Impact of the Addition of Maintenance Steroids to a Rapid Steroid Discontinuation Immunosuppressive Protocol Following Acute Renal Transplant Rejection

Swati Arora, Richard J. Marcus, Sudharani Dikkala, Kalathil K. Sureshkumar

Abstract

Objectives: **Rapid steroid discontinuation immunosuppressive protocols are increasingly used in renal transplant. The optimal immunosuppressive regimen in patients who develop acute rejection while on a rapid steroid discontinuation protocol is less clear. We examined our experience of adding maintenance steroid therapy in renal transplant recipients who developed 1 or more acute rejection episode while on a rapid steroid discontinuation protocol.**

Materials and Methods: **The outcome of 145 patients who underwent renal transplant from 2002 to 2007 and initiated a rapid steroid discontinuation protocol was analyzed. Patients were divided into the following 5 groups: (i): acute rejection × 1 and no maintenance steroids, (ii): acute rejection × 1 and started on maintenance steroids, (iii): acute rejection × 2 and no maintenance steroids (iv): acute rejection × 2 and started on maintenance steroids, and (v): no acute rejection**

Results: **Compared with patients with no acute rejection, graft survival was significantly inferior in patients who experienced 2 or more acute rejection episodes—whether they were started on maintenance steroids (*P* = .003) or not (*P* = .006)—but was similar in patients who experienced only 1 episode of acute rejection, and were started either on maintenance steroids (*P* = .87) or were continued on the rapid steroid discontinuation protocol (*P* = .69). In patients who sustained 2 episodes of acute rejection, addition of maintenance steroids had no impact on graft survival (*P* = .97).**

Conclusions: **More than 1 episode of acute rejection in renal transplant recipients on rapid steroid discontinuation protocol is associated with poor, long-term, graft survival, which remains unchanged despite starting maintenance steroids. The use of maintenance steroids may not have a positive impact on graft survival after acute rejection.**

Key words: *Graft survival, Steroid free, Acute rejection, Kidney transplant, High-risk*

Rapid steroid discontinuation immununosuppressive protocols are increasingly used in renal transplant in an attempt to avoid the long-term adverse events of corticosteroid use (1, 2). It is not clear whether rapid steroid discontinuation protocols will yield real, long-term, metabolic benefits. The recent FREEDOM trial, involving standard-risk renal transplant recipients, has shown similar 12-month biopsy proven acute rejection incidence with rapid steroid discontinuation protocol compared with standard steroid regimen (3). A 10% to 20% incidence of acute rejection has been reported with rapid steroid discontinuation protocols (4, 5). Development of acute rejection in renal transplant recipients on an rapid steroid discontinuation protocol is a marker of high immune risk. The optimal immununosuppressive regimen in those who develop acute rejection while on an rapid steroid discontinuation protocol is less clear.

Our center has been using an rapid steroid discontinuation protocol in standard-risk renal transplant recipients since December 2002. When these patients developed acute rejection, the decision whether or not to start them on maintenance steroids varied from case to case and was influenced by patient preference, clinician preference, and clinical situation.

From the Division of Nephrology and Hypertension, Allegheny General Hospital, Pittsburgh, PA
Acknowledgment : *Presented as poster at the American Society of Nephrology Renal week in Philadelphia, PA, November 2008*
Address reprint requests to: *Kalathil K Sureshkumar MD, FRCP (Glasgow), Allegheny General Hospital, Nephrology and Hypertension, 320 East North Avenue, Pittsburgh, Pennsylvania 15212, USA*
Phone*: +412-359-3319* ***Fax:*** *+412-359-4136* ***E-mail:*** *ksureshk@wpahs.org*

Experimental and Clinical Transplantation (2009) 4: 233-236

Copyright © Başkent University 2009
Printed in Turkey. All Rights Reserved.

This study sought to assess the impact of adding maintenance steroids on allograft survival in patients who developed acute rejection while on an rapid steroid discontinuation protocol.

Materials and Methods

The study protocol was approved by the Institutional Review Board. Medical records of patients who underwent renal transplant at our institution from December 2002 to September 2007 were reviewed retrospectively. Rapid steroid discontinuation protocol involved the administration of intravenous methylprednisolone 500 mg in the operating room, 250 mg on postoperative day 1, 125 mg on postoperative day 2, followed by oral prednisone 60 mg on postoperative day 3, and 30 mg on postoperative day 4. All patients on rapid steroid discontinuation protocol also received induction therapy with either rabbit antithymocyteglobulin or basiliximab. Patients younger than 60 years old without coronary artery disease or diabetes received induction therapy with antithymocyte globulin (1.5 mg/kg), in 4 intravenous doses, that were started intraoperatively (a total of 6 mg/kg) was given during hospitalization. Elderly patients and those with coronary artery disease or diabetes received basiliximab (20 mg) intraoperatively and again on day 4. Maintenance immunosuppression consisted of cyclosporine microemulsion and mycophenolate mofetil. Cyclosporine was started at 10 mg/kg pre-operatively, followed by 5 mg/kg every 12 hours. Dosages were adjusted to achieve trough concentrations of 250 to 300 ng/mL during the early posttransplant period and 150 to 200 ng/mL subsequently. Mycophenolate mofetil was started at 2 g/d and dosages were modified if adverse effects such as leukopenia and gastrointestinal disturbance occurred. Ganciclovir was used for *Cytomegalovirus* prophylaxis and trimethoprim-sulfamethoxazole for Pneumocystis prophylaxis, except in patient with sulfa allergies, in whom diamino-diphenyl sulfone was used.

