Bone Marrow Transplantation for Severe Combined Immune Deficiency

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Context Bone marrow transplantation (BMT) using stem cells obtained from a family-related, HLA-identical donor (RID) is the optimal treatment for patients with severe combined immune deficiency (SCID). In the absence of an RID, HLA-mismatched related donors (MMRDs) are often used. However, compared with RIDs, use of MMRDs for BMT is associated with reduced survival and inferior long-term immune reconstitution. Use of HLA-matched unrelated donors (MUDs) represents another potential alternative for BMT.

Objective To compare outcomes and immune reconstitution in a large cohort of patients with SCID who received RID, MUD, or MMRD BMT.

Design, Setting, and Patients Retrospective study of medical records from 94 infants diagnosed as having SCID who received BMT between 1990 and 2004 at 1 Canadian and 1 Italian pediatric referral center. Thirteen, 41, and 40 patients received RID, MUD, and MMRD BMT, respectively.

Main Outcome Measures Survival and graft failure, along with incidence of graft-vs-host disease, infections, and other complications; immune reconstitution was assessed in children who survived for more than 2 years after BMT.

Results Survival after RID BMT was highest. Twelve (92.3%) of 13 patients who received RID BMT, 33 (80.5%) of 41 who received MUD BMT, and 21 (52.5%) of 40 patients who received MMRD BMT survived. Compared with MMRD BMT, survival was significantly higher with RID (P = .008) or with MUD (P = .03). Graft failures and need for repeat BMT were more common in patients receiving MMRD BMT than in those who underwent MUD BMT. Long-term reconstitution of a full T-cell repertoire was achieved more frequently following MUD BMT (94.7%) than after MMRD BMT (61.1%) (P=.02). Acute graft-vs-host disease was documented in 73.1% of patients following MUD BMT but in only 45% after MMRD BMT (P=.009). Conversely, interstitial pneumonitis was observed more frequently after MMRD BMT (14 [35.0%] of 40) than after MUD BMT (3 [7.3%] of 41; P=.002).

Conclusion Our study suggests that in the absence of a relative with identical HLA, MUD BMT may provide better engraftment, immune reconstitution, and survival for patients with SCID than MMRD BMT.

JAMA. 2006;295:508-518 www.jama.com

Severe combined immune deficiency (SCID) is a heterogeneous group of inherited diseases with an estimated frequency of 1 in 50 000 to 100 000 live births.[1] It is characterized by significant impaired immunity leading to death in infancy unless treated by hematopoietic stem cell transplantation. The optimal treatment for most patients with SCID is bone marrow transplantation (BMT) from a related, HLA-identical donor (RID).[2] Unfortunately, such donors are found for only a minority of patients with SCID.[3,4]

As an alternative, stem cell transplantations from HLA-mismatched related donors (MMRDs) have been commonly attempted.[5] However, compiled experience of BMT for SCID from Europe revealed that in 294 recipients of MMRD BMT, 3-year survival was only 54%.[5] Furthermore, in another study, careful analysis of survival according to the degree of HLA identity showed that frank haploidentical (half-matched) transplantation resulted in only 25% to 30% long-term survival in patients with primary immunodeficiency.[6] This low success rate may reflect the intense T-cell depletion required to prevent graft-vs-host disease, which contributes to slower immune reconstitution with prolonged periods of increased susceptibility to infections.[7-9]

Human leukocyte antigen–matched unrelated donors (MUDs) represent another potential source of marrow for transplantation. There have been several reports of small groups of patients with SCID who have undergone transplantation using stem cells from MUDs, including our own experience.[5,6,10-14] However, the literature has lacked a detailed description with prolonged follow-up of a large cohort of

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patients with SCID who received MUD BMT. In addition, outcome among various phenotypes and genotypes of SCID, which may affect survival after BMT, has not been carefully analyzed.[3,15]

Recent studies have suggested a time-dependent loss of function following T cell–depleted MMRD BMT, associated with progressive lymphopenia, a restricted T-cell repertoire, decreased thymic output as indicated by reduced levels of T-cell receptor excision circles, and abnormal humoral immunity.[16,17] Little information is currently available on long-term restoration of immune function in infants with SCID treated by MUD transplantation.

Herein, we compare the long-term outcomes of a large group of patients diagnosed as having SCID who received RID, MUD, or MMRD BMT during a particular period of time.

METHODS

Patients

Two centers specializing in the management of SCID participated in this study: the Hospital for Sick Children in Toronto, Ontario, and the Department of Pediatrics at the University of Brescia, Italy. This is a retrospective analysis of data derived from patient charts and databases. All 94 patients who were diagnosed as having SCID in both centers and who received RID, MUD, or MMRD BMT between January 1, 1990, and December 31, 2004, were assessed for this study. Patients were excluded from analysis if they received BMT for HLA class II deficiency, hyper IgM syndrome, Wiskott-Aldrich syndrome, hemophagocytic lymphohistiocytosis, or X-linked lymphoproliferative disease because of the heterogeneity of clinical presentations, the selective and inconsistent nature of treatment choices, and the lack of a profound T-cell defect common to SCID. Patients were also excluded if they received another type of stem cell transplantation (eg, peripheral blood or cord blood). To assess the effect of variables such as parenteral nutrition and the introduction of new antiviral agents, which changed over the 15-year duration of the study, we evaluated survival separately during the first and second halves of the study period (1990-1997 and 1998-2004).[15] This resulted in 2 comparable groups of patients who had received either MUD or MMRD BMT in each period. The study was reviewed and approved by both hospitals' ethics boards. Written consent for participation in this study was obtained from the parents or legal guardians of all patients.

Bone Marrow Transplantation

From diagnosis until discharge, all patients were admitted to and treated in laminar-flow units.[18] Related, HLA-identical donor transplantation was the preferred treatment in both centers. In the absence of RID, in Toronto MUD BMT was offered as the preferred treatment when possible, whereas in Brescia either MMRD BMT or MUD BMT was offered. Unstable patients, defined as those who required admission to intensive care units or mechanical ventilation, were assigned to receive MMRD BMT in Brescia and MMRD BMT or MUD BMT in Toronto.

