HEMATOPOIETIC STEM-CELL TRANSPLANTATION FOR THE TREATMENT OF SEVERE COMBINED IMMUNODEFICIENCY

REBECCA H. BUCKLEY, M.D., SHERRIE E. SCHIFF, B.S., RICHARD I. SCHIFF, M.D., PH.D., M. LOUISE MARKERT, M.D., PH.D., LARRY W. WILLIAMS, M.D., JOSEPH L. ROBERTS, M.D., PH.D., LAURIE A. MYERS, M.D., AND FRANCES E. WARD, PH.D.

ABSTRACT

Background Since 1968 it has been known that bone marrow transplantation can ameliorate severe combined immunodeficiency, but data on the long-term efficacy of this treatment are limited. We prospectively studied immunologic function in 89 consecutive infants with severe combined immunodeficiency who received hematopoietic stem-cell transplants at Duke University Medical Center between May 1982 and September 1998.

Methods Serum immunoglobulin levels and lymphocyte phenotypes and function were assessed and genetic analyses performed according to standard methods. Bone marrow was depleted of T cells by agglutination with soybean lectin and by sheep-erythrocyte rosetting before transplantation.

Results Seventy-seven of the infants received T-cell–depleted, HLA-haploidentical parental marrow, and 12 received HLA-identical marrow from a related donor; 3 of the recipients of haploidentical marrow also received placental-blood transplants from unrelated donors. Except for two patients who received placental blood, none of the recipients received chemotherapy before transplantation or prophylaxis against graft-versus-host disease. Of the 89 infants, 72 (81 percent) were still alive 3 months to 16.5 years after transplantation, including all of the 12 who received HLA-identical marrow, 60 of the 77 (78 percent) who were given haploidentical marrow, and 2 of the 3 (67 percent) who received both haploidentical marrow and placental blood. T-cell function became normal within two weeks after transplantation in the patients who received unfractionated HLA-identical marrow but usually not until three to four months after transplantation in those who received T-cell–depleted marrow. At the time of the most recent evaluation, all but 4 of the 72 survivors had normal T-cell function, and all the T cells in their blood were of donor origin. B-cell function remained abnormal in many of the recipients of haploidentical marrow. In 26 children (5 recipients of HLA-identical marrow and 21 recipients of haploidentical marrow) between 2 percent and 100 percent of B cells were of donor origin. Forty-five of the 72 children were receiving intravenous immune globulin.

Conclusions Transplantation of marrow from a related donor is a life-saving and life-sustaining treatment for patients with any type of severe combined immunodeficiency, even when there is no HLA-identical donor. (N Engl J Med 1999;340:508-16.)

SEVERE combined immunodeficiency is a rare, fatal syndrome that can be due to a variety of genetic abnormalities causing profound deficiencies of lymphocytes.[1-4] Shortly after the discovery of the HLA system in 1968,[5,6] immune function was corrected in an infant with severe combined immunodeficiency by the transplantation of bone marrow from his HLA-identical sister.[7] Over the following decade, however, lethal graft-versus-host disease (GVHD) was a major problem when marrow from HLA-mismatched donors was transplanted.[1] In the late 1970s, studies in rats[8] and mice[9] revealed that allogeneic marrow or spleen cells that were depleted of T cells rescued the recipient from lethal irradiation without causing fatal GVHD, despite differences in major-histocompatibility-complex antigens between the donor and the host. Techniques developed in the early 1980s to deplete human marrow of T cells made it possible to restore immune function by marrow transplantation in patients with any form of severe combined immunodeficiency.[10-21]

Because the defect in infants with severe combined immunodeficiency is immunologic rather than hematologic, and because these infants cannot reject allografts, successful marrow transplantation for the treatment of this disease does not require chemotherapeutic conditioning before transplantation. Moreover, prophylaxis against GVHD is not necessary after transplantation of HLA-identical marrow or T-cell–depleted haploidentical marrow (in which the donor and recipient share only one of two possible HLA haplotypes). These circumstances provide a unique opportunity to study the development of T cells from donor hematopoietic stem cells, since the recipients have not received chemotherapeutic conditioning or prophylaxis against GVHD and few if any mature T cells are transplanted. We report on the outcome of hematopoietic stem-cell transplantation in 89 consecutive infants with severe combined immunodeficiency at Duke University Medical Center over the past 16.5 years and the extent of immune reconstitution in the 72 surviving patients.

