Safety and Efficacy of Alemtuzumab Induction in Highly Sensitized Pediatric Renal Transplant Recipients

Irene K. Kim, MD,¹ Jua Choi, PharmD,¹ Ashley A. Vo, PharmD,¹ Alexis Kang, BS,¹ Mitasha Patel, BS,¹ Mieko Toyoda, PhD,¹ James Mirocha, MS,² Elaine S. Kamil, MD,¹ J. Louis Cohen, MD,¹ Sabrina Louie, MPH,¹ Odette Galera, CLS,¹ Stanley C. Jordan, MD,¹ and Dechu P. Puliya, MD¹

Background. Studies show that alemtuzumab, a potent lymphocyte-depleting agent, is well tolerated in pediatric renal transplantation. We report on the use of alemtuzumab induction in highly HLA sensitized (HS) pediatric kidney transplant patients. **Methods.** Fifty pediatric renal transplants were performed from 1/2009-12/2014. 15 HS patients received IVIG (2 g/kg × 2 doses)/rituximab (375 mg/m² × 1) for desensitization with alemtuzumab induction (15-30 mg, 1 dose, subcutaneous), whereas 35 nonsensitized patients received anti-IL-2R. Graft survival and infections were compared between 2 groups. **Results.** All HS patients had received a prior transplant and were older with lower risk for viral infections due to serostatus. Patient survival was 100%, and graft outcomes were similar with mean 1-year creatinine of 1.03 ± 0.45 versus 0.99 ± 0.6 ($P = 0.48$). Although a higher incidence of acute cellular rejection was seen in HS patients receiving alemtuzumab ($P = 0.001$), there was a nonsignificant difference in antibody-mediated rejection. White blood cell and absolute lymphocyte count were significantly lower in alemtuzumab group at 30 days ($P < 0.0001$) and at 1 year ($P = 0.026$ and $P = 0.001$), respectively. There was no significant difference in bacterial, viral, or fungal infections after transplant. **Conclusions.** Alemtuzumab induction with desensitization led to nearly equivalent graft survival and functional outcomes in HS pediatric patients as nonsensitized patients receiving anti-IL-2R induction. With this small sample size, we observed significant reduction of white blood cell and absolute lymphocyte count up to 1 year posttransplant. The risk of infection was comparable between the 2 groups; however, patients who received alemtuzumab were older and at lower risk of viral infection due to serostatus.

(*Transplantation* 2017;101: 883-889)

Received 22 February 2016. Revision received 20 May 2016.

Accepted 28 May 2016.

¹ Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA.

² Biostatistics Core, Cedars-Sinai Medical Center, Los Angeles, CA.

The authors declare no funding or conflicts of interest.

I.K.K. has contributed to the conception and design of the study, data interpretation, drafting, and revising the article. J.C. has contributed to the conception of the study, data analysis, and revising the article. A.V. has contributed to the conception of the study, data analysis, and revising the article. A.K. has contributed to the conception of the study, data collection, and revising the article. M.P. has contributed to the conception of the study, data collection, and revising the article. M.T. has contributed to the conception of the study, data analysis, and revising the article. J.M. has contributed to the conception of the study, statistical analysis, and revising the article. E.S.K. has contributed to the conception of the study, data analysis, and revising the article. J.L.C. has contributed to the conception of the study, data analysis, and revising the article. S.L. has contributed to the conception of the study, data collection, and revising the article. O.G. has contributed to the conception of the study, data analysis, and revising the article. S.C.J. has contributed to the conception and design of the study, data analysis, and revising the article. D.P.P. has contributed to the conception and design of the study, data analysis, and revising the article.

Correspondence: Irene K. Kim, MD, Comprehensive Transplant Center, Cedars-Sinai Medical Center, 8900 Beverly Blvd., Los Angeles, CA 90048. (irene.kim@cshs.org).

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0041-1337/17/10104-883

DOI: 10.1097/TP.0000000000001416

If technically feasible, renal transplantation is the treatment of choice for pediatric patients with end-stage kidney disease. The majority of pediatric patients listed for transplant are nonsensitized; however, there are a growing number of children who are sensitized to HLA antigens, mainly after repeat exposure after blood transfusions.¹ It is estimated that approximately 3% of pediatric patients are HLA-sensitized and as a result, a growing number of pediatric transplant centers are developing experience with desensitization protocols for young patients.¹

Desensitization protocols using a combination of IVIG, plasma exchange, and lymphocyte-depleting agents, such as rituximab (anti-CD20), have improved the rates of transplantation in highly sensitized (HS) adult populations and are generally well tolerated.²⁻⁷ Infectious complications, including BK nephropathy, after desensitization are reported, but in 1 analysis of a large patient cohort, there were no significant differences in infections between adults who received desensitization therapy and those who did not.⁸ Pediatric patients are theoretically at higher risk for infectious complications posttransplant due to naive immune status and lack of prior exposure to infectious, such as EBV and CMV. Therefore, desensitization in pediatric patients poses a further conundrum of possible overimmunosuppression.

