

Long-term outcomes of nonconditioned patients with severe combined immunodeficiency transplanted with HLA-identical or haploidentical bone marrow depleted of T cells with anti-CD6 mAb

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Background: Between 1981 and 1995, 20 children with severe combined immunodeficiency (SCID; median age at transplant, 6.5 [range, 0.5-145] mo, 12 with serious infection) were treated with haploidentical T cell-depleted (anti-CD6 antibody) bone marrow (median number of $5.7 [0.8-18.8] \times 10^8$ nucleated cells/kg) from mismatched related donors (MMRDs), and 5 children with SCID (median age at transplant, 1.8 [0.5-5.0] mo, 1 with serious infection) were given unmanipulated bone marrow from matched related donors (MRDs). No conditioning or graft-versus-host disease (GvHD) prophylaxis was used.

Objective: To assess the outcomes of patients with SCID who received bone marrow from MMRDs or MRDs.

Methods: We reviewed the medical records of these 25 consecutive patients with SCID (4 with Omenn syndrome).

Results: Of the 20 patients who received bone marrow from MMRDs, 12 engrafted, 10 survived at a median age of 15.2 [10.0-19.1] years, 4 had chronic GvHD (lung, intestine, skin), 5 required intravenous immunoglobulin, and 8 attended school or college. Two of 5 patients who died had chronic GvHD, and 2 developed lymphoproliferative disease. Of the 5 patients who received bone marrow from MRDs, 5 engrafted, 5 survived at a median age of 23.3 [18.5-26] years, 1 had chronic GvHD (lung, skin), 2 required intravenous immunoglobulin, and 4 attended school or college.

Conclusions: Treatment of critically ill patients with SCID with anti-CD6 antibody T cell-depleted MMRD marrow resulted in an overall 50% long-term survival of patients (83% survival of those

engrafted). The principal barriers to long-term survival were delay in diagnosis, life-threatening infection, failure to engraft, and chronic GvHD. Educational goals were achieved in most of the survivors. (*J Allergy Clin Immunol* 2008;122:1185-93.)

Key words: Anti-CD6 mAb, transplantation, graft-versus-host disease, immune reconstitution, immunodeficiency, mismatched related donor

The highest survival rates after hematopoietic stem cell transplantation (HSCT) for severe combined immunodeficiency (SCID) occur when a family-related, HLA-identical donor is available, termed a matched related donor (MRD).^{1,2} Since early in the history of HSCT, the majority of bone marrow transplants (BMTs) have been performed by using a mismatched (ie, haploidentical), related donor (MMRD) because a MRD is available generally in less than 20% of patients.^{2,3} More recently, an unrelated donor who is HLA-matched (matched unrelated donor) identified from a bone marrow donor registry is sometimes used. However, in such situations, the incidence of graft-versus-host disease (GvHD) is higher than in MRD transplants.^{4,5}

T-cell depletion of donor marrow by rosetting with sheep erythrocytes and soybean lectin agglutination has been used in several centers to prevent GvHD when the only available donors were MMRDs.⁶⁻⁸ Treating with anti-CD6 mAb plus complement was one of the earliest methods of purging T cells from donor marrow.⁹⁻¹² Strategies for T-cell depletion (negative selection) are currently less used than newer techniques for positive selection of CD34⁺ cells.^{13,14}

T-cell immune reconstitution in patients with SCID may occur as long as 3 to 6 months after HSCT.^{2,3} B-cell reconstitution is often incomplete, necessitating lifelong immunoglobulin replacement therapy.^{15,16} Pretransplant conditioning with chemotherapeutic agents has been suggested to increase the chances for engraftment and immune reconstitution. Published survival outcomes vary between 46% and 62% for conditioned BMT^{7,17-20} and 78% for nonconditioned BMT.^{2,6} Several variables could explain these differences, such as the diversity of SCID phenotypes, timing of the transplant, infection status of the patient, and potential toxicity of conditioning regimens.^{2,6}

Several mAbs have been used for T-cell depletion of bone marrow grafts,²¹⁻²⁷ but use of anti-CD6 mAb for T-cell depletion of bone marrow in HSCT in a large series of patients with SCID and their long-term outcomes has not been previously reported. We reviewed the records of 25 consecutive patients with the diagnosis SCID who underwent BMT at a single center over a 15-year period (1981-1995) and describe the long-term outcomes (range, 10-27 years) of these patients.

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Abbreviations used

BMT: Bone marrow transplant
 GvHD: Graft-versus-host disease
 HSCT: Hematopoietic stem cell transplantation
 MMRD: Mismatched related donor
 MRD: Matched related donor
 NK: Natural killer
 PCP: *Pneumocystis jiroveci* pneumonia
 SCID: Severe combined immunodeficiency

METHODS**Patients**

A retrospective chart review included all 25 patients with SCID who received BMTs (20 anti-CD6 T cell–depleted MMRD and 5 MRD) between 1981 and 1995 at Texas Children's Hospital in Houston. Records were also reviewed at patient relocation centers (Los Angeles, Calif [R. Stiehm], Denver, Colo [P. Hauk], Kansas City, Mo [J. Portnoy]). The study was approved by the Institutional Review Board at Baylor College of Medicine, and parents gave informed consent.

