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Long Term Follow-Up of the Patients with Severe Combined Immunodeficiency After Hematopoietic Stem Cell Transplantation: A Single-Center Study

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ABSTRACT

Background: We aimed to evaluate hematopoietic stem cell transplantation (HSCT) related outcomes of patients with severe combined immunodeficiency (SCID).

Methods: We retrospectively collected data from SCID patients who were diagnosed, followed up and survived at least 2 years after HSCT.

Results: Forty four SCID patients were included in the study. Median age of HSCT and follow-up period after HSCT were 7.1 months and 8.7 years, respectively. Human leukocyte antigen (HLA) identical donors were used in 77.3% (n = 34) of the patients (23 siblings, six fathers, two mothers, three extended family donors), HLA 1–2 mismatched family donors in 11.3% (n = 5), and haploidentical family donors in 11.3% (n = 5). CD3 and CD19 counts were normal in more than 90% and in 45.4% at last follow-up, respectively. Intravenous immunoglobulin (IVIG) could be stopped in 72.7% (n = 32) after HSCT. B+ SCID patients had better CD19 counts than B- ($p < .001$). T cell numbers, lymphocyte proliferation, IVIG need, immunoglobulin levels, antibody responses did not differ among B- and B+ immunophenotypes. Acute graft-versus-host disease (GVHD) was less in bone marrow transplanted patients (19.4%) than peripheral stem cell (58.3%) transplanted ones ($p = .024$). There was no correlation between age at transplantation and immune reconstitution. At the last follow-up, 70.2% and 78.3% of the patients had body weight and height above 3rd percentile, respectively.

Conclusion: The immune reconstitution and the growth were normal in the majority of SCID patients after HSCT. It may be rational to use bone marrow instead of peripheral stem cell, as acute GVHD was less in bone marrow transplanted patients.

KEYWORDS
Severe combined immunodeficiency; hematopoietic stem cell transplantation; immune reconstitution

Introduction

Severe combined immunodeficiency (SCID) is a group of diseases characterized by impaired development and function of T and B cells caused by various gene defects (Buckley 2011; Picard et al. 2015). Immune system reconstitution is the only curative treatment of SCID which can be achieved by hematopoietic stem cell transplantation

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(HSCT) or gene therapy (Buckley 2010; Qasim et al. 2004). Patients without definitive therapy die due to recurrent and severe course of opportunistic infections in earlier months of life. Therefore, SCID is accepted as a pediatric emergency (Rosen 1997).

The outcome of HSCT may be related to patients' age, infections at the time of HSCT, the degree of human leukocyte antigen (HLA) compatibility of the donor, and genotype of SCID (Buckley 2011; Myers et al. 2002; Pai et al. 2014).

In this study; we evaluated HSCT-related outcome including growth and immune reconstitution of SCID patients at least after 2 years of follow-up.

Materials and methods

Among 86 SCID patients who had received a HSCT at Hacettepe University Children's Hospital, Department of Pediatric Immunology in about 20 years period (June 1994, and May 2013), 44 patients who have survived at least 2 years after HSCT were evaluated.

Registered data (age at admission and transplantation; complaints on admission; family history; anthropometric measurements at admission and last follow-up; donor types; degree of HLA match; stem cell source; donors' ages; conditioning regimen; graft-versus-host disease (GVHD) prophylaxis; acute and chronic GVHD history; underlying genetic defect; absolute lymphocyte counts, T and B cell subsets, immunoglobulin (Ig) levels at admission and last follow-up; lymphocyte proliferation with mitogens and intravenous immunoglobulin (IVIG) therapy cessation ratios at last follow-up; anti-HBs, antibody response to pneumococcal vaccine and isohemagglutinins after cessation of IVIG) were evaluated.

Immune phenotypes of the patients were categorized as B+ (B cell count, >400/mm^3) or B- (<50/mm^3) and NK+ (Natural killer cell count, >100/mm^3) or NK- (<40/mm^3) (Comans-Bitter et al. 1997).

Lymphocyte subset counts, Ig levels and lymphocyte proliferation tests were evaluated by comparing to age-matched controls.

