Alemtuzumab Induction in Deceased Donor Kidney Transplantation

Edmund Huang,[1] Yong W. Cho,[2] Rick Hayashi,[1] and Suphamai Bunnapradist[1,3]

Background. The use of alemtuzumab for induction therapy in kidney transplantation has been increasing. Herein is a report of graft outcomes associated with alemtuzumab induction from the Organ Procurement and Transplantation Network/United Network for Organ Sharing database.

Methods. A total of 14,362 deceased donor kidney transplants from 2003 to 2004 received no induction (n=4,364), antithymocyte globulin (ATG; n=4,930), interleukin-2 receptor antagonists (IL-2RA; n=4,378), or alemtuzumab (n=690). Acute rejection within the initial hospitalization, 6 months, and 1 year; graft survival; and rejection-free survival were examined. Graft and rejection-free survival of alemtuzumab recipients maintained with tacrolimus (FK) or cyclosporine (CSA), mycophenolate mofetil (MMF), and steroids versus no calcineurin inhibitors (CNI), MMF, and steroids were compared.

Results. Alemtuzumab recipients had less acute rejection during the initial hospitalization (2.3%) than no induction, ATG, and IL-2RA (7.6%, 3.4%, and 4.8%, respectively; $P<0.001$). There was increased acute rejection at 6 months and 1 year with alemtuzumab (14.5% and 19.2%) compared to no induction (12.7% and 14.8%, $P<0.001$), ATG (8.2% and 10.2%, $P<0.001$), and IL-2RA (11.1% and 13.0%, $P<0.001$) with no difference in adjusted relative risk for graft loss. Alemtuzumab recipients receiving FK or CSA, MMF, and steroids had increased graft (FK/MMF/steroids, $P<0.001$, CSA/MMF/steroids, $P=0.007$) and rejection-free survival (FK/MMF/steroids, $P<0.001$, CSA/MMF/steroids, $P=0.006$) over 24 months compared to no CNI, MMF, and steroids.

Conclusions. Despite reduced early rejection, acute rejection rates at 6 months and 1 year with alemtuzumab induction exceeded other forms of induction therapy. Maintenance with CNI-based immunosuppression may improve graft and rejection-free survival compared to CNI-free regimens among alemtuzumab recipients.

Keywords: Induction, Deceased donor, Immunosuppression, Alemtuzumab, Campath.

(*Transplantation* 2007;84: 821–828)

Alemtuzumab (Campath-1H, Berlex Laboratories, Montville, NJ) is a humanized immunoglobulin IgG1 monoclonal antibody directed against CD52, a glycoprotein expressed on circulating mononuclear cells. It was approved by the U.S. Food and Drug Administration for the treatment of B-cell chronic lymphocytic leukemia in 2001, and has been used off-label for the treatment of various diseases including rheumatoid arthritis (*1*), multiple sclerosis (*2*, *3*), and prevention of graft-versus-host disease (*4*). Its administration results in a rapid depletion of T- and B-lymphocytes, monocytes, and natural killer cells. A human in vivo study demonstrated that peripheral lymphocyte depletion occurs within 1 hour after alemtuzumab administration with gradual repopulation of lymphocytes beginning 1 month later (*5*). Although it has been observed that repopulation of B cells can be restored to above baseline levels 3 months after alemtuzumab administration (*6*), total peripheral lymphocyte counts remain at 50% of baseline levels after 12 months (*5*).

Several studies have suggested that aggressive perioperative T-cell depletion in non-human primates can induce operational tolerance and ameliorate the risk of acute rejection in kidney transplantation (*7*, *8*). Although immune tolerance has not been successfully achieved in human clinical trials, studies have used induction therapy to create a "prope" or near-tolerant state whereby allografts can be maintained with reduced immunosuppression. Calne et al. utilized such a strategy in the first published report of alemtuzumab induction, administering alemtuzumab to 13 deceased donor kidney recipients in conjunction with low-dose maintenance cyclosporine (CSA) monotherapy (target trough 75–125 μg/ml) (*9*). All 13 patients had sustained renal function between

This work was supported in part by a National Institutes of Health Training Grant T-32DK07789 and by Health Resources and Services Administration contract 234-2005-370011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does the mention of trade names, commercial products, or organizations imply endorsement by the U.S. government.

[1] Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA.

[2] National Institute of Transplantation, S. Mark Taper Foundation Transplant Center, Los Angeles, CA.

[3] Address correspondence to: Suphamai Bunnapradist, M.D., UCLA Kidney Transplant Program, 924 Westwood Blvd., Suite 860, Los Angeles, CA 90095.

E-mail: bunnapradist@mednet.ucla.edu

Received 8 March 2007. Revision requested 17 May 2007.
Accepted 16 July 2007.

ISSN 0041-1337/07/8407-821
DOI: 10.1097/01.tp.0000281942.97406.89

6 and 11 months posttransplant, and there was only one case of biopsy-proven acute rejection. Tan et al. utilized alemtuzumab induction with spaced-dose tacrolimus (FK) monotherapy in 205 living-donor renal transplant recipients and achieved 1-year acute rejection and actuarial graft survival rates of 6.8% and 98.1%, respectively (*10*).

Alemtuzumab induction has been used in conjunction with low-dose calcineurin inhibitor (CNI), CNI-free, and steroid-free regimens with comparable graft survival to conventional protocols (*11–14*). These studies have included relatively few patients with short observation periods and have reported variable acute rejection rates. The advantages of utilizing low-dose immunosuppression remain indeterminate and long-term sequelae are not known.

