

Outcomes of patients with severe combined immunodeficiency treated with hematopoietic stem cell transplantation with and without preconditioning

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Background: The effect of pretransplantation conditioning on the long-term outcomes of patients receiving hematopoietic stem cell transplantation for severe combined immunodeficiency (SCID) has not been completely determined.

Objective: We sought to assess the outcomes of 23 mostly conditioned patients with SCID and compare their outcomes with those of 25 previously reported nonconditioned patients with SCID who underwent transplantation.

Methods: In the present study we reviewed the medical records of these 23 consecutive, mostly conditioned patients with SCID who underwent transplantation between 1998 and 2007.

Results: Eighteen patients (median age at transplantation, 10 months; range, 0.8-108 months) received haploidentical mismatched related donor, matched unrelated donor, or mismatched unrelated donor transplants, 17 of whom received pretransplantation conditioning (with 1 not conditioned); 13 (72%) patients engrafted with donor cells and survive at a median of 3.8 years (range, 1.8-9.8 year); 5 (38%) of 13 patients require intravenous immunoglobulin; and 6 of 6 age-eligible children attend school. Of 5 recipients (median age at transplantation, 7 months; range, 2-23 months) of matched related donor transplants, all 5 engrafted and survive at a median of 7.5 years (range, 1.5-9.5 year), 1 recipient requires intravenous immunoglobulin, and 3 of 3 age-eligible children attend school. Gene mutations were known in 16 cases: mutation in the common γ chain of the IL-2 receptor (*IL2RG*) in 7 patients, mutation in the α chain of the IL-7 receptor (*IL7RA*)

in 4 patients, mutation in the recombina-activating gene (*RAG1*) in 2 patients, adenosine deaminase deficiency (*ADA*) in 2 patients, and adenylate kinase 2 (*AK2*) in 1 patient. Early outcomes and quality of life of the previous nonconditioned versus the present conditioned cohorts were not statistically different, but longer-term follow-up is necessary for confirmation.

Conclusions: Hematopoietic stem cell transplantation in patients with SCID results in engraftment, long-term survival, and a good quality of life for the majority of patients with or without pretransplantation conditioning. (*J Allergy Clin Immunol* 2009;124:1062-9.)

Key words: Hematopoietic stem cell transplantation, graft-versus-host disease, severe combined immunodeficiency, immune reconstitution, primary immunodeficiency, conditioning

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 pretransplantation conditioning and nonconditioning regimens are currently not well defined.

The highest success rate for HSCT in patients with SCID 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 infants with SCID. 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 with MRDs. The National Bone Marrow Registry has made matched unrelated donor (MUD) bone marrow and cord blood transplantations possible and has expanded the donor alternatives for transplantations. Because of a poor ability to mount an immune response, myeloablative conditioning of the SCID host before 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 patients with SCID without pretransplantation conditioning,⁷ and we now report on the HSCT (1998-2007) of an additional 23 patients with SCID, including 19 conditioned patients with SCID undergoing transplantation with MRD, MMRD,

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Abbreviations used

GvHD: Graft-versus-host disease
HSCT: Hematopoietic stem cell transplantation
IVIG: Intravenous immunoglobulin
MMRD: Mismatched related donor
MRD: Matched related donor
MUD: Matched unrelated donor
SCID: Severe combined immunodeficiency

MUD, or mismatched unrelated donor (MMUD) bone marrow. We summarize the outcomes of all 48 patients with SCID and analyze outcomes with regard to pretransplantation conditioning.

METHODS

Medical chart review

Records of 23 patients with SCID undergoing HSCT, 5 receiving MRD transplants and 18 receiving alternative donor transplants (10 haploidentical MMRDs, 6 MUDs, 1 MMUD, and 1 cord blood), at Texas Children's Hospital from 1998 through 2007 were reviewed. The patients receiving an MMUD transplant (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 provided informed consent.

Pretransplantation conditioning and GvHD prophylaxis

Eighteen patients receiving 29 haploidentical MMRD, MUD, or MMUD transplants from 1998 to 2007 were given pretransplantation conditioning, except for 1 patient who received an MMRD transplant and did not receive preconditioning. Five patients received 6 MRD transplants, 2 of whom were given conditioning because of older age and residual natural killer cells. Pretransplantation conditioning, including busulfan, cytarabine, antithymocyte globulin plus cyclophosphamide, or fludarabine, was performed in 13 patients (Table 1 and see Table E1 in this article's Online Repository at www.jacionline.org). Fludarabine and anti-CD52 antibody (Campath-1H) were used in 7 patients, with 1 patient also receiving cyclophosphamide and 2 patients receiving anti-CD45 mAb. Campath-1H alone was used in 1 patient. Donor PBMCs were processed for CD34⁺ cell selection with Isolex (Baxter International Inc, Deerfield, Ill, 19 grafts for 10 patients) to reduce the incidence of GvHD associated with using haploidentical MMRD grafts. Treatment of donor bone marrow with anti-CD6, anti-CD8, and anti-CD20 mAbs 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 1 cord blood products were $5.09 \times 10^8 \pm 0.7 \times 10^8$ cells/kg (mean $\pm$ 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 5 bone marrow grafts treated with mAbs for T-cell depletion was $24.9 \times 10^8 \pm 14.0 \times 10^8$ cells/kg (mean $\pm$ 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 was $0.25 \times 10^8 \pm 3.7 \times 10^6$ 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 5×10^4 cells/kg

