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Retrospective Evaluation of Rabbit Antithymocyte Globulin Induction in Heart Transplant Patients

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Background. The dosing intensity of antithymocyte globulin as induction therapy in heart transplantation remains controversial. We sought to evaluate the efficacy and safety of rabbit antithymocyte globulin at a total dose of 4.5 mg/kg compared with <4.5 mg/kg. **Methods.** This was a retrospective study of consecutive patients who underwent heart transplantation from January 2016 to December 2018 at a single quaternary care center. Exposure was defined as full antithymocyte globulin (4.5 mg/kg total) induction compared with partial (<4.5 mg/kg) induction. The primary outcome was the incidence of The International Society for Heart and Lung Transplantation 1990 acute cellular rejection grade 2 or above at 2 y. Secondary outcomes were all-cause mortality, number of infections, and time to therapeutic tacrolimus levels. Cox proportional hazard models were used to compare rejection rates and mortality. **Results.** Of 201 patients, 61 received partial and 140 received full induction. There was no difference in the cumulative incidence of cellular rejection grade 2 or above (18% versus 11.4%, $P = 0.209$) within 2 y. The adjusted hazard ratio was 1.45 (confidence interval: 0.62-3.37, $P = 0.388$) for partial compared with full induction for any grade rejection. Landmark survival analysis conditional on survival to 1 mo showed no difference in mortality ($P = 0.239$). There was no difference in the incidence of infection within 3 mo of transplant (partial 29.5% versus full 20.0%, $P = 0.140$). Both groups achieved therapeutic tacrolimus levels by day 7 after initiation. **Conclusions.** There was no difference in overall risk for any grade cellular rejection between partial or full dose induction therapy. Additionally, there was no difference in medium-term mortality from landmark survival analysis.

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INTRODUCTION

Heart transplantation is considered the gold standard treatment for end-stage heart failure.^{1,2} In the contemporary era, survival at 1 y postheart transplantation is 94.8% compared with 60% in stage D heart failure patients managed with guideline-directed medical therapy.^{3,4}

Allograft rejection, classified as hyperacute rejection, acute cellular rejection, or antibody-mediated rejection, is a major contributor to morbidity and mortality after heart transplantation.^{1,4,5} The incidence of rejection peaks at 3 to 6 mo posttransplant but may occur as early as 24 h after heart transplantation or be delayed to years later.¹ Fortunately, heart

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transplant rejections have gradually declined from 30.5% to 24.1% over the years with improvement in immunosuppressive regimens.⁴ These regimens may include a combination of induction and maintenance therapy or only maintenance therapy.⁶ In today's era, approximately 50% of heart transplant recipients receive induction.⁷

Rabbit antithymoglobulin (rATG), given as an infusion of rabbit-derived antibodies against human T cells, natural killer cells, B cells, and plasma cells, acts primarily via T-cell depletion.^{8,9} Despite a paucity of data, recent International Society for Heart and Lung Transplantation guidelines note that administration of rATG induction may be beneficial in patients at high risk for acute rejection, those with renal dysfunction whose calcineurin inhibitor therapy can be delayed, and patients with planned calcineurin inhibitor-free therapy.^{4,6,10} These recommendations are supported by limited data showing reduced rejection rates but no mortality benefit in rATG-treated patients within the first 6 mo of heart transplant.^{4,10-13} In contrast, other studies demonstrated no difference in rejection rate but rather increased risk for infection and longer recovery time of CD3 and CD2 counts.¹⁴⁻¹⁷

In addition to efficacy and safety, the optimal dose for rATG remains unknown. Doses are largely empiric with a wide variation in protocols.¹⁷ Historically, higher doses of rATG (total dose 7.5–10.5 mg/kg) resulted in low rejection rates but significantly higher infection and hematologic complications.¹⁸ rATG doses have since transitioned to total doses of at least 4.5 mg/kg;⁸ however, some institutions may administer smaller cumulative doses of 3 to 3.5 mg/kg or less for patients at low immunological risk or for those with infection before transplant.^{6,8,17} Some centers also adjust induction therapy based on sequential T-cell counts during induction.^{10,15,18}

Because of the lack of definitive trials examining the efficacy, safety, and dosing of rATG in heart transplant patients, individual and center-level variability in prescribing practices for rATG induction remains. We sought to determine the association between rejection, mortality, and rATG induction for heart transplantation at a total dose of 4.5 mg/kg compared with <4.5 mg/kg.