In this study, we conducted a retrospective analysis of deceased donor kidney transplantation using the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) database to determine graft outcomes associated with the use of alemtuzumab induction. We compared alemtuzumab induction to no antibody induction, antithymocyte globulin (ATG), and interleukin-2 receptor antagonists (IL-2RA). We also evaluated graft outcomes according to common maintenance regimens, including CNI-free protocols compared to standard triple immunosuppression.

METHODS

Using the OPTN/UNOS data as of March 23, 2006, we compared alemtuzumab to no antibody induction, ATG, and the IL-2RA, basiliximab, and daclizumab. Because there was negligible use of alemtuzumab for antibody induction before 2003, we chose to restrict the study period to those patients who received deceased donor kidney transplants from January 1, 2003 to December 31, 2004. Retransplanted patients, multi-organ transplant recipients, and patients receiving more than one type of antibody induction were excluded from the analysis. After excluding these cases, 14,362 kidney transplants remained in the study population. Transplant registration records were used to identify cases of early complications, including delayed graft function (defined as the need for dialysis within the first week after transplantation), failure of the serum creatinine to decline by at least 25% in the first day after transplantation, primary nonfunction, and acute rejection. The cumulative rate of rejection was calculated using data obtained from follow-up at hospital discharge, 6 months, and 1 year.

Cox regression model was used to estimate the relative risk for graft loss and acute rejection during the study period. In graft survival analysis, time-varying end points were graft loss or patient death. For rejection-free survival, time-varying end point was time to the first rejection episode. Recipient age, recipient gender, recipient and donor race, diabetes, peak percentage of panel reactive antibodies (pPRA), donor age, cause of donor death, cold ischemia time (CIT), extended criteria donor (ECD) kidney, number of human leukocyte antigen (HLA) mismatch, and type of induction were used for graft (Table 2) and rejection-free survival analyses (Table 2). The results of the analyses are expressed as estimated relative risk (RR) with their 95% confidence intervals and associated *P* values.

Among patients with alemtuzumab induction, fractions of patients maintained on CNI and steroid at 6 months after transplantation are listed in Table 4 according to maintenance immunosuppression regimens.

STATA version 8 (College Station, TX) was used in all statistical analyses.

RESULTS

Demographics

Table 1 shows the distribution, according to type of induction, of recipient and donor characteristics known to affect graft outcomes. In all, 69.6% of patients in the study population received antibody induction. A total of 4.8% of the overall study population received alemtuzumab induction therapy. Of those receiving antibody induction, 6.9% were induced with alemtuzumab. Compared to no induction, ATG, and IL-2RA induction groups, alemtuzumab induction was used more frequently in the following: female recipients; older recipients; diabetes; older donors; ECD grafts; and grafts with longer CIT (>24 hr). Alemtuzumab induction was less frequently used in younger recipients (age ≤20 years), black recipients, grafts from trauma death, and grafts with shorter CIT (≤12 hr).

Impact of Antibody Induction on Graft Survival

Unadjusted graft survival curves comparing induction groups are shown in Figure 1A. The graft survival rate in the alemtuzumab induction group was significantly lower than that of the IL-2RA group ($P=0.01$). The results of unadjusted and adjusted analyses of risk factors for graft loss are shown in Table 2. Statistically significant risk factors identified by univariate analysis were applied to multivariate analysis to adjust for potential confounding factors (Table 2). In multivariate analysis, recipient age greater than 60 years, black ethnicity, recipient diabetes, sensitization (pPRA>50%), black donors, donor age less than 15 or greater than 35 years old, ECD grafts, longer CIT (>24 hr), and HLA mismatched grafts (>3 mismatches) were associated with an increased risk of graft loss in our study population. After adjusting for statistically significant risk factors, multivariate analysis revealed that modality of induction was not an independent risk factor for graft loss.

Impact of Antibody Induction on Acute Rejection

An unadjusted rejection-free survival curve comparing the four induction groups is found in Figure 1B. There was a sharp decline in rejection-free survival with alemtuzumab induction beginning 6 months after transplant, culminating in a lower rejection-free survival beginning at 9 months when compared to the other induction groups. Statistically significantly risk factors in either univariate or multivariate analyses were used in multivariate rejection-free survival analysis in order to estimate adjusted relative risks for developing acute rejection. Unadjusted and adjusted analyses of risk factors for acute rejection are shown in Table 2.

In multivariate analysis, no induction (RR: 0.76, $P=0.002$), ATG (RR: 0.52, $P<0.001$), and IL-2RA (RR: 0.66, $P<0.001$) were each independently associated with a decreased risk for acute rejection when compared to alemtuzumab.

