Induction Therapies in Live Donor Kidney Transplantation on Tacrolimus and Mycophenolate With or Without Steroid Maintenance

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Abstract

Background and objectives Induction therapy with IL-2 receptor antagonist (IL2-RA) is recommended as a first line agent in living donor renal transplantation (LRT). However, use of IL2-RA remains controversial in LRT with tacrolimus (TAC)/mycophenolic acid (MPA) with or without steroids.

Design, setting, participants, & measurements The Organ Procurement and Transplantation Network registry was studied for patients receiving LRT from 2000 to 2012 maintained on TAC/MPA at discharge (n=36,153) to compare effectiveness of IL2-RA to other induction options. The cohort was initially divided into two groups based on use of maintenance steroid at time of hospital discharge: steroid (n=25,996) versus no-steroid (n=10,157). Each group was further stratified into three categories according to commonly used antibody induction approach: IL2-RA, rabbit anti-thymocyte globulin (r-ATG), and no-induction in the steroid group versus IL2-RA, r-ATG and alemtuzumab in the no-steroid group. The main outcomes were the risk of acute rejection at 1 year and overall allograft failure (graft failure or death) post-transplantation through the end of follow-up. Propensity score-weighted regression analysis was used to minimize selection bias due to non-random assignment of induction therapies.

Results Multivariable logistic and Cox analysis adjusted for propensity score showed that outcomes in the steroid group were similar between no-induction (odds ratio [OR], 0.96; 95% confidence interval [95% CI], 0.86 to 1.08 for acute rejection; and hazard ratio [HR], 0.99; 95% CI, 0.90 to 1.08 for overall allograft failure) and IL2-RA categories. In the no-steroid group, odds of acute rejection with r-ATG (OR, 0.73; 95% CI, 0.59 to 0.90) and alemtuzumab (OR, 0.53; 95% CI, 0.42 to 0.67) were lower; however, overall allograft failure risk was higher with alemtuzumab (HR, 1.27; 95% CI, 1.03 to 1.56) but not with r-ATG (HR, 1.19; 95% CI, 0.97 to 1.45), compared with IL2-RA induction.

Conclusions Compared with no-induction therapy, IL2-RA induction was not associated with better outcomes when TAC/MPA/steroids were used in LRT recipients. r-ATG appears to be an acceptable and possibly the preferred induction alternative for IL2-RA in steroid-avoidance protocols.

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Introduction

The ultimate goal of immunosuppression in kidney transplantation is to prevent acute rejection and maintain allograft function without causing adverse effects. Immunosuppressive agents are categorized as (*1*) induction therapy that is administered in the perioperative period and (2) maintenance therapy that transplant recipients require for lifelong use (1). However, optimal combinations of therapies remain controversial and the decision is mostly made in the context of the risk and benefit for each individual donor/recipient pair (2).

The most commonly used maintenance immunosuppressive combination in renal transplantation consists of tacrolimus (TAC) and mycophenolic acid (MPA) with steroids and is based on two open-label randomized studies (3,4). These agents have been part of clinical practice since the late 1990s (the TAC/MPA combination represented >90% in 2011) (5). More recently, induction therapy followed by steroid-sparing maintenance regimens with TAC/MPA alone have gained favor across all donor-recipient profiles. Induction therapy options currently comprise lymphocyte-depleting antibodies, such as polyclonal rabbit anti-thymocyte globulin (r-ATG) and monoclonal humanized anti-CD52 antibody (alemtuzumab), and nondepleting mAbs, such as basiliximab and daclizumab (both abrogate T cell activation; Supplemental Material) (6). Lymphocyte-depleting antibodies appear to be increasingly favored over IL-2 receptor antagonists (IL2-RAs) in the United States (the depleting agents were used in 57% of recipients in 2011) (5).

Lymphocyte-depleting agents are mostly used in high immunologic risk factors for acute rejection and steroid-sparing protocols. IL2-RA and no-induction therapies are primarily utilized in patients with low immunologic risk (living related donor renal transplant) (6).

Prospective randomized multicenter studies and retrospective registry analysis demonstrate that no-induction therapy can achieve acceptable acute rejection rates (10%–20% at 1 year after transplant), with allograft and patient survival similar to other induction modalities in living donor renal transplantation (LRT) (7–10). However, the current Kidney Disease Improving Global Outcomes (KDIGO) Transplant Work Group guidelines recommend IL2-RA as a first-line induction agent in all types of donor-recipient profiles to reduce risk of acute rejection and allograft loss. These recommendations are mainly based on a meta-analysis that predominantly used cyclosporine-based maintenance immunosuppression (1,11). Nevertheless, use of IL2-RA remains controversial in LRT, partially because of the low risk of rejection in this population and the utilization of more potent maintenance immunosuppression combinations such as TAC/MPA with or without steroids. To explore the added benefit of IL2-RA induction therapy in LRT recipients maintained on TAC/MPA, we conducted a retrospective cohort analysis of the Organ Procurement and Transplantation Network (OPTN) registry to compare outcomes between IL2-RA and other induction options.