MATERIALS AND METHODS

This retrospective observational study aimed to determine the prescribing pattern and safety of rATG induction at a total dose of 4.5 mg/kg compared with doses <4.5 mg/kg at University of Washington Medical Center (UWMC). UWMC is a major quaternary care referral center in the Pacific Northwest. This evaluation was approved by the University of Washington Institutional Review Board. Patient consent was not necessary, as this evaluation was retrospective and observational in nature. This study complied with the Transplantation Society ethical guidelines.

Adult patients (≥18 y old) who underwent heart transplantation and received rATG induction at UWMC from January 1, 2016, to December 31, 2018, were included. Patients who died while undergoing transplant were excluded.

Data were retrospectively obtained from electronic healthcare medical records and the UWMC transplant database. Collected data included patient demographics (recipient age, gender, calculated panel-reactive antibody level, cytomegalovirus (CMV) status, rATG induction dose, duration of cold ischemia, donor age, use of ventricular-assisted devices before transplant, number of organs transplanted, incidence of acute cellular biopsy-proven

rejection (ACR) based on the International Society for Heart and Lung Transplantation 1990 grading system, number of days before tacrolimus initiation posttransplant, number of days needed to reach the first therapeutic tacrolimus level posttransplant, incidence of infection within 3 mo of transplantation, lymphocyte counts at baseline and at 2, and 4 wk posttransplant, and all-cause mortality. Infection was defined as culture-positive bacteremia and fungemia, pneumonia based on endotracheal aspirate quantitative culture >10⁵ colony-forming units/mL (CFU/mL), bronchoalveolar lavage quantitative culture >10⁴ CFU/mL, or protected-specimen brush quantitative culture >10³ CFU/mL, urinary tract infection based on culture growth >10⁵ CFU/mL, and other documented infection types requiring antibiotics. Data for rejection and all-cause mortality were collected up to 2 y posttransplantation. A time point of 2 y posttransplant was prespecified, as events beyond this time point are less likely related to induction therapy.

Per the current postheart transplantation immunosuppression protocol at UWMC, all patients received intravenous mycophenolate mofetil 1000 mg and methylprednisolone 500 mg intraoperatively. Weight-based rATG doses of 1.5 mg/kg on postoperative day 0 and 1 mg/kg on postoperative day 1, 3, and 5 varied depending on the attending physician's clinical judgement. The administration of rATG would be held or delayed for platelets <75 × 10³/μL per institutional protocol. Other contraindications that may have warranted withholding rATG induction included active infection, hemodynamic instability, and open chest posttransplant. On postoperative day 0 and 1, all patients received intravenous methylprednisolone 125 mg every 12 h for 3 doses and intravenous or oral mycophenolate mofetil 1000 mg twice daily. Standard maintenance immunosuppression therapy included mycophenolate mofetil 1000 mg twice daily, prednisone 0.15 mg/kg twice daily, and tacrolimus (target trough 10–15 ng/mL).

The exposure for this study was defined as a full induction course of rATG (4.5 mg/kg total) versus partial induction (<4.5 mg/kg total). The primary outcome of this study was the cumulative incidence of ACR that was classified as grade 2 or above (ACR grade ≥2) within 2 y postheart transplantation. Secondary outcomes included all-cause mortality within 2 y of transplant, length of stay in the intensive care unit (ICU), and risk of infection within 3 mo of posttransplantation. Tacrolimus dosing patterns, time to achieve first therapeutic tacrolimus level, and lymphocytes at week 2 and 4 posttransplant were also examined.

Statistical Analysis

Normality was determined using Q-Q plot. For normally distributed variables, independent Student *t* test and χ^2 test were used to compare differences between continuous and categorical variables, respectively. Mood median test and Fisher exact test were used to compare differences for non normally distributed variables. Cumulative incidence curves were generated to estimate the cumulative incidence of ACR between full and partial induction groups.