METHODS

The 89 infants were from 78 families and ranged in age from newborn to 21 months at the time of diagnosis. All 89 met the

From the Departments of Pediatrics (R.H.B., S.E.S., R.I.S., M.L.M., L.W.W., J.L.R., L.A.M.) and Immunology (R.H.B., M.L.M., F.E.W.), Duke University Medical Center, Durham, N.C. Address reprint requests to Dr. Buckley at Box 2898, Duke University Medical Center, Durham, NC 27710.

criteria of the World Health Organization for the diagnosis of severe combined immunodeficiency.[3] The type of disease was determined on the basis of family history, sex, clinical features, and the results of enzyme analyses or molecular studies (Table 1).[4] The largest number of infants — 43 boys from 35 families — had X-linked severe combined immunodeficiency due to mutations of the gene encoding the common γ chain, a component of several cytokine receptors (interleukin-2, 4, 7, 9, and 15).[4,22-24] Six infants from six families had severe combined immunodeficiency due to mutations of the gene encoding Janus kinase 3 (JAK3), the primary intracellular signal transducer from the common γ chain (γ_c chain).[4,25,26] Two infants from two families had a novel type of severe combined immunodeficiency caused by mutations of the gene encoding the α chain of the interleukin-7 receptor, a cytokine required for T-cell development.[27] Thirteen infants from 11 families had severe combined immunodeficiency due to a deficiency of adenosine deaminase, a component of a purine-salvage pathway necessary for T-cell survival and function.[28] Twenty-one infants from 20 families had proven autosomal recessive inheritance but unknown mutations (including 1 with cartilage–hair hypoplasia), and 4 boys with no family history had severe combined immunodeficiency of an unknown type. The clinical characteristics of all but 13 of these infants have been reported elsewhere.[4]

The control subjects for the cellular studies were healthy adult volunteers. Immunologic monitoring was performed whenever feasible every three weeks until T-cell function was established (usually three to four months after transplantation), then every three months for the next nine months, every six months for the next two years, and once a year thereafter. The studies were undertaken with the approval of the Duke University Committee on Human Investigations, and written informed consent was obtained from the parents of the children.

Serum IgG, IgA, and IgM were quantified by single radial diffusion or nephelometry.[29] IgE was measured by double-antibody radioimmunoassay[30] or by enzyme-linked immunosorbent assay. Antidiphtheria and antitetanus antibodies were measured by tanned red-cell hemagglutination.[31] T cells, B cells, and natural killer cells were quantified by cytofluorography with the use of murine monoclonal antibodies against lineage-specific surface molecules. HLA typing was performed with a microcytotoxicity assay, cytofluorography, or a polymerase-chain-reaction assay. In vitro stimulation of lymphocytes and studies of natural-killer-cell activity were performed as described elsewhere.[12] Chimerism was detected on the basis of karyotyping, fluorescence in situ hybridization,[32] HLA typing, flow-cytometric identification of γ chain on lymphocytes, or the presence of adenosine deaminase. JAK3 deficiency was detected by immunoblotting and DNA sequencing. γ-Chain deficiency was diagnosed by the demonstration of a deleterious mutation of the γ chain of the interleukin-2 receptor.[24] Mutations of the α chain of the interleukin-7 receptor were detected by Northern blot analyses and subsequent DNA sequencing.[27]

Marrow was depleted of T cells by agglutination with soybean lectin, followed by two cycles of rosetting with sheep erythrocytes treated with aminoethylisothiuronium bromide, as described elsewhere.[10,12,33] This method reduced the number of T cells by a factor of 10,000. All the HLA-haploidentical transplants and 5 of the 12 HLA-identical transplants from related donors were depleted of T cells. Nineteen infants received one to three additional T-cell–depleted marrow transplants from either the original donor or another haploidentical relative. None of the marrow recipients received any pretransplantation chemotherapeutic conditioning or post-transplantation prophylaxis against GVHD. Two infants were treated with cyclosporine for one month because they had presented with cutaneous GVHD from transplacental transfer of maternal T cells. Three of the infants who received haploidentical marrow transplants also received placental-blood transplants from unrelated donors. Two of these children received pretransplantation conditioning because they had hematopoietic chimerism as a result of previous marrow transplants; they were also given prophylaxis against GVHD after transplantation.

The mean numbers of nucleated cells given per kilogram of the recipients' body weight are listed in Table 2. Paired t-tests, log-

TABLE 1. SURVIVAL OF 89 PATIENTS WITH SEVERE COMBINED IMMUNODEFICIENCY WHO RECEIVED TRANSPLANTS BETWEEN MAY 1982 AND AUGUST 1998.

VARIABLE	NO. OF PATIENTS	NO. SURVIVING	PERCENT SURVIVING	P VALUE*	
				WILCOXON	LOG RANK
Type of severe combined immunodeficiency				NS	NS
γ_c-Chain deficiency	43	34	79		
JAK3 deficiency	6	6	100		
Interleukin-7 receptor α deficiency	2	2	100		
Adenosine deaminase deficiency	13	11	85		
Autosomal recessive, unknown cause	20	17	85		
Cartilage–hair hypoplasia	1	1	100		
Male, unknown cause	4	1	25		
Total	89	72	81		
Race or ethnic group				<0.001	<0.001
White	69	61	88		
Black	10	5	50		
Hispanic	10	6	60		
Total	89	72	81		
Sex				0.047	0.06
Male	75	58	77		
Female	14	14	100		
Total	89	72	81		
Age at time of transplantation				0.088	NS
<3.5 mo	22	21	95		
≥3.5 mo	67	51	76		
Total	89	72	81		

*NS denotes not significant.

