

Induction and Donor Specific Antibodies in Low Immunologic Risk Kidney Transplant Recipients

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Abstract

Background Optimal induction for patients without pretransplant donor-specific antibodies (DSAs) is poorly defined. The goal of this study was to compare the incidence of *de novo* DSA (dnDSA) and graft outcomes between induction therapies in patients with a negative virtual crossmatch (VXM).

Methods A retrospective chart review was performed, identifying 782 patients with a negative VXM who underwent kidney transplantation at a single, high-volume institution between January 2013 and May 2017. Kaplan–Meier analysis was used to assess the incidence of dnDSA and allograft survival between induction therapies in this group. dnDSA is defined as the development of new post-transplant DSA, at any MFI level.

Results Induction therapy included alemtuzumab ($N=87$, 11%), basiliximab ($N=522$, 67%), and anti-thymocyte globulin (ATG; $N=173$, 22%). One-year graft survival was similar between groups (alemtuzumab, 100%; basiliximab, 98%; ATG, 99%). Incidence of acute rejection at 1 year was <2% and not different between the three groups. Alemtuzumab was associated with the highest incidence of dnDSA at 14%, compared with 5% and 8% in basiliximab and ATG groups, respectively, at 1 year ($P=0.009$). In multivariate regression analyses, alemtuzumab retained its significant association with a dnDSA HR of 2.5 (95% CI, 1.51 to 4.25; $P=0.0004$).

Conclusions In summary, alemtuzumab was associated with a higher rate of dnDSA development in patients with a negative VXM; however, this finding was not associated with rejection or graft failure.

KIDNEY360 1: 1407–1418, 2020. doi: <https://doi.org/10.34067/KID.0000122020>

Introduction

The use of immunosuppression medications as induction therapy is routine in the majority of kidney transplants, with the ultimate goal of reducing the risk of early acute rejection (1). In addition to decreased risk of early acute rejection, induction therapy can potentially confer the benefit of reducing the intensity of subsequent immunosuppression regimens (including steroid use), improving graft survival, and decreasing delayed graft function (DGF) when compared with no induction therapy (2–4). Induction therapy is of particular benefit to those at high risk of rejection, including patients who are sensitized. However, as immunosuppression therapies in transplants have evolved, the appropriate induction agent for a specific patient population has not always been clear, particularly for patients with varying immunologic risks. As with any immunosuppression regimen, inappropriate use of induction therapy can also result in infectious complications or post-transplant malignancy (5,6).

Multiple previous studies have described the benefits and risks associated with various induction regimens; however, there remains a lack of data demonstrating which induction therapy is superior in patients

with or without donor-specific antibody (DSA) (2,7,8). Patients with a high risk of rejection often have preformed DSA before transplant and, as a result, will undergo desensitization or will receive a more aggressive immunosuppression regimen after transplant. At the same time, patients without pretransplant DSA, who are deemed low risk for rejection, can subsequently develop *de novo* DSA (dnDSA) post-transplant. The presence of DSA post-transplant has already been demonstrated to have a significantly deleterious effect on graft function and survival (9,10). Therefore, it is critical to better understand the relationship between induction therapies and the development of dnDSA post-transplant. Our institution has implemented induction protocols that stratify patients on the basis of the intensity of pretransplant virtual crossmatch (VXM) (11,12). The most recent protocol divides patients into three groups: (1) negative (absence of pretransplant DSA); (2) VXM borderline positive (<1000 mean fluorescence intensity sum [MFI_{sum}]); and (3) VXM positive (≥ 1000 MFI_{sum}). The goal of this study is to compare the incidence of dnDSA and graft outcomes between induction therapies in patients with no pretransplant DSA.

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Materials and Methods

Data Source and Patient Population

This was a single-center, longitudinal, cohort study of patients undergoing kidney transplantation at our institution with alemtuzumab, anti-thymocyte globulin (ATG), or basiliximab induction between January 2013 and May 2017. This study was approved by the University of Wisconsin–Madison Minimal Risk Institutional Review Board (Health Sciences) under the title “Outcomes of Kidney Transplant Recipients” (institutional review board number is 2014-1072-CR004). Data were obtained from the prospectively collected Wisconsin Allograft Recipient Database and electronic medical records at the University of Wisconsin Hospital. Patients were excluded if they did not receive induction with alemtuzumab, rabbit ATG, or basiliximab; if they received any of the above agents in combination; if they were not tested for DSA pretransplant; and if they were <18 years old. Of the patients who met the inclusion criteria, we further identified those with a negative VXM, which indicated they did not have pretransplant DSA level, to be included in this study. Patients were then grouped according to their induction therapy (alemtuzumab, basiliximab, ATG). The choice of induction therapy in this low-risk patient population is typically made on the basis of patient-specific variables, including age, primary cause of ESKD, and a compelling indication for early steroid withdrawal (ESW). In general, at our institution, basiliximab with long-term steroid use is the induction therapy of choice for patients who are low risk. Alemtuzumab with ESW is reserved for patients <60 years old who are deemed to benefit from limited steroid use. These patients include those with sensitivities to steroids, such as individuals with diabetes or those with steroid psychosis-related symptoms. ATG with long-term steroid use is typically given to those who have autoimmune disorders as the primary cause of renal failure and those who are at risk of recurrence, such as those with IgA nephropathy or FSGS. During the study period, alemtuzumab was given as a single, intraoperative, 30-mg dose for induction. At our institution, dosing of ATG for induction involves an intraoperative dose of 1.5 mg/kg, followed by daily postoperative dosing to a goal of 4.5–6 mg/kg, dependent on compelling conditions. Basiliximab is given as a single, intraoperative, 20-mg dose, with an optional additional 20-mg dose given on postoperative day 3, per surgeon discretion. In the study presented here, 67% ($N=350$) of patients who received basiliximab induction received two doses. The post-transplant, protocolized, maintenance immunosuppressive regimen at our center is a triple drug regimen consisting of tacrolimus, mycophenolate, and corticosteroids. Institutional protocol dictates tacrolimus troughs range between 8 and 12 ng/ml for the first year after transplant. No significant differences in mean trough levels were found at 1 month, 3 months, 6 months, or 1 year. Mean (\pm SD) 3-month trough levels between induction groups were as follows: alemtuzumab, 7.8 ± 2.8 ng/ml; basiliximab, 8.2 ± 2.9 ng/ml; and ATG, 8.3 ± 3.3 ng/ml ($P=0.51$). At our institution, tacrolimus trough levels are not run any differently on the basis of steroid use in the patient. Post-transplant biopsies are not routinely performed in patients with a negative pretransplant VXM. Instead, for-cause biopsies are performed in cases of elevated creatinine or the development of DSA in patients.

Changes in maintenance immunosuppression were made if dnDSA was detected in a patient. After undergoing for-cause biopsy, patients who were identified as having rejection were treated for rejection as previously described (13). Patients who had a negative biopsy specimen after the development of dnDSA underwent optimization of tacrolimus and mycophenolate doses. Belatacept is infrequently used as a calcineurin substitute in the setting of compelling scenarios.

Data Collection and Outcomes

Primary outcomes included the development of dnDSA, graft survival, and incidence of biopsy sample-proven rejection. dnDSA was defined as the development of new post-transplant DSA, at any MFI level. Graft failure was defined as a return to dialysis, retransplantation, patient death, transplant nephrectomy, or primary nonfunction. Secondary outcomes included the incidence of cytomegalovirus (CMV) viremia, BK viremia, antibody-mediated rejection (AMR), acute cellular rejection (ACR), DGF, and length of hospital stay. CMV infection, defined as viremia *via* molecular-diagnostic testing (positive PCR) or biopsy sample-proven end organ disease *via* diagnosis code, within the study period. Molecular-diagnostic methodology was consistent throughout the study period, with the exception of the adoption of the World Health Organization international standard in 2015, which resulted in a conversion from copies per milliliter to international unit per milliliter. BK viremia was defined as borderline positive (>1000 copies/ml) and positive ($>10,000$ copies/ml). AMR and ACR were both identified as biopsy sample-proven rejection per pathology reports. Data on organ donors and recipients were collected including ethnicity, sex, age, and body mass index (BMI). Kidney Donor Profile Index (KDPI), donor type (live, donor after cardiac death, donor after brain death), and cold ischemia time (CIT) data were also collected on organ donors. CIT was calculated in deceased donors only and in all donors combined. Additional data collected on recipients of transplants included the following: blood transfusion, calculated panel-reactive antibodies (cPRA), pretransplant dialysis, and HLA mismatch.