Time zero began on the date of heart transplant. For ACR, participants were followed until an ACR event that was grade 2 or above, censored at the time of death, or end-of-study. Kaplan-Meier analysis was used to compare all-cause mortality and incidence of biopsy-proven rejection-free survival. For all-cause mortality, participants were followed until death or censored at end-of-study. Log-rank tests were used to assess differences in Kaplan-Meier and cumulative incidence curves. Cox proportional hazards models, with and without

adjustment for covariates, were used to calculate the hazard ratios (HR) and assess the association between dosing groups, ACR, and all-cause mortality. Because of potential treatment bias leading to partial versus full dose rATG induction, a prespecified landmark analysis was conducted for all-cause mortality using Cox proportional hazards model conditional on survival to 1 mo. A generalized estimating equations model with time as a factor variable was used to conduct an exploratory analysis of lymphocyte counts in relation to rATG doses. Type I error level for the generalized estimating equation model was corrected to be 0.003. Logistic regression analysis was performed to determine the relationship between lymphocyte counts and ACR. All other statistical tests were 2-sided at a significance level of 0.05. The proportional hazards assumption models were confirmed using Schoenfeld residuals. R version 3.6.0 was used to perform the statistical analysis.

RESULTS

Patient Characteristics

From January 2016 to December 2018, 216 patients were identified. After exclusion, 201 patients were included in the analysis (Figure 1). There were 61 patients in the partial rATG induction group and 140 patients in the full rATG induction group. There were no statistically significant differences in gender, CMV serology status, median duration of cold ischemic time, median donor age, use of ventricular device, number of organs transplanted, or calculated panel-reactive antibodies between the 2 groups. The only difference seen between the partial and full rATG groups was in recipient age (55 versus 50, $P = 0.005$) (Table 1).

Primary Outcome

The cumulative incidence of ACR grade ≥ 2 was 18% in the partial rATG group and 11.4% in the full rATG group ($P =$

0.205). Although not statistically significant, there was a trend toward more ACR grade ≥ 2 in the partial induction group (Figure 2). Based on the cumulative incidence curve, this separation appeared at 5 mo. Unadjusted analysis of ACR incidence between partial versus full induction at 2 y found an estimated HR of 1.64 (95% confidence interval [CI]: 0.76-3.50, $P = 0.209$). After adjusting for recipient age, gender, donor age, ICU length of stay, and pneumonia within 3 mo, the estimated HR was 1.45 (95% CI: 0.62-3.37, $P = 0.388$) (Table 2).

Among the 61 patients who received partial rATG induction, 78.7% had at least 1 occurrence of any ACR within 2 y after heart transplantation; most of these rejections were grade 1A (45.8%). For the 140 patients who received full rATG induction, 88.6% had at least 1 occurrence of ACR, of which 53.2% were grade 1A rejection. There was no statistical difference in the incidence of any ACR between partial and full rATG induction (Table S1, SDC, <http://links.lww.com/TXD/A423>).

When comparing ≤ 1.5 mg/kg, >1.5 to 2.5 mg/kg, and >2.5 to 3.5 mg/kg with the >3.5 to 4.5 mg/kg induction group, an adjusted multivariate CoxPH regression for ACR grade ≥ 2 showed no significant difference between the 4 subgroups (Table S2, SDC, <http://links.lww.com/TXD/A423>).

Survival Rates Between Partial and Full Induction Therapy

The observed, crude survival at 2 y posttransplantation for all patients was 94.5%. Survival at 2 y was 86.9% for those who received partial rATG and 97.8% for those who received full rATG induction ($P = 0.001$) (Figure S1, SDC, <http://links.lww.com/TXD/A423>); however, because of concern for potential treatment bias leading to variable rATG dosing (ie, sicker patients might have been less likely to complete induction), a prespecified landmark analysis conditional on survival to 1 mo was conducted that demonstrated no significant difference between study groups (Figure 3).