TABLE 2. MEAN NUMBERS OF NUCLEATED ALLOGENEIC CELLS TRANSPLANTED.

TYPE OF TRANSPLANT	NO. OF TRANSPLANTS	NO. OF CELLS TRANSPLANTED PER KILOGRAM OF BODY WEIGHT		
		MEAN	SD	SE
HLA-identical marrow	12	4.84×10^8	3.34×10^8	1.00×10^8
HLA-haploidentical marrow	102*	3.13×10^8	5.03×10^8	5.01×10^7
Placental blood	3	9.82×10^7	5.89×10^7	3.00×10^7

*One patient received three booster transplants, 4 received two booster transplants, and 14 received one booster transplant. All booster transplants were given without pretransplantation chemotherapy and without prophylaxis against GVHD.

rank tests, Wilcoxon's rank-sum test, and Tukey's analysis of variance were used to examine differences in survival according to sex, race (white vs. nonwhite), age at the time of transplantation, and immunologic variables.

RESULTS

Factors Influencing Survival

Of the 89 infants with severe combined immunodeficiency, 72 (81 percent) were still alive at the end of the follow-up period, which ranged from 3 months to 16.5 years (Fig. 1). None of the survivors had any evidence of susceptibility to opportunistic infections, and most were in good general health. Of these 72 children, 65 survived for 1 or more years after transplantation, 38 for 5 or more years, and 21 for 10 or more years. The median follow-up period for the surviving children was 5.6 years. All 12 recipients of marrow from HLA-identical donors, 60 of the 77 recipients of T-cell–depleted haploidentical bone marrow from a related donor, and 2 of the 3 in the latter group who were also given placental-blood transplants from unrelated donors survived.

The survival rates were similar regardless of the genetic type of severe combined immunodeficiency, except that only one of the four boys with an unknown type survived. Influences on survival include race (more white than black or Hispanic patients survived, $P<0.001$) and sex (all the girls survived, $P=0.047$) (Table 1). Of the 22 infants who received transplants before they were 3.5 months old, 21 (95 percent) survived, as compared with 51 of 67 (76 percent) who received transplants when they were 3.5 months or older ($P=0.088$).

Fifteen deaths occurred as a result of viral infections: six patients died of cytomegalovirus, three of Epstein–Barr virus, two of adenovirus, two of enteroviruses, one of parainfluenzavirus 3, and one of herpes simplex virus. One infant died of sepsis due to candida infection. Another died of an unrelated mitochondrial defect after successful marrow engraftment.

Graft-versus-Host Disease

GVHD developed in 28 of the 77 infants given T-cell–depleted haploidentical parental marrow, 6 of the 12 given HLA-identical marrow, and 2 of the 3 given placental blood. In 27 of 36 cases, this complication occurred in association with the persistence of maternal T cells that had crossed the placenta. In most cases, GVHD that developed after the administration of T-cell–depleted marrow was mild (grade I or II) and required no treatment.[34] Eight infants had grade III GVHD involving the skin, gastrointestinal tract, marrow, or a combination of these sites. Seven of these eight infants were treated with corticosteroids and cyclosporine, and one received only corticosteroids. No patient died of GVHD, but

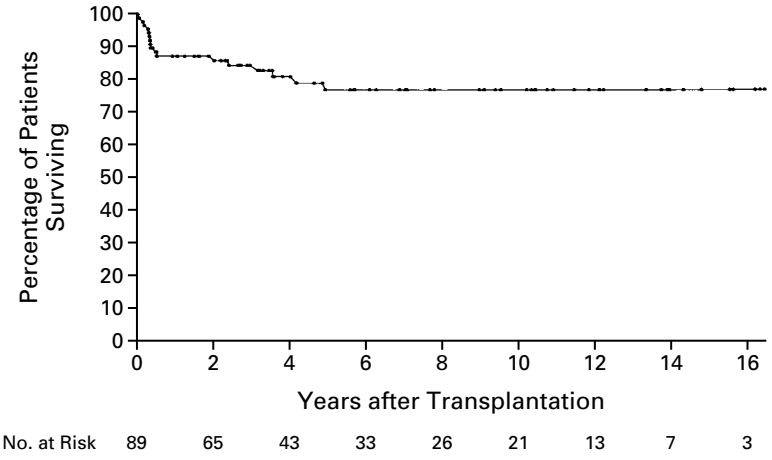

Figure 1. Kaplan–Meier Survival Curve for 89 Patients with Severe Combined Immunodeficiency Who Received Stem-Cell Transplants.