Pretransplant myeloablative conditioning, intended to eliminate residual immunity, typically included busulfan followed by cyclophosphamide.[11] Some patients also received 1 or more of the following: antithymocyte globulin, etoposide (VP16), thiotepa, melphalan, fludarabine, or methotrexate. To reduce graft-vs-host disease, MMRD bone marrow underwent ex vivo T-cell depletion using Campath IG (rat IgG2b; Wellcome Biotech, Beckenham, England) (16 patients) or $CD34^+$ selection (24 patients) as previously described,[19] while bone marrow from MUDs (41 patients) and RIDs (13 patients) was not modified. Graft-vs-host disease prophylaxis for MUD BMT consisted of cyclosporine combined with methylprednisolone and/or methotrexate.[11] In some patients, antithymocyte globulin was added.[20]

Laboratory Evaluations

Laboratory investigations for the diagnosis of SCID and for evaluating immune reconstitution after BMT included assessment of humoral and cellular immunity, as previously described.[11] Serum levels of IgG, IgM, IgA, and IgE were measured and the ability to generate antibodies to protein antigens of tetanus, polio, or hepatitis B were determined after immunization. T and B lymphocytes as well as natural killer cell markers were analyzed using flow cytometry.[21] $CD3^+$ T-lymphocyte counts of less than 1000/μL, $CD3^+CD4^+$ T-lymphocyte counts of less than 500/μL, $CD19^+$ B-lymphocyte counts of less than 50/μL, and natural killer cell counts of less than 50/μL were considered abnormal. T-cell function was assessed in vitro by comparing mitogenic responses of lymphocytes obtained from patients and healthy control individuals, as previously described.[21] Stimulation index was calculated as the ratio between stimulated and unstimulated lymphocyte responses and was considered abnormal when the patient stimulation index was less than half the response of healthy individuals. Thymic function was assessed by measuring the frequency of different T-cell receptor V_β groups and by determining T-cell receptor excision circles as recently described.[19,21] Skewed T-cell repertoire (oligoclonal) or T-cell receptor excision circles below 20 000 per 10^6 lymphocytes were considered abnormal.[19] Sequence analysis of genes typically associated with SCID was performed using standard techniques.[22,23]

Human leukocyte antigen typing to ascertain recipient-donor compatibility was performed for HLA class I (A, B) and class II (DR) using serology. Class II HLA was further analyzed by DNA hybridization with sequence-specific oligonucleotide probes.[11] To determine engraftment, the ratio between recipient and donor lymphocyte DNA was analyzed using a Y-specific probe or restriction fragment–length polymorphism.[11]

Follow-up and Complications

Patients were followed up every 2 weeks for 6 months after discharge, monthly for an additional 6 months, and then

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once every 6 to 12 months. Acute or chronic graft-vs-host disease was documented at every follow-up visit and the severity of acute graft-vs-host disease was graded according to Glucksberg et al.[24] Donor lymphocyte engraftment was determined at 1, 3, 6, 12, 18, and 24 months after BMT and yearly thereafter. Therefore, graft failure was recorded only for patients who survived more than 1 month after transplantation.[5] Graft failure was defined as an absence or progressive loss of donor lymphocytes. A period of up to 2 years after transplantation is typically required to slowly remove immune suppression prophylaxis. Therefore, long-term immune reconstitution was assessed at least 2 years after BMT and once immune suppression had been discontinued.[3]

Statistical Analysis

Survival, defined as the time from BMT to death or to last contact, was censored on December 31, 2004. Statistical analysis was performed with SAS software, version 9.1 (SAS Institute Inc, Cary, NC). Cross-classified comparisons were analyzed by χ^2 tests. Fisher exact tests were used when the expected results were 5 or fewer in cells. For comparison of continuous data, *t* tests were used and comparisons were adjusted for unequal variance. Comparison of survival rates in the treatment groups was analyzed by the log-rank test. Kaplan-Meier survival curves were constructed to graphically represent survival in the different groups. A test of proportional hazards assumption was not significant, as illustrated by the fact that the Kaplan-Meier survival curves did not cross. Two-factor Cox regressions were used to test the effect on survival of patient sex, molecular diagnosis, and the time of BMT, factors previously shown to affect prognosis.[3,5,15,25] The 2-factor models were used since the number of patients who died limited the assessment of significance with 80% power at the .05 level of significance. More than 2 factors in the same model with a sample having this number of events would have resulted in insufficient power to detect change. Differences were considered statistically significant at $P<.05$.

RESULTS

Patient Groups

Of 105 infants with SCID who received stem cell transplantation at the 2 centers during the study period, 11 were excluded. Two patients who received HLA-mismatched transplants from unrelated donors were excluded. One received a transplant from a DR-mismatched donor, while the other had a donor-recipient mixed lymphocyte reaction of 35%. A third patient, who received an unrelated bone marrow harvest that contained a low white blood cell count (likely peripheral blood), was also excluded. Also excluded from the analysis were 5 patients who received intrauterine transplants, 2 patients who received peripheral blood stem cells, and 1 patient who received a cord blood transplant.

Thirteen, 41, and 40 patients diagnosed with SCID who received RID BMT (**Table 1**), MUD BMT (**Table 2**), or MMRD BMT (**Table 3**), respectively, were included in this study. Fourteen of the MUD BMT patients have been previously reported.[11] The median ages of diagnosis were 5 months, 4 months, and 4 months, respectively. The median time from diagnosis to RID BMT was 1 month (range, 0-4 months) and the median time to MMRD BMT was 2 months (range, 0-11 months). The median time from diagnosis of SCID to MUD transplantation was 4 months (range, 1-9 months).