Materials and Methods

Design and Study Cohort

This study was a retrospective cohort analysis of the OPTN registry as of September 30, 2013, (the end of follow-up) that included all adults who received a LRT between January 1, 2000, and September 30, 2012, in the United States (n=76,266). Exclusion criteria were as follows: (*1*) pediatric patients aged <18 years; (*2*) multiorgan transplantations; (*3*) two or more previous kidney transplantations; (*4*) recipients of induction agents other than no-induction therapy, alemtuzumab, r-ATG, and IL2-RA; (*5*) patients with a positive cross-match; and (*6*) recipients of HLA zero mismatch (identical) kidneys. Data were further restricted to recipients whose maintenance immunosuppression at the time of hospital discharge was TAC and MPA. A total of 36,153 patients were included in the final analysis. The study population was initially divided into two groups based on the use of maintenance steroids at the time of hospital discharge (on-steroid [n=25,996] versus no-steroid [n=10,157] groups). Each group was further stratified into three categories according to commonly used antibody induction options: IL2-RA, r-ATG, and no-induction therapy in the steroid group versus IL2-RA, r-ATG, and alemtuzumab in the no-steroid group. The alemtuzumab category in the steroid cohort and the no-induction category in the no-steroid cohort were eliminated because of the small sample size.

Main Outcomes

The primary outcomes were incidence of acute rejection at 1 year (defined as biopsy-proven or clinically treated acute rejection) and overall allograft failure risk (graft failure or death) after transplantation (defined as return to dialysis, retransplant, or death with functioning allograft). Acute rejections were ascertained only up to 1 year after transplantation (available for all recipients), whereas overall allograft failures were included through the end of the follow-up period (September 30, 2013).

Statistical Analyses

Donor and recipient characteristics were described using frequencies or means±SDs. Comparisons between groups were made using the t test, Kruskal–Wallis test, or chi-squared test. Survival rates were estimated using the Kaplan–Meier product limit method. The log-rank test was used for comparison of the unadjusted survival curves. Logistic regression models were used to estimate the odds ratios of acute rejection. Cox regression models were used to estimate the hazard ratios associated with overall and death-censored allograft failure risk and patient mortality risk. P values < 0.05 were considered statistically significant. Statistical analyses were performed with SAS software (version 9.3; SAS Inc., Cary, NC).

Propensity Score Analyses

We controlled for potential selection bias due to nonrandom assignment of induction treatments using the propensity score (PS) method. PS is the probability that a patient would have been treated based on that patient's observed pretreatment variables. We utilized multinomial logistic regression to estimate the PS as the conditional probability of a patient receiving a certain induction treatment given pretreatment covariates including donor (age, sex, and race), recipient (age, sex, race, diabetes status, cardiovascular comorbidities, retransplant status, dialysis before transplant, and panel reactive antibodies [PRAs]), and transplant factors (donor/recipient weight ratio, HLA mismatch, and transplant year) (12). Several adjustment methods integrating the estimated PS have been suggested, including matching (13), regression adjustment (14), and weighting (12,15). In this analysis, we utilized the inverse probability of treatment weight (IPTW), in which the weights were calculated as the inverse of the PS (15). Finally, PS-weighted regression models were fitted to compare the treatment effects, controlling for selection bias.

Covariates were balanced after IPTW adjustment, that is, after performing weighted regression (with one of the covariates as outcome, induction categories as a predictor, and PS as weights), the effect of induction therapy was no longer significant. For instance, before IPTW adjustment, the variable "recipient diabetes" was significantly different among induction groups in both steroid categories (P<0.001). After adjustment, the P values for recipient diabetes were 0.77 and >0.99 in the steroid and no-steroid groups, respectively.

Results

Characteristics of the Study Cohort

Recipient, donor, and transplant characteristics for each induction category stratified by use of steroid at discharge are summarized in Tables 1 and 2, indicating clinically equitable risk factor stratification among induction categories. P values before IPTW adjustment are mostly statistically significant in Tables 1 and 2. However, all P values became statistically insignificant after IPTW adjustment, suggesting that the PS-weighting method successfully controlled for the imbalance among covariates. In the context

of steroids, compared with the no-induction and IL2-RA categories, the recipients of r-ATG were more likely to be black, were more likely to be sensitized (PRA>20%), and were more likely to have received higher HLA-mismatch (>3) kidneys. In the no-steroid group, IL2-RA induction was more likely to be used in recipients with a PRA< 20% and these patients were more likely to receive lower HLA-mismatch (<4) kidneys compared with the other two induction categories.

