Evaluation of a Weight-based Rabbit Anti-thymocyte Globulin Induction Dosing Regimen for Kidney Transplant Recipients

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Study Objective Although rabbit anti-thymocyte globulin (rATG) is commonly used as induction therapy for kidney transplantation, dosing is not standardized. Recently available findings suggest that even subtle differences in the cumulative dose of rATG induction may have an impact on acute rejection rates for patients receiving steroid-minimization maintenance immunosuppression. This investigation evaluated the potential consequences of rounding and capping rATG doses in patients receiving steroid-containing maintenance immunosuppression when calculating the dose based on actual body weight.

Design Single-center retrospective cohort study.

Setting A large academic medical center.

Patients A total of 261 adult kidney transplant recipients between July 1, 2010, and December 31, 2012, who received rATG induction and were maintained on tacrolimus, mycophenolate, and prednisone.

Methods and Measurements Incidences of biopsy-confirmed acute rejection, opportunistic infections and hematologic effects within 12 months posttransplant were assessed for patients receiving a cumulative rATG dose of 5 mg/kg or higher (5.2 ± 0.2 mg/kg, n=138) compared with those who received a cumulative rATG dose lower than 5 mg/kg (4.5 ± 0.6 mg/kg, n=123). The groups had similar baseline characteristics, immunologic risk, and indications for rATG induction. The incidence of clinically relevant biopsy-confirmed acute rejection was low and similar between the groups (8.7% for rATG of 5 mg/kg or higher vs 8.9% for rATG lower than 5 mg/kg, p=0.944). Patient survival, all-cause graft survival, and graft function did not differ between the groups. Incidences of cytomegalovirus and BK virus infection as well as the extent and duration of lymphopenia were also similar between the groups.

Conclusions In combination with triple maintenance immunosuppression consisting of tacrolimus, mycophenolate, and prednisone, modest differences in the cumulative rATG dose were not associated with increased risk of acute rejection. Measures to optimize rATG utilization present opportunities for cost-saving without sacrificing efficacy in this patient population.

Key Words rabbit anti-thymocyte globulin, kidney transplantation, induction, acute rejection, cost.
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Despite having U.S. Food and Drug Administration approval only for the treatment of acute rejection, rabbit anti-thymocyte globulin (rATG) is commonly used for induction immunosuppression in solid organ transplantation. Approximately half of adult kidney transplant recipients

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in the United States receive rATG for induction.[1] rATG induction has been compared with placebo, equine anti-thymocyte globulin, and an interleukin-2 receptor antagonist in prospective randomized controlled clinical trials.[2–4] Cumulative rATG induction doses of 7.5–12.5 mg/kg resulted in significantly decreased acute rejection rates at the potential expense of prolonged lymphocyte depletion and increased risk of opportunistic infections.[2–4] Subsequent investigations have reported that cumulative rATG doses as low as 4.5–7.5 mg/kg could be effective for induction in combination with triple immunosuppression regimens including a calcineurin inhibitor, an antiproliferative agent, and corticosteroids.[5–7] However, a recent investigation found that cumulative rATG doses of 5–6 mg/kg were associated with an increased acute rejection rate compared with cumulative doses of at least 6 mg/kg (21% vs 11%, $p<0.0418$) when combined with steroid avoidance maintenance immunosuppression.[8]

At the University of Michigan, a cumulative rATG dose of 5 mg/kg based on actual body weight is used for induction therapy. However, doses are rounded to the nearest vial size and capped at a total of 500 mg, which can result in administration of a cumulative dose lower than 5 mg/kg, especially for overweight patients. The absence of randomized controlled trials and contradictions in the available data emphasize the need for additional information to determine the optimal dose of rATG for induction in kidney transplantation, particularly when used in combination with triple immunosuppressive maintenance regimens. Therefore, this study was designed to assess effectiveness and toxicity outcomes associated with subtle differences in cumulative dose of rATG induction in patients receiving steroid-containing maintenance immunosuppression.

