ARTICLE

Effect of antithymocyte globulin source on outcomes of bone marrow transplantation for severe aplastic anemia

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ABSTRACT

For treatment of severe aplastic anemia, immunosuppressive therapy with horse antithymocyte globulin results in superior response and survival compared with rabbit antithymocyte globulin. This relative benefit may be different in the setting of transplantation as rabbit antithymocyte globulin results in more profound immunosuppression. We analyzed 833 severe aplastic anemia transplants between 2008 and 2013 using human leukocyte antigen (HLA)-matched siblings (n=546) or unrelated donors (n=287) who received antithymocyte globulin as part of their conditioning regimen and bone marrow graft. There were no differences in hematopoietic recovery by type of antithymocyte globulin. Among recipients of HLA-matched sibling transplants, day 100 incidence of acute (17% *versus* 6%, *P*<0.001) and chronic (20% *versus* 9%, *P*<0.001) graft-*versus*-host disease were higher with horse compared to rabbit antithymocyte globulin. There were no differences in 3-year overall survival, 87% and 92%, *P*=0.76, respectively. Among recipients of unrelated donor transplants, acute graft-*versus*-host disease was also higher with horse compared to rabbit antithymocyte globulin (42% *versus* 23%, *P*<0.001) but not chronic graft-*versus*-host disease (38% *versus* 32%, *P*=0.35). Survival was lower with horse antithymocyte globulin after unrelated donor transplantation, 75% *versus* 83%, *P*=0.02. These data support the use of rabbit antithymocyte globulin for bone marrow transplant conditioning for severe aplastic anemia.

Introduction

Aplastic anemia is a bone marrow failure syndrome that is almost always associated with an aberrant immune response that leads to activated type 1 cytotoxic T cells which destroy hematopoietic stem cell progenitors.[1] The current standard approach to severe aplastic anemia (SAA) includes immunosuppressive therapy

(IST) and/or allogeneic transplantation.[2] Studies of IST in SAA have shown that horse antithymocyte globulin (h-ATG) is superior to rabbit ATG (r-ATG; thymoglobulin), with both better response rates and survival.[3-6] This observation is surprising as r-ATG has been successfully used in patients who fail IST with h-ATG.[7,8] However, r-ATG is associated with a more effective depletion of lymphocytes,[9] which may be the reason for a delayed time to remission after IST with r-ATG.[10] In addition to lymphocyte depletion, r-ATG and not h-ATG enhances the number and function of regulatory T cells[11,12] which are important in suppressing immune response and maintaining tolerance. The preservation or permissive expansion of regulatory T cells could be beneficial in limiting graft-*versus*-host disease (GvHD) after allogeneic transplantation as these cells are needed for tolerance, controlling alloreactive donor lymphocytes involved in GvHD as well as innate and adaptive immune responses. These mechanistic differences between r-ATG and h-ATG may not lead to the same results following allogeneic transplantation as reported after IST, as regulatory T-cell induction and T-cell depletion may be more relevant to GvHD and graft rejection in the setting of allogeneic transplantation. We therefore sought to determine the difference, if any, in outcomes between h- and r-ATG in HLA-matched sibling and HLA-matched or mismatched unrelated donor bone marrow transplantation in SAA.

Methods

Patients

Data were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), a voluntary group of over 350 transplant centers that contribute data on consecutive transplants performed at each center with longitudinal follow up until death or loss to follow up. Eligible patients were aged 1 to 71 years old with acquired SAA, and received h- or r-ATG (thymoglobulin) transplanted with bone marrow grafts from a HLA-matched sibling or unrelated donor between 2008 and 2013 at 145 centers. Recipients of peripheral blood grafts were excluded (HLA-matched sibling n=136; unrelated donor n=140). The analysis was restricted to bone marrow transplants (BMT) as we previously showed that bone marrow is the preferred graft for SAA transplants.[13,14] The Institutional Review Board of the National Marrow Donor Program approved this study.