Anti-CD6 mAb for T-cell depletion

Donor bone marrow was filtered and treated with anti-CD6 mAb, a murine IgM mAb that binds to CD6 antigen on mature T cells. Three cycles of incubation with anti-CD6 antibody and rabbit complement were performed to remove CD6⁺ T cells. Natural killer (NK) cells and most B cells are not removed in the process. This technique has previously been shown to decrease T cells from marrow by 1.5 to 2 log₁₀.²⁸ There is a small percentage of immature CD3⁺ T cells remaining that lacks the CD6 marker.²⁹ The stem cell–enriched bone marrow, suspended in an approximately 50 mL PBS, was infused intravenously in 19 patients and intraperitoneally in 1 patient within 12 to 15 hours of the harvest date. Patients who had bone marrow failure, as evidence of failure to engraft or loss of graft, received a second (or third) anti-CD6 antibody T cell–depleted haploidentical BMT transplant. Five patients received unmanipulated MRD marrow removed from donors in a similar manner and filtered. None of the 25 patients with SCID received conditioning or posttransplant GvHD prophylaxis.

Molecular analysis

DNA extraction (Gentra Puregene Cell Kit; Qiagen, Valencia, Calif) was performed on B-cell lines, thymic tissue (autopsy), or PBMCs according to the manufacturer's instructions. Molecular analysis for SCID gene defects was performed on extracted DNA (Correlagen, Waltham, Mass; National Institutes of Health, Bethesda, Md). Adenosine deaminase levels on all patients were assessed (Baylor Cytogenetics, Houston, Tex).

Immunologic analysis

Immune reconstitution was assessed by measuring cellular immunity, CD3⁺ T cells, CD20⁺ B cells, and CD56⁺ NK cells by flow cytometry and a panel of standardized commercially available reagents according to previously published methods,^{30,31} and humoral immunity, serum IgG, IgA, and IgM levels in posttransplant survivors. *In vitro* proliferative responses to phytohemagglutinin, concanavalin A, and pokeweed mitogen were assessed, as well as response to the antigens *Candida*, streptokinase, and tetanus using a standard tritiated thymidine incorporation assay (Clinical Immunology Laboratory, Texas Children's Hospital, Houston, Tex). For a subset of survivors, antibody response was determined after immunizations. Various techniques to study chimerism, including fluorescence *in situ* hybridization with probes to detect locus DXZ1 (Xp11.1-q11.1) on the X-chromosome and locus DYZ1 (Yq12) on the Y chromosome, and short tandem repeat analysis with the patients' sorted cells, were used to determine the extent of engraftment of donor graft (Pathology Laboratory, The Methodist Hospital, Houston, Tex).

TABLE I. Clinical characteristics of patients with SCID receiving MMRD BMTs treated with anti-CD6 mAb or unmanipulated graft BMT from a MRD

	Anti-CD6 group (n = 20)	MRD group (n = 5)
No. of transplants	27*	5
Sex, male/female	16/4	2/3
Race/ethnicity		
White	14	4
Hispanic	3	0
African American	2	1
Other/unknown	1	0
Age at BMT (mo)		
<6	8	5
6-12	9	0
>12	3	0
Median (range)	6.5 (0.5-145)	1.8 (0.5-5.0)
Phenotype		
T ⁺ B ⁺ NK ⁻	13	1
T ⁺ B ⁺ NK ⁺	3	0
T ⁺ B ⁻ NK ⁺	2	4
T ⁺ B ⁻ NK ⁻	2	0
Molecular defect		
<i>IL2RG</i>	6	1
<i>RAG1</i>	1	4
Unknown	13	0

RAG1, Recombination activating gene 1.

*Three patients received 2 transplants; 2 patients received 3 transplants.

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.

RESULTS**Patient demographics**

Twenty-five patients with a diagnosis of SCID received 32 BMTs between 1981 and 1995 at our institution (Table I). Nine of the 25 patients had X-linked SCID by family history, of whom 7 had a proven molecular defect in the common γ -chain. Five had mutations in recombination activating gene 1, of which 4 were diagnosed with Omenn syndrome (Table II, patient 19; Table III, patients 21-23). Adenosine deaminase levels in all 25 patients were within the normal range. The median age at transplant was 6.5 (range, 0.5-145) months in the MMRD group and 1.8 (range, 0.5-5.0) months in the MRD group.

Transplantation, engraftment, survival, and complications

The median number of nucleated bone marrow cells infused after treatment with anti-CD6 antibody plus complement after the third lytic cycle was $5.7 (0.8-18.8) \times 10^8$ cells/kg (mean, $6.28 \times 10^8 \pm SE$, 7.69×10^7 cells/kg) among 20 patients in the MMRD group (Table II). The number of residual CD3⁺ T cells infused was $7.86 \times 10^6 \pm 1.73 \times 10^6$ cells/kg (mean $\pm SE$), and the percentage of residual CD3⁺ T cells infused was $1.25 \pm 0.30\%$ (mean $\pm SE$), calculated from flow-cytometry results available in 21 of 27 grafts treated with anti-CD6 antibody. The estimated log₁₀ reduction of CD3⁺ T cells was 1.5 to 2 after treatment with anti-CD6 mAb. No CD6⁺ T cells were detected in the infused cells.

