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High-dose individualized antithymocyte globulin with therapeutic drug monitoring in high-risk cord blood transplant

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ABSTRACT

Background: Graft-versus-host disease (GvHD) and rejection are main limitations of cord blood transplantation (CBT), more so in patients with severe inflammation or previous rejections. While rigorous T-cell depletion with antithymocyte globulin (ATG) is needed to prevent GvHD and rejection, overexposure to ATG leads to slow T-cell recovery after transplantation, especially in CBT.
Objective: To evaluate high-dose, upfront ATG with individualized dosing and therapeutic drug monitoring (TDM) in pediatric CBT for patients at high risk for GvHD and rejection.
Study design: Heavily inflamed patients and patients with a recent history of rejection were eligible for individualized high-dose ATG with real-time TDM. The ATG dosing scheme was adjusted to target a post-CBT exposure of <10 AU*day/mL, while achieving a pre-CBT exposure of 60–120 AU*day/mL; exposure levels previously defined for optimal efficacy and safety in terms of reduced GvHD and rejection, respectively. Main outcomes of interest included efficacy (target exposure attainment) and safety (incidence of GvHD and rejection). Other outcomes of interest included T-cell recovery and survival.
Results: Twenty-one patients were included ranging from 2 months to 18 years old, receiving an actual median cumulative dose of ATG of 13.3 mg/kg (range 6–30 mg/kg) starting at a median 15 days (range 12–17) prior to CBT. Dosing was adjusted in 14 patients (increased in 3 and decreased in 11 patients). Eighteen (86%) and 19 (91%) patients reached the target pre-CBT and post-CBT exposure, respectively. Cumulative incidence for acute GvHD was 34% (95% CI 23–45) and 5% (95% CI 0–10%) for grade 2–4 and grade 3–4, respectively; cumulative incidence of rejection was 9% (95% CI 2–16%). Overall survival was 75% (95% CI 65–85%).
Conclusion: Individualized high-dose ATG with TDM is feasible and safe for patients with hyperinflammation in a CBT setting. We observe high target ATG exposure attainment, good immune reconstitution (despite very high doses of ATG) and acceptable rates of GvHD and rejection.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for a variety of benign and malignant diseases. In benign indications, the main limitations of HCT include graft rejection, infections, and graft-versus-host disease (GvHD). Some transplant indications can be identified to have a higher risk for rejection and GvHD, which include those with active inflammation [1] (primary immune

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deficiencies (PID) with hyperinflammation, including chronic granulomatous disease [CGD], common variable immunodeficiency [CVID] and hemophagocytic lymphohistiocytosis [HLH]) and patients who are poly-transfused (thalassemia and bone marrow failure) due to, amongst others, anti-donor-HLA antibodies or nonablative conditioning [2,3]. These patients can be characterized as having an activated immune system, either in terms of function or counts of lymphocytes.

Lastly, patients with previous rejections may be at higher risk for future rejections. Overall, all aforementioned categories of patients may need more rigorous recipient T-cell depletion to dampen the inflammation. This could prevent the T-cell compartment into further activation leading to GvHD or rejection [4–7]. On the other hand, swift recovery of T-cells after transplantation is warranted, even more so in the immune deficiencies, in order to prevent viral reactivations and/or counter already present viral disease.

Antithymocyte globulin (ATG) is the most frequently used drug for the indication of transplant-related T-cell depletion in order to prevent GvHD and rejection [8,9]. ATG, if given some days before graft infusion, depletes recipient T-lymphocytes as mediator cells in GvHD and rejection [1,9]. However due to the long half-life, depending on dose and timing of the ATG, the graft-infused T-cells may also be exposed to ATG after graft infusion [10–13]. High ATG exposure after graft infusion is strongly related to delayed or absent T-cell reconstitution after HCT [12–16]. While the exposure to ATG before graft infusion is mainly associated with the desired pharmacological effects in preventing GvHD and rejection, a low exposure after graft infusion is mostly correlated to early T-cell recovery and survival [12,13,16,17]. A recent phase 2 clinical trial demonstrated that individualized dosing of ATG using a dosing nomogram, mainly aiming for minimal exposure after graft infusion, leads to improved T-cell reconstitution without increasing the incidence of GvHD or rejection [18].

However, patients with active inflammation and those poly-transfused may need additional protection against rejection and GvHD as compared to those without these risk factors. This protection may be acquired through higher doses of ATG in comparison to the recently published individualized dose advises [18], given relatively early before graft infusion. For safety and efficacy, this can be combined with real-time measurement of actual exposures, therapeutic drug monitoring (TDM), to ensure high ATG exposures before graft infusion while maintaining low exposures after graft infusion [13,12]. To gain maximum control over the actual ATG exposure [19], a pharmacokinetic (PK) prediction model can be applied to perform simulation studies to choose the best ATG dosing regimen, and to adjust this regimen based on the results of TDM. This is of utmost importance in cord blood transplantation, where the exposure to ATG after graft infusion has to be reduced to a minimum. Low exposure to ATG after graft infusion is strongly correlated to improved CD4+ T-cell recovery after HCT, thereby preventing viral reactivations, which is of importance especially in a cord-blood setting [12–14].

We here report the results of a clinical protocol developed to treat high-risk patients with individualized dosing of ATG combined with TDM aiming for high ATG exposure before graft infusion while minimizing exposure after transplantation [19]. By using this approach, we expected to prevent GvHD and rejection in this high-risk population, while promoting T-cell recovery.