TABLE 1. Characteristics of deceased donor kidney transplants receiving induction therapy

Variables	Levels	Total (%)	No induction (%)	ATG (%)	IL-2RA (%)	Alemtuzumab (%)	*P* value
No. of Patients			14,632	4,364	4,930	4,378	690
Recipient sex	Female	39.4	37.0	41.6	38.8	42.3	<0.001
Recipient age (years)	≤20	5.2	4.6	3.9	7.8	1.6	<0.001
	21–50	41.6	42.6	41.8	40.7	38.8	
	51–60	28.2	28.2	30.1	25.9	29.3	
	>60	25.1	24.6	24.2	25.7	30.3	
Recipient race	Black	30.7	33.4	34.7	25.3	18.4	<0.001
pPRA (%)	0–10	74.3	75.1	70.8	78.1	71.3	<0.001
	11–50	13.3	13.8	13.2	13.0	12.9	
	>50	10.5	9.5	14.3	7.8	7.0	
	Missing	1.8	1.6	1.7	1.1	8.8	
Primary ESRD	Diabetes	30.7	31.45	30.3	29.4	38.1	<0.001
Donor sex	Female	41.6	42.5	42.0	40.5	39.7	0.18
Donor race	Black	11.8	13.0	12.5	10.2	10.0	<0.001
Donor age (years)	≤15	9.5	8.3	9.4	10.6	10.7	<0.001
	16–35	34.4	34.5	32.9	37.0	28.7	
	36–55	40.0	41.3	39.7	39.4	38.7	
	>55	16.0	15.8	18.0	13.1	21.9	
Donor death	Trauma	43.8	42.3	42.3	48.4	36.2	<0.001
Donor type	ECD	16.8	16.7	19.4	13.0	23.8	<0.001
CIT (hours)	0–12	21.4	20.7	19.7	25.6	10.6	<0.001
	12–24	47.5	43.9	49.6	48.0	52.2	
	>24	17.9	17.8	18.3	17.1	20.0	
	Missing	13.3	17.6	12.5	9.3	17.3	
HLA-A,B,DR mismatch	0	13.9	14.3	12.3	15.1	15.1	0.001
	1 or 2	5.5	5.2	5.3	6.2	5.2	
	3 or 4	38.2	37.4	38.7	38.6	36.5	
	5 or 6	42.4	43.1	43.7	40.1	43.2	
Mean follow-up (months)		16.2±8.2	15.9±8.6	16.2±7.9	16.9±8.2	14.8±6.9	<0.001

Complications

Posttransplant complications are reported in Table 3. There was a higher incidence of delayed graft function (need for dialysis in the first week after transplantation) with ATG induction compared to no antibody induction, IL-2RA, and alemtuzumab. The highest percentage of failure of creatinine to decline by 25% on first day was observed in the IL-2RA group compared with those of other groups. Alemtuzumab induction was associated with a lower incidence of acute rejection during the initial hospital stay compared to no antibody induction, ATG, and IL-2RA. This effect diminished after hospital discharge. Cumulative rejection at both 6 months and 1 year with alemtuzumab induction exceeded those of no induction, ATG, and IL-2RA.

Effect of Maintenance Immunosuppression on Graft Outcomes in Alemtuzumab Recipients

At discharge from the initial hospitalization, the most common maintenance immunosuppression regimen given to alemtuzumab recipients consisted of a CNI, mycophenolate mofetil (MMF), and steroids (56.9%) (Table 4). Of CNI recipients, 65.9% were maintained on FK and 34.1% received CSA. Because immunosuppression regimens are often modified later in the course after transplantation, we examined the immunosuppression record at six months to identify those patients who underwent CNI- or steroid-withdrawal after hospital discharge. We also identified patients who were initially placed on CNI- or steroid-free protocols at discharge from the initial hospitalization. Eighty-two alemtuzumab recipients (11.9%) were discharged on a CNI-free protocol consisting of MMF and steroids. A total of 52.4% of these patients discharged on CNI-free protocols remained CNI-free at six months. 26.8% of patients initially CNI-free were subsequently started on FK within the first 6 months and 13.4% were placed on CSA. Only a small percentage of patients initially maintained on a regimen comprised of CNI, MMF, and steroids at hospital discharge underwent CNI withdrawal within the first 6 months (n=11, 2.8%). 63.7% of patients who were on FK, MMF, and steroids at hospital discharge subsequently had steroids withdrawn within 6 months. These results are summarized in Table 4.

Graft and rejection-free survival curves of other maintenance groups in Table 4 were not plotted in Figure 2 because graft survival rates of other maintenance groups (n=215) with alemtuzumab induction were not significantly different to the CNI/MMF/steroids groups (*P*=0.62 vs. FK/MMF/steroids;

TABLE 2. Estimated relative risks for graft loss acute rejection during study period

