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ORIGINAL ARTICLE

Graft Versus Host Disease Following HLA-Matched Sibling Donor Compared with Matched Related Donor for Hematopoietic Stem Cell Transplantation for the Treatment of Severe Combined Immunodeficiency Disease

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Abstract

Background One of the limiting factors for successful hematopoietic stem cell transplantation (HSCT) is graft versus host disease (GVHD). The EBMT/ESID guidelines for HSCT in severe combined immunodeficiency (SCID) recommend no GVHD prophylaxis for a matched sibling donor (MSD).

Objective To determine the risk of GVHD in MSD HSCT for SCID patients compared to matched related donor (MRD).

Methods This retrospective cohort study compares MSD with MRD and the outcome of GVHD in all SCID patients who underwent HSCT between 1993 and 2013. All statistical analyses were done using IBM SPSS statistics software.

Results One hundred forty-five SCID patients underwent 152 HSCTs while 82 (54%) received GVHD prophylaxis. GVHD occurred in 48 patients (31.5%); 20/48 (42%) had GVHD prophylaxis compared to 28/48 (58%) that did not, $P = 0.022$. Acute GVHD occurred at a higher trend in MSD, 37/120 (30.8%), compared to MRD, 6/32 (18.8%), $P = 0.17$. We also analyzed the outcome according to the period of HSCT. The first period was 1993 to 2003, 48 HSCTs, 43 MSD, 5 MRD; all patients had GVHD prophylaxis, and there was no difference in GVHD. The second period was 2004 to 2013: of 104 HSCTs, 77 had MSD and 27 had MRD; GVHD prophylaxis was used in 22.1% of MSD and 63% of MRD, $P = 0.000$. GVHD was significantly higher in the MSD (40.2%) compared to MRD (18.5%) patients, $P = 0.041$.

Conclusion GVHD prophylaxis in MSD transplant should be considered in SCID patients.

Keywords Primary immunodeficiency diseases · Severe combined immunodeficiency · Hematopoietic stem cell transplantation · Graft versus host disease · Cyclosporine

Introduction

Severe combined immunodeficiency (SCID) is a heterogeneous group of inherited diseases characterized by a substantial defect in T-cell number and function. SCID can also be associated with a defect in B-cells, natural killer (NK) cells, or both [1, 2]. Patients with classical SCID usually die during the first year of life unless they undergo hematopoietic stem cell transplantation (HSCT) [3]. Gene therapy and enzyme replacement therapy are therapeutic options for some SCID patients; however, HSCT is still the most widely available modality for a curative immune reconstitution [4]. One of the limiting factors for a successful HSCT is graft versus host disease (GVHD) [5]. The incidence of acute GVHD

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(aGVHD) is 10–80%, depending upon the risk factors present [6]. Human leukocyte antigen (HLA) compatibility is the most important risk factor for the development of GVHD. A matched sibling donor (MSD) followed by a matched related donor (MRD) are first choice donor sources for stem cells in SCID patients because of HLA compatibility and rapid donor availability. Finding an MSD or MRD is not uncommon in a population with a high consanguinity rate such as in Saudi Arabia [7, 8]. Therefore, both types of donors and the outcome of GVHD can be compared in our population. The EBMT/ESID guidelines for HSCT from an MSD in SCID patients recommend no GVHD prophylaxis [9]; however, the incidence of acute GVHD in SCID receiving HSCT from an MSD is between 23 and 50% [10, 11]. In addition, limited data are available regarding GVHD in MSD post-HSCT in SCID patients (11–16), and most previous studies are limited by small numbers of patients. Moreover, no consensus has been reached regarding GVHD prophylaxis used for patients in these studies, where the use of GVHD prophylaxis ranges from 0 to 75% of the patients. In the two largest multicenter studies by Pai et al. [11] from North America and Dvorak et al. [12] from North America and Europe, the number of MSD patients were 32 and 63, respectively, and GVHD prophylaxis was used in 75% and 40% of the patients, respectively. The incidence of acute GVHD was 23% in the study by Pai et al. [11] and 33% in the study by Dvorak et al. [12]. Although the study by Pai et al. had the largest total number of SCID patients (# 240) who underwent HSCT, MSD and MRD were used as donors in only 32 and 8 patients, respectively [11]. GVHD prophylaxis in this study was used in 75% and 88% for MSD and MRD patients, respectively [11]. Additionally, in the Pai et al. study, the GVHD rate did not differ significantly among the recipients of grafts from MSD, MRD, and recipients of grafts from other donors (T cell–depleted grafts from mismatched related donors or cord blood donors). Moreover, in other cohort studies including only 16, 13, 7, and 5 patients, the number of SCID patients who underwent HSCT from an MSD or MRD was too small to draw a conclusion [13–16]. The primary objective of this study was to determine the incidence, severity, and outcome of GVHD in SCID patients post-HSCT using MSD and MRD donors from a single center. The secondary objective was to determine the relationship of multiple independent variables as potential risk factors for GVHD outcome.