Eighty-one percent of the patients were alive at the most recent evaluation; only 12 received transplants from related identical donors.

one of the recipients of placental blood from an unrelated donor had a severe case of acute GVHD, and at the time of this writing, 2.2 years after transplantation, had chronic GVHD that required continuous cyclosporine therapy.

Engraftment and Chimerism

Genetic analyses of blood lymphocytes performed at the most recent evaluation showed that all the T cells in 68 of the 72 surviving children were of donor origin. In one child with γ_c-chain deficiency, four T-cell–depleted transplants — two from each parent — failed to engraft, but the patient is still alive at six years of age despite minimal T-cell function. Seven of nine children with adenosine deaminase deficiency who were given T-cell–depleted haploidentical marrow were alive 1.6 to 15.6 years after transplantation, with hematopoietic chimerism in six. One child with adenosine deaminase deficiency received polyethylene glycol–modified bovine adenosine deaminase after two paternal hematopoietic stem-cell transplants were rejected.

In contrast to the uniform development of T cells from donors, the B cells in most cases were derived from the recipient. However, 5 of 12 recipients of HLA-identical marrow and 21 of 60 recipients of haploidentical marrow had some donor B cells (range, 2 percent to 100 percent of all B cells; mean [±SE], 56±8 percent).

Lymphocyte Phenotypes

The infants, regardless of the genetic type of severe combined immunodeficiency, had distinct lymphocyte phenotypes before transplantation (Fig. 2A).[4] All the infants had a profound deficiency of T cells, and when T cells were present, they were usually maternal T cells that had crossed the placenta. In one infant with JAK3 deficiency, there were 8268 circulating maternal T cells per cubic millimeter at presentation. The numbers of B cells were elevated in all the infants except those with adenosine deaminase deficiency but were most elevated in infants with γ_c-chain or JAK3 deficiency ($P<0.001$). The numbers of natural killer cells were lowest in patients with γ_c-chain, JAK3, or adenosine deaminase deficiency ($P<0.001$) but were elevated in those with a deficiency in the α chain of the interleukin-7 receptor ($P<0.001$) and were normal in those with autosomal recessive disease of unknown cause and in boys with unknown types of the disease.[4]

At the most recent evaluation (Fig. 2B), the mean number of T cells in the 72 surviving children was within the normal range for those with deficiencies in the γ_c chain, in adenosine deaminase, or in the α chain of the interleukin-7 receptor and in those with severe combined immunodeficiency of unknown cause, but the number of T cells was elevated in those with the JAK3 deficiency and just below the normal range in those with the autosomal recessive type of the disease. Mean numbers of CD4+ and CD8+ T cells were within normal ranges in all groups after transplantation (data not shown). After transplantation, the mean numbers of B cells remained elevated in the children with γ_c-chain or JAK3 deficiency ($P<0.001$) but were normal in all the other children (Fig. 2B). The mean number of natural killer cells remained low in the group with γ_c-chain deficiency but was normal in the other groups.

T-Cell Function

Figure 3 shows in vitro responses to nonspecific mitogens (phytohemagglutinin, concanavalin A, and pokeweed mitogen) by unfractionated lymphocytes from children with the various types of severe combined immunodeficiency, before (Panel A) and after (Panel B) transplantation, as compared with the responses of T cells from normal adults. Remarkably, the mean responses to all three mitogens were normal in all groups after transplantation, as compared with extremely low responses before transplantation. Moreover, the lymphocytes from all groups responded poorly to allogeneic cells (indicating an absence of T-cell function) before transplantation; however, T cells from all groups responded normally to allogeneic cells, candida, and tetanus antigens after transplantation (data not shown).

B-Cell Function

B-cell function did not develop to the same extent as T-cell function. Table 3 shows the mean serum immunoglobulin concentrations before and after transplantation according to the type of disease. The presence of serum IgG before transplantation was in most cases due to the transfer of maternal antibodies across the placenta or to the administration of intravenous immune globulin, but paraproteins were present in some infants. One infant with a deficiency in the α chain of the interleukin-7 receptor had both IgG and IgA paraproteins before transplantation, as has been noted previously in patients with severe combined immunodeficiency.[36-38] At the most recent evaluation, 36 patients had normal serum IgA levels, 58 had normal IgM levels, and 33 had isohemagglutinins appropriate for the red-cell type of the host (Table 4). Forty-five children were receiving immunoglobulin-replacement therapy to prevent bacterial and common viral infections. All children who were not receiving immune globulin infusions had a demonstrated capacity to produce antibodies against one or more vaccine antigens (data not shown).