The successful use of alemtuzumab (Campath), a humanized IgG1 monoclonal antibody directed against CD52, a

glycoprotein present on T and B lymphocytes, monocytes, mononuclear cells, and natural killer cells, as an induction agent in both adult and pediatric renal transplant recipients is well described.⁹⁻¹⁴ Alemtuzumab is currently the most powerful lymphocyte-depleting agent used and in 1 recently published prospective randomized study, alemtuzumab induction resulted in lower rates of acute rejection than basiliximab in low immunological risk adult patients and had similar efficacy with rabbit antithymocyte globulin in high-risk patients.¹⁵

Building on the expertise developed for adult HS patient populations, desensitization protocols have been applied to pediatric populations.^{14,15} Preliminary data on induction with alemtuzumab in pediatric renal transplant recipients suggest the drug is well tolerated and its use offers a potential additive immunosuppressive effect on B cells, which may prove more effective in HLA-sensitized patients.^{11,12,16,17} The use of alemtuzumab in conjunction with desensitization therapy using IVIG and rituximab has not been investigated in children. Here, we sought to analyze patient and graft outcomes and infectious complications in pediatric patients who underwent renal transplantation after desensitization and alemtuzumab induction. To date, this is the largest cohort of HS pediatric patients receiving both desensitization and alemtuzumab induction ever studied.

MATERIALS AND METHODS

Study Design

Permission for this retrospective review was granted by the Cedars-Sinai Medical Center, Institutional Review Board. Between January 2009 and January 2015, the medical charts of 50 pediatric patients who underwent renal transplant were reviewed at a single institution. We compared 2 main cohorts of patients: those who were HS (PRA > 30%) and who received alemtuzumab induction after desensitization and patients who were nonsensitized and received anti-IL-2R induction.

Determination of Sensitization

Patients were considered highly sensitized if pretransplant flow cytometry PRAs were more than 30%. History of sensitizing events, including multiple blood transfusions and previous transplants, was recorded. All transplants were ABO compatible. We defined an acceptable CMX as a negative complement-dependent cytotoxicity, at least at a 1:2 dilution

of sera. Acceptable donor HLA-specific antibody levels included single antigen class I binding of less than 5000 mean fluorescent intensity (MFI) and a positive donor flow cytometry T- and B-cell crossmatch of less than 225 mean channel shifts. Solid-phase antibody analysis was also used to define the specificity of the antibodies detected, to follow the effect of desensitization, and the strength of donor-specific antibody (DSA), as reported previously.^{6,18}

Desensitization

The desensitization protocol used to treat HS pediatric patients includes IVIG 10% (2.0 g/kg, maximum 140 g per dose, on day 1 and day 30) and rituximab (375 mg/m² up to a max dose of 600 mg administered on day 7). The protocol was approved by the Cedars-Sinai Medical Center Institutional Review Board. IVIG was infused during a dialysis session, and rituximab was administered over a 6-hour period in an outpatient infusion center. The protocol for desensitization, induction, and maintenance therapy are outlined in Figure 1.

Posttransplant Immunosuppression

All patients received induction treatment. The HS patients received a single dose of alemtuzumab 15 to 30 mg subcutaneously on the day of transplant (<20 kg—15 mg dose and >20 kg—30 mg dose). Nonsensitized patients received anti-interleukin-2 receptor blocker (anti-IL-2R) with either basiliximab (2 doses) or daclizumab (5 doses).

The HS patients received a dose of IVIG at time of transplant if desensitization was completed more than 1-month prior. In addition, HS patients received an additional dose of IVIG (2 g/kg; maximum dose, 140 g) 10 to 14 days after transplantation.

Maintenance immunosuppression consisted of prednisone taper, mycophenolate mofetil (600 mg/m² in 2 divided doses), and tacrolimus adjusted to maintain target trough levels of 7 to 9 ng/mL for the first 6 months, 5 to 7 ng/mL for months 6 to 12, and 4 to 6 ng/mL thereafter.

