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blood advances

Improved survival with model-based dosing of antithymocyte globulin in pediatric hematopoietic cell transplantation

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Key Points

- Model-based dosing of ATG leads to improved survival and reduced morbidity compared with conventional fixed dosing.
- Model-based dosing is easy to implement and can improve outcome of pediatric HCT.

Antithymocyte globulin (ATG) is used in pediatric allogeneic hematopoietic cell transplantation (HCT) to prevent graft-versus-host disease (GVHD) and graft failure (GF). Poor T-cell recovery, associated with increased mortality, is the main toxicity of ATG. Model-based precision dosing of ATG (MBD-ATG) minimizes toxicity while maintaining efficacy. We report updated results of the single-arm phase 2 PARACHUTE trial investigating MBD-ATG, combined with real-world experience using identical MBD-ATG. Consecutive patients receiving a first T-cell–replete HCT for any indication were evaluated. Results were compared with historical patients receiving conventional fixed ATG dosing (FIX-ATG). Primary outcome was overall survival (OS). The MBD-ATG group consisted of 214 patients (58 trial patients; 156 real-world patients); 100 patients received FIX-ATG. MBD-ATG led to superior OS compared with FIX-ATG (hazard ratio [HR] for death, 0.56; 95% confidence interval [CI], 0.34-0.93; $P = .026$), and lower treatment-related mortality (TRM; HR, 0.51; 95% CI, 0.29-0.92; $P = .025$). Successful T-cell reconstitution (>0.05 × 10^9/L $CD4^+$ T cells twice within 100 after HCT) was improved in MBD-ATG vs FIX-ATG (87% ± 2% vs 47% ± 5%; $P < .0001$). The improved T-cell reconstitution led to lower TRM (HR, 0.19; 95% CI, 0.09-0.36; $P < .0001$). Incidence of grade 2-4 acute GVHD was comparable, whereas chronic GVHD (HR, 0.35; 95% CI, 0.17-0.72; $P = .004$) and GF (HR, 0.36; 95% CI, 0.13-0.97; $P = .044$) were both less frequent in MBD-ATG compared with FIX-ATG. MBD-ATG results in improved OS and reduced TRM, while reducing chronic GVHD and GF. This easy-to-implement approach improves outcomes after pediatric HCT, confirmatory studies are needed. The PARACHUTE trial is registered with the Dutch Trial Register as #NL4836.

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The full-text version of this article contains a data supplement.

Introduction

Hematopoietic cell transplantation (HCT) is a potentially curative treatment for malignant and nonmalignant disorders. The main limitations of HCT include graft-versus-host disease (GVHD), graft failure (GF), and infectious complications, especially viral reactivations. To reduce the risk of GVHD and GF, antithymocyte globulin (ATG) has been introduced in the conditioning regimen.[1] The addition of ATG to the conditioning regimen indeed led to a clinically relevant decrease in GVHD; however, it failed to improve overall survival (OS) in most pivotal trials.[2-5] The survival benefit through preventing GVHD is likely offset by the consequences of ATG-induced poor T-cell recovery, its main toxicity.[6] Successful T-cell recovery has been identified as a strong predictor for improved OS in a variety of HCT settings.[7-11] Successful $CD4^+$ reconstitution (CD4IR) is associated with a reduction in viral reactivations[6,12] and a lower incidence of GVHD,[10] which seem to drive this improved OS rate.

During the first 3 to 12 months after HCT, T-cell recovery depends on peripheral expansion of graft-infused T cells.[13] Depending on patient age, treatments before HCT, steroid use, and GVHD, sufficient thymic output may be absent up to years after HCT.[13] Because of its long half-life, ATG given before transplant during conditioning may be detectable, even at relatively high concentrations, at the time of graft infusion. In recent years, high exposure of the graft to ATG has been shown to negatively affect early CD4IR.[7,8,14,15] Optimizing the timing and dosing of ATG, thereby minimizing exposure to ATG after graft infusion, is therefore pivotal for improved and predictable CD4IR.[16]

ATG displays strong nonlinear pharmacokinetics (PK), as shown in a recently developed and independently evaluated population PK model.[17] Moreover, this population PK model showed that absolute lymphocyte counts (ALCs) before dosing and body weight were the main predictors of ATG clearance. Therefore, using fixed dosing for all patients can lead to overexposure or underexposure in various subgroups of the population, which may subsequently affect CD4IR and survival.[8,17] The optimal dose of ATG has not yet been defined in several randomized controlled trials in both children and adults,[2-5,18-20] which may be because of the fixed body weight–based dosing of ATG in these studies.

The recent prospective phase 2 trial (PARACHUTE) investigated model-based precision dosing of ATG (MBD-ATG; considering weight and ALC to personalize the dose); the primary end point of improved CD4IR was met, without negatively affecting GVHD and GF compared with conventional fixed ATG dosing (FIX-ATG), despite considerably lower doses administered in some patients (up to fivefold compared with historical 10 mg/kg dosing).[16] With a minimum follow-up of 1 year, the trial reported on the biomarker end point CD4IR and safety (incidence of GVHD and rejection). The trial patients currently have a minimal follow-up of 5 years, and subsequent patients have been treated with the same MBD-ATG in Utrecht and New York after the trial's closure. In this analysis, we were mainly interested in clinical outcomes with MBD-ATG, with a focus on survival. Moreover, this analysis gives insight into the long-term outcomes of a pediatric trial in HCT, which are relatively infrequently reported on.

