Alemtuzumab in Renal Retransplantation –
Transplant Outcomes and Associated
Infections

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Alemtuzumab in Renal Retransplantation – Transplant Outcomes and Associated Infections

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Abstract: Renal retransplant patients have decreased graft survival compared to primary renal transplant patients. Alemtuzumab induction is often used at the time of retransplant; however, the literature surrounding alemtuzumab induction in renal retransplant patients is limited. In this single-center, retrospective, observational study, we aimed to determine the one-year incidence of infections and transplant outcomes in renal retransplant patients who received alemtuzumab induction. Thirty-four patients who received alemtuzumab met inclusion criteria and were included in the final analysis. Twenty-two (64.7%) of these patients acquired infections. Of these, seven patients (31.8%) acquired infections that resulted in hospitalization or IV antibiotics. The most common infections were urinary tract infections (UTIs) (n=10; 29.4%), cytomegalovirus DNAemia (n=7; 20.6%), and BK virus (n=6; 17.6%). The number of patients who developed *de novo* donor specific antibodies (DSA) was n=11 (32.4%) with only one of these patients having DSA prior to retransplantation. The incidence of acute cellular rejection was 2.9% (n=1). There was no graft loss, and patient survival was 97% (n=33). There were no significant differences in infection rate or DSA development between alemtuzumab and the other induction agents, anti-thymocyte globulin (ATG) and basiliximab, among retransplanted patients. Alemtuzumab induction in renal retransplant patients resulted in similar bacterial and viral infection rates as previously reported in the literature and did not negatively impact graft and patient survival.

1. INTRODUCTION

Long-term renal allograft survival is limited with an estimated half-life of 8.8 years for deceased donors and 11.9 years for living donors.¹ Unfortunately, many patients receiving an initial renal transplant will eventually require additional transplantation. The United Network for Organ Sharing (UNOS) reported that 12,265 patients out of the 99,643 patients awaiting a kidney in 2020 were retransplants.² Compared to primary renal transplant patients, those with repeat transplantations have decreased graft survival.³ Nevertheless, a repeat renal transplant is significantly higher than those returning to dialysis following graft failure.⁴

Common reasons for graft loss include acute rejection, chronic rejection, calcineurin inhibitor nephrotoxicity, and BK virus infection.^{5,6} Following transplantation, a patient may develop donor specific antibodies (DSA) against the allograft, increasing the risk of acute rejection. Because of this, retransplant patients are often sensitized and have an increased rate of acute rejection compared to primary transplant patients.⁷ Lymphodepleting agents, such as alemtuzumab, are commonly used over IL-2 blockers in retransplant patients to offset this increased risk of acute rejection.⁸

Retransplantation is a growing segment of the transplant population with unique challenges that merit specific study. Despite the growing number of renal retransplant patients, many researchers have excluded this patient population from their clinical research trials. The literature surrounding induction with alemtuzumab, a humanized monoclonal antibody targeting CD52 on lymphocytes, in this population is limited.⁹⁻¹¹ Alemtuzumab is associated with an increased risk of DSA development compared to anti-thymocyte globulin (ATG) and interleukin-2 (IL-2) receptor blockers, possibly due to its unique ability to deplete peripheral B cells.¹² No study to date has addressed *de novo* DSA development in renal retransplant patients receiving alemtuzumab induction and the effects of this on graft rejection and other transplant outcomes. It is proposed that cumulative doses of lymphodepleting induction agents that occur in renal retransplant patients increases the risk of infection compared to primary renal

transplant patients. To date, only limited data exists concerning infectious risk of alemtuzumab induction in renal retransplant patients.^{10,11} The purpose of this study was to determine the incidence of alemtuzumab associated infections (bacterial, viral, fungal, and opportunistic infections) and to assess transplant outcomes in renal retransplant patients within 12 months of retransplant.

2. METHODS

2.1 Study Participants

This observational, retrospective cohort study included adult kidney retransplant patients who received induction with alemtuzumab, ATG, or basiliximab between April 1, 2014 and November 1, 2018 at a single, academic transplant center. Patients were excluded if they underwent a dual or ABO-incompatible transplant. This study was approved by the institutional Investigational Review Board.