Myeloablation conditioning to eliminate residual recipient immunity and facilitate donor engraftment was given to 3 (25%) of 12 patients who underwent RID BMT, 40 (97.6%) of

Table 1. Diagnosis, Complications, and Outcomes of Patients With SCID Undergoing RID BMT

Patient No.	Phenotype/ Molecular Defect	Complications and Infections After BMT	Last Posttransplantation Contact, mo	Outcome	Cause of Death	Complications at Last Contact
1	γc	AGvHD grade II	154	Alive		None
2	γc	None	96	Alive		None
3	γc	None	36	Alive		None
4	T–B+NK+	None	168	Alive		None
5	IL-7Rα	None	154	Alive		None
6	FOXP3	None	154	Alive		None
7	ZAP70	Cytomegalovirus retinitis	132	Alive		None
8	ADA	None	96	Alive		Neurologic defects
9	ADA	None	42	Alive		Neurologic defects
10	ADA	AGvHD grade I	30	Alive		None
11	ADA	Vanishing bile duct syndrome	15	Deceased	Liver failure	
12	RAG1	AGvHD grade I, AC	36	Alive		None
13	Omenn	AGvHD grade III	84	Alive		None

Abbreviations: AC, autoimmune cytopenia; ADA, significantly reduced adenosine deaminase activity; AGvHD, acute graft-vs-host disease; BMT, bone marrow transplantation; FOXP3, mutation in the *FOXP3* gene; IL-7Rα, mutation in the gene for α chain of the interleukin 7 receptor; Omenn, Omenn syndrome; RAG, mutation in the recombination-activating gene; RID, family-related, HLA-identical donor; SCID, severe combined immune deficiency; T– B+NK+, T-cell count and function reduced, B-cell count normal or increased, and natural killer cell count normal; γc, mutation in the gene for common γ chain of the interleukin 2 receptor; ZAP70, mutation in the *ZAP70* gene.

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Table 2. Diagnosis, Complications, and Outcomes of Patients With SCID Undergoing MUD BMT

Patient No.	Phenotype/ Molecular Defect	Complications and Infections After BMT	Last Posttransplantation Contact, mo	Outcome	Cause of Death	Complications at Last Contact
14	γc	Lower respiratory tract infections	136	Alive		None
15	γc	AGvHD grade I	128	Alive		None
16	γc	AGvHD grade I, AC	120	Alive		None
17	γc	AGvHD grade II, AC, myopathy	108	Alive		None
18	γc	None	70	Alive		None
19	γc	AGvHD grade I, cytomegalovirus, chorioretinitis	48	Alive		Neurologic defects
20	γc	AGvHD grade IV, CGvHD (skin), repeat MUD BMT	40	Alive		None
21	γc	AGvHD grade I	18	Alive		None
22	γc	AGvHD grade II	6	Deceased	Myocarditis	
23	JAK3	AGvHD grade I	120	Alive		None
24	JAK3	AGvHD grade III	70	Alive		None
25	JAK3	AGvHD grade II	48	Alive		None
26	T–B+NK–	AGvHD grade II, CGvHD, scleroderma	140	Alive		None
27	T–B+NK–	AGvHD grade III	108	Alive		None
28	T–B+NK–	AGvHD grade II, bronchiolitis obliterans	36	Alive		None
29	T–B+NK–	AGvHD grade IV	2	Deceased	Gastrointestinal AGvHD	
30	T–B+NK+	AGvHD grade I, CGvHD (skin)	140	Alive		None
31	T–B+NK+	None	140	Alive		None
32	T–B+NK+	AGvHD grade I, AC, CGvHD, scleroderma	23	Alive		None
33	T–B+NK+	AGvHD grade IV, CGvHD (skin, liver)	13	Deceased	Liver CGvHD	
34	CD3δ	None	40	Alive		None
35	IL-7Rα	AGvHD grade II, CGvHD, polymyositis	28	Alive		CGvHD
36	IL-7Rα	AGvHD grade I	13	Alive		None
37	IL-7Rα	AGvHD grade II, bone marrow failure, *Streptococcus viridans* infection	12	Deceased	Sepsis	
38	IL-7Rα	AGvHD grade IV	2	Deceased	Liver and gastrointestinal AGvHD	
39	RMRP	CGvHD (skin, eyes)	27	Alive		None
40	ADA	None	11	Alive		None
41	ADA	AGvHD grade III	3	Deceased	Pulmonary alveolar proteinosis	
42	T–B–NK+	AGvHD grade I	24	Alive		None
43	RAG1	AGvHD grade II	119	Alive		None
44	RAG1	AGvHD grade IV, repeat MUD BMT	1	Deceased	Gastrointestinal AGvHD	
45	RAG2	Growth delay	137	Alive		None
46	RAG2	AGvHD grade II	120	Alive		None
47	RAG2	AC, lower respiratory tract infections, *Pneumocystis jiroveci* pneumonia	81	Alive		None
48	ARTEMIS	AGvHD grade I, AC	96	Alive		None
49	ARTEMIS	Cytomegalovirus interstitial pneumonitis	1	Deceased	Cytomegalovirus interstitial pneumonitis	
50	Omenn	AGvHD (skin) (grade A-II), AC	168	Alive		None
51	Omenn	Growth delay	24	Alive		None
52	Omenn	AGvHD grade II, CGvHD, scleroderma, myocarditis	20	Alive		CGvHD
53	Omenn	AGvHD grade III, repeat MUD BMT	12	Alive		None
54	Omenn	None	1	Alive		None

Abbreviations: AC, autoimmune cytopenia; ADA, significantly reduced adenosine deaminase activity; AGvHD, acute graft-vs-host disease; ARTEMIS, mutation in the *ARTEMIS* gene; BMT, bone marrow transplantation; CD3δ, mutation in the *CD3δ* gene; CGvHD, chronic graft-vs-host disease; IL-7Rα, mutation in the gene for α chain of the interleukin 7 receptor; JAK3, mutation in the *Jak-3* gene; MUD, HLA-matched unrelated donor; Omenn, Omenn syndrome; RAG, mutation in the recombination-activating gene; RMRP, mutation RNA component of the mitochondrial RNA-processing endoribonuclease gene; SCID, severe combined immune deficiency; T–B+NK–, T-cell count and function reduced, B-cell count normal or increased, NK cells absent; 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 normal or increased, natural killer cell count normal; γc: mutation in the gene for common γ chain of the interleukin 2 receptor; ZAP70, mutation in the *ZAP70* gene.