Outcomes

Median (25th, 75th percentiles) follow-up time was 4.3 (2.1, 7.1) and 3.8 (2.0, 5.8) years for the steroid and no-steroid groups, respectively. Observed frequencies of different components of the primary outcomes are shown in Figure 1. Acute rejection was the most common outcome across induction categories for both steroid groups. In the steroid group, the recipients who received no-induction and IL2-RA therapy had a slightly higher rate of acute rejection

Table 1. Characteristics of donor, recipient and transplant factors in steroid group (*n*=25,996)

Characteristic	Steroid Induction Categories			*P* Value	
	IL2-RA	r-ATG	No Induction	Before IPTW	After IPTW
No. (%)	9741 (37.5)	8552 (32.9)	7703 (29.6)		
Donors					
Age (yr)	41.4±11.4	41.1±11.4	40.6±11.2	<0.001	0.56
Women	61.0	60.3	59.8	0.26	0.74
Race				<0.001	0.84
White	68.2	71.1	66.8		
Black	12.2	15.7	13.8		
Hispanic	14.4	9.3	14.0		
Other	5.2	3.9	5.5		
Recipients					
Age (yr)	47.4±14.3	46.8±13.7	46.6±14.1	<0.001	0.53
Women	37.0	41.3	39.2	<0.001	0.91
Race				<0.001	0.60
White	65.8	67.3	64.6		
Black	13.8	18.4	15.6		
Hispanic	14.5	9.3	14.1		
Other	5.9	5.0	5.7		
Diabetes mellitus (yes)	28.4	27.8	31.6	<0.001	0.77
Cardiovascular disease (yes)	5.8	5.8	5.3	0.33	0.97
Retransplant	2.8	2.5	4.2	<0.001	0.96
Dialysis before transplant				<0.001	0.92
Preemptive	30.7	32.1	32.2		
<1 yr	29.4	28.5	28.0		
1–3 yr	28.6	27.2	29.3		
>3 yr	11.3	12.2	10.4		
Panel reactive antibody				<0.001	1.00
<20	43.9	34.5	51.0		
20–80	3.8	7.1	4.8		
>80	0.7	2.1	1.0		
Missing	51.5	56.3	43.2		
Transplant					
Weight ratio (donor/recipient)	1.02±0.30	1.02±0.31	1.02±0.31	0.39	0.87
HLA mismatch				<0.001	1.00
1	5.9	5.3	6.1		
2	18.3	16.7	20.2		
3	29.9	28.2	31.5		
4	16.2	17.5	15.3		
5	19.3	20.9	17.4		
6	10.6	11.5	9.6		
Transplant year				<0.001	1.00
2000–2001	11.2	3.5	20.1		
2002–2003	16.1	12.0	20.2		
2004–2005	12.5	15.7	20.0		
2006–2007	15.7	16.7	13.9		
2008–2009	18.2	20.0	12.9		
2010–2012	26.3	32.2	12.9		

Data are presented as means±SD or percentages unless otherwise indicated. IL2-RA, IL-2 receptor antagonist; r-ATG, rabbit antithymocyte globulin; IPTW, inverse probability of treatment weight.

Table 2. Characteristics of donor, recipient, and transplant factors in the no-steroid group (*n*=10,157)

Characteristic	No-Steroid Induction Categories			*P* Value	
	IL2-RA	r-ATG	Alemtuzumab	Before IPTW	After IPTW
No. (%)	1,483 (14.6)	4,905 (48.3)	3,769 (37.1)		
Donors					
Age (yr)	41.7±11.4	41.6±11.5	40.6±11.5	<0.001	0.80
Women	60.9	59.7	60.8	0.51	0.93
Race				<0.001	1.00
White	71.3	71.7	65.2		
Black	8.6	11.0	12.2		
Hispanic	13.8	12.2	19.5		
Other	6.3	5.0	3.0		
Recipients					
Age (yr)	50.7±15.1	48.5±13.7	48.4±13.4	<0.001	0.36
Women	35.8	36.5	36.6	0.86	0.97
Race				<0.001	1.00
White	70.1	69.5	61.6		
Black	9.3	12.5	13.9		
Hispanic	13.8	12.3	20.2		
Other	6.8	5.7	4.5		
Diabetes mellitus (yes)	33.0	31.3	36.7	<0.001	0.97
Cardiovascular disease (yes)	5.4	7.1	4.1	<0.001	0.81
Retransplant	2.0	2.5	1.9	<0.001	0.97
Dialysis before transplant				<0.001	1.00
Preemptive	35.4	37.5	32.9		
<1 yr	26.6	28.7	29.6		
1–3 yr	29.1	24.3	27.2		
>3 yr	8.9	9.4	10.3		
Panel reactive antibody				<0.001	0.62
<20	45.6	39.1	36.2		
20–80	3.8	2.9	3.6		
>80	0.2	0.7	0.64		
Missing	50.4	57.3	59.5		
Transplant					
Weight ratio (donor/recipient)	1.01±0.33	1.00±0.31	0.99±0.30	0.02	0.89
HLA mismatch				<0.001	1.00
1	6.9	4.9	5.3		
2	21.2	16.3	17.3		
3	29.9	28.7	28.2		
4	14.0	17.2	17.3		
5	18.0	21.5	20.3		
6	9.9	11.4	11.6		
Transplant year				<0.001	0.73
2000–2001	6.5	0.1	0.0		
2002–2003	5.5	3.7	2.1		
2004–2005	17.7	15.0	10.7		
2006–2007	20.6	22.6	17.8		
2008–2009	20.8	26.2	25.2		
2010–2012	28.9	32.3	44.2		

Data are presented as means±SD or percentages unless otherwise indicated. IL2-RA, IL-2 receptor antagonist; r-ATG, rabbit antithymocyte globulin; IPTW, inverse probability of treatment weight.

at 1 year after transplantation compared with r-ATG. In the no-steroid group, acute rejection rates at 1 year were lower with r-ATG and alemtuzumab than those observed with IL2-RA. During the study period, the risks for acute rejection and graft failure steadily declined (Supplemental Figures 1 and 2). Causes of death and allograft failures are summarized in Supplemental Tables 1 and 2. Acute and chronic rejections were the most common cause of allograft failure in the IL2-RA category for both steroid groups. The cause of death was not specified in one half of the recipients. Malignancy accounted for approximately 20% of mortalities in the r-ATG arm.