Endpoints

The primary endpoint was overall survival. Death from any cause was considered an event and surviving patients were censored at last follow up. Neutrophil recovery was defined as achieving an absolute neutrophil count of $\geq 0.5 \times 10^9$/L for 3 consecutive days, and platelet recovery as achieving platelet count $\geq 20 \times 10^9$/L, unsupported by transfusion for 7 days. Incidences of grades 2 to 4 acute GvHD and chronic GvHD were based on reports from each transplant center using standard criteria.[15,16]

Statistical Methods

Analyses were undertaken separately by donor type. Within each donor group, characteristics and outcomes were compared by the formulation of ATG: h-ATG or r-ATG. Patient, disease and transplant-related characteristics were compared using the χ^2 statistic. The probability of overall survival was calculated with the Kaplan-Meier estimator,[17] and the incidence of hematopoietic recovery, infections and acute and chronic GvHD were deter-

mined using the cumulative incidence estimator[18] to accommodate competing risks. The 95% confidence interval was generated by log transformation. Cox regression models were built for acute and chronic GvHD and mortality to identify factors associated with these outcomes.[19] Variables tested included a term for ATG type (h-ATG *vs.* r-ATG), patient age (<20 *vs.* ≥20 years), sex (male *vs.* female), performance score (90 – 100 *vs.* <90), comorbidity index (0-2 *vs.* ≥3), interval between diagnosis and BMT (< 3 *vs.* ≥3 months for HLA-matched sibling and <12 months *vs.* ≥12 months for unrelated donor BMT), conditioning regimen (total body irradiation (TBI) containing regimen *vs.* non-TBI containing regimen for unrelated donor BMT and cyclophosphamide *vs.* cyclophosphamide + fludarabine for HLA-matched sibling BMT), donor-recipient HLA match (8/8 *vs.* 8/8 HLA match for unrelated donor BMT only), GvHD prophylaxis (calcineurin inhibitor with mycophenolate *vs.* with methotrexate) and BMT period (2008-2010 *vs.* 2011-2013). The final model included type of ATG regardless of level of significance and other factors that attained a *P*-value ≤0.05. All *P*-values are two-sided. There were no first-order interactions between ATG type and other factors held in the final model. Analyses were carried out using SAS software, Version 9.3 (Cary, NC, USA).

Table 1A. Characteristics of patients undergoing HLA-matched sibling transplant.

	h-ATG	r-ATG	*P*
Number of patients	278	268	
Patient age, years			0.003
Median	16 (1-69)	20 (1-67)	
<20	176 (63)	133 (50)	
20-39	65 (23)	75 (28)	
≥40	37 (13)	60 (22)	
Sex			0.45
Male	149 (54)	135 (50)	
Female	129 (46)	133 (50)	
Performance score			0.18
<90%	68 (24)	54 (20)	
90-100%	201 (72)	210 (78)	
Missing	9 (3)	4 (1)	
Comorbidity index			0.001
0-2	218 (83)	197 (93)	
3+	44 (17)	15 (7)	
Not reported	16	56	
Time from diagnosis to transplant			0.006
<6 months	223 (80)	188 (70)	
≥6 months	55 (20)	80 (30)	
Conditioning Regimen			<0.001
Cyclophosphamide + fludarabine	29 (10)	89 (33)	
Cyclophosphamide alone	249 (90)	179 (67)	
GvHD prophylaxis			0.22
Tacrolimus or cyclosporine + methotrexate	249 (90)	248 (93)	
Tacrolimus or cyclosporine + mycophenolate	29 (10)	20 (7)	
Year of transplant			0.004
2008-2010	130 (47)	158 (59)	
2011-2013	148 (53)	110 (41)	
Median follow up, median (range), months	35 (3-82)	26 (1-77)	

ATG: antithymocyte globulin; h-ATG: horse derived ATG; r-ATG: rabbit derived ATG; GvHD: graft-*versus*-host disease