Methods

Study design and patients

Children 0–18 years old receiving an allogeneic CBT with ATG as part of the conditioning regimen between November 2014 and June 2020 in the pediatric stem cell transplantation program of the University Medical Center Utrecht, later transferred to the Princess Máxima Center for Pediatric Oncology, both in Utrecht, the Netherlands, were evaluated. Patients eligible for this protocol were those defined as having a high risk for graft rejection and/or GvHD. We defined this as having PID or other benign indication with hyperinflammation (i.e., high ferritin, high inflammation parameters, cytopenia's due to inflammation before HCT), nonablative conditioning while normal protocols dictate myeloablative regimens, patients with benign disorders who received frequent transfusions over longer time periods and had high ferritin and/or iron accumulation in organs, and those with previous graft rejections or were assessed to have a high risk for graft rejection as per the discretion of the treating physician. Consecutive patients were included. There was no restriction on conditioning regimens. Clinical data were prospectively collected and entered in the clinical database. Minimum follow-up for surviving patients was 18 months. Patients were included and data were collected after obtaining written informed consent in accordance with the Declaration of Helsinki. Institutional ethical approval for sample and data collection was obtained though trial numbers 11/063-k.

Procedures

Patients received individualized dosing of ATG with TDM as described previously [19]. In short, based on the patient's body weight, lymphocyte count before the first dose of ATG and the stem cell source, simulation studies were performed using a validated population PK-model [11]. Target area under the curve (AUC) before graft infusion was 60–120 AU*day/mL, which was arbitrarily set well over the cut-off of 40 AU*day/mL that was found to be optimal in previous analysis [13,12]. The target AUC after graft infusion was <10 AU*day/mL for cord blood recipients, and was set at this value based on previous findings showing an post-HCT AUC of $<20^{13}$ and $<16^{19}$ AU*day/mL to be optimal. Based on the expected individual PK and the target exposures, dosing details including the absolute dose, starting day and number of doses of ATG were determined. The full daily dose of ATG was infused in 4 hours in all patients. Blood samples were drawn based on an optimal sampling scheme with 6 samples [19]. Timepoints for sampling included after the first dose, before and after the second and third dose, and early morning of the 4th day of ATG. On the 4th day, active ATG concentrations were measured using a validated assay [19]. Based on the measured concentrations, TDM will be performed using the population PK-model. Maximum a posteriori Bayesian estimates of individual PK-parameters were generated, and actual exposures before and after graft infusion were calculated based on these parameters (supplementary Figure S1 for an example of the simulation and TDM studies in an individual patient). Any expected over- or underexposure, both before and after graft infusion, was corrected by amendments in dosing, number of doses and/or the time between the first dose of ATG and graft infusion. In case of large (>25%) dose amendments, follow-up samples were taken to ensure adequate ATG exposures.

Conditioning regimens were given according to national and international protocols. TDM for busulfan was performed in all patients receiving a busulfan-containing conditioning regimen aiming for a cumulative AUC of 85–95 mg*h/mL. Supportive care including selective gut decontamination, other infection prophylaxis, and GvHD prophylaxis was given according to local protocols [13]. GvHD prophylaxis consisted of cyclosporin, aiming for trough levels of 150–250 μg/L, combined with prednisolone 1 mg/kg for 28 days with tapering thereafter. Patients were treated in positive-pressure, particle-free, air-filtered isolation rooms.

Assay

Full details of the assay have been described previously [19]. In summary, patient serum was diluted and incubated with Jurkat T-cells, and labelled with goat-anti-rabbit IgG biotin followed by fluorochrome-labeled streptavidin. Samples, standard curve, quality controls and negative controls were measured using flow cytometry; fluorescence was plotted against standard curves to determine the

concentrations of active ATG in patient sera. The assay was extensively validated using spiked quality control samples and negative controls. Lower limit of quantification was determined to be 0.04 AU/mL.

Outcomes

Efficacy and safety were the primary outcomes of interest for these patients. Efficacy was defined as the target attainment using the intervention of individualized dosing with TDM, and was assessed as the percentage of patients reaching desired exposures of ATG before and after CBT. Safety was assessed as the cumulative incidence of both acute GvHD and rejection. Acute GvHD was classified as per the Glucksberg criteria [20], and analyzed as the incidence of grade 2–4 and grade 3–4 acute GvHD. Rejection was defined as secondary loss of donor chimerism or having nonengraftment at 60 days after transplant.

Secondary outcomes of interest included cumulative incidence of early CD4+ T-cell recovery, defined as a CD4+ T-lymphocyte count of at least 50/μL in two consecutive measurements within 100 days after HCT. This biomarker has been proven in multiple trials to be a strong predictor for therapy related mortality (TRM) and overall survival (OS) [12–14,16,21]. Patients who did not reach 100 days of follow-up were assessed until the date of death. OS was defined as the time from transplant to last day of follow-up or death; EFS as the time from transplant to last day of follow-up or an event, defined as either death or nonengraftment. TRM was defined as death due to any other cause than relapse. Chronic GvHD was scored according to the NIH-criteria [22] and reported as moderate-severe chronic GvHD.