Acute Rejection Risk at 12 Months

Table 3 displays the results of PS-weighted and covariate-adjusted multivariable logistic regression models for acute rejection risks. Among the patients receiving steroids at discharge, the relative risk (RR) of acute rejection was significantly lower in the r-ATG category compared with IL2-RA,

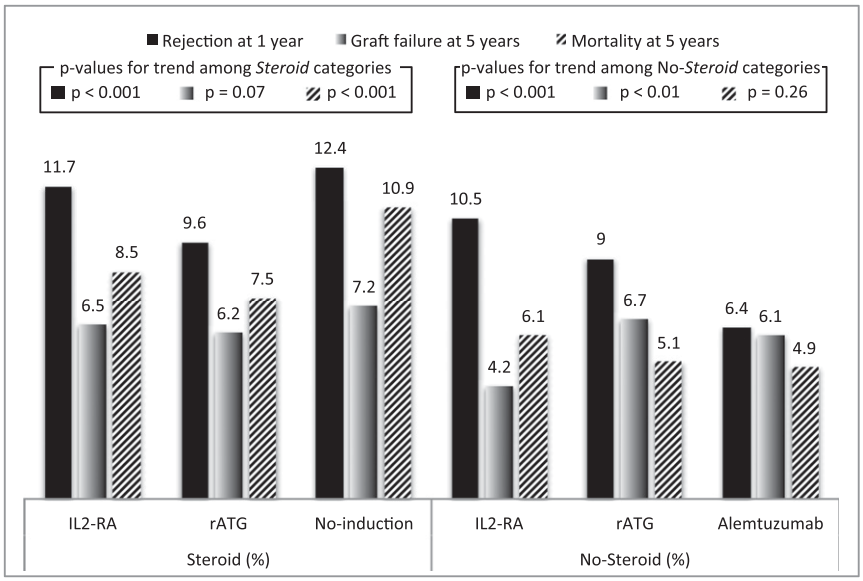

Figure 1. | Observed frequencies of outcomes by induction type, with or without steroids at discharge. IL2-RA, IL-2 receptor antagonist; r-ATG, rabbit anti-thymocyte globulin.

whereas there was no significant difference between the no-induction and IL2-RA categories. In the no-steroid group, the adjusted risk of acute rejection in patients induced with r-ATG and alemtuzumab was lower compared with those induced with IL2-RA.

Overall Allograft Failure

Unweighted Kaplan–Meier curves for overall graft survival are given in Figures 2 and 3. The survival curves did not differ across induction therapies in the steroid group, but they were significantly different in the no-steroid group. Table 4 shows the PS-weighted and covariate-adjusted multivariable Cox models for overall allograft failure. In the context of steroids, the hazard ratios for overall graft failure were not significantly different between the r-ATG and no-antibody induction categories compared with the IL2-RA category. When steroids were absent, overall allograft failure risk was statistically significantly higher with alemtuzumab but not with r-ATG compared with IL2-RA.

Discussion

In LRT, the incidence of acute rejection at 1 year decreased over the observed period of the study (2000–2012) and stayed below 15%. Short-term graft survival steadily improved at a comparable level among all induction categories including no-induction therapy over the past decade. These findings raise the following important issues: (*1*) clinical utility of induction therapy in LRT in the setting of TAC/MPA maintenance immunosuppression (9,16), and (*2*) improved outcomes that may be accounted for by other factors, such as sensitive HLA antibody detection (17–19), more sensitive cross-match techniques (20,21), implementation of virtual cross-match in 2006 (22,23), and utilization of a calculated PRA system in 2009 into a routine allocation system (19). A large sample size (a patient population ranging from 1600 to 7000) needed to detect small differences in observed outcomes among induction types is most likely prohibitive to prospective randomized trials (10). In the current literature, there are a limited number of randomized studies to compare the effectiveness of induction modalities in the setting of TAC/MPA maintenance immunosuppression, and LRT recipients are also significantly under-represented in those clinical trials. Moreover, comparison of sensitized patients using lymphocyte-depleting agents with nonsensitized patients more frequently using either no-induction or IL2-RA therapies is challenging unless advanced statistical adjustments for selection bias or stratification for immunologic risk groups are performed.

Our study constitutes the largest analysis of the OPTN registry on main outcomes in LRT recipients maintained on TAC/MPA with or without steroids since 2000. It challenges the concept of routine use of IL2-RA induction agent in all kidney transplant recipients (deceased and living), which is suggested by the KDIGO guidelines. Below, we review current recommendations and compare our findings against moderate- to high-quality evidence in the literature.