2.2 Immunosuppression/Post-transplant Care

All patients included in the study received induction therapy with one of the following agents: alemtuzumab (Campath-1H; Genzyme Corporation, Cambridge, MA) 30 mg IV and methylprednisolone 500 mg IV intraoperatively with a rapid steroid withdrawal by post-operative day four, anti-thymocyte globulin (Thymoglobulin; Genzyme Corporation, Cambridge, MA) 6 mg/kg IV given over 3 days (post-operative days 0, 1, and 2) at 2 mg/kg/day and methylprednisolone 500mg IV intraoperatively, basiliximab (Simulect, Novartis Pharmaceuticals Corporation, East Hanover, NJ) 20 mg IV given intraoperatively and on post-operative day 4 and methylprednisolone 500mg IV intraoperatively. The choice of induction agent and the use of maintenance oral steroids following retransplantation was based on patient specific factors and determined by the solid organ transplant team and the institution's immunosuppression protocol. Maintenance immunosuppression consisted of tacrolimus (Prograf; Astellas Pharma US, Deerfield, IL) or cyclosporine (Neoral; Novartis Pharmaceuticals Corporation, East

Hanover, NJ) and a mycophenolic acid derivative (Myfortic; Novartis Pharmaceuticals Corporation, East Hanover, NJ) at 540 mg by mouth twice daily or the equivalent mycophenolate mofetil dose (Cellcept; Genetech USA, Inc, South San Francisco, CA). Variations in maintenance immunosuppression from the standard regimen were made by the transplant provider on an individual basis. All calcineurin inhibitor (CNI) trough concentrations included in the analysis were drawn before the morning dose to obtain a 12-hour trough concentration and evaluated by our laboratory using liquid chromatography-mass spectrometry. Goal therapeutic trough ranges for tacrolimus were 8-10 ng/mL for months 0-3 and 6-8 ng/mL for months 4-12. Pneumocystis jiroveci pneumonia prophylaxis included sulfamethoxazole/trimethoprim 400mg/80mg by mouth daily as the first line option for 6 months following transplant. Cytomegalovirus (CMV) prophylaxis included acyclovir for 3 months for low-risk patients (donor - / recipient -), valganciclovir for 3 months for moderate-risk patients (donor + / recipient + or donor - / recipient +), and valganciclovir for 6 months for high-risk patients (donor + / recipient -). Thrush prophylaxis consisted of nystatin 10 mL (1,000,000 units) by mouth three times daily during inpatient stay.

2.3 Variables of Interest, Outcomes, and Definitions

The institutional electronic health record was utilized for data collection. The primary endpoint was the incidence of infections (bacterial, viral, fungal, and opportunistic infections) within 12 months of retransplantation with alemtuzumab induction. Infections excluded from the primary endpoint were pneumonia, cellulitis, and other skin and soft tissue infections. These infections were excluded from the primary endpoint due to reliance on clinician discretion for diagnosis, potentially leading to false-positives and false-negatives results. BK viruria and viremia were defined as the presence of BK virus in the urine or blood samples, respectively, as determined by PCR.¹³ The cut off value for BK viruria and viremia was designated as BK $\geq$ 1,000 copies/mL in the urine and plasma, respectively, or BK $\geq$ 250

copies/mL for patients who were treated for BK viremia based on clinician discretion. BK virus nephropathy (BKVN) was defined as confirmed positive renal biopsy for BKVN and histology characterized by tubular atrophy and fibrosis with an inflammatory lymphocytic infiltrate.¹³ CMV DNAemia was defined as a positive quantitative nucleic acid amplification.¹⁴ The cut off value for CMV DNAemia was designated as CMV ≥ 1000 IU/mL for asymptomatic patients or CMV ≥ 200 IU/mL for patients who were treated for CMV DNAemia based on clinician discretion. Bacteremia was defined as two out of two blood cultures positive for the same bacterial species from central line and/or peripheral line. Urinary tract infection (UTI) was defined as urine cultures that contained $\geq 10^5$ colony forming units (CFU)/mL of the same organism.¹⁵ *Clostridium difficile* (*C. difficile*) was defined as a positive PCR/nucleic acid amplification test (NAAT) for toxigenic *C. difficile* in stool samples.¹⁶ Other infections that were included in the primary endpoint were influenza, Epstein-Barr Virus (EBV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV) and fungal infections (aspergillosis, histoplasmosis, coccidioidomycosis, blastomycosis, mucormycosis, cryptococcosis, pneumocystis jiroveci pneumonia). These opportunistic infections were defined based on treatment guidelines.¹⁷⁻²³