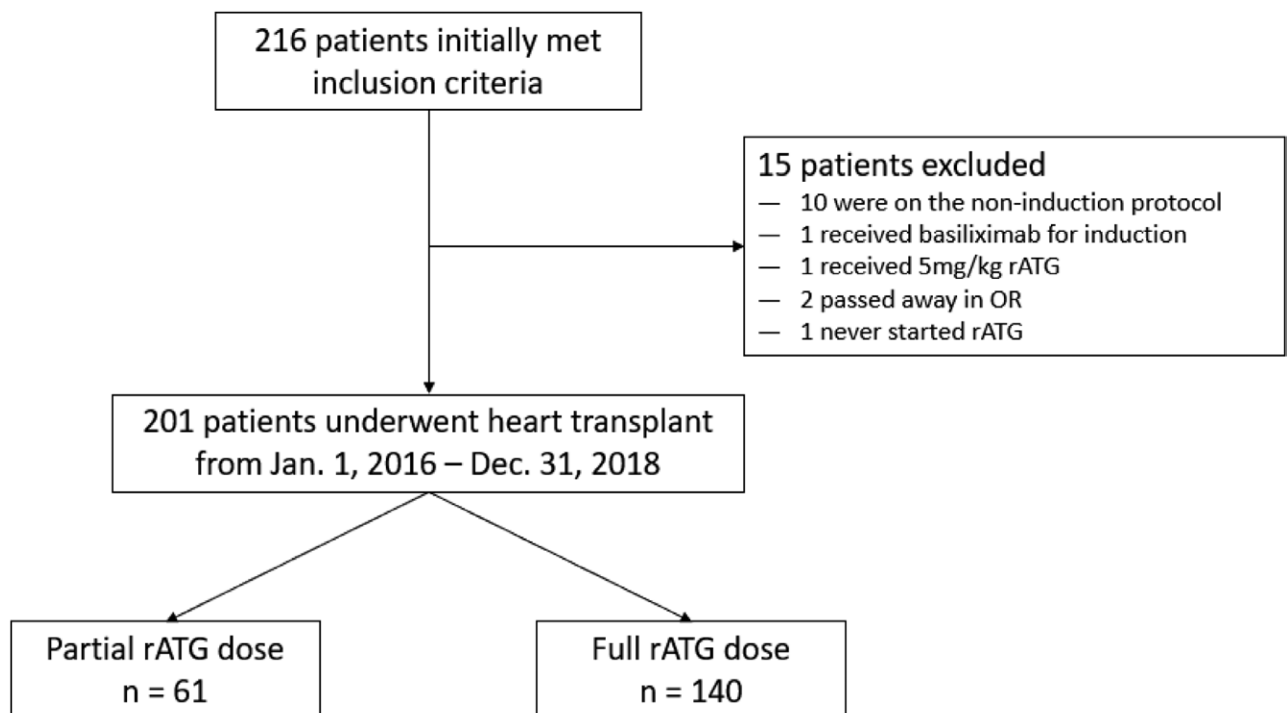


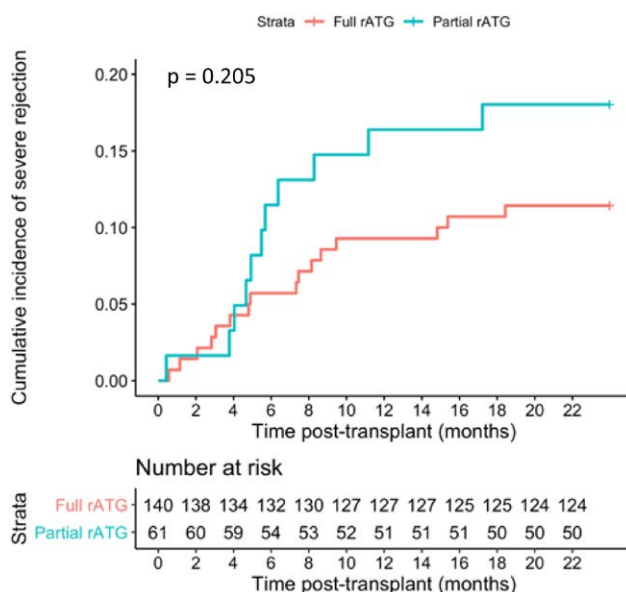
FIGURE 1. Patient screening and exclusions. OR, odds ratio; rATG, rabbit antithymoglobulin.