Natural-Killer-Cell Function

Before engraftment, the number and activity of natural killer cells were lowest in the children with γ_c-chain or JAK3 deficiency ($P<0.001$, data not shown), whereas they were higher than normal in

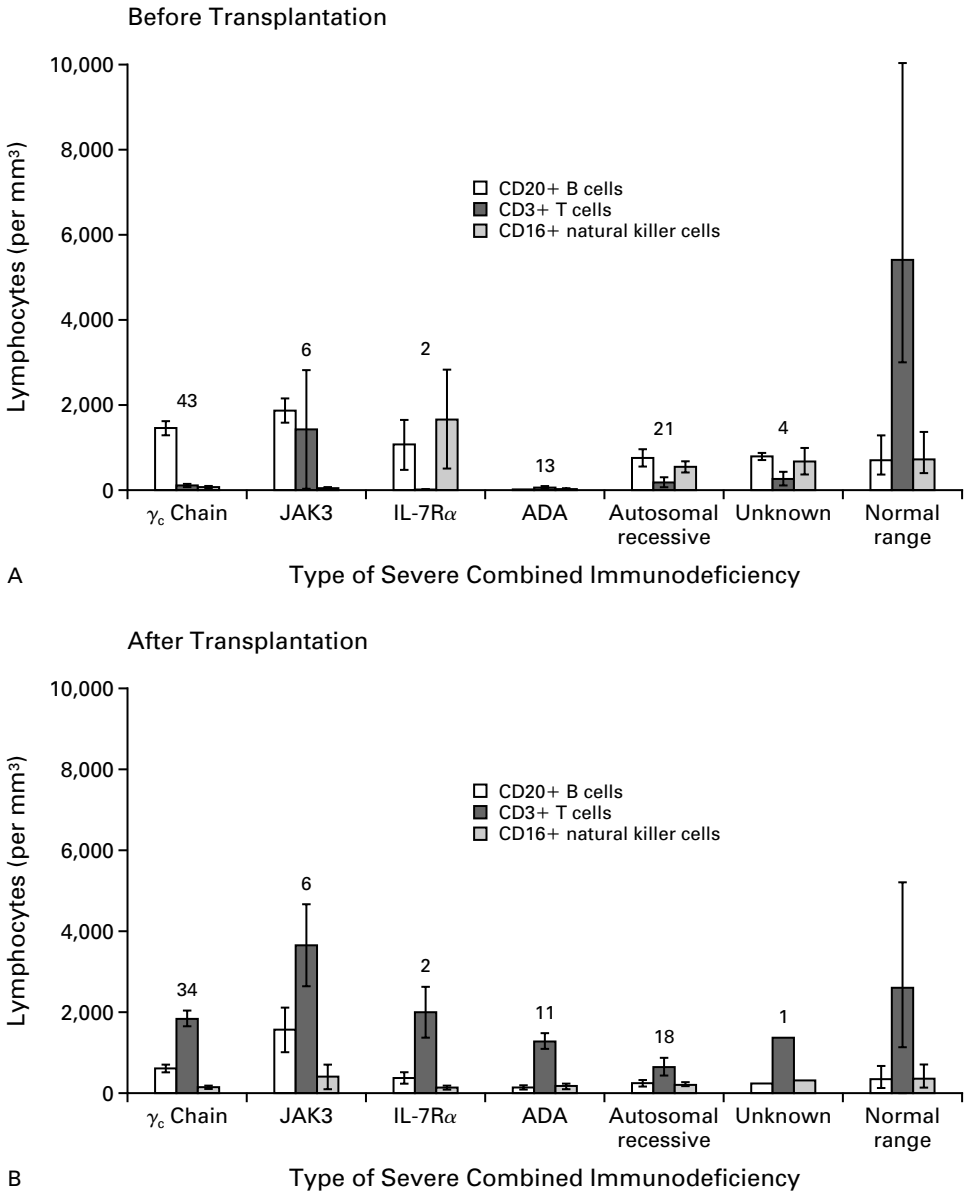

Figure 2. Mean (±SE) Numbers of CD20+ B Cells, CD3+ T Cells, and CD16+ Natural Killer Cells before Transplantation (Panel A) and at the Most Recent Evaluation after Transplantation (Panel B), According to the Type of Severe Combined Immunodeficiency.

Peripheral-blood lymphocyte counts for age-matched normal controls are from Altman.[35] The mean numbers of B and natural killer cells before transplantation in the children with γ-chain, JAK3, or adenosine deaminase deficiency were significantly different from those in normal controls (Panel A, $P<0.001$), according to the Wilcoxon and Tukey tests. The number of B cells after transplantation in the children with JAK3 or adenosine deaminase deficiency was also significantly different from that in normal controls (Panel B, $P<0.001$). The numbers above the bars indicate the number of children in each group. IL-7Rα denotes the α chain of the interleukin-7 receptor, and ADA adenosine deaminase.

those with all other types of severe combined immunodeficiency except those with adenosine deaminase deficiency. After transplantation, many of the children with γ_c-chain or JAK3 deficiency continued to have low natural-killer-cell function; natural-killer-cell activity was normal in the children with other types of severe combined immunodeficiency.

