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ORIGINAL ARTICLE

Rapid discontinuation of prednisone in kidney transplant recipients from at-risk subgroups: an OPTN/SRTR analysis

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SUMMARY

Although rapid discontinuation of prednisone (RDP) after kidney transplantation has been successful in low-risk recipients, there is concern about RDP use in recipients at increased risk for rejection or recurrent disease. Using SRTR, we compared outcomes for RDP versus maintenance prednisone-treated recipients for *all* adult 1st and 2nd transplants (n = 169 479) and the following 1st transplant subgroups: *African American* (AA); *highly sensitized;* those with a potentially *recurrent disease;* and pediatric recipients. For *all* adult 1st LD and DD transplants, RDP was associated with better patient and graft survival. For *all* LD subgroups, RDP and maintenance prednisone were associated with similar patient, graft, and death-censored (DC) graft survival. For 1st transplant DD subgroups, RDP was associated with better patient survival in AA, those with potentially recurrent disease, and pediatric recipients; graft survival with RDP was better in AAs. For adult 2nd DD transplants, RDP was associated with worse DC-graft survival. Importantly, for all differences, the effect size was small. With the exception of 2nd DD transplants, RDP protocols can be used without decreasing patient or graft survival for *subgroups* of 1st DD and LD kidney transplant recipients and for 2nd LD transplant recipients, at increased risk of rejection or recurrent disease.

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Introduction

For the first three decades of clinical kidney transplantation, high-dose prednisone was a critical component of immunosuppressive protocols [1,2]. Prednisone (500–1000 mg) was given in the operating room and then early postoperatively, followed by oral doses for long-term maintenance immunosuppression (starting as high as 2 mg/kg and then slowly tapered) combined with azathioprine [3]. Additional prednisone boluses were given for treatment of rejection episodes. Not surprisingly, prednisone-related side effects (e.g., new-onset diabetes, avascular necrosis of the hip, fractures, cataracts, hyperlipidemia, weight gain, skin changes and cushingoid appearance, and growth retardation in children) were common. When asked, transplant recipients stated that the drug they would most want eliminated from their immunosuppressive protocol was prednisone [4].

The development of new, more potent immunosuppressive drugs was followed by trials of late

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(≥3 months) post-transplant prednisone minimization or even withdrawal. In those trials, prednisone minimization or withdrawal was associated with significantly increased rates of acute rejection and of graft loss [5–8].

More recently, protocols in which prednisone is discontinued within a few days post-transplant—termed "rapid discontinuation of prednisone" (RDP) or "early steroid withdrawal" (ESW)—have been more successful. In adult recipients, RDP (as compared with protocols incorporating long-term maintenance prednisone) has been associated with an increased rate of early acute rejection episodes but has led to equivalent patient and graft survival, a better cardiovascular risk profile, and significantly fewer prednisone-related side effects [9–23]. Recent analyses reported that, when tacrolimus was used for maintenance immunosuppression in RDP protocols, there was not an increased rate of acute rejection [13,14].

Many studies of RDP have been limited to recipients at low immunologic risk. Yet certain subgroups of recipients who, if treated with RDP, would benefit from the better side effect profile might also have an increased risk of graft loss. Such subgroups include recipients known to have an increased risk of rejection (e.g., African American, highly sensitized, retransplanted, or pediatric recipients) or of disease recurrence [e.g., focal segmental glomerulosclerosis (FSGS)]. Herein, using data from the Scientific Registry of Transplant Recipients (SRTR), we analyzed the impact of RDP on patient and graft survival rates in those subgroups.

Materials and methods

Study cohort

Using the SRTR database, we analyzed the records of patients who underwent 1st and/or 2nd kidney alone transplants from January 1, 2000, through December 31, 2014. We restricted our analysis to patients who were discharged from the hospital with a functioning graft and who had typical induction [interleukin-2 (IL-2) inhibitors, thymoglobulin, alemtuzumab, or none] and maintenance immunosuppression (tacrolimus plus mycophenolate or cyclosporine plus mycophenolate) during the study period, irrespective of the use of steroids. Follow-up in this cohort continued until June 30, 2016.

Rapid discontinuation of prednisone

We took an intention-to-treat approach and defined RDP by whether or not prednisone or other steroids were part of that recipient's maintenance immunosuppression on hospital discharge.

Statistical analyses

We summarized *continuous* covariates as the median value (25th, 75th percentile); *categorical* covariates, as the frequency (percentage) by RDP status and by donation type, that is, deceased donor (DD) or living donor (LD). To test univariable differences between RDP and maintenance prednisone recipients, we used the Wilcoxon rank-sum tests (continuous covariates) and the Pearson chi-square tests (categorical covariates).

To assess the effect of RDP and adjust for confounding by indication, we fitted mixed-effect Cox proportional hazards models for overall patient survival, graft survival, and death-censored graft survival adjusting for immunosuppressive protocol; *recipient* characteristics [age, race, gender, body mass index (BMI), functional status, pretransplant dialysis (yes/no), primary disease, diabetes (yes/no), peak panel-reactive antibody (PRA) level]; *donor* characteristics [age, race, hypertension (yes/no), creatinine level, cause of death, donation type (DD vs. LD), number of human leukocyte antigen (HLA) mismatches]; and *surgical* characteristics (ischemic time). Because the proportion of subjects treated with RDP protocols increased during the study period, transplant date was included in the analysis to adjust for era effects. Because whether or not the subject was part of an RDP protocol was indicated at hospital discharge, follow-up started at the time of hospital discharge (note that subjects on RDP protocols may still be taking prednisone at discharge). In the models, we included transplant center as a random effect, to account for correlation in outcomes within center.

We analyzed the records of *all* adult 1st and 2nd transplant recipients as well as these four specific 1st transplant subgroups: adult *African American* recipients; adult *highly sensitized* (peak PRA levels ≥80%) recipients; adult recipients who had a *primary disease that can recur* post-transplant; and *pediatric* recipients. Separate models were fit for each subgroup of interest and for DDs and LDs. Additionally, we estimated the effect of RDP *within each induction regimen* by interacting RDP with induction regimen. These models additionally allow us to estimate the effect of induction regimen among recipients undergoing RDP. Because of the small number of events within each induction regimen for some of the subgroups, we pooled the three high-risk adult 1st transplant subgroups together.

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For the recurrent primary disease subgroup, using SRTR categories, we included these diagnoses: membranous glomerulonephritis, immunoglobulin A (IgA) nephropathy, FSGS, lupus, chronic glomerulonephritis, and membranous nephropathy. We estimated the effect of RDP *overall*, and *within each primary diagnosis group individually* by interacting RDP with primary disease. Additionally, we estimated the effect of RDP on the adjusted cause-specific hazard of graft loss due to disease recurrence.

To estimate adjusted survival curves, we averaged the estimated conditional survival if all recipients were to receive RDP and maintenance prednisone. For those curves, we included prednisone use on hospital discharge as a stratum in the proportional hazards model.

We multiply imputed missing data, using the full conditional specification (i.e., multivariate imputation by chained equations) [24,25]. In all, we created five complete datasets; parameter estimates from each of the complete datasets were combined using Rubin's combining rules [26].

As a sensitivity analysis, we repeated the analysis in a cohort in which we propensity-score-matched subjects undergoing RDP to those recipients receiving maintenance prednisone. Specific details are given in the Supporting Information.

Additionally, we examined the immunosuppression regimen of recipients at 6 months post-transplant and summarized the proportion taking prednisone for maintenance immunosuppression by RDP group.

For all statistical analyses, we used either SAS version 9.4 (SAS System, Cary, NC, USA) or R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). All of our statistical tests were 2-sided tests, with $P < 0.05$ indicating statistical significance.

Results

During our study period, a total of 169 479 1st and/or 2nd kidney transplant recipients met our inclusion criteria (103 628 had a DD; 65 851, LD). Mean follow-up time was 5.24 years; median, 4.61 years (25th–75th percentile: 2.2–7.6 years; maximum 16.2 years). Recipient characteristics are summarized in Table 1; the number of recipients in each subgroup is shown in Fig. 1.

The percentage of recipients in our study cohort who were treated with RDP increased from 3.1% in 2000 to 30.3% in 2014. RDP (vs. maintenance prednisone) recipients were slightly older (median age DD, 54.8 vs. 52.7 years; LD, 48.9 vs. 47.3 years), as well as more likely to be white (DD, 48.3% vs. 43.8%; LD, 67.0% vs. 66.1%), male (DD, 62.6% vs. 59.4%; LD, 62.6% vs. 60.5%), diabetic (DD, 35.1% vs. 31.4%; LD, 29.3% vs. 25.3%), a 1st transplant recipient (DD, 92.7% vs. 87.8%; LD, 95.1% vs. 90.0%), or a preemptive transplant recipient (DD, 11.7% vs. 9.7%; LD, 36.2% vs. 30.9%). In addition, RDP (vs. maintenance prednisone) recipients were more likely to be transplanted more recently (DD median transplant year 2010 vs. 2008; LD, 2010 vs. 2007) and were, therefore, more likely to receive tacrolimus for maintenance immunosuppression. Differences in donor characteristics for RDP versus maintenance prednisone recipients were generally small and clinically insignificant (Table 1).

