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# Tailored Rabbit Antithymocyte Globulin Induction Dosing for Kidney Transplantation

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**Background.** Rabbit antithymocyte globulin (rATG) is the most widely used kidney transplant induction immunotherapy in the United States. It was recently Food and Drug Administration approved for this indication with typical dose recommendations of 1.5 mg/kg for up to 7 days given via a central line. **Methods.** We theorized that reduced rATG dosing when compared with conventional dosing (6–10.5 mg/kg) is safe and effective, leading to development of a risk-stratified treatment protocol. Five-year data from a retrospective cohort of 224 adult kidney transplants (2008–2013) with follow-up through 2015 is presented. Cumulative rATG doses of 3 mg/kg were administered peripherally to nonsensitized living donor recipients, 4.5 mg/kg to nonsensitized deceased donor recipients. A subset of higher immunologic risk recipients (defined as history of prior transplant, panel reactive antibody greater than 20%, or flow cytometry crossmatch positivity) received 6 mg/kg. **Results.** There were no differences in patient or graft survival between the 3 groups. One-year rejection rates in the first 2 groups were 8.3% and 8.8%, respectively, comparable to contemporaneous rates reported to the Scientific Registry of Transplant Recipients. Dose tailoring permitted substantial cost savings estimated at US \$1 091 502. Mean length of stay fell by almost 3 days as the protocol was refined. There were no episodes of phlebitis. Infection rates were comparable with those reported to the Scientific Registry of Transplant Recipients. **Conclusions.** The novel findings of the current study include peripheral administration, reduced dosing, favorable safety, excellent allograft outcomes, and clear associative data regarding reduced costs and length of stay.

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Rabbit antithymocyte globulin (rATG; Thymoglobulin; Sanofi Genzyme, Bridgewater, NJ) is a polyclonal, T cell-depleting antibody that is the most commonly used induction

agent for kidney transplantation within the United States.<sup>1</sup> The first clinical study of rATG induction immunotherapy was reported in 1971.<sup>2</sup> Low-level development continued through the 1990s.<sup>3–6</sup> However, it was not until 1999 that the first randomized double-blind comparison of rATG versus equine ATG as induction therapy was reported.<sup>7</sup> The patients in the rATG arm received a cumulative dose of 10.5 mg/kg, experienced significantly fewer acute rejection episodes (4% vs 25%, respectively) and higher allograft survival (98% vs 83%, respectively). Since that time, a number of studies have been reported with cumulative dose ranges from 5 to 12 mg/kg.<sup>8–10</sup> Single dose (6 mg/kg) versus divided doses (1.5 mg/kg on four consecutive days) have yielded similar outcomes in terms of graft and rejection-free survival.<sup>11,12</sup> Most recently (April 2017), the Food and Drug Administration approved rATG as antibody induction therapy with doses ranging from 6 to 10.5 mg/kg. The efficacy of rATG induction when compared with various alternate strategies has been clearly defined, a detailed discussion of which is beyond the scope of this report.<sup>10,13–20</sup>

Despite the de facto enthusiasm for use of this agent, concerns about the potential adverse effects of rATG have included pancytopenia, prolonged lymphopenia, infection, and serum sickness.<sup>15,21,22</sup> Cost is also a significant issue.<sup>17,23</sup> The present study was developed with the hypothesis that tailored rATG dosing may be effective in minimizing acute rejection while simultaneously curtailing cost and adverse effects.

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**TABLE 1A.****Baseline recipient characteristics**

