Published in final edited form as:

J Allergy Clin Immunol. 2009 November ; 124(5): 1062–9.e1-4. doi:10.1016/j.jaci.2009.08.041.

Outcomes of Severe Combined Immunodeficiency Patients Treated with Hematopoietic Stem Cell Transplantation with and without Pre-conditioning

Niraj C. Patel, MD, MS^a, Javier Chinen, MD, PhD^a, Howard M. Rosenblatt, MD^b, I. Celine Hanson, MD^a, Robert A. Krance, MD^c, Mary E. Paul, MD^a, Stuart L. Abramson, MD, PhD^a, Lenora M. Noroski, MD^a, Carla M. Davis, MD^a, Filiz O. Seeborg, MD^a, Samuel B. Foster, MD^a, Kathryn S. Leung, MD^c, Betty S. Brown, MS^a, Jerome Ritz, MD^d, and William T. Shearer, MD, PhD^a

^aDepartment of Pediatrics, Section of Allergy and Immunology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX 77030, USA

^bSpecially For Children Pediatric Allergy and Immunology, Dell Children's Medical Center of Central Texas, Austin, TX 78723, USA

^cSection of Hematology and Oncology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX 77030, USA

^dDivision of Hematologic Malignancies and Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Stem Cell Institute, Harvard Medical School, Boston, MA 02115, USA

Abstract

Background—The effect of pre-transplant conditioning upon the long-term outcomes of patients receiving hematopoietic stem cell transplantation (HSCT) for severe combined immunodeficiency (SCID) has not been completely determined.

Objective—To assess the outcomes of 23 mostly conditioned SCID patients and compare their outcomes to 25 nonconditioned SCID transplanted patients previously reported.

Methods—In the present study, we reviewed the medical records of these 23 consecutive mostly conditioned SCID patients transplanted between 1998 and 2007.

Results—Eighteen patients (median age at transplant 10 [range 0.8–108] mo) received haploidentical mismatched related donor, matched unrelated donor, or mismatched unrelated donor transplants, 17 of whom received pretransplant conditioning and one was not conditioned, 13 (72%) engrafted and survive a median of 3.8 [1.8–9.8] yr, 5 of 13 (38%) require IVIG, and 6 of 6 age-eligible children attend school. Of five recipients (median age at transplant 7 [range 2–23] mo) of matched related donor transplants, all 5 engrafted and survive a median of 7.5 [range 1.5–9.5] yr, 1 requires IVIG, and 3 of 3 age-eligible children attend school. Gene mutations were

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Reprint requests: William T. Shearer, M.D., Ph.D., Department of Pediatrics, Section of Allergy and Immunology, Texas Children's Hospital, 6621 Fannin, FC 330.01, Houston, TX 77039. wtsheare@texaschildrenshospital.org. Telephone: 832-824-1274. Fax: 832-825-7131.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

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known in 16 cases: IL2 γ R in 7 patients, IL7 α R in 4 patients, RAG1 in 2 patients, ADA in 2 patients, and AK2 in 1 patient. Early outcomes and quality of life of the previous non-conditioned vs. the present conditioned cohorts were not statistically different but longer-term follow-up is necessary for confirmation.

Conclusions—HSCT in SCID patients results in engraftment, long-term survival, and a good quality of life for the majority of patients with or without pre-transplant conditioning.

Keywords

Hematopoietic stem cell transplantation; graft-versus-host disease; severe combined immunodeficiency; immune reconstitution; primary immunodeficiency; conditioning

Introduction

Hematopoietic stem cell transplantation (HSCT) is considered the treatment of choice for patients with severe combined immunodeficiency (SCID). Although many approaches to preparing the host for receiving donor marrow exist, there is no consensus for a single unified modality for transplantation. The differences of long-term outcomes using the various methods of pretransplant conditioning and non-conditioning regimens are currently not well defined.

The highest success rate for HSCT in SCID patients has come from the use of matched related donors (MRDs).^{1–5} The use of MRDs is associated with the lowest incidence of graft-versus-host disease (GvHD) in SCID infants. Because MRDs are available in less than 20% of donors,^{1,6} T cell depleted bone marrow grafts from mismatched related donors (MMRDs) are used, with a higher incidence of GvHD than MRDs. The National Bone Marrow Registry has made matched unrelated donor (MUD) bone marrow and cord blood transplants possible and has expanded the donor alternatives for transplant. Because of a poor ability to mount an immune response, myeloablative conditioning of the SCID host prior to infusion of donor marrow to reduce graft rejection is controversial and widely debated. Chemotherapy is thought to favor engraftment but carries the possibility of serious adverse effects.

We have recently reported on the bone marrow transplantation (1981–1995) of 25 SCID patients without pretransplant conditioning⁷ and we now report on the HSCT (1998–2007) of additional 23 SCID patients, including 19 conditioned SCID patients transplanted with MRD, MMRD, MUD, or mismatched unrelated donor (MMUD) bone marrow. We summarize the outcomes of all 48 SCID patients and analyze outcomes with regards to pretransplant conditioning.

