Published in final edited form as:
Transplantation. 2009 January 15; 87(1): 100–102. doi:10.1097/TP.0b013e31818c25ab.

Kidney Transplant Half-Life (t ½) After Rapid Discontinuation of Prednisone

Arthur J. Matas, MD, **Raja Kandaswamy, MD**, **Ty B. Dunn, MD**, **William D. Payne, MD**, **David E. R. Sutherland, MD, PhD**, and **Abhinav Humar, MD**
University of Minnesota

Abstract

Protocols incorporating rapid discontinuation of prednisone (RDP) after kidney transplantation have been associated with good short-term results. However, concern remains that RDP will be associated with decreased long-term graft survival rates. We compared kidney transplant half-life (t ½) for recipients treated with antibody induction, CNI, antimetabolite and RDP vs. historical controls treated with antibody induction, CNI, antimetabolite and maintenance prednisone. For both living and deceased donor recipients, we found no difference between groups. We also found no differences in rate of graft loss to acute rejection or to tubular atrophy and interstitial fibrosis. Our study suggests that long-term graft outcome is not decreased when using RDP protocols versus chronic maintenance prednisone.

Keywords

kidney transplantation; prednisone; immunosuppression

The goal of prednisone minimization protocols after kidney transplantation has been to minimize prednisone-related side effects without increasing the rates of acute rejection and of late graft loss. Historically (before 1999), most trials studied late prednisone withdrawal—i.e., ≥3 months posttransplant. The results were mixed. Single-center reports noted either good or poor results; however, large, multicenter trials and meta-analyses reported increased rates of acute rejection and graft loss after late prednisone withdrawal (1-6). These same studies showed little evidence of minimization of prednisone-related side effects.

More recently, most clinical trials have studied rapid discontinuation of prednisone (RDP) – i.e., ≤ 7 days posttransplant. Prospective randomized trials of RDP vs. maintenance prednisone have shown little or no difference in acute rejection rates and no difference in short-term graft survival rates between groups (7-13). Those and other nonrandomized trials have shown that RDP protocols are successful in minimizing prednisone-related side effects (7-17). However, concern remains that RDP will be associated with decreased long-term graft survival rates.

We herein studied the half-life (t ½)—the time it takes for ½ of the grafts functioning at 1 year to subsequently fail—and compared t ½ of recipients treated with RDP vs. historical controls treated with maintenance prednisone. Calculation of t ½ does not consider early graft loss to technical failure, early patient death, irreversible early acute rejection, or primary nonfunction. However, given that the slope of the curve of graft failure vs. time has been a straight line after 1 year, t ½ gives an estimate of long-term graft survival for grafts surviving the first year (18,19).

Corresponding author: Arthur J. Matas, MD, MMC 328, 420 Delaware St. SE, Minneapolis, MN 55455.

From September, 1999 through June 30, 2006, a total of 590 first kidney transplant recipients (423 living donor [LD], 167 deceased donor [DD]) were treated with RDP and had 1-year function. Our protocol has been described in detail elsewhere (16). In short, all recipients were treated with polyclonal antibody (Thymoglobulin), a calcineurin inhibitor (either cyclosporine or tacrolimus), an antimetabolite (either mycophenolate mofetil or sirolimus), and a 5-day course of prednisone.

Historical controls (n = 335 first transplants: 105 LD, 230 DD), who underwent a transplant from January 1, 1995, through October 31, 2000, and had 1-year function, were treated with polyclonal antibody, a calcineurin inhibitor, an antimetabolite, and long-term maintenance prednisone. Note, our program started RDP protocols in LD recipients; we only expanded the protocol to DD after showing low acute rejection rates in LDs (20). As a consequence, there is a time overlap between the RDP and maintenance prednisone groups; in addition, there is a higher percentage of DD in the controls than in the RDP group.

We calculated t ½, separately for LD and DD recipients, for those treated with RDP, and for historical controls. We first calculated t ½ for all graft loss; we then calculated t ½ for death-censored graft loss. We also determined the actuarial rates of graft loss to acute rejection, of biopsy-proven chronic rejection (tubular atrophy and interstitial fibrosis), and of death with function.