	All recipients (n = 224)*	rATG, 3 mg/kg (n = 96)	rATG, 4.5 mg/kg (n = 102)	rATG, 6 mg/kg (n = 26)
Mean age ( $\pm$ SD), y	49.6 $\pm$ 12.7	49 $\pm$ 13.5	52 $\pm$ 11.2	45 $\pm$ 14
Male sex, n (%)	151 (67.4)	63 (65.6)	74 (72.5)	14 (53.8)
White, n (%)	215 (96)	92 (95.8)	98 (96.1)	25 (96.2)
ESRD etiology				
Chronic GN	79 (35.3)	38 (39.6)	33 (32.4)	8 (30.8)
Diabetes mellitus	50 (22.3)	23 (24.0)	27 (26.5)	0
Hypertension	25 (11.2)	8 (8.3)	16 (15.7)	1 (3.8)
Obstructive uropathy	24 (10.7)	9 (9.4)	3 (2.9)	12 (46.2)
Polycystic kidney disease	26 (11.6)	8 (8.3)	16 (15.7)	2 (7.7)
Other	20 (8.9)	10 (10.4)	7 (6.9)	3 (11.4)
Preemptive, n (%)	27 (12.1)	25 (26.0)	1 (1)	1 (3.8)
Deceased donor, n (%)	118 (52.7)	4 (4.2)	93 (91.2)	21 (80.8)
History previous transplant, n (%)	37 (16.5)	1 (0.1)	13 (12.7)	23 (88.5)
Mean HLA mismatch $\pm$ SD	3.9 $\pm$ 1.6	3.4 $\pm$ 1.7	4.5 $\pm$ 1.1	3.2 $\pm$ 2.1
Mean Cumulative rATG dosage delivered ( $\pm$ SD), mg/kg	4.0 $\pm$ 1.0	3.0 $\pm$ 0	4.5 $\pm$ 0	6.1 $\pm$ 0.3
Maintenance immunosuppression, n (%)				
Calcineurin inhibitor	224 (100)	96 (100)	102 (100)	26 (100)
Antimetabolite	211 (94.2)	88 (91.7)	97 (95.1)	26 (100)
Steroid	224 (100)	96 (100)	102 (100)	26 (100)
Mean follow-up ( $\pm$ SD), mo	42.3 $\pm$ 20.0	43 $\pm$ 18.8	42 $\pm$ 20.7	39 $\pm$ 22.2

rATG, rabbit antithymocyte globulin; ESRD, end-stage renal disease; DDRT, deceased donor renal transplant; PRA, panel reactive antibody.

Sixteen years of internal quality data analyses permitted development of the risk-stratified dosing strategy that is presented herein.

## MATERIALS AND METHODS

### Study Design and Patient Population

A single-center retrospective cohort study encompassing adult kidney transplants performed at Maine Medical Center between July 1, 2008, and December 31, 2013, is presented. All patients included in the study were followed through January 1, 2015. Recipients were divided in three groups according to the administered rATG dose. Cumulative rATG doses of 3 mg/kg were administered to nonsensitized living donor recipients and 4.5 mg/kg to nonsensitized deceased donor recipients. An increased immunologic risk subgroup (defined as history of prior transplant, panel reactive antibody greater than 20%, or flow cytometry crossmatch positivity defined as a 40 and 100 channel shift for T and B lymphocytes respectively using a 1024 channel Beckman-Coulter FC-500 Cytometer) received 6 mg/kg (Table 1A). The rATG dose was calculated using the actual weight of the patients. Minor protocol deviations occurred in less than 7% of cases. The first dose of rATG given intraoperatively via a peripheral intravenous access was 1.5 mg/kg until November 2010, after which the dose was increased to 3 mg/kg to facilitate earlier discharge and to reduce length of stay (LOS). The time frame for subsequent doses of 1.5 mg/kg was dictated by clinical progress and physician discretion.

### Maintenance Immunosuppression Therapy

All patients received a cumulative loading dose of methylprednisolone 1 gram perioperatively after which prednisone was started at 30 mg daily tapering to 5 mg daily by week 10. Mycophenolate mofetil was started at 1000 mg twice

daily immediately posttransplantation, with dose adjustments for adverse effects as necessary. Tacrolimus 0.05 mg/kg was administered twice daily aiming for trough levels of 10 to 12 ng/mL for the first 3 months, and was lowered to 7 to 10 ng/mL until the end of the first year. The goal was to maintain triple immunotherapy unless adverse effects dictated otherwise.