Variables	Levels	Unadjusted RR (95% CI)	*P* values	Adjusted RR (95% CI)	*P* values
Graft loss					
Recipient age (years)	≤50	1.0		1.0	
	51–60	1.22 (1.09–1.37)	<0.001	1.11 (0.99–1.24)	0.09
	>60	1.65 (1.48–1.84)	<0.001	1.410 (1.26–1.59)	<0.001
Recipient race	Other	1.0		1.0	
	Black	1.41 (1.29–1.55)	<0.001	1.38 (1.25–1.52)	<0.001
Recipient diabetes	No	1.0		1.0	
	Yes	1.35 (1.23–1.49)	<0.001	1.23 (1.11–1.35)	<0.001
pPRA (%)	0–50	1.0		1.0	
	51–100	1.17 (1.01–1.34)	0.03	1.28 (1.11–1.48)	0.001
Donor race	Other	1.0		1.0	
	Black	1.28 (1.12–1.45)	<0.001	1.17 (1.03–1.34)	0.02
Donor age (years)	0–15	1.30 (1.09–1.56)	0.004	1.33 (1.11–1.59)	0.006
	16–35	1.0		1.0	
	36–55	1.45 (1.29–1.62)	<0.001	1.29 (1.14–1.46)	<0.001
	>55	2.17 (1.91–2.47)	<0.001	1.37 (1.14–1.65)	0.001
Trauma	No	1.0		1.0	
	Yes	0.71 (0.64–0.78)	<0.001	0.91 (0.82–1.01)	0.09
CIT (hours)	0–24	1.0		1.0	
	>24	1.22 (1.09–1.36)	0.009	1.18 (1.05–1.32)	0.004
ECD kidney	No	1.0		1.0	
	Yes	1.92 (1.73–2.13)	<0.001	1.43 (1.22–1.67)	<0.001
HLA mismatch	0	1.0		1.0	
	1–2	1.22 (0.96–1.55)	0.11	1.13 (0.89–1.44)	0.33
	3–4	1.36 (1.16–1.59)	<0.001	1.20 (1.02–1.41)	0.03
	5–6	1.55 (1.32–1.81)	<0.001	1.28 (1.08–1.50)	0.001
Induction	None	0.93 (0.75–1.15)	0.51	0.95 (0.76–1.18)	0.61
	ATG	0.84 (0.68–1.05)	0.12	0.82 (0.66–1.02)	0.07
	IL–2RA	0.76 (0.61–0.95)	0.02	0.83 (0.67–1.03)	0.10
	Alemtuzumab	1.0		1.0	
Acute rejection					
Recipient age (years)	≤50	1.0		1.0	
	51–60	0.79 (0.72–0.87)	<0.001	0.78 (0.70–0.86)	<0.001
	>60	0.69 (0.62–0.77)	<0.001	0.66 (0.59–0.74)	<0.001
Recipient sex	Male	1.0		1.0	
	Female	0.93 (0.85–1.01)	0.07	0.89 (0.82–0.97)	0.008
Recipient race	Other	1.0		1.0	
	Black	1.52 (1.40–1.65)	<0.001	1.39 (1.27–1.52)	<0.001
Recipient diabetes	No	1.0		1.0	
	Yes	0.85 (0.78–0.94)	0.001	0.91 (0.82–1.00)	0.04
pPRA (%)	0–50	1.0		1.0	
	51–100	1.22 (1.08–1.40)	0.002	1.39 (1.22–1.58)	<0.001
Donor race	Other	1.0		1.0	
	Black	1.22 (1.09–1.37)	0.001	1.05 (0.94–1.19)	0.39
Donor age (years)	0–15	1.15 (0.98–1.34)	0.09	1.14 (0.97–1.33)	0.11
	16–35	1.0		1.0	
	36–55	1.40 (1.27–1.54)	<0.001	1.30 (1.17–1.45)	<0.001
	>55	1.49 (1.32–1.69)	<0.001	1.18 (0.99–1.40)	0.06
Trauma	No	1.0		1.0	
	Yes	0.78 (0.72–0.85)	<0.001	0.92 (0.83–1.01)	0.07

TABLE 2. Continued

Variables	Levels	Unadjusted RR (95% CI)	*P* values	Adjusted RR (95% CI)	*P* values
CIT (hours)	0–12	1.0		1.0	
	13–24	1.17 (1.07–1.29)	0.001	1.22 (1.11–1.34)	<0.001
	>24	1.32 (1.17–1.48)	<0.001	1.34 (1.19–1.51)	<0.001
ECD kidney	No	1.0		1.0	
	Yes	1.44 (1.30–1.59)	<0.001	1.44 (1.24–1.66)	<0.001
HLA mismatch	0	1.0		1.0	
	1–2	1.49 (1.19–1.88)	0.001	1.41 (1.12–1.78)	0.003
	3–4	1.85 (1.59–2.17)	<0.001	1.66 (1.42–1.94)	<0.001
	5–6	2.01 (1.73–2.35)	<0.001	1.73 (1.48–2.03)	<0.001
Induction	None	0.79 (0.67–0.94)	0.007	0.77 (0.65–0.91)	0.003
	ATG	0.57 (0.48–0.68)	<0.001	0.52 (0.44–0.62)	<0.001
	IL–2RA	0.65 (0.55–0.78)	<0.001	0.67 (0.56–0.80)	<0.001
	Alemtuzumab	1.0		1.0	

TABLE 3. Complications following deceased donor kidney transplants

	No induction (%)	ATG (%)	IL-2RA (%)	Alemtuzumab (%)	*P* value
Need for dialysis in first week	901 (20.65)	1350 (27.38)	891 (20.35)	142 (20.58)	<0.001
Failure of creatinine to decline by 25% on first day	2209 (50.63)	2491 (50.53)	2483 (56.72)	335 (48.55)	<0.001
Primary nonfunction	67 (1.54)	49 (0.99)	48 (1.10)	9 (1.30)	0.096
Acute rejection during initial stay	331 (7.58)	167 (3.39)	209 (4.77)	16 (2.32)	<0.001
Cumulative rejection treatment within 6 months	400 (12.67)	310 (8.16)	374 (11.11)	84 (14.51)	<0.001
Cumulative rejection treatment within 1st year	432 (14.84)	376 (10.24)	423 (13.03)	105 (19.20)	<0.001

TABLE 4. CNI and steroid use at 6 months after transplantation among alemtuzumab recipients according to regimens at discharge

Regimen at discharge	N (%)	No CNI at 6 months (%)	CSA at 6 months (%)	FK use at 6 months (%)	No steroids at 6 months (%)	Steroids at 6 months (%)
FK/MMF/steroids	259 (37.5)	1.5	0	95.0	63.7	32.8
CSA/MMF/steroids	134 (19.4)	5.2	82.1	9.7	3.7	94.8
No CNI/MMF/steroids	82 (11.9)	52.4	13.4	26.8	12.2	80.5
Others	215 (31.2)	2.8	1.9	92.1	74.0	22.8