TABLE 1.
Baseline characteristics before heart transplantation

	Partial rATG induction (n = 61)	Full rATG induction (n = 140)	P
Gender			
Female	22 (36.1%)	46 (32.9%)	0.780
Male	39 (63.9%)	94 (67.1%)	
Recipient age, y			
Mean (SD)	55 (11)	50 (13)	0.005
Median [minimum–maximum]	53 [19–69]	57 [23–73]	
Baseline lymphocyte counts before transplant ($10 \times 3/\mu\text{L}$)			
Mean (SD)	1.29 (0.60)	1.45 (0.61)	0.084
Median [minimum–maximum]	1.17 [0.22–3.04]	1.46 [0.17–3.46]	
CMV status, D/R			
Negative/negative	11 (18.0%)	17 (12.1%)	0.702
Negative/positive	10 (16.4%)	26 (18.6%)	
Positive/negative	18 (29.5%)	40 (28.6%)	
Positive/positive	22 (36.1%)	57 (40.7%)	
Ischemia duration, h			
Mean (SD)	3.68 (1.39) ^a	3.56 (1.38) ^b	0.616
Median [minimum–maximum]	3.55 [0.75–8.10]	3.37 [0.75–7.63]	
Donor age, y			
Mean (SD)	30.6 (10.90) ^c	32.6 (11.60) ^d	0.234
Median [minimum–maximum]	27.5 [14–53]	31 [11–63]	
VAD usage before transplant			
Yes	44 (72.1%)	83 (59.3%)	0.115
No	17 (27.9%)	57 (40.7%)	
cPRA level			
0%	47 (77%)	107 (76.4%)	0.481
0%–33%	8 (13.1%)	16 (11.4%)	
34%–66%	5 (8.2%)	8 (5.7%)	
67%–100%	1 (1.6%)	9 (6.4%)	
Organ(s) transplanted			
Heart	59 (96.7%)	134 (95.7%)	0.737
Heart and kidney	2 (3.3%)	6 (4.3%)	

^aData from 11 patients were missing.^bData from 15 patients were missing.^cData from 1 patient was missing.^dData from 3 patients were missing.

cPRA, calculated panel-reactive antibody; CMV, cytomegalovirus; rATG, rabbit antithymoglobulin; VAD, ventricular assist device.

**FIGURE 2.** Cumulative incidence curve of acute cellular rejection ≥ 2 between partial and full induction. rATG, rabbit antithymoglobulin.

After adjusting for recipient age, gender, donor age, ICU length of stay, and pneumonia, the estimated HR for all-cause mortality at 2 y between the induction groups was 3.31 (95% CI: 0.74–14.86, $P = 0.119$), which was not statistically significant (Table 2). Similarly, an adjusted Cox proportional hazards regression adjusted for recipient age, gender, and donor age with landmark analysis conditional on survival to 1 mo showed a nonstatistically significant estimated HR of 2.30 (95% CI: 0.44–12.11, $P = 0.323$).

To note, 8 out of the 210 study patients received combined heart and kidney transplantations. Seven of the 8 heart-kidney-transplanted patients survived to at least 2 y posttransplant and did not experience ACR ≥ 2 within the first 2 y. One patient expired because of pulmonary embolism and pneumonia.

Causes of Death

A total of 11 patients died within 2 y of transplantation. Seven out of 11 (63.6%) patients died within the first month of transplant, of which they received partial rATG induction (1.5–3.5 mg/kg). The causes of death were multifactorial with multi-organ system failure (MOSF) (6/7) being the most common, followed by primary graft dysfunction (5/7), and lastly by

TABLE 2.**Cox proportional regression model for mortality and ACR**

	All-cause mortality at 2 y			ACR at 2 y		
	HR	CI	P	HR	CI	P
Partial vs full induction (unadjusted)	6.55	1.74-24.71	0.005 ^a	1.64	0.76-3.5	0.209
Partial vs full induction (adjusted) ^b	3.31	0.74-14.8	0.119	1.45	0.62-3.37	0.388

^aStatistically significant $P < 0.05$.

^bAdjusted HR: age, gender, donor age, ICU length of stay, pneumonia within 3 mo.