Statistical analysis was performed using the IBM SPSS 22.0 software. Numerical variables were summarized by mean ± standard deviation or median (minimum-maximum) as appropriate. Normality of the numerical variables was determined by Shapiro-Wilks test. Because numerical variables in the dataset have skewed distribution, nonparametric Kruskal-Wallis and Mann-Whitney U test were used to compare independent groups. Differences between groups in terms of categorical variables were examined by the Chi-square test or Fisher's exact test. *P* value less than 0.05 was considered statistically significant.

Results

Clinical

Forty four patients (19 females, 25 males) were evaluated in this study. Characteristics of the patients on admission are shown in Table 1. Median age on admission and at HSCT were 5 months (0–25 months) and 7.1 months (23 days-32.8 months) respectively. Median follow-up period after HSCT was 8.7 years (2–21 years) and median age at the last follow-up was 9.1 years (3.1–21.6 years).

Table 1. Characteristics of the patients.

Characteristics	All patients (n = 44)
Demographic characteristics	
*Sex — no. (%)	
Male	25 (56.8%)
Female	19 (43.2%)
*Age at transplantation — no. (%)	
≤6 months	19 (43.2%)
>6 months	25 (56.8%)
*Parental consanguinity — no. (%)	37 (84.1%)
*Post-HSCT follow-up time	
≥10 years	19 (43.2%)
5–10 years	12 (27.3%)
2–5 years	13 (29.5%)
Complaints and clinical findings on admission — no. (%)	
Chronic diarrhea	24 (54.5%)
Oral candidiasis	23 (52.3%)
Recurrent pneumonia	22 (50%)
Malnutrition	22 (50%)
Family history (for SCID)	10 (22.7%)
Rash	6 (13.6%)
Failure to thrive	2 (4.5%)
Urinary tract infection	2 (4.5%)
Otitis media	1 (2.3%)
Immunological characteristics on admission	
*Cell phenotype — no. (%)	
T-B-NK+	26 (59.1%)
T-B+ NK-	15 (34.1%)
T-B+ NK+	3 (6.8%)
*Genetic defects identified — no. (%)	34 (77.3%)
Artemis gene	8
IL2RG	7
RAG2	7
RAG1	6
Cernunnos	2
JAK3	2
IL7RA	1
DNA-PKcs	1

Immunological characteristics on admission	All patients (*n* = 44)	B- SCID patients(*n* = 26)	B+ SCID patients (*n* = 18)
*T-cell immunity			
Low absolute lymphocyte count	37 (84.1%)	21 (80.8%)	16 (88.9%)
*B-cell immunity			
Low CD19+ count	26 (59.1%)	26 (100%)	0
Low IgA level	18/43 (41.9%)	11/25(44%)	7 (38.9%)
Low IgM level	29/13(67.4%)	18/25(72%)	11 (61.1%)
Low IgG level[1]	12/27 (44.4%)	6/15(40%)	6/13(50%)

[1]Patients who had received IVIG before admission to our clinic are excluded for IgG levels.

Most common complaints on admission were diarrhea (54.5%), oral candidiasis (52.3%) and recurrent pneumonia (50%).

Body weight, height and head circumference of the patients on admission were less than 3rd percentile according to age and sex in 51.2%, 28.2% and 34.4%, respectively.

Immunophenotypes

Twenty six (59.1%), 15 (34.1%) and three (6.8%) patients were T-B-NK+, T-B+NK- and T-B +NK+, respectively. Twenty six patients (59.1%) were B- and 18 (%40.9) were B+ SCID according to B cell counts.

On admission, 37 patients (84.1%) had low, six (13.6%) had normal and one (2.3%) had high absolute lymphocyte counts. CD19 counts, IgA, IgM and IgG levels were low in 26 patients (59.1%), 18 (41.9%), 29 (67.4%), and 12 (44.4%) on admission, respectively. Absolute lymphocyte counts and Ig levels on admission did not vary between B- and B+ immunophenotypes.

Genetics

A genetic defect causing SCID was identified in 34 of 44 patients (77.3%). The most common phenotype of SCID was T-B-NK+ caused by mutations in *RAG1/RAG2* (% 38.2) followed by mutations in Artemis (23.5%) and *IL2RG* genes (20.6%) (Sanal and Tezcan 2011).