Anti-HLA Antibody Screening by Solid-Phase Fluorescent Beads

DSAs were detected pre- and post-transplant using Lumines single antigen beads (One Lambda, Canoga Park, CA), performed according to the manufacturer's instructions with a reduced volume of beads (3 versus 5 μ l) (14). In our program, we do not rely on strict MFI cutoffs to assign HLA antibody specificities. Instead, antibodies were identified using multiple criteria, including patterns of epitope reactivity, MFI value, specific bead behaviors, and assay background, as described previously (15). All DSAs detected in this study had MFI values >100 . DSAs were classified as *de novo* if they appeared after transplantation and were not detected in pretransplant samples. Because pretransplant antibodies did not need to meet a minimum MFI threshold to be “identified,” *de novo* antibody identified in this study is less likely to be due to increases in weak pretransplant DSA. Previous studies have established that low levels of DSA (MFI <1000) can result in AMR, which

indicates that low levels of DSA are clinically significant and should be followed (13).

The strength of dnDSA was represented as the sum of the MFI value (MFI_{sum}) of all DSAs. Since 2014, routine post-transplant monitoring of DSA was performed on all recipients of transplants at 6 and 12 months, and annually thereafter. Patients with a pretransplant cPRA greater than zero were tested at an additional 3-week time point. Patients with dnDSA underwent transplant biopsy. All patients undergoing renal transplant biopsy for other reasons had DSA testing done as a part of the biopsy visit. The yearly DSA monitoring included patients transplanted before 2014 (16). Median MFI_{sum} of dnDSA and the 25th–75th interquartile range (IQR) was calculated using the first values that were found to be positive for HLA class 1 and class 2. Immuno-dominant DSA was determined as the specificity with the highest MFI value when first detected as positive.

Statistical Analyses

Statistical analysis was performed with SAS software, and *P* values <0.05 were considered statistically significant. Differences between induction groups were assessed with

ANOVA for continuous variables and the Fisher exact tests for nominal variables. The methods of Kaplan and Meier were used to estimate the incidence of dnDSA, graft survival, patient survival, rejection, CMV viremia, and BK viremia; rates were compared between induction groups using log-rank tests. Multivariable analyses were carried out using Cox proportional hazards regression models. After initial multivariable analyses were run, significant variables were included in an additional multivariable analysis to determine the relative effect of each variable on dnDSA development. The chi-squared was used for nominal variables.

A propensity-score matching analysis was also performed to help control for clinical differences between groups. Due to the size of each population and the need to control for many variables, the alemtuzumab cohort (*N*=87) was matched to a combined basiliximab/ATG cohort (*N*=348) on a 1:4 basis.

Results

A total of 1147 patients underwent kidney transplantation from January 2013 to May 2017. Of these patients, 195 were

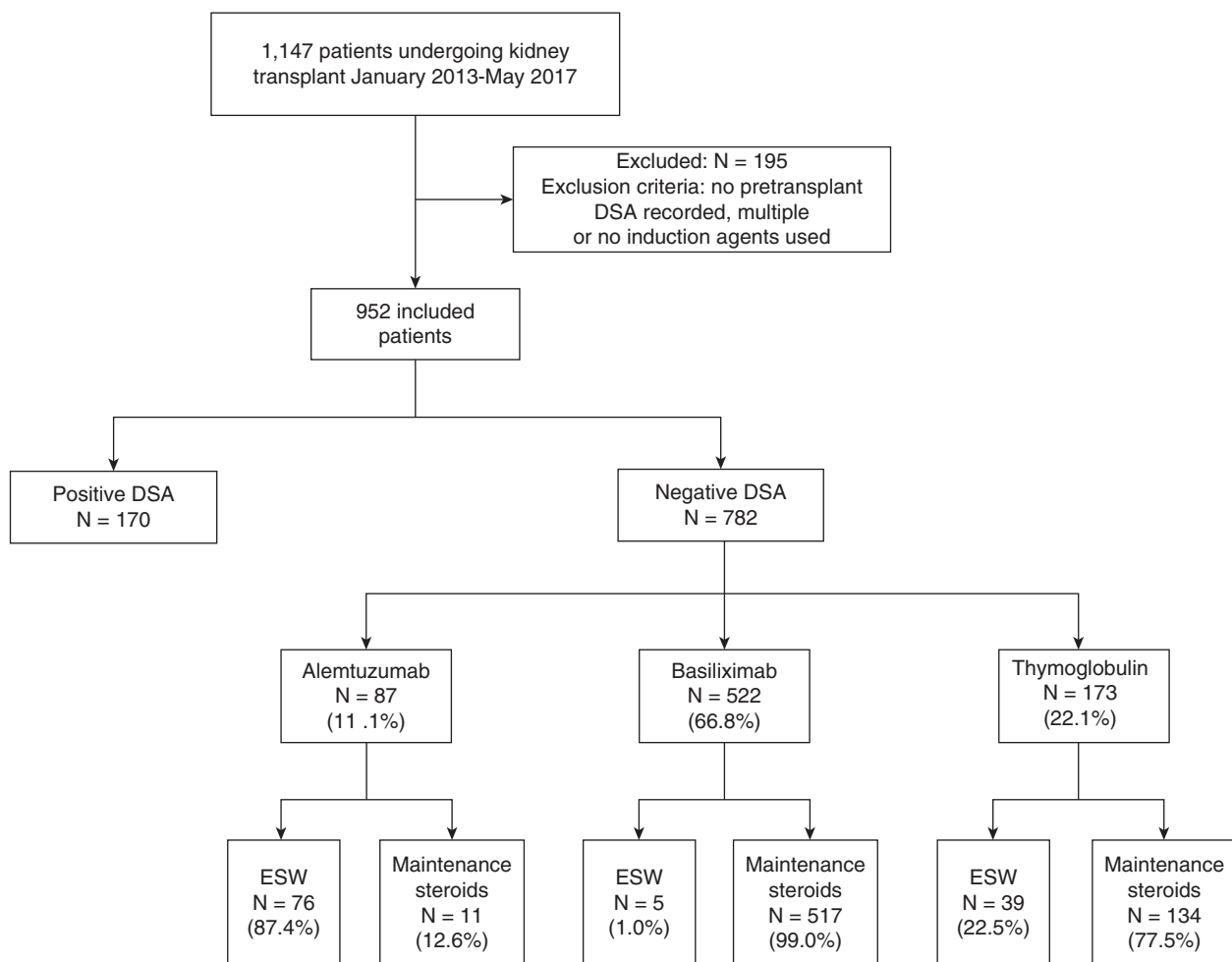


Figure 1. | Study flowchart of kidney transplant population. Patients were excluded if DSA was not tested for pretransplant or no induction agents were used. DSA, donor specific antibody; ESW, early steroid withdrawal.

excluded on the basis of the criteria listed above. Of the 952 included patients, 782 patients were identified as having a negative VXM and were included in this study. The majority of patients received basiliximab at 67% ($N=522$); 11% ($N=87$) received alemtuzumab and 22% ($N=173$) received ATG (Figure 1).