Materials and Methods

This retrospective single-center cohort study included adult kidney transplant patients who received a living or deceased donor graft at the University of Michigan between July 1, 2010, and December 31, 2012. All included patients received rATG induction and were maintained on tacrolimus, mycophenolate, and prednisone. According to the institutional protocol, indications for rATG induction included African-American race, living unrelated kidney transplant, panel reactive antibody higher than 20%, presence of donor-specific antibody, and marginal graft function within 24 hours posttransplant defined as urine output less than 0.5 ml/kg/hour, a decline in serum creatinine less than 10% from pretransplant baseline, or a need for hemodialysis. Patients who received a prior or simultaneous nonrenal transplant, underwent desensitization, experienced primary graft nonfunction, expired within 7 days of transplantation, and those who received a positive crossmatch graft, investigational medications, or rATG for nonprotocol indications were excluded. Eligible patients were divided into two groups: those who received a cumulative rATG dose of 5 mg/kg or more (group I) and those who received less than 5 mg/kg (group II) based on preoperative actual body weight.

Induction with rATG consisted of 1.5 mg/kg on postoperative day (POD) 0 and POD 1, followed by 2 mg/kg on POD 2, for a cumulative dose of 5 mg/kg. Doses were rounded to the nearest vial size (25 mg) and capped at 150 mg for 1.5 mg/kg on POD 0 and POD 1 and 200 mg for 2 mg/kg on POD 2. Dose alterations were not allowed for patients with leukopenia or thrombocytopenia. In patients with marginal graft function, rATG induction was initiated postoperatively upon assessment of urine output and serum creatinine. For the other indications, the first dose of rATG was given intraoperatively before reperfusion of the kidney graft. Corticosteroids were administered according to the following schedule: methylprednisolone intravenous 500 mg intraoperatively followed by oral prednisone starting at 100 mg on POD 1 with gradual taper to 10 mg by POD 30. Further reduction of prednisone to 5 mg was done at the discretion of the transplant nephrologist. Tacrolimus 0.05 mg/kg orally (PO) every 12 hours was initiated within 24 hours of transplantation with trough targets of 8–12 ng/ml for POD 0–90, 6–10 ng/ml for POD 91–120, and 4–8 ng/ml beyond POD 121. Mycophenolate mofetil 1000 mg orally (PO) every 12 hours was initiated on POD 0. All patients received prophylaxis for fungal infection (nystatin suspension) and *Pneumocystis jiroveci* infection (trimethoprim/sulfamethoxazole or inhaled pentamidine) for 1 month. Patients at risk for cytomegalovirus (CMV) infection received antiviral prophylaxis with valganciclovir according to the institutional protocol.

The primary end point was incidence of biopsy-confirmed acute rejection (BCAR) grade 1A or greater within 12 months posttransplant as determined by Banff histologic criteria.[9] Secondary outcomes included incidences of CMV, BK viremia (BKV) and BK virus nephropathy (BKVN), patient and graft survival, graft function assessed by serum creatinine at 12 months, and hematologic effects including leukopenia, thrombocytopenia, and lymphopenia. Per protocol, BKV screening by polymerase chain reaction (PCR) occurs at 1, 2, 3, 6, 9, and 12 months posttransplant. CMV PCR was performed in conjunction with signs and symptoms suggestive of CMV infection. The Student unpaired *t* test and one-way analysis of variance were used to compare continuous variables. Categorical variables were compared using the χ^2 test. All statistical analyses were performed using SPSS 21 (IBM, Armonk, NY). This investigation was approved by the University of Michigan institutional review board.

Results

Among 474 kidney transplants performed between July 1, 2010, and December 31, 2012, 261 were included in the final analysis (Figure 1). With the exceptions of weight and body mass index (BMI), the groups were well matched with respect to demographics and immunologic risk factors (Table 1). The average rATG dose in group I was 5.2 ± 0.2 mg/kg compared with 4.5 ± 0.6 mg/kg for group II ($p<0.001$), and no patient received more than 6 mg/kg of rATG. Two patients in group II did not complete all three doses of rATG due to intolerance (respiratory distress and rash for one patient and hypotension for the other patient); these patients received single doses of 1.3 and 1.4 mg/kg, respectively. Tacrolimus trough concentrations in the first week posttransplant were similar. All patients were maintained on a steroid-containing regimen, and most of them continued the triple maintenance immunosuppression through 12 months (Table 2). There were no differences in the distribution of indications for rATG induction (Table 3). The 24 patients who received rATG for marginal graft function did not have another indication for induction and therefore received only steroids intraoperatively (group I, 8.7% vs group II, 9.8%; $p=0.767$). The overall incidence of marginal graft function was 31% and did not differ between the groups (group I, 31% vs group II, 31%; $p=0.963$).