Results

Patient, disease and transplant characteristics

Patient, disease and transplant characteristics of the study population are shown in Tables 1A (HLA-matched sibling donors) and 1B (unrelated donors) by type of ATG. No patient received ATG-Fresenius or Lymphoglobuline h-ATG. HLA-matched sibling BMT recipients of h-ATG were younger, more likely to have a higher comorbidity index, receive a transplant within 6 months from diagnosis, receive cyclophosphamide as the sole chemotherapeutic agent and to be transplanted after 2010. There were no differences in regards to sex, performance score, conditioning regimen and GvHD prophylaxis. Table 1B shows recipients of HLA-matched or mismatched unrelated donor BMT. The only difference in characteristics was the BMT conditioning regimen. Although most recipients of unrelated donor BMT received low-dose TBI, recipients of h-ATG were more likely to receive cyclophosphamide with TBI, and recipients of r-ATG were more likely to

receive cyclophosphamide and fludarabine with TBI. The dose of ATG was available for approximately half of HLA-matched sibling and unrelated donor transplants; the median dose of h-ATG was 90 mg/kg (range 60 mg/kg – 150 mg/kg) and that for r-ATG was 9 mg/kg (range 6 mg/kg – 15 mg/kg) for both donor types.

Hematopoietic Recovery

The probability of neutrophil recovery at day 28 was not different for h-ATG and r-ATG for HLA-matched sibling BMT, 86% (95% confidence interval (CI) 82-90) and 89% (95% CI 85-92), P=0.43 or unrelated donor BMT, 90% (95% CI 84-94) and 88% (82-92), P=0.59, respectively. The corresponding median time to neutrophil recovery for h-ATG and r-ATG for HLA-matched sibling BMT was 18 and 17 days and for unrelated donor BMT, it was 19 days, regardless of type of ATG. Similarly, the probability of platelet recovery at 100 days was not different for h-ATG and r-ATG for HLA-matched sibling BMT, 95% (95% CI 92-97) and 92% (95% CI 87-95), P=0.14 and

Table 1B. Characteristics of patients undergoing unrelated donor transplant

	h-ATG	r-ATG	P
Number of patients	126	161	
Patient age, years			0.33
Median	21 (2-67)	20 (<1-66)	
<20	57 (45)	82 (51)	
≥20	69 (55)	79 (49)	
Sex			0.53
Male	68 (54)	81 (50)	
Female	58 (46)	80 (50)	
Performance score			0.34
<90%	34 (27)	35 (22)	
90-100%	91 (73)	122 (78)	
Missing	1	4	
Comorbidity index			0.55
0-2	92 (74)	122 (77)	
3+	32 (26)	36 (23)	
Missing	2	3	
Time from diagnosis to transplant			0.47
Median (range), months	9 (2-210)	10 (1-298)	
<12 months	78 (62)	93 (58)	
≥12 months	48 (38)	68 (42)	
Conditioning Regimen			<0.001
Cyclophosphamide + fludarabine + TBI 200 cGy	39 (31)	99 (61)	
Cyclophosphamide + fludarabine	15 (12)	29 (18)	
Cyclophosphamide +TBI 200 cGy	57 (45)	21 (13)	
Cyclophosphamide alone	15 (12)	12 (7)	
Donor-Recipient HLA match			0.31
8/8 HLA match	101 (80)	121 (75)	
7/8 HLA match	25 (20)	40 (25)	
GvHD prophylaxis			0.43
Tacrolimus or cyclosporine + methotrexate	108 (86)	143 (89)	
Tacrolimus or cyclosporine + mycophenolate	18 (14)	18 (11)	
Year of transplant			0.49
2008-2010	52 (41)	60 (37)	
2011-2013	74 (59)	101 (63)	
Median follow up, median (range), months	35 (11-73)	26 (4-77)	

ATG: antithymocyte globulin; h-ATG: horse derived ATG; r-ATG: rabbit derived ATG; GvHD: graft-*versus*-host disease; HLA: human leukocyte antigen; TBI: total body irradiation.

unrelated donor BMT, 81% (95% CI 74-88) and 88% (95% CI 83-93), *P*=0.10. The corresponding median time to platelet recovery for h-ATG and r-ATG for HLA-matched sibling BMT was 24 and 25 days and for unrelated donor BMT it was 27 and 26 days, respectively.