Patients Who Received Alemtuzumab Were Significantly Younger and Less Sensitized

Demographic data and baseline characteristics for recipients of kidney transplants are presented in Table 1. Patients who received alemtuzumab were significantly younger, with a mean age of 47.9 ± 12.3 years compared with 54.9 ± 12.9 and 51.2 ± 12.8 years in the basiliximab and ATG groups, respectively ($P < 0.001$). Patients who received alemtuzumab were more likely to be White, at 82%, compared with 76% of patients on basiliximab and 71% of patients on ATG ($P < 0.01$). No difference was seen in sex or BMI between groups. Notably, patients who received alemtuzumab were less sensitized compared with both basiliximab and ATG groups, as evidenced by fewer blood transfusions ($P < 0.02$) and a lower cPRA ($P < 0.001$). Additionally, there were significantly more patients in the ATG induction group who had undergone a previous kidney transplant, at 22% ($N=38$), compared with 8% ($N=42$) in the basiliximab and 9% ($N=8$) in the alemtuzumab induction groups ($P < 0.001$).

Patients Who Received Alemtuzumab Were More Likely Recipients of Live-Donor Transplants

Demographic data and baseline characteristics of organ donors are listed in Table 2. Patients who received alemtuzumab were more likely to receive a live donor kidney with low KDPI compared with basiliximab and ATG groups ($P < 0.0006$). Mean (\pm SD) KDPI in the alemtuzumab group was $41\% \pm 28\%$, although this was only significantly lower than the basiliximab group, which had a mean (\pm SD) of $51\% \pm 28\%$. Overall, the mean CIT in the alemtuzumab group was significantly lower at 12.9 ± 7.1 hours when compared

with basiliximab (14.9 ± 6.4 hours) and ATG (15.6 ± 7.4 hours), which is likely a reflection of the alemtuzumab group being more likely to receive a live donor kidney ($P < 0.05$). When live donors were excluded, no significant CIT difference existed between induction groups. The mean age at donation, sex, or BMI were not significantly different between groups.

Highest Incidence of dnDSA Seen in Patients Who Received Alemtuzumab

The overall incidence of dnDSA at 1 year in patients who received a kidney transplant with no pretransplant DSA during this period was 7%. At 1-year post-transplant, 14% of patients who received alemtuzumab as induction therapy developed dnDSA (Table 3). This incidence of dnDSA is significantly higher than the incidence seen in the basiliximab and ATG induction groups ($P = 0.0009$). At 1 year, the basiliximab group had the lowest incidence of dnDSA at 5%; ATG demonstrated an incidence of 8% (Figure 2). Fifty percent of the dnDSA that developed in the alemtuzumab induction group was HLA class 1 alone, 25% was class 2 alone, and 25% was both class 1 and 2. The basiliximab induction group primarily developed class-2 dnDSA (44%), whereas the ATG induction group primarily developed class-1 dnDSA (43%) ($P = 0.36$) (Figure 3). An additional analysis was performed to compare rates of dnDSA development in patients who received ESW in the alemtuzumab ($N=76$) and ATG ($N=39$) induction groups. When controlling for ESW, the alemtuzumab induction group still developed dnDSA at a greater rate compared with the ATG group at 1 year (15% versus 5%; $P < 0.02$) (Figure 4). Tacrolimus trough levels were not significantly different between groups at 3 months. The mean 3-month trough levels for each group were as follows: alemtuzumab, 7.8 ± 2.8 ng/ml; basiliximab, 8.2 ± 2.9 ng/ml; and ATG, 8.3 ± 3.3 ng/ml ($P = 0.51$).

When analyzed in a multivariate analysis, including baseline characteristics, steroid withdrawal, and belatacept use, alemtuzumab demonstrated a 4.2-increased risk of dnDSA development relative to ATG (hazard ratio [HR], 4.2; 95%

Table 1. Baseline characteristics of recipients

Recipient Characteristics (total $N=782$)	Alemtuzumab ($N=87$)	Basiliximab ($N=522$)	ATG ($N=173$)	<i>P</i> Value
Sex, <i>n</i> (%)				0.45
Male	59 (68)	356 (68)	109 (63)	
Female	28 (32)	166 (32)	64 (37)	
Race, <i>n</i> (%)				0.01
White	71 (82)	395 (76)	123 (71)	
Black	7 (8)	65 (12)	34 (20)	
Other	9 (10)	62 (12)	16 (9)	
Age at transplant (yr), mean (range)	47.9 (18.6–69.6)	54.9 (20.8–81.4)	51.2 (18.8–73.0)	<0.001
BMI (kg/m^2), mean (range)	29.2 (19.2–40.4)	28.6 (16.3–47.6)	28.3 (16.3–40.8)	0.44
Blood transfusion, <i>n</i> (%)	25 (29)	229 (44)	86 (50)	<0.02
Previous kidney transplant, <i>n</i> (%)	8 (9)	42 (8)	38 (22)	<0.001
Pretransplant dialysis, mo	21.6	26.6	26.0	0.75
End cPRA, % mean \pm SD	7.7 \pm 22.6	12.6 \pm 27.0	24.7 \pm 37.6	<0.001
HLA mismatch, mean \pm SD (out of 6)	4.0 \pm 1.5	3.9 \pm 1.5	3.8 \pm 1.7	0.69
Belatacept, <i>n</i> (%)	21 (24)	1 (0.2)	17 (10)	<0.001
Early steroid withdrawal, <i>n</i> (%)	76 (87)	5 (1)	39 (23)	<0.001

ATG, anti-thymocyte globulin; BMI, body mass index; cPRA, calculated panel-reactive antibody.

Table 2. Baseline characteristics of donors

Donor Characteristics (total N=782)	Alemtuzumab (N=87)	Basiliximab (N=522)	ATG (N=173)	P Value
Sex, n (%)				0.26
Male	41 (47)	294 (56)	92 (53)	
Female	46 (53)	228 (44)	81 (47)	
Race, n (%)				0.86
White	80 (92)	475 (91)	154 (89)	
Black	2 (2)	19 (4)	5 (3)	
Other	5 (6)	28 (5)	14 (8)	
Donor type, n (%)				0.0006
Live	47 (54)	177 (34)	57 (33)	
DBD	26 (30)	250 (48)	71 (41)	
DCD	14 (16)	95 (18)	45 (26)	
Age at donation (yr), mean (range)	43.3 (6.0–69.0)	44.4 (1.0–76.0)	42.7 (4.0–74.0)	0.34
BMI (kg/m ²), mean (range)	27.8 (15.1–59.9)	28.0 (12.2–60.6)	28.7 (12.7–63.3)	0.46
KDPI, %±SD	41±28	51±26	49±28	0.10
CIT (h), mean (range)	12.9 (1.0–27.2)	14.9 (0.5–34.7)	15.6 (1.0–40.9)	0.06
Deceased donor only CIT (h), mean (range)	15.6 (6.7–27.2)	15.6 (4.5–34.7)	16.7 (2.5–40.9)	0.25

ATG, anti-thymocyte globulin; DBD, donation by brainstem death; DCD, donation by cardiac death; BMI, body mass index; KDPI, Kidney Donor Profile Index; CIT, cold ischemia time.

CI, 1.57 to 11.04; $P=0.004$). Basiliximab was not associated with an increased risk of dnDSA development. Black patients demonstrated a 2.4-increased risk of dnDSA development relative to White patients (HR, 2.4; 95% CI, 1.42 to 4.02; $P=0.001$), and older age at transplant demonstrated a decrease in risk of dnDSA development (HR, 0.98; 95% CI, 0.96 to 0.99; $P=0.01$) (Table 4). In a multivariate model containing alemtuzumab, Black race, age at transplant, and hospital length of stay, alemtuzumab retained its strong association with the incidence of dnDSA (HR, 2.5; 95% CI, 1.51 to 4.25; $P=0.0004$) (Table 5).