Infection Prophylaxis

All transplant patients received cytomegalovirus prophylaxis with IV ganciclovir (5 mg/kg per day, administered daily postoperatively as an inpatient), followed by oral valganciclovir ($7 \times \text{BSA} \times \text{serum creatinine/day}$) for 6 months of total

FIGURE 1. Pediatric desensitization protocol and alemtuzumab use in highly sensitized pediatric renal transplant recipients.

treatment.¹⁹ Dose of valganciclovir was adjusted to renal function and white blood cell (WBC) count. All patients received *Pneumocystis jiroveci* pneumonia and bacterial prophylaxis with trimethoprim-sulfamethoxazole (2 mg/kg of the Trimethoprim component) for 6 months. The HS patients received fluconazole (2 mg/kg daily), whereas nonsensitized patients received nystatin (5–10 mL swish and swallow, 4 times daily) for fungal prophylaxis.

Acute Allograft Rejection Episodes

Protocol biopsies were not performed. Renal allograft biopsies were performed in the context of acute allograft dysfunction defined as an unexplained variation in serum creatinine levels higher than 20% of baseline levels, unexplained proteinuria, or rise in DSA levels. Diagnoses of acute cell-mediated rejection (CMR) and antibody-mediated rejection (AMR) were made based on Banff '97 and Banff 2013 criteria.^{20,21} Patients diagnosed with acute CMR were treated with 3 days of intravenous steroids at 10 mg/kg per dose. Patients with concomitant AMR received 2 mg/kg of IVIG followed 1 to 2 weeks later, by rituximab, 375 mg/m².

Posttransplant Infection and Immune Monitoring

All patients underwent protocol viral monitoring (cytomegalovirus (CMV), Epstein-Barr virus (EBV), and BK virus by quantitative real-time polymerase-chain reaction (PCR)) every 3 months for the first year after transplant and then every 3 to 12 months based on serostatus. Viremia was defined as blood leukocyte CMV- and EBV-PCR titers of 50 copies/PCR or more, and plasma BK-PCR titers of 2500 copies/mL or greater.²² Urine was not monitored. Patients who developed viremia (CMV, EBV, or BK) were initially treated with reduction of mycophenolate mofetil by 30%. Blood counts, rejection, graft survival, and incidence of all infections were analyzed. Kidney biopsies were performed only if clinically indicated.

DSA was monitored for the HS patients routinely every 3 months posttransplant for the first year. After the first year, the DSA was monitored annually if there were no DSAs detected or every 3 months if DSAs were detected. DSAs were not routinely monitored in the nonsensitized group receiving anti-IL-2R induction unless they were noted to have AMR on biopsy for cause. Strength of DSA was defined based on MFI as: less than 5000, weak; 5000 to 10 000, moderate; and greater than 10 000 MFI, strong.

Study Assessments and Statistical Analysis

The 2 groups analyzed were HS pediatric patients who received alemtuzumab induction and nonsensitized pediatric patients who received anti-IL-2R induction. Numerical variables were summarized by mean $\pm$ standard deviation or median (range). Group differences on numerical variables were assessed by the independent samples *t* test (normally distributed variables) or the Wilcoxon rank sum test (non-normally distributed variables). Categorical variables were summarized by frequency and percent and were compared across groups by the Fisher exact test. Freedom from events (graft loss and rejection) was estimated by the Kaplan-Meier method and was compared across groups by the log-rank test. A 2-sided 0.05 significance level was used throughout. Statistical calculations were made using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient Demographics

Between January 2009 and January 2015, 50 pediatric patients underwent kidney transplantation, receiving either alemtuzumab induction (30%, *n* = 15) or anti-IL-2R blockade (70%, *n* = 35). Of the patients receiving anti-IL-2R therapy, only 8% (*n* = 3) received daclizumab and the rest received basiliximab. All HS patients were sensitized from previous kidney transplants. The mean class I and II PRA in patients receiving alemtuzumab was $64.4 \pm 28.2\%$ and $69.6 \pm 24.3\%$, respectively, compared with nonsensitized patients with a mean PRA of 0%. There were no significant differences in race, sex, type of transplant (ie, living versus deceased donor), and etiology of renal disease. Patient demographic information is represented in Table 1.