Booster Transplants

In an attempt to overcome poor B- or T-cell function or resistance to engraftment, "booster" transplants were given to 20 of the 89 patients (22 percent). None of these patients received chemotherapy beforehand, and the method of T-cell depletion was the same as that used initially. Fifteen children re-

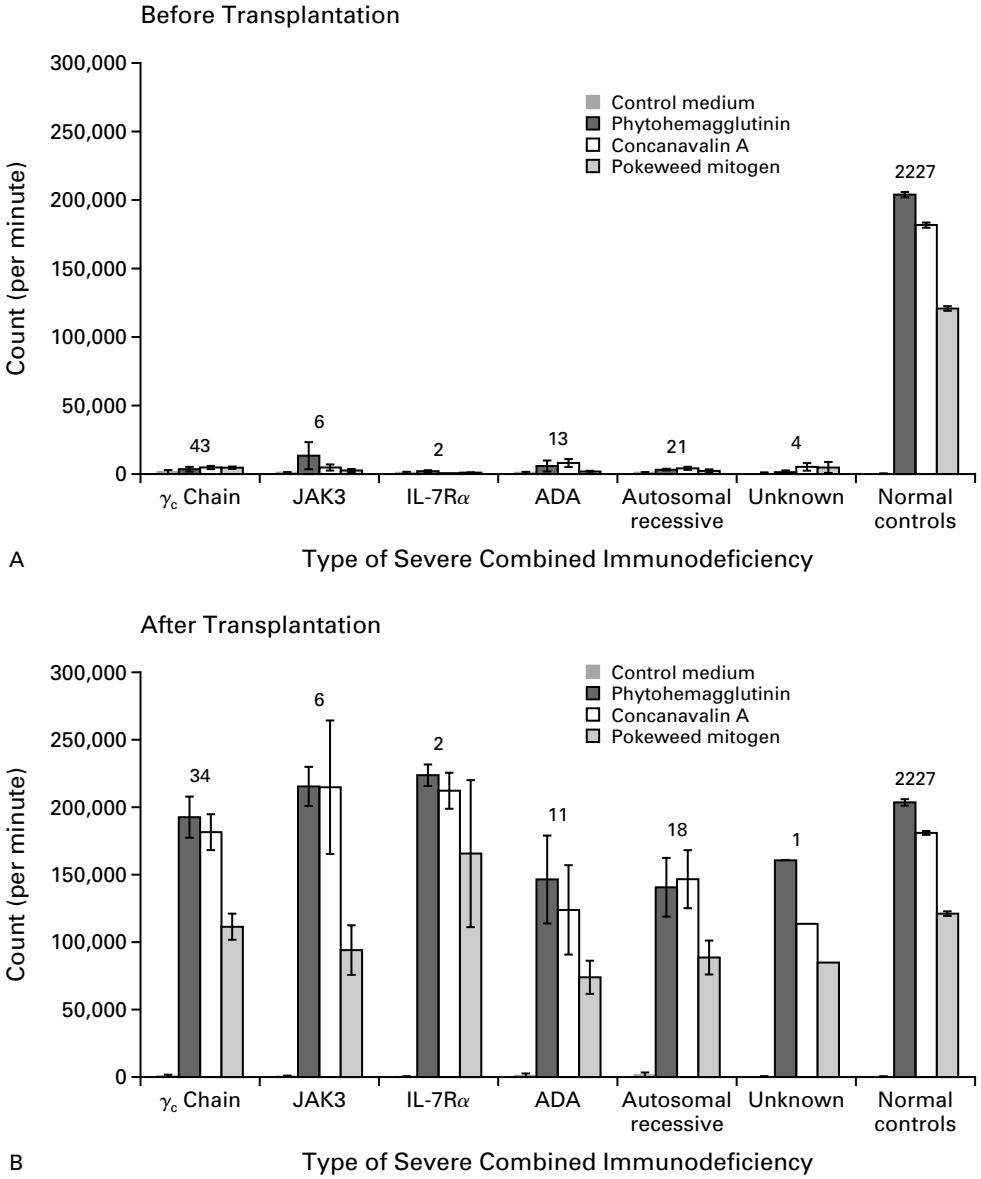

Figure 3. Tritium-Labeled Thymidine Incorporated by Proliferating Lymphocytes in Response to Phytohemagglutinin, Concanavalin A, and Pokeweed Mitogen, before Transplantation (Panel A) and at the Most Recent Evaluation after Transplantation (Panel B), According to the Type of Severe Combined Immunodeficiency.

Values are mean (±SE) counts per minute. Counts per minute for normal controls are shown for comparison. The numbers over the bars indicate the number of children in each group, with the exception of those over the set of bars on the far right, which indicate the number of normal controls. IL-7Rα denotes the α chain of the interleukin-7 receptor, and ADA adenosine deaminase.

ceived booster transplants from the parental donor who supplied the initial transplant; six of these children died of opportunistic viral infections. Four received booster transplants from the other parent; all four survived. In addition, one patient received a blood transfusion from an identical twin who had undergone successful transplantation of marrow from their father. Immune function improved in all but three of the survivors who received booster transplants.