The adjusted hazard ratio (HR) for patient survival, death-censored graft survival, and graft survival for RDP versus maintenance prednisone recipients is given in Fig. 1 and Table 2. For *all adult (LD and DD) 1st transplant recipients*, RDP (vs. maintenance prednisone) recipients had a better patient survival rate [DD, HR = 0.91, 95% confidence interval (CI) = 0.87–0.96; LD, HR = 0.87, CI = 0.80–0.93) and a better graft survival rate (DD, HR = 0.95, CI = 0.92–0.99; LD, HR = 0.92, CI = 0.87–0.97). The 10-year adjusted patient survival rate for RDP versus maintenance prednisone recipients was 68.9% vs. 67.9% for DD recipients and 82.2%; vs. 81.0% for LD recipients (Table 3). The death-censored graft survival rate did not significantly differ for RDP versus maintenance prednisone recipients (DD, HR = 0.97, CI = 0.92–1.03; LD, HR = 0.96, CI = 0.89–1.03).

RDP-treated (vs. maintenance prednisone) 1st DD transplant recipients in the following subgroups had better patient survival: adult *African Americans* (HR = 0.91, CI = 0.83–0.99), adults with a *primary disease that can recur* (HR = 0.85, CI = 0.74–0.97), and *pediatric* recipients (HR = 0.56, CI = 0.33–0.96). But the differences in the 10-year adjusted patient survival for RDP versus maintenance prednisone in those subgroups were generally modest: adult *African Americans,* 72.0% vs. 70.7%; adults with a *primary disease that can recur* 82.2% vs. 81.3%; and *pediatric* recipients, 97.0% vs. 94.9% (Table 3, Figs S1 and S2). For 1st LD transplant recipients, we found no significant differences for RDP versus maintenance prednisone in any subgroup although effect estimates were generally similar in magnitude in LDs as in DDs. The death-censored graft survival rate significantly differed for RDP versus maintenance prednisone recipients only in the *adult 2nd DD* subgroup (HR = 1.23, CI = 1.08–1.40). For that subgroup, the 10-year adjusted death-censored graft survival rate was 66.1% for RDP vs. 69.1% for maintenance prednisone recipients (Table 3, Fig. S3).

Table 1. Clinical and demographic information among recipients (a) and donors (b) included in the cohort by donor type and maintenance prednisone

(a) Recipient characteristics													
	Deceased donor recipients							Living donor recipients					
	Maintenance prednisone			Rapid discontinuation of prednisone				Maintenance prednisone			Rapid discontinuation of prednisone		
	Median or Frequency	(25th, 75th centile) or percent	Percent Missing	Median or Frequency	(25th, 75th centile) or percent	Percent Missing	*P*-value	Median or Frequency	(25th, 75th centile) or percent	Percent missing	Median or frequency	(25th, 75th centile) or percent	Percent missing	*P*-value
Age (Years)	52.7	(41.2, 61.8)	0	54.8	(43.4, 63.2)	0	<0.001	47.3	(34.5, 57.8)	0	48.9	(35.9, 59.1)	0	<0.001
Race														
Black or African American	26038	32.9	0	7047	28.8	0	<0.001	6962	15.0	0	2389	12.3	0	<0.001
Hispanic/Latino	12114	15.3		3527	14.4			6091	13.1		2928	15.1		
Asian	4882	6.2		1568	6.4			2020	4.3		818	4.2		
White	34645	43.8		11819	48.3			30722	66.1		12968	67.0		
Other or Multiracial	1497	1.9		491	2.0			699	1.5		254	1.3		
Gender														
Female	32108	40.6	0	9156	37.4	0	<0.001	18383	39.5	0	7230	37.4	0	<0.001
Male	47068	59.4		15296	62.6			28111	60.5		12127	62.6		
Transplant number														
First	69531	87.8	0	22665	92.7	0	<0.001	41859	90.0	0	18416	95.1	0	<0.001
Second	9645	12.2		1787	7.3			4635	10.0		941	4.9		
Primary diagnosis														
Type I diabetes	3687	4.7	0	896	3.7	0	<0.001	3169	6.8	0	1304	6.7	0	<0.001
Type II diabetes	15428	19.5		5821	23.8			6060	13.0		3197	16.5		
FSG	5514	7.0		1619	6.6			3782	8.1		1568	8.1		
Hypertension	18800	23.7		5879	24			6982	15.0		3190	16.5		
IGA	2984	3.8		1011	4.1			3437	7.4		1462	7.6		
Other	26056	32.9		6881	28.1			18044	38.8		6212	32.1		
Polycystic kidneys	6707	8.5		2345	9.6			5020	10.8		2424	12.5		
BMI (kg/m^2)	27.1	(23.4, 31.2)	7.1	27.5	(23.8, 31.7)	5.5	<0.001	26.3	(22.8, 30.5)	7.7	26.9	(23.1, 31.3)	5.4	<0.001
Assistance needed														
None	56831	76.4	6.1	18285	76.7	2.5	<0.001	36133	84.7	8.2	15610	83.0	2.8	<0.001
Some	16808	22.6		5192	21.8			6253	14.7		2983	15.9		
Total	715	1.0		355	1.5			281	0.7		223	1.2		

Table 1. Continued.

(a) Recipient characteristics														
	Deceased donor recipients							Living donor recipients						
	Maintenance prednisone			Rapid discontinuation of prednisone				Maintenance prednisone			Rapid discontinuation of prednisone			
	Median or Frequency	(25th, 75th centile) or percent	Percent Missing	Median or Frequency	(25th, 75th centile) or percent	Percent Missing	*P*-value	Median or Frequency	(25th, 75th centile) or percent	Percent missing	Median or frequency	(25th, 75th centile) or percent	Percent missing	*P*-value
Preemptive Tx														
No	71082	90.3	0.5	21497	88.3	0.5	<0.001	31771	69.1	1	12268	63.8	0.7	<0.001
Yes	7678	9.7		2843	11.7			14235	30.9		6954	36.2		
Diabetes														
No	53754	68.6	1.1	15654	64.9	1.3	<0.001	34317	74.7	1.2	13417	70.7	1.9	<0.001
Yes	24550	31.4		8471	35.1			11614	25.3		5570	29.3		
Peak PRA	3	(0, 35)	2.2	0	(0, 20)	1.8	<0.001	0	(0, 9)	4.9	0	(0, 5)	3.3	<0.001
Cold ischemia time (Hrs)	16.7	(11.5, 22.2)	5.6	16.9	(11.4, 23)	3.5	<0.001	1	(1, 2)	25.8	1	(0.7, 2)	27.5	<0.001
HLA mismatch														
0	9391	11.9	0	2611	10.7	0	<0.001	3885	8.4	0.9	1514	7.9	0.8	<0.001
1	945	1.2		243	1.0			2617	5.7		1023	5.3		
2	3983	5.0		1031	4.2			8003	17.4		3191	16.6		
3	10946	13.8		3114	12.7			12815	27.8		5139	26.8		
4	20304	25.7		6497	26.6			6763	14.7		2941	15.3		
5	22660	28.6		7473	30.6			7802	16.9		3487	18.2		
6	10923	13.8		3481	14.2			4188	9.1		1911	10.0		
Immunosuppression														
Campath, CSA+MMF	235	0.3	0	101	0.4	0	<0.001	121	0.3	0	75	0.4	0	<0.001
Campath, Tac+MMF	3156	4.0		6917	28.3			1297	2.8		6208	32.1		
IL-2, CSA+MMF	5573	7.0		290	1.2			4198	9.0		230	1.2		
IL-2, Tac+MMF	17970	22.7		2172	8.9			13671	29.4		2527	13.1		
None, CSA+MMF	3376	4.3		173	0.7			3094	6.7		132	0.7		
None, Tac+MMF	14735	18.6		2665	10.9			10026	21.6		1906	9.8		
Thymo, CSA+MMF	2302	2.9		444	1.8			1028	2.2		502	2.6		
Thymo, Tac+MMF	31829	40.2		11690	47.8			13059	28.1		7777	40.2		

Table 1. Continued.