TABLE II. Outcomes of patients with SCID who received a MMRD transplant pretreated with anti-CD6 antibody

Patient no., sex	Molecular diagnosis or phenotype	Donor, HLA match (no./ total)	Age at diagnosis (mo)	Pre-HSCT complications	Age at HSCT (mo)	Engraftment	GvHD, grade (II-IV), Sk/Liv/Gi	Outcome/ age, cause of death	If alive, age at last follow-up (y)	Complications at follow-up, if alive
1, M	X-SCID	Sister, 3/6	1		145	No	aGvHD, grade II, Gi	Deceased at 12 y, gastrointestinal bleeding, EBV PTLD		
2, M	T ⁺ B ⁺ NK ⁻	Mother, 4/6	23	PCP, chronic diarrhea, thrush, candidal dermatitis	24	Yes	cGvHD	Deceased at 17 y, cGvHD		
3, M	X-SCID	Mother, 3/6	2	Diarrhea, transplacentally transferred maternal T cells RxC6mAb	2	No	aGvHD, grade III, Sk/Liv, cGvHD	Deceased at 3 mo, polymicrobial sepsis, aGvHD		
4, M	T ⁺ B ⁺ NK ⁻	Mother, 3/6	4	PCP, transplacentally transferred maternal T cells RxC6mAb	4	Yes	aGvHD, grade II, Sk/Liv, cGvHD	Deceased at 10 y, cGvHD		
5, M	X-SCID	Mother, 3/6	0.5	Transplacentally transferred maternal T cells RxC6mAb	0.75	No	aGvHD, grade II, Sk/Liv/Gi	Deceased at 5 mo, cGvHD, collagen vascular disease		
6, M	T ⁺ B ⁺ NK ⁻	Mother, 4/6	0.25	CMV viremia	0.5	Yes		Alive, home-bound	18	Seizure disorder, blindness, neurogenic bladder, cutaneous candidiasis
7, M	X-SCID	Father, 3/6	7		8	Yes	aGvHD, grade II, Sk/Liv/Gi	Alive, in college	18	Warts
8, M	X-SCID	Father, 3/6	8		8, 12	Yes	aGvHD, grade II, Sk/Liv/Gi	Alive, in high school	16	Autoimmune fasciitis, ganglion cysts, obesity
9, M	X-SCID	Father, 3/6	3	PCP, thrush	4	Yes	cGvHD	Alive, in high school	16.3	Short stature, warts, bronchiolitis obliterans, cGvHD
10, F	T ⁺ B ⁺ NK ⁻	Mother, 4/6, Aunt, 3/6	7		8, 12, 20	Yes	aGvHD, grade II, Sk, cGvHD	Alive, in high school	14.75	Asthma, hearing loss, warts, vitiligo, alopecia, chronic hepatitis B infection, cGvHD
11, M	X-SCID	Father, 3/6	8	PCP	8	Yes	aGvHD, grade II, Sk/Gi, cGvDH	Alive, in high school	14.75	Chronic colitis, cGvHD
12, M	X-SCID	Mother, 3/6	5	PCP	6	No	aGvHD, grade IV, Sk/Gi	Deceased at 18 mo, pseudomonal and enterococcal sepsis		
13, M	T ⁺ B ⁺ NK ⁻	Mother, 3/6	4	PCP	4.5	Yes		Alive, in high school	14	Mild hearing loss
14, M	T ⁺ B ⁺ NK ⁺	Father, 3/6	6	Invasive mycosis, thrush	7	Yes		Alive, up to 1994, LTFU	10	Well
15, F	T ⁺ B ⁺ NK ⁺	Mother, 3/6, Father, 3/6	4	Chronic diarrhea, candidal esophagitis, PCP	20, 21	No	aGvHD, grade II, Sk/Gi	Deceased at 22 mo, pseudomonal and candidal sepsis		

(Continued)

TABLE II. (Continued)

Patient no., sex	Molecular diagnosis or phenotype	Donor, HLA match (no./ total)	Age at diagnosis (mo)	Pre-HSCT complications	Age at HSCT (mo)	Engraftment	GvHD, grade (II-IV), Sk/Liv/Gi	Outcome/ age, cause of death	If alive, age at last follow-up (y)	Complications at follow-up, if alive
16, M	T ⁺ B ⁺ NK ⁺	Mother, 4/6	5	PCP	6	Yes		Alive, in middle school	11.75	Warts, asthma, obesity
17, F	T ⁺ B ⁺ NK ⁺	Father Mother, 3/6, 3/6	0.5	Rotavirus	1, 5	No		Deceased at 8 mo, disseminated <i>Aspergillus</i>		
18, M	T ⁺ B ⁺ NK ⁺	Father Father Mother, 3/6, 3/6	5	RSV pneumonia, CMV viremia, thrombophlebitis, candidal dermatitis, transplacentally transferred maternal T cells	11, 15, 19	No		Deceased at 2 y, EBV PTLN		
19, F	<i>RAG1</i> , Omenn syndrome	Father, 4/6	2.5	<i>Listeria</i> sepsis and meningitis, purulent otitis, transplacentally transferred maternal T cells	3	No	aGvHD, grade III, Sk	Deceased at 5 mo, aGvHD, PCP		
20, M	T ⁺ B ⁺ NK ⁺	Father, 4/6	6	PCP	7	Yes	cGvHD	Alive, home-bound	15.3	Bronchiolitis obliterans, short stature, deafness, food aversion, hypertension, spongiotic dermatitis, cGvHD