### Antimicrobial Prophylaxis

Bacterial and *Pneumocystis jirovicii* pneumonia prophylaxis was achieved with trimethoprim-sulfamethoxazole single-strength daily for 1 year. For patients allergic to sulfa products, inhaled pentamidine or oral atovaquone were administered. Oral candida prophylaxis included clotrimazole or oral nystatin for the first month posttransplantation. For cytomegalovirus (CMV) prophylaxis, choice and duration of antiviral depended on the donor and recipient risk profile. CMV negative patients receiving a CMV positive donor kidney received 24 weeks of valganciclovir. CMV positive

**TABLE 1B.**  
Exclusion criteria<sup>a</sup>

	n
No immunosuppression	2
1 Identical Twin Transplant	
1 Kidney transplant from prior bone marrow donor	
IL-2R induction therapy	5
rATG therapy interrupted	3
Graft thrombosis	4
Death within 1 month of transplant	3
Total	17

<sup>a</sup> Two hundred twenty-four of the initial 241 adult patients transplanted in the study period (93%) were included in the analysis. Six pediatric transplant recipients were also excluded.

**TABLE 2.**  
Outcomes based on the cumulative rATG dosages

	All recipients (n = 224)	rATG, 3 mg/kg (n = 96)	rATG, 4.5 mg/kg (n = 102)	rATG, 6 mg/kg (n = 26)
Mean serum creatinine at 1 y ( $\pm$ SD), mg/dL	1.5 $\pm$ 0.6	1.5 $\pm$ 0.5	1.5 $\pm$ 0.5	1.8 $\pm$ 0.9
No. biopsies	87 (39%)	33 (34%)	34 (33%)	20 (76%)
No. patients with one or more biopsies, n (%)	71 (31.7)	29 (30.2)	27 (26.5)	15 (57.7)
Mean time to first biopsy ( $\pm$ SD), d	118 $\pm$ 102	144 $\pm$ 110	116 $\pm$ 100	71 $\pm$ 69
DSA screen, n (%)	97 (43.3)	46 (47.9)	34 (33.3)	17 (65.4)
DSA positivity, n (%)	16 (7.1)	7 (7.3)	6 (5.9)	3 (11.4)
Class I	18 (8.0)	10 (10.4)	4 (3.9)	4 (15.4)
Class II				
No. patients with BPAR, n (%)	21 (9.4)	8 (8.3)	9 (8.8)	4 (15.4)
No. BPAR episodes	29 (12.9%)	9 (9.3%)	13 (12.7%)	7 (26.9%)
Death-censored graft survival				
1-year, n (%)	224 (100)	96 (100)	102 (100)	26 (100)
End-of-study, * n (%)	212 (94.6)	90 (93.8)	99 (97.1)	23 (88.5)
Deaths at 1 y, n (%)	8 (3.6)	2 (2.1)	4 (3.9)	2 (7.7)
Deaths at the end of study, n (%)	15 (6.7)	4 (4.2)	9 (8.8)	2 (7.7)

\* End-of-study, January 1, 2015.

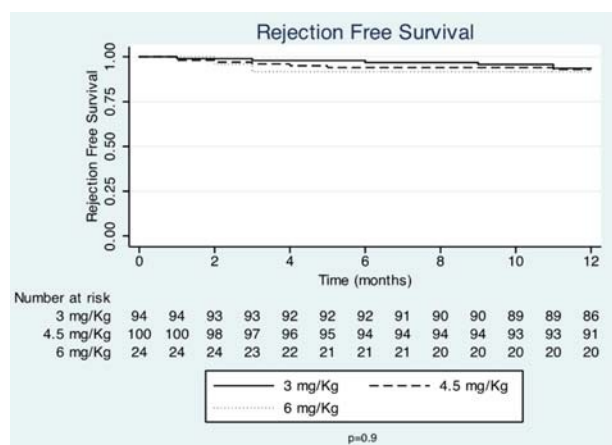
"At risk" patients (retransplant, prior acute rejection, increased PRA) were screened for DSA. DSA also tested for cause (AKI, proteinuria). DSA defined as > 1000 MFI for detection of HLA Ab. BPAR, biopsy proven acute rejection.

recipients received 12 weeks of valganciclovir. Seronegative recipients of seronegative allografts received 12 weeks of acyclovir to prevent non-CMV herpes infection. Antiviral agents were dosed according to the estimated glomerular filtration rate.

### Statistical Analysis

The primary outcome of the study was biopsy-proven acute rejection (BPAR) within the first year posttransplant. The secondary outcomes included patient survival, graft survival, costs and LOS. Patient demographics, baseline characteristics and primary outcome were summarized using descriptive statistics. Kaplan-Meier analysis was used to estimate rejection-free survival as well as graft and patient survival. Log-rank test was used to compare survival distributions.