(a) Recipient characteristics													
	Deceased donor recipients							Living donor recipients					
	Maintenance prednisone			Rapid discontinuation of prednisone				Maintenance prednisone			Rapid discontinuation of prednisone			
	Median or Frequency	(25th, 75th centile) or percent	Percent Missing	Median or Frequency	(25th, 75th centile) or percent	Percent Missing	*P*-value	Median or Frequency	(25th, 75th centile) or percent	Percent missing	Median or frequency	(25th, 75th centile) or percent	Percent missing	*P*-value
Tx Year	2008	(2004, 2012)	0	2010	(2007, 2012)	0	<0.001	2007	(2003, 2011)	0	2010	(2007, 2012)	0	<0.001
Among second Tx recipients														
Previous graft survival (years)														
0–1	1610	16.7	0	312	17.5	0	<0.001	312	6.7	0	73	7.8	0	0.017
1–5	2556	26.5		488	27.3			728	15.7		165	17.5		
5–10	2528	26.2		460	25.7			1284	27.7		234	24.9		
10–15	1279	13.3		266	14.9			1041	22.5		227	24.1		
15+	501	5.2		108	6.0			573	12.4		132	14.0		
Unknown	1171	12.1		153	8.6			697	15.0		110	11.7		
Previous cause of graft failure														
Acute rejection	905	9.4	0	151	8.4	0	0.011	271	5.8	0	60	6.4	0	0.005
Chronic rejection	3314	34.4		611	34.2			1493	32.2		267	28.4		
Graft thrombosis	521	5.4		97	5.4			127	2.7		25	2.7		
Other	1447	15.0		329	18.4			654	14.1		162	17.2		
Primary failure	377	3.9		72	4.0			115	2.5		17	1.8		
Recurrent disease	448	4.6		85	4.8			223	4.8		66	7.0		
Unknown	2633	27.3		442	24.7			1752	37.8		344	36.6		

Table 1. Continued.

(b) Donor characteristics														
	Deceased donor recipients							Living donor recipients						
	Prednisone at discharge			Rapid discontinuation of prednisone				Prednisone at discharge			Rapid discontinuation of prednisone			
	Median or frequency	(25th, 75th centile) or percent	Percent missing	Median or frequency	(25th, 75th centile) or percent	Percent missing	*P*-value	Median or frequency	(25th, 75th centile) or percent	Percent missing	Median or frequency	(25th, 75th centile) or percent	Percent missing	*P*-value
Age (years)	39	(23, 51)	0	40	(24, 51)	0	<0.001	41	(32, 49)	0	41	(32, 50)	0	0.003
Race														
Black or African American	10632	13.4	0	3368	13.8	0	<0.001	6124	13.2	0	2084	10.8	0	<0.001
Hispanic/ Latino	11104	14.0		2938	12.0			5985	12.9		2860	14.8		
Asian	1869	2.4		508	2.1			1726	3.7		659	3.4		
White	54760	69.2		17436	71.3			32019	68.9		13517	69.8		
Other or multiracial	788	1.0		201	0.8			640	1.4		237	1.2		
Gender														
Female	31597	39.9	0	9770	40.0	0	0.898	27865	59.9	0	11592	59.9	0	0.917
Male	47579	60.1		14682	60.0			18629	40.1		7765	40.1		
Hypertension														
No	58898	74.8	0.6	17600	72.4	0.6	<0.001							
Yes	19814	25.2		6710	27.6									
Creatinine (mg/dL)	0.9	(0.7, 1.3)	0.1	1.0	(0.7, 1.3)	0.1	<0.001							
Cause of death														
Anoxia	34635	43.7	0	10397	42.5	0	<0.001							
Stroke	16573	20.9		5825	23.8									
Other	27968	35.3		8230	33.7									
Cardiac death														
Yes	70652	89.2	0	21232	86.8	0	<0.001							
No	8513	10.8		3217	13.2									

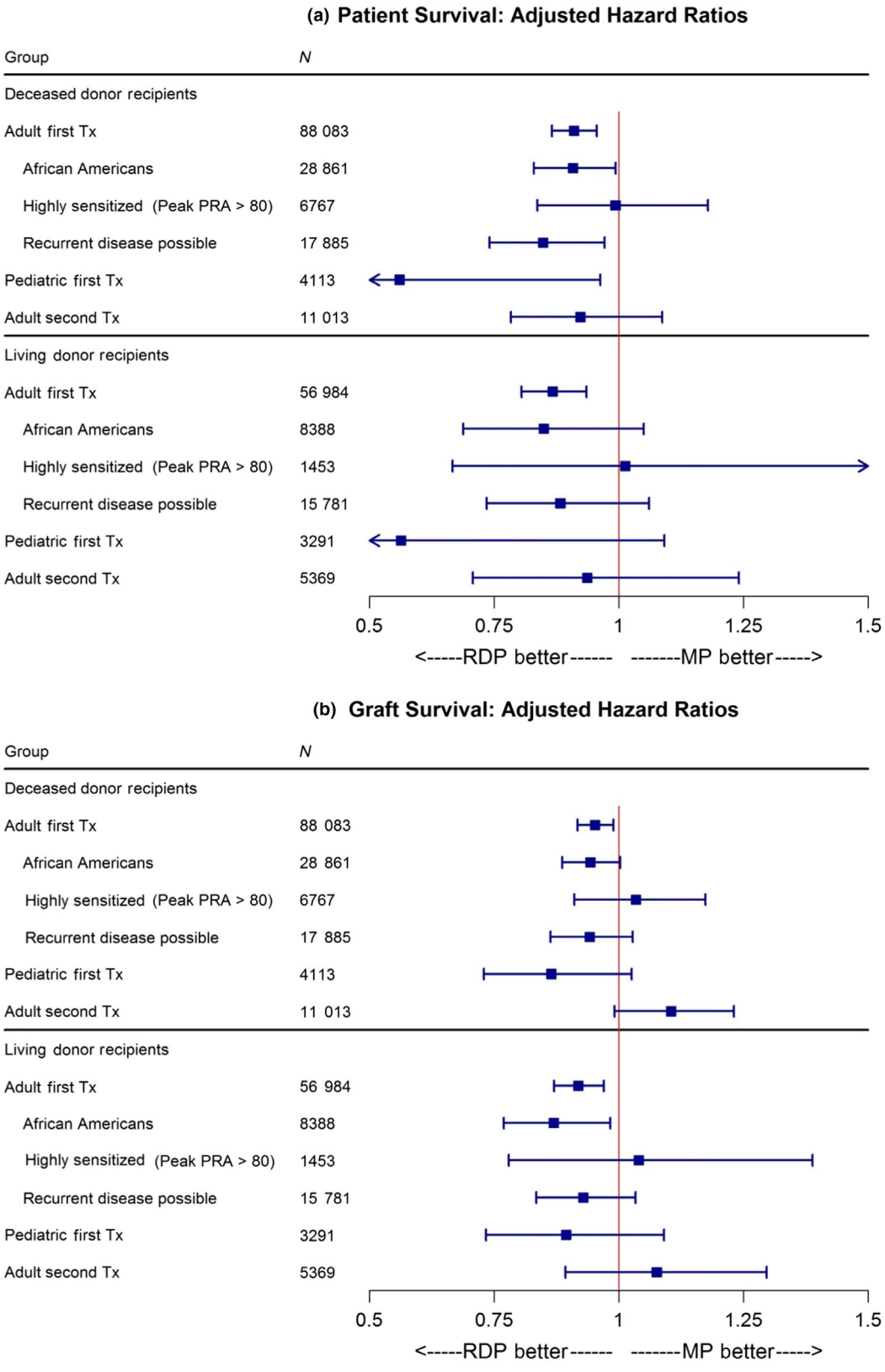

Figure 1 Adjusted hazard ratios and 95% confidence intervals comparing rapid discontinuation of prednisone to maintenance prednisone at discharge for (a) overall patient survival, (b) graft survival, and (c) death-censored graft survival among different subgroups. Hazard ratios <1 indicate better outcomes for rapid discontinuation of prednisone. RDP: rapid discontinuation of prednisone; MP: maintenance prednisone; Tx: transplant.