aGvHD, Acute GvHD; cGvHD, chronic GvHD; CMV, cytomegalovirus; F, female; LFTU, lost to follow-up; M, male; PTLN, posttransplant lymphoproliferative disease; *RAG1*, mutation in recombination activating gene 1; *RxCD6mAb*, treated with anti-CD6 mAb; *Sk/Liv/Gi*, skin/liver/gastrointestinal; X-SCID, X-linked SCID.

Engraftment occurred in 12 of 20 (60%) patients who received monoclonal anti-CD6 antibody-treated mismatched related marrow (Table II). Five of 20 (25%) patients in the MMRD group were retransplanted, with 2 patients receiving an additional third transplant; 2 of these 5 patients engrafted. The overall survival for engrafted patients in the MMRD group was 10 of 12 (83%). At the most recent follow-up period (April 2007 to June 2008), with patients ranging in age from 13.5 to 27 years, the Kaplan-Meier curve (Fig 1) showed 50% (10 of 20) survival for patients who received anti-CD6 antibody-treated MMRD bone marrow, whereas 100% (5 of 5) survival is shown for patients who received unmanipulated MRD bone marrow. Overall, 15 of 25 patients (60%) survived.

Twelve of the 20 patients in the MMRD group presented with life-threatening infections (Table II). Their infectious complications present at the time of initial diagnosis included *Pneumocystis jirovecii* pneumonia (PCP) in 9 patients, invasive bacterial infections in 2 patients, cytomegalovirus viremia in 2 patients, and invasive fungal infection in 1 patient. Of 8 patients who died within an average of 6 months (range, 1-13 months) after transplantation, the causes of mortality included EBV post-transplant lymphoproliferative disease (n = 2), polymicrobial sepsis (n = 2), polymicrobial sepsis with grade IV GvHD (n = 1), chronic GvHD with superimposed collagen vascular disease (n = 1), PCP with concurrent GvHD (n = 1), and invasive aspergillosis infection (n = 1). One of 5 patients in the MRD group presented with a life-threatening infection (concurrent staphylococcal and streptococcal sepsis; Table III). No deaths occurred in the MRD group.

Acute GvHD (grade I-IV) was present in all patients (only grades II-IV are listed in Table II). Eleven of the 20 patients in

the MMRD group had grade II to IV acute GvHD. Seven of 11 patients (4 with grade II, 2 with grade III, and 1 with grade IV) were treated with methylprednisolone alone (n = 2; grade II), anti-CD6 mAb plus methylprednisolone (n = 3; grade II-III), anti-CD3 mAb and methylprednisolone (n = 1; grade III), or methylprednisolone and cyclosporine (n = 1; grade IV). One of 7 of these patients (patient 7; Table II) survived. None of these 25 patients received routine GvHD prophylaxis. Chronic GvHD in skin, intestine, and lung at the most recent follow-up (range 14.8-16.3 years) was present in 4 patients who received a MMRD graft. Four patients in the MRD group developed acute GvHD (grade I-II) that did not require treatment; 1 had chronic GvHD (lung, skin) at the most recent follow-up.

Transplacentally transferred maternal T cells was confirmed in 5 of 5 patients investigated in the MMRD group (Table II; patients 3, 4, 5, 18, and 19), with a median number of CD3⁺ T cells present at diagnosis of 180 (range, 123-1725) cells/ μ L. Three of these 5 patients presented with life-threatening infections. Three patients who died (3 months and 5 and 10 years posttransplantation, respectively) received anti-CD6 mAb to treat transplacentally transferred maternal T cells before to transplantation. Only 1 of the 5 patients engrafted, and all 5 patients died after BMT, with a median time of 5 months posttransplantation (range, 1-166 months).

Long-term complications

A higher frequency of long-term complications was present in the MMRD group (Table II) and included gastrointestinal disorders in 3 patients (chronic hepatitis B infection, protein-losing enteropathy,

TABLE III. Outcomes of patients with SCID who received a MRD transplant without conditioning