HSCT characteristics and outcome

Bone marrow was given in 31 patients (70.4%), peripheral stem cell in 12 (27.3%) and umbilical cord blood in one (2.3%). Human leukocyte antigen identical HSCT was performed in 77.3% of the patients (23 matched siblings, six matched fathers, two matched mothers, three matched extended family donors), HLA 1–2 mismatched family donors in five (11.3%), and haploidentical family donors in five (11.3%).

Conditioning regimen (myeloablative) and GVHD prophylaxis were used in four and nine patients, respectively. Acute GVHD was seen in two (22.2%) of nine patients who received GVHD prophylaxis.

The overall incidence of acute and chronic GVHD were 31.8% (14/44) and 6.8% (3/44) respectively. The incidence did not differ significantly between B- and B+ SCID patients. Furthermore, the incidence did not differ according to the HLA match status. Acute GVHD developed in 35.3% (12/34) and 20% (1/5) of HLA identical and haploidentical transplants, respectively. All of the acute GVHD cases were grade 1–2 and transient. Chronic GVHD developed in 8.8% (3/34) of HLA identical transplants. Moreover, only one patient had limited chronic GVHD and none of them had generalized type.

Acute GVHD incidence was low in bone marrow transplanted patients (6/31, 19.4%) compared to peripheral stem cell transplanted ones ((7/12, 58.3%) (p = .024). When only patients transplanted from HLA identical donors were evaluated, acute GVHD was again less in bone marrow tranplanted (6/27, 22.2%) than peripheral stem cell transplanted (5/6, 83.3%) patients (p = .010).

Acute/chronic GVHD incidence did not significantly differ according to transplantation age (<6 months versus ≥6 months) (p = .53/p = 1.0), and donor's age (<18 years versus ≥18 years old) (p = .085/p = .54).

After follow-up [8.7 years (2–21 years)]; absolute lymphocyte counts, CD3, CD4, CD8 counts were normal in 90.9%, 95.4%, 88.1% and 97.6% of the patients, respectively. When only patients transplanted from HLA identical donors without conditioning regimen were

evaluated, CD3 and CD4 counts were normal in 93.8% (30/32) and 90.3% (28/31) of the patients, respectively. Absolute lymphocyte counts, CD3, CD4, and CD8 counts were similar after HSCT in B- and B+ immunophenotypes. Furthermore, CD16-56 count was lower after HSCT in NK- patients compared with NK+ patients ($p = .011$).

CD19 counts were normal in 45.4% (20/44) of the patients at the last follow-up [8.7 years (2–21 years)]. B+ SCID (14/18, 77.8%) patients had better CD19 counts than B- SCID (6/26, 23.1%) after HSCT ($p < .001$). Although CD19 counts were normal in 45.4% (n = 20), monthly IVIG therapy could be ceased in 72.7% of the patients (n = 32). Additionally, IVIG therapy was stopped in 79.4% and 40% of the patients who had HLA identical and haploidentical HSCT, respectively. Immunoglobulin A levels were normal in 59.1% (26/44) of the patients at the last follow-up. When only patients transplanted from HLA identical donors were evaluated, IgA levels were normal in 70.6% (24/34). Although B + SCID patients had better CD19 counts than B- SCID; IVIG cessation ratios and Ig levels did not vary between B- and B+ immunophenotypes.

CD3, CD4, CD8, CD16-56, CD19 counts, and Ig levels were not significantly different between the patients transplanted before and after 6 months.

After IVIG therapy was stopped, patients were vaccinated. Pneumococcal antibody response was normal in six out of 12 (50%), anti-HBs was positive in 15 out of 28 (53.6%) and isohemoagglutinin titers were normal in seven out of nine patients (77.8%) (5/7 of B- SCID and 2/2 of B+ SCID patients) after cessation of IVIG. B- SCID (12/17, 70.6%) patients had better protective response to hepatitis B vaccine at the last follow-up when compared with B+ SCID (3/11, 27.3%) patients ($p = .025$). Although not significant, pneumococcal vaccine response was also better in B- SCID (4/5) patients than B+ (2/7).

Phytohemagglutinin, concanavalin A and ionomycin-induced lymphocyte proliferation were normal, respectively, in 94.6% (n = 33), 94.3% (n = 33) and 91.2% (n = 31) of the patients. CD4+ CD45RO was ≥%50 in 42.9% of the patients who were over 5 years of age at the last follow-up (7/14 of B- SCID and 5/14 of B+ SCID patients).