Alemtuzumab Not Associated with Inferior Rejection or Graft Survival Rates

Despite the significant difference of dnDSA incidence, there was no association between induction agent and the incidence of biopsy sample–proven rejection, overall actuarial graft survival, or patient survival. Patients were followed for a mean of 2.4 years. Episodes of rejection were further characterized as AMR or ACR on the basis of biopsy-

specimen results. No episodes of AMR at 1 year occurred in patients receiving alemtuzumab; low incidences of 0.4% and 2% were seen in the basiliximab and ATG groups, respectively. The incidence of ACR was greater than AMR across all groups; however, these results were still not statistically significant (Figure 5). Importantly, the development of dnDSA and occurrence of ACR and AMR did not correspond with a higher rate of graft loss. Patients who received alemtuzumab had 100% graft survival at 1 year; similarly, the basiliximab and ATG groups demonstrated graft survival rates of 98% and 99%, respectively (Table 3). In multivariate analyses, induction therapy had no significant effect on graft survival, patient survival, or any type of rejection (Supplemental Tables 1–5).

We performed a propensity-score matching analysis to control for clinical differences seen among groups. Graft survival, patient survival, rejection incidence, and dnDSA development were measured outcomes. Groups were matched on a 1:4 basis between alemtuzumab cohort ($N=87$) and combined basiliximab/ATG cohort ($N=348$).

Table 3. Comparison of outcomes by induction group

Variable	Alemtuzumab	Basiliximab	ATG	P Value
Development of dnDSA at 1 yr, % (<i>n</i>)	14 (12)	5 (27)	8 (14)	0.0009
Graft survival at 1 yr, %	100	98	99	0.81
Rejection at 1 yr, %				
AMR	0.0	0.4	2	0.64
ACR	6	5	5	0.66
CMV viremia at 1 yr, %	37	22	38	0.0003
BK viremia at 1 yr, %				
BK >1000	21	25	24	0.45
BK >10,000	15	17	12	0.24
Delayed graft function, %	4	8	6	0.18
Length of hospital stay (d), mean±SD	4.3±1.7	5.1±3.0	5.1±2.1	0.02

ATG, anti-thymocyte globulin; dnDSA, *de novo* donor-specific antibody; AMR, antibody-mediated rejection; ACR, acute cellular rejection; CMV, cytomegalovirus.

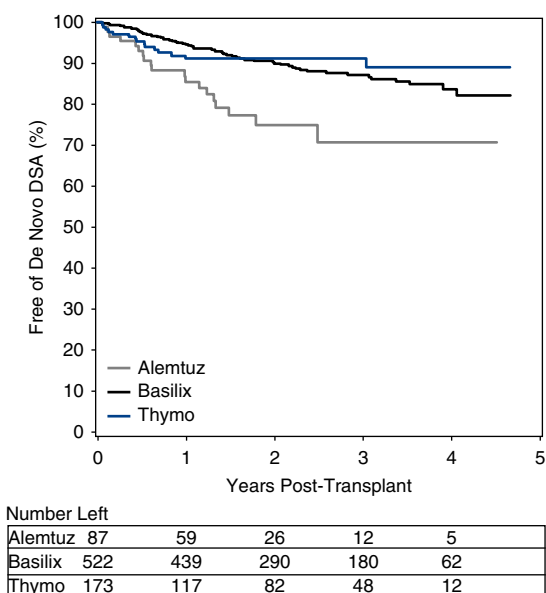


Figure 2. | Kaplan–Meier curves comparing the development of *de novo* DSA by induction group. Table under the graph indicates the number of patients remaining in each induction group over time. Alemtuz, alemtuzumab; basilix, basiliximab; thymo, thymoglobulin.

The alemtuzumab group had a significantly higher 1-year rate of dnDSA development at 15% compared with 5% in the combined basiliximab/ATG group ($P=0.0004$). No significant difference was seen for all other outcomes.

ATG Associated with Significantly Greater Incidence of CMV Viremia but Not BK Viremia

Incidence of CMV and BK viral infection were examined between induction groups. The depletion induction agents had significantly higher incidence of CMV viremia on univariate analysis than that seen in the basiliximab group

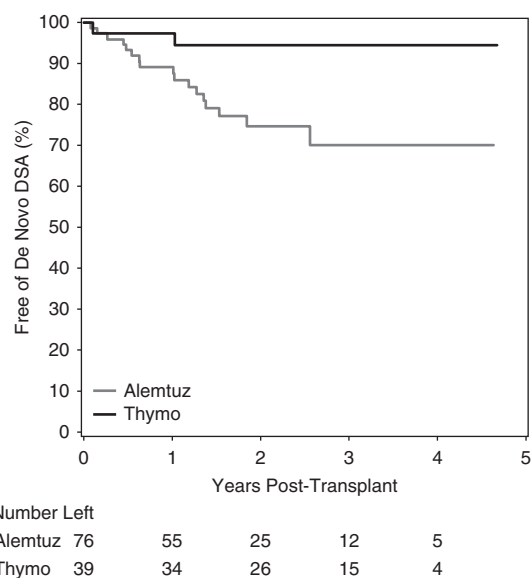


Figure 4. | Kaplan–Meier curves comparing the development of *de novo* DSA in patients who received early steroid withdrawal. Table under the graph indicates the number of patients remaining in each induction group over time. Alemtuz, alemtuzumab; thymo, thymoglobulin.

(ATG, 38%; alemtuzumab, 37%; basiliximab, 22%; $P<0.0003$) (Table 3). There was no difference in incidence of CMV viremia on univariate analysis between ATG and alemtuzumab groups ($P=0.83$). In a multivariate analysis, basiliximab conferred a protective benefit against CMV viremia (HR, 0.6; 95% CI, 0.41 to 0.78; $P=0.0004$), alemtuzumab was not significantly different from the referent ATG in CMV risk (HR, 0.9; 95% CI, 0.54 to 1.67; $P=0.85$) (Supplemental Tables 6–8). The incidence of BK viremia was not statistically significantly different at either borderline positivity (BK >1000 copies/ml; alemtuzumab, 21%; basiliximab, 25%; ATG, 24%; $P=0.45$) or positive (BK >10,000 copies/

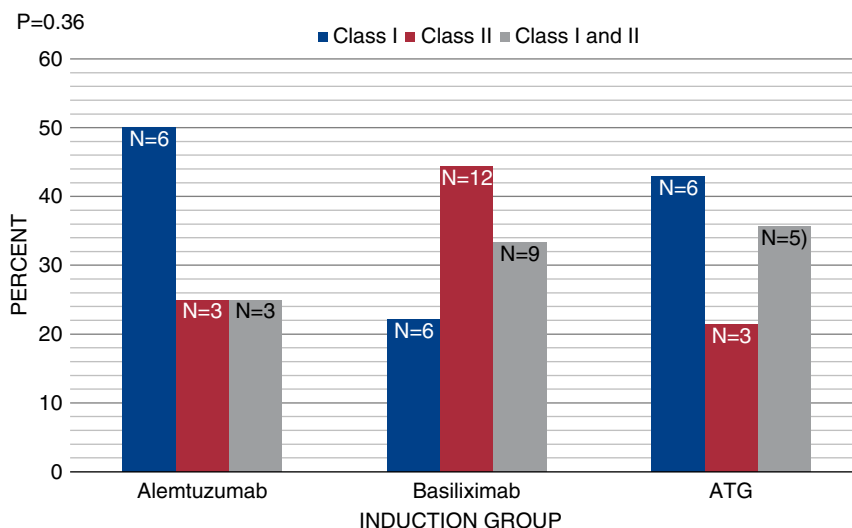


Figure 3. | Development of dnDSA by class in induction group. ATG, anti-thymocyte globulin; dnDSA, *de novo* DSA.