Patient no., sex	Molecular diagnosis/phenotype	Donor, HLA match (no./total)	Age at diagnosis of SCID (mo)	Pre HSCT complications	Age at HSCT (mo)	Engraftment	aGvHD, grade (II-IV), Sk/Liv/Gi	Outcome/cause of death	If alive, age at last follow-up (y)	Complications at last follow-up, if alive
21, F	<i>RAG1</i> , Omenn syndrome	Father, 6/6	4		5	Yes		Alive, in college	27	Precancerous skin lesions
22, F	<i>RAG1</i> , Omenn syndrome	Sister, 6/6	0.5		1.5	Yes		Alive, completed high school	23	Well
23, F	<i>RAG1</i> , Omenn syndrome	Sister, 6/6	0.5	Staphylococcal and streptococcal sepsis	1.75	Yes	aGvHD, grade II, Sk, cGvHD	Alive, home-bound	19	Alopecia, chronic lung disease, bronchiolitis obliterans, bronchiectasis, sleep apnea, pituitary microadenoma, adrenal insufficiency, mental retardation, seizures, galactorrhea, amenorrhea, dental caries, myopia, cGvHD
24, M	<i>RAG1</i>	Sister, 6/6	3.5	Rotavirus	4	Yes		Alive, completed college	25.25	Well
25, M	X-SCID	Sister, 6/6	0.25	Pneumonia, palatal ulcer	0.5	Yes		Alive, completed college	21	Rhinitis, warts

aGvHD, Acute GvHD; cGvHD, chronic GvHD; F, female; HSCT, hematopoietic stem cell transplant; M, male; *RAG1*, mutation in recombination activating gene 1; Sk/Liv/Gi, skin/liver/gastrointestinal; X-SCID, X-linked SCID.

and food aversion), growth abnormalities in 2 patients (short stature), respiratory abnormalities in 4 patients (bronchiolitis obliterans in 2, asthma in 2), dermatologic manifestations in 6 patients (viral warts in 4 patients, and autoimmune vitiligo and autoimmune fasciitis each in 1 patient), and hearing loss ranging from mild to complete in 3 patients. Among patients in the MRD group (Table III), there were dermatologic manifestations in 2 patients (viral warts and autoimmune skin disease), and 1 patient had multiple problems including endocrine, respiratory, and neurodevelopmental systems. There were no lymphomas present in any of the survivors.

Immune reconstitution

At last follow-up, 7 of 10 survivors in the MMRD group and 3 of 5 survivors in the MRD group had CD3⁺ T-cell numbers within the normal range (Fig 2, A and D; Table IV). Lymphocyte responses to phytohemagglutinin, concanavalin A, or pokeweed mitogen were normal in 7 of 10 patients in the MMRD group and 2 of 5 patients in the MRD group (Table IV). Lymphocyte response to *Candida*, streptokinase, or tetanus was normal in 8 of 8 patients evaluated in the MMRD group and 3 of 5 patients in the MRD group. Chimerism studies were available on 8 of the 15 survivors (7 in the MMRD group and 1 in the MRD group; Table IV). All 8 patients showed evidence of donor T-cell engraftment, and 4 of these 7 patients (3 in the MMRD group and 1 in the MRD group) demonstrated some evidence of donor granulocyte or B-cell engraftment at last measurement.

Those on intravenous immunoglobulin replacement therapy at the time of this report included 5 of 10 (50%) in the MMRD group and 2 of 5 (40%) in the MRD group (Table IV). IgG levels were within the normal range in 8 of 10 patients evaluated (80%) in the MMRD group and 3 of 4 (75%) in the MRD group; both IgA and IgM levels were normal in 6 of 9 (66%) in the MMRD group and 2 of 4 (50%) in the MRD group. Antibody responses

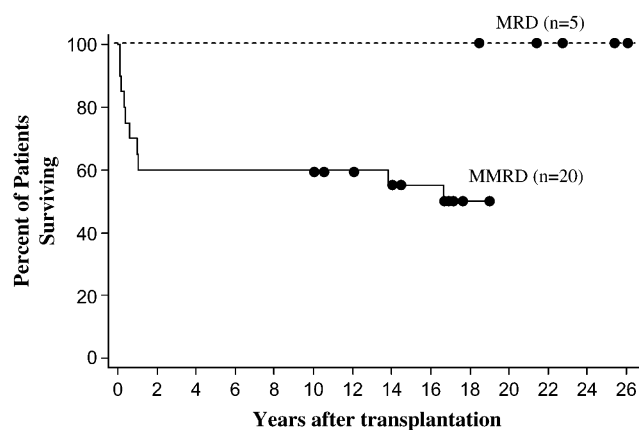


FIG 1. Kaplan-Meier curve demonstrating survival of patients with SCID, including 20 patients whose donor bone marrow was treated with anti-CD6 mAb (solid line) and 5 patients who received unmanipulated bone marrow (dotted line).

were adequate to the following antigens: diphtheria (>0.10 IU/mL) or tetanus (>0.10 IU/mL) in 5 of 5 patients evaluated in the MMRD group and 2 of 2 in the MRD group, *Streptococcus pneumoniae* (>1.0 µg/mL) in 5 of 5 in the MMRD group and 2 of 2 in the MRD group, and *Haemophilus influenzae* type b (>0.15 µg/mL) in 3 of 3 patients in the MMRD group (Table IV).

Natural killer cell counts were persistently normal in 3 of 10 (30%) of patients in the MMRD group and 4 of 5 (80%) in the MRD group (Fig 2, B and E). CD19⁺ B-cell numbers were within the normal range in 7 of 10 (70%) patients in the MMRD group and 1 of 5 (20%) in the MRD group (Fig 2, C and F). Naive CD4⁺CD45RA⁺ T-cell counts were normal in 2 of 9 (22%) in the MMRD group (median, 289; range, 273-305 cells/µL) and 1 of 5 (25%) in the MRD group (287 cells/µL; data not shown).