Methods

Medical Chart Review

Records of 23 HSCT SCID patients, 5 MRD and 18 alternative donor (10 haploidentical MMRD, 6 MUD, 1 MMUD, 1 cord blood) at Texas Children's Hospital from 1998–2007 were reviewed. The patients receiving a MMUD (HLA 5/6 match) and cord blood (HLA 6/6 match) were placed and analyzed with the MUD group. The study was approved by the Institutional Review Board at Baylor College of Medicine and parents gave informed consent.

Pretransplant Conditioning and GvHD Prophylaxis

Eighteen patients receiving 29 haploidentical MMRD, MUD, or MMUD transplants from 1998 to 2007 were given pretransplant conditioning, except for one patient who received a MMRD transplant and did not receive pre-conditioning. Five patients received 6 MRD transplants, two of whom were given conditioning because of older age and residual NK cells. Pretransplant conditioning, including busulfan, cytarabine, antithymocyte globulin plus cyclophosphamide or fludarabine, was performed in 13 patients (see Tables I, E-1). Fludarabine and anti-CD52 antibody (Campath-1H) were used in 7 patients, with one patient also receiving cyclophosphamide and two patients receiving anti-CD45 monoclonal antibody. Campath-1H alone was used in one patient. To reduce the incidence of GvHD associated to using haploidentical MMRD grafts, donor peripheral blood mononuclear cells were processed for CD34⁺ cell selection with the Isolex[®] (19 grafts for 10 patients). Treatment of donor bone marrow with anti-CD6, anti-CD8, and antiCD20 monoclonal antibodies was alternatively done (5 grafts for 3 patients). The number of infused mononuclear bone marrow derived cells and residual CD3⁺ T cells among 14 unmodified bone marrow and one cord blood products were $5.09 \times 10^8 \pm 0.7 \times 10^8$ cells/kg (median $\pm$ SE) and $3.8 \times 10^7 \pm 1.0 \times 10^7$ cells/kg, respectively.

The number of total cells and residual CD3⁺ T cells infused using five bone marrow grafts treated with monoclonal antibodies for T cell depletion were $24.9 \times 10^8 \pm 14.0 \times 10^8$ cells/kg (median $\pm$ SE) and $7.6 \times 10^7 \pm 3.4 \times 10^7$ cells/kg, respectively. The number of infused CD34⁺-enriched peripheral derived blood stem cells and residual CD3⁺ T cells among 18 products were $0.25 \times 10^8 \pm 3.7 \times 10^6$ cells/kg and $4.1 \times 10^4 \pm 1.5 \times 10^4$ cells/kg, respectively. GvHD prophylaxis for non-MRD recipients, used when residual CD3⁺ T cells were $\geq 5 \times 10^4$ cells/kg, included cyclosporine (2.5 mg/kg) or tacrolimus (0.03 mg/kg) alone or combined with methylprednisolone.

Molecular Analysis

Molecular analysis for SCID gene defects was performed on extracted DNA (Correlagen, Waltham, MA; NIH, Bethesda, MD; Gene DX, Gaithersburg, MD). Adenosine deaminase levels on all patients were assessed (Baylor Cytogenetics, Houston, TX).

Immunologic Analysis

Immune reconstitution was assessed by measuring cellular immunity and humoral immunity according to previously published methods.⁷⁻⁹ Donor engraftment was determined on peripheral blood and/or bone marrow using fluorescence *in-situ* hybridization probes for sex chromosomes (sex-mismatched transplants) or polymerase chain reaction amplification of specific polymorphic DNA sequences (short tandem repeats).

Long Term Complications

Outcomes and long-term complications, including gastrointestinal, skin, respiratory, developmental, cardiovascular, endocrinologic, and neurologic manifestations were assessed. Educational goals were measured by recording the patient's performance in school.

Statistical Analysis

The standard chi square test was used to test differences between percentages and the Fisher's exact test was used when one or more expected values was less than 5 (STATA 9.0 for Windows). Survival at fixed time points was compared using the log-rank test. A *p*-value less than 0.05 was considered statistically significant.