ACR, acute cellular rejection; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

infection (4/7). The other 4 patients received total rATG doses of 3.5 to 4.5 mg/kg. Of the 4 patients, 1 died from rejection, infection, and MOSF; another died from infection and MOSF; 1 died from an oncologic event; and 1 suffered from ESRD requiring dialysis posttransplant, which led to withdrawal of care (Table S3, SDC, <http://links.lww.com/TXD/A423>).

Further Analysis of Outcomes

When comparing the patients who received partial versus full rATG induction, the average number of days before tacrolimus initiation was 2.5 d versus 2.1 d ($P = 0.044$), respectively. The median number of days before tacrolimus initiation of 2 d was not statistically significant between both groups. The average number of days to reach therapeutic tacrolimus levels was 7.4 d in the partial group and 6.9 d in the full induction group (Table 3). The percentage of patients with infection within 3 mo of transplant was not significantly different between the partial and full rATG induction group, 29.5% versus 20.0% ($P = 0.140$). Occurrence of pneumonia was numerically higher in the partial rATG induction group (Table S4, SDC, <http://links.lww.com/TXD/A423>). Patients who received partial rATG induction also remained in the ICU longer than those who received full induction (9.5 versus 6.0 d, $P < 0.001$) (Table 3).

Exploratory Analysis of Lymphocyte Counts

When stratified by rATG doses, there was no statistically significant difference in average lymphocyte count at baseline across the 4 dosing quartiles. All groups showed a significant reduction in mean lymphocyte counts at 2 wk post heart transplantation compared with their respective baseline values (Figure S2, SDC, <http://links.lww.com/TXD/A423>). Lymphocyte counts were most depleted from baseline in the >3.5 to 4.5 mg/kg group when compared with other induction groups at 2 wk, with an average difference of -1.23 thousand/microliter (Table 4). There were no significant differences in mean lymphocyte counts at weeks 2 and 4 between those who received >3.5 to 4.5 mg/kg, >2.5 to 3.5 mg/kg, and >1.5 to 2.5 mg/kg of rATG therapy (Table 5). A statistically significant difference of 0.43 thousand/microliter was seen between average lymphocyte counts when comparing >3.5 to 4.5 mg/kg and ≤1.5 mg/kg rATG at week 2 ($P < 0.001$).

A logistic regression analysis adjusted by the 4 weight-based induction groups did not demonstrate a relationship between lymphocyte counts and ACR ≥2 at 2 wk (odds ratio, 1.66 [95% CI: 0.33-6.97], $P = 0.505$) and at 4 wk (odds ratio, 4.10 [95% CI: 0.84-19.8], $P = 0.075$) (Table S5, SDC, <http://links.lww.com/TXD/A423>).

Reasons for Partial rATG Induction

Several scenarios were identified to have led to partial induction in our study population. The most common causes

were thrombocytopenia (92.7%) and leukopenia (24.4%) (Figure S3, SDC, <http://links.lww.com/TXD/A423>).

DISCUSSION

In this study, we found the following: (1) there was no statistically significant difference in the cumulative incidence of ACR grade ≥2 over 2 y postheart transplantation between the partial and full rATG induction groups; (2) there was no difference in all-cause mortality at 2 y conditional on survival to 1 mo; (3) infection incidence within 3 mo of transplant and time to therapeutic tacrolimus levels were not significantly different between both groups.

The current evaluation contributes to the literature regarding rATG induction therapy in the heart transplant population. Compared with previous studies, it contained more granular data to examine the differences in efficacy and safety for various rATG doses in heart transplantation.^{14,18,19,20}

There was no difference between the overall incidence of any grade ACR between partial or full induction. Furthermore, there was no statistically significant difference in the cumulative incidence of ACR grade ≥2 between partial and full rATG induction; however, there appears to be a trend toward more rejection grade ≥2 with total rATG doses <4.5 mg/kg, which may have been influenced by the higher incidence of grade 3A rejection seen with partial rATG induction. This trend toward more rejection with rATG doses lower than 4.5 mg/kg was