The study was deemed exempt from the Institutional Review Board as it involved collection and analysis of existing data in such a manner that subjects could not be identified.

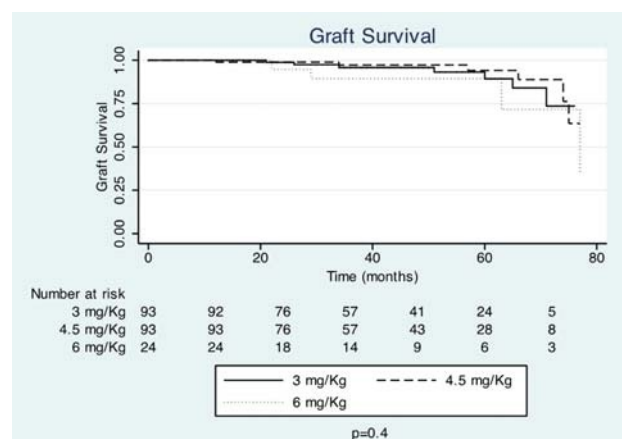


**FIGURE 1.** Kaplan-Meier curves for rejection-free survival for the 3 rATG groups indicate that there was no difference between the groups.

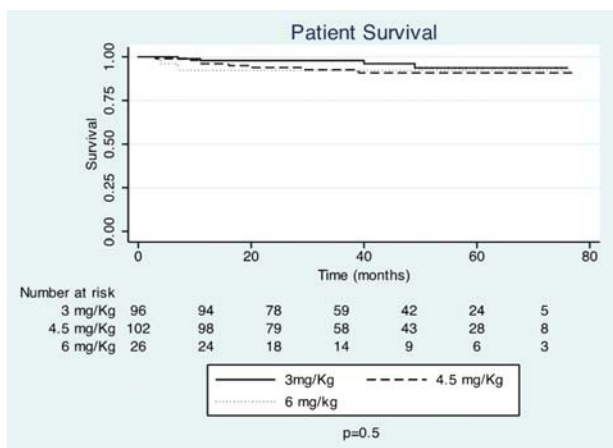
### RESULTS

The patient demographics are described in Table 1A. Importantly, 224 of the initial 241 patients transplanted in the study period (93%) were included in the analysis. Seventeen patients were excluded for various reasons described in Table 1B. The median follow-up was 42 months. Consistent with the demographics of northern New England, 96% of patients were Caucasian. All patients had negative crossmatches, both by CDC and flow cytometry.

The outcomes of the groups based on the cumulative rATG dosing are described in Table 2 and Figures 1 to 3. There were no significant differences in rejection, graft or patient survival between the 3 groups. The mean serum creatinine at 1 year was 1.5 mg/dL for all patients. However, the increased immunologic risk group who received higher dose rATG (6 mg/kg) was smaller, underwent numerically (if not significantly) more allograft biopsies, had earlier time to biopsy, more donor-specific antibodies (DSA), more rejection, and had higher serum creatinine levels at 1 year as expected.



**FIGURE 2.** Kaplan-Meier curves for graft survival for the 3 rATG groups indicate no difference between the 3 groups.



**FIGURE 3.** Kaplan-Meier curves for patient survival for the 3 rATG groups indicate no difference between the 3 groups.

Detailed analysis of allograft rejection is described in Tables 3A and 3B. There were 29 BPAR episodes (12.9%) in 21 patients (9.4%). Thirty-eight percent of the rejections were antibody mediated, most of which were treated with plasmapheresis and IVIg. Sixty-two percent were T-cell mediated, most of

which were treated with lympholytic doses of methylprednisolone and augmented maintenance immunotherapy. These rejection rate was lower than that seen in historic controls (approximately 20%, data not shown) who had not received rATG induction therapy.