Statistical analysis

Duration of follow-up was defined as the time from HCT to the last visit for patients alive at time of analysis, or to death. Cumulative incidence curves were used for the endpoints of CD4+ immune reconstitution, acute and chronic GvHD and rejection. Survival parameters including OS, EFS and TRM were also analyzed in patients with or without successful CD4+ immune reconstitution. Probabilities of EFS and OS were calculated using the Kaplan-Meier method; a two-sided log- rank test was used for univariable comparisons. Variables in univariable analyses with a P value less than 0·1 were selected for multivariable analyses on the basis of the relatively small population; a P value less than 0·05 was considered statistically significant. Factors included in multivariable analysis included recipient data (age, sex, underlying disease) as well as transplantation details (human leukocyte antigen disparity, patient and donor viral serology status of cytomegalovirus and Epstein-Barr virus). We did not analyze exposures to ATG (both before and after HCT) as a predictor for outcome, as because of the TDM this was not an independent predictor. Statistical analyses were done using R version 4.0.5.

Results

Patients and dosing

A total of 21 patients were included (Table 1). Median age at time of transplant was 5.6 years (range 2 months to 18 years). For most patients it was their first transplant (n = 18; 86%), 3 patients received a second transplant (14%). Most frequent underlying disease included immune deficiencies (n = 13; 62%) and bone marrow failure syndromes (n = 4; 19%). Myeloablative conditioning was used in the majority of patients (n = 17; 81%); 4 patients (19%) received reduced intensity conditioning. The intended median cumulative starting dose of ATG was 15mg/kg (range 8–50 mg/kg) starting median 15 days before HCT (range 12–17 days) and was intended to be given over a median of 5 doses (range 3–10 doses; Table 1).

Primary outcome of interest

Following TDM, dosing was adjusted in 14 patients, which led to an increase in cumulative dose in 3 patients, while the cumulative dose was reduced in 11 patients (Figure 1). Actual cumulative dose of ATG was 13.3 mg/kg (range 6–30 mg/kg), starting 15 days before CBT (range 12–17 days). Desired pre-HCT ATG exposures were reached in 18/21 (87%) patients; 3 patients had slight over-exposure pre-HCT. The desired target post-HCT exposure of 0–10 AU*day/mL was reached in 19/21 (91%) patients; the remainder 2 patients had post-HCT ATG exposures of 11 and 12 AU*day/mL, respectively.

In this high-risk group of patients, the observed rates of rejection and severe acute GvHD were relatively low. The incidence of acute GvHD grade 2–4 was 34% (95% CI 23–45%; Figure 2A), however only 5% (95% CI 0–10%) experienced grade 3–4 acute GvHD (Figure 2A). In multivariable analysis, no predictors for grade 2–4 acute GvHD were found, while higher age was associated with a higher incidence of grade 3–4 acute GvHD. All patients showed neutrophil engraftment at a median of 13 days post-HCT (range 11–31 days). We observed 2 patients (patients 15 and 18 in Table 1) with rejection, both due to late secondary graft loss, making the cumulative incidence of rejection 9% (95% CI 2–16%; Figure 2B). In patient 15, the graft loss was preceded by a cytomegalovirus reactivation. In patient 18, who had HLA antibodies before HCT, no clear cause for rejection was found, in particular no antidonor HLA antibodies were found.

Secondary outcomes of interest

Successful CD4+ IR was observed in 77% (95% confidence interval [CI] 68–86%; Figure 3A); 2 patients died and 2 patients had graft-failure before 100 days; none of these had CD4 IR at the time of event. Both patients with slight overexposure post-HCT reached successful CD4+ IR. Median time to reach successful CD4+ IR was 16.5 days post-HCT (range 6–63 days) in patients meeting the endpoint. There was no significant difference in CD4+ IR when split for the different underlying diagnosis, but the analysis is limited by small numbers. No multivariable predictors for CD4+ IR were identified.

The OS in the cohort was 75% (95% CI 65–85%; Figure 3B). Causes of death were gut GvHD or colitis with refractory sepsis 6 months after HCT (patient 2), encephalopathy 7 months after HCT (patient 8), fungal infection at 5 weeks (patient 10), unknown cause after discharge at 2.5 months after HCT (patient 12), and pulmonary infection or bronchitis obliterans at 9 months (patient 13).

In multivariable analysis, successful CD4+ IR was observed to be the only predictor for OS (hazard rate [HR] 0.073, 95% CI 0.011–0.48, P = 0.0066; supplemental Table S1). Of note, underlying disease was not a predictor for OS in this analysis. All observed deaths were therapy related, making the cumulative incidence of TRM 25% (95% CI 15–35%). Successful CD4+ IR was the only significant multivariable predictor for TRM (HR 0.073, 95% CI 0.013–0.39, P = 0.0025). EFS was 66% (95% CI 56–76%; Figure 3B), with no multivariable predictors identified (the Cox proportional hazard model did not converge for successful CD4+ IR). Cumulative incidence of chronic GvHD was 9% (95% CI 3–15%), with patient-donor CMV disparity being a multivariable predictor for a higher incidence (HR 0.50, 95% CI 0.27–0.95, P = 0.034).

Discussion

We show that high-dose, individualized ATG with TDM is feasible, leads to predictable and accurate exposures to ATG, and is safe in high-risk patients receiving cord blood transplants. In this real-world experience treating a heterogeneous cohort in terms of disease and conditioning regimens, the procedure is successful in preventing severe acute GvHD and rejection, and leads to an acceptable OS in this very high-risk group of patients.

Table 1
Patient and dosing details.