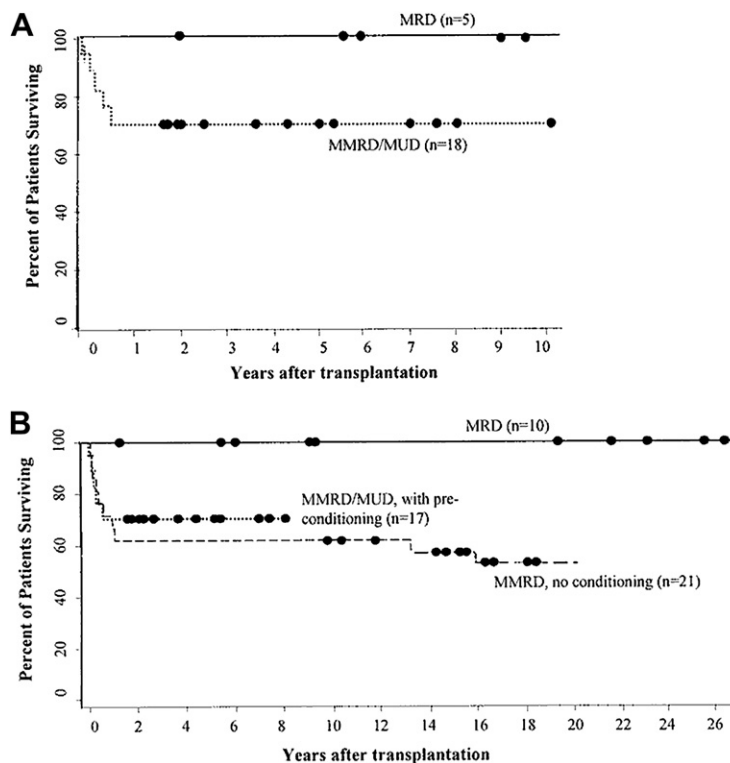


FIG 1. A, Kaplan-Meier curve analyzing the survival of patients with SCID, including 18 patients who received MMRD or MUD transplants and 5 patients who received MRD transplants. B, Kaplan-Meier curve demonstrating survival of patients with SCID, including 21 patients who received MMRD transplants without host preconditioning, 17 patients who received MMRD/MUD transplants with host preconditioning, and 10 patients who received MRD transplants. The illustration contains data from 23 patients from this study and 25 patients from a previous study.⁷

TABLE I. Outcomes of 18 patients with SCID (17 pretransplantation conditioned) who received MMRD or MUD HSCT from 1998 through 2007

Patient no., sex	Phenotype, molecular diagnosis	Donor, HLA match (no./total), T-cell depletion, cell selection	Age at diagnosis (mo)	Pre-HSCT infections
1, male	T ⁺ B ⁺ NK ⁻ , <i>IL2RG</i>	Mother 3/6‡	0.1	None
2, female	T ⁻ B ⁻ NK ⁺ , <i>RAG1</i>	#1 Father 3/6, ‡#2 father‡	0.25	PCP, salmonella, group B sepsis, rhinovirus, <i>Mycobacterium chelonae</i> -induced pneumonia, cutaneous candidiasis
3, male	T ⁻ B ⁻ NK ⁺	#1 Mother 4/6, ‡#2 mother,‡ #3 mother, CD34 ⁺ isolation	0.25	None
4, female	T ⁻ B ⁻ NK ⁺	#1 Mother 3/6, CD34 ⁺ isolation, #2 mother, CD34 ⁺ isolation, #3 brother 3/6, CD34 ⁺ isolation	0.1	<i>Proteus</i> and <i>Pseudomonas</i> species-induced pneumonia, PCP, and CMV
5, female	T ⁻ B ⁺ NK ⁺	#1 MUD, 6/6, #2 MUD, CD34 ⁺ isolation	2	<i>Enterobacter cloacae</i> -induced pneumonia, <i>Bipolaris</i> species-induced pneumonia, oral thrush, RSV-induced pneumonia
6, male	T ⁻ B ⁺ NK ⁺ , <i>IL7RA</i>	#1 Mother 3/6, CD34 ⁺ isolation, #2 father 3/6, CD34 ⁺ isolation, #3 father (boost), CD34 ⁺ isolation	9.5	PCP, adenovirus diarrhea
7, male	T ⁻ B ⁺ NK ⁺ , <i>IL7RA</i>	#1, Father 3/6, CD34 ⁺ isolation, #2 father (boost)	6	PCP, adenovirus, rotavirus
8, male	T ⁻ B ⁺ NK ⁻ , <i>IL2RG</i>	Mother 3/6, CD34 ⁺ isolation	5.5	<i>Candida</i> species, nocardia
9, male	T ⁻ B ⁻ NK ⁻ , <i>ADA</i> ⁻	MMUD 5/6	0.1	Varicella zoster disseminated
10, male	T ⁻ B ⁺ NK ⁻ , <i>IL2RG</i>	#1, Mother 4/6, CD34 ⁺ isolation, #2 mother, CD34 ⁺ isolation, #3 father 3/6, CD34 ⁺ isolation	0.1	PCP, RSV, rotavirus, <i>Enterobacter cloacae</i> -induced bacteremia, <i>Klebsiella</i> species-induced UTI and bacteremia, CMV-induced pneumonia
11, female	T ⁻ B ⁻ NK ⁻ , <i>ADA</i> ⁻	MUD 6/6	38	Recurrent pneumonia, Parvovirus
12, male	T ⁻ B ⁺ NK ⁻ , <i>IL2RG</i>	Mother 3/6, CD34 ⁺ isolation	0.1	None
13, male	T ⁻ B ⁺ NK ⁻	MUD 6/6	6	PCP
14, male	T ⁻ B ⁺ NK ⁻ , <i>IL2RG</i>	#1 MUD 6/6, #2 MUD	13	Disseminated varicella
15, female	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-induced pneumonia
16, male	T ⁻ B ⁺ NK ⁻ , <i>IL2RG</i>	MUD 6/6	7	Rotavirus, PCP
17, female	T ⁻ B ⁻ NK ⁻ , <i>AK2</i>	MUD 6/6	1	Omphalitis, enterococcal UTI, CONS, gram-negative bacteremia, CMV
18, male	T ⁻ B ⁺ NK ⁻ , <i>IL2RG</i>	Mother 3/6, CD34 ⁺ isolation	5.5	RSV