Although HS pediatric patients who received alemtuzumab were on average older than nonsensitized patients who received anti-IL-2R induction (15.7 ± 5.3 years vs 11.6 ± 6.3 years, *P* = 0.039), there was a wide age distribution in both groups. The youngest HS pediatric patient who underwent desensitization and alemtuzumab induction was 2 years old at the time of transplantation and 4 patients younger than 12 years received alemtuzumab as induction at the time of transplant.

Assessment of Patient and Graft Survival

Patient survival was 100% in both groups. Graft survival was similar in both groups, where $83.9 \pm 10.5\%$ of the

TABLE 1.

Pretransplant patient characteristics

Variables	Alemtuzumab (N = 15)	IL-2R (N = 35)	P
Age, mean $\pm$ SD	15.7 $\pm$ 5.3	11.9 $\pm$ 6.1	0.039
Age, median (range)	18 (2-21)	14 (1-20)	0.012
Sex (female), n (%)	6 (40)	18 (51.4)	0.54
Race (%)			0.22
White	7 (46.7)	7 (20)	
African American	0	4 (11.4)	
Hispanic	7 (46.7)	21 (60)	
Asian	1 (6.7)	1 (2.9)	
Other/unknown	0	2 (5.9)	
Type of transplant, living (%)	1 (6.7)		>0.99
Cause of end-stage renal disease			0.146
Glomerulonephritis	2	14	
Obstructive uropathy	5	11	
Other	8	10	
Class I PRA, mean	64.4 $\pm$ 28.2	0	
Class II PRA, mean	69.6 $\pm$ 24.3	0	
Viral status (CMV)			0.20 ^a
+/+	7	9	
+/-	2	14	
-/-	3	7	
-/+	3	4	
Unknown		1	
Viral status (EBV)			0.103 ^a
+/+	12	19	
+/-	1	12	
-/-	0	0	
-/+	2	3	
Unknown		1	

^aThe *P* value is for the whole distribution, not for any specific comparison.

TABLE 2.**Posttransplant patient characteristics**

Variables	Alemtuzumab (N = 15)	Percent	Anti-IL-2R (N = 35)	Percent	P
Mean, follow-up $\pm$ SD, d	1051.4 $\pm$ 671.8		1248.4 $\pm$ 517.1		0.32
Patient survival		100		100	
% Graft survival					
1 y		92.3 $\pm$ 7.4 ^a		94.3 $\pm$ 3.9 ^a	0.89
2 y		83.9 $\pm$ 10.5 ^a		91.3 $\pm$ 4.8 ^a	0.56
3 y		83.9 $\pm$ 10.5 ^a		91.3 $\pm$ 4.8 ^a	0.56
Serum creatinine, mg/dL					
12 mo	1.03 $\pm$ 0.45		0.99 $\pm$.60		0.48
3 y	0.87 $\pm$ 0.40		0.87 $\pm$ 0.57		>0.99
Rejections (within 1 y) and 1-y freedom from rejection					
All	8	46.7 ^a	8	77.1 ^a	0.003
Antibody-mediated rejection	2	86.7 ^a	4	88.6 ^a	0.34
Cell-mediated rejection	7	53.3 ^a	4	88.6 ^a	0.001
WBC mean count (1000/UL)					
Baseline	6.87 $\pm$ 1.83		8.21 $\pm$ 3.18		0.24
Day 1	8.11 $\pm$ 3.59		11.14 $\pm$ 3.96		0.017
Day 7	5.45 $\pm$ 2.27		10.25 $\pm$ 4.34		0.0003
Day 30	4.3 $\pm$ 2.17		9.28 $\pm$ 3.22		<0.0001
Day 180	5.73 $\pm$ 2.86		7.41 $\pm$ 2.90		0.049
Day 365	5.76 $\pm$ 2.63		8.07 $\pm$ 2.44		0.026
Absolute lymphocyte mean count (1000/UL)					
Baseline	2.23 $\pm$ 0.83		3.02 $\pm$ 1.63		0.20
Day 1	0.17 $\pm$ 0.22		1.12 $\pm$ 1.18		<0.0001
Day 7	0.07 $\pm$ 0.08		2.99 $\pm$ 2.51		<0.0001
Day 30	0.15 $\pm$ 0.16		3.94 $\pm$ 2.26		<0.0001
Day 180	0.73 $\pm$ 0.54		2.55 $\pm$ 1.11		<0.0001
Day 365	1.49 $\pm$ 2.12		2.97 $\pm$ 1.24		0.001
Infections					
Bacterial	7	46.7 ^a	19	54.2 ^a	0.76
Fungal	0		0		
Viral	3	20 ^a	12	34.2 ^a	0.50