Patient and graft outcomes did not differ significantly between the groups. At 12 months posttransplant, 98.6% of patients in group I were alive compared with 98.4% in group II ($p=0.908$). All-cause graft survival was 95.7% in group I and 97.6% for group II ($p=0.399$). Graft function as measured by serum creatinine at 12 months was also similar (group I, 1.4 ± 0.7 mg/dl vs group II, 1.5 ± 1.0 mg/dl;

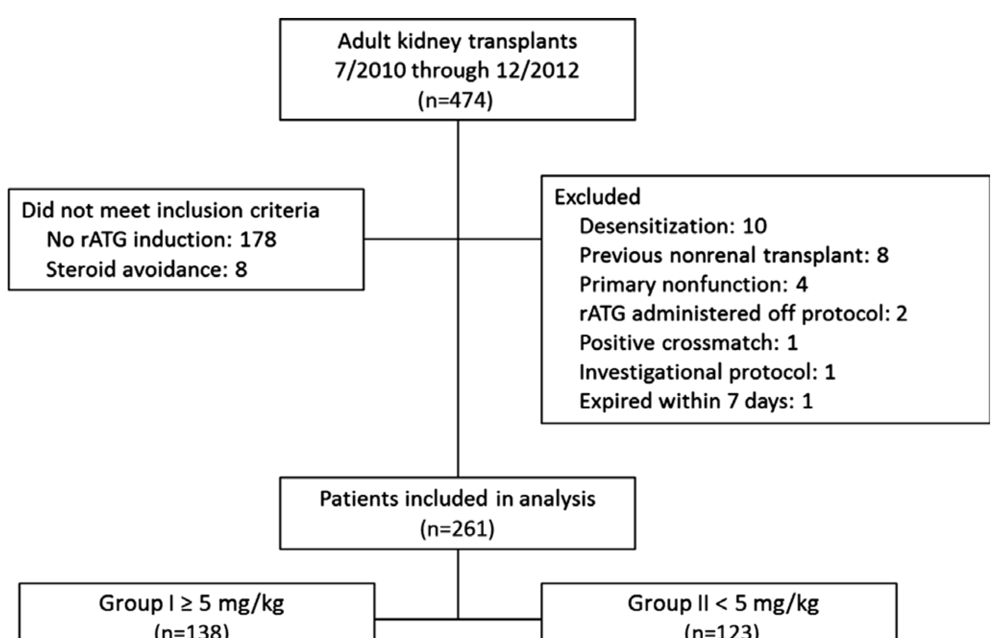

Figure 1. Study population. rATG = rabbit anti-thymocyte globulin.

Table 1. Baseline Characteristics

	Group I (n=138)	Group II (n=123)	p value
Age, yrs, mean ± SD	50.3 ± 14.1	50.5 ± 11.9	0.918
Male, n (%)	82 (59.4)	76 (61.8)	0.696
ABW, kg, mean ± SD	80.3 ± 13.8	94.6 ± 24.4	< 0.001
IBW, kg, mean ± SD	64.4 ± 11.5	66.8 ± 10.9	0.084
BMI, kg/m^2, mean ± SD	27.6 ± 4.8	31.3 ± 6.9	< 0.001
Follow up, days, mean ± SD	661 ± 263	717 ± 260	0.087
Indication for transplant, n (%)			
HTN	28 (20.3)	25 (20.3)	0.588
DM	28 (20.3)	26 (21.1)	
HTN and DM	15 (10.9)	14 (11.4)	
PCKD	10 (7.2)	14 (11.4)	
GN	16 (11.6)	19 (15.4)	
FSGS	10 (7.2)	8 (6.5)	
Other	31 (22.5)	17 (13.8)	
Donor, n (%)			
DDKT	84 (61.9)	63 (51.2)	0.187
LRKT	8 (5.8)	13 (10.6)	
LUKT	46 (33.3)	47 (38.2)	
African-American, n (%)	46 (33.3)	33 (26.8)	0.282
PRA > 20%, n (%)	57 (41.3)	49 (39.8)	0.810
DSA, n (%)	26 (18.1)	26 (21.1)	0.643
Retransplantation, n (%)	14 (17.4)	16 (13.0)	0.326
CMV high-risk (D+/R−), n (%)	33 (23.9)	28 (22.8)	0.884