Patient, transplant, and conditioning									*Starting dose of ATG*				*Adjusted dose of ATG*			
Patient	Diagnosis	Age (years)	Body weight (kg)	Baseline lymphocyte counts (x10^9/L)	Transplant	HLA match	CD34+ Cell Dose (10^6 cells/kg)	Conditioning Regimen	Cumulative dose (mg/kg)	Daily dose (mg/kg)	Starting day relative to HCT (days)	Number of doses	Cumulative dose (mg/kg)	Daily dose (mg/kg)	Starting day relative to HCT (days)	Number of doses
1	MDS with prior neuroblastoma	9.6	25	1.2	First	5/6	0.29	BuFluClo	8	2	−13	4	11	3 × 2, 1 × 5	−13	4
2	CVID with cytopenia and colitis	12.3	38	0.3	First	4/6	0.56	BuFlu	8	2	−15	4	15	3 × 2, 3 × 3	−15	6
3	X-ALD	9.1	24	0.1	Second	4/6	0.34	FluTreo	8	2	−12	4	6	3 × 2	−17	3
4	CVID with cytopenia	11.8	44	3.7	First	4/6	2	BuFlu	12	3	−14	4	14	3 × 3, 1 × 5	−14	4
5	Beta thalassemia, AML, 2 previous rejections	5.6	20	0.5	Second	5/6	0.77	BuFluClo	12	2	−15	6	8	4 × 2	−15	4
6	MLD with previous solid tumor	14	45	2.8	First	6/6	0.19	BuFlu	12	2	−14	6	8	4 × 2	−14	4
7	RCC polytransfusee	7.3	35	2.7	First	5/6	0.27	FluTreo	15	3	−15	5	9	3 × 3	−15	3
8	HLH	7.4	28	2.7	First	5/6	0.75	BuFlu	15	3	−12	5	12	4 × 3	−12	4
9	PID with autoinflammation of unknown origin	0.6	6	2	Second	5/6	0.84	BuFlu	20	5	−12	4	15	3 × 5	−12	3
10	SCID with Ruthmund Thompson syndrome	0.5	5	0.9	First	6/6	0.52	FluTreo	20	3.3	−15	6	13.3	4 × 3.333	−15	4
11	PID with autoinflammation of unknown origin	0.5	7	0.5	First	5/6	0.54	BuFlu	25	5	−15	5	20	4 × 5	−15	4
12	HLH	0.3	4	1.3	First	5/6	1.28	BuFlu	25	4.2	−12	6	16.4	4 × 4.1	−12	4
13	Epidermolysis Bullosa	0.8	10	4	First	5/6	0.76	BuFlu	40	5	−15	8	25	5 × 5	−13	5
14	HLH	0.2	3	3.2	First	5/6	1.77	BuFlu	50	5	−14	10	20	4 × 5	−14	4
15	Beta Thalassemia	18	64	0.9	First	4/6	0.4	BuFlu	9	3	−17	3	-	-	-	-
16	AML with HLH	1.3	10	0.5	First	5/6	1.2	BuFluClo	12	3	−14	4	-	-	-	-
17	CGD	13.9	31	1.2	First	4/6	0.37	BuFlu	12	4	−17	3	-	-	-	-
18	Severe aplastic anemia with HLA antibodies	5.6	21	2	First	5/6	0.48	FluCy	12.5	2.5	−15	5	-	-	-	-
19	HLH	2.6	14	2.3	First	5/6	0.87	BuFluEto	20	4	−16	5	-	-	-	-
20	CGD	1	10	4	First	5/6	1.27	BuFlu+TBI	30	5	−15	6	-	-	-	-
21	CGD	1.1	8	5.1	First	6/6	1.25	BuFlu	30	5	−15	6	-	-	-	-

MDS, myelodysplastic syndrome; CVID, combined variable immune deficiency; X-ALD, x-linked adrenoleukodystrophy; AML, acute myeloid leukemia; MLD, metachromatic leukodystrophy; RCC, refractory cytopenia of childhood; HLH, hemophagocytic lymphohistiocytosis; CGD, chronic granulomatous disease; BuFlu, busulfan/fludarabine; BuFluClo, busulfan/fludarabine/clofarabine, FluTreo, fludarabine/treosulfan; FluCy, fludarabine/cyclophosphamide; BuFluEto, busulfan/fludarabine/etoposide; TBI, total body irradiation.

