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ASSESSMENT OF RABBIT ANTITHYMOCYTE GLOBULIN DOSING AND CLINICAL OUTCOMES IN KIDNEY TRANSPLANTATION

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ABSTRACT

Purpose: Optimal dosing of rabbit antithymocyte globulin (rATG) remains undefined and varies between transplant centers. Previously the Methodist University Hospital Transplant Institute (MUHTI) based rATG dosing on kidney graft function (GF) following transplantation, but now utilizes risk stratification (RS) to guide dosing. The study aim was to evaluate outcomes of the RS dosing protocol in kidney transplant recipients as compared to the GF protocol. **Methods:** A retrospective chart review was done to identify adult patients who underwent single-organ kidney transplantation at the MUHTI and received rATG induction using the GF or RS protocol. The following 1 year outcomes were compared between groups: mean cumulative rATG induction dose, SCr and eGFR, patient and graft survival, episodes of biopsy-proven acute rejection, and infection with BK Polyoma virus and/or cytomegalovirus. Fisher's exact test was used to analyze categorical variables and student's t-test was used for continuous variables. A Kaplan-Meier analysis was used to compare patient and graft survival. **Results:** Of the 100 patients studied, 50 were dosed under the GF protocol and 50 were dosed using the RS protocol. The mean cumulative rATG dose in the GF group was 7.4 ± 2 mg/kg compared to 5.4 ± 1 mg/kg in the RS group ($p<0.05$). At 1 year renal function was significantly better in the RS group versus the GF group ($p<0.05$) and patient and graft survival were similar between groups $p>0.05$). There was a higher incidence of acute rejection in the RS group (14%) versus the GF group (8%); however, this difference was not statistically significant. The incidence of infection with BK Polyoma virus and cytomegalovirus were similar between groups ($p>0.05$). **Conclusion:** The RS dosing protocol for rATG improved renal outcomes without compromising patient or graft survival and led to a decrease in the mean cumulative rATG dose in kidney transplant recipients.

KEYWORDS: Rabbit antithymocyte globulin (rATG), risk stratification, kidney transplant this study was presented at the ACCP Annual Meeting, Albuquerque, NM, October 13-16, 2013.

INTRODUCTION

Rabbit antithymocyte globulin (rATG) has become a standard part of the immunosuppressive regimen in transplant centers across the nation. This polyclonal antibody is currently FDA-approved for the prophylaxis and treatment of acute rejection (AR).[1] The efficacy and safety of rATG induction for kidney transplantation was previously reported.[2,3,4]

Kidney transplant recipients at increased risk of AR may derive the most benefit from induction therapy. Risk factors for AR include: human leukocyte antigen (HLA) mismatches, younger recipient age, older donor age, African-American (AA) ethnicity (in the United States), panel reactive antibody (PRA) >30%, presence of a donor-specific antibody (DSA), blood group incompatibility, delayed graft function (DGF), cold ischemia time (CIT) >24 hours, and prior transplant.[5] In addition, a current or peak PRA ≥ 20% is also considered a risk factor for AR.[6]

Several studies have compared rATG (Thymoglobulin; Sanofi-Aventis, Laval, Quebec, Canada) dosing among both low risk and high risk kidney transplant recipients.[7-13] These results suggest that a cumulative rATG dose ≤6 mg/kg may successfully prevent AR in low risk recipients[10-12], whereas patients at high risk may require up to 7.5 mg/kg.[8,13] Despite this evidence and its widespread use, the optimal dosing of rATG remains undefined and varies between transplant centers.

Previously at the Methodist University Hospital Transplant Institute (MUHTI), the rATG dosing protocol was primarily based on kidney allograft function following transplantation.[14,15] The cumulative rATG dosing varied from 4.5 mg/kg for recipients with

immediate graft function to ~11 mg/kg in those with delayed graft function. On August 24, 2010, MUHTI implemented a new protocol which utilized risk stratification to guide dosing of rATG induction in kidney transplant recipients. This protocol allows patients at low immunologic risk to receive a cumulative rATG dose of ≤4.5 mg/kg and up to 6 mg/kg in those at high risk.