Methods

Study design and patients

The MBD-ATG group consisted of patients enrolled in the PARACHUTE trial[16] (Dutch Trial Register number NL4836), as well as consecutive patients who were treated per the PARACHUTE trial protocol after its conclusion as the best available care in Utrecht (Princess Máxima Centre for Pediatric Oncology) and New York (Memorial Sloan Kettering Cancer Center [MSK]). In short, all consecutive real-world patients receiving their first T-replete unrelated HCT in the pediatric transplant units for any indication, who did not receive serotherapy in past 3 months, were eligible (full inclusion criteria in the supplemental Methods). Although the inclusion criteria for those treated in the trial were stringent in terms of remission and performance status, some real-world patients underwent transplant while not being in complete remission (CR) or having poor performance status.

As per the protocol of the PARACHUTE trial, outcomes were compared with a well-documented historical cohort of patients previously reported,[8] who received FIX-ATG. Inclusion criteria for patients in the FIX-ATG group were identical to that of the MBD-ATG group. FIX-ATG patients were recruited between 1 April 2004 and 1 April 2012. The outcome data for these consecutive controls were prospectively collected. No major changes were implemented in treatment protocols between the historical controls and the MBD-ATG group regarding conditioning regimens (except for patients with acute lymphoblastic leukemia treated after 2018 who received total body irradiation (TBI)-based rather than chemotherapy-based conditioning), therapeutic drug monitoring (busulfan and cyclosporin), donor hierarchy, GVHD prophylaxis, infection prophylaxis, and nursing protocols.

The minimum follow-up for all patients was 12 months. Ethical committee approval for data collection was acquired as described for controls[8]; for the PARACHUTE-trial through trial number 14-672/G-M; and for real-world patients through trial numbers 19-379 (MSK) and 11/063-k (Utrecht). The study is registered with the Dutch Trial Register (NL4836).

Procedures

Patients in the MBD-ATG group received ATG (Thymoglobulin; Genzyme, Cambridge, MA) according to a MBD-ATG nomogram based on body weight, ALCs before the first ATG dose, and graft source (supplemental Table 1 for bone marrow and peripheral blood stem cells [PBSCs]; supplemental Table 2 for cord blood). The cumulative dose of ATG varied from 2 to 10 mg/kg and was given over 1 to 4 days, starting 9 days before HCT. The goal of the MBD-ATG regimen was to achieve low exposure to ATG after graft infusion (<20 AU × d/mL in cord blood transplants; <50 AU × d/mL in bone marrow and PBSC transplants) to optimize successful CD4IR and thereby aiming to improve OS. The FIX-ATG cohort received ATG in a dose of 10 (± 1) mg/kg starting day 5 (± 1) days before transplantation (supplemental Figure 1).[16]

Conditioning regimens were given according to national and international treatment protocols. Therapeutic drug monitoring was used for regimens containing busulfan, aiming at a cumulative area under the curve of 80 to 100 mg × h/L. Reduced-intensity conditioning was reserved for patients with severe aplastic anemia and Fanconi anemia. GVHD prophylaxis, infection prophylaxis, and selective gut decontamination were given according to local

protocols.[8] High-risk patients (cord blood recipients or cytomegalovirus [CMV]-seronegative donor) treated from 2022 received letermovir as CMV prophylaxis. GVHD prophylaxis consisted of cyclosporin, targeted at trough levels of 200 to 250 µg/L (Máxima and MSK before 2022), or tacrolimus, targeted at trough levels of 8 to 12 µg/L (MSK since 2022), combined with either prednisolone 1 mg/kg (cord blood at Máxima), mofetil mycophenolate (cord blood at MSK), or methotrexate 10 mg/m^2 on days 1, 3, and 6 (bone marrow and peripheral blood transplants in both centers). The management for GVHD did change over the years, with several new agents including ruxolitinib, vedolizumab, and etanercept being introduced.

Patients were treated in high-efficiency, particle-free, air-filtered, positive-pressure isolation rooms. Routine blood evaluations were performed for cell counts, extensive chemistry, and therapeutic drug monitoring, with once weekly viral loads. None of the above-mentioned procedures, other than ATG dosing, changed over time during the treatment of historical controls, trial patients, and those treated after trial completion.

Outcomes

The primary end point of this analysis was OS. Secondary end points included successful CD4IR, event-free survival (EFS), acute GVHD, chronic GVHD, GF, and viral reactivations of CMV, adenovirus (AdV), and Epstein-Barr virus (EBV). Viral reactivations were evaluated as both the actual incidence of viral reactivations and the incidence of viral reactivations that were treated with systemic antiviral drugs.

