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The Natural History of Children with Severe Combined Immunodeficiency: Baseline Features of the First Fifty Patients of the Primary Immune Deficiency Treatment Consortium Prospective Study 6901

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Abstract

The Primary Immune Deficiency Treatment Consortium (PIDTC) consists of 33 centers in North America. We hypothesized that the analysis of uniform data on patients with severe combined immunodeficiency (SCID) enrolled in a prospective protocol will identify variables that contribute to optimal outcomes following treatment. We report baseline clinical, immunologic, and genetic features of the first 50 patients enrolled, and the initial therapies administered, reflecting current practice in the diagnosis and treatment of both typical ($n = 37$) and atypical forms ($n = 13$) of SCID.

From August 2010 to May 2012, patients with suspected SCID underwent evaluation and therapy per local center practices. Diagnostic information was reviewed by the PIDTC eligibility review panel, and hematopoietic cell transplantation (HCT) details were obtained from the Center for International Blood and Marrow Transplant Research.

Most patients (92%) had mutations in a known SCID gene. Half of the patients were diagnosed by newborn screening or family history, were younger than those diagnosed by clinical signs (median 15 vs. 181 days; $P = <0.0001$), and went to HCT at a median of 67 days vs. 214 days of life ($P =$

<0.0001). Most patients (92%) were treated with HCT within 1–2 months of diagnosis. Three patients were treated with gene therapy and 1 with enzyme replacement.

The PIDTC plans to enroll over 250 such patients and analyze short and long-term outcomes for factors beneficial or deleterious to survival, clinical outcome, and T- and B-cell reconstitution, and which biomarkers are predictive of these outcomes.

Keywords

Severe Combined Immunodeficiency; Hematopoietic Cell Transplantation; Newborn Screening

Introduction

Severe combined immunodeficiency disease (SCID) includes a heterogeneous group of genetic conditions characterized by profound deficiencies of T (and in some types, B and NK cell) numbers and function [1–4]. SCID can be identified at birth by newborn screening through quantification of T-cell receptor excision circles (TRECs) in a dried blood spot [5, 6]. If untreated, infants with SCID succumb early in life from severe and recurrent infections. The standard treatment for SCID is allogeneic hematopoietic cell transplantation (HCT), preferably from an HLA-matched relative [7], though for certain genetic subtypes, either enzyme replacement therapy (ERT) or gene transfer (GT) are potential options [8, 9]. In patients lacking an HLA-matched relative, two major controversies exist in the field of HCT for treatment of SCID: 1) the choice of alternative donor – unrelated adult or umbilical cord blood (UCB) versus T-cell depleted haploidentical related donor; and 2) whether or not to utilize pre-HCT conditioning [10]. These various approaches may have significant impact on survival, the duration and quality of post-HCT immune reconstitution (T-cell only vs. combined T- and B-cell function), and short- and long-term side-effects [11–13]. In addition, the various genetic subtypes may respond differently to the different approaches to transplant, such as the increased risk of late-effects following alkylating conditioning in patients with radiosensitive forms of SCID [14, 15]. There has never been a randomized controlled trial comparing the outcomes of patients with SCID or atypical SCID receiving HCT from different donor sources or different conditioning intensities, and the published studies often report different clinical endpoints, making comparisons difficult [16–23].

The Primary Immune Deficiency Treatment Consortium (PIDTC) was formed to address fundamental questions regarding the optimal diagnosis, management, and follow-up of patients with SCID and other immunologic defects. It consists of 13 centers in North America with a special interest in primary immunodeficiencies (PID), in addition to 20 centers of the Pediatric Blood and Marrow Transplant Consortium (PBMT), all of whom care for patients with PID. The hypothesis for the PIDTC 6901 prospective observational natural history study is that the uniform collection and analysis of pre-, peri-, and post-treatment data on patients with SCID will lead to the identification of those variables that contribute to the best outcomes following HCT, ERT, or GT. We report the baseline clinical, immunologic, and genetic features, and the initial therapy received, for the first 50 SCID and SCID atypical patients enrolled in the 6901 prospective study over a 21-month timeframe, thus reflecting current practice in the diagnosis and treatment of SCID.