The secondary endpoints consisted of acute rejection, patient and graft survival, and development of *de novo* DSA within 12 months of retransplantation with alemtuzumab. Additional secondary endpoints included the presence of infections, acute rejection, patient and graft survival, and development of *de novo* DSA within 12 months of retransplantation with ATG induction, and the presence of infections, acute rejection, patient and graft survival, and development of *de novo* DSA within 12 months of retransplantation with basiliximab induction. Acute rejection was defined as either acute cellular rejection (ACR), antibody-mediated rejection (AMR), or mixed acute rejection as determined by renal biopsy. Development of *de novo* DSA was defined as the development of new anti-HLA antibodies against the donor determined by total mean fluorescent intensity (MFI) ≥ 1000 .

2.4 Statistical Analysis

Descriptive statistics were used to determine the primary and secondary endpoints. Categorical values were reported as counts and percentage of the population and continuous values were reported as median (minimum – maximum). The Fisher's Exact Test was used to detect statistical differences in outcomes between alemtuzumab and the other induction agents used in the study, ATG and basiliximab. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics 26 (Armonk, NY).

3. RESULTS

3.1. Cohort Characteristics

During the study period, 45 patients received a renal retransplant and were included in the final analysis: 34 patients received alemtuzumab induction, five patients received ATG induction, and six patients received basiliximab induction. Patient characteristics are listed in Table 1. Many of the patients were sensitized in the alemtuzumab group with n=15 (44.1%) having cPRA between 80-100% and n=11 (32.4%) developing DSA after receiving the first renal transplant. No patients receiving ATG had DSA at any point prior to retransplant whereas approximately one-third of the patients who received basiliximab (n=2; 33.3%) had DSA prior to retransplant. The median time in between subsequent transplants in the alemtuzumab group was 171 months. The majority of patients received tacrolimus/mycophenolate mofetil (MMF) dual therapy or tacrolimus/MMF/prednisone triple therapy for maintenance immunosuppression within 12 months of retransplantation (Table 2).

3.2 Infectious Outcomes

Of the 34 patients included in the alemtuzumab group, 22 (64.7%) acquired infections within 12 months of retransplantation (Table 3). Of these, seven patients (31.8%) acquired infections that resulted in hospitalization or IV antibiotics. Seven patients (20.6%) acquired CMV DNAemia and six patients (17.6%) acquired BK virus. Of these, three patients had BK viremia, two patients had BK virus nephropathy, and one patient had BK viruria. One patient acquired adenovirus 169 days after retransplantation and one patient acquired rhinovirus 358 days after retransplantation. Ten patients in the alemtuzumab group (29.4%) acquired urinary tract infections (UTIs). Of these ten patients, three patients acquired two UTIs each within 12 months. The organisms that were isolated include *Escherichia coli* (n=4), *Klebsiella pneumoniae* (n=3), *Staphylococcus epidermidis* (n=2), *Candida albicans* (n=1), *Candida glabrata* (n=1), *Enterobacter* (n=1), and *Pseudomonas aeruginosa* (n=1). One patient acquired *Escherichia coli* bacteremia caused by dissemination of UTI 63 days after retransplantation. One patient acquired *Clostridium difficile* 97 days after retransplantation. Of the five patients who received ATG, one (20%) acquired an infection, BK viremia, within 12 months of retransplantation (Table 3). Of the six patients who received basiliximab induction, four (66.7%) acquired infections within 12 months of retransplantation (Table 3). One patient in the basiliximab group acquired CMV DNAemia, one patient acquired BK viruria, one patient acquired adenovirus, and one patient acquired Epstein-Barr Virus. The total number of infections acquired in the alemtuzumab group was not significantly different from the number acquired in the ATG group ($p=0.139$) or the basiliximab group ($p=1.000$).