^aPercentages and standard error computed from Kaplan-Meier analysis.

patients in the alemtuzumab group compared with 91.3 $\pm$ 4.8% in the anti-IL-2R group had functional grafts at 3 years ($P = 0.56$, Table 2). In the alemtuzumab group, there were 2 graft losses within the first 2 years posttransplant. One patient lost her graft secondary to recurrent episodes of CMR after decrease in immunosuppression to treat CMV and BK infection, whereas another patient lost his graft to recurrence of focal segmental glomerulosclerosis. Three patients receiving anti-IL-2R induction lost their grafts in the early postoperative period: 2 patients secondary to graft thrombosis, and a third patient lost his graft secondary to recurrent (focal segmental glomerulosclerosis). Kaplan-Meier curves were created to demonstrate that there was no difference in graft survival over 6 years after transplant ($P = 0.56$) between patients who received alemtuzumab versus anti-IL-2R induction (Figure 2).

Graft function was similar between both groups. Twelve-month mean serum creatinine was 1.03 $\pm$ 0.45 mg/dL for patients receiving alemtuzumab versus 0.99 $\pm$ 0.60 mg/dL in the anti-IL-2R group ($P = 0.48$). Three-year creatinine was also similar with good graft function (Table 2).

Rejection

Highly sensitized pediatric patients receiving desensitization and alemtuzumab had a higher incidence of total rejection episodes, including both CMR and AMR ($P = 0.003$,

Table 2). Kaplan-Meier curves further support these findings; however, when CMR versus AMR were examined independently, there was no difference in AMR between the 2 groups ($P = 0.34$) at 1 year posttransplant. Of note, 1 patient receiving alemtuzumab induction had concurrent AMR and CMR.

FIGURE 2. Graft survival. Kaplan-Meier graft survival curve demonstrates that no significant difference in graft survival between pediatric patients who received alemtuzumab induction versus anti-IL-2 R induction.

FIGURE 3. Kaplan-Meier curves demonstrate freedom from rejection between patients who received alemtuzumab induction versus anti-IL-2R induction. There were significantly more rejection events, total and cell-mediated rejection, in the alemtuzumab group (A, B); however, there was no difference in AMR between the 2 groups (C).

To further illustrate the similar incidence of AMR in both groups, Kaplan-Meier curves after the incidence of rejection over 5 years showed greater CMR and total rejection episodes in patients receiving alemtuzumab induction, but again, no difference was seen in AMR over 6 years ($P = 0.59$, Figure 3). Despite a higher incidence of overall rejection in HS patients, there was no significant difference in graft survival between the 2 groups.

Among HS patients, 7 (46%) of 15 patients had moderate to strong DSA (either class 1 or class 2 or both) at the time of transplant. Three of these 7 patients (42.8%) had a decrease in or resolution of DSAs posttransplant. Three patients with persistence of DSA developed AMR. One patient remained stable (with only moderate cw7 DSA). None of the HS patients who developed only CMR had DSA greater than 5000 MFI. Among nonsensitized patients, 2 (5.7%)

of 35 patients who developed AMR had de novo DSA posttransplant.

Monitoring of Blood Counts

Routine immune monitoring was performed in patients for up to 1 year posttransplant. Baseline WBC counts were similar in both groups before transplant (6.87 vs 8.21 1000/UL, $P = 0.24$). As expected, after induction, the alemtuzumab group had significant depletion in total WBC counts observed up to a year posttransplant (Table 2). At day 30, the mean WBC count in the alemtuzumab group was 4.3 ± 2.17 versus 9.28 ± 3.22 1000/UL, $P < 0.0001$. In addition, baseline absolute lymphocyte count (ALC) levels at the time of transplant were similar in both groups (2.23 vs 3.02 1000/UL, $P = 0.2$). After induction, patients receiving alemtuzumab had a dramatic reduction in ALC compared with patients in

FIGURE 4. Lymphocyte depletion. Box plots demonstrate a significant difference in both WBC (A, B, C) and ALC (D, E, F) at 30, 180, and 365 days for patients who received alemtuzumab induction.

the anti-IL-2R induction group, observed out to 365 days posttransplant (Figure 4). One third of the HS patients receiving alemtuzumab induction ($n = 5$) required mycophenolate dose adjustment for leukopenia in the first 3 months posttransplant.