METHODS

Study Population

From August 2010 to May 2012, patients with suspected typical or atypical SCID underwent diagnostic evaluation and therapy per local center practice. This study was approved by the

Institutional Review Boards of each center and was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. The trial is registered at www.clinicaltrials.gov as NCT01186913.

After signed informed consent was obtained, data were submitted to the PIDTC eligibility and stratification review panel. Patients in Stratum A have typical SCID (defined as $<300/\mu\text{L}$ T cells – or T cells of maternal origin – AND $<10\%$ of lower limit of normal T cell function as measured by response to phytohemagglutinin [PHA]) with intention to treat with HCT. Patients in Stratum B have an atypical form of SCID, either: 1) leaky SCID (defined as T cell numbers $<1000/\mu\text{L}$ if ≤ 2 years of age, $<800/\mu\text{L}$ if 2–4 years of age, or $<600/\mu\text{L}$ if >4 years of age, without maternal lymphocytes, AND either 10–30% of the lower limit of normal T cell functional response to PHA or absent proliferative responses to *Candida* and post-vaccination tetanus toxoid), or a pathologic mutation in a known SCID gene; or 2) Omenn Syndrome (defined as generalized skin rash, $<30\%$ of the lower limit of normal T cell functional responses to PHA, $>80\%$ of T cells with a CD45RO^+ phenotype, and absence of maternal lymphocytes, or a genotype consistent with Omenn); or 3) Reticular Dysgenesis (defined as $<300/\mu\text{L}$ T cells, $<10\%$ of lower limit of normal T cell functional response to PHA, sensorineural deafness and either neutrophils $<200/\mu\text{L}$ despite administration of granulocyte-colony stimulating factor (G-CSF) or a mutation in *AK2*). Patients in Stratum C have ADA-deficient SCID with intention to treat with ERT or GT, or X-linked SCID with intention to treat with GT. Patients were excluded if they were human-immunodeficiency-virus 1 positive by PCR, had DiGeorge Syndrome, MHC Class I or II antigen deficiency, a non-SCID primary immunodeficiency disease, or a metabolic condition that imitates SCID.

Clinical & Laboratory Investigation

The patients' history and laboratory findings were evaluated for the presence of transplacentally-transferred maternal T cells, opportunistic infections, autoimmunity, failure to thrive, and other organ dysfunction. Baseline quality-of-life evaluations were performed. The diagnostic work-up performed at the local centers included lymphocyte phenotyping (CD3, CD4, CD8, CD45RA, CD45RO, CD19/20, CD16/56), in vitro lymphocyte proliferation to phytohemagglutinin (PHA), and quantitative immunoglobulins. Testing for T-cell Receptor Rearrangement Excision Circles (TRECs) and T-cell receptor spectratyping was performed at the PIDTC core lab [5, 24]. Spectratyping results were scored for the number of peaks observed in each of 24 V families, and defined as absent, oligoclonal (1–4 peaks), or polyclonal (≥ 5 peaks), with normal being ≥ 20 polyclonal families. Transplacental maternal engraftment was evaluated using fluorescent in situ hybridization or short tandem repeats. Additional samples were archived for future studies.

Genetic Assessment

As part of the standard diagnostic work-up, patients had genotyping performed at a CLIA-approved or research laboratory. All mutation reports were reviewed centrally to confirm the pathologic nature of the mutation. For those patients without a locally-identified mutation, a sample of pre-HCT genomic DNA was submitted to the PIDTC core lab for evaluation using a custom research sequencing platform [25].