Infections

Data on infections post-transplant was available for approximately 25% of HLA-matched siblings and 50% of unrelated donor transplant recipients. Those infections considered included bacterial, viral, fungal and parasitic within the first 100 days after transplantation. The incidence of any infection did not differ by type of ATG. Among recipients of HLA-matched sibling donor transplants, the day 100 cumulative incidence of infection was 67% (95% CI 53 – 77) and 74% (58 – 85) after h-ATG and r-ATG, respectively (*P*=0.41). The corresponding rates following unrelated donor transplantation were 72% (95% CI 56 -83) and 84% (95% CI 73 – 91), *P*=0.13. Regardless of donor type, bacterial and viral infections were predominant, and there were no differences in the proportion of bacterial, viral and fungal infection by type of ATG (*data not shown*). There were no parasitic infections reported.

Epstein-Barr virus (EBV) associated lymphoproliferative disease

EBV-associated lymphoproliferative disease was uncommon. Among recipients of HLA-matched sibling donor BMT, only 1 patient developed EBV-associated lymphoproliferative disease after h-ATG compared to 6 patients after r-ATG. Among recipients of unrelated donor BMT, 4 patients developed EBV-associated lymphoproliferative disease after h-ATG compared to 13 patients after r-ATG. This limited number of events prevented us from calculating the incidence of EBV-associated lymphoproliferative disease.