Results

Patient Demographics and Molecular Diagnoses

Twenty-three patients with SCID received a total of 35 transplants and 3 boosts (Table E-2) between 1998 and 2007. The source of hematopoietic stem cells were bone marrow (n=19), peripheral blood stem cells (n=18), and cord blood (n=1, Table I, patient 17). The median age at first transplant for 23 SCID patients was 10 [range 0.8–108] months: 10 [range 1–108] months for the MMRD/MUD group, and 7 [range 2–23] months for the MRD group. Molecular defects were known in 16 of 23 patients (Table E-2). Twelve of the 18 patients in the MMRD/MUD group were B⁺ SCID, compared with four of five in the MRD group. (Table E-2)

Engraftment and Survival

Among 18 recipients of MMRD/MUD transplants (Table I), all but one (patient 1) received pretransplant conditioning. Six of these patients had low residual CD3⁺ T cells in their grafts and did not receive GvHD prophylaxis. One patient received conditioning after twice failing to engraft (Table I, patient 3). Engraftment and survival occurred in 13/18 (72%, 95% CI, 46%–89%) MMRD/MUD transplant recipients and 5/5 (100%, 95% CI, 46%–100%) MRD transplant recipients. (p=0.4) (Kaplan-Meier curve, Figure 1A). Survival among conditioned MMRD recipients, 7/10 (70%), was similar to the MUD recipients, 5/7 (71%). Medians follow-up among MRD, MMRD and MUD recipients were 7.5 [range 1.5–9.5] yr, 4.3 [range 1.8–8] yr and 2 [range 1.8–7] yr, respectively. Five patients died between 1 to 7 months (mean 4 months) post-transplant and none after one year post-transplant. Two of these patients received 3 donor lymphocyte infusions to treat viral infections (Table I, patients 9,15).

Life-threatening infection prior to transplantation was present in 15/18 patients (Table I) in the MMRD/MUD group and included *Pneumocystis jiroveci* pneumonia (PCP, n=7), bacteremia (n=3), candidal infection (n=2), and disseminated viral infections with cytomegalovirus (CMV, n=3), rotavirus (n=4), respiratory syncytial virus (RSV, n=3), adenovirus (n=2), varicella zoster virus (n=2), parvovirus (n=1), and parainfluenza (n=1)

Among recipients of MRD transplants, 3/5 patients (Table E-1) presented with life-threatening infections prior to transplantation, including rotavirus (n=2) and varicella zoster virus (n=1).

Graft versus Host Disease

Acute GvHD grade II–IV occurred in 2/18 (11%) MMRD/MUD (1 non-conditioned) patients, (Table I, patients 7, 15), and one patient expired despite treatment of the GvHD. Acute GvHD did not occur in the MRD group. None of the 23 transplant recipients has developed chronic GvHD.

Transplacentally-transferred maternal T cells were present in two patients in the MMRD/MUD group (Table I, patients 17,18). Patient 17 presented with skin GvHD before HSCT due to maternal cells.

Long-term Complications

Among survivors in the MMRD/MUD group with conditioning (Table I, patients 2–18), complications included respiratory diseases (asthma, n=3), dermatologic conditions (eczema, n=2; warts, n=1), infectious complications (chronic HHV6, n=1), hematologic abnormalities (anemia, n=4, autoimmune in two cases and iron-deficient in two cases), gastrointestinal disorder (eosinophilic enterocolitis, n=1), speech delay (n=2), and dental

caries (n=1). Two patients had hearing loss before treatment (Table I, patients 11, 17). Among patients in the MRD group (Table E-1), there were respiratory abnormalities (asthma, n=2), dermatologic manifestations (viral source warts, n=1), infectious complication (chronic HHV6, n=1), obesity (n=2), and dental caries (n=1). There were no neoplasias present in any of the survivors.

Immunologic reconstitution

The average period of the last evaluation from the time of transplant was 38.9 [range 12–118] mo for 13 survivors (Table II, patients 1,3–8,11–13,16–18) who received MMRD/MUD transplants, and 70.0 [range 14–106] mo for 5 survivors (Table II, patients 19–23) who received MRD transplants. At the last follow up, 8/13 survivors in the MMRD/MUD group and 3/5 in the MRD group had CD3⁺ T cell numbers within the normal range (Figure E-1 A,D) (Table II). The percentages of patients with CD3⁺ T cell numbers within the normal range at 1, 3 and 5 year post-transplant follow up were 61%, 66% and 60% in the MMRD/MUD group; and 40%, 75% and 75% in the MRD group. These differences were not statistically significant. Lymphocyte proliferative responses to phytohemagglutinin were normal or above 80% of lower limit of normal in 12/13 patients in the MMRD/MUD group and 5 of 5 in the MRD group. Antigen-specific lymphocyte proliferation was demonstrated against at least one antigen in all patients. Donor-host chimerism was established within one year post-HSCT and did not change in the 18 survivors. Studies performed in sorted PBMC cells demonstrated that T cell engraftment was present in all survivors, and 9/13 patients in the MMRD/MUD group and 5/5 in the MRD group had some evidence of B cell engraftment. Of those survivors with B⁺ SCID phenotype, 6/10 (60%) in the MMRD/MUD group and 4/4 (100%) in the MRD group had evidence of B cell engraftment, compared with 3/3 (100%) in the MMRD/MUD and 1/1 (100%) in the MRD group with B[−] SCID phenotype.