Infectious Complications and Management

Virologic risk for CMV and EBV was examined in both the HS patients receiving alemtuzumab induction and nonsensitized patients receiving anti-IL-2R induction. In general, nonsensitized patients receiving anti-IL-2R therapy were virologically more immune-naïve to HS patients. Thirty-three percent ($n = 5$) were CMV negative and 6.7% ($n = 1$) were EBV negative in the alemtuzumab group at the time of transplant compared with 60% ($n = 21$) CMV-negative and 34% ($n = 12$) EBV-negative in the anti-IL-2R group (Table 1).

There were no graft losses secondary to BK nephropathy in both cohorts. As mentioned above, 1 HS patient receiving alemtuzumab induction developed CMV and BK viremia early after transplant while on prophylactic valganciclovir. The patient's peak CMV titer was 2800 copies/PCR and the patient's BK viremia peak 2.5×10^4 copies/mL. After reduction of the patient's MMF dose and initiation of treatment dose with valganciclovir, the patient had improved viremia; however, 3 weeks later, the patient experienced a rise in her creatinine level, prompting allograft biopsy showing acute cellular rejection. Despite treatment with steroids, the patient continued to have recurrent episodes of acute CMR and eventually lost her graft 1 year after initial development of viremia.

There was no difference in bacterial and viral infections ($P = 0.76$ and 0.5 , respectively; Table 2). There were no cases of posttransplant lymphoproliferative disorder in patients who received alemtuzumab induction. One patient, who received anti-IL-2R induction, developed tonsillar posttransplant lymphoproliferative disorder requiring immunosuppressive adjustment.

DISCUSSION

Highly sensitized patients who develop AMR have been shown to suffer from early graft loss and higher graft failure rates.^{16,23} The development of desensitization protocols has enabled transplantation in these patients; however, protocols for pediatric highly sensitized patients, who stand to benefit the most from longer graft survival, are scarce. There are remarkably few case series and no clinical trials of desensitization and induction immunosuppressive regimens in pediatric kidney transplantation on which to base clinical recommendations. As pediatric patients with end-stage renal disease have the greatest potential benefit of life-years from their allograft, it is important to gain expertise in pediatric desensitization and transplant immunotherapy to maximize graft longevity and minimize adverse events.

The rationale for alemtuzumab induction in HS pediatric recipients at our center was based on favorable outcomes with alemtuzumab use at other transplant centers in nonsensitized pediatric patients, along with our positive experience using alemtuzumab in our HS adult population.^{14,18,24} There are several observed and theoretical benefits to alemtuzumab induction. First, several clinical trials have demonstrated a reduced incidence of rejection compared to other induction modalities. Nonsensitized adult patients randomized to alemtuzumab induction demonstrated lower rates of cellular rejection compared to patients receiving basiliximab, although

it failed to show any difference in graft survival.⁹⁻¹² There is also a theoretical benefit of improving graft function by enabling calcineurin minimization, but again, this strategy failed to demonstrate a significant benefit in graft function or survival.¹² Lastly, alemtuzumab use theoretically has benefit for both T and B cell-mediated pathways and therefore, is may be more appealing in patients with a higher risk profile of AMR, although this has never been corroborated in a randomized-control trial.^{14,15}

The HS pediatric patients desensitized in this study were older with a mean age of 15.7 years; however, our protocol for desensitization and alemtuzumab induction was applied to a wide range of HS pediatric recipients. Our youngest HS patient to receive alemtuzumab induction was 2 years old at the time of transplant, and at 4 years posttransplant, she continues to have good graft function with a creatinine of 0.8 mg/dL. Like prior studies examining alemtuzumab induction in pediatric patients,^{17,25-30} alemtuzumab was well tolerated with no patient deaths or significant difference in graft loss compared with nonsensitized patients receiving anti-IL-2R induction in our pediatric patients.

There are several key differences with historical studies that make alemtuzumab induction in our cohort unique. First, unlike prior studies researching alemtuzumab induction in the pediatric patient population,^{17,24} 100% of our patients receiving alemtuzumab induction were highly HLA-sensitized with a mean class I and II PRA of 64.4% and 69.6%, respectively. Shapiro et al,¹⁷ who have published one of the largest series of alemtuzumab induction in pediatric patients, had only 3.8% of their patients who were HS with a PRA greater than 20%. Interestingly, Kaabak et al²⁵ used alemtuzumab induction in ABO-incompatible pediatric renal transplant recipients who underwent pretransplant plasmapheresis but no desensitization therapy was used. Lastly, this study followed a consistent protocol of desensitization therapy with both IVIG and rituximab and alemtuzumab induction. Pirojsakul et al³¹ published their experience transplanting 4 HS pediatric patients where all patients received rituximab, IVIG, and bortezomib for desensitization, but induction therapy used a varied combination of plasmapheresis, alemtuzumab induction, and antithymocyte globulin.