Characteristics of the RDP and historical groups are shown in Table 1. For LD recipients, we found no significant differences between the RDP and historical groups. But for DD recipients, the RDP group had a significantly increased percentage of recipients with type 1 diabetes ($p<.05$) and with a low panel-reactive antibody (PRA) level ($p<.05$).

T ½ is shown separately for DD and LD recipients in Table 2. For both DD and LD recipients, we found no significant difference in t ½ or in death-censored t ½ between the RDP recipients and historical groups. For LD recipients, we found no difference in the actuarial rates of graft loss to acute rejection, of tubular atrophy and interstitial fibrosis, or of death with function (Table 3); for DD recipients, the RDP group had a significantly lower rate of death with function ($p=.04$). Considering only actuarial rates of graft loss for LDs after the first year, we found no difference between LD groups; for DDs, there was a trend ($p=.07$) to a lower rate of death with function.

The benefits of prednisone-free immunosuppression are intuitively obvious. Prednisone is associated with numerous side effects including hypertension, diabetes, cataracts, avascular necrosis, fractures, and changes in skin, mood, and appearance. Treatment of prednisone-related side effects in transplant recipients is expensive for the health care system (21). And, when surveyed, recipients state that the immunosuppressive drug they would most like to *not* take is prednisone (22).

Recent prospective randomized trials of maintenance prednisone vs. RDP have shown little or no increase in acute rejection rates with RDP (7-13). Short-term patient and graft survival rates, and renal function, have been similar between the RDP and maintenance groups. Our current study suggests that long-term graft function will be similar for those on RDP protocols and on maintenance prednisone.

The historical concern about long-term graft function with prednisone-free maintenance immunosuppression is based on the results of 1 multicenter Canadian study (23). In that study, recipients on prednisone and cyclosporine who had good graft function were randomized at 3 months posttransplant to either continue on the 2 drugs or switch to cyclosporine monotherapy. For the first 500 to 600 days after randomization, that study's authors found there were no significant differences between the 2-drug and prednisone withdrawal groups; but, thereafter,

the prednisone withdrawal group had significantly worse graft function. Of importance, acute rejection episodes were not documented, so that it is unknown whether some (or all) of the difference between the 2 groups was related to an increased rate of acute rejection after prednisone withdrawal. Other studies involving prednisone withdrawal at 3 months have reported an increased rate of acute rejection in their prednisone withdrawal group (1-6).

Prednisone is an antiinflammatory drug, so there is a theoretical concern that the kidney grafts of prednisone-free recipients might more rapidly deteriorate in association with tubular atrophy and interstitial fibrosis. But, to date, large randomized trials (albeit with limited follow-up) have not shown any increase in graft dysfunction in any of the RDP groups. In our study, with longer follow-up, we found no difference in t ½ between the RDP and historical groups.

One limitation of our study is the assumption that the curve of graft failure (after 1 year) vs. time will be a straight line after RDP, as it has been for recipients on maintenance prednisone. It is possible, long-term, that the curve of graft failure vs. time will differ for RDP recipients. Only continued, long-term, follow-up investigation will answer this question.

A second limitation is related to actuarial analysis; Meier-Kriesche et al. showed that real half-lives were shorter than projected half-lives (24). This observation is of less of a concern in our study in that the control group has only been followed slightly longer than the RDP group and we are not relying on projected half-lives for our analysis. A third limitation is the use of historical controls. Given that transplant results are improving, use of current controls (or a randomized study) may demonstrate different results. Finally, as noted in Table 1, over 80% of our recipients are white; our observation may not apply to an African American population.

We found no significant difference for LD recipients in the actuarial rates of graft loss to acute rejection, tubular atrophy and interstitial fibrosis, or of death with function; for DD recipients, the RDP group had a significantly lower rate of graft loss to death with function. Recently, in a long-term follow-up study, Vanrenterghem et al. noted that the total dose of steroids was related to cardiovascular complications (25).