Those requiring intravenous immunoglobulin (IVIG) at the time of this report included 5/13 (38%) survivors in the MMRD/MUD group. Three of these 5 patients have received HSCT less than 24 months ago. One of the other two patients has engrafted donor B cells. (Table II, patient 12). IgA and IgM levels were normal, with the exception of undetectable IgA in 3 patients in the MMRD/MUD group. Antibody responses to immunizations were adequate to the following antigens: diphtheria (>0.10 IU/mL) or tetanus (>0.10 IU/mL) in 7/7 patients evaluated in the MMRD/MUD group and 4/4 in the MRD group, *Streptococcus pneumoniae* (>1.0 µg/mL) in 6/7 in the MMRD/MUD and 4/4 in the MRD group, and *Haemophilus influenzae* type b (>0.15 µg/mL) in 4/5 patients in the MMRD/MUD group and 4/4 in the MRD group (Table II).

NK cell counts at the most recent evaluation were normal in 7/13 (54%) patients in the MMRD/MUD group and 4/5 (80%) in the MRD group (Figure E-1 B,E). CD19⁺ B cell numbers were normal at last follow up in 8/13 (62%) patients in the MMRD/MUD group and 4/5 in the MRD group (Figure E-1 C,F). At the one-year post-transplant follow up visit, naïve CD4⁺CD45RA⁺ T cell counts were normal in 6/13 (46%) patients in the MMRD/MUD group (median 432 cells/uL, range [16–2035]) and 3/5 (60%) in the MRD group (median 1009 cells/uL, range [8–1256]) (data not shown).

Health and Educational Accomplishment

HSCT in SCID patients resulted in a good quality of life for the majority of survivors. Of 13 MMRD/MUD survivors, 6/6 (100%) age-eligible children attend school. Of 5 MRD survivors, 3/3 (100%) age eligible children attend school.

Comparison between SCID Patients Given Conditioning or No Conditioning Prior to HSCT

We analyzed the present patient cohort together with the cohort we have previously published to examine the use of pre-transplant conditioning.

Survival

Figure 1B presents a Kaplan-Meier curve representing the survival of 48 SCID patients given HSCT transplants in our center including nonconditioned MMRD recipients⁷, conditioned MMRD and MUD recipients, and MRD recipients of whom 2 received pre-conditioning. The Kaplan-Meier survival estimates were calculated at 1, 3 and 5 years post-transplantation, resulting in the cumulative survival of 7/10 (70%; 95% confidence interval [CI], 34%–93%) for the conditioned MMRD children and 5/7 (71%; 95% CI, 25%–100%) for conditioned MUD children given HSCT for all three time points ($P=0.99$ by the log-rank test). Without pre-transplant conditioning, a comparable MMRD group yielded a cumulative survival at 1, 3, and 5 years post-transplantation of 13/21 (62%; 95% CI, 46%–87%). The entire MRD group survived (100%, 95% CI, 46%–100%), and their survival difference with each of the other groups was statistically significant. ($P=0.04$) Patients with the B⁻ cell phenotype treated with a MMRD graft and no conditioning had the lowest survival rate (Table III).

Graft-versus-host Disease

GvHD grades II–IV occurred in 2/17 (12%) in conditioned MMRD and MUD patients who also received GvHD prophylaxis, compared to 11/21 (52%) of nonconditioned MMRD recipients who did not receive GvHD prophylaxis ($P=0.02$, Table I, III). Chronic GvHD was reported in 5 of the 11 survivors in the nonconditioned MMRD group, but not in the other patient groups. Three of these presented between 1–3 years after HSCT and the other two after 6 and 8 years.

Long-term Complications

A trend towards increased frequency of complications was present in the MMRD group with no conditioning compared to the conditioned MMRD/MUD group and MRD group (Table III), including autoimmune (fasciitis, vitiligo), dermatologic (warts), endocrine (short stature), gastrointestinal (protein losing enteropathy, chronic hepatitis B infection, food aversion), neurologic (hearing loss), and respiratory systems (asthma, bronchiolitis obliterans). Because this increased frequency could be attributed to differences in follow up time, we reviewed the occurrence of these complications at 1 and 5 year after HSCT. In 11 patients who received MMRD grafts without conditioning, at 1 year after HSCT, 10 had complications as a result of infections pre-transplant such as CMV retinitis or chronic GvHD. At year 5 post-transplant, this proportion did not change. Other complications were added over time, for example, in four patients, chronic GvHD of the lung was diagnosed not earlier than 7 years of age. Two of these patients died at ages 10 and 17 years-old. Of 12 SCID patients who received MMRD or MUD grafts after being conditioned, at one year post-transplant 7 had long-term complications and 4 of 5 patients had complications at the 5 year post-transplant follow up. In the MRD group, only 1 of 10 patients had long-term complications at one year, and 4 of 9 had chronic illnesses at the 5-year visit post transplant.