OS was defined as the time between HCT and last follow-up or death; EFS as the time between HCT and last visit or event, in which death, relapse, and GF are considered events. Surviving patients were censored at the date of last follow-up. Treatment-related mortality (TRM) was defined as death because of causes other than relapse; relapse-related mortality (RRM) as death because of relapse of malignancy (only applicable in those with malignant underlying diseases). Successful CD4IR was defined as CD4$^+$ T-cell count of at least 0.05 × 10^9 cells per L at 2 consecutive measurements within 100 ± 3 days after transplantation, in line with previous reports associating this cellular marker with improved OS.[7-11] Acute GVHD (both grade 2-4 and grade 3-4) was graded according to the Glucksberg criteria[21]; chronic GVHD was graded according to the National Institutes of Health criteria.[22] GF was defined as having either nonengraftment (not reaching 0.5 × 10^9/L donor neutrophils) or secondary graft rejection. In case of nonengraftment, the time to nonengraftment is arbitrarily set at 60 days after graft infusion. Viral reactivations were defined as having a viral load of >1000 copies per mL for CMV, AdV, or EBV; treated viral reactivations were defined as any reactivation requiring systemic antiviral therapy as per the treating physician, usually based on viral load in the context of timing, donor serostatus, and immune recovery.

Statistical analysis

We performed a per-protocol analysis, only excluding patients treated in the PARACHUTE trial with major protocol violations. All patients, including those with early events, were considered for all end points. The end points OS and EFS were evaluated using Kaplan-Meier curves with a 2-sided log-rank test for statistical analysis; cumulative incidence curves were estimated for CD4IR, TRM, RRM, relapse incidence, acute and chronic GVHD, GF, and viral reactivations in a competing risk setting, in which Gray test was used for univariate analysis. Multivariable analyses were performed to identify predictors of outcomes, including recipient (age, sex, patient and donor serology status of CMV and EBV, and underlying disease) and transplantation (HLA disparity and stem cell source) predictors. Nearly all patients with malignancy as underlying disease underwent transplant with negative measurable (or minimal) residual disease (acute lymphoblastic leukemia) or complete hematological remission (acute myeloid leukemia). As such, measurable (or minimal) residual disease and remission status were not included in the multivariable analyses for relapse. In multivariable analysis, hazard ratios (HRs) were calculated using either Cox proportional hazard models or Fine-Gray competing risk regressions. Considered competing events were death from other causes (for TRM, RRM, relapse, GVHD, GF, and viral reactivations) or death, GF, and relapse (for CD4IR). Causes of death were investigated for a relationship with ATG; deaths likely attributability to ATG were defined as death because of viral disease, whereas deaths possibly related to ATG were defined as having GVHD and GF as the cause of death. CD4IR was explored as a potential predictor for survival parameters (OS, EFS, and TRM). The retrospective character of the FIX-ATG controls could introduce bias. To address this, we analyzed OS with each of the intervention groups split at their respective median treatment year, indicating that outcome was improved over time because of other factors than ATG dosing; and we analyzed successful CD4IR as a driver of survival differences because this biomarker was found to be highly predictive of survival.[7,8,10-12] Variables in univariate analysis with a P value <.05 were selected for multivariable analysis; a multivariable P value <.05 was considered statistically significant. Data analysis was performed using R version 4.0.5.

Results

Patients

Between 1 July 2015 and 22 August 2018, the PARACHUTE trial enrolled 64 patients, of whom 6 patients were excluded from the analysis because of major protocol violations and/or fulfilling exclusion criteria, making a total of 58 patients.[16] After the trial's completion, 124 patients were treated with MBD-ATG in the Princess Máxima Centre between 25 September 2018 and 17 August 2022; and a further 32 patients in Memorial Sloan Kettering Cancer Centre between 4 March 2019 and 1 June 2022. A total of 214 patients were included in the MBD-ATG group (Table 1). The median age of the MBD-ATG group was 8.4 years (interquartile range [IQR], 4.2-13.8); most patients (61%) received a bone marrow graft, and the most frequent underlying disease groups were malignancies (51%) and bone marrow failure (BMF; 33%). The median follow-up in the MBD-ATG group was 3.5 years (range, 1.0-8.1 years). The median cumulative dose in the MBD-ATG group was 8.5 mg/kg (IQR, 6.0-10.0). Within the MBD-ATG cohort, dosing was not significantly different between patients treated in the PARACHUTE trial and those treated after trial completion in both centers (median dose, 8.7 mg/kg, 8.1 mg/kg, and 9.7 mg/kg in trial, Utrecht, and New York patients, respectively; P = .88). The FIX-ATG group consisted of 100 patients, with a median age of 6.1 years (IQR, 2.0-11.6); most received bone