The purpose of this study is to evaluate the outcomes of a risk stratified (RS) dosing protocol for rATG in kidney transplant recipients as compared to the previous graft function (GF) protocol.

METHODS

Study Design and Patients

This was a retrospective review of adult patients who underwent kidney transplantation at Methodist University Hospital from January 1, 2008 to April 30, 2012. All patients received rATG induction therapy perioperatively. Patients were excluded if they received combined organ transplants, were treated with alternative induction therapy, or experienced graft loss within the first week posttransplant. Patients transplanted prior to August 24, 2010 were in the GF protocol group, while those transplanted on or after this date were in the RS group. Patients were randomly selected until 50 patients were identified for each group during the study period. This study was approved by the University of Tennessee Health Science Center Institutional Review Board.

Immunosuppression Protocol

Induction therapy with rATG was initiated intraoperatively for both protocols using an intravenous (IV) dose of 1.5 mg/kg based on the patient's actual body weight at the time of transplant. Postoperatively, patients received additional doses of 1.5 mg/kg according to the GF or RS dosing protocol. In the GF protocol, kidney transplant recipients with immediate graft function were given rATG 1.5 mg/kg/day for 3 doses and 7 doses for slow/delayed graft function.[14,15] Slow graft function was defined as <30% decrease in serum creatinine by postoperative day 3. Delayed graft function was defined as requiring hemodialysis within the first week of transplant. In the RS protocol, rATG 1.5 mg/kg/day for 3 doses was given for low risk and 4 doses for high risk kidney transplant recipients. Recipients were categorized as high risk if the following recipient/donor factors were present: prior transplant, prior desensitization, panel reactive antibody > 40%, positive donor specific antibody, positive B cell flow crossmatch, or serum creatinine reduction < 30% on postoperative day 3.

African American recipients with a donor age > 50 and 6 human leukocyte antigen (HLA) mismatches were also considered high risk. Doses were adjusted for leukopenia (white blood cell count 2000-4000 cells/m^3) and/or thrombocytopenia (platelets 50,000-100,000 cells/m^3). Doses were held for severe leukopenia (white blood cell count <2000 cells/m^3) or severe thrombocytopenia (platelets <50,000 cells/m^3). Patients were premedicated with acetaminophen, diphenhydramine and steroids prior to each infusion.

Patients also received methylprednisolone 500 mg preoperatively, followed by a steroid taper to a goal of prednisone 5 mg daily by 30 to 60 days posttransplant. Mycophenolate mofetil was started at 500 mg twice a day on the day of transplant and titrated to a goal of 2000 mg daily in divided doses as tolerated. Tacrolimus was started per transplant nephrologist preference. A trough level of 8-10 ng/mL was targeted for living donor recipients and 10-12 ng/ml for deceased donor and high risk recipients for the first three months, 8-10 ng/mL for months 3 through 6, and 7-9 ng/mL for months 6-12. All patients received an antifungal (nystatin, fluconazole, or clotrimazole), antiviral (valganciclovir or acyclovir), and Pneumocystitis jiroveci pneumonia prophylaxis (sulfamethoxazole-trimethoprim, dapsone, or pentamidine) following transplantation. For sulfa allergic patients, ciprofloxacin was used for urinary tract infection prophylaxis for the first two months post transplant.

Definition of Study End Points

The primary endpoint was renal outcomes based on serum creatinine (SCr) and calculated estimated glomerular filtration rate (eGFR) at 1, 3, 6, and 12 months. Estimated GFR (eGFR) was calculated using the abbreviated MDRD equation.