Steroid Maintenance

The KDIGO guidelines recommend induction therapy (a biologic agent, either a lymphocyte-depleting agent or IL2-RA, at the time of transplant) in all kidney transplant recipients (1A equals high-quality evidence) and IL2-RA as the first-line agent (1B equals moderate-quality evidence). However, supportive evidence in the current literature since the guidelines were published is unclear, mostly because of heterogeneity in the recipient's immunologic risks and difference in maintenance immunosuppressive agents (choice of calcineurin inhibitors and antiproliferative agents).

A large meta-analysis (32 studies, n=5854), mainly including cyclosporine-based maintenance immunosuppression (30 of 32), compared IL2-RA induction to placebo (no induction). The authors demonstrated that biopsy-proven acute rejection was reduced by 28% (RR, 0.72; 95% confidence

Table 3. Comparison of the estimated association of induction treatments on acute rejection at 1 year using multivariable logistic regression models

Multivariable Model	Induction Type	OR (95% CI)	*P* Value
Steroid			
Logistic regression			
	IL-2 RA	1	
	r-ATG	0.80 (0.71 to 0.89)	<0.001
	No induction	1.04 (0.92 to 1.16)	0.55
PS-weighted logistic regression			
	IL-2 RA	1	
	r-ATG	0.78 (0.70 to 0.88)	<0.001
	No induction	0.96 (0.86 to 1.08)	0.48
No Steroid			
Logistic regression			
	IL-2 RA	1	
	r-ATG	0.72 (0.58 to 0.90)	0.004
	Alemtuzumab	0.52 (0.40 to 0.66)	<0.001
PS-weighted logistic regression			
	IL-2 RA	1	
	r-ATG	0.73 (0.59 to 0.90)	0.004
	Alemtuzumab	0.53 (0.42 to 0.67)	<0.001

Adjusted for donor factors (age, sex, and race), recipient factors (age, sex, race, cardiovascular morbidity, panel reactive antibody, retransplant status, and dialysis status) and transplant factors (donor/recipient weight ratio, HLA mismatch, and transplant year). PS, propensity score; IL2-RA, IL-2 receptor antagonist; r-ATG, rabbit anti-thymocyte globulin; OR, odds ratio; 95% CI, 95% confidence interval.

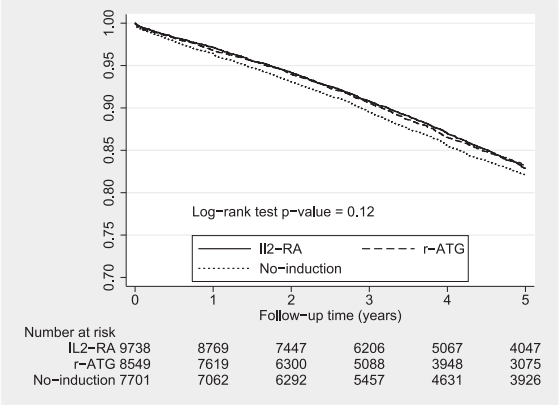

Figure 2. | Unweighted Kaplan–Meier survival estimates for induction types with steroid. IL2-RA, IL-2 receptor antagonist; r-ATG, rabbit anti-thymocyte globulin.

interval [95% CI], 0.64 to 0.81) and overall allograft failure was reduced by 25% (RR, 0.75; 95% CI, 0.62 to 0.90) (11,24). The rate of acute rejection at 1 year after transplant was 38% in the placebo/no-induction group and 27% in the IL2-RA arm. In a subgroup analysis, the outcomes were not different when use of cyclosporine and TAC maintenance regimens were compared. However, two pivotal large prospective studies reported significantly lower rates of biopsy-proven rejection at 1 year among kidney transplant recipients receiving IL2-RA induction and TAC/MPA maintenance (15.4% and 7.5%, respectively) (3,4). A registry analysis (n=26,686) compared IL2-RA induction use to no-induction therapy in primary LRT recipients discharged on TAC/MPA/prednisone maintenance (9). The incidence of rejection at 1 year was significantly different between groups (11.6% for IL2-RA versus 13% for no-induction therapy), but this did not translate into a graft or patient survival benefit.

In our study, based on the multivariable logistic and Cox regression analyses adjusted for PS weighting and covariates, IL2-RA neither decreased the incidence of acute rejection rate nor did it improve overall graft survival after transplant compared with no-induction therapy. However, one does not truly know whether the IL2-RA cohort was treated the same as the no-induction cohort in terms of maintenance immunosuppression (especially target TAC levels and MPA dosing). It is possible that LRT recipients maintained on TAC/MPA with steroids are at low risk for acute rejection and graft loss, and the advantage of using IL2-RA induction may be too small. In this setting, especially considering adverse effects and cost, no-induction therapy is a reasonable option. By contrast, compared with IL2-RA, r-ATG decreased the RR of acute rejection by 22%, but it did not improve graft survival. It is a plausible strategy to limit the use of r-ATG to patients at increased risk for acute rejection to keep a favorable balance between benefits and serious adverse effects.