Analysis of rATG cost is described in Figure 4 and Table 4. Cost expenditure was derived based on a purchasing price of US \$697 per 25 mg vial of rATG. A total of US \$2 272 220 was spent on rATG for these 224 patients averaging US \$10 143 per patient. The mean cost per patient was US \$7667 in the 3-mg/kg rATG group, US \$11 152 in the 4.5-mg/kg group, and US \$15 334 in the 6-mg/kg rATG group. Dose tailoring permitted substantial cost savings on rATG alone estimated at US \$1 091 502 over the study period compared with routine rATG dosing of 6 mg/kg.

To streamline care, minimize duration of cytokine release symptoms and thus promote patient education and early discharge, the intraoperative rATG dose was increased from 1.5 to 3 mg/kg starting November 2010. Since making the change, the average length of hospital stay has declined from 6.8 to 4.0 days (Figure 5).

Infection rates within the first year posttransplantation were surveyed periodically during this period. Overall infection rates did not change during the study and were similar

**TABLE 3A.**

**Pathology according to the Banff 1997 classification with 2005 update**

Rejection type	Criteria	All episodes (n = 29)	rATG, 3 mg/kg	rATG, 4.5 mg/kg	rATG, 6 mg/kg
AMR	All AMR	11 (37.9%)	2 (6.9%)	4 (13.8%)	5 (17.2%)
Borderline	C4d-, changes suspicious for changes	1	0	1	0
Grade I	C4d+, acute-tubular necrosis-like	8	2	3	3
Grade II	C4d+, capillary polymorphonuclear leukocytes, and/or thrombosis	2	0	0	2
Grade III	C4d+, transmural arteritis, fibrinoid necrosis	0	0	0	0
Chronic	C4d+, capillary double contours, peritubular capillary multilayers	0	0	0	0
TCMR	All TCMR	18 (62.1%)	7 (24.1%)	9 (31.0%)	2 (6.9%)
Borderline	Suspicious for rejection	4	1	3	0
Grade I	Interstitial inflammation (>25% of parenchyma) Moderate or severe tubulitis (>4 lymphocytes per tubular cross section)	13	5	6	2
Grade II	Intimal arteritis	1	1	0	0
Grade III	Transmural arteritis and/or fibrinoid necrosis with lymphocytes	0	0	0	0
Chronic	Features of chronic and acute rejection	0	0	0	0

AMR, antibody-mediated (humoral) rejection; TCMR, T cell-mediated rejection.

**TABLE 3B.**

**Allograft rejection management**

	All rejection episodes	rATG, 3 mg/kg	rATG, 4.5 mg/kg	rATG, 6 mg/kg
AMR				
Plasmapheresis	11	2	4	5
Pulse dose steroids	11	2	4	5
Ecuzumab	1	0	0	1
TCMR				
Thymoglobulin	4	1	3	0
Pulse dose steroids	13	5	6	2
Augmentation of maintenance immunosuppression	16	7	7	2

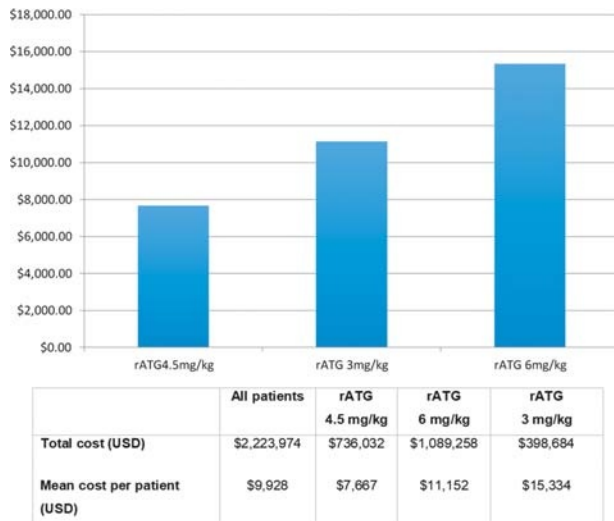


FIGURE 4. Mean cost per patient for those receiving rATG 3, 4.5, and 6 mg/kg.