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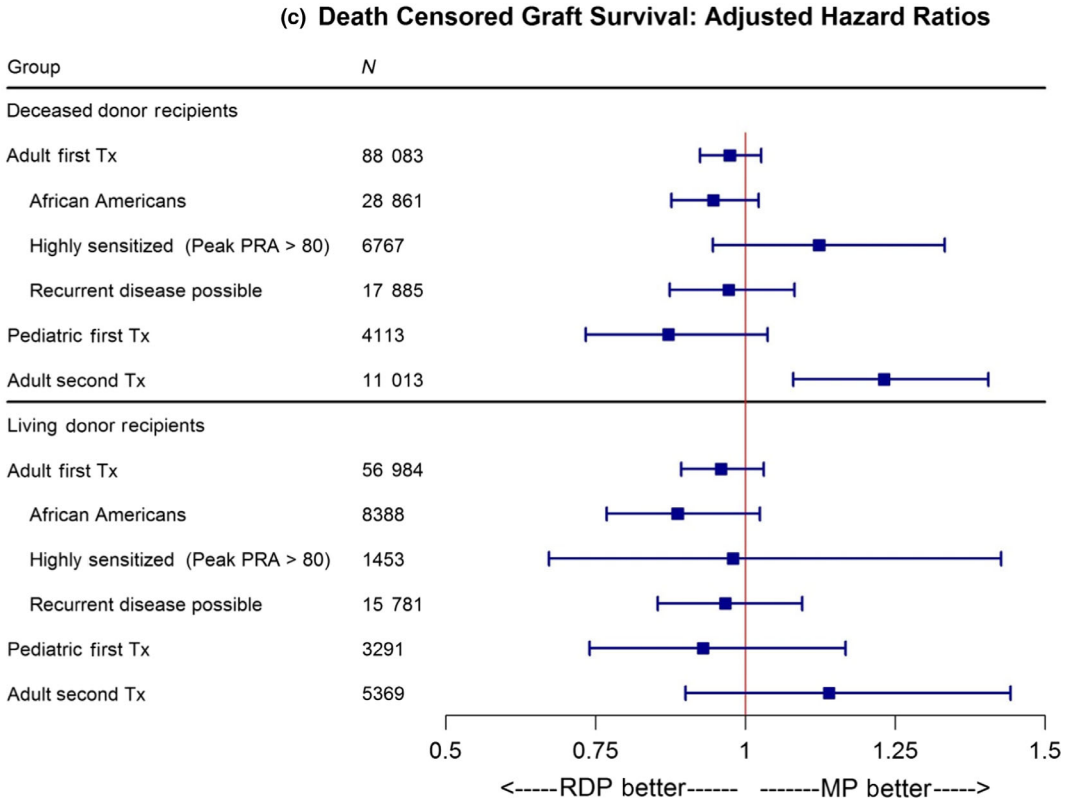

Among the subgroups, the effect of RDP relative to maintenance prednisone on graft survival was generally in between the effect on death-censored graft survival and on patient survival (significantly better for LD *African Americans*; no difference other subgroups) (Fig. 1).

Estimates of the effect of RDP versus maintenance prednisone were very similar in the propensity-score-matched analysis (see Table S2).

When recipients with potentially recurrent diseases were analyzed *by disease entity*, the effect of RDP on death-censored graft survival, graft survival, and patient survival was generally nonsignificant; for some primary diagnoses, the effect of RDP was even protective (Table 4a–c). However, for recipients with IgA nephropathy (but not any of the other primary diagnoses we studied), the cause-specific hazard of graft loss due to disease recurrence was higher among DD recipients for RDP (vs. maintenance prednisone) recipients (HR = 1.83, CI = 1.01–3.30) (Table 4d). Of importance, however, for those with IgA nephropathy, there was no difference in the overall risk of graft loss.

Table 5 gives the adjusted hazard ratio (HR) for patient survival, death-censored graft survival, and graft survival for RDP versus maintenance prednisone recipients by induction regimen. Across most subpopulations and endpoints, there was no significant difference in the effect of RDP among different induction regimens (see composite *P* in Tables 5a–c). Importantly for all subpopulations and endpoints, with the exception of death-censored graft survival for *adult 2nd DD* subgroup, RDP was associated with significantly improved survival or no significant difference in survival among recipients receiving thymoglobulin, IL-2 inhibitors, or campath for induction. Table 6 compares the effect of induction regimen within recipients undergoing RDP protocols. In subgroups where there was a significant difference, recipients receiving thymoglobulin for induction had the most favorable outcomes; no induction, the least favorable.

Among those with graft survival and follow-up longer than 6 months, 83% subjects had current maintenance immunosuppression data available at 6 months post-transplant. Of those with data available, 94% of recipients in the maintenance prednisone group had prednisone as part of their

Table 2. Adjusted hazard ratios and 95% confidence intervals comparing rapid discontinuation of prednisone to maintenance prednisone at discharge for (a) overall patient survival, (b) graft survival, and (c) death-censored graft survival among different subgroups of deceased donor recipients and living donor recipients

Subpopulation	HR	95% CI	*P*
(a) Overall patient survival			
Deceased donor recipients			
Adult first Tx	0.91	(0.87, 0.96)	<0.001
Adult African American first Tx	0.91	(0.83, 0.99)	0.035
Highly sensitized adult first Tx	0.99	(0.84, 1.18)	0.935
Adult w/possible recurrent Dz, first Tx	0.85	(0.74, 0.97)	0.017
Pediatric first Tx	0.56	(0.33, 0.96)	0.036
Adult second Tx	0.92	(0.78, 1.09)	0.336
Living donor recipients			
Adult first Tx	0.87	(0.80, 0.93)	<0.001
Adult African American first Tx	0.85	(0.69, 1.05)	0.130
Highly sensitized adult first Tx	1.01	(0.67, 1.54)	0.954
Adult w/possible recurrent Dz, first Tx	0.88	(0.73, 1.06)	0.182
Pediatric first Tx	0.56	(0.29, 1.09)	0.088
Adult second Tx	0.94	(0.71, 1.24)	0.647
(b) Graft survival			
Deceased donor recipients			
Adult first Tx	0.95	(0.92, 0.99)	0.011
Adult African American first Tx	0.94	(0.89, 1.00)	0.061
Highly sensitized adult first Tx	1.03	(0.91, 1.17)	0.608
Adult w/possible recurrent Dz, first Tx	0.94	(0.86, 1.03)	0.177
Pediatric first Tx	0.86	(0.73, 1.03)	0.095
Adult second Tx	1.10	(0.99, 1.23)	0.071
Living donor recipients			
Adult first Tx	0.92	(0.87, 0.97)	0.002
Adult African American first Tx	0.87	(0.77, 0.98)	0.025
Highly sensitized adult first Tx	1.04	(0.78, 1.39)	0.791
Adult w/possible recurrent Dz, first Tx	0.93	(0.83, 1.03)	0.174
Pediatric first Tx	0.89	(0.73, 1.09)	0.270
Adult second Tx	1.08	(0.89, 1.30)	0.444
(c) Death-censored graft survival			
Deceased donor recipients			
Adult first Tx	0.97	(0.92, 1.03)	0.317
Adult African American first Tx	0.95	(0.88, 1.02)	0.160
Highly sensitized adult first Tx	1.12	(0.95, 1.33)	0.186
Adult w/possible recurrent Dz, first Tx	0.97	(0.87, 1.08)	0.605
Pediatric first Tx	0.87	(0.73, 1.04)	0.120
Adult second Tx	1.23	(1.08, 1.40)	0.002
Living donor recipients			
Adult first Tx	0.96	(0.89, 1.03)	0.251
Adult African American first Tx	0.89	(0.77, 1.02)	0.102
Highly sensitized adult first Tx	0.98	(0.67, 1.43)	0.912
Adult w/possible recurrent Dz, first Tx	0.97	(0.85, 1.09)	0.591
Pediatric first Tx	0.93	(0.74, 1.17)	0.526
Adult second Tx	1.14	(0.90, 1.44)	0.278

Hazard ratios <1 indicate better outcomes for rapid discontinuation of prednisone.