Steroid Avoidance

Early steroid avoidance has gained interest over the past decade in the United States, mainly to minimize metabolic side effects and negative effects on quality of life. Steroids have been a mainstay of immunosuppression for decades, and data evaluating minimization of steroids are sparse. In addition, many of the side effects attributed to steroids have been observed with higher doses. The association of low-dose steroid protocols (prednisone 5 mg daily) with

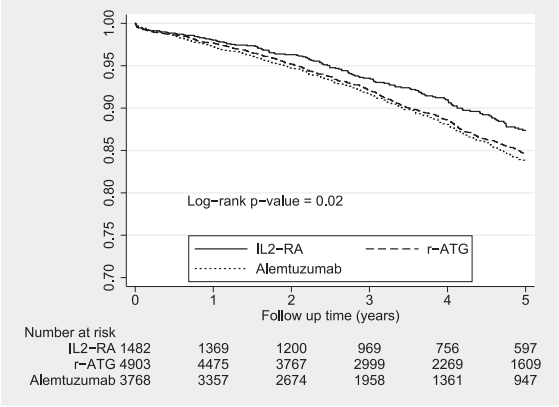

Figure 3. | Unweighted Kaplan–Meier survival estimates for induction types without steroid. IL2-RA, IL-2 receptor antagonist; r-ATG, rabbit anti-thymocyte globulin.

steroid cessation (7 days) versus chronic low-dose steroid in a randomized double-blinded study (32). At 5 years, the authors did not observe any difference in primary end points. In the corticosteroid cessation group, biopsy-proven rejection was significantly higher in recipients inducted with IL2-RA (24.4%) compared with r-ATG (14.4%). A recent meta-analysis (n=1934) included eight randomized clinical trials of early steroid withdrawal in kidney transplant recipients treated with r-ATG or IL2-RA induction and calcineurin inhibitors (TAC or cyclosporine A)/MPA with or without steroid-maintenance immunosuppression (33). Compared with conventional steroid use, when TAC and MPA were used, the no-steroid arm was not associated with higher acute rejection (RR, 1.06; 95% CI, 0.79 to 1.42), death (RR, 1.09; 95% CI, 0.50 to 2.37), and graft loss (RR, 1.29; 95% CI, 0.71 to 2.34). Similar findings were observed in a prospective, randomized multicenter trial (Thymoglobulin in Renal Transplantation for Induction and Minimization of Steroids study, n=153), which evaluated early

Table 4. Comparison of the estimated association of induction treatments on overall allograft failure through the end of the follow-up using multivariable Cox regression models

Multivariable Model	Induction Type	HR (95% CI)	*P* Value
Steroid			
Cox regression			
	IL-2 RA	1	
	r-ATG	1.00 (0.91 to 1.09)	0.93
	No induction	1.00 (0.91 to 1.09)	0.92
PS-weighted Cox regression			
	IL-2 RA	1	
	r-ATG	0.99 (0.91 to 1.08)	0.79
	No induction	0.99 (0.90 to 1.08)	0.76
No Steroid			
Cox regression			
	IL-2 RA	1	
	r-ATG	1.14 (0.93 to 1.39)	0.21
	Alemtuzumab	1.21 (0.98 to 1.49)	0.07
PS-weighted Cox regression			
	IL-2 RA	1	
	r-ATG	1.19 (0.97 to 1.45)	0.01
	Alemtuzumab	1.27 (1.03 to 1.56)	0.02

Adjusted for donor factors (age, sex, and race), recipient factors (age, sex, race, cardiovascular morbidity, panel reactive antibody, retransplant status, and dialysis status) and transplant factors (donor/recipient weight ratio, HLA mismatch, and transplant year). PS, propensity score; IL2-RA, IL-2 receptor antagonist; r-ATG, rabbit anti-thymocyte globulin; HR, hazard ratio; 95% CI, 95% confidence interval.

major side effects is not well defined. Early steroid withdrawal studies were associated with high rejection rates and graft failures (25–27); however, incorporation of antibody induction into standard immunosuppression protocols produced acceptable results (28–31). The KDIGO guidelines also suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for kidney transplant recipients at high immunologic risk for rejection prevention (2B equals a moderate evidence suggestion).

Woodle *et al.* compared outcomes (graft failure, death, acute rejection) of adult renal transplant recipients (LRT comprising 58% of the study cohort, n=386) who received antibody induction, TAC/MPA maintenance immunosuppression, and early corticosteroid withdrawal in LRT recipients who received r-ATG induction and TAC/MPA maintenance (8). In another steroid withdrawal randomized controlled trial (TAC/MPA maintenance regimen), Hanaway *et al.* stratified recipients based on their immunologic risk; low-risk patients (n=335) were randomized to alemtuzumab or basiliximab, whereas high-risk patients (n=139) received alemtuzumab or r-ATG (34). The incidence of rejection at 1 year in the low-risk group was lower with alemtuzumab versus basiliximab (3% versus 20%, $P<0.001$) and similar among high-risk patients (10% for alemtuzumab versus 13% for r-ATG, P=0.53). Nevertheless, these differences in the lower rejection rates did not translate to better death-censored graft survival or function.