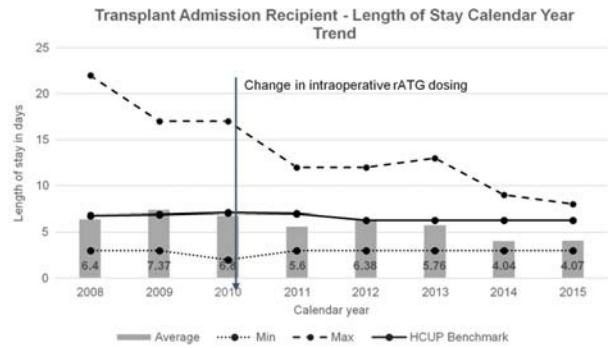
to those reported to the Scientific Registry of Transplant Recipients (data not shown).

**DISCUSSION**

This cohort study demonstrates that in standard immunologic-risk living and deceased donor recipients, cumulative rATG doses of 3 and 4.5 mg/kg, respectively, associates with excellent patient survival, graft survival, and low 1-year allograft rejection rates. Furthermore, allograft function, allograft survival, and patient survival at 1 year were comparable between the various rATG dosing groups. Dose tailoring permitted substantial cost savings compared with routine rATG dosing of 6 to 10.5 mg/kg as recommended in the Thymoglobulin package insert.

The overall rejection rate in the entire cohort was 9%, with living donor recipient rejection rate of 7.5% and deceased donor recipient rejection rate of 11%, comparable with that reported by the United States Renal Data System contemporaneously.<sup>1</sup> The present rejection rates are far lower than institutional historic controls who had not received rATG induction therapy. The administration of rATG 3 mg/kg intraoperatively was associated with a substantive reduction in LOS. We believe this is due to a combination of less frequent dosing and also minimization of adverse events related to cytokine release, thus promoting patient education which in turn facilitates discharge planning.

Several studies have directly compared cumulative rATG dosing with outcomes, all of which used higher doses than we are describing. The initial landmark study by Brennan et al<sup>7</sup> in 1996 was conducted using doses starting at 10.5 mg/kg



HCUP- Healthcare cost and utilization project

HCUP benchmark for length of stay after kidney transplantation is 6.1 days.

FIGURE 5. Index kidney transplantation admission recipient length of hospital stay by calendar year before and after change in intraoperative rATG dosing.

wherein recipients received 1.5 mg/kg per day for seven consecutive days. Subsequent reports have yielded rejection rates of 10% or less albeit with higher rATG dosing than we have used. For example, Agha et al<sup>13</sup> compared their historical 7-day regime in 48 patients with a modified 3-day regime in 40 patients resulting in cumulative dosing of 6 mg/kg. Similarly, Gurk-Turner et al<sup>24</sup> performed a retrospective cohort study of 96 adult subjects who received between 5.7 and 10 mg/kg rATG. Klem et al<sup>25</sup> reported a study in which cumulative rATG doses of 4.5 and 6 mg/kg were administered. Rogers et al<sup>26</sup> reported their experience with two different rATG induction dosing and early steroid withdrawal with dosing ranges of 4.1 to 5.1 mg/kg. Single-dose administration of rATG 6 mg/kg has also been evaluated. For example, Stevens et al<sup>11,12</sup> reported results of their experience of rATG 6 mg/kg single dose versus same total dose divided in 4 days. Again, low rejection rates with favorable safety parameters were obtained using higher doses than we report.

The advantages of this study compared with the published literature include large population size, robust follow-up over a long period and tight adherence to the treatment regimen. We identified a lower risk group that may benefit from reduced rATG dosing. The chief drawbacks include the retrospective nature of the study and the predominantly Caucasian study population. The data on the small, higher immunologic risk group are included for the sake of completeness. The numerically, if not statistically, higher incidences of DSA, biopsies, and rejection in this increased risk group are acknowledged.

In conclusion, the novel findings of the current study of reduced rATG induction therapy include peripheral administration, much reduced dosing compared with other reports, favorable safety, excellent allograft outcomes, and clear associative data regarding reduced costs and LOS.

**TABLE 4.** Total and mean cost of rATG per cumulative dose received

	All patients (n = 224)	rATG, 3 mg/kg (n = 96)	rATG, 4.5 mg/kg (n = 102)	rATG, 6 mg/kg (n = 26)
Total cost of rATG, US \$	2 272 220	736 032	1 137 504	398 684
Mean cost of rATG per patient, US \$	10 143	7667	11 152	15 334

## ACKNOWLEDGMENTS

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