Table 1. Patient characteristics

	MBD-ATG	FIX-ATG	*P* value	MBD-ATG (PARACHUTE)	MBD-ATG (Utrecht)	MBD-ATG (New York)
No. of patients, N	214	100		58	124	32
Age at transplant, y	8.4 (4.2-13.8)	6.1 (2.0-11.6)	.07	7.4 (2.8-13.2)	8.9 (5.0-13.9)	5.8 (3.8-13.8)
Male sex, n (%)	121 (57)	41 (41)	.011	29 (50)	68 (55)	24 (75)
Cumulative dose of ATG, mg/kg						
All patients	8.5 (6.0-10.0)	10.0 (10.0-10.0)	<.001	8.7 (6.4-10.0)	8.1 (6.0-10.0)	9.7 (7.3-10.0)
Cord blood only	6.5 (5.0-10.0)	10.0 (10.0-10.0)	<.001	7.8 (5.3-10.0)	6.0 (4.0-9.5)	7.8 (5.1-9.7)
Bone marrow/peripheral blood only	9.7 (7.8-10.0)	10.0 (10.0-10.0)	<.001	9.1 (8.0-10.0)	9.4 (7.1-10.0)	9.9 (8.1-10.1)
Starting day before HCT, d	9 (9-9)	5 (5-5)	<.001	9 (9-9)	9 (9-9)	9 (9-9)
Graft source, n (%)			<.001			
Bone marrow	130 (61)	48 (48)		29 (50)	81 (65)	20 (62)
Cord blood	83 (39)	42 (42)		29 (50)	42 (34)	12 (38)
PBSCs	1 (0)	10 (10)		0 (0)	1 (1)	0 (0)
Diagnosis, n (%)			<.001			
Malignancy	110 (51)	42 (42)		20 (34)	73 (59)	17 (53)
PID	11 (5)	24 (24)		8 (14)	0 (0)	3 (9)
BMF	71 (33)	8 (8)		18 (31)	42 (34)	11 (34)
Benign non-PID	22 (10)	26 (26)		12 (21)	9 (7)	1 (3)
Match grade, n (%)			.0023			
Matched	145 (68)	53 (53)		37 (64)	84 (68)	24 (75)
Mismatched	69 (32)	47 (47)		21 (36)	40 (32)	8 (25)
Follow-up	3.5 (2.5-5.0)	15.4 (14.1-17.2)	<.001	6.7 (5.5-7.7)	3.0 (2.1-4.0)	2.6 (2.0-3.0)
Year of transplant	2020 (2018-2021)	2008 (2006-2009)	<.001	2016 (2015-2018)	2020 (2019-2021)	2021 (2020-2021)

Values represent median (IQR), unless otherwise specified. Matched: 10/10 in bone marrow and PBSCs and 6/6 in cord blood.
PID, primary immune deficiency.

marrow (48%), and the most frequent underlying disease group was malignancy (42%). The median follow-up for the FIX-ATG group was 15.4 years (range, 11.7-19.0). The median cumulative dose of ATG was 10.0 mg/kg (IQR, 10.0-10.0) in the FIX-ATG group. All patients in both treatment groups received T-cell–replete grafts; no haplo-identical transplants were included.

Primary outcome: survival

OS was significantly higher in the MBD-ATG group than the FIX-ATG group (HR for death, 0.56; 95% confidence interval [CI], 0.34-0.93; $P = .026$; Table 2; Figure 1A; supplemental Table 3). The diagnosis group of BMF was the only multivariable predictor of improved outcome, with malignancies as reference. A significantly higher survival was noted after MBD-ATG than fixed dosing for both malignant and nonmalignant diseases (supplemental Figure 6) and when only evaluating real-world patients (supplemental Figure 7). The survival advantage in the MBD-ATG group was mainly due to reduced TRM, with an incidence of 12% ± 2% compared with 24% ± 4% in the controls (HR, 0.51; 95% CI, 0.29-0.92; $P = .025$; Figure 1B; Table 2). No other multivariable predictors were identified for TRM. RRM was not significantly different between both groups. No differences were found in OS and TRM between patients treated before and after the median treatment year in each group (2008 and 2020 for FIX-ATG and MBD-ATG, respectively; supplemental Figure 2). We further investigated the causes of death in relation to ATG (supplemental Table 4). Of the 100 patients in the FIX-ATG group, 11 deaths were likely attributable to ATG (9 without successful CD4IR), whereas 4 deaths were possibly related. Of the 214 patients in the MBD-ATG group, 3 deaths were likely related to ATG (1 without successful CD4IR), and 9 deaths were possibly related.

Primary outcomes: role of successful CD4IR in survival

Given the retrospective nature of the analysis, we further investigated whether improvements in CD4IR, which is the direct toxicity of ATG, affected survival. This would indicate that the differences in outcome are due to MBD-ATG rather than improvements in the standard of care. We found that achieving successful CD4IR was a strong predictor of TRM ($P < .0001$; Figure 2B). In both the MBD-ATG and FIX-ATG groups, patients without successful CD4IR had comparably high rates of TRM ($P = .76$). On the contrary, patients with successful CD4IR in the MBD-ATG and FIX-ATG groups had comparably low rates of TRM ($P = .36$). To further test the role of successful CD4IR in TRM, we introduced CD4IR along with all other predictors in the multivariable model for TRM. Here, successful CD4IR was found to be a strong predictor of TRM (HR, 0.18; 95% CI, 0.09-0.36; $P < .0001$), whereas treatment group was not (HR, 0.98; 95% CI, 0.52-1.86; $P = .96$). A landmark sensitivity analysis, excluding those who died before 100 days and resetting the time of origin to 100 days after HCT, shows comparable results (supplemental Figure 3).