Dz, disease; Tx, transplant; HR, hazard ratio; CI, confidence interval.

maintenance immunosuppression protocol at 6 months post-transplant. (Additionally, 97% reported taking prednisone for maintenance immunosuppression during the reporting period between discharge and 6 months post-transplant.) Overall, 81% of subjects undergoing RDP

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Table 3. Adjusted 5- and 10-year (a) overall patient survival, (b) graft survival, and (c) death-censored graft survival for patients undergoing rapid discontinuation of prednisone and maintenance prednisone at discharge for among different subgroups of deceased donor recipients and living donor recipients

	% 5-year survival		% 10-year survival	
Subpopulation	RDP (%)	MP (%)	RDP (%)	MP (%)
(a) Overall patient survival				
Deceased donor recipients				
Adult first Tx	86.6	85.0	68.9	67.9
Adult African American first Tx	87.9	85.9	72.0	70.7
Highly sensitized adult first Tx	86.5	85.8	69.4	68.2
Adult w/possible recurrent Dz, First Tx	92.3	91.3	82.1	81.2
Pediatric first Tx	98.4	97.2	97.0	94.9
Adult second Tx	88.1	88.2	75.5	75.8
Living donor recipients				
Adult first Tx	93.4	82.4	82.2	81.0
Adult African American first Tx	93.5	92.0	85.3	82.9
Highly sensitized adult first Tx	90.2	91.7	79.1	79.0
Adult w/possible recurrent Dz, First Tx	96.4	96.1	91.0	89.6
Pediatric first Tx	99.3	97.4	98.2	95.0
Adult second Tx	93.3	93.0	85.5	82.4
(b) Graft survival				
Deceased donor recipients				
Adult first Tx	76.1	74.4	51.6	50.5
Adult African American first Tx	72.6	70.0	47.2	45.2
Highly sensitized adult first Tx	75.0	74.2	49.5	50.1
Adult w/possible recurrent Dz, first Tx	79.9	78.7	60.0	58.3
Pediatric first Tx	79.4	77.7	55.4	57.1
Adult second Tx	73.6	75.1	51.6	54.5
Living donor recipients				
Adult first Tx	86.4	84.9	67.4	65.5
Adult african american first Tx	81.8	77.1	61.9	55.6
Highly sensitized adult first Tx	77.6	82.8	62.4	59.3
Adult w/possible recurrent Dz, first Tx	87.9	86.6	71.2	70.1
Pediatric first Tx	88.7	85.6	67.9	68.8
Adult second Tx	83.2	83.5	69.6	64.5
(c) Death-censored graft survival				
Deceased donor recipients				
Adult first Tx	86.0	85.3	72.5	71.1
Adult African American first Tx	80.9	79.3	63.5	61.1
Highly sensitized adult first Tx	84.1	84.6	68.1	70.9
Adult w/possible recurrent Dz, first Tx	85.6	84.8	72.0	70.3
Pediatric first Tx	80.4	78.9	56.8	59.0
Adult second Tx	81.4	83.4	66.1	69.1
Living donor recipients				
Adult first Tx	91.7	91.0	80.5	79.5
Adult African American first Tx	86.2	82.8	70.7	65.9
Highly sensitized adult first Tx	84.4	88.6	75.3	73.2
Adult w/possible recurrent Dz, first Tx	90.5	89.6	77.6	77.7
Pediatric first Tx	89.0	87.0	68.3	71.0
Adult second Tx	88.6	89.0	80.8	77.0

Dz, disease; Tx, transplant.

remained prednisone free during the first 6 months post-transplant; Table 7 gives the percentage by donation type and subpopulation. The percentage remaining prednisone free was slightly larger for living donor recipients than deceased donor recipients across all subgroups, and among adult, second transplant recipients, the percentage returning to prednisone was approximately double

Table 4. Adjusted hazard ratios and 95% confidence intervals comparing rapid discontinuation of prednisone to maintenance prednisone at discharge for (a) graft failure due to recurrent disease, (b) death-censored graft survival, (c) graft survival, and (d) overall patient survival among different primary diagnoses

Subpopulation	HR	95% CI	*P*
(a) Overall patient survival			
Deceased donor recipients			
Membranous glomerulonephritis	0.64	(0.41, 0.99)	0.047
IgA nephropathy	0.79	(0.57, 1.11)	0.170
FSGS	0.98	(0.80, 1.22)	0.888
Lupus	0.79	(0.54, 1.16)	0.229
Chronic glomerulonephritis	0.95	(0.75, 1.21)	0.690
Membranous nephropathy	0.91	(0.45, 1.84)	0.800
Living donor recipients			
Membranous glomerulonephritis	1.03	(0.64, 1.67)	0.900
IgA nephropathy	1.04	(0.71, 1.51)	0.844
FSGS	0.84	(0.63, 1.12)	0.238
Lupus	0.61	(0.34, 1.07)	0.087
Chronic glomerulonephritis	0.80	(0.56, 1.16)	0.246
Membranous nephropathy	1.12	(0.49, 2.56)	0.781
(b) Graft survival			
Deceased donor recipients			
Membranous glomerulonephritis	0.73	(0.56, 0.96)	0.026
IgA nephropathy	1.02	(0.84, 1.23)	0.869
FSGS	0.95	(0.83, 1.09)	0.438
Lupus	1.04	(0.84, 1.28)	0.737
Chronic glomerulonephritis	0.99	(0.84, 1.16)	0.869
Membranous nephropathy	1.15	(0.73, 1.83)	0.545
Living donor recipients			
Membranous glomerulonephritis	1.24	(0.94, 1.64)	0.131
IgA nephropathy	1.02	(0.84, 1.24)	0.826
FSGS	0.91	(0.77, 1.07)	0.236
Lupus	0.76	(0.58, 1.00)	0.046
Chronic glomerulonephritis	0.73	(0.57, 0.92)	0.009
Membranous nephropathy	1.06	(0.60, 1.87)	0.852
(c) Death-censored graft survival			
Deceased donor recipients			
Membranous glomerulonephritis	0.77	(0.55, 1.07)	0.122
IgA nephropathy	1.12	(0.90, 1.39)	0.321
FSGS	0.93	(0.78, 1.09)	0.359
Lupus	1.09	(0.86, 1.38)	0.482
Chronic glomerulonephritis	0.97	(0.78, 1.20)	0.772
Membranous nephropathy	1.48	(0.83, 2.65)	0.184
Living donor recipients			
Membranous glomerulonephritis	1.37	(0.99, 1.90)	0.055
IgA nephropathy	1.02	(0.82, 1.26)	0.871
FSGS	0.95	(0.79, 1.15)	0.617
Lupus	0.88	(0.66, 1.18)	0.395
Chronic glomerulonephritis	0.66	(0.49, 0.89)	0.007
Membranous nephropathy	1.26	(0.62, 2.56)	0.523
(d) Graft failure due to recurrent disease			
Deceased donor recipients			
Membranous glomerulonephritis	1.58	(0.79, 3.18)	0.196
IgA nephropathy	1.83	(1.01, 3.30)	0.045
FSGS	0.66	(0.41, 1.07)	0.090
Lupus	0.62	(0.19, 2.04)	0.428
Chronic glomerulonephritis	1.01	(0.49, 2.06)	0.980
Membranous nephropathy	0.42	(0.05, 3.49)	0.425

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Table 4. Continued.

Subpopulation	HR	95% CI	*P*
Living donor recipients			
Membranous glomerulonephritis	0.85	(0.44, 1.64)	0.624
IgA nephropathy	1.27	(0.78, 2.06)	0.335
FSGS	0.52	(0.33, 0.82)	0.005
Lupus	0.24	(0.03, 1.83)	0.169
Chronic glomerulonephritis	0.47	(0.16, 1.40)	0.176
Membranous nephropathy	0.57	(0.12, 2.70)	0.477

Hazard ratios <1 indicate better outcomes for rapid discontinuation of prednisone.

FSGF, focal segmental glomerulosclerosis; IgA, immunoglobulin A; lupus, systemic lupus erythematosus; HR, hazard ratio; CI, confidence interval.

the percentage among adult, first transplant recipients.

Discussion

When first introduced, RDP was shown to have similar short-term patient and graft survival rates, as compared with maintenance prednisone; however, concern remained that RDP would be associated with increased rates of *late* deterioration of kidney graft function and graft loss. But to date, *no study, review, or meta-analysis* has reported decreased rates of long-term patient and/or graft survival with RDP [9–23]. Two prospective randomized studies comparing RDP with maintenance prednisone found no significant difference in patient survival, graft survival, or renal function at 5 years post-transplant. [15,22] In a single-center analysis of 1st and 2nd transplant recipients, we found no difference in 15-year patient or graft survival between those on RDP and those on maintenance prednisone [27]. In a subanalysis of that study, we compared recipients with *at least 5-year graft survival* on RDP (n = 859) versus maintenance prednisone (n = 317) and found no difference between groups in patient or graft survival between 5 and 15 years post-transplant. In our current analysis of SRTR data, we found that—although effect sizes were small—*overall*, for 1st DD and 1st LD transplant recipients, RDP (vs. maintenance prednisone) was associated with better patient survival, better graft survival, and similar death-censored graft survival rates (Fig. 1).

Most early studies of RDP were limited to low-risk recipients [15,18–23], and many transplant centers have hesitated to use RDP for recipients known to have an increased risk of rejection or of disease recurrence. Because each center has a small number of recipients in each of those increased risk subgroups, single-center studies provide limited information. Analyses, to date, suggest that in those higher-risk subgroups, RDP did not decrease patient or graft survival rates [28–41].