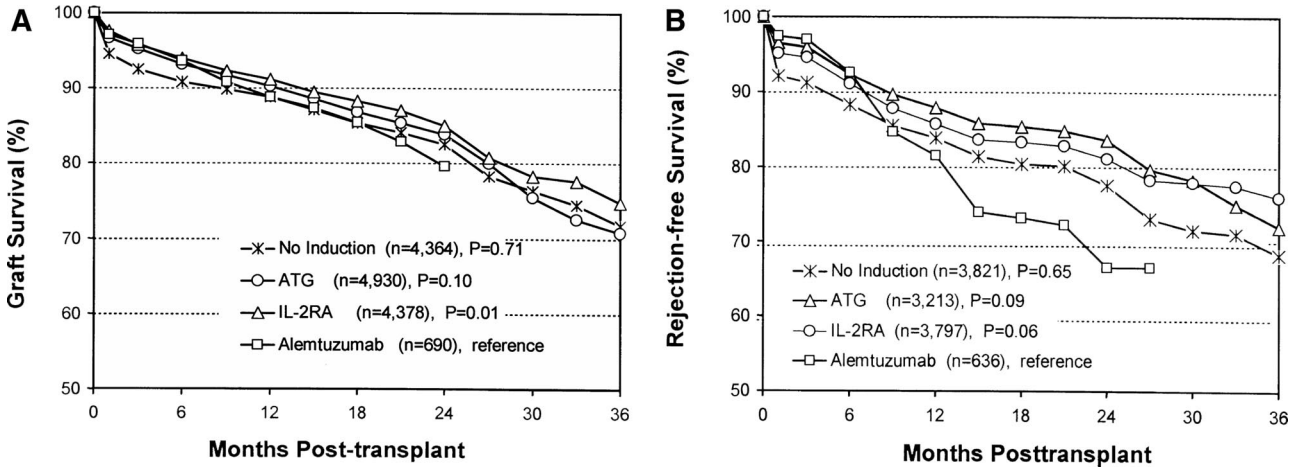

FIGURE 1. (A) Unadjusted graft survival according to type of induction. (B) Unadjusted rejection-free survival according to type of induction.

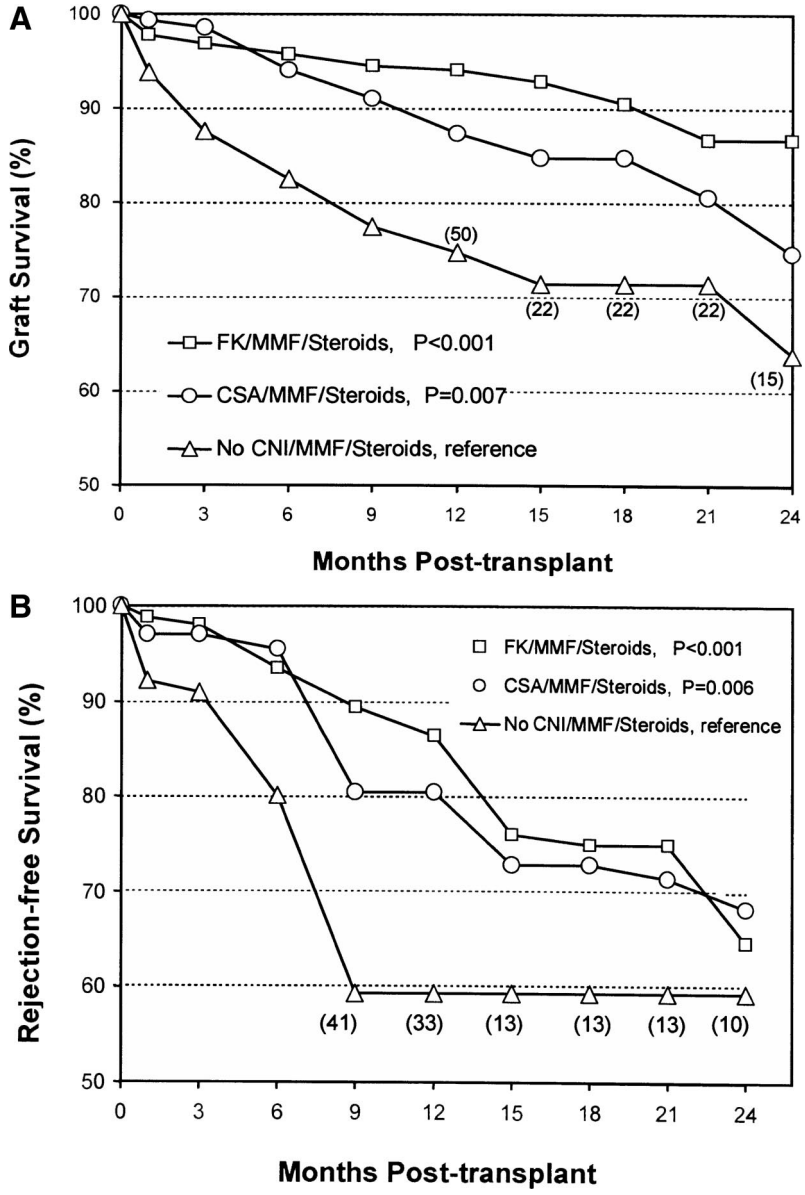

FIGURE 2. (A) Effect of maintenance regimens on graft survival in patients receiving alemtuzumab induction. (B) Effect of maintenance regimens on rejection-free survival in patients receiving alemtuzumab induction.