Table 2. Multivariable analysis

Variable	HR	95% CI	*P* value	Significance level
OS (HR for death)				
Fixed dosing	1			
Model-based dosing	0.56	0.34-0.93	.026	*
TRM				
Fixed dosing	1			
Model-based dosing	0.51	0.29-0.92	.025	*
RRM				
Fixed dosing	1			
Model-based dosing	0.47	0.20-1.13	.090	.
Successful $CD4^+$ immune reconstitution				
Fixed dosing	1			
Model-based dosing	2.92	2.02-4.22	<.0001	****
EFS (HR for events)				
Fixed dosing	1			
Model-based dosing	0.64	0.42-0.97	.035	*
Relapse incidence				
Fixed dosing	1			
Model-based dosing	0.92	0.46-1.84	.82	
Incidence of grade 2-4 acute GVHD				
Fixed dosing	1			
Model-based dosing	1.58	0.86-2.89	.14	
Incidence of moderate-severe chronic GVHD				
Fixed dosing	1			
Model-based dosing	0.35	0.17-0.72	.0040	**
Incidence of GF				
Fixed dosing	1			
Model-based dosing	0.36	0.14-0.96	.040	*
Incidence of AdV reactivations				
Fixed dosing	1			
Model-based dosing	0.41	0.20-0.81	.011	*
Incidence of EBV reactivations				
Fixed dosing	1			
Model-based dosing	0.17	0.07-0.38	<.0001	****
Incidence of CMV reactivations				
Fixed dosing	1			
Model-based dosing	0.82	0.44-1.54	.54	
Incidence of treated AdV reactivations				
Fixed dosing	1			
Model-based dosing	0.31	0.13-0.76	.010	*
Incidence of treated EBV reactivations				
Fixed dosing	1			
Model-based dosing	0.11	0.04-0.31	<.0001	****
Incidence of treated CMV reactivations				
Fixed dosing	1			
Model-based dosing	0.49	0.25-0.99	.046	*

Overview of multivariate analyses.
***<0.0005.
. <0.1.
*<0.05.
**<0.005.
****<0.0001.

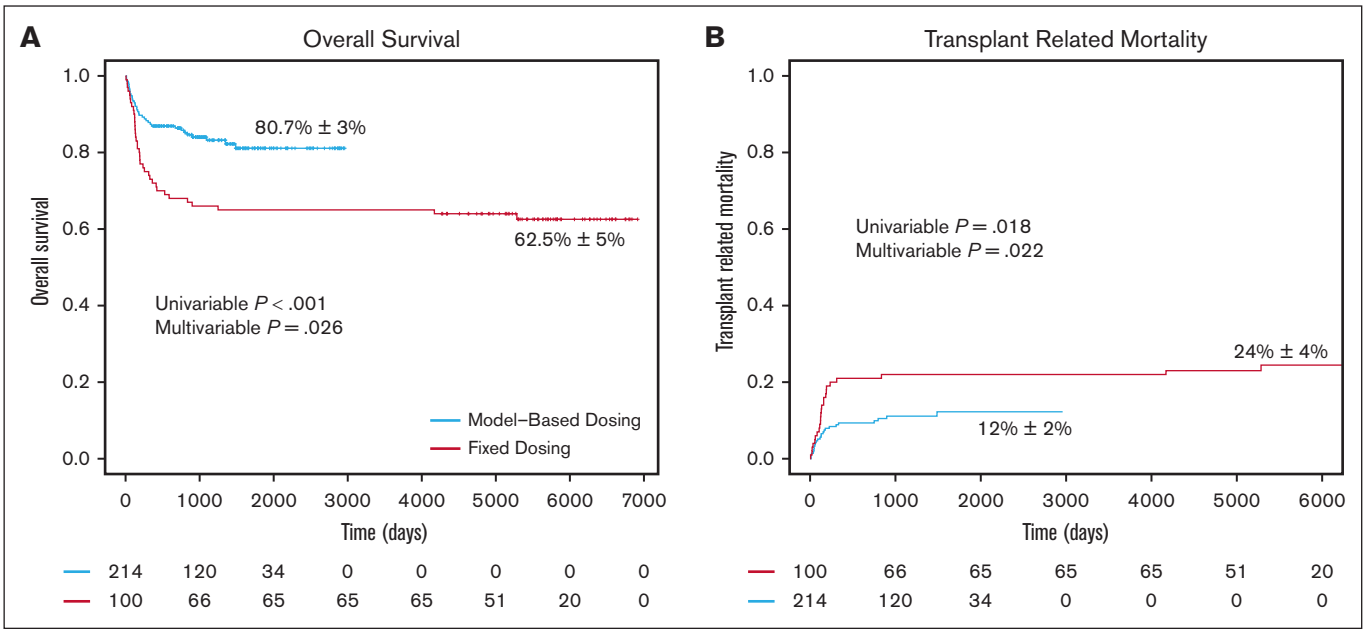

Figure 1. Survival. OS (A) and cumulative incidence of TRM (B) in model-based dosing (blue curves) and fixed dosing (red curves).