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Table 3. Diagnosis, Complications, and Outcomes of Patients With SCID Undergoing MMRD BMT

Patient No.	Phenotype/ Molecular Defect	Complications and Infections After BMT	Last Posttransplantation Contact, mo	Outcome	Cause of Death	Complications at Last Contact
55	γc	AGvHD grade I	73	Alive		None
56	γc	AGvHD grade I	44	Alive		None
57	γc	Disseminated cytomegalovirus	6	Deceased	Cytomegalovirus	
58	γc	Disseminated cytomegalovirus	5	Deceased	Cytomegalovirus	
59	γc	Multiorgan failure	2	Deceased	Multiorgan failure	
60	γc	*Pneumocystis jiroveci* interstitial pneumonitis	1	Deceased	*P jiroveci* interstitial pneumonitis	
61	γc	*P jiroveci* interstitial pneumonitis	1	Deceased	*P jiroveci* interstitial pneumonitis	
62	JAK3	None	156	Alive		None
63	JAK3	Repeat MMRD BMT	148	Alive		None
64	JAK3	Lower respiratory tract infections	142	Alive		Recurrent respiratory infections
65	JAK3	AGvHD grade I	117	Alive		None
66	JAK3	Repeat MMRD BMT, AGvHD grade I, dystonia	100	Alive		None
67	JAK3	Repeat MMRD BMT, lower respiratory tract infections	56	Alive		None
68	JAK3	2 Repeat MMRD BMTs	22	Deceased	AC	
69	JAK3	AGvHD grade II	32	Alive		None
70	JAK3	Interstitial pneumonitis	1	Deceased	Interstitial pneumonitis	
71	T–B+NK+	None	59	Alive		None
72	T–B+NK+	AGvHD grade I	30	Alive		None
73	T–B+NK+	AGvHD grade II, CGvHD scleroderma	29	Deceased	Encephalitis	
74	T–B+NK+	Repeat MMRD BMT, interstitial pneumonitis	6	Deceased	Interstitial pneumonitis	
75	T–B+NK+	Repeat MMRD BMT	6	Deceased	Cerebral edema	
76	T–B+NK+	Repeat MMRD BMT, AC	5	Alive		None
77	T–B+NK+	Interstitial pneumonitis	1	Deceased	Interstitial pneumonitis	
78	T–B-NK+	AGvHD grade II	84	Alive		None
79	T–B-NK+	Interstitial pneumonitis	17	Deceased	Interstitial pneumonitis	
80	RAG1	Diplegia, AC	119	Alive		Diplegia
81	RAG1	AGvHD grade II, lower respiratory tract infections	108	Alive		None
82	RAG1	AGvHD grade IV, AC	100	Alive		None
83	RAG1	AGvHD grade II, cytomegalovirus, repeat MMRD BMT	24	Alive		None
84	RAG1	AGvHD grade III, repeat MMRD BMT	12	Alive		None
85	RAG1	AGvHD grade IV, CGvHD (lung), repeat MMRD BMT	5	Deceased	CGvHD (lung)	
86	RAG1	AGvHD grade I, interstitial pneumonitis	2	Deceased	Cytomegalovirus interstitial pneumonitis	
87	RAG2	Interstitial pneumonitis	1	Deceased	Interstitial pneumonitis	
88	ARTEMIS	AGvHD grade IV	134	Alive		None
89	ARTEMIS	AGvHD grade III, repeat MMRD BMT	12	Deceased	AC	
90	ARTEMIS	Interstitial pneumonitis	6	Deceased	Interstitial pneumonitis	
91	ARTEMIS	AGvHD grade II	6	Alive		None
92	ARTEMIS	Interstitial pneumonitis	1	Deceased	Interstitial pneumonitis	
93	Omenn	2 Repeat MMRD BMTs, AGvHD grade IV	81	Alive		None
94	Omenn	Interstitial pneumonitis	2	Deceased	Interstitial pneumonitis	

Abbreviations: AC, autoimmune cytopenia; AGvHD, acute graft-vs-host disease; ARTEMIS, mutation in the *ARTEMIS* gene; BMT, bone marrow transplantation; CGvHD, chronic graft-vs-host disease; IL-7Rα, mutation in the gene for α chain of the interleukin 7 receptor; JAK3, mutation in the *Jak-3* gene; MMRD, HLA-mismatched related donor; Omenn, Omenn syndrome; RAG, mutation in the recombination-activating gene; SCID, severe combined immune deficiency; 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 normal or increased, natural killer cell count normal; γc, mutation in the gene for common γ chain of the interleukin 2 receptor.

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41 who underwent MUD BMT, and 32 (80%) of 40 who underwent MMRD BMT.

Survival After BMT

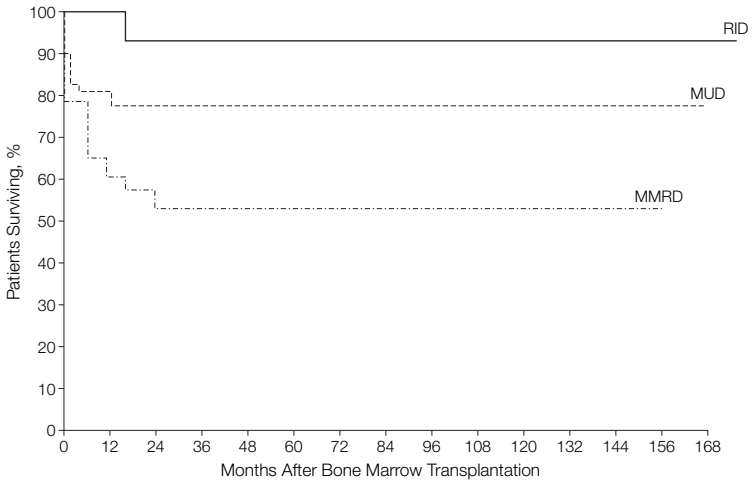
Patients were followed up for a median of 96 months (range, 15-168 months), 40 months (range, 1-168 months), and 24 months (range, 1-156 months) after RID, MUD, and MMRD transplantation, respectively. No patients were lost to follow-up. Twelve of 13 RID BMT patients (92.3%), 33 of 41 MUD BMT patients (80.5%), and 21 of 40 MMRD BMT patients (52.5%) survived (FIGURE). Survival following MUD BMT was significantly better ($P=.03$) than with MMRD BMT (TABLE 4). While survival of RID BMT recipients was also significantly better than that of MMRD BMT recipients ($P=.008$), survival after RID BMT and MUD BMT was not statistically different.