Acute and Chronic GvHD

Grade II-IV acute GvHD was higher with h-ATG compared to r-ATG after HLA-matched sibling BMT (Table 2A). Acute GvHD risk was lower for patients aged less than 20 years and for males. Recipients of h-ATG reported grade II (n=24) and grade III (n=21) acute GvHD whereas r-ATG only reported grade II (n=16) acute GvHD. The day 100 incidence of acute grade II-IV GvHD adjusted for patient age and sex was 17% (95% CI 13 – 21) with h-ATG and 6% (95% CI 3 – 9) with r-ATG, *P*<0.001 (Figure 1A). Chronic GvHD was also higher with h-ATG compared to r-ATG after HLA-matched sibling BMT and it was lower for those aged less than 20 years and for males, independent of the type of ATG (Table 2A). The severity of chronic GvHD did not differ by type of ATG (*P*=0.15). Among recipients of h-ATG, 47 reported chronic GvHD, and severity was reported as limited (n=18) and extensive (n=29). Among recipients of r-ATG, 21 reported chronic GvHD, and severity was reported as limited (n=12) and extensive (n=9). The 3-year incidence of chronic GvHD adjusted for patient age and sex was 20% (95% CI 15 – 25) with h-ATG and 9% (95% CI 6 – 14) with r-ATG, *P*<0.001 (Figure 1B).
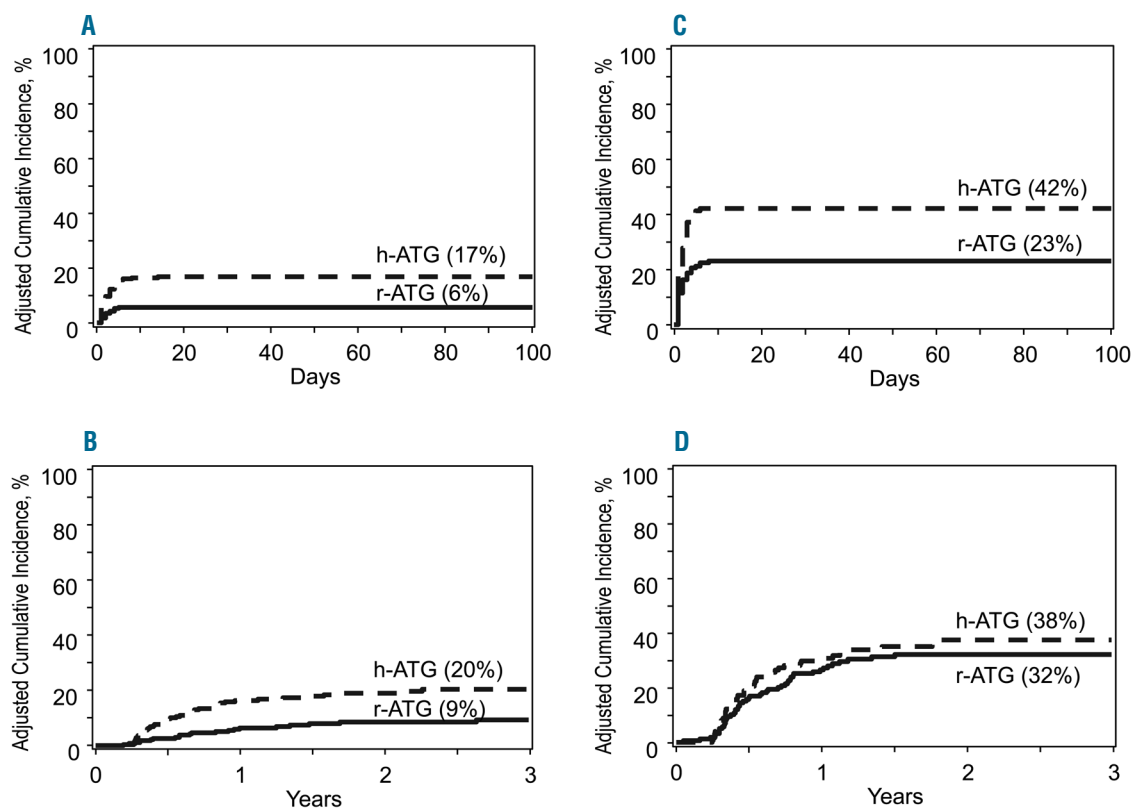
Figure 1. Acute and chronic graft-*versus*-host disease (GvHD). The adjusted cumulative incidence of grade II – IV acute GvHD (A) and chronic GvHD (B) after HLA-matched sibling transplant, and grade II – IV acute GvHD (C) and chronic GvHD (D) after unrelated donor transplant. h-ATG: horse derived ATG; r-ATG: rabbit derived ATG.

Among recipients of unrelated donor BMT, grade II-IV acute GvHD was higher with h-ATG compared to r-ATG (Table 2B). The risk of acute GvHD was higher for recipients of a single HLA locus mismatched unrelated donor BMT. Recipients of h-ATG reported grade II (n=23) and grade III-IV (n=32) and those who received r-ATG reported grade II (n=25) and grade III-IV (n=14) acute GvHD. The day 100 incidence of acute grade II-IV GvHD adjusted for donor-recipient HLA match was 42% (95% CI 34 – 50) with h-ATG and 23% (95% CI 17 – 29) with r-ATG, *P*<0.001 (Figure 1C). Restricting the population to 8/8 HLA-matched transplants, the day 100 incidence of grade II-IV acute GvHD was 20% (95% CI 12-30%) with h-ATG and 10% (95% CI 5-16%) with r-ATG (*P*=0.05). The risk of chronic GvHD after unrelated donor BMT did not differ by type of ATG (Table 2B). However, the severity of chronic GvHD differed by ATG type in that recipients of h-ATG were more likely to report extensive chronic GvHD (*P*=0.01). Of the 43 patients with chronic GvHD who received h-ATG, the severity was reported as limited (n=14) and extensive (29); 49 patients with chronic GvHD who received r-ATG reported its severity as limited (n=29)

and extensive (n=20). Patients aged 20 years or older, and the addition of mycophenolate to tacrolimus or cyclosporine rather than methotrexate were factors associated with a higher risk of chronic GvHD (Table 2B). Donor-recipient HLA match was not associated with a risk of chronic GvHD. The 3-year incidence of chronic GvHD adjusted for patient age and GvHD prophylaxis was 38% (95% CI 29 – 46) with h-ATG and 32% (95% CI 25 – 40) with r-ATG, *P*=0.35 (Figure 1D).