At last follow-up [8.7 years (2–21 years)], 70.2% (26/37) and 78.3% (29/37) of the patients had body weight and height above 3rd percentile according to age and sex, after a median follow-up of 8.5 years (2–17.7 years), and 13.8% (4/29) had head circumference less than 3rd percentile. Out of four patients whose body weight, height and head circumference were less than 3rd percentile; two had Cernunnos deficiency, the underlying genetic defect was not found in other two patients who did not have any transplant-related complications. One of the patients with Cernunnos deficiency had acute GVHD.

There were two patients with Cytomegalovirus retinitis and one patient with idiopathic thrombocytopenic purpura diagnosed after HSCT as post-transplant morbidity.

Characteristics of transplantation and donors are shown in Table 2 and immunological characteristics at last follow-up in Table 3. The detailed individual characteristics of the patients are provided in Supplementary Table.

Discussion

On admission, absolute lymphocyte counts were low in 84.1% of the patients. Possibly depending on the presence of maternal IgG, IgG levels were in normal ranges in most (55.6%) of the patients. Therefore, typical clinical warning signs and lymphopenia are more important for the suspicion of SCID than other laboratory findings, such as Ig levels.

Table 2. Donor and transplant characteristics.

Characteristics	All patients (n = 44)	Identical donors (n = 34)	Mismatched donors (n = 5)	Haploidentical donors (n = 5)
		number (percent)		
Graft type				
Bone marrow	31 (70.4%)	27 (79.4%)	2 (40%)	2 (40%)
Peripheral stem cell	12 (27.3%)	6 (17.64%)	3 (60%)	3 (60%)
Umbilical cord blood	1 (2.3%)	1 (2.94%)	0	0
GVHD prophylaxis				
None	35 (79.5%)	31 (91.2%)	2 (40%)	2 (40%)
Cyclosporine	8 (18.2%)	2 (5.9%)	3 (60%)	3 (60%)
Steroid	1 (2.3%)	1 (2.9%)	0	0
Conditioning regimen				
None	40 (91%)	32 (94.1%)	5 (100%)	3 (60%)
Myeloablative	4 (9%)	2 (5.9%)	0	2 (40%)

Table 3. Immunologic characteristics at last follow-up.

	All patients (n = 44)	B- SCID patients (n = 26)	B+ SCID patients (n = 18)
		number (percent)	
*T-cell immunity			
Normal absolute lymphocyte count	40 (90.9%)	22 (84.6%)	18 (100%)
Normal CD3+ count	42 (95.4%)	24 (92.3%)	18 (100%)
Normal CD4+ count	37/42 (88.1%)	21/25 (84%)	16/17 (94.1%)
Normal CD8+ count	41/42 (97.6%)	24/25 (96%)	17/17 (100%)
*B-cell immunity			
Normal CD19+ count	20 (45.4%)	6 (23.1%)	14 (77.8%)
Normal IgA level	26 (59.1)	18 (69.2%)	8 (44.4%)
Normal IgM level	27 (61.4%)	15 (57.7%)	12 (66.7%)
Normal IgG level[1]	18/32 (56.3%)	11/20 (55%)	7/12 (58.3%)

[1]Patients whose IVIG therapy were not stopped at last follow-up are excluded for IgG levels.

Normal growth was observed in the majority of SCID patients after HSCT. Most of our patients had HLA identical HSCT which were performed without conditioning. We assumed that the patients tranplanted without conditioning did not have severe infections and achieved rapid engraftment, so their growth was not affected.

In the United States, IL2RG genetic defect was found in 19% of SCID patients who were diagnosed by newborn screening whereas it is nearly half in published cohorts (Kwan et al. 2014). The IL2RG ratio in the genetic defects detected in our study is 20.6%. The most common genetic defects are; *RAG1/2* (38.2%) and Artemis (23.5%). Genetic defects related to molecules involved in DNA repair mechanisms inherited as autosomal recessive trait are frequently seen in our population. This may be attributed to the high consanguineous marriage frequency in Turkey (18.5%) (Kaplan et al. 2016). Although consanguineous marriage is a disadvantage for the occurrence of autosomal recessive SCID, it also provides increased chance to find a HLA identical donor in the family.