Transplantation of patients with a B– SCID phenotype has previously been associated with poor prognosis.[3,5,15] However, in this study, the survival of patients with B– SCID after MUD BMT was 84.6% (11/13), not significantly different from the 78.6% (22/28) survival for patients with B+ SCID. Similarly, the survival of patients with B– SCID who were treated with MMRD BMT was 52.9% (9/17), practically identical to the 52.1% survival for patients with B+ SCID (12/23).

Eight (61.5%), 28 (68.3%), and 29 (72.5%) patients who received RID, MUD, or MMRD BMT, respectively, were males. Seven (87.5%), 21 (75.0%), and 13 (44.8%) survived, compared with 5 (100%) of 5 females receiving RID BMT ($P=.62$), 12 (92.3%) of 13 females receiving MUD BMT ($P=.19$), and 8 (72.7%) of 11 females receiving MMRD BMT ($P=.11$). Two-factor Cox regression found that patient sex had no significant effect on posttransplant survival. Similarly, using the same method, analysis of specific molecular defects causing SCID did not affect survival.

The rate of survival, at least with MUD transplants, was not affected by transplant center. Eighteen (75%) of 24 patients survived after receiving MUD BMT at the Hospital for Sick Children, which was not significantly different from the 88.2% (15/17) who survived after MUD BMT at the University of Brescia ($P=.26$). Only 2 patients received MMRD BMT at the Hospital for Sick Children, precluding statistical comparison. Similarly, the effect on survival of whether BMT was performed in the first or second half of the study period was tested using 2-factor Cox regression. In the earlier period, 5 (83.3%) of 6 with RID BMT, 16 (80.0%) of 20 with MUD BMT, and 9 (45%) of 20 with MMRD BMT survived. This was not different from the 7 of 7 (100%) ($P=.46$), 17 of 21 (80.9%) ($P=.62$), and 12 of 20 (60%) ($P=.26$) patients surviving in the later period.

Figure. Survival of Patients With SCID Who Received a Bone Marrow Transplant From a RID, MUD, or MMRD



No. at Risk					
RID	13	13	12	8	5
MUD	41	33	26	17	10
MMRD	40	23	19	12	4

For patients who received multiple transplants, survival was calculated from the date of the last transplantation. RID indicates family-related, HLA-identical donor; MUD, HLA-matched unrelated donors; and MMRD, HLA-mismatched related donor.

Table 4. Outcomes Following BMT for Severe Combined Immune Deficiency

	No. of Patients/Total (%)			*P* Value		
	RID BMT	MUD BMT	MMRD BMT	RID vs MUD	RID vs MMRD	MUD vs MMRD
Survival	12/13 (92.3)	33/41 (80.5)	21/40 (52.5)	.90	.008	.03
Fatal interstitial pneumonitis	0/13	1/41 (2.4)	11/40 (27.5)	.76	.03	.001
Graft failure	0/13	3/41 (7.3)	12/40 (30.0)	.43	.02	.009
Acute graft-vs-host disease	4/13 (30.7)	30/41 (73.1)	18/40 (45.0)	.008	.28	.009
Abnormal T-cell receptor diversity	3/8 (37.5)	1/19 (5.3)	7/18 (38.9)	.07	.65	.02

Abbreviations: BMT, bone marrow transplantation; MMRD, HLA-mismatched related donor; MUD, HLA-matched unrelated donor; RID, family-related, HLA-identical donor.

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An unstable clinical condition at time of diagnosis has traditionally been one of the major arguments to proceed with transplantation urgently. In our study, the 2 patients who received RID BMT after being clinically unstable survived. Among the 81 patients who received MUD or MMRD BMT, there were only 9 clinically unstable patients, 3 at Brescia and 6 at the Hospital for Sick Children. Four of the 6 unstable patients at Toronto were stabilized and subsequently treated with MUD BMT; 3 (75%) survived. Five patients received urgent MMRD BMT, 1 (20%) of whom survived.

Complications Following BMT

Complications after RID, MUD, or MMRD BMT are detailed in Tables 1, 2, and 3, respectively, and summarized in Table 4. Lower respiratory tract infections and interstitial pneumonitis were diagnosed in 3 (7.3%) of 41 patients and 14 (35.0%) of 40 patients following MUD and MMRD BMT, respectively ($P=.002$). Importantly, interstitial pneumonitis was the most common cause of death after transplantation, particularly after MMRD BMT. It caused death in 11 (27.5%) of the 40 patients who received MMRD BMT but only in 1 (2.4%) of the 41 patients who received MUD BMT ($P=.001$). Respiratory complications were not reported in patients who received RID BMT.

Acute graft-vs-host disease was documented in 30 (73.1%) of 41 patients who received MUD BMT, compared with 18 (45%) of 40 patients after MMRD BMT ($P=.009$). Acute graft-vs-host disease also occurred in 4 (30.8%) of the 13 patients who received RID BMT, which was significantly less than after MUD BMT ($P=.008$) but not significantly different from MMRD BMT. However, grade III or higher acute graft-vs-host disease was seen in only 9 (21.9%) of 41 patients following MUD BMT compared with 6 (15.0%) of 40 patients after MMRD BMT, a difference that was not statistically significant. Acute graft-vs-host disease was the most common cause of death among MUD BMT recipients (3 [7.3%] of 41 patients) yet was not significantly different than in recipients of MMRD BMT (0 of 40 patients).

Chronic graft-vs-host disease, which most often involved the skin and mucous membranes, was diagnosed in 8 of 35 patients after MUD BMT, compared with 2 of 31 who received MMRD BMT ($P=.06$). After MUD BMT, 1 patient developed fatal graft-vs-host disease of the liver, while another had bone marrow failure that may have been associated with chronic graft-vs-host disease. Chronic graft-vs-host disease of the lungs was the cause of death in 1 patient after MMRD BMT. No RID transplant patients developed chronic graft-vs-host disease.