Treatment Details

Data on HCT details, including donor type, stem cell source and processing, conditioning, and graft-versus-host disease (GVHD) prophylaxis, were recorded in the Center for International Blood and Marrow Transplant (CIBMTR) research database and linked to the PIDTC database via a data-sharing agreement. The conditioning regimens were divided into four categories, none, serotherapy only, reduced intensity (RIC), and myeloablative (MAC),

as defined by the CIBMTR guidelines [26]. Treatment details for patients in Stratum B & C were collected on forms harmonized with those of the CIBMTR.

Statistical Analysis

Descriptive statistics were calculated as median and range for quantitative variables or frequencies and percentiles for categorical variables. Comparisons between groups were done using the nonparametric Mann-Whitney test for quantitative variables and the Fisher's exact test for categorical variables. Analyses were done using SAS version 9.2. Significant differences are defined as a *P* value ≤ 0.05 .

RESULTS

Clinical Characteristics at SCID Diagnosis

Fifty patients with typical SCID (*N*=37) or atypical SCID (*N*=13) were enrolled in the PIDTC 6901 prospective trial during the first 21 months it was open, and 46 of them went to HCT. This represents 47% of the total number of HCTs for similar disorders reported to the CIBMTR from North American centers during that time frame. The presenting clinical characteristics of the first 50 patients are shown in Table I. These patients originated from 17 centers, 5 of whom were located in one of the 6 states routinely performing newborn screening (NBS) for SCID during this time period. Patients with typical SCID (Strata A + C) were less likely to be Caucasian (non-Hispanic) or Asian, compared to patients with atypical SCID (Stratum B; *P* = 0.016). Patients with typical SCID were diagnosed at a younger age (median: 34 days; range: 0–304 days) compared to those with atypical SCID (median age at diagnosis: 74 days; range: 0–4916 days), though the difference was not significant (*P* = 0.121). Patients identified by NBS or through positive family history (FH) of immunodeficiency were younger (median: 14 days of age; range 0–80) than those diagnosed by clinical features (median: 179 days of age, range 36–4916; *P* < 0.001). Patients with typical SCID were also more likely to be diagnosed due to FH (27%) or positive NBS (32%), as compared to those with atypical SCID, who were more often found due to the presence of clinical features, such as an opportunistic infection (54%) or other signs, including rashes (23%) (*P* = 0.047). The types of opportunistic infections that developed prior to the diagnosis of SCID are shown in Figure 1, with some patients presenting with more than one organism. Transplacentally-transferred maternal T cell engraftment was common in certain subtypes of typical SCID, but was rarely associated with GVHD (9% of those with maternal T cells). Autoimmunity was more common in those with atypical SCID (46%), which presented with thrombocytopenia (*n* = 2), hemolytic anemia (*n* = 1), rash (*n* = 1), hepatitis (*n* = 1), and vitiligo (*n* = 1), compared to typical SCID (3%), in which only 1 patient had neutropenia (*P* < 0.001). No patient had significant cardiac or renal dysfunction at diagnosis, though 14% of typical SCID and 23% of atypical SCID had pulmonary dysfunction (oxygen requirement) prior to onset of therapy (*P* = 0.413).

Immunologic Status at SCID Diagnosis

The immunologic status of the 50 patients at the time of diagnosis is shown in Table 2. Various SCID genotypes exhibited the expected immunophenotypic differences in B and NK cell numbers. Patients with typical SCID as a group had significantly lower numbers of CD3 cells, all T cell subsets, and PHA response compared to those with atypical SCID (*P* < 0.001 for CD3, CD4, CD8, CD45RO, and PHA, *P* = 0.001 for CD45RA). The median CD3 count was $20 \times 10^6/\text{L}$ (range 0–8898) for those patients with detectable maternal engraftment (*n*=11) compared to a median of $3.5 \times 10^6/\text{L}$ (range 0–30) for those without maternal engraftment (*n*=10; *P* = 0.08). The majority of T cells in patients with atypical SCID were of the CD45RO memory phenotype (median: 98%; range: 24–100%). IgE levels were higher in patients with atypical SCID (median: 196 IU/mL; range: 0–20400) compared