Our study showed that there was a higher incidence of acute cellular rejection in patients treated with alemtuzumab induction, contrary to the literature.¹⁵ The main difference, however, is that these studies demonstrating lower acute rejection with alemtuzumab induction were studies conducted in nonsensitized patients. Another explanation for the higher incidence of CMR observed in our study is that mycophenolate mofetil maintenance immunosuppression was often minimized due to the significant lymphopenia, resulting from alemtuzumab induction. One third of the pediatric patients receiving alemtuzumab required reduction in the dose mycophenolate mofetil, making them more susceptible to rejection. It is also important to note that most rejection episodes in our HS pediatric patients were within the first year posttransplant and were successfully treated with return to baseline creatinine, resulting in no significant difference in graft function, which was monitored out to 1 year posttransplant.

The initial experience with alemtuzumab in children showed ALCs that remained less than 50% of baseline 12 months after transplantation²⁸⁻³⁰ and some reports of depletion out to 24 months postinduction.¹⁷ Similarly, significant depletion in

both mean WBC count and ALCs were observed in our HS pediatric patients receiving alemtuzumab, which was seen out to 1 year posttransplant. Despite significant lymphocyte depletion, the HS pediatric patients did not suffer from more bacterial, viral, or fungal infections. Both HS and nonsensitized patients received infectious prophylaxis, but HS patients did receive stronger antifungal prophylaxis (fluconazole vs nystatin). Furthermore, HS patients receiving alemtuzumab were older and significantly less viral-naïve compared with younger, nonsensitized patients, which may have put them at an immune advantage. Use of IVIG, which also carries antiviral properties, could also be a cause in reducing incidence of infection in our HS patients.

There are some obvious limitations to this study. Because there are relatively few HS pediatric patients, our sample size, although larger than other previously published case series, is small. Furthermore, our HS patients tended to be older and at somewhat lower virologic risk than the nonsensitized patients. Thus, given the small sample size and the fact that the HS population appeared to have been at lower risk for CMV and EBV disease, this study may not have been able to appreciate differences in virologic risk associated with the use of alemtuzumab had it been used in more children at risk for primary CMV and EBV infection.

In summary, subcutaneous alemtuzumab induction in HS pediatric patients who received desensitization with IVIG and rituximab was well tolerated and associated with excellent graft and patient survival. There was comparable renal function with a nonsignificant difference in AMR rates and rates of infectious complications over 5 years compared with nonsensitized patients receiving anti-IL-2R induction.