Secondary endpoints included patient and graft survival at each time point, episodes of biopsy-proven acute rejection (BPAR), BK virus (BKV) and/or cytomegalovirus (CMV) within the first year posttransplant, total cost of rATG administered as induction and for the treatment of BPAR within the first year posttransplant, length of initial hospital stay, and readmission to MUHTI within the first 90 days posttransplant. Infectious episodes of BKV and/or CMV were determined by a positive serum PCR. RATG costs were based on the current cost of therapy at Methodist University Hospital. BPAR was classified by the pathologist utilizing BANFF criteria.[16]

Statistical Analysis

Endpoints were compared between groups using the Fisher's exact test for categorical data and the t-test for parametric continuous data. For nonparametric continuous data, Mann-Whitney test was utilized. The Grubbs tests were used to detect any significant outliers. Survival analysis was performed utilizing the Kaplan-Meier technique. Statistical significance was defined as a *P* value less than 0.05. Statistical analysis was performed with SPSS 21.0 (IBM Corp., Armonk, NY).

RESULTS

Of the 109 patients screened, 4 were excluded because they were lost to follow-up, 3 experienced early graft loss, and 2 received alternative induction therapy. Of the

100 patients who met inclusion criteria, 50 were dosed under the GF protocol and 50 were dosed using the RS protocol. Baseline recipient characteristics were similar between groups with the exception of mean BMI (Table 1). The population was predominantly male (61%) and African American (73%). The leading causes of renal failure were hypertension and diabetes (66% and 22%, respectively), and 14% of patients had received a previous kidney transplant. Mean BMI was 30.0 ± 5.3 kg/m^2 in the GF protocol group vs. 26.6 ± 4.5 kg/m^2 in the RS group ($p<0.05$). Donor and transplant characteristics were also similar between groups (Table 2). The mean cumulative rATG dose in the GF protocol group was 7.4 ± 2 mg/kg compared to 5.4 ± 1 mg/kg in the RS group ($p<0.05$). A majority of patients were discharged on prednisone and mycophenolate (Table 3). Only 56% of the GF group were started on tacrolimus by the time of discharge as compared to 98% of the RS group ($p<0.05$).

Primary Outcome

Renal function was significantly better in the RS protocol group as compared to the GF protocol group at all time points. Mean serum creatinine was significantly higher in GF group vs. the RS group at 1 month posttransplant (2 vs. 1.6 mg/dL), at 3 months posttransplant (1.8 vs. 1.5 mg/dL), at 6 months posttransplant (1.7 vs. 1.4 mg/dL), and at 12 months posttransplant 1.7 vs. 1.5 mg/dL), respectively (Figure 1). Calculated eGFR was significantly lower in the GF protocol group as compared to the RS group at 1 month postransplant (46.7 vs. 57.4 mL/min/1.73 m^2), at 3 months posttransplant (48.7 vs. 61.2 mL/min/1.73 m^2), at 6 months posttransplant (52.4 vs. 61.8 mL/min/1.73 m^2), and at 12 months posttransplant (49.7 vs. 59.8 mL/min/1.73 m^2), respectively (Figure 2).

Secondary Outcomes

Patient and graft survival were similar between groups at all time points (Figures 3, 4). There was a higher incidence of BPAR in the RS protocol group vs. the GF group, (14% vs. 8%, respectively). However, this difference was not statistically significant. Interestingly, there were no episodes of antibody mediated or mixed BPAR in the GF group. The RS group had one patient with an antibody mediated rejection, while 3 patients had a mixed rejection episode (Table 4). Patients in the RS group also experienced more infections with BKV vs. the GF group (42% vs. 22%, respectively); however, this difference was not statistically significant. Episodes of CMV infection were similar between groups (Table 5).

The cost of rATG induction was significantly higher in the GF group vs. the RS group ($10,985 vs. $7,222, respectively; $p<0.05$). On the other hand, four patients required treatment with rATG for BPAR within the first year posttransplant. The mean rATG cost for BPAR treatment was $7,611 for these patients (Table 6). Length of initial hospital stay and readmission within 90 days of transplant were similar between groups (Table 7).