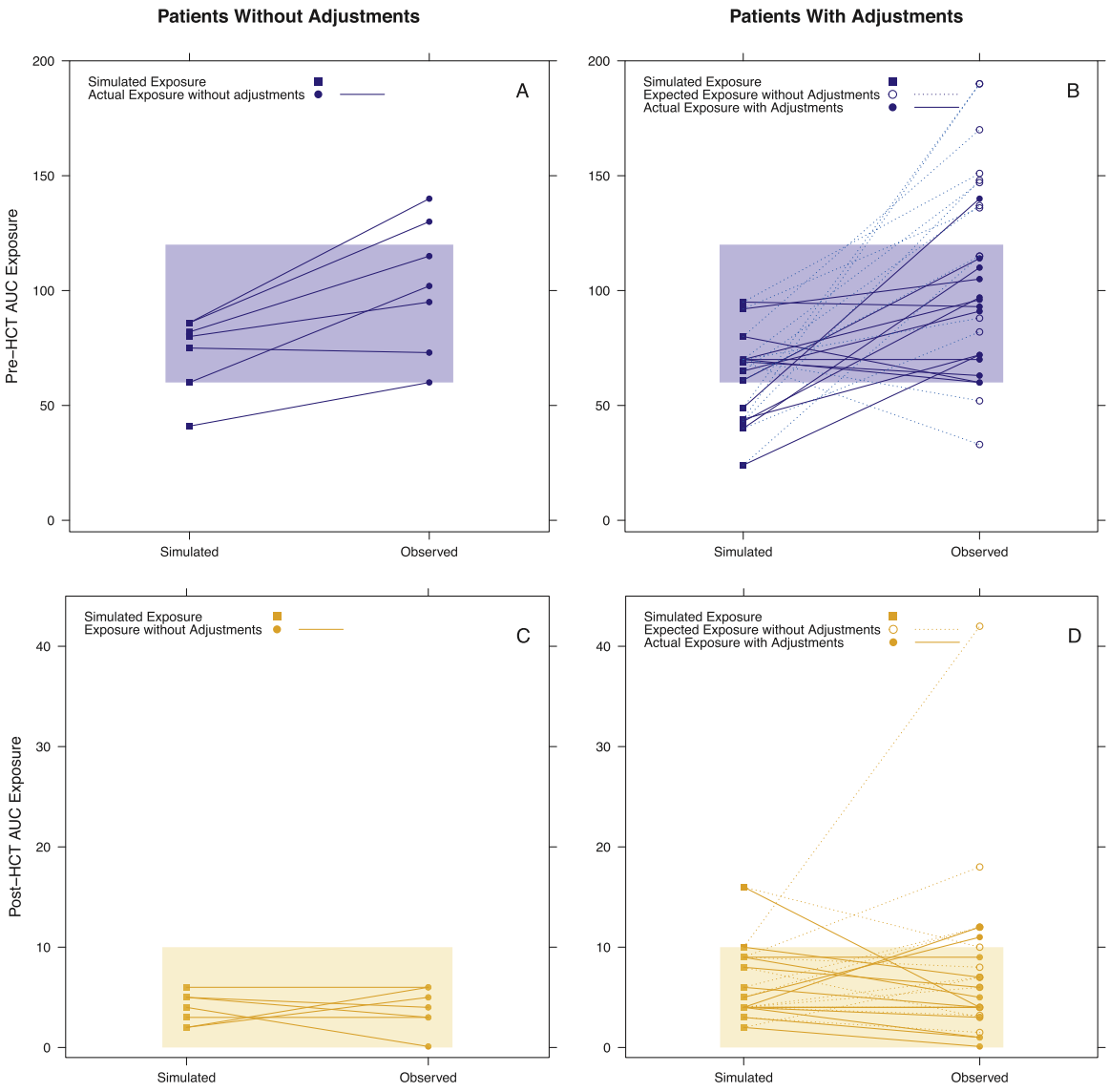

Figure 1. Exposure to ATG before graft infusion (panels A&B) and after graft infusion (panels C&D) for those without dose adjustments (panels A&C) and with dose adjustments (panels B&D). Connected dots represent the simulated exposure and the observed exposure in the same patient (blue: exposure before graft infusion; green: exposure after graft infusion for bone marrow recipients; orange: exposure after graft infusion for cord blood recipients). The solid lines represent actual exposures, the dotted lines the exposures if no dose adjustments based on TDM would take place. Blue areas: optimal exposure before graft infusion (60–120 AU*day/mL); yellow areas: optimal exposure after graft infusion for cord blood recipients (0–16 AU*day/mL).

To our best knowledge, this is the first paper to report on tailored ATG with TDM.

Current studies in the aforementioned categories of patients undergoing HCT show variable outcomes. In non-SCID immune deficiencies the reported survival rates in recent studies are 48% [23], 86% [24] and 85–93% [25,26] in CVID, HLH and CGD, respectively. Nevertheless, we feel that the results of our current study are in line, especially taking into account that we used cord blood as stem cell source. The use of cord blood transplantation in HLH is associated with a lower survival than when using bone marrow grafts (55% [27] versus 86% [24]), while in CGD the survival after cord blood transplant is 62% [26]. In patients with thalassemia major, current survival rates of 93% are reached with bone marrow/peripheral blood, however there are still problems with rejection (nonengraftment [4.2%] and second transplantation [7%]) [28] . Survival rates in unrelated cord blood transplantation in thalassemia in literature vary from 88 to 62% with disease free survival of 74–21% [29,30].

The population PK and the therapeutic window of ATG have been eluded in the previous years, with the main focus on Thymoglobulin [10–13]. The therapeutic window in a cord blood setting based on previous literature was >40 and <10 AU*day/L for pre- and post-HCT ATG exposure, respectively [13,12]. As a high pre-HCT exposure was mainly correlated with prevention of GvHD and rejection, i.e., the main goals in the current setting, we arbitrarily set the desired pre-HCT exposure to 60–120 AU*day/L to ensure adequate effects, while maintaining the exposure of <10 AU*day/mL post-HCT. In previous analyses, we did not identify differences in the optimal ATG exposures to prevent GvHD and rejection based on stem cell source. As such, upfront high dose ATG may also be beneficial when using bone marrow for the same high-risk indications. However, the optimal post-HCT exposure to ATG in bone marrow recipients seems to be less critical in order to ensure adequate T-cell recovery (<50 AU*day/mL as compared to <10 AU*day/mL in cord blood) [13]. Therefore, TDM in a bone marrow setting may prove unnecessary as less precision in dosing is required, even when using upfront high dose ATG.