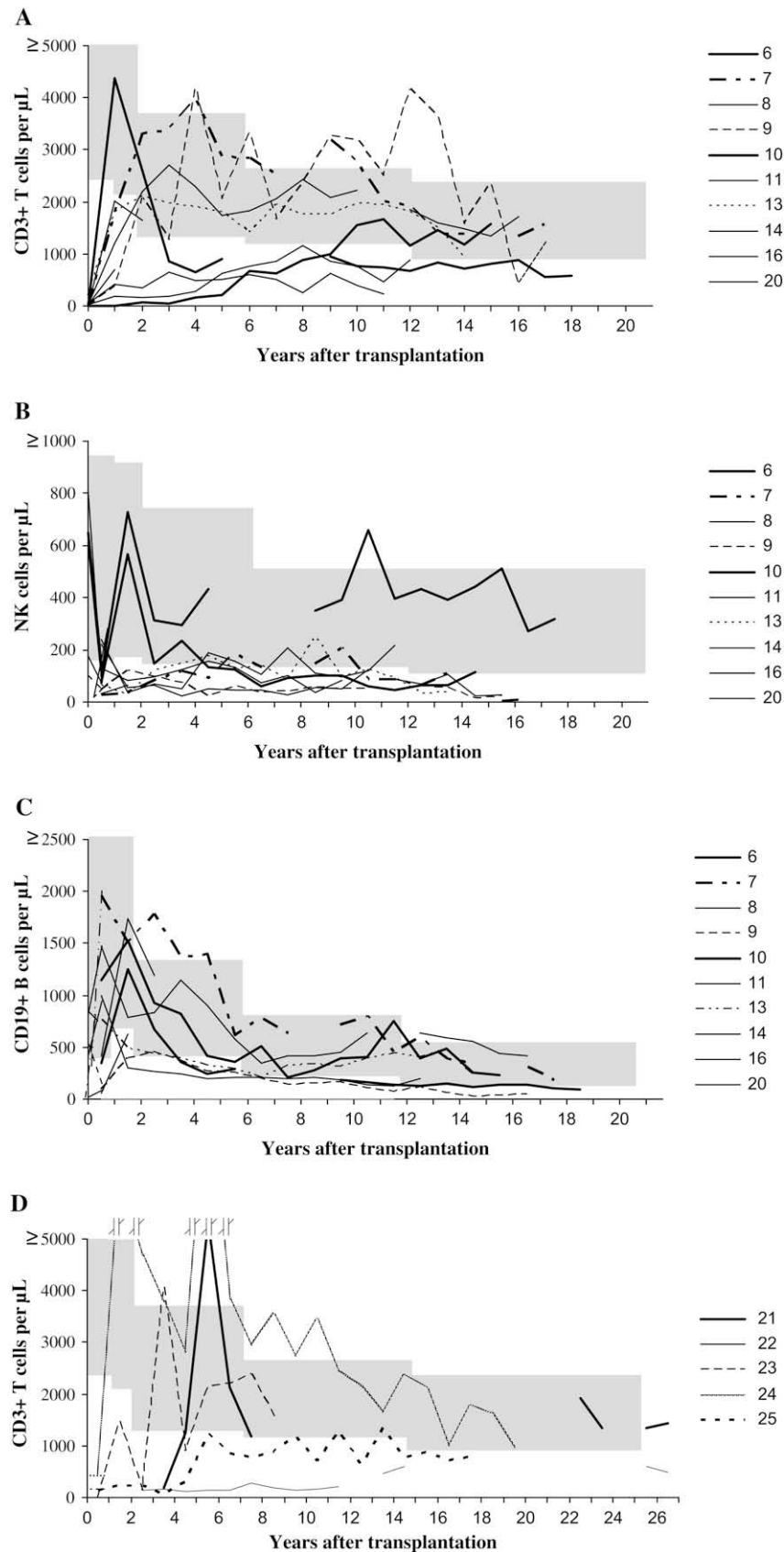


FIG 2. Lymphocytes in patients with SCID: CD3⁺ T cells (**A**), NK⁺ cells (**B**), and CD19⁺ B cells (**C**) in 10 survivors who received anti-CD6 T cell-depleted bone marrow; and CD3⁺ T cells (**D**), NK⁺ cells (**E**), and CD19⁺ B cells (**F**) in 5 survivors who received unmanipulated bone marrow. The 10th and 90th percentile normal values are represented by shaded areas.³¹