Patients on rapid steroid discontinuation protocol who developed 1 or more acute rejection episodes were identified. A diagnosis of acute rejection was made on the basis of allograft biopsy findings, or when there was a greater than 25% increase in serum creatinine from baseline in the absence of other causes. Acute rejection was treated with intravenous pulse methylprednisolone 250 to 500 mg daily for 3 to 5 days. If the renal biopsy also showed positive C4d immunostaining, patients received additional therapy with plasmapheresis and intravenous immunoglobulin. Few of these patients subsequently were started on maintenance steroids following the acute rejection. The decision to start maintenance steroids was based on clinical situation, severity of rejection, physician, and patient preference. Graft survival was estimated using Kaplan-Meier analysis with a log-rank test, and *P* value less than .05 was considered statistically significant.

Results

A total of 345 patients underwent renal transplant from December 2002 to September 2007, of which 316 patients were initiated on rapid steroid discontinuation protocol. During a mean follow-up of 33.8 ± 1.5 months, 84 patients on rapid steroid discontinuation protocol developed acute rejection. These patients were divided into the following groups: (i) 1 episode of acute rejection and not started on maintenance steroids (n=46), (ii) 1 episode of acute rejection and started on maintenance steroids (n=10), (iii) 2 or more episodes of acute rejection and not started on maintenance steroids (n=13), and (iv) 2 or more episodes of acute rejection and started on maintenance steroids (n=15). From the 232 patients who were on rapid steroid discontinuation protocol and did not develop acute rejection, 61 patients were randomly chosen to represent the control group (group v). The control group was designed to include roughly 3 times the average number of patients in each of the other groups to make the groups

Table 1. Demographic characteristics.

Patient groups	1 (n=46)	2 (n=10)	3 (n=13)	4 (n=15)	5 (n=61)
Donor age (y)	38	32	37	40	37
Deceased donors (%)	36	8	13	14	49
ECD kidneys (%)	23	3	10	9	33
Recipient age (y)	52	46	55	51	52
Diabetes (%)	14	2	4	6	17
Mean PRA (%)	2 ± 9	14 ± 20	3 ± 9	4 ± 6	5 ± 15
HLA mismatch	3.6	3.9	4.2	4.4	4
DGF (%)	12	2	4	6	11
CIT (hours)	20	19	26	26	21
Graft loss (%)	5	1	5	6	5
Time to first AR (months)	5.6	4.9	1.8	2.4	NA

Abbreviations: AR, acute rejection; CIT, cold ischemia time; DGF, delayed graft function; ECD, expanded criteria donor; HLA, human leukocyte antigen; PRA, panel reactive antibody

comparable. Thus, a total of 145 patients were included in the final analysis (120 deceased and 25 living-donor transplants) including 84 patients who developed acute rejection during the follow-up.

Demographic characteristics of the different groups are shown in Table 1. Sixty-four percent of the acute rejection episodes were biopsy-proven. There were 74 episodes of acute rejection in the first posttransplant year, indicating an acute rejection rate of 23%. Mean age was 37 ± 17 years for the donors and 52 ± 12 years for the recipients. Cold ischemia time was significantly higher in patients who developed 2 or more acute rejection episodes compared with patients who developed only 1 acute rejection episode (26 hours vs 20 hours) ($P < .05$). Expanded criteria donor kidney use (68% vs 46%) ($P = .1$), and the incidence of delayed graft function (35% vs 25%) ($P = .44$), were higher, and time to first acute rejection episode was shorter (2.1 ± 2.8 months vs 5.5 ± 9.4 months) ($P = .06$) in patients who developed 2 or more acute rejection episodes, but did not reach statistical significance.

Graft survival in patients with 1 acute rejection episode was not significantly inferior compared with patients who experienced no acute rejection ($P = .68$), but it was superior, compared with patients who developed 2 or more episodes of acute rejection ($P = .004$) (Figure 1). Graft survival of the different groups is shown in Figure 2. Compared with patients with no acute rejection, graft survival was significantly inferior in patients who experienced 2 or more acute rejection episodes whether they were started on maintenance steroids ($P = .003$) or not ($P = .006$). Conversely, graft survival was not significantly different between patients with no acute rejection episodes, and those who experienced 1 episode of acute rejection and were either started on maintenance steroids ($P = .87$) or were continued on the rapid steroid discontinuation protocol ($P = .69$). Despite adding maintenance steroids, graft survival was inferior in patients who developed 2 episodes of acute rejection compared with those who experienced only 1 episode of acute rejection and were not started on maintenance steroids ($P = .02$). In patients who sustained 2 episodes of acute rejection, addition of maintenance steroids had no impact on graft survival ($P = .97$).