Table 1: Baseline Patient Characteristics.

Characteristic	GF Protocol (n = 50)	RS Protocol (n = 50)	*P* value
Mean ± SD age at transplant, yr	49.7 ± 11.6	49.2 ± 12.6	0.824
Male, no. (%) patients (pts)	30 (60)	31 (62)	1.000
African American, no. (%) pts	38 (76)	35 (70)	0.653
Mean ± SD BMI (kg/m^2)	30.0 ± 5.3	26.6 ± 4.5	0.0009
BMI > 30 kg/m^2, no. (%) pts	26 (52)	13 (26)	0.013
Cause of renal failure, no. (%) pts Hypertension Diabetes IgA nephropathy Polycystic kidney disease Graft failure, previous transplant Other/unknown	 34 (68) 12 (24) 2 (4) 4 (8) 6 (12) 5 (10)	 32 (64) 10 (20) 3 (6) 2 (4) 8 (16) 11 (22)	NS
Panel reactive antibody > 40%	5 (10)	12 (24)	NS

Table 2: Donor and Transplant Characteristics.

Characteristic	GF Protocol (n = 50)	RS Protocol (n = 50)	*P* value
Mean ± SD cold ischemic time, hr	15.7 ± 8.8	12.7 ± 9.0	NS
Donor source, no. (%) pts Living Standard criteria donor (SCD) Extended criteria donor (ECD) Donation after cardiac death (DCD)	 9 (18) 30 (60) 7 (14) 4 (8)	 15 (30) 23 (46) 5 (10) 7 (14)	NS
Donor > 50 years old, no. (%) pts	14 (28)	12 (24)	NS
6 HLA mismatch, no. (%) pts	12 (24)	6 (12)	NS
Delayed graft function, no. (%) pts	10 (20)	3 (6)	NS

Table 3: Comparison of immunosuppression between groups.

Characteristic	GF Protocol (n = 50)	RS Protocol (n = 50)	*P* value
Mean ± SD cumulative rATG dose, mg/kg*	7.41 ± 2.0	5.35 ± 1.1	0.0001
Prednisone upon discharge, no. (%) pts	50 (100)	48 (96)	NS
Mycophenolate agent upon discharge, no. (%) pts	50 (100)	49 (98)	NS
Tacrolimus upon discharge, no. (%) pts	28 (56)	49 (98)	0.0001

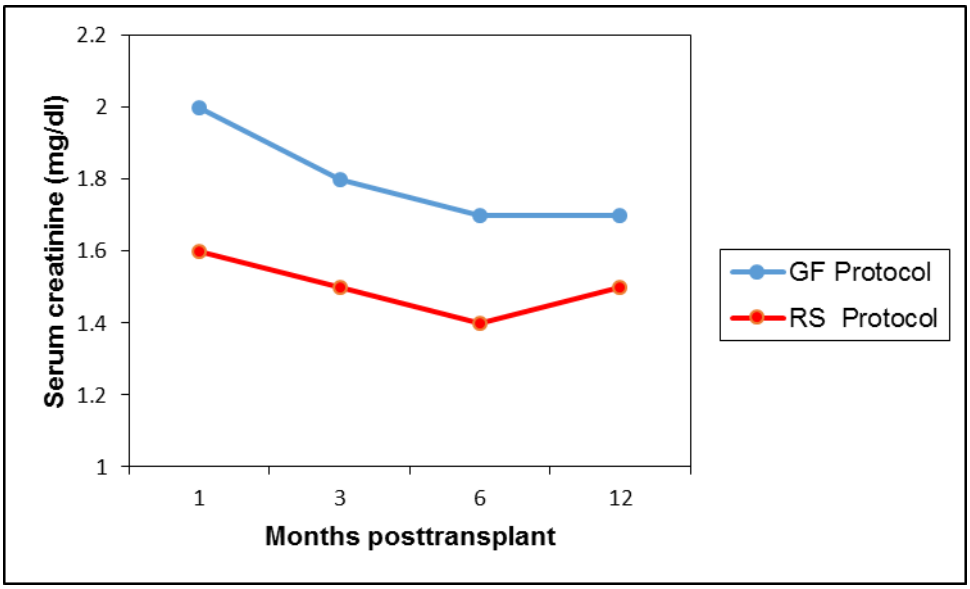

Figure 1: Comparison of serum creatinine in GF and RS protocols.