Overall Survival

Among recipients of HLA-matched sibling BMT, there was no difference in survival by type of ATG (Table 2A). Mortality risk was higher for patients aged 40 years or older and when the interval from diagnosis to BMT was longer than 3 months. The 3-year probability of overall survival adjusted for age and the interval between diagnosis and BMT was 90% (95% CI 85 – 93) and 89% (95% CI 85 – 92), *P*=0.67, with h-ATG and r-ATG, respectively (Figure 2A). There were no differences in the causes of death by ATG type (*P*=0.11). Graft failure and infection were the predominant cause of death after h-ATG and r-

Table 2A. Risk factors outcomes after HLA-matched sibling transplant.

	Number	Hazard Ratio (95% Confidence Interval)	P
Acute graft-*versus*-host disease			
Type of ATG			
r-ATG	267	1.00	
h-ATG	277	3.34 (1.87-5.96)	<0.001
Age at transplant, years			
<20	308	1.00	
20-39	140	2.38 (1.33- 4.28)	0.004
≥40	96	2.83 (1.47-5.42)	0.002
Sex			
Female	261	1.00	
Male	283	1.82 (1.07-3.07)	0.026
Chronic graft-*versus*-host disease			
Type of ATG			
r-ATG	259	1.00	
h-ATG	270	2.55 (1.51-4.31)	<0.001
Age at transplant, years			
<20	303	1.00	
20-39	135	4.38 (2.53-7.58)	<0.001
≥40	91	3.49 (1.77-6.85)	<0.001
Sex			
Female	252	1.00	
Male	277	2.05 (1.23-3.39)	0.006
Overall survival			
Type of ATG			
r-ATG	268	1.00	
h-ATG	278	0.92 (0.53-1.59)	0.76
Age at HCT, years			
<20	309	1.00	
20-39	140	1.56 (0.72-3.40)	0.26
≥40	97	4.90 (2.49-9.66)	<0.001
Time from diagnosis to transplant			
<3 months	350	1.00	
≥3 months	196	2.43 (1.34-4.40)	0.004

ATG: antithymocyte globulin; h-ATG: horse derived ATG; r-ATG: rabbit derived ATG; HLA: human leukocyte antigen; HCT: hematopoietic cell transplantation.

ATG. There were 23 deaths among recipients of h-ATG; graft failure (n=8), infection (n=5), GvHD (n=4), pneumonitis/organ failure (n=4), and the cause of death was not reported for 2 patients. There were 30 deaths among recipients of r-ATG; graft failure (n=16), infection (n=8), GvHD (n=3), myelodysplastic syndrome (n=1), bleeding (n=1), and the cause of death was not reported for 2 patients.

Among recipients of unrelated donor BMT, the risk of mortality was higher with h-ATG compared to r-ATG (Table 2B). Mortality risk was higher for patients with a comorbidity score of 3 or greater and 1 HLA locus mismatched unrelated donor BMT. The 3-year probability of overall survival adjusted for the comorbidity score and HLA match was 75% (95% CI 67 – 81) and 83% (95% CI 76 – 88) with h-ATG and r-ATG, respectively (Figure 2B). There were no differences in the causes of death by ATG type (P=0.26). There were 32 deaths among recipients of h-ATG; graft failure (n=6), infection (n=7), GvHD (n=13) and organ failure (n=6). There were 25 deaths among recipients of r-ATG; graft failure (n=7), infection (n=8), GvHD (n=4), pneumonitis/organ failure (n=5), and EBV-associated lymphoproliferative disease (n=1).