Table 4. Risk of development of dnDSA

Variable	Multivariate Analysis	
	HR (95% CI)	P Value
Induction group		
Anti-thymocyte globulin	1	
Alemtuzumab	4.2 (1.57 to 11.04)	0.004
Basiliximab	1.2 (0.67 to 2.26)	0.50
Race		
White	1	
Black	2.4 (1.42 to 4.02)	0.001
Other	1.6 (0.89 to 3.02)	0.12
Donor type		
Live	1	
DBD	0.9 (0.53 to 1.58)	0.75
DCD	1.7 (0.95 to 3.02)	0.07
Age at transplant (yr)	0.98 (0.96 to 0.99)	0.01
End cPRA	1.0 (0.99 to 1.01)	0.94
Transplant to discharge (d)	1.1 (1.00 to 1.14)	0.05
Maintenance steroids	1.7 (0.59 to 4.59)	0.34
Belatacept	1.6 (0.61 to 4.19)	0.34

dnDSA, *de novo* donor-specific antibody; HR, hazard ratio; DBD, donation by brainstem death; DCD, donation by cardiac death; cPRA, calculated panel-reactive antibody.

ml; alemtuzumab, 15%; basiliximab, 17%; ATG, 12%; $P=0.24$) between groups on univariate analysis. On multivariate analysis where ATG was the referent, there was also no difference in risk of BK virus on the basis of induction type (alemtuzumab, HR, 1.6; 95% CI, 0.68 to 3.98; $P=0.27$; basiliximab, HR, 1.3; 95% CI, 0.76 to 2.13; $P=0.36$) (Figure 6).

Other outcome measurements include DGF and length of hospital stay. Overall rates of DGF were low at <10%. The basiliximab induction group had the highest DGF incidence among groups at 8%; however, this was not statistically significant (4% alemtuzumab versus 8% basiliximab versus 6% ATG; $P=0.18$). The mean length of hospital stay was lowest in the alemtuzumab group at 4.3 days compared with 5.1 days in both the basiliximab and ATG groups ($P<0.02$) (Table 3).

Among Those Who Developed dnDSA, Graft Survival and Rejection Rates Are Equivalent between Induction Groups

Lastly, we further characterized outcomes among those who developed dnDSA at 1 year between the induction groups (Table 6). The alemtuzumab induction group had the lowest median MFI_{sum} of 1179 (IQR, 640.3–2335) for

dnDSA compared with basiliximab (median MFI_{sum}, 2264; IQR, 1231–8252) and ATG (median MFI_{sum}, 2138; IQR, 752.3–5642). However, no statistically significant difference of median MFI_{sum} was found between groups ($P=0.27$). The average number (\pm SD) of DSAs contributing to the MFI_{sum} was similar between groups (alemtuzumab, 1.6 ± 0.9 ; basiliximab, 2.1 ± 1.9 ; thymoglobulin, 2.0 ± 1.6 ; $P=0.70$). Mean time (\pm SD) to development of dnDSA post-transplant was longest in the basiliximab group at 198.6 ± 95.3 days, but was not different from the other induction groups (alemtuzumab, 172.1 ± 112 days; ATG, 163.2 ± 104.9 days; $P=0.53$). The majority of patients who developed dnDSA in the alemtuzumab induction group were on the ESW protocol (83%, $N=10$), whereas 100% ($N=27$) of the patients in the basiliximab and 86% ($N=12$) of the patients in the ATG induction groups who developed dnDSA were on maintenance steroids ($P<0.001$). Graft survival at 1 year was excellent between all three induction groups. The alemtuzumab induction group had the lowest overall graft survival at 75% ($N=9$); however, this was not significantly different from other groups. The highest rate of AMR at 1 year was seen in the alemtuzumab induction group (17%; $N=2$), with the highest overall AMR rate demonstrated in the basiliximab induction group (19%; $N=5$). At 1 year, 42% ($N=5$) of the patients on alemtuzumab with dnDSA developed ACR compared with 30% ($N=8$) and 21% ($N=3$) in the basiliximab and ATG groups, respectively ($P=0.53$). Changes in MFI levels of the immunodominant dnDSA are represented in Figure 7 for each patient who developed rejection during the study period.

Discussion

Here, we present the results of a retrospective study examining the development of dnDSA and kidney allograft outcomes between the induction therapies alemtuzumab, basiliximab, and ATG in patients with low immunologic risk. Our results suggest that patients with no pretransplant DSA who receive alemtuzumab induction therapy are more likely to form dnDSA than those who receive basiliximab or ATG. This association was independent of other risk factors, including Black race, age at transplant, and hospital length of stay. Length of hospital stay was likely lowest in the alemtuzumab group due to the significantly higher rate of living donors, which has previously been shown to be associated with shorter hospital stays (17). Notably, the increased incidence of dnDSA in those receiving alemtuzumab was not associated with a significantly higher incidence of biopsy sample-proven rejection compared with other induction groups at 1 year. Although basiliximab demonstrated a lower rate of dnDSA development compared with ATG at 1 year, the rates between these two groups were not significantly different when evaluated in the controlled analysis. ATG was found to have a significantly higher incidence of CMV viremia. Despite these differences in the development of dnDSA and CMV viremia, no single induction therapy was associated with a superior overall graft survival rate.

Current induction regimens commonly include the use of the T lymphocyte-depleting agents ATG or alemtuzumab or nondepleting agents, such as basiliximab. Each of these agents carries its own set of risks and benefits. ATG,

Table 5. Alemtuzumab is associated with greatest risk of dnDSA development

Variable	Multivariate Analysis	
	HR (95% CI)	P Value
Alemtuzumab	2.5 (1.51 to 4.25)	0.0004
Black race	2.3 (1.44 to 3.77)	0.0006
Age at transplant (yr)	0.98 (0.96 to 0.99)	0.004
Transplant to discharge (d)	1.1 (1.01 to 1.14)	0.03

dnDSA, *de novo* donor-specific antibody; HR, hazard ratio.