3.3 Infectious Outcomes Associated with Steroid Use

The number of patients who received alemtuzumab induction and on maintenance prednisone at the time of transplant, 3 months, 6 months, 9 months, and 12 months following retransplant were n=12 (35.3%), n=17 (50%), n=17 (50%), n=16 (47.1%), and n=18 (54.5%), respectively. The average

prednisone dose for those on maintenance steroids was $7.1 \text{ mg} \pm 7.2 \text{ mg}$ at time of transplant, $5.9 \text{ mg} \pm 2.0 \text{ mg}$ at 3 months, $5.6 \text{ mg} \pm 1.7 \text{ mg}$ at 6 months, $7.5 \text{ mg} \pm 8.8 \text{ mg}$ at 9 months, and $5.4 \text{ mg} \pm 1.8 \text{ mg}$ at 12 months post-transplant. Of the 22 patients who developed an infection within 12 months of retransplantation, eleven (50%) had received steroids prior to or during the time that they acquired their infection. The two patients who developed BK nephropathy were on maintenance steroids at the time of diagnosis. The remaining eleven patients (50%) who acquired an infection within 12 months of retransplantation did not receive maintenance steroids. The majority of the infections in the steroid free group were UTIs ($n=7$; 53.8%) and the majority of the infections in the steroid maintenance group were viral ($n=10$; 71.4%); however, the difference in the rate in viral infections between the two groups was not significant ($p=0.128$). Additional infections that occurred are shown in Figure 1.

3.4 Transplant Outcomes

The incidence of acute cellular rejection within 12 months of retransplantation with alemtuzumab induction was 2.9% ($n=1$) and occurred 49 days after retransplant. No patients developed antibody mediated rejection or mixed rejection. Eleven patients (32.4%) developed *de novo* DSA towards their retransplanted renal graft within 12 months of retransplantation with alemtuzumab with only one of these patients having DSA at any point prior to retransplantation. The average time to *de novo* DSA development was 130 days, and the average MFI was 3,492 (1,186 – 20,075). There was no graft loss, and patient survival was 97% ($n=33$) with one death due to unknown causes within 12 months of retransplantation with alemtuzumab. There was no acute rejection and graft and patient survival was 100% in both the ATG and basiliximab induction groups. Two patients in the ATG group and one patient in the basiliximab group developed DSA within 12 months of retransplantation with none of these patients having DSA at any point prior to retransplantation. The occurrence of the development of *de*

novo DSA in the alemtuzumab group was not significantly different from the ATG group ($p=1.000$) or the basiliximab group ($p=0.648$).

4. DISCUSSION

The most common infections acquired in our cohort were urinary tract infections, CMV DNAemia, and BK viremia. No patients experienced invasive fungal infections (candidiasis, PJP, aspergillus, mucor, etc). This is in contrast to a recent retrospective study by Descourouez et al that reported a substantial number of fungal infections (46.8%) and bacterial infections (18.7%) in renal retransplant patients that received alemtuzumab induction.¹¹ However, several factors were different between this study and our study that might have impacted the difference in infection rates. First, the average time in between subsequent transplants for our patients was 170 months. In contrast, patients in the Descourouez et al study who received alemtuzumab for induction had an average of 20 months in between subsequent transplants. In addition, the majority of patients in the Descourouez et al study received two 30-mg doses of alemtuzumab for induction therapy whereas our center used a single 30mg dose of alemtuzumab for induction therapy. The higher dose of alemtuzumab, as well as the shorter time frame in between subsequent transplants, could be the reason why an increased proportion of patients experienced fungal and bacterial infections in the Descourouez et al studied compared to our study.

A larger, retrospective study by Schold et al found the risk of BK virus for retransplant patients who received alemtuzumab was 4%.¹⁰ This is in contrast to our study which found 17.6% of patients acquired BK virus and is closer to the results in the Descourouez et al study that found the rate of BK virus to be 12.5%. Neither the Schold et al study nor the Descourouez et al study stratified patients based on steroid use during their analysis of infectious outcomes. Our study found that the use of maintenance steroids following alemtuzumab therapy did not increase the risk of acquiring infections compared to a

steroid-free maintenance interval, indicating that the use of steroids for additional immunosuppression may not lead to negative outcomes from an infection standpoint.