Materials and Methods

This study was a retrospective review of medical records and the bone marrow transplant central data unit. The study includes all SCID patients who underwent HSCT from MSD or MRD at King Faisal Specialist Hospital and Research Center (KFSHRC), Riyadh, Saudi Arabia, between 1993 and 2013. The central data unit contributes data on allogeneic transplants to the European Group for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplantation Research (CIBMTR). SCID was defined according to the criteria by the primary immunodeficiency treatment consortium experience in the USA [1]. aGVHD was defined as grade I, II–IV, or III–IV per the Consensus guidelines [17]. HLA matching was determined for all donors and recipients by serology prior to 1996 and by molecular DNA typing; low-resolution class I was from 2005 and high-resolution class II was from 1996. MSD donors were defined as HLA-identical sibling donors, and MRD donors as HLA-identical nonsibling family donors. Stem cells sources were from the bone marrow for all HSCT except for four HSCTs where the source was peripheral blood in three and sibling cord in one patient. The stem cells from the bone marrow donors were RBC or plasma depleted depending on ABO mismatch, and otherwise were unmanipulated or T cell depleted. The study was approved by the institutional research review board.

Statistical Analysis

The analyses included descriptive statistics to calculate the mean and standard deviation for numeric variables (age, age at symptoms onset, age at diagnosis, age of HSCT, and time from diagnosis to HSCT); frequencies and percents for categorical variables (gender, pre-HSCT viral infections, GVHD prophylaxis, conditioning, graft evaluation, and the presence or absence of GVHD diagnosis and mortality); and comparisons between both groups (MSD vs MRD) by a Student's *t* test for continuous variables and a chi-squared test or a Fisher's exact test, as appropriate, for categorical variables. Additionally, analysis with a 10-year cutoff for two different periods, 1993 to 2003 and 2004 to 2013, was undertaken. All tests were two-sided and the threshold for statistical significance was set to $P < .05$. Odds ratios were calculated, and their respective 95% CIs are presented. Risk factors were identified and added in a univariate/multivariate setting using Logistic regression analysis was used to predict the probability of occurrence of GVHD. All statistical analysis was carried out using IBM SPSS statistic software for Windows, version 20.

Results

Patient Characteristics

One hundred forty-five SCID patients who underwent 152 HSCTs were eligible for analysis. Male patients were 49.7% of the patient population, the mean age of symptoms onset was 2.9 months, and the mean age of diagnosis was 7.39 months. The pre-HSCT CMV and EBV viremia were

present in 12.4% and 4.1% of the patients, respectively. BCGitis occurred in 33.8% of the patients and was localized in 37% and disseminated in 63%. The predominant SCID phenotype was T-B-NK+ in 57.9% of the patients. Both groups (MSD and MRD) had comparable demographic characteristics (Table 1).

Transplantation Characteristics

Of the 152 HSCTs, 120 (79%) were from MSD and 32 (21%) were from MRD donors. Six patients had two HSCTs and one patient had three HSCTs. In the MSD, the same gender donor was used in 45% of the HSCT. The MRD was a father, a mother, an uncle, a cousin, and an aunt at a rate of 10, 10, 9, 2, and 1 HSCT, respectively. The mean age at which the patients underwent HSCT was 12.7 months. Both the mean age at HSCT and mean time to HSCT were higher in MRD compared to MSD; however, this difference was not a significant (Table 1). Overall, 82 HSCTs (53.3%) had GVHD prophylaxis, 60 were in the MSD, and 22 in the MRD group (Table 1). The GVHD prophylaxis was cyclosporine alone, cyclosporine plus methotrexate, cyclosporine plus mycophenolate, or cyclosporine plus steroids in 59, 19, 2, and 2 HSCT cases, respectively. Chemotherapy conditioning was used in 58 HSCTs (38%). MRD HSCTs were more likely to receive chemotherapy conditioning (56.2% vs 33.3% $p = 0.029$). The chemotherapy was myeloablative (busulfan and cyclophosphamide) for 45 HSCTs (35 in MSD and 10 in MRD) and reduced intensity conditioning (fludarabine, melphalan, and ATG) in 13 HSCTs (5 in MSD and 8 in MRD). The conditioning regimen and the GVHD prophylaxis were decided as per the EBMT/ESID guidelines and as permitted by the clinical status of the patient.