Discussion

Our study shows poor graft survival in renal transplant recipients who developed more than 1 episode of acute rejection while maintained on an rapid steroid discontinuation regimen. This is consistent with previous studies that showed an association between multiple acute rejection episodes and increased risk for poor allograft outcome (6, 7). In our patients who developed more than 1 episode of acute rejection, the addition of maintenance steroids did not have a positive effect on long-term graft survival.

After the first acute rejection episode, close immune monitoring and immunosuppression modification are warranted to minimize the risk of a further acute rejection episode to improve long-term graft survival. However, the optimal maintenance

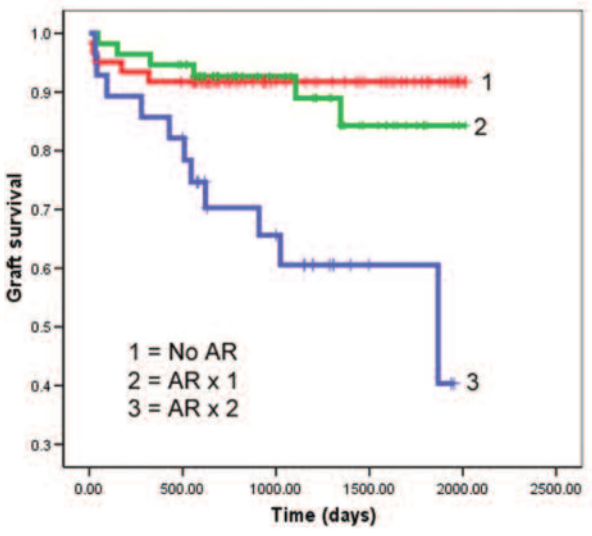

Figure 1. Graft survival rates based on AR episodes

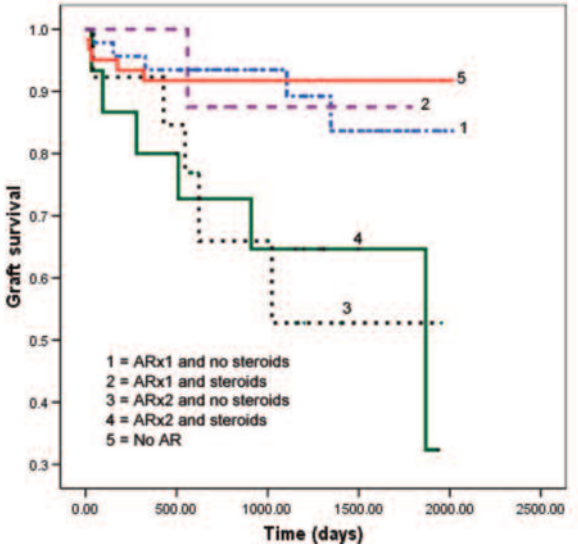

Figure 2. Graft survival rates in the 5 groups

immunosuppression regimen in these patients is less clear. Adding maintenance steroids to an rapid steroid discontinuation regimen following a first acute rejection episode did not decrease the risk of a second acute rejection episode in 1 study (8). Retrospective analysis, small sample size, and lack of biopsy-proven acute rejection in a subset of patients are limitations of our study. Owing to a small sample size, we did not incorporate the severity of biopsy-proven acute rejection into the analysis.

In summary, the development of acute rejection in renal transplant recipients on an rapid steroid discontinuation protocol indicate a high immune risk. How to alter the immunosuppression in these patients is less clear. A multicenter, randomized study, with large sample size may give definitive answers.

References

1. Luan FL, Steffick DE, Gadegbeku C, Norman SP, Wolfe R, Ojo AO. Graft and patient survival in kidney transplant recipients selected for de novo steroid-free maintenance immunosuppression. Am J Transplant. 2009;9(1):160-168.
2. Augustine JJ, Hricik DE. Steroid sparing in kidney transplantation: changing paradigms, improving outcomes, and remaining questions. Clin J Am Soc Nephrol. 2006;1(5):1080-1089.
3. 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(2):307-316. Erratum in: Am J Transplant. 2008;8(5):1080.
4. Anil Kumar MS, Heifets M, Fyfe B, et al. Comparison of steroid avoidance in tacrolimus/mycophenolate mofetil and tacrolimus/sirolimus combination in kidney transplantation monitored by surveillance biopsy. Transplantation. 2005;80(6):807-814.
5. Rostaing L, Cantarovich D, Mourad G, et al. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. Transplantation. 2005;79(7):807-814.
6. Kyllönen LE, Salmela KT, Eklund BH, et al. Long-term results of 1047 cadaveric kidney transplantations with special emphasis on initial graft function and rejection. Transpl Int. 2000;13(2):122-128.
7. Basadonna GP, Matas AJ, Gillingham KJ, et al. Early versus late acute renal allograft rejection: impact on chronic rejection. Transplantation. 1993;55(5):993-995.
8. Humar A, Gillingham K, Kandaswamy R, Payne W, Matas A. Steroid avoidance regimens: a comparison of outcomes with maintenance steroids versus continued steroid avoidance in recipients having an acute rejection episode. Am J Transplant. 2007;7(8):1948-1953.