Three retrospective studies were conducted that evaluated transplant outcomes in renal retransplant patients receiving alemtuzumab induction. The reported 1-year acute rejection rates in these studies were higher than the acute rejection rate of our study. Our study found a lower rate of rejection, 2.9%, compared to other studies (10-25%).⁹⁻¹¹ The majority of the patients in our study did not have DSA prior to retransplant, which could account for the low acute rejection rate seen in our study. Approximately half of our patients were on maintenance steroids within 12 months of retransplant, which would result in greater immunosuppression and possibly less acute rejection compared to the other studies. However, approximately half of the patients who received alemtuzumab induction in the Santos et al study received maintenance steroids and almost all of the patients in the Schold et al and the Descourouez et al studies received maintenance steroids following alemtuzumab induction.

Our study was the first to analyze how the development of *de novo* DSA in renal retransplant patients who received alemtuzumab induction influenced acute rejection rates. Development of *de novo* DSA in the alemtuzumab group was 32.4% (n=11) with n=1 of these patients having DSA prior to retransplant. A similar rate of *de novo* DSA development has previously been reported in primary renal transplant patients. A study by Todeschini et al found 50% of primary renal transplant patients who received alemtuzumab induction developed *de novo* DSA within 12 months of transplant, despite no history of DSA prior to transplant.¹² Similar to our study, none of the patients in the Todeschini et al study who developed DSA experienced antibody mediated rejection within 12 months of transplant. This suggests that, although retransplant patients have a higher chance of being sensitized compared to primary transplant patients, development of DSA following alemtuzumab induction may not lead to an increased risk of antibody mediated rejection in the short-term. Long-term follow-up is needed to see if these results remain consistent after one-year post-retransplantation.

The limitations of this study are inherent to the design of a retrospective cohort study. Observational studies carry the risk for confounding bias. To reduce this bias, we performed stratification and analysis of subgroups that we thought may contribute to this type of bias, i.e. the use or absence of steroids for maintenance immunosuppression. Small sample sizes, particularly in the ATG and basiliximab treatment groups, may result in our study lacking adequate statistical power to note differences in outcomes between the alemtuzumab group and the ATG and basiliximab groups. With the knowledge gained from this project, it could add to the growing body of literature surrounding retransplant patients to help institutions assess the risks and benefits of choosing alemtuzumab as an induction agent. Future studies including larger sample sizes and longer follow-up would be warranted given the favorable outcomes in this study.

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TABLES AND FIGURES

Table 1. Clinical and Demographic Characteristics of Patients			
	N = 34	N = 5	N = 6
Baseline Characteristics	Alentuzumab	ATG	Basiliximab
Gender			
Male	22 (65%)	4 (80%)	3 (50%)
Race			
Caucasian	21 (61.8%)	2 (40%)	3 (50%)
African American	10 (29.4%)	3 (60%)	2 (33.3%)
Hispanic	2 (5.9%)	0	1 (16.7%)
American Indian	1 (2.9%)	0	0
Age^a	49 (25 - 66)	56 (52 - 65)	40 (22 - 56)
Etiology of Renal Disease			
Hypertension	6 (17.6%)	1 (20%)	0
Diabetes	6 (17.6%)	2 (40%)	0
Chronic Glomerulonephritis	3 (8.8%)	0	0
IgA Nephropathy	4 (11.8%)	1 (20%)	1 (16.7%)
ANCA Vasculitis	2 (5.9%)	0	0
Goodpasture's Syndrome	2 (5.9%)	0	0
Interstitial Nephritis	2 (5.9%)	0	0
Polycystic Kidney Disease	3 (8.8%)	0	1 (16.7%)
Other	6 (17.6%)	1 (20%)	4 (66.7%)
Months between subsequent transplants^a	171 (27-306)	212 (69 - 257)	152 (53 - 302)
Reason for retransplant			
Chronic Rejection	19 (55.9%)	3 (60%)	1 (16.7%)
Acute Rejection	6 (17.6%)	0	0
Infections	2 (5.9%)	0	1 (16.7%)
Rejection (Unknown Type)	2 (5.9%)	0	0
Acute Tubular Necrosis	2 (5.9%)	0	0
Calcineurin Inhibitor Toxicity	1 (2.9%)	0	1 (16.7%)
Recurrent Disease	0	1 (20%)	2 (33.3%)
Other	2 (5.9%)	1 (20%)	1 (16.7%)
cPRA at time of transplant			
0-20%	3 (8.8%)	0	2 (33.3%)
20-40%	1 (2.9%)	0	0
40-60%	4 (11.8%)	0	0
60-80%	1 (2.9%)	0	0
80-100%	15 (44.1%)	1 (20%)	0
Not reported	10 (29.4%)	4 (80%)	4 (66.7%)
DSA prior to re-transplant			
Yes	11 (32.4%)	0	2 (33.3%)
Donor relationship			
Living related	5 (14.7%)	2 (40%)	1 (16.7%)
Living unrelated	6 (17.6%)	0	3 (50%)
Deceased	23 (67.6%)	3 (60%)	2 (33.3%)