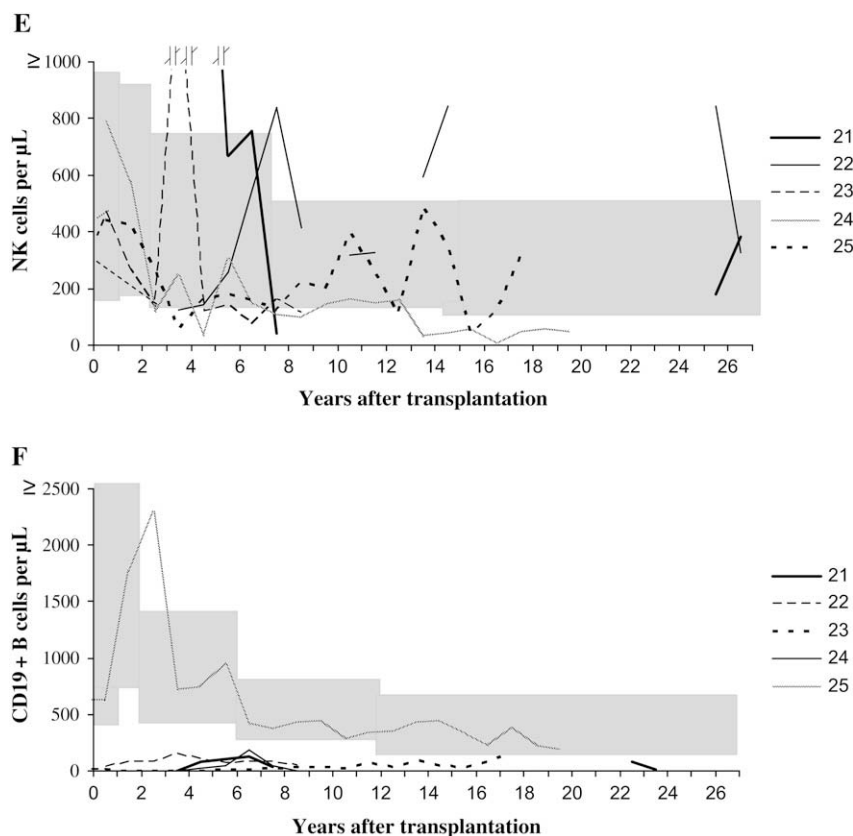


FIG 2. (Continued)

Health and educational accomplishment

Of the 10 MMRD survivors, 8 were attending or had attended school or college, and 2 were being home-educated (Table II). Of the 5 MRD survivors, 4 attended school, and 1 was home-educated (Table III). Three patients in the MRD group performed at the college level, and with the exception of 1 patient, those in the MMRD group were not old enough to attend college. One survivor in the MMRD group, who was hepatitis B surface antigen–positive at pregnancy, delivered a healthy infant. The infant received hepatitis B immunoglobulin and hepatitis B vaccination at delivery, and currently the infant remains hepatitis B surface antigen–negative. One survivor in the MRD group had 2 children, ages 3 and 1 year. All 3 children were age-appropriate for developmental milestones and were in good physical health.

DISCUSSION

Age at transplant

Among patients with SCID, the median age at the time of transplant was 6.5 months in the MMRD group and 1.8 months in the MRD group. Other published studies have shown a similar range of ages at transplant.^{6,16,17,32} Younger age at the time of transplant has been associated with improved outcomes in patients with SCID,^{6,33} and this has also been true here.

Pretransplant infection

Infectious, life-threatening infections were present in 12 (60%) of 20 patients with SCID before HSCT, with PCP present in the majority (9 patients). Of those with life-threatening infections, 6

(50%) of 12 patients in the MMRD group died, compared with none in the MRD group (1 with a life-threatening infection). The development of opportunistic infections, particularly pulmonary infection, before transplant has been associated with significantly poorer outcomes.^{32,34}

GvHD

Pretreatment of the donor graft with anti-CD6 mAb followed by complement lyses mature T cells, a subset of B cells, and monocytes, but not NK cells. Two other methods that have been used to deplete T cells from donor grafts include alemtuzumab or Campath-1M (Millenium Pharmaceuticals, Inc., Cambridge, Mass, and ILEX Pharmaceuticals, LP, San Antonio, Tex), anti-CD52 mAbs that remove T cells, most B cells, and NK cells, but not monocytes,²² and soybean lectin agglutination of donor marrow followed by rosetting with sheep erythrocytes, which remove T cells and NK cells.^{2,6} Generally, antibody depletion of T cells from donor bone marrow is between 1.5 and 2 log₁₀,²⁸ whereas soybean lection agglutination removal of T cells can be >2 log₁₀.^{2,6} The incidence of grade II to IV acute GvHD after treatment with anti-CD6 mAb in this study was 11 of 20 (55%), of which 3 patients developed grade III to IV. Published series of Campath-1M depletion and soybean lectin agglutination methods resulted in GvHD incidences of 27% and 36%, respectively.^{2,6,22} After anti-CD6 antibody treatment, a small percentage of CD3⁺ T cells remain in the infused marrow. Donor T cells (in excess of 1×10^5 cells/kg, as was the case with our patients) have been associated with GvHD in other HSCT recipients.^{35,36} However, it is not known whether