Sk/Liv/Gi, Skin/liver/gastrointestinal; T⁻B⁺NK⁻, T-cell count and function reduced, B-cell count normal or increased, and natural killer cell count reduced; *IL2GR*, mutation in the common γ chain of the IL-2 receptor; T⁻B⁻NK⁺, T-cell count and function reduced, B-cell count reduced, natural killer cell count normal; *RAG*, mutation in the recombinase-activating gene; PCP, *Pneumocystis jirovecii*-induced pneumonia; CMV, cytomegalovirus; T⁻B⁺NK⁺, T-cell count and function reduced, B-cell count normal or increased, and natural killer cell count normal; RSV, respiratory syncytial virus; *IL7RA*, mutation in the α chain of the IL-7 receptor; *HHV6*, human herpes virus 6; *aGvHD*, acute graft-versus-host disease; *ADA*⁻, adenosine deaminase deficiency; UTI, urinary tract infection; *AK2*, adenylate kinase 2; CONS, coagulase-negative staphylococcus; *AIHA*, autoimmune hemolytic anemia; Bu, busulfan; Cy, cytoxan; araC, cytarabine; ATG, antithymocyte globulin; C-1H, campath-1H; pred, prednisone; Flu, fludarabine; CSA, cyclosporine; FK, tacrolimus; Mel, melphalan; TBI, total body irradiation. *Treatment with steroids, daclizumab, infliximab, tacrolimus, mycophenylate, and methylprednisolone.

†Donor lymphocyte infusions administered to patient.

‡Anti-CD6, anti-CD8, and anti-CD20 antibodies.

§Anti-CD45 antibody.

¶Bu/Cy/araC/ATG or C-1H, CSA/pred.

||Flu/C-1H, $\pm$ CSA or FK.

#Flu/Cy/C-1H, $\pm$ CSA or FK.

**Flu/Bu or Mel/C-1H, FK.

††Flu/TBI/C-1H, FK.

‡‡C-1H.

