14. Thiery A, Mourad G, Büchler M, et al. Steroid avoidance with early intensified dosing of enteric-coated mycophenolate sodium: A randomized multicentre trial in kidney transplant recipients. Nephrol Dial Transplant 2012;27:3651-9.
15. Vincenti F, Schena FP, Paraskevas S, et al. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. Am J Transplant 2008;8:307-16.
16. Vítko S, Klinger M, Salmela K, et al. Two corticosteroid-free regimens-tacrolimus monotherapy after basiliximab administration and tacrolimus/mycophenolate mofetil-in comparison with a standard triple regimen in renal transplantation: Results of the Atlas study. Transplantation 2005;80:1734-41.
17. Gaber AO, Moore LW, Alloway RR, et al. Acute rejection characteristics from a prospective, randomized, double-blind, placebo-controlled multicenter trial of early corticosteroid withdrawal. Transplantation 2013;95:573-9.
18. Roostaing L, Cantarovich D, Mourad G, et al. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. Transplantation 2005;79:807-14.
19. Vincenti F, Monaco A, Grinyo J, Kinkhabwala M, Roza A. Multicenter randomized prospective trial of steroid withdrawal in renal transplant recipients receiving basiliximab, cyclosporine microemulsion and mycophenolate mofetil. Am J Transplant 2003;3:306-11.
20. Meulen CG, van Riemsdijk I, Hené RJ, et al. Steroid-withdrawal at 3 days after renal transplantation with anti-IL-2 receptor alpha therapy: A prospective, randomized, multicenter study. Am J Transplant 2004;4:803-10.
21. Sureshkumar KK, Thai NL, Hussain SM, Ko TY, Marcus RJ. Influence of induction modality on the outcome of deceased donor kidney transplant recipients discharged on steroid-free maintenance immunosuppression.
22. Woodle ES; Fujisawa Steroid Withdrawal Study Group. A randomized, double-blinded, placebo-controlled trial of early corticosteroid cessation versus chronic corticosteroid maintenance therapy. Am J Transplant 2005;5 Suppl 11:540.

23. Birkeland SA. Steroid-free immunosuppression after kidney transplantation with antithymocyte globulin induction and cyclosporine and mycophenolate mofetil maintenance therapy. Transplantation 1998;66:1207-10.

24. Woodle ES, First MR, Pirsch J, et al. 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;248:564-77.

25. Knight SR, Morris PJ. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. Transplantation 2010;89:1-4.

26. Bloembergen WE, Port FK, Mauger EA, Briggs JP, Leichtman AB. Gender discrepancies in living related renal transplant donors and recipients. J Am Soc Nephrol 1996;7:139-44.

27. Hardinger KL, Brennan DC, Klein CL. Selection of induction therapy in kidney transplantation. Transpl Int 2013;26:662-72.

28. Kuo HT, Huang E, Emami S, et al. Effects of antibody induction on transplant outcomes in human leukocyte antigen zero-mismatch deceased donor kidney recipients. Transplantation. 2012;93:493-502.

29. Sheashaa HA, Bakr MA, Rashad RH, et al. Ten-year follow-up of basiliximab induction therapy for live-donor kidney transplant: A prospective randomized controlled study. Exp Clin Transplant 2011;9:247-51.

Date of manuscript receipt: 7 October 2018.
Date of revised copy receipt: 23 February 2019.
Date of final acceptance: 24 February 2019.