Discussion

This analysis of a large, prospectively reported cohort of patients directly compared the utility of h-ATG with r-ATG in transplant conditioning regimens for SAA. Data reported to the CIBMTR in recent years show that 75% of HLA-matched sibling donor and 77% of unrelated donor transplants include ATG in the transplant conditioning regimen. As we have previously demonstrated the superiority of bone marrow to peripheral blood as a graft source in SAA,[13,14] this study was restricted to bone marrow grafts. Our findings support r-ATG (thymoglobulin) as the preferred type of ATG compared to h-ATG for HLA-matched sibling and unrelated donor BMT for SAA. With r-ATG there was less acute GvHD with both HLA-matched sibling and unrelated donor BMT and less chronic GvHD after HLA-matched sibling BMT. This is not surprising as r-ATG has a more potent immune suppressive effect and spares T-regulatory cells more effectively compared to h-ATG. Although survival was similar with h-ATG and r-ATG in HLA-matched sibling BMT, there was a survival advantage with r-ATG in the setting of unrelated donor BMT. The observed survival rate of 83% in the current analysis with r-ATG after unrelated donor BMT is consistent with that reported from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0301) in which about 75% of patients received r-ATG.[20] In that trial, h-ATG was only used for patients who could not tolerate r-ATG.

Our findings are in keeping with smaller studies that have assessed differences in ATG formulations in allogeneic transplantation. Atta *et al.* also showed that r-ATG was associated with less GvHD, but more fungal infec-

Table 2B. Risk factors associated with Risk factors outcomes after unrelated donor transplant.

	Number	Hazard Ratio (95% Confidence Interval)	P
Acute graft-*versus*-host disease			
Type of ATG			
r-ATG	160	1.00	
h-ATG	124	2.20 (1.47-3.35)	<0.001
Donor recipient HLA match			
Matched	220	1.00	
1 locus Mismatch	64	1.91 (1.23-2.97)	0.004
Chronic graft-*versus*-host disease			
Type of ATG			
r-ATG	158	1.00	
h-ATG	120	1.36 (0.90-2.04)	0.147
Age at transplant, years			
<20	138	1.00	
≥20	140	1.58 (1.05-2.39)	0.030
GvHD prophylaxis			
Tacrolimus or cyclosporine + methotrexate	245	1.00	
Tacrolimus or cyclosporine + mycophenolate	33	2.31 (1.39-3.84)	0.001
Overall survival			
Type of ATG			
r-ATG	158	1.00	
h-ATG	124	1.90 (1.12-3.24)	0.0183
Comorbidity index			
0-2	214	1.00	
3+	68	4.85 (2.85-8.27)	<0.001
Donor-recipient HLA match			
Matched	219	1.00	
1 locus Mismatch	63	1.96 (1.09-3.54)	0.0250

ATG: antithymocyte globulin; h-ATG: horse derived ATG; r-ATG: rabbit derived ATG; HLA: human leukocyte antigen; GvHD: graft-*versus*-host disease.
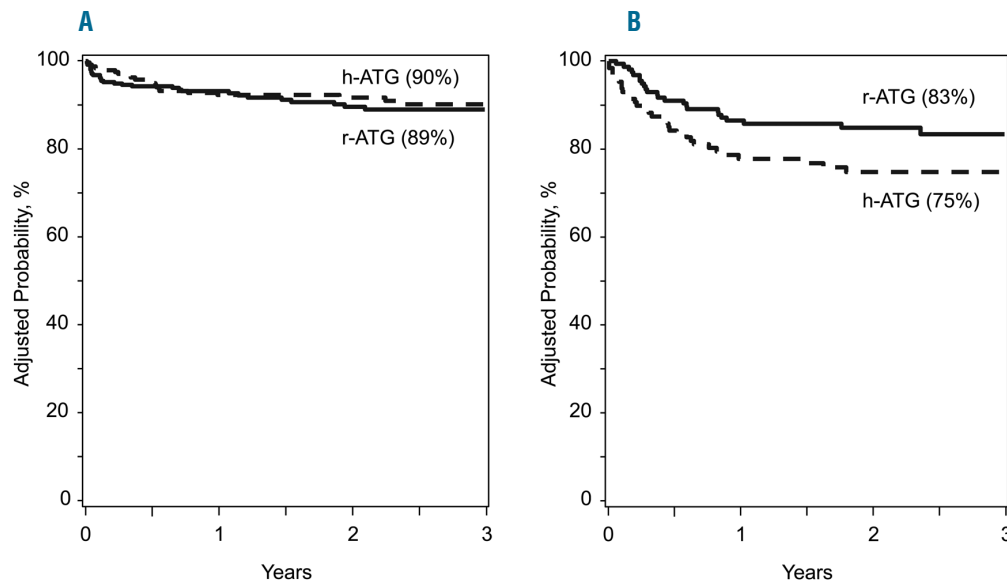
Figure 2. Overall survival. The probability of overall survival after HLA-matched sibling transplant adjusted for age and time from diagnosis to transplant (A) and unrelated donor transplant adjusted for comorbidity index and donor-recipient HLA match (B). h-ATG: horse derived ATG; r-ATG: rabbit derived ATG.