GVHD

All types of GVHD were diagnosed in 48 out of the 152 total HSCTs (31.6%). The MSD group showed a trend for more GVHD diagnoses than MRD; however, this difference was not significant (34.2% vs 21.9% $P = 0.18$) (95% CI 0.58 to 3.21). Out of the 48 GVHD, 20 (42%) received GVHD prophylaxis and 28 (58%) did not, $P = 0.022$. Moreover, a trend toward more acute GVHD (aGVHD) was seen in HSCT from MSD compared to MRD (30.8% vs 18.8%, $P = 0.17$)

Table 1 Patient characteristics for 145 children with severe combined immunodeficiency who received either MSD or MRD HSCT

Variable	Total (*n* 145)	MSD (*n* 114)	MRD (*n* 31)	*P* value
Pretransplantation characteristics				
Male number (%)	72 (49.7)	58 (50.9)	14 (45.2)	0.572*
Mean age of symptoms onset (months) (SD)	2.9 (8.1)	2.82 (7.4)	3.29 (10.4)	0.508**
Mean age of diagnosis (months) (SD)	7.39 (15.5)	7.37 (16.1)	6.60 (11.4)	0.711**
Pre-HSCT CMV infection number (%)	18 (12.4)	14 (12.3)	4 (12.9)	1***
Pre-HSCT EBV infection number (%)	6 (4.1)	3 (2.6)	3 (9.7)	0.11***
Pre-HSCT BCGitis	49 (33.8)	40 (35.1)	9 (29)	0.527*
SCID phenotype, *n* (%)				0.84***
T-B-NK+	84 (57.9)	63 (55.3)	21 (67.6)	
T-B+NK+	18 (12.4)	16 (14)	2 (6.5)	
T-B+NK-	1 (0.7)	1 (0.9)	0	
Leaky SCID	10 (6.9)	8 (7)	2(6.5)	
Omenn syndrome	12(8.3)	9(7.9)	3 (9.7)	
ADA deficiency	16 (11)	13 (11.4)	3 (9.7)	
ZAP-70 deficiency	4 (2.8)	4 (3.5)	0	
Transplantation characteristics,				
HSCT number (%)	152	120 (79)	32 (21)	
Mean age by months of HSCT (SD)	12.7(25.1)	12.5(26.1)	13.64(20.8)	0.981**
Mean time by months from diagnosis to HSCT (SD)	3.75(8.7)	3.42 (9.2)	4.95 (7.2)	0.376**
GVHD prophylaxis number (%)	82 (54)	60 (50)	22 (68.8)	0.059*
Conditioning (%)	58 (38)	40 (33.3)	18 (56.2)	0.017*

ADA adenosine deaminase

*Chi-squared

***t* test

***Fisher's exact test

(Table 2). Grade I aGVHD was diagnosed in 14 (11.7%) of the 120 MSD compared to 3 (9.4%) of the MRD, whereas grade II-IV was diagnosed in 17 (14.2%) of the MSD compared to 3 (9.4%) of the MRD. Grade III–IV was only diagnosed in MSD in 6 patients (5%). Chronic GVHD (cGVHD) was slightly higher in MSD compared to MRD (Table 2). The most common site of GVHD was the skin followed by the gut, liver and other sites (lung, eye) at rates of 87%, 36%, 10% and 10%, respectively. Other secondary outcomes, such as engraftment evaluation, mortality during the first 100 days and overall survival, showed no significant differences between the MSD and MRD patients (Table 2). Maternal cell engraftment (MCE) detected by a short tandem repeat (STR) was positive in 7 out of the 23 patients who had the test. Six patients with positive MCE were in the MSD group and one was in the MRD group. Only 2/7 patients with MCE had aGVHD. In the MSD group, no difference was detected in GVHD incidence between the same and mismatch gender HSCT (37% vs 31.8%, $P = 0.54$). In the MRD group, GVHD was diagnosed when the donor was a father, a mother, and an aunt, in 3, 3, and 1 HSCT, respectively. Further analysis of the 41 patients who developed any grade GVHD showed no significant difference whether the patients received no conditioning and no prophylaxis, conditioning, prophylaxis, or with no conditioning and prophylaxis at a rate of 44.1%, 22, 5, and 28.6, respectively ($P = 0.071$).