to those with typical SCID (median: 3 IU/mL; range: 0–79), though the difference was not significant ($P=0.464$). TRECs were extremely low in all tested patients, of both classic and atypical SCID types. Results of spectratyping analysis of T cell receptor diversity were available for 8 patients with typical SCID, who had a median of 0.5 polyclonal V families (range: 0–20; normal: 20 polyclonal families). One patient with typical SCID due to an *IL2RG* mutation and high-level transplacentally-transferred maternal T cells had near normal spectratyping. Spectratyping was available for 5 patients with atypical SCID, who had a median of 10 polyclonal V families (range: 2–18), with the difference from typical SCID not quite significant ($P=0.073$).

Genetic Analysis

The majority of patients (92%) with a clinical SCID phenotype had pathogenic mutations located in genes known to be responsible for SCID, as shown in Table 3. No mutations in known SCID-causing genes were found in 1 patient with immunologic criteria of typical SCID associated with multiple intestinal atresias [27]. Three patients with Omenn Syndrome have not had a mutation identified to date, while 3 had mutations in *RAG1* or *RAG2*.

Treatment of SCID

The majority of patients ($n=46$; 92%) with SCID or SCID atypical were initially treated with HCT, while 3 patients were treated with GT and 1 with ERT. The HCT donor type, conditioning regimen, and GVHD prophylaxis regimen are shown in Tables 4a and 4b. Patients diagnosed by FH or NBS went to HCT at a younger median age of 67 days (with 74% receiving HCT at less than 3.5 months of age) compared to a median of 214 days (with 17% receiving HCT at less than 3.5 months of age) for those diagnosed by clinical signs ($P<0.001$). However, there was no difference in time from diagnosis to HCT for those diagnosed by FH/NBS vs. clinical signs (median 56 vs. 43 days, respectively; $P=0.28$). For all 46 transplanted patients, the time from diagnosis to HCT was approximately 1 month for HLA-matched related donors (MRD; median 25 days, range 4–151 days; $n=7$) or mismatched related donors (MMRD; median 29 days, range 16–110 days; $n=12$), compared to 2 months for unrelated adult donors (URD; median 61 days, range 30–221 days; $n=13$) or umbilical cord blood (UCB; median 60 days, range 24–147 days; $n=14$) donors ($P=0.0185$ for related vs. unrelated).

The donor types and conditioning regimens were dissimilar between those with typical SCID and atypical SCID. Typical SCID patients underwent HCT from a MRD (12%), MMRD (36%), URD (18%) and UCB (34%). Patients with atypical SCID underwent HCT from a MRD (23%), URD (54%), or UCB (23%), with no patient undergoing MMRD HCT ($P=0.011$). No pre-HCT chemotherapy was used in the majority (63%) of patients who were treated by HCT from a MRD or MMRD, compared to very few (7%) of those with a URD or UCB donor ($P<0.001$). Patients with typical SCID and atypical SCID were equally likely to receive fully myeloablative conditioning (MAC, 52% vs. 46%), however only patients with typical SCID received either no conditioning (30%) or serotherapy alone (12%), while the majority of patients with atypical SCID received RIC (54%; $P<0.001$). Only 3 of the 16 typical SCIDs who received related donor transplants received MAC (19%) whereas 14 of the 17 typical SCIDs who received MUD transplants received MAC (82%; $P<0.001$).

With a short median follow-up of 9.2 months (range, 3.3–17.5 months) from HCT, 6 patients have expired, for an estimated 1-year overall survival of 86% (95% CI, 72–94%). Further subgroup comparisons of survival will be possible when the entire study has accrued with sufficient follow-up time. All 4 patients treated with GT or ERT are still alive, with a median follow-up of 15.7 months (range, 10.6–28.5 months) from diagnosis.