DISCUSSION

Our study demonstrates that the transplantation of either HLA-identical or T-cell–depleted HLA-haploidentical bone marrow is highly effective in reconstituting T-cell immunity in patients with severe combined immunodeficiency, regardless of the genetic type. No chemotherapeutic conditioning was required to ensure engraftment, because the recipients had virtually no T cells at the time of transplan-

TABLE 3. SERUM IMMUNOGLOBULIN CONCENTRATIONS BEFORE AND AFTER TRANSPLANTATION, ACCORDING TO THE TYPE OF SEVERE COMBINED IMMUNODEFICIENCY.*

TYPE OF SEVERE COMBINED IMMUNODEFICIENCY	IgG		IgA		IgM		IgE	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
	mg/dl		mg/dl		mg/dl		IU/ml	
γ_c-Chain deficiency								
No. of patients	*43*	*34*	*43*	*34*	*43*	*34*	*37*	*29*
Mean	411	717	3	37	23	71	7	11
SD	363	355	6	72	28	68	18	22
SE	55	61	1	12	4	12	3	4
JAK3 deficiency								
No. of patients	*6*	*6*	*6*	*6*	*6*	*6*	*6*	*6*
Mean	328	843	4	64	28	149	116	20
SD	359	355	7	72	12	84	272	23
SE	147	145	3	29	5	34	111	9
Interleukin-7 receptor α deficiency								
No. of patients	*2*	*2*	*2*	*2*	*2*	*2*	*1*	*2*
Mean	2233	1053	202	54	83	89	1	3
SD	282	583	285	24	4	8		2
SE	200	413	202	17	3	6		2
Adenosine deaminase deficiency								
No. of patients	*13*	*11*	*13*	*11*	*13*	*11*	*9*	*10*
Mean	312	751	34	67	108	59	5	93
SD	189	225	65	59	362	37	6	245
SE	52	68	18	18	100	11	2	78
Autosomal recessive, unknown cause								
No. of patients	*21*	*18*	*21*	*18*	*21*	*18*	*18*	*16*
Mean	471	882	16	49	44	70	38	40
SD	504	612	27	66	71	53	111	74
SE	110	144	6	16	15	13	26	19
Male, unknown cause								
No. of patients	*4*	*1*	*4*	*1*	*4*	*1*	*4*	*1*
Mean	223	722	1	54	13	105	21	85
SD	222		3		16		34	
SE	111		1		8		17	

*The normal values for serum immunoglobulin concentrations at the age of six months are as follows: IgG, 192 to 515 mg per deciliter; IgA, 12 to 31 mg per deciliter; IgM, 39 to 92 mg per deciliter; and IgE, 0 to 200 IU per milliliter (0 to 480 μg per liter).[29] To convert values for serum IgE to micrograms per liter, multiply by 2.4. The differences in mean IgG and IgA concentrations before and after transplantation were significant for the patients with γ_c-chain deficiency, adenosine deaminase deficiency, or the autosomal recessive form of severe combined immunodeficiency ($P<0.03$ by paired t-test), and the difference in the mean IgM concentration before and after transplantation was significant for the patients with γ_c-chain or JAK3 deficiency ($P<0.02$ by the paired t-test).

tation. Eliminating the need for such conditioning prevents the problems associated with chemotherapeutic agents, including neutropenia, the need for red-cell and platelet transfusions, mucositis, veno-occlusive disease, lung disease (induced by busulfan), growth suppression, sterility, and a 15 percent risk of subsequent cancer.[39] Although prophylaxis against GVHD was not used except for a one-month regimen of cyclosporine given to two infants who presented with GVHD and two who received placental-blood transplants, clinically significant GVHD was rarely seen. Since most of the infants did not receive cyclosporine as prophylaxis against GVHD, T-cell function developed without hindrance.

T-cell function was normal within two weeks after transplantation of unfractionated HLA-identical marrow as a result of the transfer of mature donor T cells. By contrast, normal function did not develop until three to four months after the transplantation of T-cell–depleted marrow, irrespective of whether the marrow was HLA-identical or haploidentical.[12] Three to four months is the average time required for donor stem cells to become phenotypically and functionally mature T cells in a recipient.[12,21] In our study, T-cell function often developed much earlier in the neonatal recipients and in the children with maternal T cells that had crossed the placenta, but it developed later in some children who had high numbers of natural killer cells at presentation. In the children who received placental-blood transplants from unrelated donors, T cells were present immediately after transplantation, but T-cell function was suppressed by the large doses of corticosteroids and cyclosporine needed to prevent or treat GVHD.