Age at HSCT (mo)	Conditioning, GvHD prophylaxis	Engrafted	GvHD, Sk/Liv/Gi	Outcome/age, cause of death	Age at last follow-up (y)	If alive, complications at follow-up
0.75	None	Yes	None	Alive, in elementary school	9.75	Asthma, migraines, protein-losing enteropathy, warts, IgA deficiency
6, 7	#1, #2 none	No	None	Death at 7 mo, PCP, <i>Enterococcus faecalis</i> -induced sepsis		
1, 5, 23	#1 None, #2 none, #3	Yes	None	Alive, in elementary school	7.5	Asthma, fire ant hypersensitivity
10, 12, 14	#1, ‡‡#2, ¶ #3	Yes	None	Alive, in elementary school	8	
5, 13	#1, #2 none	Yes	None	Alive, in elementary school	5.25	Allergic rhinitis, eczema, poor growth, dental caries
13, 15, 17	#1, #2, ¶ #3 none	Yes	None	Alive, in elementary school	5	Speech delay, chronic HHV6 infection, reactive airway disease
9,10	#1, ¶#2 none	Yes	aGvHD, skin	Alive, well	4.25	Asthma
12		Yes	None	Alive, well	3.75	IgA deficiency
108		No	None	Death at 111 mo, adenovirus enterocolitis and sepsis		
8, 9, 10.5	#1, ¶#2, ##3#	No	None	Death at 12 mo, RSV-induced pneumonia and sepsis		
53	††	Yes	None	Alive, in elementary school	7	Asthma, eczema
1.5		Yes	None	Alive, well	2.5	Anemia
12		Yes	None	Alive, well	2	Anemia
16, 18	#1, ¶#2¶§	No	None	Death at 19 mo, culture-negative sepsis		
	#1, ¶#2, ¶#3 none	No	aGvHD, grade IV, Sk/Gi*	Death at 19 mo, HHV6-induced pneumonitis, aGvHD, sepsis		
12, 13						
10	**	Yes	None	Alive, well	2	None
4		Yes	None	Alive, well	1.75	AIHA
						eosinophilic enterocolitis
8	¶,§	Yes	None	Alive, well	1.75	Reactive airway disease, IgA deficiency

kg or greater, included cyclosporine (2.5 mg/kg) or tacrolimus (0.03 mg/kg) alone or combined with methylprednisolone.

Molecular analysis

Molecular analysis for SCID genetic defects was performed on extracted DNA (Correlagen, Waltham, Mass; National Institutes of Health, Bethesda, Md; Gene DX, Gaithersburg, Md). Adenosine deaminase levels in all patients were assessed (Baylor Cytogenetics, Houston, Tex).

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, bone marrow, or both by using fluorescence *in situ* hybridization probes for sex chromosomes (sex-mismatched transplants) or PCR 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 χ^2 test was used to test differences between percentages, and the Fisher exact test was used when 1 or more expected values was less than 5 (STATA 9.0 for Windows). Survival at fixed time points was compared by using the log-rank test. A *P* value of less than .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 (see Table E2 in this article's Online Repository at www.jacionline.org) between 1998 and 2007. The source of hematopoietic stem cells was bone marrow (*n* = 19), peripheral blood stem cells (*n* = 18), or cord blood (*n* = 1; Table I, patient 17). The median age at first transplantation for 23 patients with SCID was 10 months (range, 0.8-108 months): 10 months (range, 1-108 months) for the MMRD/MUD group and 7 months (range, 2-23 months) for the MRD group. Molecular defects were known in 16 of 23 patients (see Table E2). Twelve of the 18 patients in the MMRD/MUD group had B⁺ SCID compared with 4 of 5 in the MRD group (see Table E2).

Engraftment of donor cells and survival

Among 18 recipients of MMRD/MUD transplants (Table I), all but 1 (patient 1) received pretransplantation 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 donor cell engraftment failed twice (Table I, patient 3). Donor cell engraftment and survival occurred in 13 (72%; 95% CI, 46% to 89%) of 18 MMRD/MUD transplant recipients and 5 (100%; 95% CI, 46% to 100%) of 5 MRD transplant recipients (*P* = .4, Kaplan-Meier curve; Fig 1, A). Survival among conditioned MMRD recipients (7/10 [70%]) was similar to that seen among MUD recipients (5/7 [71%]). Median follow-up among MRD, MMRD, and MUD recipients was 7.5 years (range, 1.5-

9.5 years), 4.3 years (range, 1.8-8 years), and 2 years (range, 1.8-7 years), respectively. Five patients died between 1 and 7 months (mean, 4 months) after transplantation, and none died 1 year after transplantation. Two of these patients received 3 donor lymphocyte infusions to treat viral infections (Table I, patients 9 and 15).

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

Among recipients of MRD transplants, 3 of 5 patients (see Table E1) presented with life-threatening infections before transplantation, including rotavirus (*n* = 2) and varicella zoster virus (*n* = 1).

GvHD

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

Transplacentally transferred maternal T cells were present in 2 patients in the MMRD/MUD group (Table I, patients 17 and 18). Patient 17 presented with skin GvHD before HSCT caused by 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 human herpes virus 6 infection, *n* = 1), hematologic abnormalities (anemia, *n* = 4, autoimmune in 2 cases and iron deficient in 2 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 and 17). Among patients in the MRD group (see Table E1), there were respiratory abnormalities (asthma, *n* = 2), dermatologic manifestations (viral source warts, *n* = 1), infectious complication (chronic human herpes virus 6 infection, *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 transplantation was 38.9 months (range, 12-118 months) for 13 survivors (Table II, patients 1, 3-8, 11-13, and 16-18) who received MMRD/MUD transplants, and 70.0 months (range, 14-106 months) for 5 survivors (Table II, patients 19-23) who received MRD transplants. At the last follow-up, 8 of 13 survivors in the MMRD/MUD group and 3 of 5 in the MRD group had CD3⁺ T-cell numbers within the normal range (see Fig E1, A and D, in this article's Online Repository at www.jacionline.org; Table II). The percentages of patients with CD3⁺ T-cell numbers within the normal range at 1, 3, and 5 years after transplantation follow-up were 61%, 66%, and 60% in the MMRD/MUD group and 40%, 75%, and 75% in the MRD group, respectively. These differences were not statistically significant. Lymphocyte proliferative responses to PHA were normal or greater than 80% of