Discussion

The PIDTC 6901 study was designed to collect prospectively, in a uniform fashion, patient and donor characteristics, in addition to treatment characteristics and outcomes, of children with SCID or SCID atypicals in North America. A wide range of approaches has been utilized in the centers that provide care to these patients, and the rarity of these patients has limited our understanding of the optimal conditions for the safe achievement of effective immune reconstitution.

In a short period of time, we have collected detailed clinical and immunologic features of patients presenting with SCID or its atypicals at multiple centers throughout North America. However, a limitation of this study is that some centers opened the trial at varying time points, having captured the details of only 47% of patients with SCID transplanted in North America and reported to CIBMTR, we cannot be certain that the sample is truly representative. Now that all centers are fully activated, a more representative population will be available for future study.

We have demonstrated that in the states where NBS is available, patients with SCID were typically diagnosed at less than a month of age, and the majority (74%) proceeded to transplant by 3.5 months of age, a time point that has been shown to be associated with superior outcomes [12, 16]. Despite this success, at the national level as many as 50% of patients with SCID are still diagnosed later in life, after developing opportunistic infections or other clinical signs, often associated with pulmonary dysfunction, and this has been associated with worse survival [11, 21, 28].

As built into our definitions, patients with typical SCID typically had very low T cell numbers (though very high amounts were occasionally seen due to maternally-transferred T cells) and function, with very low endogenous (i.e., non-IgG) immunoglobulin levels. Patients with atypical forms of SCID often had some detectable T cells, though these were primarily of the CD45RO memory/activated phenotype, and had some residual T cell function as measured by proliferation to PHA. The presence of elevated IgE was a common feature of atypical SCID, as previously reported [29]. We also noted that the T cell repertoire of patients with typical SCID generally is characterized by very low numbers of V families that express normal polyclonal CDR3 distribution, while the T cell repertoire in patients with atypical forms of SCID is characterized by a larger number of polyclonal V families, albeit 50% fewer than in normal individuals. More data need to be accumulated to extend these observations, which could ultimately form the basis for an additional criterion for delineating atypical forms of SCID, as well as representing a new tool for assessing the functional diversity of the immune system after HCT. Among patients with typical SCID, the distribution of identified genetic mutations matched with previously published reports [21, 30], while hypomorphic or leaky mutations in *RAG1/2* genes accounted for the majority of atypical forms of SCID.

For patients lacking a MRD and treated with HCT, the choice of donor was almost equally split between a MMRD (using *ex vivo* T-cell depletion to prevent GVHD), a 7/8 adult URD, or a 5/6 UCB (typically given pre-transplant conditioning and GVHD prophylaxis with both a calcineurin inhibitor and an additional agent). Those patients receiving cells from MMRD generally went to HCT about 1 month faster than those receiving cells from a URD or UCB, likely reflecting the time needed to perform a URD/UCB search. Further follow-up will be necessary to determine whether this faster time to HCT is associated with superior outcomes, or if the closer HLA-matching in the URD/UCB donors alternatively produces better outcomes that justify the prolonged time to transplant. This debate may also change over time as more patients are diagnosed by NBS and thus can receive prophylaxis

against the typical opportunistic infections that have classically increased the urgency to proceed with HCT in order to achieve immune reconstitution. Long-term follow-up studies will be needed to assess whether use of a conditioning regimen (a common practice in patients who received HCT from UCB or URD) is associated with a higher rate of late effects.

Future directions for the PIDTC 6901 trial will include continued prospective enrollment with a goal of accumulating over 200 patients with typical SCID and 50 patients with leaky SCID. We will then be able to begin analysis of both short and long-term outcomes of therapy. One of our aims will be to identify which factors are beneficial or deleterious to survival, T- and B-cell immune reconstitution, and clinical outcome early after HCT for SCID, as well as to identify early biomarkers that are predictive of those outcomes. Cognitive and behavior abnormalities are particularly important targets to be studied [31]. These data will eventually shape the design of future prospective clinical trials testing the approaches with the best outcomes and least degree of toxicity.