In our multivariable PS-weighted analysis of LRT recipients maintained on TAC/MPA without steroids at discharge, induction with r-ATG and alemtuzumab lowered the RR of acute rejection, compared with IL2-RA, by 27% and 47%, respectively. Only alemtuzumab significantly increased the RR of overall graft failure after transplant by 27%, as previously shown in another OPTN/United Network for Organ Sharing (UNOS) analysis (35).

We agree with the KDIGO suggestion that, in the setting of steroid withdrawal, lymphocyte-depleting agents are more effective for decreasing risk of rejection and r-ATG seems to be safer and preferable over alemtuzumab to minimize graft loss and death. Nevertheless, in terms of pharmacoeconomics, IL2-RA induction is initially less costly, compared with r-ATG, as a result of shorter initial hospitalization and lower serious infectious complications (36). However, this initial higher cost can easily be offset by reducing hospitalization rates for acute rejection episodes and preventing graft failures. Clinicians should base their induction choice on the risk/benefit ratio for each recipient.

Cost

Alemtuzumab offers a significant cost savings compared with r-ATG and IL2-RA based on the average wholesale price (Red Book Online 2014, http://www.redbook.com/redbook/online). The cost of a typical course of alemtuzumab induction (typically 30 mg intravenously ×1) was $2118 in 2010. Alemtuzumab is no longer commercially available but is distributed only under research protocols with an institutional review board approval by its manufacturer. Basiliximab (IL2-RA) is usually administered as two doses of 20 mg (postoperative days 0 and 4) and costs $6489.14 (20-mg unit price $3244.57). Thymoglobulin (r-ATG) is typically given as four doses of 1.5 mg/kg (1.5 mg/kg×70 kg×4 doses=420 mg for a 70-kg standard adult patient) and costs $13,554.95 (unit price $797.35 per 25-mg vial, 17 vials×$797.35=$13,554.95). One should also keep in mind that these values are the costs of the drugs but they do not reflect the cost of administration, inpatient hospital stay, incidence, and cost of induction therapy–related complications.

Strengths and Limitations of the Study

The large sample size powers our study to detect small differences in the outcomes. Minimization of selection bias in patients undergoing different induction treatments (approximation to randomization) was mostly achieved by using PS weighting. Despite these strengths, our study has some limitations that are inherent in observational studies using registry data. Definitions and reporting of acute rejection episodes are left to the discretion of individual transplant centers, which are likely to be underreported. The lack of maintenance immunosuppression doses and trough levels (TAC) in the OPTN/UNOS database can introduce bias in acute rejection rates as a result of the difference in TAC/MPA exposure among induction categories. Finally, rate of malignancy and infectious complications could not be accurately assessed.

In LRT, when TAC/MPA/steroids are used, IL2-RA induction does not improve the outcomes compared with no-induction therapy. r-ATG appears to be an acceptable and preferred induction alternative for IL2-RA in steroid-avoidance protocols.

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Disclosures

None.

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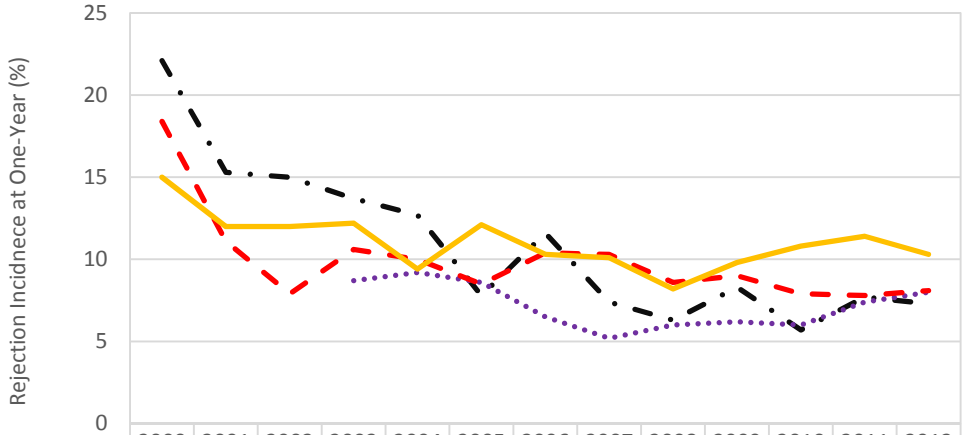
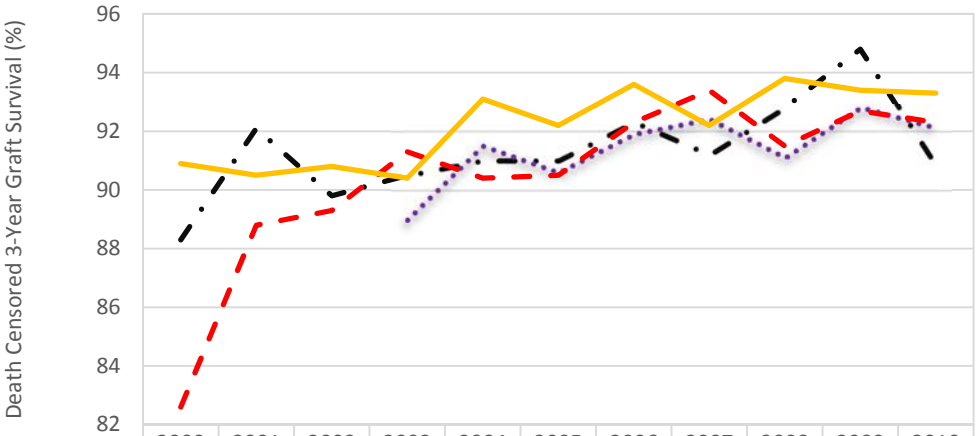
SUPPLEMENTAL FIGURES:

Figure S1. Acute rejection incidence at one-year by induction type and transplant year in the entire cohort.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
No induction	22.1	15.3	15	13.7	12.7	7.8	11.6	7.4	6.3	8.3	5.7	7.7	7.3
Alemtuzumab				8.7	9.2	8.6	6.5	5.2	6	6.2	6	7.4	8
rATG	18.4	11.1	7.9	10.6	10	8.5	10.4	10.3	8.6	9	7.9	7.8	8.1
IL2-RA	15	12	12	12.2	9.4	12.1	10.3	10.1	8.2	9.8	10.8	11.4	10.3

Figure S2. Three-year death censored graft survival by induction type and transplant year in the entire cohort.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
No induction	88.3	92.1	89.8	90.5	91	91	92.3	91.2	92.8	94.8	90.8
Alemtuzumab				89	91.5	90.6	91.9	92.4	91.1	92.8	92.1
rATG	82.6	88.8	89.3	91.3	90.4	90.5	92.3	93.4	91.5	92.7	92.3
IL2-RA	90.9	90.5	90.8	90.4	93.1	92.2	93.6	92.2	93.8	93.4	93.3

SUPPLEMENTAL TABLES:

Table S1. Causes of death in LRT recipients

Cause of death	IL2-RA	r-ATG	No induction	P-value
Steroid (N=2,450)				**<0.001**
Graft failure (%)	1.3	0.9	1.2	
Infection (%)	15.2	8.2	11.2	
CVS (%)	25.2	22.8	22.5	
Malignancy (%)	14.3	17.9	10.5	
Other (%)	44.1	50.4	54.7	

Cause of death	IL2-RA	r-ATG	Alemtuzumab	P
No-steroid (N=574)				**<0.001**
Graft failure (%)	2.1	0.7	0.0	
Infection (%)	7.5	13.9	8.9	
CVS (%)	17.0	26.4	17.7	
Malignancy (%)	19.2	23.6	14.1	
Other (%)	54.3	35.4	59.4	

Table S2. Causes of allograft failure in LRT recipients.

Cause of graft failure	IL2-RA	r-ATG	No induction	P-value
Steroid (N=2,813)				**<0.001**
Acute and chronic Rejection (%)	**57.0**	48.4	51.2	
Infection including BK (%)	6.8	6.5	5.7	
Surgical complications (%)	2.3	3.8	3.1	
Recurrent disease (%)	9.7	12.0	8	
Primary failure (%)	3.5	3.6	7.5	
Other (%)	20.7	25.7	24.6	

Cause of graft failure	IL2-RA	r-ATG	Alemtuzumab	P
No-steroid (N=781)				0.072
Acute and chronic Rejection (%)	**52.3**	46.6	43.7	
Infection including BK (%)	4.5	10.0	7.2	
Surgical complications (%)	4.5	5.9	2.9	
Recurrent disease (%)	8.1	5.6	10.4	
Primary failure (%)	3.6	4.1	2.2	
Other (%)	27.0	27.9	33.7	

Induction Therapies:

Basiliximab (Novartis, East Hannover, New Jersey, US) is currently only IL2-RA preparation available in the US, approved by the FDA in 1998.[1] Basiliximab is chimeric monoclonal antibody (75% human and 25% murine protein) which primarily abrogates T cell proliferation by binding to alpha subunit of IL2 receptor (CD25), a major growth factor for activated T lymphocytes.[2]

Alemtuzumab (Campath, Genzyme–Sanofi, New Jersey, US) is a humanized monoclonal rat antibody which targets CD52, a glycoprotein expressed on all mononuclear cells and male germ lines, and causes prolonged intense depletion of T and B cell lymphocytes, macrophages, monocytes, natural killers.[3] It initially received the FDA approval in 2001 in the treatment of B-cell chronic lymphocytic leukemia. Kidney transplantation has been one of its off label uses to treat and prevent rejection, especially in the calcineurin inhibitor (CNI) and steroid minimization protocols, since 1998. The drug was withdrawn from the market in 2012 to relicense for another indication, Multiple Sclerosis, but the FDA declined the application in 2013. It is currently available free to transplant centers through a special registry program.

rATG is a purified immunoglobulin derived from rabbit after immunization with human thymocyte that comprise cytotoxic antibodies directed against multiple antigens (CD2, CD3, CD4, CD8, CD18, CD25, CD44, CD45, HLA-DR, HLA Class I heavy chains, and B2 micro-globulin) expressed on human T lymphocytes.[4] Thymoglobulin (Genzyme-Sanofi, Cambridge, Massachusetts, US) was approved for treatment of acute rejection in renal transplantation in 1998, but not as an induction agent yet.

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