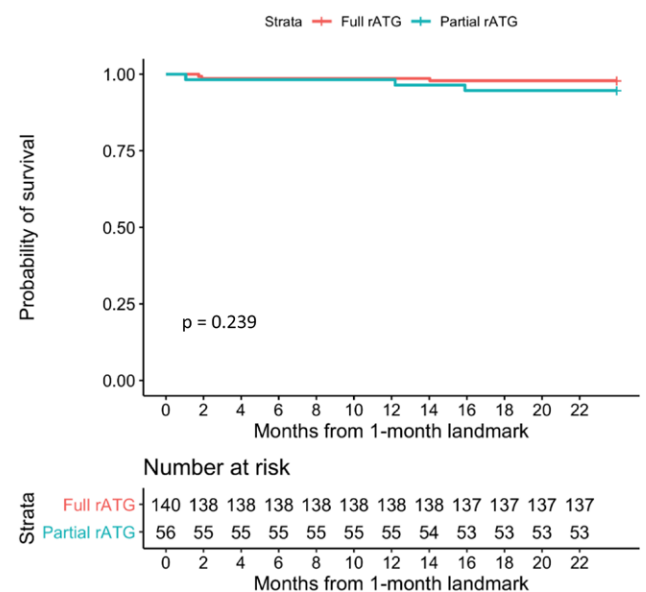


FIGURE 3. Landmark analysis conditional on survival to 1 mo for all-cause mortality. rATG, rabbit antithymoglobulin.

TABLE 3.
Comparison of secondary outcomes

	Partial rATG induction (n = 61)	Full rATG induction (n = 140)	P
Secondary outcomes			
Average number of days before tacrolimus initiation	2.5	2.1	0.044
Median number of days before tacrolimus initiation (IQR)	2 (2–3)	2 (1–2)	0.107
Average days to therapeutic tacrolimus level	7.4	6.9	0.459
Median days to therapeutic tacrolimus level (IQR)	6 (5–9)	6 (5–8)	0.774
Number of patients with at least 1 infection within 3 mo (%)	18 (29.5)	28 (20)	0.140
Median duration of ICU length of stay, d (IQR)	9.5 (6.8–14.3)	6 (4–7)	<0.001

ICU, intensive care unit; IQR, interquartile range; rATG, rabbit antithymoglobulin.

TABLE 4.
Lymphocyte counts between baseline and week 2 for each induction group

		≤1.5 mg/kg	>1.5–2.5 mg/kg	>2.5–3.5 mg/kg	>3.5–4.5 mg/kg
Week 2 vs baseline (10 × 3/μL)	Estimated average difference	–0.52	–0.932	–1.19	–1.23
	95% CI	–0.83 to –0.20	–1.18 to –0.686	–1.42 to –0.96	–1.33 to –1.13
	P	0.001	≤0.001	≤0.001	≤0.001

CI, confidence interval.

TABLE 5.
Comparison of mean lymphocyte counts (10 × 3/μL) between rATG dosing quartiles

Comparison groups		Baseline	Week 2	Week 4
≤1.5 mg/kg vs >3.5–4.5 mg/kg	Estimated average difference	–0.29	0.43	0.17
	95% CI	–0.62 to 0.05	0.27–0.59	–0.05 to 0.39
	P	0.094	<0.001	0.130
>1.5–2.5 mg/kg vs >3.5–4.5 mg/kg	Estimated average difference	–0.23	0.07	0.10
	95% CI	–0.52 to 0.05	–0.06 to 0.19	–0.07 to 0.32
	P	0.111	0.290	0.193
>2.5–3.5 mg/kg vs >3.5–4.5 mg/kg	Estimated average difference	0.07	0.11	0.13
	95% CI	–0.18, 0.32	–0.07 to 0.29	–0.002 to 0.25
	P	0.585	0.223	0.053

CI, confidence interval; rATG, rabbit antithymoglobulin.

similarly seen by Aliabadi et al. Aliabadi et al¹⁴ conducted a retrospective, single-center study that compared differences in mortality, ACR, and infection among various rATG doses in 523 heart transplant patients over 13 y. The incidence of ACR per 1000 patient-years was 54.8 (95% CI: 33.9–83.8) for doses <4.5 mg/kg and 19.6 (11.1–31.4) for doses between 4.5 and 7.5 mg/kg. These results suggest that rATG doses of at least 4.5 mg/kg may be needed for lower rates of rejection postheart transplantation. A significant difference of the current study is the relatively lower doses of rATG used compared with the study by Aliabadi et al, with our highest dose (4.5 mg/kg) equivalent to their second lowest dose group. We show that even lower doses appear to potentially be acceptable without observed differences in ACR or mortality.