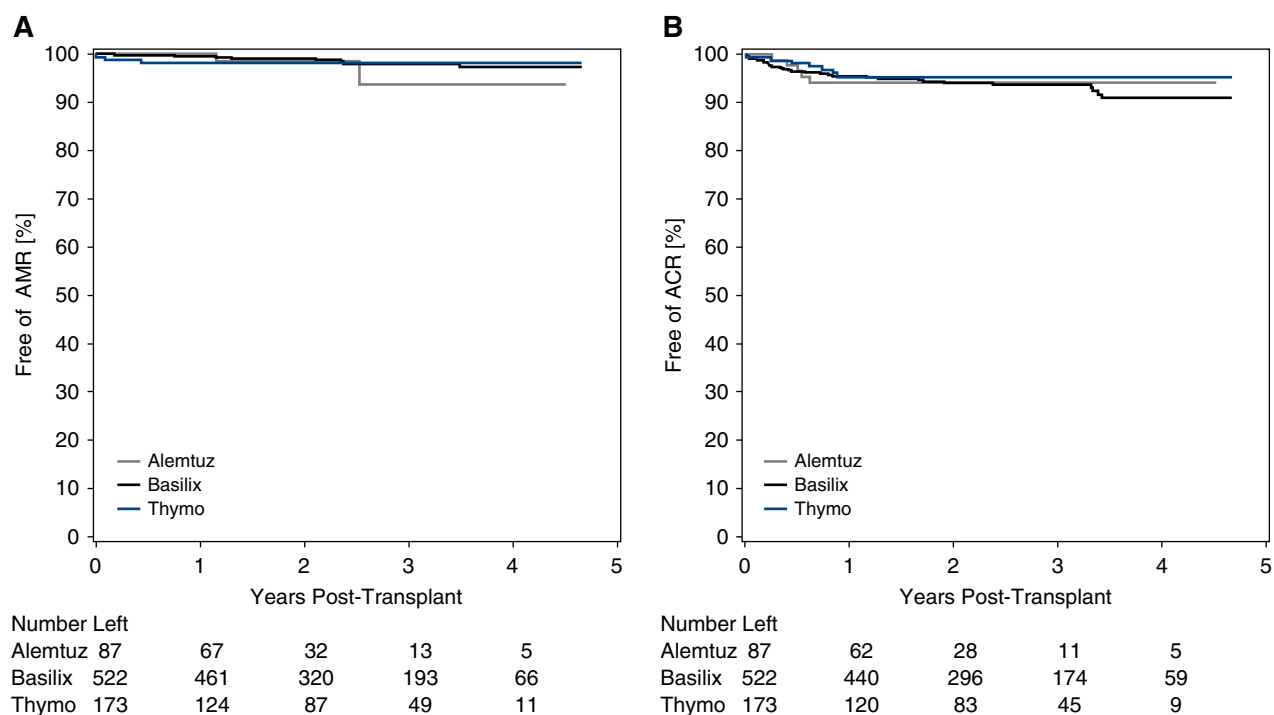


Figure 5. | Kaplan–Meier curves comparing the incidence of (A) AMR and (B) ACR by induction group. Table under the graph indicates the number of patients remaining in each induction group over time. ACR, acute cellular rejection; alemtuz, alemtuzumab; AMR, antibody-mediated rejection; basilix, basiliximab; thymo, thymoglobulin.

a polyclonal T lymphocyte-depleting antibody made in rabbits, has been associated with a decreased risk of acute rejection and increased survival, particularly among patients at high immunologic risk, but has significant side effects, including increased opportunistic infections, thrombocytopenia, and leukopenia (2,18–21). Alemtuzumab is a humanized mAb that targets the cell-surface marker CD52, resulting in the long-term depletion of T lymphocytes

and a more transient depletion of B lymphocytes and monocytes (22). Alemtuzumab has been shown to be effective when used as an induction agent in a steroid-free maintenance regimen (23). In contrast to ATG and alemtuzumab, basiliximab is a nondepleting mAb that inhibits T-lymphocyte activation through the blockade of the cell surface receptor IL-2. Single-dose basiliximab has been shown to be an effective induction agent for patients at low immunologic risk, and has

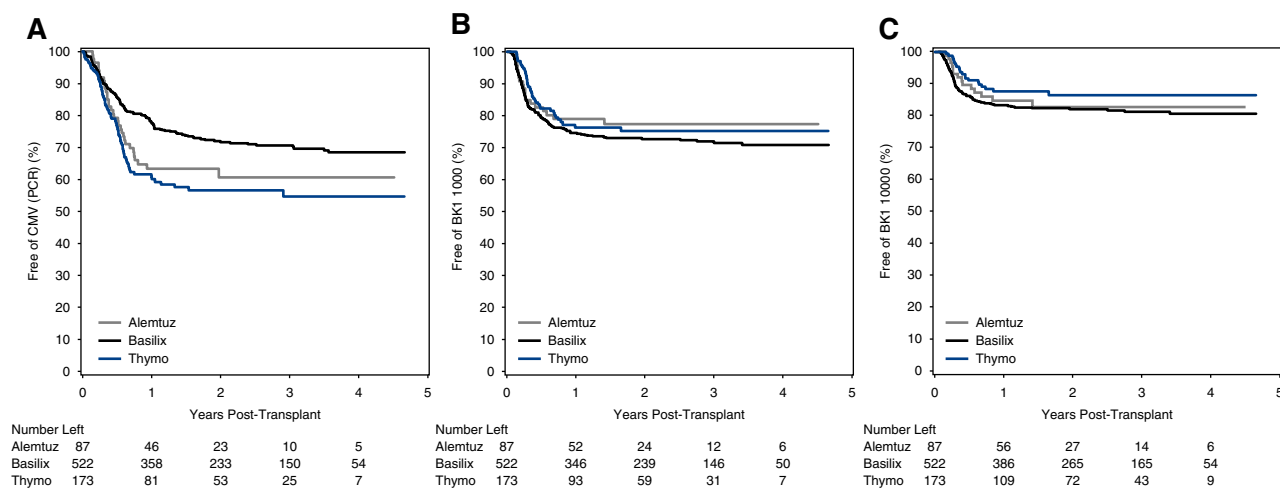


Figure 6. | Kaplan–Meier curves comparing the development of (A) CMV viremia, (B) BK viral load >1000 copies/ml, and (C) BK viral load >10,000 copies/ml by induction group. Table under the graph indicates the number of patients remaining in each induction group over time. Alemtuz, alemtuzumab; basilix, basiliximab; CMV, cytomegalovirus; thymo, thymoglobulin.

Table 6. Comparison of outcomes in patients who developed dnDSA by induction group

Variable	Alemtuzumab (N=12)	Basiliximab (N=27)	ATG (N=14)	P Value
Development of dnDSA at 1 yr, % (n)	14 (12)	5 (27)	8 (14)	0.0009
Sum MFI of dnDSA at first test, median (interquartile range)	1179 (640.3–2335)	2264 (1231–8252)	2138 (752.3–5642)	0.27
Number of DSA contributing to sum MFI, mean±SD	1.6±0.9	2.1±1.9	2.0±1.6	0.70
Days to development of dnDSA, mean±SD	172.1±112	198.6±95.3	163.2±104.9	0.53
Steroid status, % (n)				<0.001
Early steroid withdrawal	83 (10)	0 (0)	14 (2)	
Maintenance steroids	17 (2)	100 (27)	86 (12)	
Graft survival at 1 yr, % (n)	100 (12)	96 (26)	100 (14)	0.61
Graft survival overall, % (n)	75 (9)	93 (25)	93 (13)	0.24
Rejection at 1 yr, % (n)				
AMR	17 (2)	15 (4)	14 (2)	0.98
ACR	42 (5)	30 (8)	21 (3)	0.53
Rejection overall, % (n)				
AMR	17 (2)	19 (5)	14 (2)	0.94
ACR	42 (5)	33 (9)	21 (3)	0.53

dnDSA, *de novo* donor-specific antibody; ATG, anti-thymocyte globulin; MFI, mean fluorescence intensity; AMR, antibody-mediated rejection; ACR, acute cellular rejection.

previously been associated with fewer infectious complications; however, it was associated with a higher incidence of acute rejection in recipients at moderate to high risk compared with ATG (24–27).

Despite the fact that alemtuzumab was not associated with inferior graft outcomes or increased risk of rejection at 1 year, the increased incidence of dnDSA associated with alemtuzumab use in patients with no pretransplant DSA remains a significant finding. Previous studies have demonstrated a strong association between dnDSA development and graft failure (9,28). The delay between dnDSA production and resulting clinical manifestations, such as proteinuria, elevated creatinine, or biopsy specimen-proven rejection is likely a result of antibody damage through chronic repetitive injury to the allograft (10,28–30). Therefore, sufficient time after antibody production is required before the manifestation of allograft injury or failure. The presence of dnDSA before clinical detection represents one explanation for no difference in outcomes among those who received alemtuzumab induction in our study.

Additionally, it is important to note the HLA class-specific antibodies that developed in each induction group,

because not all dnDSAs are equal. The development of HLA class-2 antibodies have previously been associated with a greater risk of AMR compared with HLA class-1 antibodies. In our cohort, 75% of patients who developed dnDSA in the alemtuzumab group formed HLA class-1 dnDSA compared with 56% of those in the basiliximab group and 79% of those in the ATG group. One explanation for preserved outcomes between groups may be that the increase in dnDSA in the alemtuzumab group was primarily HLA class 1. In addition to having the highest rate of dnDSA development, median MFI_{sum} was not significantly lower in the alemtuzumab induction group. Although no difference in patient or graft survival was noted at 1 year, it is important to note that the HLA class-1 dnDSA that developed, regardless of induction group, could potentially affect long-term graft outcomes.