Other noteworthy posttransplant complications included infections, autoimmune hematopoietic disorders, and neurologic abnormalities. Following RID BMT, 1 patient had cytomegalovirus retinitis, which improved with treatment. Significant infections after MUD BMT included fatal *Streptococcus viridans* sepsis in 1 patient and fatal cytomegalovirus-associated interstitial pneumonitis in another. Cytomegalovirus chorioretinitis was detected in 1 patient, while another developed *Pneumocystis jiroveci* pneumonia after treatment with rituximab. Among the patients who received MMRD bone marrow, 2 had fatal disseminated cytomegalovirus infection and 2 died of *P jiroveci*–associated pneumonitis. Autoimmune hematopoietic disorders occurred in 6 and 5 patients following MUD and MMRD transplantation, respectively. In addition, after MUD BMT, 2 patients developed myocarditis, while 1 case each of polymyositis and bronchiolitis obliterans were recorded. Neurologic disorders were observed in 4 patients who received MMRD BMT.

In contrast with the high frequency of complications shortly after transplantation, late complications were rare. They included neurologic defects in 1 MUD, 1 MMRD, and 2 RID BMT patients. Two patients had chronic graft-vs-host disease after MUD BMT and 1 patient had recurrent lower respiratory tract infections after MMRD BMT. No patient had autoimmune phenomena or malignancy.

Engraftment and Long-term Immune Reconstitution

No patient who received RID bone marrow experienced graft failure, while it was observed in 3 of 41 patients who received MUD BMT (7.3%). Repeated MUD BMT in these patients led to full engraftment in 2 of the patients, while the third died shortly after transplantation. Among the 40 patients who received MMRD BMT, 12 (30.0%) lost the donor graft and required a second MMRD transplant, a significantly higher rate of graft loss than with MUD BMT ($P=.009$). The repeated MMRD BMT led to complete donor engraftment in only 4 patients. Two patients underwent a third MMRD BMT, 1 of which was successful.

To evaluate long-term immune reconstitution, data were analyzed from 12 RID BMT (TABLE 5), 26 MUD BMT (TABLE 6), and 18 MMRD BMT patients (TABLE 7) who had survived for 2 years or more after transplantation. The median time from transplantation to the most recent immune function evaluation was 96 months for RID BMT (range, 30-168 months), 90 months for MUD BMT (range, 24-168 months), and 92 months for MMRD BMT (range, 30-156 months). As expected, complete donor lymphocyte engraftment was demonstrated in only 3 (25%) of 12 patients after RID BMT because myeloablative conditioning typically is not required prior to transplantation. Complete donor engraftment was documented in 23 (88.5%) of 26 MUD BMT patients and in 12 (66%) of 18 MMRD patients, a difference ($P=.08$) that did not achieve statistical significance.

Intravenous immunoglobulin replacement therapy was still required in 1 RID, 1 MUD, and 2 MMRD BMT patients. All BMT patients (RID, MUD, or MMRD) who did not receive intravenous immunoglobulin were able to produce antibodies to tetanus, polio, and hepatitis B vaccines.

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Lymphocyte subsets and lymphocyte function were analyzed in 12 RID, 26 MUD, and 18 MMRD BMT patients, with no significant statistical difference between MUD and MMRD. Similarly, there was no difference in achieving normal T-cell receptor excision circles. In contrast, while a normal distribution of T-cell receptor

Table 5. Immune Reconstitution After RID BMT for Severe Combined Immune Deficiency

Patient No.	Time Since BMT, mo	Lymphocytes, $\times 10^6/\mu L$					Stimulation Index	T-Cell Receptor Diversity	T-Cell Receptor Excision Cycles/10^6 Lymphocytes
		Total	$CD3^+$ T Cells	$CD3^+CD4^+$ T Cells	$CD3^+CD8^+$ T Cells	$CD19^+$ B Cells			
1	156	3630	2610	290*	1340	330	Normal	ND	Normal
2	96	3000	2340	1020	1020	660	Normal	Oligoclonal*	Normal
3	36	3600	2630	1510	950	890	Normal	ND	ND
4	168	1900	1100	610	360	270	Normal	Oligoclonal*	Low*
5	156	5700	4160	2680	800	850	Normal	Normal	Normal
6	156	1100	650*	330*	230	260	Normal	Oligoclonal*	Very low*
7	132	2500	1250	620	530	920	Normal	ND	ND
8	96	2100	1720	590	500	250	Normal	Normal	Low*
9	42	600	400*	250*	150	100	Reduced*	ND	ND
10	30	2000	1820	1020	680	80	Normal	Normal	Normal
12	36	3200	2560	960	1150	30*	Normal	Normal	Normal
13	84	1400	690*	390*	210	290	Normal	Normal	Normal

Abbreviations: BMT, bone marrow transplantation; ND, not determined; RID, family-related, HLA-identical donor.
*Abnormality.

Table 6. Immune Reconstitution After MUD BMT for Severe Combined Immune Deficiency

Patient No.	Time Since BMT, mo	Lymphocytes, $\times 10^6/\mu L$					Stimulation Index	T-Cell Receptor Diversity	T-Cell Receptor Excision Cycles/10^6 Lymphocytes
		Total	$CD3^+$ T Cells	$CD3^+CD4^+$ T Cells	$CD3^+CD8^+$ T Cells	$CD19^+$ B Cells			
14	142	2900	2580	460*	1160	180	Normal	Normal	Normal
15	120	3800	2584	1440	940	798	Normal	Normal	ND
16	120	2700	2270	864	1270	320	Normal	ND	ND
17	108	2200	1500	890	440	500	Normal	ND	ND
18	70	2000	1640	660	740	240	Normal	Normal	ND
19	54	5200	3540	1720	1560	1100	Normal	Normal	Normal
20	40	3080	2125	1300	620	680	Normal	ND	ND
23	126	2300	1950	940	780	275	Normal	Normal	Normal
24	76	1800	1460	630	468	180	Normal	Normal	Normal
25	54	3140	2000	1200	590	820	Normal	Oligoclonal*	Normal
26	36	3810	2360	610	1752	650	Normal	Normal	ND
27	114	3100	2360	1650	560	560	Normal	Normal	Normal
28	36	2500	1750	1050	600	330	Normal	Normal	ND
30	140	2340	1520	800	608	440	Normal	Normal	ND
31	140	2100	1640	588	500	270	Normal	Normal	ND
34	40	2700	1800	1000	730	460	Normal	Normal	ND
35	28	3200	1980	1470	400	380	Normal	ND	ND
39	27	7700	4620	2500	1310	2460	Normal	ND	ND
42	24	3700	2770	2030	670	440	Normal	Normal	Low*
43	125	2080	1560	830	380	360	Normal	ND	Normal
45	143	3100	2170	1360	650	590	Normal	Normal	Normal
46	120	6800	5440	2500	2720	1088	Normal	ND	ND
47	87	2100	1760	630	1030	21*†	Normal	Normal	Normal
48	90	5220	4280	2250	1930	574	Normal	Normal	Normal
50	168	2600	1800	860	620	440	Normal	Normal	ND
51	24	4200	2690	1600	800	880	Normal	Normal	Normal