The observed difference in mortality was higher at 2 y for the partial induction group; however, adjusted landmark analysis for mortality conditional on survival to 1 mo showed no difference between the 2 groups. This suggests that the increased mortality seen in the partial rATG group occurred before 1 mo and was related to sicker patients receiving partial rather than full induction. When taking this into account, there was no difference in mortality. This finding was consistent with the observation published by Aliabadi et al. They

did not observe a statistically significant difference in survival between rATG doses of 4.5 to 7.5 mg/kg and <4.5 mg/kg. A trend toward higher mortality was similarly seen for patients who received <4.5 mg/kg of rATG (HR 1.56, 95% CI: 0.95–2.56).¹⁴ Jarmi et al¹⁹ also demonstrated no survival difference when comparing rATG induction to no induction.

There was no difference in the degree of lymphocyte depletion between the 4 rATG dosing quartiles of >3.5 to 4.5 mg/kg, >2.5 to 3.5 mg/kg, >1.5 to 2.5 mg/kg, and ≤1.5 mg/kg at baseline and week 4. There was, however, a significant difference in average lymphocytes at week 2 when comparing the lowest and highest rATG induction groups. The overall lack of difference observed in mean lymphocyte counts suggests that the majority of rATG doses used at UWMC cause similar degrees of lymphocyte depletion and that lymphocyte count may not correlate with the rejection rates seen between the induction groups.

Leukopenia and thrombocytopenia appeared to be the most common reasons for partial rATG induction. Other patient-specific conditions, such as fever, concern for infection, and hemodynamic instability, were also identified. Management of the posttransplant patient can be challenging when balancing risk for rejection with risk for other adverse events. The lack of

difference in any grade ACR and conditional survival between partial and full induction supports that lower rATG doses may potentially be safe and alleviates concerns with dose reduction in sick patients who may not tolerate full induction.

This retrospective evaluation has several limitations to be considered. As with any observational study, residual confounding cannot be excluded. We adjusted for relevant covariables and used a landmark analysis to minimize this limitation. Additionally, the study population was relatively small. Larger studies may be feasible with registries or multicenter data, but the level of granularity achieved in this study would be difficult in larger studies. Second, patients who received partial rATG induction might have received different doses of glucocorticoids and mycophenolate mofetil, which could have influenced the observed rejection rates; the potential differences in immunosuppressant doses were not accounted for in this evaluation; however, patients in both study groups achieved a therapeutic tacrolimus level of 10 to 15 ng/mL at day 7 after initiation, suggesting that maintenance immunosuppression was not a significant confounder. Third, the time to infection relative to rATG induction was not investigated, so the causal pathway between rATG induction and risk of pneumonia could not be ascertained. Fourth, because of the retrospective nature of this evaluation, not all patients had complete lymphocyte data at weeks 2, 3, and 4. Fifth, CMV infection rate was not investigated in this study, though the association between CMV infection, a common viral infection that occurs postsolid organ transplantation, and rATG therapy is well established in solid organ transplant patients;²¹ however, administering rATG doses <4.5 mg/kg would likely not reduce the incidence of CMV disease.²² Furthermore, our center requires CMV prophylaxis for all patients, which would make early CMV infection unlikely. Lastly, approximately 95% of the heart transplant recipients at our institution received induction therapy; hence, without a control group that did not receive induction in the absence of contraindications, we could not conclude that no induction would yield similar findings as those who received lower rATG doses. Therefore, a prospective randomized controlled study is needed to address whether induction therapy would improve outcomes in heart transplant patients.

CONCLUSION

In summary, we compared the efficacy and safety between partial versus full rATG induction at a single, high-volume heart transplant center. We find that total rATG doses <4.5 mg/kg compared with a cumulative dose of 4.5 mg/kg showed no significant difference in any ACR or mortality conditional on survival to 1 mo.

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