TABLE II. Immunologic evaluation of SCID survivors after HSCT (1998-2007)

Patient no.	Last evaluation after HSCT (mo)	CD3 ⁺ T cells/mL	PHA/ConA/PWM response† (× 1000)	Can/SK/Tet response (× 1000)	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	1,042*	60*/32*/26*	5.2/0*/0.4*	(100/0)	Yes	456*	<4*	14*	<4	ND
3	55	682*	213/ /55	5.4/ /18.9	(84/45)	No	761	200	81	7.7	Pr, Ps
4	38	2,011	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	2,412	339/255/151	34/0.5*/78.4	(100/100)	No	1,180	106	191	104*	Pr, Ps
7	41	1,545	385/278/119	13/0.3*/68.1	(100/100)	No	1,260	73	141	223*	Pr
8	34	5,622	360/263/140	1.2/0.8/38.5	(100/29)	No	835	<6*	62.6	<4	Pr, Ps
11	30	1,851	202/141/77	12.8/0*/81.0	(100/100)	No	1,210	220	195	306	Pr
12	29	4,047	248/47*/96	17.3/0.1*/61	(100/19)	Yes	355*	73	207	<4	ND
13	12	1,071*	141*/52*/68	0.7/0*/1.2	(100/0)	No	932	32	115	8.3	Pr, Ps
16	14	2,576	353/154/130	3.9/22.5/6.6	(100/0)	Yes	614	17	52	<4	ND
17	17	1,517*	358/293/71	4.8/ /1.2	(100/100)	Yes	852	81	87	ND	ND
18	14	2,799	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	1,090	250	100	1330*	Pr, Ps
20	106	2,880	135*/12*/57	19.2/.2*/4.7	(100/3)	No	1,090	295	99	12	Pr, Ps
21	65	3,141	323/212/48	21.9/.3*/77	(100/90)	No	1,240	219	215	92*	Pr, Ps
22	60	2,074	323/159/58	0.2*/0.1*/38	(100/100)	No	980	83	152	<4	Pr, Ps
23	14	1,026*	320/ /78	64.6/ /0*	(97/5)	Yes	506	124	111	229*	ND

ConA, Concanavalin A; PWM, pokeweed mitogen; Can, *Candida* species; SK, streptokinase; Tet, tetanus; Pr, protein; Ps, polysaccharide; ND, data not available.

*Abnormal values.

†Normal values: PHA (10 µg/mL) = 165,549 to 307,659 counts/min; ConA (50 µg/mL) = 93,548 to 245,877 counts/min; PWM (100 µg/mL) = 42,095 to 138,816 counts/min.

‡Protective antibody titers present.

the lower limit of normal in 12 of 13 patients in the MMRD/MUD group and 5 of 5 patients in the MRD group. Antigen-specific lymphocyte proliferation was demonstrated against at least 1 antigen in all patients. Donor-host chimerism was established within 1 year after HSCT and did not change in the 18 survivors. Studies performed in sorted PBMCs demonstrated that T-cell engraftment was present in all survivors, and 9 of 13 patients in the MMRD/MUD group and 5 of 5 patients in the MRD group had some evidence of B-cell engraftment. Of those survivors with the B⁺ SCID phenotype, 6 (60%) of 10 in the MMRD/MUD group and 4 (100%) of 4 in the MRD group had evidence of B-cell engraftment compared with 3 (100%) of 3 in the MMRD/MUD and 1 (100%) of 1 in the MRD group with the B⁻ SCID phenotype.

Those requiring intravenous immunoglobulin (IVIG) at the time of this report included 5 (38%) of 13 survivors in the MMRD/MUD group. Three of these 5 patients have received HSCT less than 24 months ago. One of the other 2 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 of 7 patients evaluated in the MMRD/MUD group and 4 of 4 patients in the MRD group, *Streptococcus pneumoniae* (>1.0 µg/mL) in 6 of 7 patients in the MMRD/MUD and 4 of 4 patients in the MRD group, and *Haemophilus influenzae* type b (>0.15 µg/mL) in 4 of 5 patients in the MMRD/MUD group and 4 of 4 in the MRD group (Table II).

Natural killer cell counts at the most recent evaluation were normal in 7 (54%) of 13 patients in the MMRD/MUD group and 4 (80%) of 5 patients in the MRD group (see Fig E1, B and E). CD19⁺ B-cell numbers were normal at the last follow-up in 8 (62%) of 13 patients in the MMRD/MUD group and 4 of 5 patients in the MRD group (see Fig E1, C and F). At the 1-year

posttransplantation follow-up visit, naive CD4⁺CD45RA⁺ T-cell counts were normal in 6 (46%) of 13 patients in the MMRD/MUD group (median, 432 cells/µL; range, 16-2035 cells/µL) and 3 (60%) of 5 patients in the MRD group (median, 1,009 cells/µL; range, 8-1256 cells/µL; data not shown).