ABW = actual body weight; BMI = body mass index; CMV = cytomegalovirus; D = donor; DDKT = deceased donor kidney transplant; DM = diabetes mellitus; DSA = donor-specific antibody; FSGS = focal segmental glomerulosclerosis; GN = glomerulonephritis; HTN = hypertension; IBW = ideal body weight; LRKT = living related kidney transplant; LUKT = living unrelated kidney transplant; PCKD = polycystic kidney disease; PRA = panel reactive antibody; R = recipient; SD = standard deviation.

Table 2. Maintenance Immunosuppression

	Group I (n=138)	Group II (n=123)	p value
Mean tacrolimus level on POD 3–7, ng/ml, mean ± SE	8.8 ± 4.8	9.1 ± 4.2	0.573
Mean tacrolimus level on POD 3–7 ≥ 8 ng/ml, n (%)	72 (52.2)	68 (55.3)	0.615
Immunosuppression at 12 mo			
TMP, n (%)	124 (89.9)	114 (92.7)	0.859
TP, n (%)	10 (7.2)	6 (4.9)	
mTOR, n (%)	3 (2.2)	2 (1.6)	
Other, n (%)	1 (0.7)	1 (0.8)	

mTOR = mammalian target of rapamycin (i.e., any regimen containing everolimus or sirolimus); POD = postoperative day; SE = standard error; TMP = tacrolimus, mycophenolate and prednisone; TP = tacrolimus and prednisone.

p=0.583). No significant differences in the primary endpoint of BCAR ≥ 1A, recurrent BCAR, or antibody-mediated rejection were observed (Table 4). Similarly, no significant difference in BCAR ≥ 1A was found when patients were stratified based on BMI (Table 5). Cumulative rATG dose was not associated with a difference in time to BCAR ≥ 1A within the first 12 months (Figure 2).

Table 3. Indications for Rabbit Anti-thymocyte Globulin Induction

	Group I (n=138)	Group II (n=123)	p value
African-American, n (%)	46 (33.3)	33 (26.8)	0.282
LUKT, n (%)	46 (33.3)	47 (38.2)	0.411
PRA > 20%, n (%)	57 (41.3)	49 (39.8)	0.810
DSA, n (%)	26 (18.1)	26 (21.1)	0.643
Number of indications			
Two, n (%)	30 (21.7)	30 (24.4)	0.510
Three, n (%)	10 (7.2)	5 (4.1)	
Marginal graft function only, n (%)[a]	12 (8.7)	12 (9.8)	0.927

DSA = donor-specific antibody; LUKT = living unrelated kidney transplant; PRA = panel reactive antibody.
[a]Patients without other indications who developed marginal graft function received the first dose of rabbit anti-thymocyte globulin (rATG) postoperatively. For the other patients, rATG was initiated intraoperatively.

Table 4. Biopsy-confirmed Acute Rejection at 12 months

	Group I (n=138)	Group II (n=123)	p value
BCAR grade ≥ 1A, n (%)	12 (8.7)	11 (8.9)	0.994
BCAR grade			
BCAR grade 1, n (%)	6 (4.3)	9 (7.3)	0.304
BCAR grade 2, n (%)	5 (3.6)	1 (0.8)	0.130
BCAR grade 3, n (%)	1 (0.7)	1 (0.8)	0.935
Recurrent BCAR grade ≥ 1A, n (%)	10 (7.2)	3 (2.4)	0.075
Antibody-mediated rejection, n (%)	5 (3.6)	2 (1.6)	0.319

BCAR = biopsy-confirmed acute rejection.

Regarding the toxicity-related outcomes, no differences in CMV (group I, 8.0% vs group II, 9.8%; p=0.385), BKV (group I, 10.9% vs group II, 10.6%; p=0.550) or BKVN (group I, 4.3% vs group II, 4.1%; p=0.579) were observed. The incidences of lymphopenia, thrombocytopenia, and leukopenia did not differ significantly between the groups (Figure 3). rATG induction depleted circulating lymphocytes to fewer than 500 cells/mm^3, and lymphocyte depletion was sustained until POD 90 in almost 40% of patients. The degree and duration of lymphopenia was not different between the groups.