Abbreviations: BMT, bone marrow transplantation; MUD, HLA-matched unrelated donor; ND, not determined.
*Abnormality.
†Following treatment with anti-CD20 monoclonal antibody.

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variable β chain expression was demonstrated in 18 (94.7%) of 19 MUD BMT patients, it was found in only 11 (61.1%) of 18 MMRD BMT patients (P=.02).

COMMENT

Severe combined immunodeficiency is a fatal disease unless treated with stem cells capable of reconstituting a normal immune system.[17] The best treatment results have been achieved by using family member donors who are HLA-identical to the recipient.[4,5] In agreement with previous studies, we report here a 92.3% long-term survival rate for patients who received RID BMT. Unfortunately for most patients with SCID, including more than 85% of our patients, such donors are not available and other solutions, such as MMRD or MUD BMT, must be considered.[4] Herein we have described and compared the outcomes between groups of 41 and 40 SCID patients who received MUD BMT and MMRD BMT, respectively, during the same period and in the same centers. This study, which contains the largest group of patients with SCID to have undergone MUD BMT, reveals a survival rate of 80.5% for MUD BMT, which is consistent with or better than results previously reported with smaller cohorts.[6,11,13,14]

Survival of patients undergoing MMRD BMT has been reported to vary between 45% and 78%[5,25,26] and, indeed, in this study, we show a survival rate of 52.5%. The differences between these reports may reflect variability in patient selection, techniques of T-cell depletion, or, alternatively, inconsistent definition of criteria for HLA matching.[6] Our study, which details large groups of SCID patients treated in 2 centers, has provided a unique opportunity for direct and detailed comparison of MMRD BMT and MUD BMT, showing a significant survival advantage for patients who received MUD transplants.

Our study shows that MUD BMT not only leads to a significant increase in survival of SCID but also results in excellent long-term immune reconstitution. The ultimate purpose of BMT for patients with SCID is to fully restore immune function and return patients to normal unrestricted lives indefinitely. More than 80% of the patients who received a MUD transplant showed robust immune reconstitution. Humoral immunity was also completely reconstituted in all but 1 patient (who had not received pretransplant conditioning). Importantly, none of the long-term survivors had evidence of increased susceptibility to infections or malignancy. In contrast, close to one third of MMRD BMT recipients required a second transplant because of graft failure, and 38.9% of long-term survivors had abnormal distribution of T-cell receptor variable β chain expression. Our findings are in agreement with recent reports detailing immune dysfunction following MMRD BMT for SCID.[16,27,28] To avoid severe graft-vs-host disease, a rigorous depletion of donor T cells is required with MMRD BMT.[2,29] Unfortunately, this necessary T-cell depletion may contribute to delayed and abnormal engraftment, resulting in increased incidence of infection or immune dysregulation.[7-9,25,30]

Perceived limitations of MUD BMT as a therapy have been the delay in treatment dictated by the time

Table 7. Immune Reconstitution After MMRD BMT for Severe Combined Immune Deficiency

Patient No.	Time Since BMT, mo	Lymphocytes, × 10^6/μL: Total	CD3$^+$ T Cells	CD3$^+$CD4$^+$ T Cells	CD3$^+$CD8$^+$ T Cells	CD19$^+$ B Cells	Stimulation Index	T-Cell Receptor Diversity	T-Cell Receptor Excision Cycles/10^6 Lymphocytes
55	73	5400	4293	2187	1986	1009	Normal	Normal	Normal
56	44	2950	2675	1435	1184	147	Normal	Normal	Normal
59	34	3800	2505	1079	1389	1233	Normal	Normal	Normal
62	156	1900	1668	649	850	209	Normal	Normal	Low*
63	148	1200	861*	343*	480	298	Normal	Oligoclonal*	Normal
64	142	4990	4467	454*	3820	31*	Reduced*	Oligoclonal*	Low*
65	117	3900	2125	1314	780	787	Normal	Oligoclonal*	Normal
66	100	3100	2833	1235	1478	881	Normal	Normal	Low*
67	56	5510	4070	2288	1583	676	Normal	Normal	Normal
69	30	3000	2235	1461	782	621	Normal	Oligoclonal*	Normal
70	32	2600	1838	1157	594	525	Normal	Oligoclonal*	Normal
71	59	4100	2779	1517	1086	602	Normal	Normal	Normal
78	84	2160	1660	608	950	208	Normal	Normal	Normal
80	119	2700	2235	831	1360	81	Normal	Oligoclonal*	Very low*
81	108	2900	2033	979	987	257	Normal	Normal	Normal
82	100	2920	2262	1089	1075	380	Normal	Normal	Normal
88	134	3500	2310	1417	810	843	Normal	Normal	Normal
93	81	2700	1606	569	952	529	Reduced*	Oligoclonal*	Very low*

Abbreviations: BMT, bone marrow transplantation; MMRD, HLA-mismatched related donor; ND, not determined.
*Abnormality.