African American recipients

African American kidney transplant recipients have higher rates of acute rejection and lower rates of graft survival, as compared with Caucasian recipients [42]. Many reasons have been proposed for this disparity, which is likely multifactorial, including worse HLA matching, the presence of polymorphisms associated with more rapid metabolism of immunosuppressive drugs, as well as lower income and reduced access to care [42]. Studies of *late* prednisone withdrawal in African Americans have shown a marked, statistically significant increase in acute rejection episodes [7].

Taber *et al.*, [28] using Organ Procurement and Transplantation Network (OPTN) data from 2000 through 2009, compared the impact of RDP versus maintenance prednisone in African Americans (n = 26 582). They found that RDP was associated with a better patient survival rate and equivalent graft survival rate. However, in their subgroup analyses, they found an increased rate of graft loss and increased mortality in four RDP-treated African American subgroups: those who did *not* undergo cytolytic induction, those *not* on tacrolimus, those *not* on mycophenolate, and those with delayed graft function.

Highly sensitized recipients

Sureshkumar *et al.*, [29] using OPTN data from 2000 through 2008, grouped DD kidney recipients (n = 42 851) by peak PRA levels and analyzed the impact of RDP (vs. maintenance prednisone), adjusting

for confounding variables. For those with peak PRA levels >60%, RDP (vs. maintenance prednisone) was associated with similar patient and graft survival rates, but with a lower death-censored graft survival rate.

Pediatric recipients

In single-center studies of pediatric kidney transplant recipients, RDP has been shown to decrease prednisone-related side effects and to improve the cardiovascular risk profile. Similar to adult studies, pediatric studies have found that RDP and maintenance prednisone were associated with equivalent patient and graft survival rates. However, in contrast to adult studies, pediatric studies have not found any association between RDP and increased rates of acute rejection [30–32]. Moreover, in a single-center study, Chavers *et al.* [33] reported that RDP was not associated with an increased risk of graft loss to disease recurrence. Additionally, two recent multicenter prospective randomized studies, as well as two recent reviews and meta-analyses—all involving pediatric recipients—found no difference in patient and graft survival rates in RDP versus maintenance prednisone recipients [31,32,34,35].

Recipients with an increased risk of disease recurrence

Four large registry analyses—2 using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry (1988 through 2007; and 1985 through 2014) and 2 using OPTN data (1990 through 2003; and 2000 through 2014)—showed that recipients with IgA nephropathy had equivalent patient and death-censored graft survival rates with RDP versus maintenance prednisone [36–39]. However, RDP recipients had increased risks of IgA nephropathy recurrence and of graft loss to recurrence. We know of no registry reports showing an association between RDP and an increased risk of recurrence of other glomerular diseases. Clayton *et al.*, [36] using the ANZDATA Registry, reported that RDP recipients had no increased risk of recurrence of FSGS, membranous nephropathy, or membranoproliferative glomerulonephritis. A more recent ANZDATA analysis with a median follow-up time of 8.6 years produced similar findings [37].

Our current analyses of SRTR data, with substantially more recipients in each subgroup and with longer follow-up, support the above observations. For each of our subgroups, with the exception of 2nd DD transplant recipients, recipients treated with RDP protocols did as well or better as those maintained on long-term prednisone. In our subgroup analyses of 1st DD transplant recipients, we found that RDP was associated with a better *patient survival rate* for adult African Americans, for adults with a primary disease that can recur, and for pediatric recipients. For 1st LD transplant recipients, we found no significant difference in patient survival for RDP versus maintenance prednisone recipients. *Graft survival* was better for 1st transplant RDP-treated African American LD recipients; however, in all other 1st transplant LD or DD subgroups studied, we found no significant difference between RDP versus maintenance prednisone in graft or death-censored graft survival. In the subgroup of recipients with IgA nephropathy, we found (as did the above investigators) that RDP was associated with an increased risk of graft loss to disease recurrence (but *not* with a significant increased risk of graft loss overall). Similar to the ANZDATA analyses, we found that with RDP there was no increase in graft loss to disease recurrence in other potentially recurrent diseases (Table 4).

Importantly, for most of these increased risk subgroups, our data suggest that the major benefit of RDP (compared with maintenance prednisone) is improved patient survival with little difference in death-censored graft survival, consistent with other investigators' observations that RDP protocols were associated with a better cardiovascular risk profile [9–14,43].

Other investigators have looked at recipients in other at-risk groups—delayed graft function; expanded-criteria DD recipients—and similarly found no significant differences in outcome with RDP versus maintenance prednisone [40,41].

Retransplant recipients

We know of no previous registry studies of RDP in retransplant recipients. In our registry analyses, we found that for 2nd DD and LD recipients, RDP and maintenance prednisone were associated with similar patient and graft survival rates. However, for 2nd DD recipients (but not for 2nd LD recipients), RDP was associated with worse death-censored graft survival.

Induction immunosuppression

Rapid discontinuation of prednisone use raises two questions regarding induction. First, is RDP successful regardless of induction? Our analyses, although limited by small numbers in some subgroups, suggest that RDP can be used with any induction protocol without decreasing graft survival. Second, is there a best

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Table 5. Adjusted hazard ratios and 95% confidence intervals comparing rapid discontinuation of prednisone to maintenance prednisone at discharge for (a) overall patient survival, (b) graft survival, and (c) death-censored graft survival by induction regimen among different subgroups of deceased donor recipients and living donor recipients

Subpopulation	Induction	HR	95% CI	*P*	Composite *P*
(a) Overall patient survival					
Deceased donor recipients					
Adult first Tx	Thymoglobulin	0.85	(0.80, 0.91)	<0.001	0.028
	IL-2 inhibitors	1.00	(0.90, 1.11)	0.957	
	Campath	0.89	(0.78, 1.02)	0.087	
	None	0.98	(0.88, 1.09)	0.704	
High-risk adult first Tx	Thymoglobulin	0.87	(0.78, 0.96)	0.006	0.484
	IL-2 inhibitors	0.96	(0.79, 1.16)	0.667	
	Campath	0.93	(0.77, 1.12)	0.434	
	None	0.99	(0.85, 1.16)	0.922	
Pediatric first Tx	Thymoglobulin	0.37	(0.14, 0.99)	0.048	0.746
	IL-2 inhibitors	0.64	(0.25, 1.70)	0.374	
	Campath	NA	NA	NA	
	None	0.85	(0.24, 3.02)	0.805	
Adult second Tx	Thymoglobulin	0.92	(0.74, 1.14)	0.452	0.400
	IL-2 inhibitors	1.25	(0.81, 1.92)	0.319	
	Campath	0.75	(0.51, 1.11)	0.148	
	None	0.92	(0.62, 1.35)	0.665	
Living donor recipients					
Adult first Tx	Thymoglobulin	0.88	(0.79, 0.98)	0.018	0.566
	IL-2 inhibitors	0.80	(0.69, 0.92)	0.002	
	Campath	0.92	(0.72, 1.18)	0.518	
	None	0.91	(0.78, 1.06)	0.215	
High-risk adult first Tx	Thymoglobulin	1.05	(0.87, 1.26)	0.631	0.352
	IL-2 inhibitors	0.84	(0.63, 1.12)	0.242	
	Campath	0.82	(0.54, 1.26)	0.369	
	None	0.80	(0.59, 1.09)	0.163	
Pediatric first Tx	Thymoglobulin	0.59	(0.19, 1.78)	0.346	0.982
	IL-2 inhibitors	0.48	(0.18, 1.30)	0.149	
	Campath	0.00	NA	NA	
	None	0.35	(0.04, 3.04)	0.343	
Adult second Tx	Thymoglobulin	0.97	(0.67, 1.41)	0.881	0.898
	IL-2 inhibitors	0.89	(0.45, 1.78)	0.750	
	Campath	0.76	(0.41, 1.41)	0.379	
	None	1.04	(0.52, 2.08)	0.918	
(b) Graft survival					
Deceased donor recipients					
Adult first Tx	Thymoglobulin	0.89	(0.84, 0.93)	<0.001	<0.001
	IL-2 inhibitors	1.07	(0.98, 1.16)	0.119	
	Campath	0.89	(0.81, 0.97)	0.012	
	None	1.07	(0.99, 1.16)	0.074	
High-risk adult first Tx	Thymoglobulin	0.90	(0.84, 0.97)	0.006	0.062
	IL-2 inhibitors	1.03	(0.90, 1.17)	0.670	
	Campath	0.92	(0.81, 1.04)	0.190	
	None	1.06	(0.95, 1.18)	0.321	
Pediatric first Tx	Thymoglobulin	0.99	(0.78, 1.26)	0.938	0.040
	IL-2 inhibitors	0.91	(0.69, 1.20)	0.503	
	Campath	0.35	(0.17, 0.75)	0.006	
	None	0.67	(0.44, 1.02)	0.063	
Adult second Tx	Thymoglobulin	1.13	(0.98, 1.30)	0.083	0.544
	IL-2 inhibitors	1.28	(0.92, 1.80)	0.145	
	Campath	1.09	(0.84, 1.40)	0.514	
	None	0.96	(0.74, 1.24)	0.730	

Table 5. Continued.