Immunologic Reconstitution

Donor T cells were present in 100% of survivors in both conditioned and nonconditioned HSCT recipients. Donor B cells were present in 8/12 (67%) conditioned MMRD/MUD

recipients, 5/11 (45%) nonconditioned MMRD recipients, and 7/10 (70%) MRD recipients. These estimates were not statistically different and did not change over follow up time.

Health and Educational Achievement

School attendance and educational goals were achieved in the majority of survivors. All 9 age eligible patients in the MRD group attend school or college. All 5/5 (100%) age eligible children in the MMRD/MUD group who received conditioning attend school, and 9/11 (82%) age eligible children in the MMRD group without conditioning attend school (one attends college). Two patients in the MMRD group without pre-conditioning gave birth to three healthy infants.

Discussion

We describe the long-term outcomes of 23 children with SCID who received HSCT (19 with conditioning) from 1998–2007. We have previously reported 25 patients with SCID transplanted without conditioning from 1981–1995.⁷ We found increased survival of MMRD/MUD patient groups receiving conditioning compared to the nonconditioned MMRD group; however the differences did not achieve statistical significance (possibly due to the relatively small patient numbers).

The median age at transplant of the recent cohort was 3.5 months older for the patients receiving MMRD/MUD grafts and 5.2 months older for patients receiving MRD transplants (trend not significant). We found an apparent higher frequency of life-threatening infections in the conditioned group, likely reflecting advances in microbial pathogen detection of this more recently transplanted group or the later age at transplantation compared to the nonconditioned MMRD recipients.

Engraftment and survival were 100% in MRD recipients, including two with conditioning. All patients who engrafted survived. The survivals of patient groups not receiving MRD grafts were lower than MRD groups, as expected. We did not find significant differences in survival among the non-MRD groups, regardless of the use of pre-transplant conditioning. Mortality occurred in the first year post-transplantation, except for 2 patients from the MMRD group with no conditioning who presented with chronic GvHD of the lung and progressive lung disease, and died after 10 years post-transplant. No effect on survival of the type of graft, cell dose or SCID type was identified.

GvHD grades II–IV were less frequent in the MMRD/MUD group with conditioning than in the MMRD group without conditioning. The difference seen between these groups may be due to differences in T cell depletion methods, as evidenced by the lower number of residual CD3⁺ T cells infused in the conditioned MMRD group, as well as the use of GvHD prophylaxis.

The proportion of patients affected with long-term complications was high and was not different according to the different HSCT modalities; however, examining these complications in detail revealed that while most patients who received MMRD/MUD with conditioning and MRD grafts are affected by illnesses of mild to moderate severity such as asthma and eczema; some of those who received MMRD grafts without conditioning presented with severe chronic conditions such as bronchiolitis obliterans and protein-losing enteropathy. Progress in medical care over time allowing early diagnosis and intervention may have influenced this outcome.

Comparison with other published reports

Engraftment rates similar to ours have been reported for conditioned MMRD recipients (59–70%)^{13,15,16}, for nonconditioned MMRD recipients (78%)^{1,10}, and for MRD recipients (100%)^{10,13} regardless of conditioning. The survival rate of 92–100% of MRD in other published studies^{1,2,10,11} is similar to the survival rate in this report. Maintenance of long-term T cell reconstitution, as occurred in our study, has been reported for patients up to 25 years post-transplantation.² We found an apparent lower survival rate for SCID patients with a B[−] phenotype than those with a B⁺ phenotype, unless given a MRD transplant, which is also supported by the literature.^{12,14,15,17}

No significant differences of donor B cell engraftment regarding the use of conditioning were found. There were less patients with donor B cell engraftment in those who did not receive conditioning than those who did; however there were also more B⁺ SCID in this group (17/21) than in the most recent cohort (11/17). The majority of patients who lack donor B cells and require IVIG have the B⁺ SCID phenotype, which is in agreement with the notion of difficulty of B cell engraftment in this subset of patients.¹⁴ Conditioning did not appear to reduce dependence on IVIG infusion among haploidentical recipients.

Most of the survivors in both nonconditioned and conditioned group have attained educational goals and maintain a good quality of life, which is similar (88–100%) to other reports in the literature.^{4,11}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank Dr. Jennifer Puck for providing *IL2γR* sequence analysis and Nirmi Parikh for assistance with EBV-transformed B-cell lines. Support for this study came from the General Clinical Research Center (grant RR-0188), the Immunology Research Fund, and the David Fund, Texas Children's Hospital. We thank Rosalind Gary and Janelle Allen for assistance in the preparation of the manuscript.

Abbreviations used

HSCT	Hematopoietic stem cell transplantation
SCID	severe combined immunodeficiency
GvHD	Graft-versus-host disease
MRD	Matched related donor
MMRD	Mismatched related donor
MUD	Matched unrelated donor

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Figure 1.