Health and educational accomplishment

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

Comparison between patients with SCID given conditioning or no conditioning before HSCT

We analyzed the present patient cohort together with the cohort we previously published to examine the use of pretransplantation conditioning.

Survival. Fig 1, B, presents a Kaplan-Meier curve representing the survival of 48 patients with SCID undergoing HSCT transplantations in our center, including nonconditioned MMRD recipients,⁷ conditioned MMRD and MUD recipients, and MRD recipients, of whom 2 received preconditioning. The Kaplan-Meier survival estimates were calculated at 1, 3, and 5 years after transplantation, resulting in the cumulative survival of 7 (70%; 95% CI, 34% to 93%) of 10 for the conditioned MMRD children and 5 (71%; 95% CI, 25% to 100%) of 7 for conditioned MUD children undergoing HSCT for all 3 time points ($P = .99$, log-rank test). Without pretransplantation conditioning, a comparable MMRD group yielded a cumulative survival at 1, 3, and 5 years after transplantation of 13 (62%; 95% CI, 46% to 87%) of 21. The entire MRD group survived (100%; 95% CI, 46% to 100%), and their survival difference with each of the other groups was statistically significant ($P = .04$). Patients with the B⁻ cell

TABLE III. Comparison of outcomes in 48 patients with SCID undergoing transplantation with and without pretransplantation conditioning from 1981 through 2007*

	MMRD group, no condition- ing (n = 21)	MMRD/MUD group, with conditioning (n = 17)	MRD group (n = 10)
Survival at 1 y after HSCT			
B ⁻ SCID	1/4 (25%)	4/6 (67%)	5/5 (100%)
B ⁺ SCID	12/17 (71%)	8/11 (73%)	5/5 (100%)
GvHD			
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

phenotype treated with an MMRD graft and no conditioning had the lowest survival rate (Table III).

GvHD. GvHD grades II to IV occurred in 2 (12%) of 17 conditioned MMRD and MUD recipients who also received GvHD prophylaxis compared with 11 (52%) of 21 of nonconditioned MMRD recipients who did not receive GvHD prophylaxis ($P = .02$, Tables I and 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 and 3 years after HSCT, and the other 2 presented after 6 and 8 years, respectively.

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

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 (67%) of 12 conditioned MMRD/MUD recipients, 5 (45%) of 11 nonconditioned MMRD recipients, and 7 (70%) of 10 MRD recipients. These estimates were not statistically different and did not change over follow-up.

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. Five (100%) of 5 age-eligible children in the MMRD/MUD group who received conditioning attend school, and 9 (82%) of 11 age-eligible children in the MMRD group without conditioning attend school (1 attends college). Two patients in the MMRD group without preconditioning gave birth to 3 healthy infants.

DISCUSSION

We describe the long-term outcomes of 23 children with SCID who received HSCT (19 with pretransplantation conditioning) from 1998 through 2007. We have previously reported on 25 patients with SCID undergoing transplantation without conditioning from 1981 through 1995.⁷ We found increased survival of MMRD/MUD patient groups receiving pretransplantation conditioning compared with that seen in the nonconditioned MMRD group; however, the differences did not achieve statistical significance (possibly because of the relatively small patient numbers).

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

Donor cell engraftment and survival were 100% in MRD recipients, including 2 with conditioning. All patients who were donor cell 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 pretransplantation conditioning. Mortality occurred in the first year after 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 more than 10 years after transplantation. No effect on survival of the type of graft, cell dose, or SCID type was identified.

GvHD grades II to IV were less frequent in the MMRD/MUD group with pretransplantation conditioning than in the MMRD group without conditioning. The difference seen between these groups might 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 although most patients who received MMRD/MUD with pretransplantation 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 pretransplantation 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 might have influenced this outcome.

Engraftment rates similar to ours have been reported for pretransplantation conditioned MMRD recipients (59% to 70%),¹⁰⁻¹² for nonconditioned MMRD recipients (78%),^{1,13} and for MRD recipients (100%),^{10,13} regardless of pretransplantation conditioning. The survival rate of 92% to 100% of MRD recipients in other published studies^{1,2,10,14} 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 after transplantation.² We found an apparently lower survival rate for patients with SCID with a B⁻ phenotype than those with a B⁺ phenotype, unless given an MRD transplant, which is also supported by the literature.^{11,15-17}

No significant differences in donor B-cell engraftment regarding the use of pretransplantation conditioning were found. There were fewer patients with donor B-cell engraftment among those who did not receive conditioning than among those who did; however, there was 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.¹⁶ Pretransplantation conditioning did not appear to reduce dependence on IVIG infusion among haploidentical recipients.