Subpopulation	Induction	HR	95% CI	*P*	Composite *P*
Living donor recipients					
Adult first Tx	Thymoglobulin	0.92	(0.85, 0.99)	0.031	0.244
	IL-2 inhibitors	0.88	(0.79, 0.98)	0.015	
	Campath	0.85	(0.72, 1.00)	0.053	
	None	1.00	(0.90, 1.12)	0.937	
High-risk adult first Tx	Thymoglobulin	0.97	(0.86, 1.09)	0.640	0.110
	IL-2 inhibitors	0.88	(0.74, 1.06)	0.177	
	Campath	0.80	(0.63, 1.02)	0.069	
	None	1.12	(0.94, 1.33)	0.214	
Pediatric first Tx	Thymoglobulin	0.85	(0.59, 1.22)	0.376	0.993
	IL-2 inhibitors	0.90	(0.65, 1.23)	0.500	
	Campath	0.98	(0.22, 4.29)	0.979	
	None	0.91	(0.55, 1.49)	0.700	
Adult second Tx	Thymoglobulin	1.10	(0.86, 1.41)	0.433	0.443
	IL-2 inhibitors	0.75	(0.43, 1.29)	0.294	
	Campath	1.05	(0.69, 1.60)	0.829	
	None	1.34	(0.84, 2.15)	0.219	
(c) Death-censored graft survival					
Deceased donor recipients					
Adult first Tx	Thymoglobulin	0.89	(0.83, 0.96)	0.002	<0.001
	IL-2 inhibitors	1.11	(0.99, 1.25)	0.074	
	Campath	0.90	(0.80, 1.02)	0.109	
	None	1.14	(1.03, 1.27)	0.013	
High-risk adult first Tx	Thymoglobulin	0.89	(0.81, 0.97)	0.012	0.056
	IL-2 inhibitors	1.04	(0.88, 1.23)	0.669	
	Campath	0.96	(0.82, 1.12)	0.59	
	None	1.10	(0.96, 1.26)	0.182	
Pediatric first Tx	Thymoglobulin	1.04	(0.81, 1.33)	0.758	0.015
	IL-2 inhibitors	0.90	(0.67, 1.20)	0.478	
	Campath	0.33	(0.15, 0.70)	0.004	
	None	0.64	(0.41, 0.99)	0.045	
Adult second Tx	Thymoglobulin	1.26	(1.06, 1.50)	0.008	0.423
	IL-2 inhibitors	1.13	(0.71, 1.82)	0.600	
	Campath	1.45	(1.05, 2.00)	0.023	
	None	1.01	(0.74, 1.38)	0.952	
Living donor recipients					
Adult first Tx	Thymoglobulin	0.94	(0.85, 1.04)	0.225	0.180
	IL-2 inhibitors	0.96	(0.83, 1.10)	0.547	
	Campath	0.83	(0.68, 1.02)	0.084	
	None	1.09	(0.94, 1.25)	0.267	
High-risk adult first Tx	Thymoglobulin	0.95	(0.83, 1.10)	0.503	0.044
	IL-2 inhibitors	0.90	(0.73, 1.12)	0.354	
	Campath	0.84	(0.64, 1.11)	0.216	
	None	1.26	(1.03, 1.54)	0.023	
Pediatric first Tx	Thymoglobulin	0.86	(0.59, 1.25)	0.438	0.979
	IL-2 inhibitors	0.96	(0.69, 1.33)	0.799	
	Campath	0.90	(0.20, 4.00)	0.895	
	None	0.94	(0.57, 1.57)	0.822	
Adult second Tx	Thymoglobulin	1.14	(0.84, 1.55)	0.392	0.687
	IL-2 inhibitors	0.76	(0.35, 1.65)	0.488	
	Campath	1.31	(0.76, 2.26)	0.332	
	None	1.30	(0.69, 2.44)	0.424	

Hazard ratios <1 indicate better outcomes for rapid discontinuation of prednisone. Composite *P* tests whether or not the effect of RDP protocols was significantly different among the induction regimens. High-risk recipients include those who are African American, highly sensitized, or have possibly recurrent disease.

Tx, transplant; HR, hazard ratio; CI, confidence interval.

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Table 6. Adjusted hazard ratios and 95% confidence intervals comparing induction regimens within participants undergoing rapid discontinuation of prednisone protocols for (a) overall patient survival, (b) graft survival, and (c) death-censored graft survival among different subgroups of deceased donor recipients and living donor recipients

Subpopulation	Induction	HR	95% CI	*P*	Composite *P*
(a) Overall patient survival					
Deceased donor recipients					
Adult first Tx	Thymoglobulin (reference)	1.00	–	–	0.090
	IL-2 inhibitors	1.13	(1.01, 1.26)	0.040	
	Campath	1.09	(0.99, 1.20)	0.086	
	None	1.11	(0.99, 1.24)	0.082	
High-risk adult first Tx	Thymoglobulin (reference)	1.00	–	–	0.697
	IL-2 inhibitors	1.07	(0.88, 1.31)	0.508	
	Campath	1.07	(0.93, 1.24)	0.352	
	None	1.09	(0.91, 1.30)	0.340	
Pediatric first Tx	Thymoglobulin (reference)	1.00	–	–	0.879
	IL-2 inhibitors	1.26	(0.35, 4.55)	0.720	
	Campath	1.10	(0.12, 9.73)	0.932	
	None	1.84	(0.42, 8.09)	0.417	
Adult second Tx	Thymoglobulin (reference)	1.00	–	–	0.670
	IL-2	1.27	(0.80, 2.01)	0.314	
	Campath	0.93	(0.65, 1.32)	0.674	
	None	0.96	(0.63, 1.46)	0.845	
Living donor recipients					
Adult first Tx	Thymoglobulin (reference)	1.00	–	–	0.442
	IL-2 inhibitors	0.89	(0.76, 1.04)	0.153	
	Campath	1.01	(0.88, 1.17)	0.885	
	None	1.01	(0.86, 1.20)	0.888	
High-risk adult first Tx	Thymoglobulin (reference)	1.00	–	–	0.329
	IL-2 inhibitors	0.87	(0.64, 1.20)	0.402	
	Campath	0.80	(0.62, 1.04)	0.100	
	None	0.81	(0.58, 1.13)	0.208	
Pediatric first Tx	Thymoglobulin (reference)	1.00	–	–	0.899
	IL-2 inhibitors	1.21	(0.33, 4.46)	0.774	
	Campath	1.67	(0.33, 8.36)	0.534	
	None	0.70	(0.07, 6.75)	0.760	
Adult second Tx	Thymoglobulin (reference)	1.00	–	–	0.827
	IL-2 inhibitors	0.97	(0.46, 2.06)	0.939	
	Campath	0.79	(0.45, 1.40)	0.419	
	None	1.09	(0.51, 2.33)	0.826	
(b) Graft survival					
Deceased donor recipients					
Adult first Tx	Thymoglobulin (reference)	1.00	–	–	<0.001
	IL-2 inhibitors	1.19	(1.09, 1.30)	<0.001	
	Campath	1.13	(1.05, 1.22)	0.001	
	None	1.19	(1.09, 1.30)	<0.001	
High-risk adult first Tx	Thymoglobulin (reference)	1.00	–	–	0.023
	IL-2 inhibitors	1.14	(0.99, 1.31)	0.066	
	Campath	1.12	(1.02, 1.24)	0.024	
	None	1.17	(1.04, 1.32)	0.011	
Pediatric first Tx	Thymoglobulin (reference)	1.00	–	–	0.204
	IL-2 inhibitors	0.84	(0.61, 1.17)	0.311	
	Campath	0.64	(0.35, 1.15)	0.133	
	None	0.68	(0.43, 1.06)	0.090	
Adult second Tx	Thymoglobulin (reference)	1.00	–	–	0.664
	IL-2	1.06	(0.75, 1.50)	0.741	
	Campath	0.97	(0.77, 1.21)	0.760	
	None	0.85	(0.64, 1.12)	0.257	

Table 6. Continued.