A. Kaplan-Meier Curve analyzing the survival of patients with SCID, including 18 patients who received MMRD or MUD transplants (——), and 5 patients who received MRD transplants (——). **B.** Kaplan-Meier Curve demonstrating survival of patients with SCID, including 21 patients who received MMRD transplants without host pre-conditioning (——), 17 patients who received MMRD/MUD transplants with host pre-conditioning (-----), and 10 patients who received MRD transplants (——). Figure contains data from 23 patients from this study and 25 patients from a previous study.⁷

Table 1
Outcomes of 18 SCID patients (17 conditioned) who received MMRD or MUD HSCT from 1998–2007.

Patient, Sex	Phenotype, Molecular Diagnosis	Donor, HLA Match (No./total), T cell depletion, Cell Selection	Age at diagnosis (mo)	Pre-HSCT Infections	Age at HSCT (mo)	Conditioning, GvHD prophylaxis	Engrafted	GvHD, Sk/Liv/Gi	Outcome/ Age, Cause of Death	Age at Last Follow Up (yr)	If Alive, Complications at Follow up
1, M	T ⁺ B ⁺ NK ⁻ , IL2 γ R	Mother 3/6 ϵ	0.1	None	0.75	None	Yes	None	Alive, in elementary school	9.75	Asthma, migraines, protein-losing enteropathy, warts, IgA def
2, F	T ⁺ B ⁺ NK ⁺ , RAG1	#1 Father 3/6 ϵ , #2 Father ϵ	0.25	PCP, salmonella, Group B sepsis, rhinovirus, Mycobacterium chelonae pneumonia, cutaneous candidiasis	6, 7	#1 <i>a</i> , #2 None	No	None	Death at 7 months, PCP, enterococcus faecalis sepsis		
3, M	T ⁺ B ⁺ NK ⁺	#1 Mother 4/6 ϵ , #2 Mother ϵ , #3 Mother, CD34 ⁺ Isolation	0.25	None	1, 5, 23	#1 none, #2 none, #3 <i>a</i>	Yes	None	Alive, in elementary school	7.5	Asthma, fire ant hypersensitivity
4, F	T ⁺ B ⁺ NK ⁺	#1 Mother 3/6, CD34 ⁺ Isolation, #2 Mother, CD34 ⁺ Isolation, #3 Brother 3/6, CD34 ⁺ Isolation	0.1	Proteus and Pseudomonas Pneumonia, PCP and CMV	10, 12, 14	#1 <i>f</i> , #2 <i>b</i> , #3 <i>a</i>	Yes	None	Alive, in elementary school	8	
5, F	T ⁺ B ⁺ NK ⁺	#1 MUD, 6/6, #2 MUD, CD34 ⁺ Isolation	2	Enterobacter cloacae pneumonia, Bipolaris pneumonia, oral thrush, RSV pneumonia	5, 13	#1 <i>a</i> , #2 None	Yes	None	Alive, in elementary school	5.25	Allergic rhinitis, eczema, poor growth, dental caries
6, M	T ⁺ B ⁺ NK ⁺ , IL7R α	#1 Mother 3/6, CD34 ⁺ Isolation, #2 Father 3/6, CD34 ⁺ Isolation, #3 Father (boost), CD34 ⁺ Isolation	9.5	PCP, adenovirus diarrhea	13, 15, 17	#1 <i>a</i> , #2 <i>b</i> , #3 None	Yes	None	Alive, in elementary school	5	Speech delay, chronic HHV6 infection, reactive airway disease
7, M	T ⁺ B ⁺ NK ⁺ , IL7R α	#1, Father 3/6, CD34 ⁺ Isolation, #2 Father (boost)	6	PCP, adenovirus, rotavirus	9,10	#1 <i>b</i> , #2 None	Yes	aGvHD, skin	Alive, well	4.25	Asthma
8, M	T ⁺ B ⁺ NK ⁻ , IL2 γ R	Mother 3/6, CD34 ⁺ Isolation	5.5	Candida, nocardia	12	<i>a</i>	Yes	None	Alive, well	3.75	IgA deficiency
9, M	T ⁺ B ⁺ NK ⁻ , ADA ⁻	MMUD 5/6	0.1	Varicella zoster disseminated	108	<i>a</i>	No	None	Death at 111 mo, adenovirus		