Our findings are supported by Todeschini *et al* (7). In this single-center, matched-cohort study comparing alemtuzumab with combined low-dose ATG/basiliximab, Todeschini *et al*. (7) found alemtuzumab to be associated with a higher incidence of dnDSA, inferior graft function, and B-lymphocyte phenotypic changes that correlated with

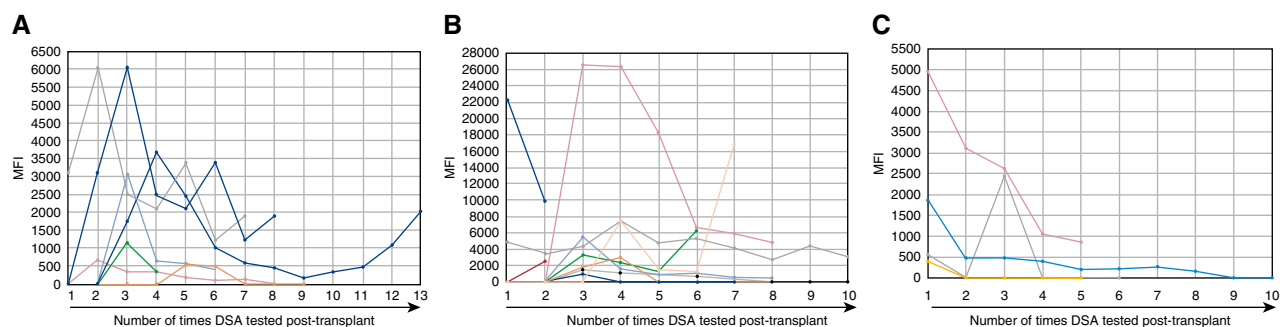


Figure 7. | MFI trend of immunodominant DSA in patients who developed rejection. Immunodominant DSA was defined as the DSA with the highest mean fluorescence intensity (MFI) value when first detected as positive. Each line represents one patient who developed rejection. (A) Alemtuzumab (N=7), (B) basiliximab (N=10), (C) ATG (N=4).

dnDSA development. The authors hypothesized the B-cell depletion with alemtuzumab led to a dysregulated repopulation in the post-transplant follow-up period that was not seen in the ATG/basiliximab cohort, which may be due to elevated B-cell activating factor levels in patients treated with alemtuzumab. In this study, the development of dnDSA was ultimately found to be associated with worse long-term graft function. This association between dnDSA development and worse long-term graft function supports the concept that an extended period is required before the clinical effects (*i.e.*, graft failure) of dnDSA are evident (31). Therefore, patients who develop dnDSA in the post-transplant period may require extended surveillance for graft injury or failure (7).

Alemtuzumab has also frequently been associated with secondary autoimmune disease when given to patients with multiple sclerosis. The mechanism underlying this phenomenon is thought to be related to faster B-lymphocyte than T-lymphocyte recovery after alemtuzumab administration. The recovered B lymphocytes then allow for unregulated B-lymphocyte expansion and antibody production in response to self-antigens. B-lymphocyte repopulation also coincided with increased serum B-cell activating factor, which has been seen in both transplant populations and in other B lymphocyte-related autoimmune disorders (32–34). This mechanism, in addition to the findings by Todeschini *et al.* (7), further support the association of alemtuzumab and dnDSA development seen in our study.

It is important to note that alemtuzumab is often given with the intention of limiting maintenance immunosuppression that is administered. Specifically, steroid use is associated with numerous complications. In our study population, 87% of patients who received alemtuzumab and 23% of patients who received ATG as induction therapy were placed on an ESW protocol and, therefore, did not receive steroids as part of their maintenance immunosuppression regimen. When controlling for maintenance steroid use, the alemtuzumab group still developed dnDSA at the significantly higher rate of 14% compared with 5% in the ATG group at 1 year ($P < 0.02$). No significant differences in tacrolimus trough levels were seen between groups; this is an important finding and requires further investigation. These findings indicate dnDSA development in the alemtuzumab group likely cannot be attributed to lack of maintenance steroid use but may be affected by tacrolimus trough levels.

Limitations

There are several limitations to address in this study. Although several patient factors are taken into consideration when choosing induction therapy in this low-risk group, the choice of induction therapy is ultimately up to the treating physician, which allows for varying degrees of selection bias. Although this study did not find alemtuzumab to be associated with a significantly higher incidence of biopsy sample-proven rejection compared with other groups at 1 year, subclinical rejection and chronic AMR could still develop at varying rates between induction groups beyond this time period. Our current practice is for patients who develop dnDSA to undergo a protocol kidney biopsy; therefore, patients who have developed

rejection after the development of dnDSA in this cohort have been captured. Lastly, this study is limited by the inherent biases associated with retrospective studies.

The widespread use of induction therapy has resulted in significantly reduced rates of rejection in kidney transplant, which is ultimately associated with improved graft survival. Various induction therapies and subsequent maintenance regimens are each associated with potential risks and benefits when used in particular patient populations. Specifically, special attention must be given to patients with low and high immunologic risk for rejection. In a low-risk patient population, we have demonstrated an increased risk of dnDSA production without an association of inferior graft outcomes, including biopsy sample-proven rejection and graft failure, with alemtuzumab when compared with basiliximab and ATG. Additionally, ATG was associated with increased risk of CMV viremia. Despite the overall equivalent outcomes between induction groups, the association of dnDSA development with alemtuzumab induction therapy may warrant increased surveillance in this patient population. Further studies examining long-term follow-up are required.

Disclosures

All authors have nothing to disclose.

Funding

None.

Author Contributions

N. Bath, J. Descourouez, T. Ellis, D. Hager, M. Jorgenson, D. Kaufman, and R. Redfield were responsible for investigation; N. Bath, D. Hager, and M. Jorgenson were responsible for data curation; N. Bath, L. Hidalgo, G. Levenson, and D. Mandelbrot were responsible for formal analysis; N. Bath, S. Parajuli, and R. Redfield wrote the original draft; J. Descourouez, A. Djamali, D. Kaufman, G. Levenson, D. Mandelbrot, S. Parajuli, and R. Redfield were responsible for methodology; A. Djamali was responsible for resources; A. Djamali, D. Kaufman, D. Mandelbrot, and R. Redfield conceptualized the study; A. Djamali, D. Kaufman, S. Parajuli, and R. Redfield provided supervision; L. Hidalgo was responsible for validation; and all authors reviewed and edited the manuscript.

Supplemental Material

This article contains the following supplemental material online at <http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000122020/-/DCSupplemental>.

Supplemental Table 1. Risk of kidney graft survival.

Supplemental Table 2. Risk of patient survival.

Supplemental Table 3. Risk of rejection.

Supplemental Table 4. Risk of antibody mediated rejection.

Supplemental Table 5. Risk of acute cellular rejection.

Supplemental Table 6. Risk of CMV viremia.

Supplemental Table 7. Risk of BK >1000 copies/ml.

Supplemental Table 8. Risk of BK >10,000 copies/ml.

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Received: January 13, 2020 **Accepted:** October 1, 2020

Supplemental Digital Content:

Supplemental Table 1. Risk of kidney graft survival. DBD, donation by brainstem death.