$P=0.10$ vs. CSA/MMF/steroids). Similarly, rejection-free survival rates of other maintenance groups were not significantly different to the CNI/MMF/steroids groups ($P=0.83$ vs. FK/MMF/steroids; $P=0.85$ vs. CSA/MMF/steroids).

Figure 2A shows that patients discharged on CNI had superior graft survival compared to those on CNI-free protocols (FK/MMF/steroids, $P<0.001$; CSA/MMF/steroids, $P=0.007$). Patients maintained on FK/MMF/steroids had superior graft survival rates compared to CSA/MMF/steroids ($P=0.03$).

Figure 2B shows that patients discharged on a CNI had superior rejection-free survival compared to those on a CNI-free protocol (FK/MMF/steroids, $P<0.001$; CSA/MMF/steroids, $P=0.006$). Rejection-free survival rates of patients maintained on FK/MMF/steroids were not significantly different to the CSA/MMF/steroids group ($P=0.59$).

DISCUSSION

With introduction of newer induction agents, the use of antibody induction in kidney transplantation has increased annually since 1997 (*15*). The use of alemtuzumab for kidney transplantation has also been increasing, particularly in the years 2003–2004 (*15*) despite limited data on its efficacy. To date, there are only two prospective, randomized controlled trials of alemtuzumab induction in kidney transplantation involving a total of 50 alemtuzumab recipients in the literature. Vathsala et al. reported a randomized trial of 20 patients who received alemtuzumab induction and low-dose CSA monotherapy (target trough 90–110 ng/ml) compared to 10 patients who received standard-dose CSA (target trough 180–225 ng/ml), azathioprine, and corticosteroids (*16*). The incidence of acute rejection, serum creatinine, graft and patient survival were comparable between the two groups at 6 months. Perhaps because of a small sample size and short duration of follow-up, no improvement in renal function or reduction in infectious complications could be demonstrated in the alemtuzumab group despite reduced exposure to CNI over the course of the study period. Ciancio et al. compared 90 deceased donor transplants, randomizing 30 patients to each of three arms: ATG or daclizumab induction with

full-dose FK (target trough 8–10 ng/ml), full-dose MMF (2 g/day), and methylprednisolone or alemtuzumab induction with low-dose FK (target trough 4–7 ng/ml at 1 month and 4–6 ng/ml at 6 months and thereafter), half-dose MMF (1 g/day), and no steroids (*17*). There was an equivalent rate of acute rejection at one year (16.7%) and no difference in patient and graft survival among the three groups. Despite targeting lower FK doses in the alemtuzumab group, mean FK trough levels in the alemtuzumab group did not differ from the daclizumab group. Additionally, because of leukopenia, the mean dose of MMF administered to the alemtuzumab group during the study was lower than that targeted by the study protocol. Six of 30 patients in the alemtuzumab group (20%) required at least temporary corticosteroid therapy for graft dysfunction. These reasons may explain why no difference in creatinine clearance or infectious complications was observed among the three groups in this analysis.

Inducing perioperative lymphocyte depletion with antilymphocyte antibodies is one strategy used to delay the administration of CNI, thus avoiding the acute nephrotoxic effects of CNI. This is often done when delayed graft function is anticipated (*18*, *19*). We found that that there was an increased use of alemtuzumab in recipients at higher risk for delayed graft function, including ECD kidneys and donor kidneys with greater than 24 hr of CIT. Additionally, alemtuzumab was more often used in recipients with diabetes, perhaps in an attempt to avoid or reduce FK exposure.

Our study found that alemtuzumab induction was associated with a lower rate of acute rejection during the initial hospital stay compared to no antibody induction, ATG, and IL-2RA (2.3 vs. 7.6 vs. 3.4 vs. 4.8%, $P<0.001$), an effect that was lost by 6 months posttransplant. By 1 year, the cumulative incidence of acute rejection with alemtuzumab induction exceeded that of no antibody induction, ATG, and IL-2RA (19.2% vs. 14.8 vs. 10.2 vs. 13.0%, $P<0.001$). This is similar to data derived from the 2006 OPTN/Scientific Registry of Renal Transplant Recipients (SRTR) Annual Report, with reported overall first-year rejection rates in the United States of 13% in 2003 and 12% in 2004 (*20*). Furthermore, multivariate analysis revealed that alemtuzumab induction was independently associated with an increased risk for acute rejection during the study period compared to no antibody induction (RR: 1.30, $P=0.003$). In contrast, both ATG and IL-2RA induction resulted in a lower risk for acute rejection compared to no antibody induction (RR: 0.68, $P<0.001$ and RR: 0.87, $P=0.008$). Watson et al. described similar findings in a retrospective analysis of alemtuzumab induction used in 33 deceased donor kidney transplants (*21*). In comparison to a contemporaneous control group in whom the majority did not receive antibody induction, there was comparable graft and rejection-free survival at five years. The median time to first rejection episode was prolonged in the alemtuzumab group (170 vs. 21 days). Rejection-free survival curves suggested that alemtuzumab induction was associated with increased late rejection, particularly occurring after one year posttransplant. It should be noted that patients in the alemtuzumab group were maintained on half-dose CSA monotherapy (target trough 75–125 ng/ml) compared to conventional maintenance immunosuppression consisting of CSA, azathioprine, and prednisolone in the control group.