Patient, Sex	Phenotype, Molecular Diagnosis	Donor, HLA Match (No./total), T cell depletion, Cell Selection	Age at diagnosis (mo)	Pre-HSCT Infections	Age at HSCT (mo)	Conditioning, GvHD prophylaxis	Engrafted	GvHD, Sk/Liv/Gi	Outcome/ Age, Cause of Death	Age at Last Follow Up (yr)	If Alive, Complications at Follow up
enterocolitis and sepsis											
10, M	T ⁻ B ⁺ NK ⁻ , IL2 γ R	#1, Mother 4/6, CD34 ⁺ Isolation, #2 Mother, CD34 ⁺ Isolation, #3 Father 3/6, CD34 ⁺ Isolation	0.1	PCP, RSV, Rotavirus, Enterobacter cloacae bacteremia, Klebsiella UTI and bacteremia, CMV pneumonia	8, 9, 10.5	#1 <i>b</i> , #2 <i>c</i> , #3 <i>c</i>	No	None	Death at 12 months, RSV pneumonia and sepsis		
11, F	T ⁻ B ⁻ NK ⁻ , ADA ⁻	MUD 6/6	38	Recurrent pneumonia, Parvovirus	53	<i>e</i>	Yes	None	Alive, in elementary school	7	Asthma, eczema
12, M	T ⁻ B ⁺ NK ⁻ , IL2 γ R	Mother 3/6, CD34 ⁺ Isolation	0.1	None	1.5	<i>a</i>	Yes	None	Alive, well	2.5	Anemia
13, M	T ⁻ B ⁺ NK ⁻	MUD 6/6	6	PCP	12	<i>a</i>	Yes	None	Alive, well	2	Anemia
14, M	T ⁻ B ⁺ NK ⁻ , IL2 γ R	#1 MUD 6/6, #2 MUD	13	Disseminated varicella	16,18	#1 <i>b</i> , #2 <i>b</i> §	No	None	Death at 19 months, culture-negative sepsis		
15, F	T ⁻ B ⁺ NK ⁻	#1 Father 4/6, CD34 ⁺ Isolation, #2 Father, CD34 ⁺ Isolation, #3 Father (boost), CD34 ⁺ Isolation	10	Serratia, enterobacter, and parainfluenza type 4 pneumonia	12,13	#1 <i>b</i> , #2 <i>d</i> , #3 None	No	aGvHD, Grade IV, Sk/Gi*	Death at 19 mo, HHV6 pneumonitis, aGvHD, sepsis		
16, M	T ⁻ B ⁺ NK ⁻ , IL2 γ R	MUD 6/6	7	Rotavirus, PCP	10	<i>d</i>	Yes	None	Alive, well	2	None
17, F	T ⁻ B ⁻ NK ⁻ , AK2	MUD 6/6	1	Omphalitis, enterococcal UTI, CONS, gram-negative bacteremia, CMV	4	<i>a</i>	Yes	None	Alive, well	1.75	AIHA Eosinophilic enterocolitis
18, M	T ⁻ B ⁺ NK ⁻ , IL2 γ R	Mother 3/6, CD34 ⁺ Isolation	5.5	RSV	8	<i>b</i> §	Yes	None	Alive, well	1.75	Reactive airway disease, IgA deficiency

* Treatment with steroids, dactilizumab, infliximab, tacrolimus, mycophenylate, methylprednisolone;;

‡ Donor lymphocyte infusions administered to patient;

€ = anti-CD6, anti-CD8, and anti-CD20 antibodies;

§ = anti-CD45 antibody;

a = Bu/Cy/araC/ATG or C-1H, CSA/pred
b = Flu/C-1H, ±CSA or FK;
c = Flu/Cy/C-1H, ±CSA or FK;
d = Flu/Bu or Mel/C-1H, FK;
e = Flu/TBI/C-1H, FK;
f = C-1H

Abbreviations: Ab, antibody; AK2, adenylate kinase 2; araC, cytarabine; aGvHD, acute graft-versus-host disease; ADA[−], adenosine deaminase deficiency; AIHA, autoimmune hemolytic anemia; ATG, antithymocyte globulin; Bu, busulfan; C-1H, campath-1H; CMV, cytomegalovirus; CONS, coagulase negative staphylococcus; CSA, cyclosporine; Cy, cytoxan; F, female; FK, Tacrolimus; Flu, fludarabine; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplant; HHV6, human herpes virus 6; IL2γR, mutation in the common gamma chain of the interleukin-2 receptor; IL7Rα, mutation in the alpha chain of the interleukin-7 receptor; M, male; Mel, melphalan; MMRD, mismatched related donor; MUD, matched unrelated donor; PCP, *Pneumocystis jiroveci* pneumonia; RAG, mutation in the recombination activating gene; RSV, respiratory syncytial virus; RD, reticular dysgenesis; SCID, severe combined immunodeficiency; Sk/Liv/Gi, Skin/Liver/Gastrointestinal; TBI, total body irradiation; T[−]B⁺NK⁺, T cell count and function reduced, B cell count normal or increased, and natural killer cell count normal; T[−]B[−]NK⁺, T cell count and function reduced, B cell count normal or increased, and natural killer cell count reduced; UTI, urinary tract infection.

Table II

Immunologic evaluation of SCID survivors after HSCT (1998–2007).