Secondary outcomes: CD4IR, EFS, and relapse

CD4IR was significantly improved in the MBD-ATG group compared with the FIX-ATG group, with 87% ± 2% of patients receiving MBD-ATG achieving successful CD4IR compared with 49% ± 5% in FIX-ATG (HR, 2.92; 95% CI, 2.02-4.22; $P < .0001$; Figure 2A). This is also true when separately analyzing bone marrow/PBSC transplants and cord blood transplants (supplemental Figure 8). Of note, the difference in incidence between treatment groups was larger in cord blood transplants than bone marrow/PBSC transplants. Immune disorders were associated with worse CD4IR in multivariable analysis. EFS was significantly better in the MBD-ATG group (HR for events, 0.64;

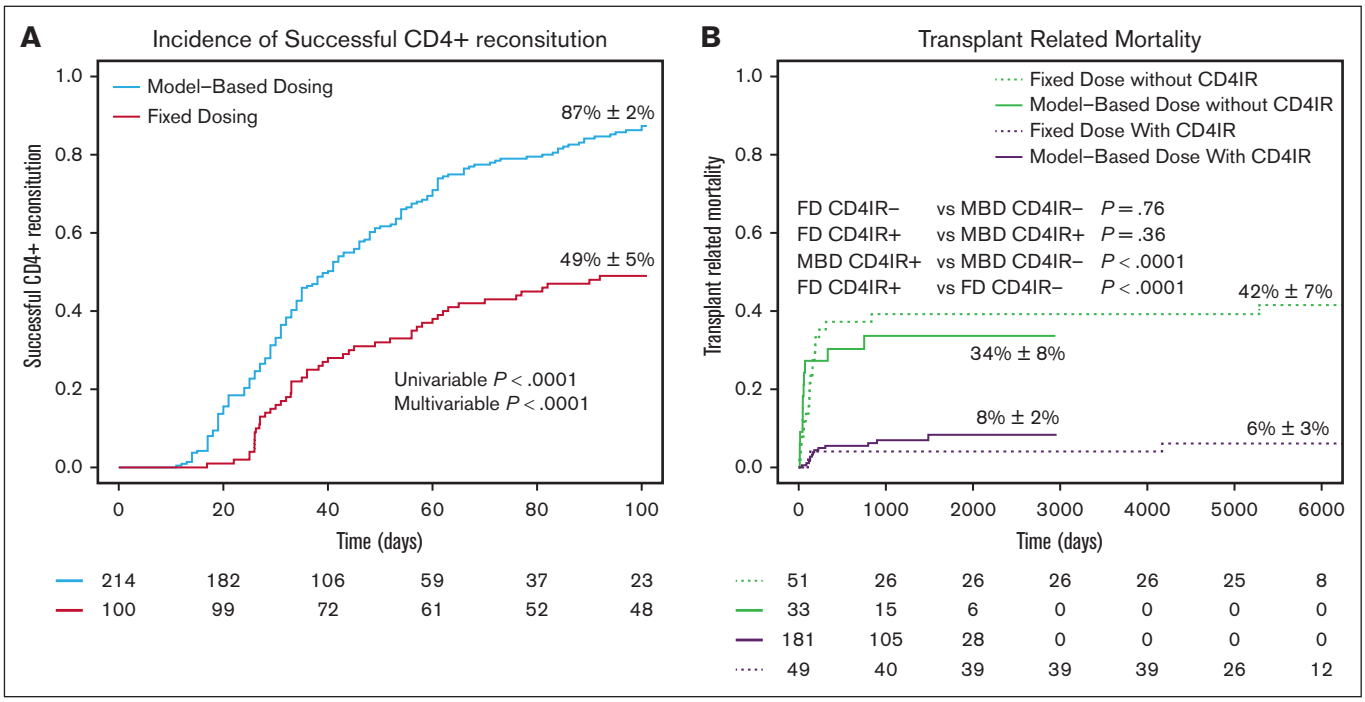

Figure 2. CD4$^+$ immune reconstitution and TRM. (A) Cumulative incidence of successful CD4$^+$ immune reconstitution (CD4$^+$ T-cell count of at least 0.05 × 10^9 cells per L at 2 consecutive measurements within 100 (± 3) days after transplantation; CD4IR) in model-based dosing (blue curves) and fixed dosing (red curves). (B) Cumulative incidence of TRM stratified for treatment group and CD4IR. Green lines represent unsuccessful CD4IR (model-based dosing in solid lines; fixed dosing in dashed lines); purple lines, successful CD4IR (model-based dosing, solid lines; fixed dosing, dashed lines).