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Figure 1. Opportunistic Infections at Time of SCID Diagnosis

Bacterial (*Pseudomonas*, n = 2; *E. coli*, n = 1; *S. pneumoniae*, n = 1; methicillin-resistant *S. aureus*, n = 1; *C. difficile*, n = 1); Viral (Respiratory syncytial virus, n = 3; rotavirus, n = 3; enterovirus, n = 1; Varicella-zoster virus, n = 1)

Table 1

Clinical Characteristics at SCID Diagnosis by Immunophenotype

	T-B+NK-	T-B-NK+	T-B+NK+	ADA-SCID	SCID with IA	Typical SCID Overall	Omenn	Leaky SCID	RD
	n = 22	n = 5	n = 6	n = 3	n = 1	n = 37	n = 6	n = 6	n = 1
Age in days (median, range)	24 (0-224)	97 (44-304)	23 (0-200)	56 (36-163)	76	34 (0-304)	67 (44-196)	730 (0-4916)	0
Gender (M / F)	20 / 2	2 / 3	3 / 3	2 / 1	1 / 0	28 / 9	1 / 5	2 / 4	1 / 0
Race / Ethnicity									
White / Non-Hispanic	7 (32%)	2 (40%)	1 (17%)	1 (33%)	1	12 (32%)	4 (66%)	4 (66%)	0
White / Hispanic	4 (18%)	3 (60%)	2 (33%)	0	0	9 (24%)	0	0	0
African American	4 (18%)	0	0	1 (33%)	0	5 (14%)	0	0	0
Asian or Pacific Islander	3 (14%)	0	0	0	0	3 (8%)	2 (34%)	1 (17%)	1
Native American	0	0	0	1 (33%)	0	1 (3%)	0	0	0
Other	4 (18%)	0	3 (50%)	0	0	7 (19%)	0	1 (17%)	0
Trigger for Diagnosis									
Family History	8 (36%)	0	2 (33%)	0	0	10 (27%)	0	1 (17%)	1
Newborn Screen	8 (36%)	2 (40%)	2 (33%)	0	0	12 (32%)	0	1 (17%)	0
Infection	6 (27%)	3 (60%)	1 (17%)	3 (100%)	1	14 (38%)	3 (50%)	4 (66%)	0
Other (Rash, etc.)	0	0	1 (17%)	0	0	1 (3%)	3 (50%)	0	0
Maternal Engraftment	7/15 (47%)	2/3 (66%)	2/2 (100%)	0/1	NT	11/21 (52%)	0/6	0/3	0/1
GVHD	0	1	0	0	0	1 (3%)	NA	NA	NA
Autoimmunity	1 (5%)	0/4	0	0	0	1 (3%)	4 (67%)	2 (33%)	0
Failure to Thrive	2 (9%)	1 (20%)	2 (33%)	3 (100%)	1	9 (24%)	2 (33%)	2 (33%)	1
Pulmonary Dysfunction	3 (14%)	1 (20%)	1 (17%)	1 (33%)	0	6 (17%)	2 (33%)	1 (17%)	0
Mechanical Ventilation	3 (14%)	0	1 (17%)	0	0	4 (11%)	1 (17%)	1 (17%)	0