Patient	Last evaluation post HSCT (mo)	CD3 ⁺ T cells/ml	PHA/ConA/P WM response [†] (×1,000)	Can/SK/Tet response (×1,000)	T cell/B cell donor chimerism (%/%)	IVIg treatment	IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)	IgE (IU/ml)	Response to Vaccines (Pr) (Ps) ‡
1	118	1042*	60*/32*/26*	5.2/0*/0.4*	(100/0)	Yes	456*	<4*	14*	<4	ND
3	55	682*	213/1/55	5.4/18.9	(84/45)	No	761	200	81	7.7	Pr, Ps
4	38	2011	220/117/113	16/0*/0.4*	(100/100)	No	908	86	191	41	ND
5	58	936*	270/150/67	3.2/0.3*/61	(100/100)	No	998	168	240	98	Pr
6	46	2412	339/255/151	34/0.5*/78.4	(100/100)	No	1180	106	191	104*	Pr, Ps
7	41	1545	385/278/119	13/0.3*/68.1	(100/100)	No	1260	73	141	223*	Pr
8	34	5622	360/263/140	1.2/0.8/38.5	(100/29)	No	835	<6*	62.6	<4	Pr, Ps
11	30	1851	202/141/77	12.8/0*/81.0	(100/100)	No	1210	220	195	306	Pr
12	29	4047	248/47*/96	17.3/0.1*/61	(100/19)	Yes	355*	73	207	<4	ND
13	12	1071*	141*/52*/68	0.7/0*/1.2	(100/0)	No	932	32	115	8.3	Pr, Ps
16	14	2576	353/154/130	3.9/22.5/6.6	(100/0)	Yes	614	17	52	<4	ND
17	17	1517*	358/293/71	4.8/1.2	(100/100)	Yes	852	81	87	ND	ND
18	14	2799	174/105/47	0.2*/0.1*/3	(97/0)	Yes	625	<6*	29*	<4	ND
19	105	670*	302/117/80	69/1.3/20.7	(100/96)	No	1090	250	100	1330*	Pr, Ps
20	106	2880	135*/12*/57	19.2/2.2*/4.7	(100/3)	No	1090	295	99	12	Pr, Ps
21	65	3141	323/212/48	21.9/3*/77	(100/90)	No	1240	219	215	92*	Pr, Ps
22	60	2074	323/159/58	0.2*/0.1*/38	(100/100)	No	980	83	152	<4	Pr, Ps
23	14	1026*	320/1/78	64.6/0*	(97/5)	Yes	506	124	111	229*	ND

* abnormal values

‡ protective antibody titers present

† normal values: PHA (10 µg/ml) = 165,549–307,659 counts per minute (cpm); ConA (50 µg/ml) = 93,548–245,877cpm; PWM (100 µg/ml) = 42,095–138,816cpm

Abbreviations: Can, candida; ConA, concanavalin A; D, donor; HSCT, hematopoietic stem cell transplant; IVIG, intravenous immunoglobulin; ND, data not available; PHA, phytohemagglutinin; Pr, Protein; Ps, Polysaccharide; PWM, pokeweed mitogen; SCID, severe combined immunodeficiency; SK, streptokinase; Tet, tetanus

Table IIIComparison of outcomes in 48 transplanted SCID patients with and without conditioning from 1981–2007.[†]

	MMRD group, no conditioning (n=21)	MMRD/MUD group, with conditioning (n=17)	MRD group (n=10)
Survival at 1 Year Post-HSCT			
B⁻ SCID	1/4 (25%)	4/6 (67%)	5/5 (100%)
B⁺ SCID	12/17 (71%)	8/11 (73%)	5/5 (100%)
Graft-versus-host Disease:			
Grade II–IV	11/21 (52%)	2/17 (12%)	1/10 (10%)
Survived	4/11 (36%)	1/2 (50%)	1/1 (100%)
Long-Term Complications in Survivors:	(n=11)	(n=12)	(n=10)
Autoimmune	2 (18%)	1 (8%)	1 (10%)
Dermatologic	4 (36%)	3 (25%)	2 (20%)
Endocrine	2 (18%)	0 (0%)	1 (10%)
Gastrointestinal	4 (36%)	0 (0%)	0 (0%)
Hematologic	0 (0%)	2 (17%)	0 (0%)
Neurologic	3 (27%)	2 (17%)	1 (10%)
Respiratory	5 (45%)	6 (50%)	3 (30%)
Immunoreconstitution in Survivors	(n=11)	(n=12)	(n=10)
Donor T cell	11 (100%)	12 (100%)	10 (100%)
Donor B cell	5 (45%)	8 (67%)	7 (70%)
Health and Educational Achievement:			
School in age eligible children	9/11 (82%)	5/5 (100%)	8/8 (100%)

[†] = Table contains data from 23 patients from this study and 25 patients from a previous study.⁷