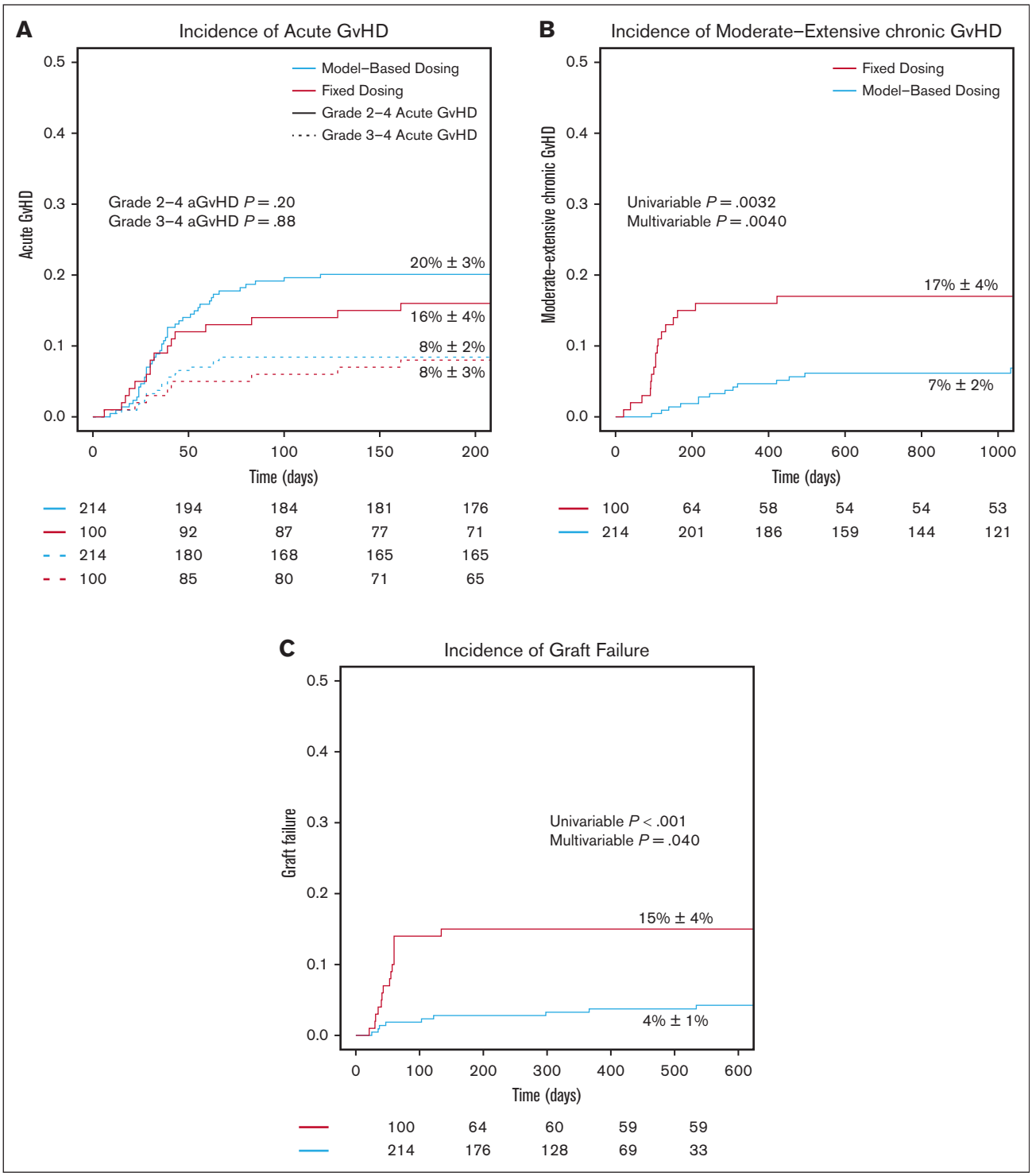

Figure 3. GVHD and GF. Cumulative incidence of acute GVHD grade 2 to 4 (solid lines) and grade 3 to 4 (dashed lines; A), moderate-severe chronic GVHD (B), and GF (C) according to model-based dosing vs fixed dosing.

95% CI, 0.42-0.97; $P = .035$). Donor mismatch was identified as a multivariable predictor of worse EFS. Relapse rate was not affected by treatment group or any other multivariable predictor. Relapse incidence was also not affected by treatment group when evaluating only those with myeloid or lymphoblastic leukemia.

Secondary outcomes: GVHD and GF

The incidence of acute GVHD grade 2 to 4 (HR, 1.58; 95% CI, 0.86-2.89; $P = .14$) and grade 3 to 4 (HR, 1.06; 95% CI, 0.46-2.43; $P = .88$) did not differ between groups (Figure 3A). However, the incidence of moderate-severe chronic GVHD was significantly

lower in the MBD-ATG group (HR, 0.35; 95% CI, 0.17-0.72; $P = .0040$; Figure 3B). No other predictors of chronic GVHD could be identified in the multivariable analysis. Chronic GVHD, however, was not affected by CD4IR, potentially because of relatively low number of events. The observed incidence of GF was lower in the MBD-ATG group than the FIX-ATG group (HR, 0.36; 95% CI, 0.14-0.96; $P = .040$; Figure 3C), with immune deficiencies, BMF, and donor mismatch being predictors of a higher incidence of GF.

Secondary outcomes: viral reactivations

The incidence of viral reactivations was lower in the MBD-ATG group than the FIX-ATG group for AdV (HR, 0.41; 95% CI, 0.20-0.81; $P = .011$) and EBV (HR, 0.17; 95% CI, 0.07-0.38; $P < .0001$; supplemental Figure 4). There was no statistically significant difference in the incidence of CMV between groups. The incidence of viral reactivations that required systemic treatment was further reduced in the MBD-ATG group compared with the FIX-ATG group, for AdV (HR, 0.31; 95% CI, 0.13-0.76; $P = .010$), EBV (HR, 0.11; 95% CI, 0.04-0.31; $P < .0001$), and CMV (HR, 0.49; 95% CI, 0.25-0.99; $P = .046$; supplemental Figure 5).