Most of the survivors in both the nonconditioned and conditioned groups have attained educational goals and maintain a good quality of life, which is similar (88% to 100%) to other reports in the literature.^{4,14}

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Clinical implications: HSCT in patients with SCID with and without pretransplantation conditioning appears to yield favorable outcomes.

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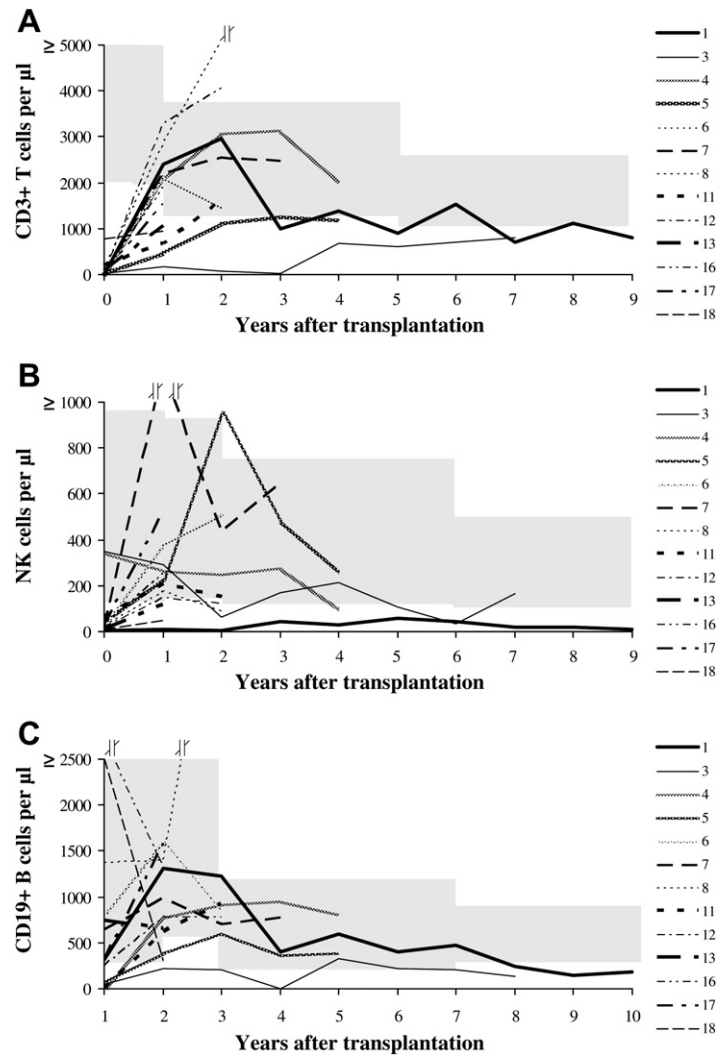


FIG E1. Lymphocytes in patients with SCID: CD3⁺ T cells (**A**), NK⁺ cells (**B**), and CD19⁺ B cells (**C**) in 13 survivors who received MMRD/MUD bone marrow and CD3⁺ T cells (**D**), NK⁺ cells (**E**), and CD19⁺ B cells (**F**) in 5 survivors who received unmanipulated bone marrow. The 10th and 90th percentile normal values are represented by shaded areas.⁹