Clinical application of pharmacokinetic studies for agents used as serotherapy in the setting of allogeneic HCT are infrequently described. Only descriptive PK studies are published for Grafalon

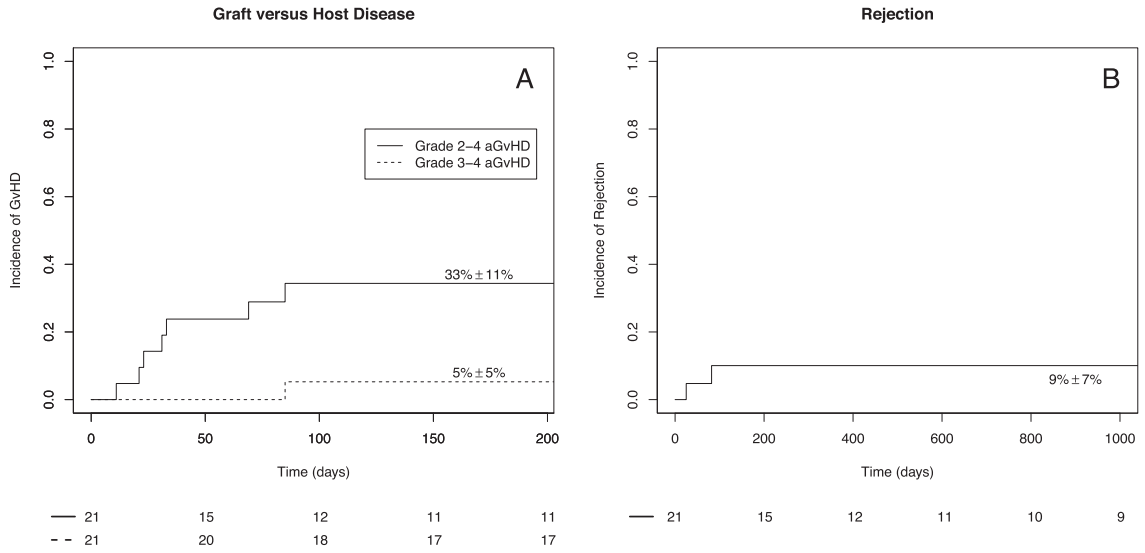

Figure 2. Safety. Panel A: Grade 2–4 acute GvHD (solid lines), grade 3–4 acute GvHD (dashed lines); Panel B: graft failure.

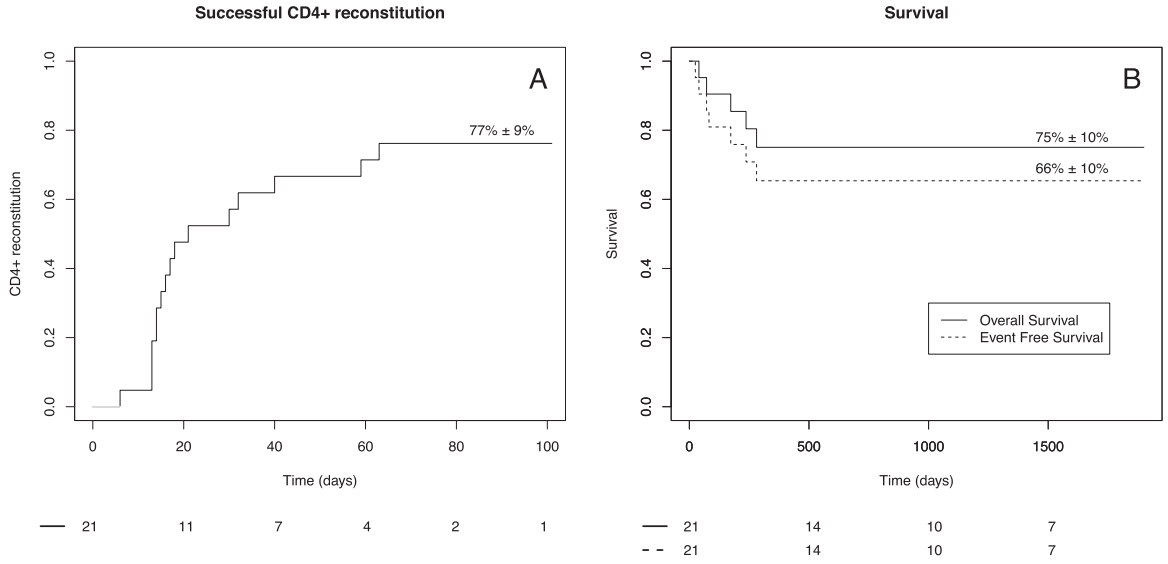

Figure 3. Clinical outcomes. Panel A: Cumulative incidence curve of T-cell recovery (>50/uL CD4+ T-cells before day +100 in 2 consecutive samples). Panel B: Overall survival (solid lines) and Event Free Survival (dashed lines).

[31]. Since different types of ATG are not biosimilar, due to their different production processes, the population PK parameters cannot be extrapolated to other ATGs. For alemtuzumab, a monoclonal anti-CD52 antibody used for the same indication, some studies are available describing the population PK [32–34], the therapeutic window [35,36], and TDM [34]. Although concentrations were only measured well after the full intended dose was given, an extra dose of alemtuzumab was given when patients were to fall below the therapeutic window [34]. In the current study, we employed TDM to correct for over- and underexposure, which ensures both safety and efficacy.

Limitations of this study include the relatively low number of patients treated in this protocol and the heterogeneity of underlying diseases and conditioning regimens. We did however include consecutive patients meeting the criteria for inclusion in this protocol. A limitation of this approach is the applicability of ATG TDM in other transplant centers. Concentrations of the active fraction of ATG need to be measured for TDM, for which one would need a cell-based flow cytometry assay. While these kinds of assays may not be available in all centers, we recently published an elaborate description of our method for measuring active ATG. Furthermore, as ATG is quite stable, centers could ship serum or plasma samples to expert laboratories with validated assays in order to measure ATG. Another option may be the recently proposed LC-MS/MS for ATG [37], but this method still requires clinical validation.