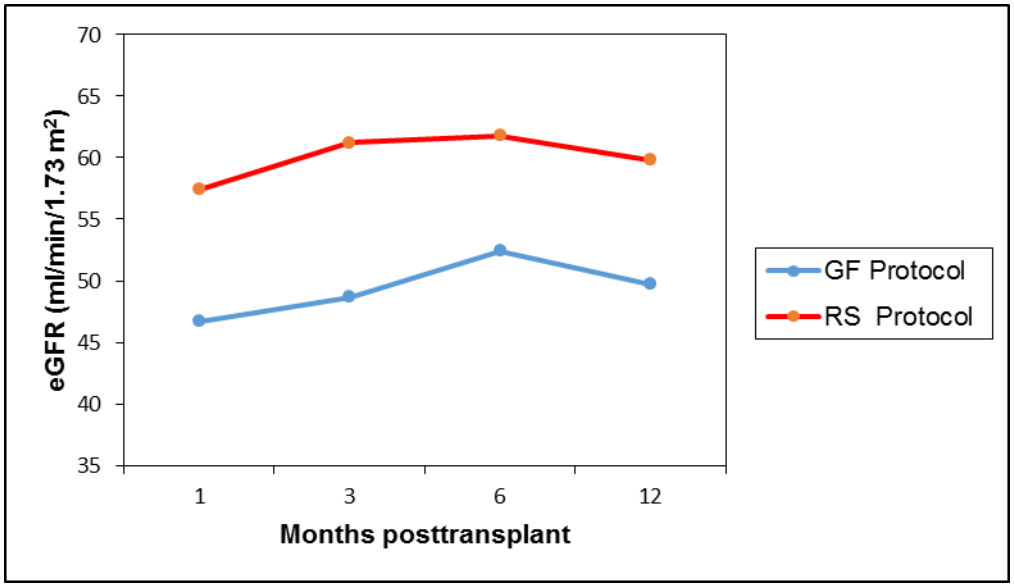

Figure 2: Comparison of eGFR in GF and RS protocols.

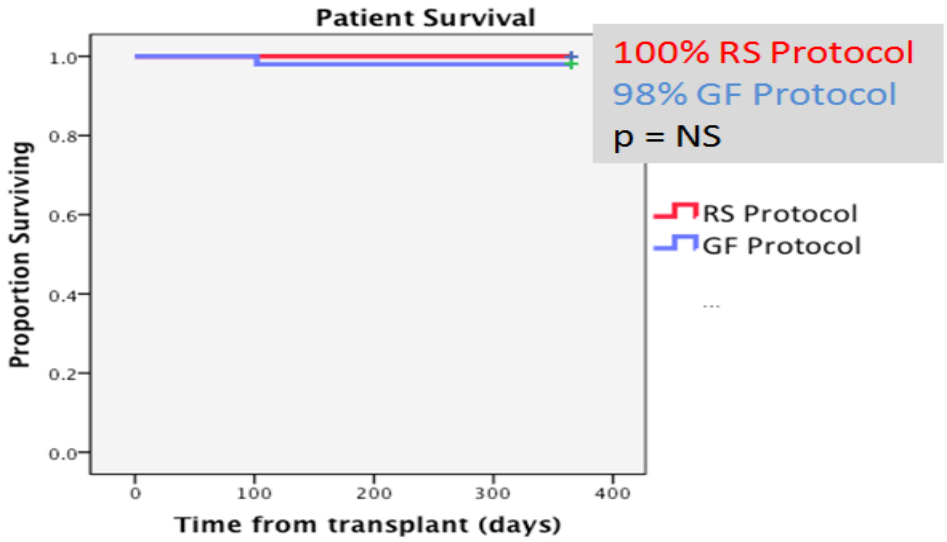

Figure 3: Kaplan-Meier curve comparison of patient survival.