DCD, donation by cardiac death. cPRA, calculated panel reactive antibody

Variable	Multivariate Analysis	
	HR (95% CI)	<i>P</i> value
Induction group	1	
• Anti-thymocyte globulin	3.83 (0.42-35.01)	0.23
• Alemtuzumab	1.01 (0.40-2.53)	0.98
• Basiliximab		
Race	1	
• White	0.53 (0.16-1.77)	0.30
• Black	0.58 (0.18-1.91)	0.37
• Other		
Donor type	1	
• Live	1.52 (0.65-3.56)	0.33
• DBD	2.33 (0.94-5.80)	0.07
• DCD		
Age at transplant, years	1.03 (0.99-1.06)	0.07
End cPRA	0.99 (0.98-1.01)	0.34
Transplant to discharge, days	1.07 (0.99-1.16)	0.10
Maintenance steroids	3.50 (0.35-34.96)	0.29
Belatacept	0.91 (0.08-10.13)	0.94

Supplemental Table 2. Risk of patient survival. DBD, donation by brainstem death. DCD, donation by cardiac death. cPRA, calculated panel reactive antibody

Variable	Multivariate Analysis	
	HR (95% CI)	<i>P</i> value
Induction group	1	
• Anti-thymocyte globulin	3.6 (0.08-168.32)	0.51
• Alemtuzumab	0.5 (0.14-1.63)	0.24
Race	1	
• White	0.3 (0.04-2.76)	0.32
• Black	0.0 (0.0-)	0.99
• Other		
Donor type	1	
• Live	4.3 (1.04-17.34)	0.04
• DBD	2.0 (0.35-11.31)	0.44
• DCD		
Age at transplant, years	1.1 (1.02-1.13)	0.01
End cPRA	0.99 (0.97-1.01)	0.26
Transplant to discharge, days	1.0 (0.84-1.17)	0.95
Maintenance steroids	23.8 (0.23-2475.58)	0.18
Belatacept	9.99 (0.31-325.89)	0.20

Supplemental Table 3. Risk of rejection. DBD, donation by brainstem death. DCD, donation by cardiac death. cPRA, calculated panel reactive antibody

Variable	Multivariate Analysis	
	HR (95% CI)	<i>P</i> value
Induction group		
• Anti-thymocyte globulin	1	
• Alemtuzumab	0.4 (0.07-2.60)	0.36
• Basiliximab	1.3 (0.43-4.0)	0.63
Race		
• White	1	
• Black	2.1 (0.65-6.68)	0.22
• Other	2.4 (0.85-6.50)	0.10
Donor type		
• Live	1	
• DBD	0.4 (0.16-0.96)	0.04
• DCD	0.1 (0.01-0.91)	0.04
Age at transplant, years	1.0 (0.95-1.01)	0.20
End cPRA	1.0 (0.99-1.02)	0.19
Transplant to discharge, days	0.7 (0.48-1.01)	0.054
Maintenance steroids	1.8 (0.27-11.53)	0.56
Belatacept	3.6 (0.61-22.15)	0.16

Supplemental Table 4. Risk of antibody mediated rejection. DBD, donation by brainstem death. DCD, donation by cardiac death. cPRA, calculated panel reactive antibody

Variable	Multivariate Analysis	
	HR (95% CI)	<i>P</i> value
Induction group		
• Anti-thymocyte globulin	1	
• Alemtuzumab	2.3 (0.23-22.8)	0.48
• Basiliximab	0.4 (0.09-1.86)	0.25
Race		
• White	1	
• Black	0.9 (0.10-7.51)	0.88
• Other	2.0 (0.41-10.12)	0.39
Donor type		
• Live	1	
• DBD	0.3 (0.07-1.47)	0.14
• DCD	0.5 (0.08-2.74)	0.41
Age at transplant, years	1.0 (0.95-1.04)	0.81
End cPRA	1.0 (0.97-1.01)	0.40
Transplant to discharge, days	1.0 (0.71-1.32)	0.82
Maintenance steroids	16.3 (0.69-387.66)	0.08
Belatacept	6.9 (0.38-125.07)	0.19

Supplemental Table 5. Risk of acute cellular rejection. DBD, donation by brainstem death. DCD, donation by cardiac death. cPRA, calculated panel reactive antibody

Variable	Multivariate Analysis	
	HR (95% CI)	<i>P</i> value
Induction group		
• Anti-thymocyte globulin	1	
• Alemtuzumab	0.9 (0.22-3.22)	0.81
• Basiliximab	1.9 (0.69-5.31)	0.21
Race		
• White	1	
• Black	2.0 (0.83-4.92)	0.12
• Other	2.0 (0.84-4.61)	0.12
Donor type		
• Live	1	
• DBD	0.7 (0.31-1.46)	0.32
• DCD	0.9 (0.34-2.41)	0.85
Age at transplant, years	1.0 (0.96-1.01)	0.22
End cPRA	1.0 (0.99-1.01)	0.54
Transplant to discharge, days	0.7 (0.55-0.97)	0.03
Maintenance steroids	1.1 (0.23-5.55)	0.88
Belatacept	5.4 (1.36-22.11)	0.02

Supplemental Table 6. Risk of CMV viremia. DBD, donation by brainstem death. DCD, donation by cardiac death. cPRA, calculated panel reactive antibody

Variable	Multivariate Analysis	
	HR (95% CI)	<i>P</i> value
Induction group		
• Anti-thymocyte globulin	1	
• Alemtuzumab	0.9 (0.54-1.67)	0.85
• Basiliximab	0.6 (0.41-0.78)	0.0004
Race		
• White	1	
• Black	0.9 (0.57-1.27)	0.43
• Other	1.2 (0.85-1.83)	0.26
Donor type		
• Live	1	
• DBD	1.1 (0.82-1.59)	0.44
• DCD	1.5 (1.07-2.23)	0.02
Age at transplant, years	1.0 (1.001-1.02)	0.04
End cPRA	1.0 (1.0-1.01)	0.04
Transplant to discharge, days	1.02 (0.97-1.07)	0.43
Maintenance steroids	0.8 (0.48-1.50)	0.56
Belatacept	0.6 (0.29-1.20)	0.15

Supplemental Table 7. Risk of BK >1,000 copies/mL. DBD, donation by brainstem death.

DCD, donation by cardiac death. cPRA, calculated panel reactive antibody

Variable	Multivariate Analysis	
	HR (95% CI)	<i>P</i> value
Induction group		
• Anti-thymocyte globulin	1	
• Alemtuzumab	1.4 (0.68-2.81)	0.38
• Basiliximab	1.0 (0.70-1.55)	0.84
Race		
• White	1	
• Black	1.4 (0.94-2.09)	0.10
• Other	1.1 (0.68-1.70)	0.75
Donor type		
• Live	1	
• DBD	1.0 (0.74-1.47)	0.81
• DCD	0.7 (0.45-1.11)	0.13
Age at transplant, years	1.0 (1.00-1.03)	0.02
End cPRA	1.0 (0.99-1.0)	0.35
Transplant to discharge, days	1.0 (0.97-1.07)	0.43
Maintenance steroids	1.7 (0.83-3.67)	0.15
Belatacept	1.5 (0.70-3.42)	0.28

Supplemental Table 8. Risk of BK >10,000 copies/mL. DBD, donation by brainstem death. DCD, donation by cardiac death. cPRA, calculated panel reactive antibody

Variable	Multivariate Analysis	
	HR (95% CI)	<i>P</i> value
Induction group		
• Anti-thymocyte globulin	1	
• Alemtuzumab	1.6 (0.68-3.98)	0.27
• Basiliximab	1.3 (0.76-2.13)	0.36
Race		
• White	1	
• Black	1.8 (1.14-2.94)	0.01
• Other	1.4 (0.84-2.42)	0.19
Donor type		
• Live	1	
• DBD	1.0 (0.68-1.61)	0.84
• DCD	0.79 (0.46-1.36)	0.40
Age at transplant, years	1.0 (1.0-1.03)	0.02
End cPRA	1.0 (0.99-1.003)	0.23
Transplant to discharge, days	1.0 (0.92-1.06)	0.64
Maintenance steroids	1.3 (0.51-3.13)	0.61
Belatacept	0.9 (0.32-2.64)	0.88