In conclusion, we show that individualized high dose ATG with TDM is feasible and safe for patients in the setting of hyperinflammation prior to CBT setting. We observe high target ATG exposure attainment, and good immune reconstitution (despite very high doses of ATG). This approach is a promising method to improve outcomes in this very high-risk patient group, not only in CB, but also for other graft sources, and should thus be further explored.

Data Sharing

No data can be shared, since patients did not give consent for data sharing.

Declaration of Competing Interest

CL reports honoraria for a lecture from Genzyme (related to this topic). JJB reports honoraria from BlueRock, Avrobio, Sobi, Bluebird bio, Medexus, and Omeros for consulting (not related to this topic) and from Sanofi (related to this topic), and participation on a data safety monitoring board for Advanced Clinical. All other authors declare no competing interests.

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Author Contributions

RA, JJB, CL and SN designed the clinical protocol; AV, MB, JJB, CL were treating phycisians; RA, JJB and CL performed data collection; RA, LE, AL, KK and SN analyzed the data. RA, CL and SN prepared the manuscript. All authors reviewed the manuscript and vouch for the accuracy and completeness of the data and analyses. RA and SN had access to the raw data.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcyt.2024.02.015.

References

[1] Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet 2009;373:1550–61.
[2] Ciurea S, Cao K, Fernandez-Vina M, Kongtim P, Malki M, Fuchs E, et al. The European Society for Blood and Marrow Transplantation (EBMT) consensus guidelines for the detection and treatment of donor specific anti-HLA antibodies (DSA) in haploidentical hematopoietic. Bone Marrow Transpl 2018;53:521–34.
[3] Morin-Zorman S, Loiseau P, Taupin JL, Caillat-Zucman S. Donor-specific anti-HLA antibodies in allogeneic hematopoietic stem cell transplantation. Front Immunol 2016;7:1–6.
[4] Ouachée-Chardin M, Elie C, de Saint Basile G, Le Deist F, Mahlaoui N, Picard C, et al. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single-center report of 48 patients. Pediatrics 2006;117:e743–50.
[5] Baker KS, Filipovich AH, Gross TG, Grossman WJ, Hale GA, Hayashi RJ, et al. Unrelated donor hematopoietic cell transplantation for hemophagocytic lymphohistiocytosis. Bone Marrow Transplant 2008;42:175–80.
[6] Horwitz ME, Barrett AJ, Brown MR, Carter CS, Childs R, Gallin JI, et al. Treatment of chronic granulomatous disease with nonmyeloablative conditioning and a T-cell–depleted hematopoietic allograft. N Engl J Med 2001;344:881–8.
[7] Jacobsohn DA, Duerst R, Tse W, Kletzel M. Reduced intensity haemopoietic stem-cell transplantation for treatment of non-malignant diseases in children. Lancet (London, England) 2004;364:156–62.
[8] Storek J, Mohty M, Boelens JJ. Rabbit anti–T cell globulin in allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2015;21:959–70.
[9] Mohty M. Mechanisms of action of antithymocyte globulin: T-cell depletion and beyond. Leukemia 2007;21:1387–94.
[10] Admiraal R, Nierkens S, de Witte MA, Petersen EJ, Fleurke G, Verrest L, et al. Association between anti-thymocyte globulin exposure and survival outcomes in adult unrelated haemopoietic cell transplantation: a multicentre, retrospective, pharmacodynamic cohort analysis. Lancet Haematol 2017;4:e183–91.
[11] Admiraal R, van Kesteren C, Jol-van der Zijde CM, van Tol MJD, Bartelink IH, Bredius RGM, et al. Population pharmacokinetic modeling of Thymoglobulin® in children receiving allogeneic-hematopoietic cell transplantation (HCT): towards improved survival through individualized dosing. Clin Pharmacokinet 2015;54:435–46.
[12] Admiraal R, Lindemans CA, van Kesteren C, Bierings MB, Versluys AB, Nierkens S, et al. Excellent T-cell reconstitution and survival depend on low ATG exposure after pediatric cord blood transplantation. Blood 2016;128:2734–41.
[13] Admiraal R, van Kesteren C, Jol-van Der Zijde CM, Lankester AC, Bierings MB, Egberts TC, et al. Association between anti-thymocyte globulin exposure and CD4 + immune reconstitution in paediatric haematopoietic cell transplantation: a multicentre , retrospective pharmacodynamic cohort analysis. Lancet Haematol 2015;2:e194–203.
[14] Admiraal R, de Koning C, Lindemans CA, Bierings MB, Wensing AMJ, Versluys AB, et al. Viral reactivations and associated outcomes in context of immune reconstitution after pediatric hematopoietic cell transplantation. J Allergy Clin Immunol 2017;140:1643–50.
[15] Van Roessel I, Prockop S, Klein E, Boulad F, Spitzer B, Kung A, et al. Early CD4+ T cell reconstitution as predictor for outcomes after allogenic hematopoietic cell transplantation. Cytotherapy 2020;22:503–10.
[16] Lakkaraja M, Scordo M, Mauguen A, Cho C, Devlin S, Ruiz JD, et al. Antithymocyte globulin exposure in CD341 T-cell–depleted allogeneic hematopoietic cell transplantation. Blood Adv 2022;6:1054–63.