Only 6 of 12 survivors of HLA-identical transplantation and 18 of 60 survivors of haploidentical

TABLE 4. HUMORAL IMMUNE STATUS AT THE MOST RECENT EVALUATION.

TYPE OF SEVERE COMBINED IMMUNODEFICIENCY	DONOR B CELLS	NORMAL IgA CONCENTRATIONS	NORMAL IgM CONCENTRATIONS	ISOAGGLUTININS	INTRAVENOUS IMMUNE GLOBULIN THERAPY
			no. of patients		
γ_c-Chain deficiency	17	11	24	9	27
JAK3 deficiency	1	3	6	5	3
Interleukin-7 receptor α deficiency	0	2	2	2	0
Adenosine deaminase deficiency	3	9	10	6	5
Autosomal recessive, unknown cause	4	10	15	10	10
Male, unknown cause	1	1	1	1	0
Total	26	36	58	33	45

transplantation had some donor B cells (2 percent to 100 percent of total B cells). At the time of the last evaluation, 45 of the 72 surviving children were receiving immunoglobulin-replacement therapy to prevent bacterial and common viral infections, because the capacity to produce protective antibodies had not yet been demonstrated. However, IgA and isohemagglutinins were detected in 11 of these 45 children, suggesting that they may eventually be able to discontinue immunoglobulin-replacement therapy.

Recent progress in identifying the molecular causes of severe combined immunodeficiency permitted us to study mutations of the disease in relation to the outcome of hematopoietic stem-cell transplantation. Most of the children with γ_c-chain or JAK3 deficiency who did not have any evidence of donor-derived B cells continued to have poor B-cell function, as demonstrated by the absence of isotype switching after immunization with bacteriophage ϕX174 (data not shown) and the absence of normal production of IgA, IgM, IgE, and isohemagglutinins in vivo. Thus, normal stem cells that matured in the children with γ_c-chain or JAK3 deficiency developed into normal T cells but did not often develop into normal B cells; the host B cells in these children probably failed to function because they lacked normal cytokine receptors. In contrast, a majority of the children with a deficiency in adenosine deaminase or the α chain of the interleukin-7 receptor and those with autosomal recessive severe combined immunodeficiency of unknown molecular cause had good host B-cell function, indicating that these mutations did not adversely affect B-cell function.

Before transplantation, the number and function of natural killer cells were lowest in the infants with γ-chain or JAK3 deficiency, whereas they were higher than normal in the infants with most other types of severe combined immunodeficiency. After transplantation, most of those with γ-chain or JAK3 deficiency continued to have very low numbers of natural killer cells and low cell function, whereas the number and activity of natural killer cells were normal in the patients with the other types of the disease.

The ability to give half-matched (haploidentical), T-cell–depleted parental marrow to infants with severe combined immunodeficiency has been a remarkable therapeutic advance, but it is not a perfect treatment. During the three to four months needed for donor stem cells to develop into mature, functioning T cells, the infant is susceptible to viral infections. Chemotherapy administered before transplantation fails to accelerate immune reconstitution, heightens the susceptibility of the recipient to infection, and necessitates the use of cyclosporine, which prolongs the T-cell deficiency.[40] The poor B-cell function in children with γ_c-chain or JAK3 deficiency in whom donor B cells do not develop has led some physicians to use pretransplantation conditioning. However, chemotherapy does not guarantee that donor B cells will develop, and the risks associated with chemotherapy outweigh the potential for the development of B-cell function.[40] Resistance to engraftment was overcome in all but three of our patients by the use of booster T-cell–depleted transplants from a parent, without chemotherapeutic conditioning before transplantation.

Placental-blood transplantation from unrelated donors is fraught with problems because of the risk of GVHD. Moreover, in most institutions where placental-blood transplantation is performed for the treatment of severe combined immunodeficiency, chemotherapy is given before the procedure and prophylaxis against GVHD is given for nine months afterward.[41,42] These treatments heighten the risk of infection. In utero transplantation of stem cells from related donors does not appear to offer any advantage over transplantation performed soon after birth. The mother would probably not be used as a donor of an in utero transplant because of the risks associated with anesthesia during pregnancy. The invasive procedures required for in utero stem-cell transplantation carry risks, and it is not possible to detect or treat either a graft-versus-graft reaction or GVHD in utero.[43,44]

Severe combined immunodeficiency, a disorder that is fatal if untreated, is a pediatric emergency that could be routinely diagnosed at birth.[4] White-cell counts in cord blood and differential counts calculated manually can be used to detect the lymphopenia that is almost invariably present in infants with this disorder, and appropriate immunologic tests can then be performed. A prenatal diagnosis can often be made when there is a family history of the disease. If stem cells from a relative can be transplanted in the first 3.5 months of life, before infections develop, there

is a high (95 percent) probability of success. In summary, transplantation of HLA-identical or T-cell–depleted haploidentical marrow from related donors is a life-saving treatment in patients with any type of severe combined immunodeficiency.

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