In conclusion, the potential benefit of RDP protocols after kidney transplant is the minimization of prednisone-related side effects. Our study suggests that kidney allograft t ½ will be similar on RDP and with chronic maintenance prednisone protocols.

Acknowledgments

We thank Mary Knatterud for editorial assistance and Stephanie Daily for preparation of the manuscript.

Supported by NIH grant #DK 13083

References

1. 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(6):1300. [PubMed: 8130356]
2. Kasiske BL, Chakkera HA, Louis TA, Ma JZ. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. Am Soc Nephrol 2000;11(10):1910.
3. Ahsan N, Hricik D, Matas A, R, et al. Prednisone withdrawal in kidney transplant recipients on cyclosporine and mycophenolate mofetil—a prospective randomized study. Steroid Withdrawal Study Group. Transplantation 1999;68(12):1865. [PubMed: 10628766]
4. Vanrenterghem Y, Lebranchu Y, Hene R, Oppenheimer F, Ekberg H. Double-blind comparison of two corticosteroid regimens plus mycophenolate mofetil and cyclosporine for prevention of acute renal allograft rejection. Transplantation 2000;70(9):1352. [PubMed: 11087152]

5. Pascual J, Quereda C, Zamora J, Hernández D. Spanish Group for Evidence-Based Medicine in Renal Transplantation. Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolate mofetil: a meta-analysis of randomized, controlled trials. Transplantation 2004;78(10):1548. [PubMed: 15599321]
6. Pascual J, Quereda C, Zamora J, Hernández D. Spanish Group for Evidence-Based Medicine in Renal Transplantation. Updated metaanalysis of steroid withdrawal in renal transplant patients on calcineurin inhibitor and mycophenolate mofetil. Transplant Proc 2005;37(9):3746. [PubMed: 16386525]
7. Ter Meulen CG, van Riemsdijk I, Hene RJ, et al. Steroid-withdrawal at 3 days after renal transplantation with anti-IL-2 receptor therapy: a prospective, randomized, multicenter study. Am J Transplant 2004;4:803. [PubMed: 15084178]
8. Rostaing L, Cantarovich D, Mourad G, et al. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. Transplantation 2005;79:807. [PubMed: 15818323]
9. Vitko 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(12):1734. [PubMed: 16378069]
10. Woodle ES. TRIMS Study Group. A randomized, prospective, multicenter comparative study evaluating a thymoglobulin-based early corticosteroid cessation regimen in renal transplantation (TRIMS). Am J Transplant 2006;6(suppl):294.abstract
11. Vincenti F, Schena FP, Paraskevas S, Hauser IA, Walker RG, Grinyo J. FREEDOM Study Group. 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. [PubMed: 18211506]
12. Laftavi MR, Stephan R, Stefanick B, et al. Randomized prospective trial of early steroid withdrawal compared with low-dose steroids in renal transplant recipients using serial protocol biopsies to assess efficacy and safety. Surgery 2005;137:364–371. [PubMed: 15746793]
13. Woodle ES for the Astellas Steroid Withdrawal Study Group. A randomized, double blind, placebo controlled trial of early corticosteroid cessation versus chronic corticosteroids: five year results. American Transplant Congress 2008 abstract. Am J Transplant. in press
14. Montagnino G, Sandrini S, Iorio B, et al. A randomized exploratory trial of steroid avoidance in renal transplant patients treated with everolimus and low-dose cyclosporine. Nephrol Dial Transplant 2008;23(2):707. [PubMed: 17890244]
15. Kumar MS, Heifets M, Moritz MJ, et al. Safety and efficacy of steroid withdrawal two days after kidney transplantation: analysis of results at three years. Transplantation 2006;81(6):832. [PubMed: 16570004]
16. Matas AJ, Kandaswamy R, Humar A, et al. Long-term immunosuppression, without maintenance prednisone, after kidney transplantation. Ann Surg 2004;240:510. [PubMed: 15319722]
17. Sarwal MM, Vidhun JR, Alexander SR, et al. Continued superior outcomes with modification and lengthened follow-up of a steroid-avoidance pilot with extended daclizumab induction in pediatric renal transplantation. Transplantation 2003;76:1331. [PubMed: 14627912]
18. Opelz G, Mickey MR, Terasaki PI. Calculations on long-term graft and patient survival in human kidney transplantation. Transplant Proc 1977;9(1):27. [PubMed: 325765]
19. Gjertson DW, Terasaki PI. The large center variation in half-lives of kidney transplants. Transplantation 1992;53(2):357. [PubMed: 1738930]
20. Matas AJ, Ramcharan T, Paraskevas S, et al. Rapid discontinuation of steroids in living donor kidney transplantation: a pilot study. Am J Transplant 2001;1(3):278. [PubMed: 12102262]
21. 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(5):829. [PubMed: 10213637]
22. Prasad GV, Nash MM, McFarlane PA, Zaltzman JS. Renal transplant recipient attitudes toward steroid use and steroid withdrawal. Clin Transplant 2003;17(2):135–9. [PubMed: 12709080]
23. 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(5):645–57. [PubMed: 1521210]