[17] Scordo M, Bhatt V, Hilden P, Smith M, Thoren K, Cho C, et al. Standard antithymocyte globulin dosing results in poorer outcomes in overexposed patients after ex vivo CD34+ selected allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2019;25:1526–35.
[18] Admiraal R, Nierkens S, Bierings MB, Bredius RGM, Van Vliet I, Jiang Y, et al. Individualised dosing of anti-thymocyte globulin in paediatric unrelated allogeneic haematopoietic stem-cell transplantation (PARACHUTE): a single-arm , phase 2 clinical trial. Lancet Haematol 2022;9:e111–20.
[19] Meesters-Ensing JI, Admiraal R, Ebskamp L, Lacna A, Boelens JJ, Lindemans CA, et al. Therapeutic drug monitoring of anti-thymocyte globulin in allogeneic stem cell transplantation: proof of concept. Front Pharmacol 2022;13:1–8.
[20] Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 1974;18:295–304.
[21] de Koning C, Prockop S, van Roessel I, Kernan N, Klein E, Langenhorst J, et al. CD4+ T-cell reconstitution predicts survival outcomes after acute graft-versus-host-disease: a dual-center validation. Blood 2021;137:848–55.
[22] Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005;11:945–56.
[23] Wehr C, Gennery AR, Lindemans C, Schulz A, Hoenig M, Marks R, et al. Multicenter experience in hematopoietic stem cell transplantation for serious complications of common variable immunodeficiency. J Allergy Clin Immunol 2015;135:988–997.e6.
[24] Greental Ness Y, Kuperman AA, Stein J, Yacobovich J, Even-Or E, Zaidman I, et al. Improved transplant outcomes with myeloablative conditioning for hemophagocytic lymphohistiocytosis in HLA-matched and mismatched donors: a national multicenter retrospective study. Bone Marrow Transplant 2021;56:2088–96.
[25] Güngör T, Teira P, Slatter M, Stussi G, Stepensky P, Moshous D, et al. Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. Lancet 2014;383:436–48.
[26] Chiesa R, Wang J, Blok HJ, Hazelaar S, Neven B, Moshous D, et al. Hematopoietic cell transplantation in chronic granulomatous disease: a study of 712 children and adults. Blood 2020;136:1201–11.
[27] Furtado-Silva JM, Paviglianiti A, Ruggeri A, Boelens JJ, Veys P, Ahmari AA, et al. Risk factors affecting outcome of unrelated cord blood transplantation for children with familial haemophagocytic lymphohistiocytosis. Br J Haematol 2019;184:397–404.
[28] Lüftinger R, Zubarovskaya N, Galimard JE, Cseh A, Salzer E, Locatelli F, et al. Busulfan–fludarabine- or treosulfan–fludarabine-based myeloablative conditioning for children with thalassemia major. Ann Hematol 2022;101:655–65.
[29] Ruggeri A, Eapen M, Scaravadou A, Cairo MS, Bhatia M, Kurtzberg J, et al. Umbilical cord blood transplantation for children with thalassemia and sickle cell disease. Biol Blood Marrow Transplant 2011;17:1375–82.
[30] Jaing TH, Hung IJ, Yang CP, Chen SH, Chung HT, Tsay PK, et al. Unrelated cord blood transplantation for thalassaemia: a single-institution experience of 35 patients. Bone Marrow Transplant 2012;47:33–9.
[31] Oostenbrink LVE, Jol-Van Der Zijde CM, Kielsen K, Jansen-Hoogendijk AM, Ifversen M, Müller KG, et al. Differential elimination of anti-thymocyte globulin of Fresenius and Genzyme impacts T-cell reconstitution after hematopoietic stem cell transplantation. Front Immunol 2019;10:1–11.
[32] Admiraal R, Jol-van der Zijde C, Furtado Silva J, Knibbe C, Lankester A, Boelens J, et al. Population pharmacokinetics of alemtuzumab (Campath) in pediatric hematopoietic cell transplantation: towards individualized dosing to improve outcome. Clinical Pharmacokinetics 2019;58:1609–20.
[33] Mould DR, Baumann A, Kuhlmann J, Keating MJ, Weitman S, Hillmen P, et al. Population pharmacokinetics-pharmacodynamics of alemtuzumab (Campath) in patients with chronic lymphocytic leukaemia and its link to treatment response. Br J Clin Pharmacol 2007;64:278–91.
[34] Dong M, Emoto C, Fukuda T, Arnold DE, Mehta PA, Marsh RA, et al. Model-informed precision dosing for alemtuzumab in paediatric and young adult patients undergoing allogeneic haematopoietic cell transplantation. Br J Clin Pharm 2022;88:248–59.
[35] Marsh RA, Lane A, Mehta PA, Neumeier L, Jodele S, Davies SM, et al. Alemtuzumab levels impact acute GVHD, mixed chimerism, and lymphocyte recovery following alemtuzumab, fludarabine, and melphalan RIC HCT. Blood 2016;127:503–13.
[36] Chandra S, Chandrakasan S, Dávila Saldaña BJ, Bleesing JJ, Jordan MB, Kumar AR, et al. Experience with a reduced toxicity allogeneic transplant regimen for non-CGD primary immune deficiencies requiring myeloablation. J Clin Immunol 2021;41:89–98.
[37] El Amrani M, Admiraal R, Willaert L, Ebskamp-van Raaij LJC, Lacna AM, Hack CE, et al. Quantification of T cell binding polyclonal rabbit anti-thymocyte globulin in human plasma with liquid chromatography tandem-mass spectrometry. AAPS J 2020;22:43. https://doi.org/10.1208/s12248-020-0419-6.