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required to obtain bone marrow and the concern of failing to identify a donor in the registries.[31] However, the latter concern has been greatly alleviated by the continuous expansion of the international unrelated donor base.[32] For all but 1 patient (who was of African origin), we were able to find an acceptable donor. The median time from diagnosis to MUD BMT in this study was only 4 months. This is shorter than previously reported,[33] probably due to the expansion and improvement of bone marrow donor registries.[34] Still, the median time from diagnosis to transplantation in the MMRD BMT group was only 2 months. However, 30% of patients receiving MMRD BMT required repeat transplantation. Thus, the actual median time from diagnosis to final MMRD transplantation increased by 1 month, eliminating some of the potential advantage of MMRD. In addition, the need for repeated transplantation frequently led to reexposure of patients to myeloablation.

It has also been suggested that prolonged hospitalization of patients prior to transplantation might expose them to increased risk. However, our experience has been strikingly different. We did not observe clinical deterioration while waiting for a transplant, and no patient was lost because of such delay. On the contrary, in many cases we used this time to control infections and to improve patients' nutritional status, factors well known to affect outcome.[35] Even among patients who required assisted ventilation prior to MUD BMT, we did not observe increased mortality. In addition, mortality rates were not different for patients who were rushed to receive MMRD transplant because of a perceived urgency in clinical condition vs those who were in stable clinical condition. Together these results may challenge the instinct to rush to BMT while patients are clinically unstable, especially when myeloablation is prescribed.

A major complication of bone marrow transplantation in SCID is life-threatening infection, especially of the lower respiratory tract.[6,25] We show here that interstitial pneumonitis, most frequently caused by viral or fungal infections, was far more common in MMRD BMT recipients than in MUD BMT ($P=.002$). Indeed, interstitial pneumonitis was the most common cause of death among MMRD recipients, resulting in 27.5% patient mortality. A second significant threat to patients with SCID who receive transplants from donors other than RID is graft-vs-host disease. Between 45% and 85% of children are reported to develop acute graft-vs-host disease following MUD BMT,[36,37] despite various combinations of prophylactic treatments. Consistent with these data, 73.1% of the patients in our series developed acute graft-vs-host disease. Although acute graft-vs-host disease was transient and limited to the skin in most MUD BMT patients, it was the major cause of death in patients who did not survive. In some patients, graft-vs-host disease erupted or worsened when rapid reductions in immunosuppressive prophylactic treatments were attempted, emphasizing the need to establish strict guidelines to assist in the management of graft-vs-host disease when this procedure is used.

Acute graft-vs-host disease has been reported at lower incidence (46%-66%) after MMRD BMT.[38,39] In full agreement, 45% of the patients in our MMRD BMT group developed acute graft-vs-host disease, significantly lower than the frequency of acute graft-vs-host disease in MUD BMT recipients. However, there was no significant difference in the frequency of grade III or higher acute graft-vs-host disease between patients receiving MUD and MMRD transplants. Assessment of larger groups of patients with high-grade acute graft-vs-host disease will be required to reveal whether there is a significant difference in the pathogenesis and consequences of graft-vs-host disease arising from MUD and MMRD BMT. We anticipate that future improvements in graft-vs-host disease prophylaxis, such as the use of antithymocyte globulin, and graft-vs-host disease treatment will help reduce the morbidity and mortality associated with graft-vs-host disease, further improving the success of MUD BMT.

In addition to our primary analysis, we also identified the molecular and functional causes of SCID in more than 65% of our patients, thereby enabling some comparison of MUD BMT and MMRD BMT according to phenotypic or genetic defect. We found that the survival of patients with B– SCID, such as those with Omenn syndrome or mutations in the *RAG-1*, *RAG-2*, and *ARTEMIS* genes, was not different from the survival of B+ SCID. Previous studies had shown disappointing outcomes, with as low as 35% disease-free survival for those with B– SCID undergoing MMRD BMT.[5,15] Thus, MUD BMT may be a particularly attractive alternative for patients with B– SCID, although further study with larger patient groups will be required to confirm these findings.

This study has a number of limitations. It was conducted at only 2 centers and, therefore, generalizability is unknown. A relatively small number of patients were included, especially limiting subgroup analyses. Patients were not randomly assigned to MUD vs MMRD BMT, and unmeasured confounders may have influenced the outcomes.

In conclusion, we have demonstrated that MUD BMT has an 80% cure rate for SCID and is associated with long-term robust immune reconstitution, suggesting that this mode of treatment may be an important therapeutic alternative for patients with SCID when RID is not available. The continuing expansion of donor registries, advances in HLA analysis, and better management of graft-vs-host disease are expected to further improve outcomes of MUD transplantation.

Author Contributions: The first 2 authors, Dr Grunebaum and Dr Mazzolari, contributed equally. Dr Roifman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Grunebaum, Porta, Notarangelo, Roifman.
Acquisition of data: Grunebaum, Mazzolari, Porta, Dallera, Atkinson, Reid, Notarangelo, Roifman.
Analysis and interpretation of data: Grunebaum, Mazzolari, Porta, Reid, Notarangelo, Roifman.

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Statistical analysis: Grunebaum, Notarangelo.
Obtained funding: Notarangelo, Roifman.
Administrative, technical, or material support: Mazzolari, Dallera.
Study supervision: Grunebaum, Mazzolari, Porta, Notarangelo, Roifman.

Financial Disclosures: None reported.
Funding/Support: Mutation analysis performed by Dr Notarangelo was partially supported by the Nocivelli Foundation. The MIUR-FIRB (grant RBNE01899JJ-003 to Dr Notarangelo) partially supported mutation analysis in infants with T– B+ SCID and the AFM-Telethon (grant GATA0203 to Dr Notarangelo) partially supported mutation analysis in infants with T– B– SCID. The European Union (EURO-POLICY-PID grant 006411) and the MIUR-COFIN 2004 to Dr Notarangelo partially supported data collection. In addition, the Audrey and Donald Campbell Chair of Immunology, University of Toronto, provided partial salary support for Dr Roifman. The Canadian Immunodeficiency Society partially supported data collection at the Hospital for Sick Children and the Jeffrey Modell Foundation partially supported the molecular analysis.
Role of the Sponsors: The sources of support for this study had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, or preparation, review, or approval of the manuscript.

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