Secondary Analysis for Two Time Periods

In a secondary group analysis, we compared both MSD and MRD during two different time periods: the first time period (1993 to 2003) had 48 HSCTs with 43 in the MSD and 5 in the MRD group. During this period, all patients received GVHD prophylaxis and no significant differences were detected in GVHD in both groups (Table 3). During the second time period (2004 to 2013), there were 104 HSCTs, with 77 in the MSD and 27 in the MRD group. During this period, the use of GVHD prophylaxis was much less in the MSD compared to the MRD group (22.1% vs 63%, $P = 0.000$). The primary outcome of GVHD was significantly increasingly diagnosed in the MSD group (40.2%), with an odds ratio of 1.31 (95% CI 1.081 to 1.61), compared to the MRD group (18.5%), with an odds ratio of 0.30 (95% CI 0.078 to 1.17), $P = 0.041$ (Table 3). In addition, a trend was observed for more aGVHD in the MSD compared to MRD group (37.7% vs 18.5% $P = 0.068$); however, no significant differences were detected in cGVHD, engraftment, or mortality during the first 100 days and overall survival between both groups (Table 3).

Upon logistic regression analysis, GVHD prophylaxis (independent variables) was significantly associated with a 2.2 times benefit in aGVHD (CI 95% 1.11–4.49, $P = 0.023$). Other independent variables (sex, HLA type, CMV, EBV, BCGitis, conditioning, age at HSCT, and SCID phenotype) that may also influence GVHD were not significant (Table 4). Among the 49 patients with BCGitis, GVHD was diagnosed in 17 patients (35%). The risk of GVHD was not significantly different in patients with BCGitis compared to patients without BCGitis (35% vs 31%, $P = 0.67$).

Discussion

An HLA-matched sibling followed by a matched related donor are the first-choice donors for HSCT in SCID patients. This study demonstrates a trend toward a higher rate of GVHD in MSD compared to MRD HSCT for SCID patients. This finding was associated with the use of GVHD prophylaxis confirmed in a univariate analysis, which was independent of the HLA type via multivariate analysis (Table 4). Consistently, a recent study by Pai et al. [11] reported no

Table 2 Primary and secondary outcomes

Variable	Total HSCT (*n* 152)	MSD (*n* 120)	MRD (*n* 32)	*P* value
GVHD number (%)	48 (31.6)	41 (34.2)	7 (21.9)	0.18*
Acute GVHD				
All grade (%)	43 (28.3)	37 (30.8)	6 (18.8)	0.17*
Grade I (%)	17 (11.1)	14(11.7)	3 (9.4)	1**
Grade II–IV (%)	20 (13.1)	17(14.2)	3 (9.4)	0.57**
Grade III–IV (%)	6 (3.9)	6 (5)	0	0.34**
Chronic GVHD (%)	14(9.2)	11(7.2)	3 (9.4)	0.97*
Engraftment (%)	128 (84.2)	101 (84.2)	27 (84.4)	0.921**
Nonengraftment (%)	12 (7.9)	10 (8.3)	2 (6.2)	
Patient deaths *** (%)	12 (7.9)	9 (7.5)	3 (9.4)	
Overall survival (%)	117 (80.7)	90 (78.9)	27 (87.1)	0.308*

*Chi-squared

**Fisher's exact test

***Died during the first 100 days before complete engraftment evaluation

Table 3 Comparing the outcome of GVHD in MSD and MRD HSCT in SCID patients transplanted within two different time periods

Variable	1993 to 2003 (n 48)		*P* value	2004 to 2013 (n 104)		*P* value
	MSD n 43	MRD n 5		MSD n 77	MRD n 27	
GVHD prophylaxis (%)	43 (100)	5 (100)		17 (22.1)	17 (63)	0.000*
Conditioning (%)	28 (65)	4 (80)	0.65**	12 (15.5)	14 (51.8)	0.0002*
GVHD (%)	10 (23.3)	2 (40)	0.587**	31 (40.2)	5 (18.5)	0.041*
Acute GVHD						
All grade (%)	8 (18.6)	1 (20)	1**	29 (37.7)	5(18.5)	0.068*
Grade I (%)	4 (9.3)	0	1**	10 (13)	3 (11.1)	1**
Grade II–IV (%)	4 (9.3)	1 (20)	0.43**	13 (16.9)	2 (7.4)	0.34**
Grade III–IV (%)	0	0		6 (7.8)	0	0.33**
Chronic GVHD (%)	2 (4.7)	1 (20)	0.28**	9 (11.7)	2 (7.4)	0.72*
Engraftment (%)	35 (81.4)	4 (80)	0.423**	66 (85.7)	23 (85.1)	1**
Nonengraftment (%)	5 (11.6)	0		5 (6.5)	2 (7.4)	
Died patients*** (%)	3 (7)	1 (20)		6 (7.7)	2 (7.4)	
Overall survival (%)	33 (82.5)	4 (80)	1**	57 (77)	23 (88)	0.20 *