We found that the majority of patients receiving alemtuzumab induction are maintained on a CNI, MMF, and steroids at discharge. Almost twice as many patients were maintained on FK than CSA. 8.7% of alemtuzumab recipients were discharged from the initial hospitalization on a CNI-free protocol and 46.7% of these remained CNI-free at 6 months. CNI-free maintenance regimens were associated with both decreased rejection-free and graft survival at all time points compared to conventional triple therapy with a CNI, MMF, and steroids. Because OPTN/UNOS does not provide dosing information, it is unknown if patients receiving CNI were maintained on low versus standard dose CNI. Our data suggests that alemtuzumab recipients should be maintained on a CNI, although it is still unknown whether low-dose CNI results in similar outcomes as standard doses.

The majority of alemtuzumab recipients maintained on steroid-free protocols had steroids withdrawn subsequent to discharge from the initial hospitalization. Only 15 patients were steroid-free at hospital discharge, 14 of whom remained steroid-free at 6 months. Of the patients who were discharged on FK, MMF, and steroids, 63.9% subsequently underwent steroid withdrawal within the first 6 months. When comparing patients on a steroid withdrawal protocol of FK and MMF compared to FK, MMF, and steroids and CSA, MMF, and steroids, patients in the steroid withdrawal group had improved rejection-free (90.5% vs. 67.2% and 80.5%, respectively) and graft survival (98.1% vs. 91.6% and 88.1%, respectively). The majority of patients who had steroids withdrawn within the first 6 months had a low rate of rejection and excellent graft survival. However, longer follow-up is needed to assess the long-term of impact of steroid-free protocols in alemtuzumab induction.

One of the major findings of our study is that there is an increase in late rejection observed with alemtuzumab induction. The increased rate of rejection in these recipients is likely a result of a net state of under-immunosuppression. One explanation for this observation may simply relate to inadequate maintenance immunosuppression, particularly in patients maintained on CNI-minimization regimens. The use of MMF may be limited in alemtuzumab recipients due to leukopenia. It has been reported that the incidence of acute rejection is inversely correlated with exposure to mycophenolic acid, measured by mycophenolic acid area under the curve (*22*). However, we could not address the frequency and associated impact of MMF dose reduction in our analysis, as dose information is not captured in the OPTN/UNOS database. Furthermore, it is still unclear if immunosuppression minimization could yet be possible with alternative dosing of alemtuzumab. There is limited experience with repeated doses of alemtuzumab in the late posttransplant period (*6*). Given the increasing use of alemtuzumab for induction therapy, prospective studies investigating varying doses of alemtuzumab induction with different maintenance regimens are necessary to evaluate the optimal use of alemtuzumab induction.

Other immunologic factors may contribute to increased rejection rates observed with alemtuzumab induction. Although alemtuzumab has profound lymphocyte-depleting properties, monocyte depletion is more gradual and less sustained (*5*). A monocytic-predominant tubulitis has been described in cases of early acute rejection after alemtuzumab induction (*5*). It has also been suggested that $CD45RO^+$

memory T cells are incompletely depleted by alemtuzumab and may play a prominent role in the development of acute rejection after alemtuzumab induction (*6*). Additionally, there have been reports of acute humoral rejection occurring after alemtuzumab induction (*12*, *23*). This may potentially be mediated by B cells, which have been noted to repopulate to levels beyond baseline after depletion by alemtuzumab (*6*).

Although we observed an increase in acute rejection in the alemtuzumab group occurring after 6 months, we did not see a difference in graft survival over 3 years compared to no induction, IL-2RA, and ATG. It remains to be seen whether differences in graft survival will become apparent over a longer observation period. The association between late acute rejection and decreased long-term graft survival has been previously documented. Sijpkens et al. reported that 10-year graft survival rates censored for causes of graft loss other than chronic rejection were reduced for patients who developed late acute rejection (greater than 3 months after transplant) compared to those who did not have acute rejection and those who developed acute rejection within the first 3 months (45% vs. 94% and 86%) (*24*).

We acknowledge some limitations of our study. First, this is a retrospective analysis and is therefore susceptible to inherent bias. Second, we could not account for patients who were maintained on lower levels of CNI compared to standard-dose CNI. There is no data from clinical trials on optimal dosing and frequency of alemtuzumab administration. This data also does not exist in the OPTN/UNOS database. We observed an increase in late rejection in alemtuzumab recipients, which may be a reflection of inadequate maintenance immunosuppression or may relate to inadequate depletion of monocytes, $CD45RO^{+}$ memory T-cells, or repopulating B-cells. The effect of reduced maintenance immunosuppression on long-term graft survival will need to be addressed in future studies over a longer period of follow-up.

In conclusion, the use of alemtuzumab induction was associated with reduced rates of acute rejection during the initial hospitalization compared to no induction, IL-2RA, and ATG. However, this benefit was not sustained 6 months and 1 year after transplant. This finding may reflect a tendency to reduce maintenance immunosuppression in patients who receive alemtuzumab induction. Among alemtuzumab recipients, there is decreased rejection-free and graft survival in patients not maintained on a calcineurin-inhibitor. Steroid withdrawal may be considered in patients who receive alemtuzumab induction therapy, although it remains unclear which factors will predict how patients will fare once steroids are withdrawn. Despite increased acute rejection episodes associated with alemtuzumab induction, there is comparable graft survival between alemtuzumab, no antibody induction, ATG, and IL-2RA. Further studies are necessary to assess long-term graft outcomes of alemtuzumab induction and to further identify predictive factors that will guide the selection of maintenance immunosuppression regimens.