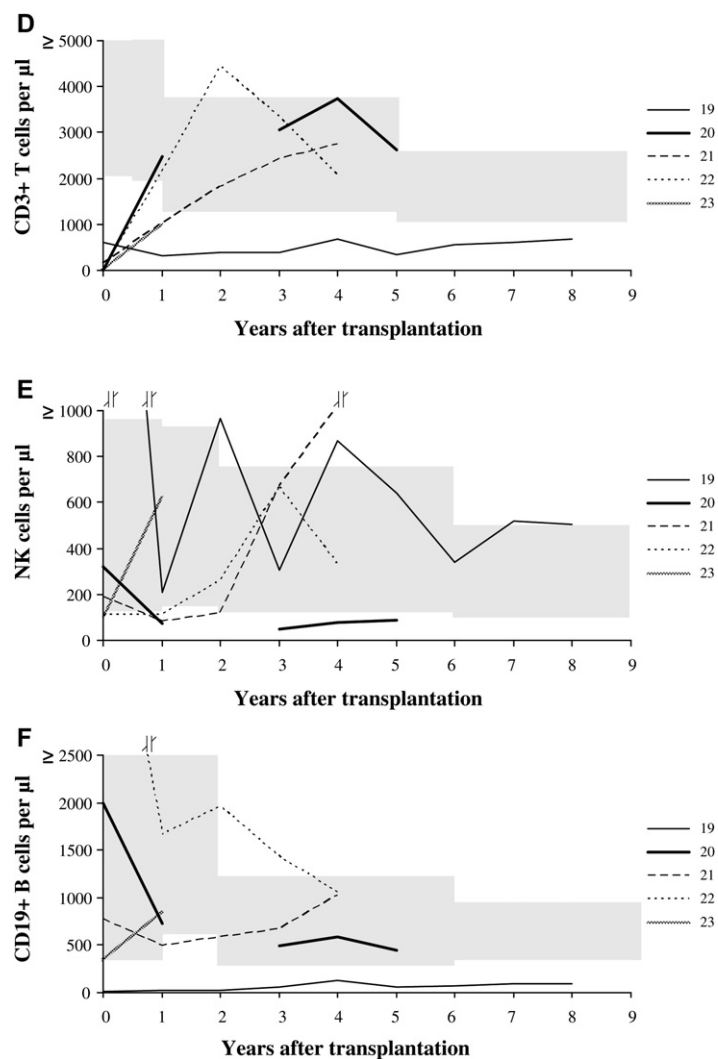


FIG E1. (Continued)

TABLE E1. Outcomes of 5 patients with SCID (2 conditioned) who received MRD HSCT from 1998 through 2007

Patient no., sex	Phenotype, molecular diagnosis	Donor, HLA match (no./total)	Age at diagnosis (mo)	Pre-HSCT infections	Age at HSCT (mo)	Conditioning, GvHD prophylaxis	Engrafted	GvHD	Outcome/age, cause of death	Age at last follow-up (y)	Complications at follow-up
19, male	T ⁻ B ⁻ NK ⁺ , <i>RAG1</i>	# 1 Sister, 6/6, #2 sister	0.1	Pneumonia	3, 8	None	Yes	None	Alive, in elementary school	9	Obesity, asthma, dental caries
20, male	T ⁻ B ⁺ NK ⁻	Sister, 6/6	6	Rotavirus, oral thrush, <i>Escherichia coli</i> -induced UTI	7	None	Yes	None	Alive, in elementary school	9.5	Asthma, warts
21, female	T ⁻ B ⁺ NK ⁺	Sister, 6/6	13.5	Disseminated varicella zoster	23	*	Yes	None	Alive, in elementary school	7.5	Obesity, cataracts
22, female	T ⁻ B ⁺ NK ⁺ , <i>IL7RA</i>	Brother, 6/6	10.5	Rotavirus	14	*	Yes	None	Alive, in daycare	5	Well
23, male	T ⁻ B ⁺ NK ⁺ , <i>IL7RA</i>	Sister, 6/6	0.25	HHV6	2	None	Yes	None	Alive, well	1.5	HHV6 reactivation

T⁻B⁻NK⁺, T-cell count and function reduced, B-cell count reduced, and natural killer cell count normal; *RAG*, mutation in the recombina-activating gene; T⁻B⁺NK⁺, T-cell count and function reduced, B-cell count normal or increased, and natural killer cell count normal; *UTI*, urinary tract infection; *HHV6*, human herpes virus 6; *Bu*, busulfan; *Cy*, cytoxan; *araC*, cytarabine; *ATG*, antithymocyte globulin; *CSA*, cyclosporine.

*Bu/Cy/araC/ATG or Campath-1H, CSA/prednisone.

TABLE E2. Characteristics of 23 patients with SCID who received HSCT from 1998 through 2007

	MMRD group, no conditioning (n = 1)	MMRD/MUD group, with preconditioning (n = 17)	MRD group, no preconditioning (n = 3)	MRD group, with preconditioning (n = 2)
No. of transplantations	1	28	4	2
Sex (%)				
Male (65)	1	11	3	0
Female (35)	0	6	0	2
Race/ethnicity (% of patients)				
White (17)	0	4	0	0
Hispanic (70)	0	11	3	2
African American (13)	1	2	0	0
Age at first transplantation (% of patients)				
<6 mo (30)	1	4	2	0
6-12 mo (44)	0	9	1	0
>12 mo (26)	0	4	0	2
Median (mo [range])	0.8	10 (1-108)	3 (2-7)	18.5 (14-23)
Phenotype (% of patients)				
$T^+B^+NK^-$ (40)	1	7	1	0
$T^+B^+NK^+$ (30)	0	4	1	2
$T^+B^-NK^+$ (17)	0	3	1	0
$T^+B^-NK^-$ (13)	0	3	0	0
Molecular defect (% of patients)				
$IL2RG$ (30)	1	6	0	0
$RAG1$ (9)	0	1	1	0
$IL7RA$ (17)	0	2	1	1
ADA^- (9)	0	2	0	0
$AK2$ (5)	0	1	0	0
Unknown (30)	0	5	1	1

$T^+B^+NK^-$, T-cell count and function reduced, B-cell count normal or increased, and natural killer cell count reduced; $T^+B^+NK^+$, 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 reduced, natural killer cell count normal; $T^+B^-NK^-$, T-cell count and function reduced, B-cell count reduced, natural killer cell count reduced; $IL2RG$, mutation in the common γ chain of the IL-2 receptor; RAG , mutation in the recombinaase-activating gene; $IL7RA$, mutation in the α chain of the IL-7 receptor; ADA^- , adenosine deaminase deficiency; $AK2$, adenylate kinase 2.