24. Meier-Kriesche HU, Schold JD, Kaplan B. Long-term renal survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? Am J Transplant 2004;4(8): 1289–95. [PubMed: 15268730]

25. Vanrenterghem YF, Claes K, Montagnino G, et al. Risk factors for cardiovascular events after successful renal transplantation. Transplantation 2008;85(2):209–16. [PubMed: 18212625]

Table 1

Characteristics of First Kidney Transplant Recipients

	Deceased donor recipients		Living donor recipients	
	Historical control	RDP[+]	Historical control	RDP[+]
Primary disease (%)				
Type 1 diabetes	16%	32%[*]	33%	32%
Type 2 diabetes	15%	16%	8%	10%
Polycystic kidney disease	12%	7%	11%	12%
% female	41%	40%	34%	40%
% white	80%	78%	94%	93%
Mean age years (±S.E.)	51±13	51±13	43±11	42±10
Graft PRA[#] level (%)				
0%	78%	84%[*]	89%	88%
1-10%	4%	3%	4%	6%
11-50%	8%	6%	5%	5%
>50%	14%	8%	2%	2%
Donor gender, % female	45%	43%	62%	60%
Donor race, % white	94%	93%	95%	93%
Donor mean age, years (± S.E.)	39±17	36±16	43±11	42±10

[+] RDP = rapid discontinuation of prednisone

[#] PRA = panel-reactive antibody

[*] $p<.05$ vs. deceased donor historical controls

S.E. = standard error

Table 2

Kidney Graft Half-life (t ½) (± S.E.)

	Historical controls	RDP
Deceased donor recipients		
T ½ (95% C.I.)	8.9±0.8 years (7.3, 10.6 years)	15.0±3.3 years (8.6, 21.4 years)
Death-censored t ½ (95% C.I.)	17.2±2.2 years (12.8, 21.6 years)	22.5±6 years (10.7, 34.3 years)
Living donor recipients		
T ½ (95% C.I.)	14.7±2.5 years (9.8, 19.6 years)	16.1±2.2 years (11.7, 20.4 years)
Death-censored t ½ (95% C.I.)	25.0±5.6 years (14.0, 35.9 years)	33.4±6.7 years (20.3, 46.5 years)

[+] RDP = Rapid discontinuation of prednisone

C.I. = confidence interval

S.E. = standard error

Table 3

Six-Year Actuarial Graft Loss Rates

	Historical controls	RDP[+]
Deceased donor recipients	n=230	n=167
Acute rejection	1.7%	4.3%
TA/IF[*]	6.1%	7.1%
Death with function	12.2%	5.4%[**]
Living donor recipients	n=105	n=423
Acute rejection	1.2%	0.6%
TA/IF	3.2%	4.2%
Death with function	9.2%	9.3%

[+] RDP = Rapid discontinuation of prednisone

[*] TA/IF – tubular atrophy/interstitial fibrosis

[**] p = .05