REFERENCES

1. Isaacs JD, Manna VK, Rapson N, et al. CAMPATH-1H in rheumatoid arthritis–an intravenous dose-ranging study. *Br J Rheumatol* 1996; 35: 231.
2. Coles AJ, Wing MG, Molyneux P, et al. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. *Ann Neurol* 1999; 46: 296.
3. Moreau T, Coles A, Wing M, et al. CAMPATH-IH in multiple sclerosis. *Mult Scler* 1996; 1: 357.
4. Hale G, Slavin S, Goldman JM, et al. Alemtuzumab (Campath-1H) for treatment of lymphoid malignancies in the age of nonmyeloablative conditioning? *Bone Marrow Transplant* 2002; 30: 797.
5. Kirk AD, Hale DA, Mannon RB, et al. Results from a human renal allograft tolerance trial evaluating the humanized CD52-specific monoclonal antibody alemtuzumab (CAMPATH-1H). *Transplantation* 2003; 76: 120.
6. Marcos A, Eghtesad B, Fung JJ, et al. Use of alemtuzumab and tacrolimus monotherapy for cadaveric liver transplantation: with particular reference to hepatitis C virus. *Transplantation* 2004; 78: 966.
7. Thomas JM, Neville DM, Contreras JL, et al. Preclinical studies of allograft tolerance in rhesus monkeys: A novel anti-CD3-immunotoxin given peritransplant with donor bone marrow induces operational tolerance to kidney allografts. *Transplantation* 1997; 64: 124.
8. Knechtle SJ, Vargo D, Fechner J, et al. FN18-CRM9 immunotoxin promotes tolerance in primate renal allografts. *Transplantation* 1997; 63: 1.
9. Calne R, Friend P, Moffatt S, et al. Prope tolerance, perioperative campath 1H, and low-dose cyclosporin monotherapy in renal allograft recipients. *Lancet* 1998; 351: 1701.
10. Tan HP, Kaczorowski DJ, Basu A, et al. Living donor renal transplantation using alemtuzumab induction and tacrolimus monotherapy. *Am J Transplant* 2006; 6: 2409.
11. Calne R, Moffatt SD, Friend PJ, et al. Campath IH allows low-dose cyclosporine monotherapy in 31 cadaveric renal allograft recipients. *Transplantation* 1999; 68: 1613.
12. Knechtle SJ, Pirsch JD, H Fechner JJ, et al. Campath-1H induction plus rapamycin monotherapy for renal transplantation: Results of a pilot study. *Am J Transplant* 2003; 3: 722.
13. Flechner SM, Friend PJ, Brockmann J, et al. Alemtuzumab induction and sirolimus plus mycophenolate mofetil maintenance for CNI and steroid-free kidney transplant immunosuppression. *Am J Transplant* 2005; 5: 3009.
14. Kaufman DB, Leventhal JR, Axelrod D, et al. Alemtuzumab induction and prednisone-free maintenance immunotherapy in kidney transplantation: Comparison with basiliximab induction–long-term results. *Am J Transplant* 2005; 5: 2539.
15. Huang E, Cho YW, Shah T, et al. Alemtuzumab induction in kidney transplantation. *Clin Transpl* 2005: 343.
16. Vathsala A, Ona ET, Tan SY, et al. Randomized trial of Alemtuzumab for prevention of graft rejection and preservation of renal function after kidney transplantation. *Transplantation* 2005; 80: 765.
17. Ciancio G, Burke GW, Gaynor JJ, et al. A randomized trial of three renal transplant induction antibodies: Early comparison of tacrolimus, mycophenolate mofetil, and steroid dosing, and newer immune-monitoring. *Transplantation* 2005; 80: 457.
18. Pallet N, Anglicheau D, Martinez F, et al. Comparison of sequential protocol using basiliximab versus antithymocyte globulin with high-dose mycophenolate mofetil in recipients of a kidney graft from an expanded-criteria donor. *Transplantation* 2006; 81: 949.
19. Knight RJ, Kerman RH, Schoenberg L, et al. The selective use of basiliximab versus thymoglobulin in combination with sirolimus for cadaveric renal transplant recipients at low risk versus high risk for delayed graft function. *Transplantation* 2004; 78: 904.
20. Andreoni KA, Brayman KL, Guidinger MK, et al. Kidney and pancreas transplantation in the United States, 1996–2005. *Am J Transplant* 2007; 7 Suppl 1: 1359.
21. Watson CJ, Bradley JA, Friend PJ, et al. Alemtuzumab (CAMPATH 1H) induction therapy in cadaveric kidney transplantation–efficacy and safety at five years. *Am J Transplant* 2005; 5: 1347.
22. van Gelder T, Hilbrands LB, Vanrenterghem Y, et al. A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. *Transplantation* 1999; 68: 261.
23. Hill P, Gagliardini E, Ruggenenti P, Remuzzi G. Severe early acute humoral rejection resulting in allograft loss in a renal transplant recipient with Campath-1H induction therapy. *Nephrol Dial Transplant* 2005; 20: 1741.
24. Sijpkens YW, Doxiadis, II, Mallat MJ, et al. Early versus late acute rejection episodes in renal transplantation. *Transplantation* 2003; 75: 204.