tions and cytomegalovirus (CMV) reactivation.[21] The overall mortality rate, however, was not different between r-ATG and h-ATG, with more infectious related deaths with r-ATG and more GvHD related deaths with h-ATG. As the current analyses used data reported to an observational registry, data on infectious complications were not collected consistently. However, infection was reported as the primary cause of death in 22% of patients who received h-ATG and 25% of patients who received r-ATG following HLA-matched sibling and unrelated donor BMT. One death was attributed to EBV-associated post-transplant lymphoproliferative disorder in a patient who received r-ATG and unrelated donor BMT.

In addition to the effect of the type of ATG on acute and chronic GvHD and survival, the current analyses identified several modifiable factors that may improve outcomes both after HLA-matched sibling and unrelated donor BMT. In the setting of HLA-matched sibling BMT, delaying transplant beyond 3 months from diagnosis, regardless of patient age, results in higher mortality.[22] Therefore, initiating a donor search at diagnosis is highly desirable and unlikely to delay the initiation of IST by more than 2-3 weeks in the event that a matched sibling is not available. Older patients are less likely to have a sustained response to IST, thus offering BMT early may mitigate some of the mortality risks associated with a longer waiting period to BMT. In the setting of unrelated donor BMT, selecting a HLA-matched donor lowered the risk for acute GvHD and mortality.[23] Consistent with reports after reduced intensity conditioning transplants for hematologic malignancies, the addition of mycophenolate rather than methotrexate to a calcineurin inhibitor for GvHD prophylaxis resulted in a two-fold increase in the risk of contracting chronic GvHD.[24]

A limitation of the current study is that the choice of treatment strategy, including whether to use h-ATG or r-ATG, and the dose and timing of ATG, was at the discretion of the treating physician and/or transplantation center and therefore subject to bias. This may have also been influenced by the availability of different ATG formulations at various centers. Others have noted that the timing of ATG and dose have been noted to be important in outcomes of engraftment, infection rates and survival post-BMT.[25,26] These studies have shown that higher doses of ATG are associated with lower rates of GvHD but higher rates of infection, including post-transplant lymphoproliferative disorder. A limitation of the current analyses is the lack of information on timing and dose. In addition, there may likely be other unmeasured or unknown factors that may have affected GvHD rates and survival. Due to the prohibitive costs of conducting multi-site trials, we often rely on observational registry data, such as that used in the study herein, to address some of the issues that may or may not be associated with outcomes. Nevertheless, we performed carefully controlled comparisons of the effects of r-ATG and h-ATG considering known prognostic factors. In patients undergoing HLA-matched sibling and unrelated donor BMT, survival was excellent regardless of type of ATG, and these findings may stimulate trials that test ATG type and dose for SAA transplants. The higher rates of GvHD associated with h-ATG support using r-ATG as opposed to h-ATG in order to lower the burden of morbidity in bone marrow transplantation for SAA.

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