REFERENCES

- Shapiro R, Sarwal MM. Pediatric kidney transplantation. *Pediatr Clin North Am*. 2010;57:393–400.
- Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. *N Engl J Med*. 2008;359:242–251.
- Vo AA, Sinha A, Haas M, et al. Factors predicting risk for antibody-mediated rejection and graft loss in highly human leukocyte antigen sensitized patients transplanted after desensitization. *Transplantation*. 2015;99:1423–1430.
- Montgomery RA, Lonze BE, King KE, et al. Desensitization in HLA-incompatible kidney recipients and survival. *N Engl J Med*. 2011;365:318–326.
- Vo AA, Peng A, Toyoda M, et al. Use of intravenous immune globulin and rituximab for desensitization of highly HLA-sensitized patients awaiting kidney transplantation. *Transplantation*. 2010;89:1095–1102.
- Jordan SC, Tyan D, Stablein D, et al. Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IG02 trial. *J Am Soc Nephrol*. 2004;15:3256–3262.
- Stegall MD, Gloor J, Winters JL, et al. A comparison of plasmapheresis versus high-dose IVIG desensitization in renal allograft recipients with high levels of donor specific alloantibody. *Am J Transplant*. 2006;6:346–351.
- Kahwaji J, Sinha A, Toyoda M, et al. Infectious complications in kidney-transplant recipients desensitized with rituximab and intravenous immunoglobulin. *Clin J Am Soc Nephrol*. 2011;6:2894–2900.
- Margreiter R, Klempnauer J, Neuhaus P, et al. Alemtuzumab (Campath-1H) and tacrolimus monotherapy after renal transplantation: results of a prospective randomized trial. *Am J Transplant*. 2008;8:1480–1485.
- Chan K, Taube D, Roufosse C, et al. Kidney transplantation with minimized maintenance: alemtuzumab induction with tacrolimus monotherapy—an open label, randomized trial. *Transplantation*. 2011;92:774–780.
- Friend PJ. *Transplant Res*. 2013;2(Suppl 1):S5.
- Hanaway MJ, Woodle ES, Mulgaonkar S, et al. Alemtuzumab induction in renal transplantation. *N Engl J Med*. 2011;364:1909–1919.
- Nankivell BJ, Borrows RJ, Fung CL, et al. The natural history of chronic allograft nephropathy. *N Engl J Med*. 2003;349:2326–2333.
- Vo AA, Wechsler EA, Wang J, et al. Analysis of subcutaneous (SQ) alemtuzumab induction therapy in highly sensitized patients desensitized with IVIG and rituximab. *Am J Transplant*. 2008;8:144–149.
- Nourelddeen T, Albekioni Z, Machado L, et al. Alemtuzumab induction and antibody-mediated rejection in kidney transplantation. *Transplant Proc*. 2014;46:3405–3407.
- Gillen DL, Stehman-Breen CO, Smith JM, et al. Survival advantage of pediatric recipients of a first kidney transplant among children awaiting kidney transplantation. *Am J Transplant*. 2008;8:2600–2606.
- Shapiro R, Ellis D, Tan HP, et al. Alemtuzumab pre-conditioning with tacrolimus monotherapy in pediatric renal transplantation. *Am J Transplant*. 2007;7:2736–2738.
- Lai CH, Cao K, Ong G, et al. Antibody testing strategies for deceased donor kidney transplantation after immunomodulatory therapy. *Transplantation*. 2011;92:48–53.
- Vaudry W, Ettenger R, Jara P, et al. Valganciclovir dosing according to body surface area and renal function in pediatric solid organ transplant recipients. *Am J Transplant*. 2009;9:636–643.
- Solez K, Benediktsson H, Cavallo T, et al. Report of the Third Banff Conference on Allograft Pathology (July 20–24, 1995) on classification and lesion scoring in renal allograft pathology. *Transplant Proc*. 1996;28:441–444.
- Solez K, Colvin RB, Racusen LC, et al. Banff 07 classification of renal allograft pathology: updates and future directions. *Am J Transplant*. 2008;8:753–760.
- Toyoda M, Thomas D, Ahn G, et al. JC polyomavirus viremia and progressive multifocal leukoencephalopathy in human leukocyte antigen-sensitized kidney transplant recipients desensitized with intravenous immunoglobulin and rituximab. *Transpl Infect Dis*. 2015;17:838–847.
- Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *Am J Transplant*. 2012;12:1157–1167.
- Ge S, Pao A, Vo A, et al. Immunologic parameters and viral infections in patients desensitized with intravenous immunoglobulin and rituximab. *Transpl Immunol*. 2011;24:142–8.
- Kaabak MM, Babenko NN, Samsonov DV, et al. Alemtuzumab induction in pediatric kidney transplantation. *Pediatr Transplant*. 2013;17:168–178.
- Velez C, Zuluaga G, Ocampo C, et al. Clinical description and evolution of renal transplant pediatric patients treated with alemtuzumab. *Transplant Proc*. 2011;43:3350–3354.
- Sung J, Barry JM, Jenkins R, et al. Alemtuzumab induction with tacrolimus monotherapy in 25 pediatric renal transplant recipients. *Pediatr Transplant*. 2013;17:718–725.
- Knechtle SJ. Present experience with Campath-1H in organ transplantation and its potential use in pediatric recipients. *Pediatr Transplant*. 2004;8:106–112.
- De Serres SA, Mfarrej BG, Magee CN, et al. Immune profile of pediatric renal transplant recipients following alemtuzumab induction. *J Am Soc Nephrol*. 2012;23:174–182.
- Bartosh SM, Knechtle SJ, Sollinger HW. Campath-1H use in pediatric renal transplantation. *Am J Transplant*. 2005;5:1569–1573.
- Pirojsakul K, Desai D, Lacelle C, et al. Management of sensitized pediatric patients prior to renal transplantation. *Pediatr Nephrol*. 2016.