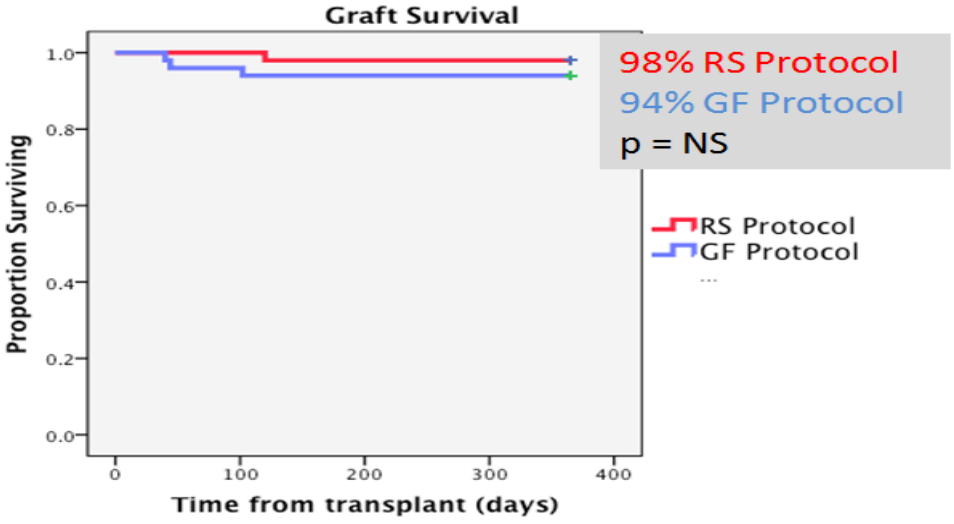

Figure 4: Kaplan-Meier curve comparison of graft survival.

Table 4: Comparison of biopsy-proven acute rejection episodes.

Type of BPAR	GF Protocol (n = 50)	RS Protocol (n = 50)	*P* value
Overall, no. (%) pt	4 (8)	7 (14)	NS
T-cell Mediated, no. (%) pt	4 (8)	3 (6)	NS
Antibody Mediated, no. (%) pts	0 (0)	1 (2)	NS
Mixed (T-cell + Antibody Mediated), no. (%) pts	0 (0)	3 (6)	NS

Table 5: Episodes of BK and CMV viremia.

Type of Infection	GF Protocol (n = 50)	RS Protocol (n = 50)	*P* value
BKV	11 (22)	21 (42)	0.0537
CMV	11 (22)	7 (14)	NS

Table 6: Cost of rATG.

	GF Protocol (n = 50)	RS Protocol (n = 50)	*P* value
Mean rATG induction cost, $	$10,985.64	$7,222.28	<0.0001
Mean rATG BPAR cost, $	n = 0 $0.00	n = 4 $7,611.30	<0.0001

Table 7: Length of Initial Hospital Stay / Readmission.

	GF Protocol (n = 50)	RS Protocol (n = 50)	*P* value
Mean ± SD length of initial stay, days	7.1 ± 2.4	6.4 ± 3.4	NS
Readmission within 90 days of transplant, no. (%) pts	21 (42)	21 (42)	NS

DISCUSSION

Previous studies have shown that kidney transplant recipients at high risk of developing acute rejection may require more intensive induction therapy when compared to patients at low risk.[6,11] This is the first known study to evaluate the outcomes of a risk stratified dosing protocol for rATG induction therapy. The results suggest that this patient-specific protocol improves renal outcomes when compared to a dosing protocol based on graft function.