In most European and North American countries, HSCT from HLA identical donor is infrequent (Buckley 2004). However, in our study, HLA identical HSCT was performed in 77.3% (34/44) of the patients.

The incidence of grade 1–2 acute and chronic GVHD in patients who received HLA identical HSCT were respectively 35.3% and 8.8%, similar to the literature (Dvorak et al. 2014). So acute and chronic GVHD may be seen even in HLA identical HSCT.

In the study of Heimall et al., there was no significant difference in rates of GVHD when comparing bone marrow versus cord blood versus peripheral stem cell sources in unconditioned related donor patients (Heimall et al. 2017). But acute GVHD was less in bone marrow transplanted patients than peripheral stem cell transplanted ones (p = .024) in our study. Therefore, it may be rational to use bone marrow instead of peripheral stem cell if possible.

In the study of Pai et al., CD3 and CD4 counts were normal in 70% and 39% of the patients at 2–5 years after HSCT, respectively. Also, CD3 and CD4 counts were normal in 76% and 48% of the patients who received HLA identical sibling HSCT, respectively (Pai et al. 2014). In our study, CD3 and CD4 counts after HSCT [8.7 years (2–21 years)] were normal in more patients compared with previous studies. Absolute lymphocyte counts, CD3, CD4, CD8 counts and lymphocyte proliferation with mitogens were normal in 90.9%, 95.4%, 88.1%, 97.6% and more than 90% of the patients, respectively, at last follow-up. Hence, T cell reconstitution was found to be normal in more than 90% of the patients compared to normal reference values by age.

In the study of Pai et al., B cells (CD19 or CD20 counts) were normal in 52%, and IgA levels were normal in 56% of the patients [96% (22/23) in matched siblings, 34% in mismatched related and 72% in unrelated donors] in the post-transplant period at 2–5 years. (Pai et al. 2014). In our study, B cells (CD19 counts) were normal in fewer patients at the last follow-up compared with the study of Pai et al.; however, most of the patients (32/44, 72.7%) were IVIG-free. Pai et al. reported that IVIG therapy was stopped in 54% of the patients and the rate of IVIG therapy cessation and IgA levels were significantly greater in HLA identical HSCT (Pai et al. 2014). In our study, IVIG therapy was stopped in more patients which may be attributed to higher ratio of HLA identical HSCT.

In the study of Scarselli et al., four out of five (80%) and two out of three patients (66.7%) had protective antibody titers for pneumococcal and hepatitis B vaccines after HSCT at last follow-up, respectively. Isohemagglutinin titers were normal in two out of four patients (50%) beyond one year post-transplantation (Scarselli et al. 2015). In our study, pneumococcal vaccine response and anti-HBs positivity seem to be lower, whereas isohemagglutinin titers are better compared with the study of Scarselli. But number of the patients are not enough for a fair comparison.

In the study of Railey et al., patients those transplanted before 3.5 months of age had a lower rate of clinical problems such as infections, developmental delay, diarrhea, attention deficit hyperactivity disorder, failure to thrive, and need for booster transplants (Railey et al. 2009). In our study, we compared the immune reconstitution and GVHD incidence of patients who were transplanted before and after 6 months of age. CD3, CD4, CD8, CD16-56 and CD19 counts, IVIG need, Ig levels and GVHD incidence did not differ between the patients transplanted before and after 6 months.

Conclusion

The immune reconstitution and the growth were normal in the majority of SCID patients after HSCT. Most of our patients had HLA identical HSCT which were performed without conditioning. We assumed that the patients tranplanted without conditioning did not have severe infections and achieved rapid engraftment, so their growth was not affected. There

was no correlation between the age at transplantation and T and B cell reconstitution. Better CD3 and CD4 counts, and higher cessation of IVIG therapy than the previous studies can be attributed to the higher ratio of HLA identical HSCT. Besides, it may be rational to use bone marrow instead of peripheral stem cell as the stem cell source, as acute GVHD was less in patients with bone marrow (6/31, 19.4%) than peripheral stem cell (7/12, 58.3%) transplantation (p = .024).

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Declarations of interest

The authors declare that they have no declarations of interest.

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