Table 2

Immunologic Status at SCID Diagnosis by Immunophenotype

	T-B+NK- n = 22	T-B-NK+ n = 5	T-B+NK+ n = 6	ADA-SCID n = 3	SCID with 1A n = 1	Typical SCID Overall n = 37	Omenn n = 6	Leaky SCID n = 6	RD n = 1
Absolute Lymphocyte Count ($\times 10^9/L$)	2058 (360–10720)	400 (280–1401)	1123 (202–3510)	57 (22–136)	1220	1220 (22–10720)	4920 (861–17000)	1229 (400–11070)	3160
CD3 ($\times 10^6/L$)	11 (0–8898)	25 (3–168)	2 (0–111)	4 (3–6)	74	10 (0–8898)	3535 (672–10164)	386 (45–7985)	1918
CD4 ($\times 10^6/L$)	3 (0–1307)	20 (3–196)	2 (0–95)	4 (3–4)	85	4 (0–1307)	1887 (474–8639)	182 (31–442)	1675
CD45RA ($\times 10^6/L$)	0 (0–57)	3 (0–57)	0 (0–5)	0	21	0 (0–57)	46 (11–313)	14 (0–78)	0
CD45RO ($\times 10^6/L$)	1 (0–1294)	28 (17–155)	0 (0–95)	3 (2–3)	65	2 (0–1294)	1975 (161–8466)	139 (31–397)	1675
CD8 ($\times 10^6/L$)	3 (0–750)	0 (0–28)	2 (0–7)	9 (2–27)	24	3 (0–750)	300 (37–1525)	166 (18–4033)	600
PHA (% control)	0 (0–11)	4 (1–20)	0 (0–1)	1 (0–2)	3	0 (0–20)	18 (1–82)	5 (0–27)	100
TRECs (#uL)	0 (0–11)	0 (0–0)	0 (0–0)	0	11	0 (0–11)	0 (0–0)	0 (0–0)	0
B Cells ($\times 10^6/L$)	1496 (320–3847)	3 (0–186)	773 (164–2655)	2 (0–7)	830	NA	3 (0–1052)	1 (0–2041)	822
IgG (mg/dL), pre-IVIG	610 (30–1020)	371 (36–686)	572 (326–891)	292 (56–329)	0	539 (0–1020)	489 (371–608)	674 (474–874)	1030
IgM (mg/dL)	14 (5–58)	5 (4–89)	18 (11–67)	0 (0–3)	5	11 (0–89)	15 (0–95)	22 (4–147)	0
IgA (mg/dL)	6 (0–25)	9 (7–24)	6 (0–7)	0	0	6 (0–25)	7 (0–63)	20 (0–165)	0
IgE (IU/mL)	2 (0–79)	8 (1–38)	0 (0–4)	5 (5–5)	NT	3 (0–79)	4467 (0–20400)	0 (0–874)	1
NK Cells ($\times 10^6/L$)	28 (0–968)	300 (258–939)	249 (28–386)	16 (9–37)	207	NA	641 (43–6268)	106 (40–298)	32

Table 3

Genetic Mutations Identified in Patients with SCID

	Typical	Atypical	Overall
IL-2RG	20	0	20
JAK3	2	1	3
RAG-1/2	5	8	13
IL-7R	3	0	3
CD3delta	3	0	3
ADA	3	0	3
SCID with IA	1 [*]	0	1 [*]
AK2	0	1	1
Unknown	0	3 [^]	3 [^]
Total	37	13	50

^{*} Phenotypic diagnosis (mutation not yet identified)

[^] All with Omenn Syndrome

HCT Characteristics for 36 Patients with Typical SCID

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HCT Characteristics for 13 Patients with Atypical SCID

Table 4b

Donor Type	Conditioning Type					GVHD Prophylaxis				Median Days from Diagnosis to HCT (range)	
	n	None	Serotherapy-only	RIC	MAC	None	TCD	CI Only	CI + Other		
Related											
MRD BM / PBSC	3	0	0	0	0	3	0	0	1	2	96 (11–151)
MMRD TCD BM/PBSC	0	0	0	0	0	0	0	0	0	0	NA
Unrelated											
7/8 URD BM/PBSC	7	0	0	0	4	3	0	0	0	7	45 (30–221)
5/6 UCB	3	0	0	0	3	0	0	0	1	2	62 (38–123)