Discussion

We present the results of a large cohort of pediatric HCT recipients treated with MBD-ATG in the setting of a clinical trial and subsequent real-world experience. We found that OS is significantly improved with MBD-ATG compared with FIX-ATG, mainly driven by the reduced incidence of TRM. The reduction in TRM is attributable to markedly decreased incidence of clinically relevant viral reactivations because of better CD4IR. Here, we confirm previous findings[16] showing that MBD-ATG, which encompasses a reduced dose of ATG in most patients (median, 16%) that is given earlier (day −9 vs −5 in the fixed dosing), was not different in preventing acute GVHD compared with FIX-ATG, whereas the observed incidence of GF and chronic GVHD was twofold to threefold lower.

Limitations of the study include an imbalance in underlying diseases, with underrepresentation of immune deficiencies and overrepresentation of BMF in the MBD-ATG group compared with the FIX-ATG group. This is mainly because of the character of the transplant program in Utrecht, focusing on malignancies, BMF, and inborn errors of metabolism. The New York program was more comparable with the FIX-ATG cohort in terms of underlying diseases, providing more balance to the MBD-ATG cohort. Another limitation is the very limited number of patients receiving a PBSC transplant treated with MBD-ATG, which hinders any firm conclusions in this setting. However, MBD-ATG in an external center reporting on 30 patients with PBSC transplants leads to comparable improvement in TRM.[23] The most important limitation, however, is the use of historical controls. Although clinical protocols and supportive care guidelines have not significantly changed over the years, it is hard to fully standardize daily clinical practice over a longer time period. However, our study clearly suggests that it is improvements in CD4IR and not the general improvements over time that explain the improved survival rates of MBD-ATG compared with FIX-ATG. We demonstrated that the improvement in TRM is driven by attaining successful CD4IR; successful CD4IR was vastly improved with MBD-ATG. TRM was comparable in those with and without successful CD4IR, regardless of treatment group (Figure 2B). Moreover, the multivariable model showed that after including CD4IR as a predictor of TRM, no additional effect of treatment group was identified. Finally, we demonstrate that there was no improvement in outcome over time within each treatment group (supplemental Figure 2). This thus strongly suggests that MBD-ATG–induced improved OS is due to improved CD4IR rather than improvements in general HCT treatment protocols. A randomized controlled trial comparing MBD-ATG with FIX-ATG with OS or TRM as the primary end point would obviously be the most optimal comparison. However, based on previous results, we considered this to be unethical. FIX-ATG likely leads to overexposure to ATG in older children and those with very low ALC.[17,24] This is in line with developmental[25] as well as antibody[26] PK. Given the suggested importance of avoiding overexposure to ATG after HCT[7,8] and subsequent poor CD4IR,[7,8,10-12] we decided in accordance with the ethical board recommendation to design the PARACHUTE trial as a single-arm trial with historical controls.

The lower incidence of GF and chronic GVHD with MBD-ATG is in line with previous findings.[16] Furthermore, the finding that successful CD4IR is associated with lower chronic GVHD is in line with previous results.[10,11,27,28] Moreover, successful CD4IR at the time of onset of acute GVHD also seems important for the ability to control GVHD.[10] We hypothesize that the protective effect of CD4IR on the development of GVHD may be due to better reconstitution of regulatory T cells. This needs to be confirmed in immune reconstitution subset analyses.

Since the publication of the PARACHUTE trial, MBD-ATG has been implemented in other centers and multicenter trials (eg, SCRIPT-AML [trial ID NCT05477589] and COG trials AAML1831 and ASCT2031 [trial IDs NCT04293562 and NCT05457556, respectively]). The dosing nomogram is generally considered to be easy to implement in other centers, with comparable results in terms of CD4IR.[23] The MBD-ATG dosing nomogram is practical, accessible, and easy to use. The use and implementation of the nomogram do not add financial costs; the costs associated with the 4-day earlier hospital admission will likely be counterbalanced by reduced costs because of lower incidences of viral reactivations, chronic GVHD, GF, and TRM with MBD-ATG. Still, even with MDB-ATG, not all patients achieve CD4IR. This is in part due to the unexplained uncertainty in the ATG PK model; we know that, even with MBD-ATG, a percentage of patients will be out of range. With increasing knowledge and data gathered in the upcoming years, we hope to finetune the PK model further. Other factors that could contribute to not reaching CD4IR include exposure to other conditioning agents such as fludarabine.

In conclusion, MBD-ATG in pediatric HCT recipients leads to significantly improved OS because of lower TRM compared with FIX-ATG in a historical cohort. The latter is due to reduced toxicity after MBD-ATG, with lower incidences of viral reactivations, GF, and chronic GVHD. These results need to be confirmed in other transplant settings for a more general implementation, for example, adult transplantation, PBSC transplants, haplo-identical transplants, T-cell–depleted transplants, and the posttransplant cyclophosphamide platform including ATG.

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Authorship

Contribution: R.A., S.N., M.B.B., Y.J., C.M.Z., J.J.B., and C.A.L. designed the trial; R.A., Y.J., C.A.L., and J.J.B. analyzed the data and prepared the manuscript; R.A. and C.A.L. verified the data; and all authors reviewed the manuscript and vouch for the accuracy and completeness of the data, and they were responsible for patient inclusion, data collection, and patient registration, and they had access to the statistical reports and had the final responsibility for the decision to submit for publication.

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