TABLE IV. T-cell and B-cell function of 15 survivors with SCID after HSCT

Patient no.	Last evaluation post-BMT (mo)	CD3 ⁺ T cells/mL	PHA/ConA/PWM (×1000) response	Cand/SK/Tet (×1000) response	T-cell/B-cell donor chimerism (%/%)	IVIG treatment	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)	Response to vaccines (Pr, Ps) [†]
Anti-CD6 T cell–depleted haploidentical BMT patients										
6	229	663*	161/126/85	2.3/2.2/8.2	(100/90)	No	904	285	206	Pr, Ps
7	199	1576	286/192/81	20.4/2.1/15.1	(100/11)	Yes	797	<15*	15*	—
8	193	1705	100/39/22	—	—	No	629	216	81.2	Pr, Ps
9	188	1336	20/9/9*	2.3/ /0	(93/0)	Yes	839	<15*	29.8*	—
10	182	1573	214/141/57	2.6/.8/.05	(100/0)	No	1440	172	97	Pr, Ps
11	171	905	79/ /64*	—	—	Yes	450*	—	—	—
13	168	930	82/ /16*	45.3/0 /1.57	(100/12)	No	869	82	154	Pr, Ps
14	40	1669	89/98/69	3.2/5.9/0	(100/0)	No	579*	65	130	Pr, Ps
16	148	889*	250/204/67	1.35/ /3.41	(100/0)	Yes	1280	91.7	63.9	—
20	129	232*	121/ /61	13/ /0	—	Yes	606	1.1*	1.7*	—
Match-related BMT patients										
21	312	4496	11/20/3*	61/ /.60	—	Yes	1060	173	11*	—
22	92	1568	24/12/41*	0.3/0/0*	—	No	—	—	—	—
23	222	562	203/35/38	3.1/.12/10.4	—	No	890	113	197	Pr, Ps
24	305	610	52/ /50*	.06/ /.2.70*	—	Yes	332*	80*	<5*	—
25	253	1040	356/109/75	13.4/9.4/5.4	(97/97)	No	1140	305	113	Pr, Ps

Note: — indicates test not done.

Cand, *Candida*; PHA, phytohemagglutinin; Pr, protein; Ps, polysaccharide; PWM, pokeweed mitogen; SK, streptokinase; Tet, tetanus; IVIG, intravenous immunoglobulin.

*Abnormal values.

†Protective antibody titers present.

the CD6[−] T-cell subset, thought to be immature, can similarly cause GvHD. In addition, the presence of NK cells, which anti-CD6 antibody does not remove, has also been associated with GvHD.^{37,38} Patients did not receive GvHD prophylaxis in this study, and 13 patients in the MMRD group (9 with grade I and 4 with grade II-IV) improved without treatment. Of note, 3 MRD survivors diagnosed with Omenn syndrome (Table III; patients 21-23) had successful T-cell immune reconstitution without pretransplant conditioning. This result contrasts with the view that patients with Omenn syndrome require myeloablative conditioning for a successful outcome.¹⁷

Engraftment

Engraftment occurred in 60% of patients who received anti-CD6 antibody–depleted MMRD marrow. This is similar to the rates of engraftment (59% to 70%) for patients who received a MMRD transplant regardless of conditioning.^{17,22,39} When survivors of MMRD recipients (with some MRD recipients) who received no conditioning were assessed, a higher rate of engraftment was determined (96%)^{2,6} compared with our study. Engraftment of B cells was much lower, as seen in BMT regimens with or without conditioning.^{15,16,40} Data from 5 MRD recipients and 10 MMRD recipients were available to evaluate long-term immune reconstitution. Replacement therapy with intravenous immunoglobulin was still required in 2 of 5 (40%) MRD (2 T[−]B[−]NK⁺) and 5 of 10 (50%) MMRD (3 T[−]B⁺NK[−], 1 T[−]B⁺NK⁺, 1 T[−]B[−]NK⁺) transplants. Most of these patients present with the B⁺ phenotype, confirming the notion of the difficulty of engrafting donor B cells in patients with SCID with this phenotype.³²

Survival and quality of life

In our study, all 5 of 5 MRD recipients who received no conditioning are currently alive. This outcome is similar to the 92% to

100% survival in other published studies.^{2,6,18} Of the 20 patients in the MMRD group, there were 10 survivors (50%) at the most recent follow-up, which compares to 46% to 62% of patients who received T cell–depleted bone marrow with conditioning in other studies^{17,20,22,34} and 78% of patients who received T cell–depleted bone marrow without conditioning in 1 center.^{2,6} Another development that has widened the choice of T-cell reconstitution in severely immune deficient children is the use of matched unrelated donors, usually with conditioning of patients, yielding survivals of approximately 80%.^{17,41} Umbilical cord blood transplantation offers another mode of therapy for these patients.⁴² The lower survival rate seen in the population of MMRD recipients could be attributed to multiple factors, including GvHD incidence, the older patient population at the time of transplant, and severe pretransplant infections.^{2,6,15,32,33} In our subset of patients with SCID with a B⁺ phenotype, survival in MMRD recipients was 9 of 16 (56%) and 1 of 1 in MRD recipients, compared with only 1 of 4 (25%) in MMRD and 4 of 4 in MRD recipients with a B[−] phenotype. Similar observations of differences in survival rates between B⁺ and B[−] SCID phenotypes has been noted in other studies,^{16,22,32,34} suggesting the B[−] phenotype is associated with a poorer prognosis unless they are given HLA-identical unfractionated marrow transplants.

Most of the survivors have attained educational goals and maintain a good quality of life. A few have become parents of healthy children.

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Clinical implications: Early transplantation of T cell–depleted MMRD bone marrow in infection-free, nonconditioned children with SCID results in long-term survival with a good quality of life.

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