Values are reported as median (range) or n (%)

^a: median (minimum – maximum)

ATG: Antithymocyte globulin

cPRA: calculated Panel Reactive Antibodies

DSA: Donor Specific Antibodies

Table 2: Maintenance Immunosuppression used in Alemtuzumab Patients

Maintenance Immunosuppression	At transplant N (%)	3 months N (%)	6 months N(%)	9 months N(%)	12 months N (%)
Triple therapy (tac, pred, MMF)	12 (35.3%)	14 (41.2%)	13 (38.2%)	12 (35.3%)	14 (42.4%)
Triple therapy (tac, pred, aza)	0	1 (2.9%)	1 (2.9%)	0	1 (3%)
Dual therapy (tac, MMF)	22 (64.7%)	17 (50%)	16 (47.1%)	17 (50%)	15 (45.5%)
Dual therapy (tac, aza)	0	0	0	1 (2.9%)	0
Dual therapy (tac, pred)	0	1 (2.9%)	2 (5.9%)	3 (8.8%)	3 (9.1%)
Dual therapy (siro, pred)	0	1 (2.9%)	1 (2.9%)	1 (2.9%)	0
Monotherapy (tac)	0	0	1 (2.9%)	0	0

tac: tacrolimus

MMF: mycophenolate mofetil

Pred: prednisone

Aza: azathioprine

Siro: sirolimus

Table 3: Infections within 12 Months of Retransplantation

Infections	Mean time to infection (min - max) (days)	N (%)	Mean viral copies (min - max)
ALEMTUZUMAB			
Viral Infections			
CMV DNAemia	152 (22-282)	7 (20.6%)	4,463 IU/mL (315 - 13,183)
BK Virus			
BK Viremia	181 (92-346)	3 (8.8%)	24,347 copies/mL (2,400 - 35,641)
BK Viruria	197	1 (2.9%)	1,679,530 copies/mL
BK Nephropathy	137	2 (5.9%)	-
Other Viral			
Adenovirus	169	1 (2.9%)	-
Rhinovirus	358	1 (2.9%)	-
Bacterial Infections			
Urinary Tract Infection	126 (9-350)	10 (29.4%)	-
Bacteremia	63	1 (2.9%)	-
Clostridium difficile	97	1 (2.9%)	-
ATG			
Viral Infections			
BK Viremia	252	1 (20%)	409 copies/mL
BASILIXIMAB			
Viral Infections			
CMV DNAemia	238	1 (16.7%)	40,641 IU/mL
BK Virus			
BK Viruria	274	1 (16.7%)	1,070,159 copies/mL
Other Viral			
Adenovirus	251	1 (16.7%)	-
Epstein-Barr Virus	22	1 (16.7%)	15,000 copies/mL

ATG: Anti-thymocyte globulin

CMV: Cytomegalovirus

Figure 1. Infection Rate Based on the Use or Absence of Steroid Maintenance Therapy Following Alemtuzumab Induction

UTI: Urinary Tract Infection

BKV: BK Virus

CMV: Cytomegalovirus