The utilization of an RS dosing protocol led to a decrease in the mean rATG induction dose, resulting in an average savings of $3,763.36 per patient. However, overall financial savings were achieved with the GF protocol (average savings $3,847.94 per patient), especially when considering rejection episodes. Additional doses of rATG were necessary to treat rejection episodes in the RS dosing protocol, whereas rejection episodes in the GF protocol responded to steroids. In other words, rejection severity was greater for patients in the RS protocol, but similar graft and patient survival were achieved.

In addition, the mean BMI was noted to be significantly higher in the GF group vs. the RS group (30 ± 5.3 vs. 26.6 ± 4.5 kg/m^2, $p<0.05$). Both protocols utilized weight-based dosing for rATG (1.5 mg/kg), therefore the difference in BMI may have contributed to the differences in mean rATG dose. Previous studies have shown that obese kidney transplant recipients (defined by NIH and WHO guidelines as a BMI $\geq$ 30 kg/m^2) are at an increased risk of delayed graft function, wound complications, prolonged hospitalizations, and acute rejection.[12-15] However, recent data suggests that obesity does not affect patient and graft survival.[17-20] It is unclear whether the difference in BMI observed in this study represents clinical significance and can account for renal outcomes.

Despite overall mean dose reduction, there was a higher incidence of BKV infection in the RS group. When comparing the two protocols, we noticed that the urinary quantitative BKV DNA PCR was monitored more frequently under the RS protocol as compared to the previous GF protocol. About 50% of patients in each group who experienced rejection had an infection with BKV or CMV prior to the rejection episode. Therefore,

the increased incidence of BKV infections may explain the higher incidence of rejection in the RS group.

Although the RS group experienced a higher incidence of rejection, renal function was significantly better vs. the GF group at each time point within the first year posttransplant. However, this may be influenced by graft function immediately following the transplant as patients in the RS group were noted to have better renal function upon discharge when compared to the GF group (SCr: 3.3 vs. 6.4 mg/dL; eGFR 37.1 vs. 17.9 mL/min/1.73 m^2, respectively). Similarly, Tsapepas et. al. also reported an increased incidence of acute rejection when comparing kidney recipients receiving 5-6 mg/kg or ≥ 6 mg/kg of rATG induction. Authors concluded that renal outcomes were similar but suggested utilization of ≥ 6 mg/kg of rATG induction to prevent rejection and decrease cost of additional rATG for treatment of rejection.[21] However, this study utilized steroid avoidance whereas our study includes steroids as part of a triple therapy maintenance regimen.

In contrast, Klem et al. utilized a similar triple therapy maintenance regimen with reduced dose rATG induction in high risk patients; however, patients with delayed graft function were excluded from the study. Authors concluded that reduced dose (~4.5 mg/kg) was as effective as (~6 mg/kg) for selected kidney transplant recipients.[22] Our study differs due to the inclusion of delayed graft function patients and evaluation of rejection risk for each patient in order to determine rATG dosing in our RS protocol. This is important because kidney recipients with delayed graft function have been associated with an increased risk of rejection as well as graft loss posttransplant.[23-24] However, with rATG induction, similar renal outcomes have been reported in this subpopulation.[25]

We acknowledge that there are several limitations of this study. The retrospective design may allow for the collection of rATG dosing deviations from each protocol. However, since a transplant pharmacist frequently ordered rATG doses daily for the team per protocol, deviations were likely minimal. In addition, our sample may be too small to detect differences between groups for secondary outcomes. Therefore, a prospective study would be recommended to further support our results. We only evaluated short term outcomes, but it would be interesting to see if these dosing protocols had an effect on renal function and posttransplant complications beyond 1 year.

CONCLUSION

With a multitude of treatment options available, it is pertinent to tailor immunosuppression regimens based on several patient- and transplant-specific factors. In this study, the utilization of a risk stratified dosing protocol for rATG improved renal outcomes in kidney transplant recipients without compromising patient or graft survival within the first year posttransplant.

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