Discussion

The rATG induction dose that provides adequate protection from acute rejection with

Table 5. Biopsy-confirmed Acute Rejection Stratified by Body Mass Index

	BMI ≤ 24.9 kg/m^2 (n=68)	BMI 25 – 29.9 kg/m^2 (n=81)	BMI 30 – 34.9 kg/m^2 (n=65)	BMI ≥ 35 kg/m^2 (n=47)	p value
BCAR grade ≥ 1A, n (%)	5 (7.4)	7 (8.6)	9 (13.8)	2 (4.3)	0.328
rATG dose, mg/kg, mean ± SD	5.0 ± 0.5	5.0 ± 0.2	4.9 ± 0.5	4.4 ± 0.6	< 0.001

BCAR = biopsy-confirmed acute rejection; BMI = body mass index; rATG = rabbit anti-thymocyte globulin.

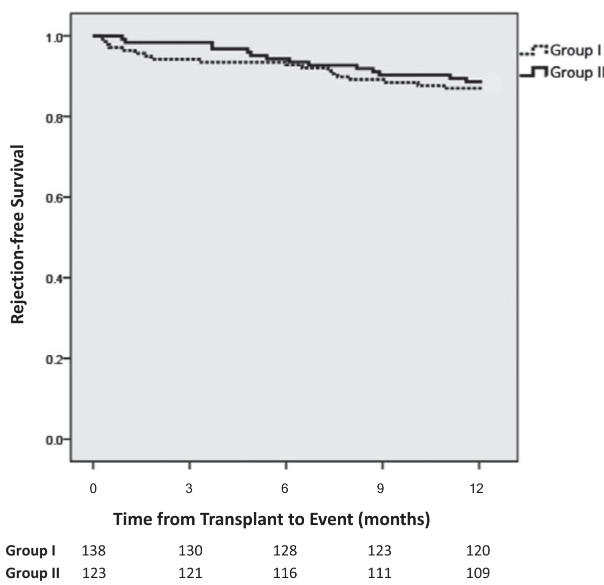

Figure 2. Kaplan-Meier graph illustrating overall rejection-free survival according to rabbit anti-thymocyte globulin induction dose (group I ≥ 5 mg/kg and group II < 5 mg/kg). Time to event includes time to an episode of biopsy-confirmed acute rejection ≥ 1A, graft loss, or death—whichever occurred earlier.

minimal hematologic and infectious complications is a subject of ongoing investigation. This investigation provided additional evidence regarding weight-based dosing strategies for rATG induction in adult kidney transplant recipients with immunologic risk factors. In our cohort, rATG induction at a cumulative dose of 5 mg/kg given in combination with tacrolimus-based steroid-containing triple maintenance immunosuppression was effective in preventing acute rejection. The overall incidence of 12-month BCAR was lower than 9%, and the small difference in rATG dose due to rounding and capping did not appear to have a significant impact on the rejection rate. The difference in rATG dose was not associated with changes in opportunistic infections, hematologic toxicities, or duration of lymphopenia.

Previous studies using various rATG doses in combination with triple maintenance immunosuppression regimens consisting of a calcineurin inhibitor, an antiproliferative agent, and steroids reported similar acute rejection rates to those in the current study. One study reported that rATG doses were commonly halved or held for leukopenia or thrombocytopenia when a cumulative dose of 10.5 mg/kg was given over a 7-day course.[5] Therefore, they compared this historical control group to patients receiving a reduced cumulative dose of 6 mg/kg over a 3-day course and found no significant difference in BCAR at 12 months (4.2% for 10.5 mg/kg vs 5% for 6 mg/kg, p=1.0). Additionally, the patients receiving 6 mg/kg had a significantly shorter length of stay than those receiving 10.5 mg/kg (6 vs 8 days, p=0.002). A different study in adult kidney transplant patients reported that the incidence of BCAR at 12 months was similar (9.5% for more than 7.5 mg/kg vs 8.8% for 7.5 mg/kg or less; p=0.9) between patients who received a target cumulative rATG dose of 7.5 mg/kg (10.3 ± 2.1 mg/kg) and those who received 7.5 mg/kg or less (5.7 ± 1.6 mg/kg).[6] Another investigation comparing lower cumulative doses of 6 mg/kg given over 4 days and 4.5 mg/kg given over 3 days also reported no significant difference in acute rejection rates at 12 months (11% for 6 mg/kg vs 10% for 4.5 mg/kg; p=1.0).[7] The median length of stay was significantly shorter for the patients receiving the 3-day regimen (3 vs 4 days; p=0.004). These studies provided the foundation for the 3-day rATG induction dosing strategy at our center.