*Chi-squared

**Fisher's exact test

***Died during the first 100 days before completion of the engraftment evaluation

significant differences in GVHD according to donor type. No type or grade of GVHD is uncommon post-HSCT in SCID patients, even in the presence of an MSD donor, as our data showed a cumulative incidence of 31.5%, which is similar to the previously reported incidences in two multicenter studies by Pai et al. [11] and Dvorak et al. [12] of 31% and 37%, respectively. The majority of transplant centers in the presence of a full matched sibling donor do not precondition typical SCID patients with chemotherapy, as the rate of rejection is very low [4]; however, no consensus has been reached with regard to GVHD prophylaxis. The use of GVHD prophylaxis ranged from 0 to 100% in MSD transplants from different centers [11–15]. In our data, GVHD prophylaxis was used in 100% of patients during the first period (1993–2003) and decreased to 22.1% during the second period (2004–2013) in MSD HSCT for SCID. We also found a decrease in the use of chemotherapy conditioning between the periods (65% vs 16%) (Table 3). Moreover, GVHD prophylaxis during the second period was more likely to be used in MRD compared to MSD (63% vs 22.1%, respectively, $P = 0.000$). This difference in the use of GVHD prophylaxis resulted in more patients having GVHD in the MSD group (40.2%) compared to MRD (18.5%), $P = 0.041$. GVHD prophylaxis in our study was associated with a 2.2 times benefit to prevent GVHD (Table 4). We could not identify potential risk factors, e.g., HLA type, pretransplant infections, conditioning, or SCID phenotype, associated with GVHD, which may be due to the sample size. A larger sample size from multicenter data is needed for future studies. Grade II–IV aGVHD was seen in 14.2% of patients, in contrast to 23% and 22% in the MSD

Table 4 Univariate and multivariate analysis for aGVHD and associated factors

Independent variable	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Gender	0.95	0.47–1.92	0.90	–	–	–
Age at HSCT	1	0.98–1.01	0.99	–	–	–
HLA type	0.54	0.21–1.35	0.18	0.60	0.23–1.54	0.29
CMV	0.95	0.33–2.71	0.92	–	–	–
EBV	2.47	0.28–21.7	0.41	–	–	–
BCGitis	0.85	0.41–1.77	0.67	–	–	–
GVHD prophylaxis	2.24	1.11–4.49	*0.023*	2.13	1.05–4.31	0.034
Conditioning	0.56	0.27–1.16	0.12	–	–	–
SCID subclass	0.84	0.69–1.03	0.10	–	–	–

patient cohorts from Pai et al. and Dvorak et al., respectively. This difference might be explained by the predominant NK+ SCID phenotype in our cohort. NK cell counts were shown to be inversely correlated with the incidence of grade II–IV aGVHD [18]; however, grade III–IV was seen in 5% of the patients, similar to other MSD HSCT of SCID cohorts [11, 12]. GVHD is known to be associated with mortality and morbidity, and our data showed that 25% of the patients who died posttransplantation had GVHD. This finding was also previously shown in a European report focusing on the long-term results of HSCT in primary immunodeficiency patients showing that GVHD was the main cause of death in 25% of the cases [19]. The SCID phenotype in our dataset was not found to be a significant risk factor in the development of GVHD. Of the patients in our study, 66% had a T-B-NK+/Omenn syndrome phenotype. This SCID phenotype has a heterogeneous molecular basis. The abundant NK-cell numbers of the recipient type may affect posttransplant immune reconstitution; however, their role remains to be fully defined [20], and therefore, the results might not be applicable to other types of typical SCID in other populations. This study is limited by its nature as a retrospective analysis of the BMT database registry. Multiple confounding factors that may influence the GVHD outcome could not be analyzed, although this study had the largest number of patients with SCID who underwent MSD HSCT. Nevertheless, a multicenter controlled prospective study with a larger sample size will allow for a more robust analysis.

In conclusion, this study provides additional analyses on the incidence of GVHD in MSD and MRD HSCT for SCID patients. This incidence is modified primarily by the use of GVHD prophylaxis and independent of the HLA type. Finally, contrary to the EBMT/ESID guidelines, SCID patients may require additional consideration regarding GVHD prophylaxis even when MSD donors are used.

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Compliance with Ethical Standards

The study was approved by the institutional research review board.

Conflict of Interest The authors declare that they have no conflicts of interest.

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