Subpopulation	Induction	HR	95% CI	*P*	Composite *P*
Living donor recipients					
Adult first Tx	Thymoglobulin (reference)	1.00	–	–	0.270
	IL-2 inhibitors	0.98	(0.87, 1.10)	0.746	
	Campath	1.06	(0.95, 1.17)	0.283	
	None	1.10	(0.98, 1.24)	0.114	
High-risk adult first Tx	Thymoglobulin (reference)	1.00	–	–	0.487
	IL-2 inhibitors	0.99	(0.82, 1.20)	0.923	
	Campath	1.03	(0.88, 1.21)	0.680	
	None	1.15	(0.95, 1.39)	0.140	
Pediatric first Tx	Thymoglobulin (reference)	1.00	–	–	0.941
	IL-2 inhibitors	1.11	(0.74, 1.66)	0.626	
	Campath	1.14	(0.67, 1.93)	0.629	
	None	1.13	(0.65, 1.96)	0.656	
Adult second Tx	Thymoglobulin (reference)	1.00	–	–	0.36
	IL-2 inhibitors	0.70	(0.39, 1.25)	0.228	
	Campath	0.86	(0.60, 1.25)	0.429	
	None	1.24	(0.75, 2.05)	0.412	
(c) Death-censored graft survival					
Deceased donor recipients					
Adult first Tx	Thymoglobulin (reference)	1.00	–	–	<0.001
	IL-2 inhibitors	1.25	(1.10, 1.42)	0.001	
	Campath	1.20	(1.09, 1.33)	<0.001	
	None	1.27	(1.13, 1.43)	<0.001	
High-risk adult first Tx	Thymoglobulin (reference)	1.00	–	–	0.003
	IL-2 inhibitors	1.19	(0.99, 1.43)	0.057	
	Campath	1.22	(1.07, 1.38)	0.003	
	None	1.27	(1.09, 1.48)	0.002	
Pediatric first Tx	Thymoglobulin (reference)	1.00	–	–	0.128
	IL-2 inhibitors	0.81	(0.58, 1.13)	0.214	
	Campath	0.61	(0.33, 1.12)	0.110	
	None	0.64	(0.41, 1.01)	0.058	
Adult second Tx	Thymoglobulin (reference)	1.00	–	–	0.669
	IL-2	0.83	(0.51, 1.34)	0.437	
	Campath	1.01	(0.78, 1.32)	0.927	
	None	0.85	(0.61, 1.19)	0.343	
Living donor recipients					
Adult first Tx	Thymoglobulin (reference)	1.00	–	–	0.248
	IL-2 inhibitors	1.03	(0.88, 1.20)	0.742	
	Campath	1.11	(0.97, 1.27)	0.120	
	None	1.14	(0.98, 1.34)	0.096	
High-risk adult first Tx	Thymoglobulin (reference)	1.00	–	–	0.100
	IL-2 inhibitors	1.00	(0.79, 1.27)	0.986	
	Campath	1.14	(0.95, 1.37)	0.154	
	None	1.29	(1.03, 1.61)	0.024	
Pediatric first Tx	Thymoglobulin (reference)	1.00	–	–	0.933
	IL-2 inhibitors	1.12	(0.74, 1.70)	0.597	
	Campath	1.10	(0.63, 1.90)	0.739	
	None	1.17	(0.67, 2.05)	0.583	
Adult second Tx	Thymoglobulin (reference)	1.00	–	–	0.774
	IL-2 inhibitors	0.67	(0.30, 1.50)	0.335	
	Campath	1.00	(0.63, 1.57)	0.989	
	None	1.09	(0.56, 2.14)	0.794	

Thymoglobulin is the reference induction regimen for all analysis. Hazard ratios <1 indicate better outcomes for the given induction regimen compared to thymoglobulin. Composite *P* tests whether or not the effect of any induction regimen differed from the others. High-risk recipients include those who are African American, highly sensitized, or have possibly recurrent disease.

Tx, transplant; HR, hazard ratio; CI, confidence interval.

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Table 7. Percentage of recipients undergoing RDP who remained prednisone free for maintenance immunosuppression during the first 6 months post-transplant (a subject was not considered prednisone free if he/she was either prescribed prednisone for maintenance immunosuppression at 6 months or receiving maintenance prednisone during the reporting period between discharge and 6 months post-transplant)

Subpopulation	Deceased donor (%)	Living donor (%)
Adult first Tx	81.1	83.7
Adult African American first Tx	77.8	80.4
Highly sensitized adult first Tx	74.1	77.4
Adult w/possible recurrent Dz, first Tx	79.4	81.2
Pediatric first Tx	83.3	85.9
Adult second Tx	63.6	64.6

The table includes those with graft survival and follow-up longer than 6 months and immunosuppression data available at 6 months post-transplant.

Dz, disease; Tx, transplant.

approach to induction when RDP is used? We found that, in subgroups showing differences, thymoglobulin induction provided the best outcome; no induction, the worst.

We did an "intention-to-treat analysis" of kidney transplant recipients discharged from the hospital on RDP and did not further subdivide our recipients by whether or not they restarted prednisone. This was done to mimic the analysis of the corresponding target randomized trial [44]. Schold *et al.*, [45] using SRTR data from 2002 through 2008 to study RDP, noted: (i) Recipients who received depleting antibodies for induction, followed by tacrolimus and MMF for maintenance, were significantly *less likely* to restart prednisone; (ii) the proportion of recipients who restarted prednisone decreased from 47% in 2002 to 16% in 2008; and (iii) transplant centers that used RDP in most of their recipients were less likely to have them restart prednisone, as compared with centers that limited RDP use. In our current analysis, including high-risk groups, 81% remained prednisone free at 6 months.

Our analyses have several limitations. First, although this study of RDP protocols has the longest follow-up of any reported in the literature (maximum follow-up in this study was 16.2 years), the majority of subjects had less than 5-year follow-up. A longer follow-up time may show a difference between RDP and maintenance prednisone. Second, as noted above, more recent recipients were more likely to have been treated with RDP, thus potentially the effect of RDP may be confounded by era. However, transplant date was adjusted for in the analyses. Third, we adjusted for many potential confounders in the outcome models. It is possible that some confounders are not properly adjusted for in the analysis or that some confounders are not captured in the SRTR registry data. Importantly, a propensity-score matching analysis produced very similar estimates of the effect of RDP (see Supporting Information). Taken together, the data strongly suggest that prednisone-free maintenance immunosuppression should be considered for patients in these potentially higher-risk subgroups.

Although we grouped all RDP recipients, a number of previous studies have clearly shown that both induction and maintenance protocols affect RDP outcomes [13,14]. Over time, a larger proportion of RDP recipients have been treated with induction as well as with tacrolimus and mycophenolate. Future studies could focus on recipients treated with these protocols. Fourth, recipients' maintenance immunosuppression at discharge may have been misclassified. In particular, recipients who were given prednisone for a short, fixed duration after transplant (e.g., 7 days), may have been discharged from the hospital before prednisone was discontinued and, therefore, misclassified as on maintenance prednisone. However, we found more than 94% recipients in the maintenance prednisone group had prednisone as part of their maintenance immunosuppression protocol at 6 months post-transplant suggesting the overwhelming proportion of recipients in the maintenance prednisone group were correctly classified. Finally, we considered numerous statistical analyses and did not correct for multiple significance tests.

It is intuitive that recipients who receive no prednisone or who have their prednisone discontinued in the first post-transplant week will have fewer prednisone-related complications. And numerous studies have reported fewer prednisone-related complications in recipients treated with RDP protocols [9–16]. However, early studies reporting significantly fewer prednisone-related complications with RDP compared it with contemporary or historical cohorts treated with relatively large maintenance prednisone doses. Today, most centers using maintenance prednisone use much lower doses. No large studies, to our knowledge, have compared RDP with low-dose maintenance prednisone, whose side effects might be less striking. Nonetheless, even low-dose prednisone has been associated with loss

of bone mineral density and with an increased rate of fractures [46,47].

To date, there is not a one-size-fits-all immunosuppressive protocol. RDP protocols, when used in low-risk recipients, have been associated with minimization of prednisone-related side effects *without decreasing* short- or long-term patient or graft survival. Our current analyses, using SRTR data, suggest that RDP can similarly be successful in some groups thought to be at increased risk for rejection or recurrent disease. Additional studies are necessary in other potentially high-risk subgroups.

Authorship

David Vock designed and performed the research/study, collected and analyzed the data, and wrote the paper. Arthur Matas designed and performed the research/study, analyzed the data, and wrote the paper.

Conflicts of interest

The authors have declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Adjusted overall patient survival curves for RDP and MP after discharge.

Figure S2. Adjusted graft survival curves for RDP and MP after discharge.

Figure S3. Adjusted death censored graft survival curves for RDP and MP after discharge.

Table S1. Clinical and demographic information among recipients (a) and donors (b) included in the propensity-matched cohort.

Table S2. Estimated hazard ratios from a propensity-score matched cohort comparing rapid discontinuation of prednisone to maintenance prednisone at discharge

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