A more recent rATG induction dosing investigation observed an increase in acute rejection with cumulative doses of 5–6 mg/kg, raising concern particularly for centers targeting total doses in this range.[8] In contrast to these findings, which evaluated different cumulative rATG doses administered in combination with a steroid-avoidance maintenance regimen, the results presented in our study align with prior rATG induction dosing investigations using similar triple maintenance immunosuppression. Our findings also address the uncertainty regarding potential consequences of underdosing rATG in overweight patients. The absence of any clinically

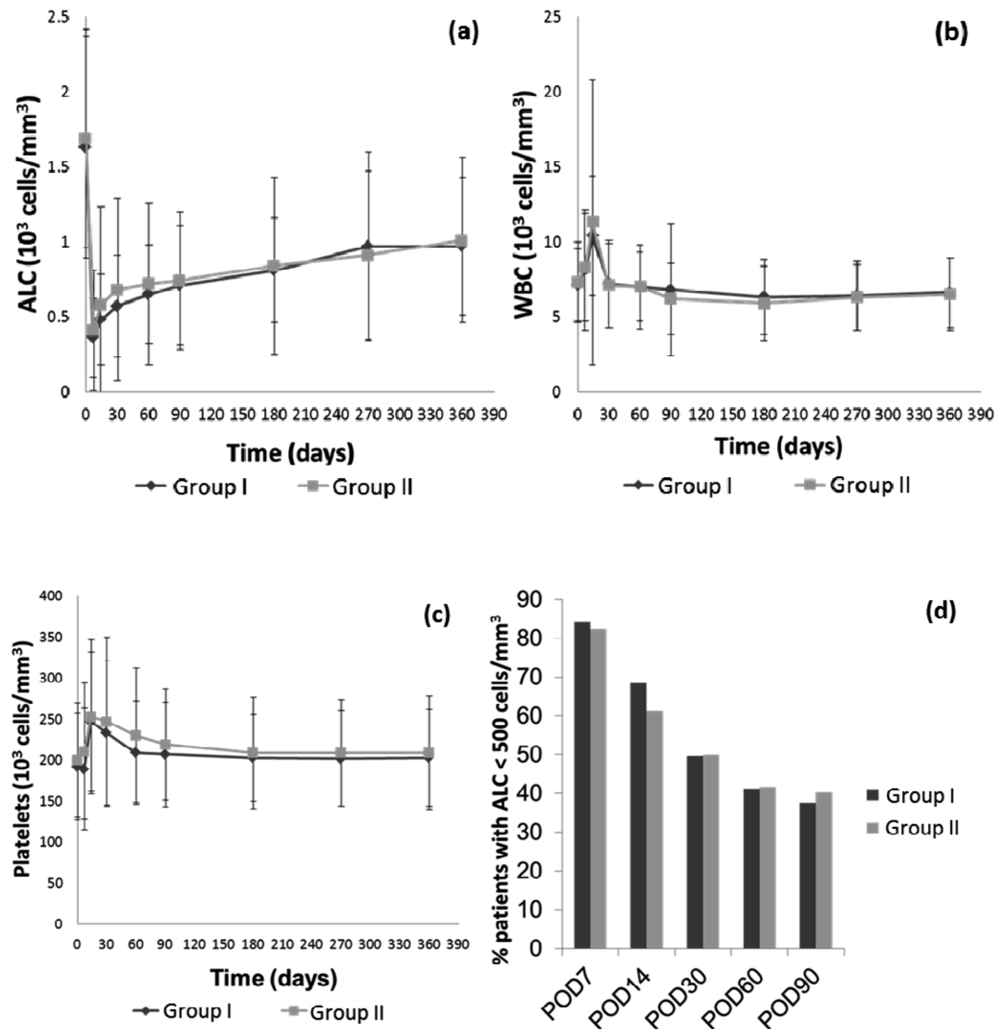

Figure 3. Hematologic effects of rabbit anti-thymocyte globulin induction following transplant (group I ≥ 5 mg/kg and group II < 5 mg/kg): (a) absolute lymphocyte counts (ALCs), (b) total white blood cell (WBC) counts, (c) platelet counts, and (d) patients with ALCs below 500 cells/mm^3. POD = postoperative day.

significant difference in both safety and efficacy between average doses of 4.5 mg/kg compared with 5.2 mg/kg provides reassurance for the use of doses in this range, which are known to cause fewer adverse events and may offer cost-saving advantages as well.

We have observed variations in the weight used for rATG dose calculation. In most patients, preoperative weight was used to determine all three doses of rATG. Weight often increased postoperatively due to fluid overload, so that higher doses of rATG were given when actual body weight on the day of rATG administration was used for the dose calculation. Our findings suggest that modest variation in rATG induction dosing due to rounding and capping may not significantly compromise short-term outcomes, provided that patients receive approximately 5 mg/kg based on preoperative actual body weight. During the 30-month period of this investigation, a total of 104,800 g rATG were administered to 261 patients. If all doses were based on preoperative actual body weight, only 103,225 g rATG would have been needed. Standardizing the dosing weight could reduce rATG utilization by 1575 g over 30 months. At a wholesale acquisition cost of $664.46/25 g vial,[10] dosing rATG based on the preoperative weight rather than the current weight translates to an annual cost savings of $6415 per 100 patients.

This investigation is limited by the retrospective nonrandomized single-center design. Confounders such as adherence to maintenance immunosuppression regimen or mycophenolate dose adjustment were not captured. Although there was no difference in the average tacrolimus levels during the first week posttransplant, the exposure to tacrolimus preceding any episodes of rejection is unknown. Because no patient in our study cohort received a cumulative rATG dose higher than 6 mg/kg, any differences that may exist with higher doses could not be detected.

Dividing patients based on the cumulative rATG dose also assigned those with higher BMI to group II (less than 5 mg/kg). Obesity is characterized as a chronic inflammatory condition during which adipocytes produce proinflammatory cytokines that promote T-cell proliferation.[11] Therefore, obese patients may have an inherently increased risk of rejection. An analysis identified 27,377 kidney transplant recipients with complete anthropometric data available in a national registry.[12] When compared with patients who had a normal BMI (18.5–24.9 kg/m^2), obese patients (BMI 30–34.9 kg/m^2) were more likely to experience acute rejection before discharge (odds ratio [OR] [95% confidence interval (CI), 1.19 [1.04–1.36]) and morbidly obese patients (BMI of 35 kg/m^2 or higher) were more likely to experience acute rejection prior to discharge and at 6 and 12 months posttransplant (OR [95% CI], 1.5 [1.3–1.86], 1.28 [1.11–1.49], and 1.2 [1.09–1.55], respectively). A single-center observational study of 1151 kidney transplant recipients found an increased risk of acute rejection for patients in the highest BMI strata (35 kg/m^2 or higher) compared with those who had a BMI 20–24.9 kg/m^2 (HR [95% CI], 2.19 [1.37–3.49]).[13] However, these findings have not been reproduced consistently in other studies. A meta-analysis that included 11 studies representing 3307 patients found no association between obesity and acute rejection (relative risk [95% CI], 0.95 [0.82–1.11]).[14] Our study included 47 patients with a BMI in the range previously associated with increased risk of rejection (35 kg/m^2 or higher), and these patients received a lower dose of rATG compared with those with a BMI lower than 35 kg/m^2. We did not observe any differences in BCAR when patients were stratified by BMI (Table 5).

Although the recipients at highest immunologic risk were excluded, including those who were ABO incompatible, positive crossmatch, and those receiving desensitization or steroid avoidance, our study population was diverse and included highly sensitized patients as well as those with multiple immunologic risk factors (Table 3). The results of this investigation suggest that modest differences in rATG induction dose are not associated with increased risk of acute rejection when a cumulative dose of 5 mg/kg is targeted in combination with triple maintenance immunosuppression. Therefore, it is reasonable to determine the rATG dose based on actual body weight with rounding and capping in this patient population to minimize toxicity as well as cost.

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