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B-cell function in severe combined immunodeficiency after stem cell or gene therapy: A review

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Activity Objectives

1. To understand the variability of posttransplantation B-cell reconstitution in patients with severe combined immunodeficiency (SCID).
2. To appreciate the implications of pre–bone marrow transplantation conditioning in patients with SCID.

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Although bone marrow transplantation has resulted in life-saving T-cell reconstitution in infants with severe combined immunodeficiency (SCID), correction of B-cell function has been more problematic. This review examines B-cell reconstitution results presented in 19 reports from the United States and Europe on posttransplantation immune reconstitution in patients with SCID over the past 2 decades. The analysis considered whether pretransplantation conditioning regimens were used, the overall survival rate, the percentage with donor B-cell chimerism, the percentage with B-cell function, and the percentage of survivors requiring immunoglobulin replacement. The survival rates were higher at those centers that did not use pretransplantation conditioning or posttransplantation graft-versus-host disease prophylaxis. The percentage of survivors with B-cell chimerism, function, or both was higher and the percentage requiring immunoglobulin replacement was lower at those centers that used pretransplantation conditioning. However, there were substantial numbers of patients requiring immunoglobulin replacement at all centers. Thus pretransplantation conditioning does not guarantee that B-cell function will develop. Because most infants with SCID either present with serious infections or are given diagnoses as newborns, one must decide whether there is justification for using agents that compromise innate immunity and have intrinsic toxicities to gain B-cell immune reconstitution. (J Allergy Clin Immunol 2010;125:790-7.)

Key words: *Severe combined immunodeficiency, adenosine deaminase deficiency, Janus kinase 3 deficiency, recombinase activating genes 1 and 2 deficiencies, IL-7 receptor α chain deficiency, DNA protein kinase catalytic subunit, graft-versus-host disease, hematopoietic stem cell transplantation, immunoglobulin therapy, matched unrelated donor*

Severe combined immunodeficiency (SCID) is a fatal syndrome of diverse genetic cause characterized by profound deficiencies of T- and B-cell function and, in some types, also of natural killer cells and function.[1] This condition is uniformly fatal in the first 2 years of life unless immune reconstitution can be accomplished.[1-5] SCID is currently known to be caused by mutations in at least 13 different genes. X-linked SCID is caused by defects in the common γ chain (Table I).[6] Mutations in the genes encoding adenosine deaminase (ADA),[7] Janus kinase 3,[8] the IL-7 receptor α chain,[9] recombinase-activating gene (RAG) 1 or 2,[10] CD45,[11,12] Artemis,[13] ligase IV,[14] DNA protein kinase catalytic subunit,[15] CD3δ,[16] CD3ε,[17] or CD3ζ[18] also result in SCID and are inherited as autosomal recessive traits (Table I).

In the 42 years since the first transplantation was performed in 1968, the standard treatment for all forms of SCID has been ***allogeneic*** bone marrow transplantation.[19] For the first decade, an

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Terms in boldface and italics are defined in the glossary on page 791.

Abbreviations used
ADA: Adenosine deaminase
GVHD: Graft-versus-host disease
IL-7Rα: IL-7 receptor α chain
IVIG: Intravenous immunoglobulin
RAG: Recombinase-activating gene
SCID: Severe combined immunodeficiency
TREC: T-cell receptor recombination excision circle
UCSF: University of California, San Francisco

HLA-identical related donor transplant was required to avoid lethal ***graft-versus-host disease*** (GVHD). However, rigorously T cell–depleted transplantations have been possible from HLA-***haploidentical*** related donors since 1981 and, more recently, from matched unrelated donors. The principal causes of death in such infants have been fatal viral infections present at the time of referral.[1,5] Some centers use myeloablative conditioning, usually with busulfan and cyclophosphamide, before transplantation (mostly in infants who do not have an HLA-identical donor) and immunosuppressive drugs after transplantation to prevent or ameliorate GVHD. However, because they all lack T cells, infants with all genetic types of SCID given T cell–depleted HLA-identical or haploidentical bone marrow stem cells with or without pretransplantation chemoablation or posttransplantation GVHD prophylaxis develop phenotypically and functionally normal, genetically donor T cells at between 90 and 120 days after transplantation.[2-4,20-23] Finally, in recent years, gene therapy has been attempted with some success in patients with X-linked and ADA-deficient SCID.

Several reports have been published within the past decade on the long-term outcomes of patients with SCID who received bone marrow transplants.[2,4,5,24-30] Borghans et al[25] found that 11 of 19 patients with SCID followed up to 25 years after conditioned bone marrow transplantation had no evidence for a decrease in T-cell immunity or thymic output, as measured based on T-cell receptor recombination excision circles (TRECs); however, those patients with SCID who had low thymic output soon after transplantation continued to have decreased long-term T-cell reconstitution. Mazzolari et al[27] reported on the long-term immune reconstitution and clinical outcome of 40 patients with severe T-cell immunodeficiency who survived for up to 11 years after hematopoietic stem cell transplantation. Thirty-five percent of the 40 patients had low levels of TRECs at their last follow-up, and oligoclonality of the T-cell repertoire was demonstrated in 27.5% of the patients. Cavazzana-Calvo et al[26] and Friedrich et al[28] reported findings similar to those of Mazzolari et al[27] and speculated that use of a conditioning regimen before hematopoietic stem cell transplantation for SCID is necessary for thymic output at greater than 16.3 years after transplantation. However, Patel et al[30] reported sustained T-cell function in 15 long-term SCID survivors (up to 26 years) of nonconditioned bone marrow transplantations. Even more recently, our group reported that (in 128 SCID survivors of bone marrow transplantations since 1982) T-cell function and TREC levels had been sustained for more than 2 decades, providing evidence of continued thymic output at more than 20 years after transplantation in the absence of both pretransplantation conditioning and posttransplantation GVHD prophylaxis.[2,4,5] Although bone marrow transplantation has resulted in life-saving T-cell reconstitution in most patients with SCID, correction of B-cell function has been more problematic. This review

GLOSSARY

ALLOGENEIC: Denotes cells or tissues that are genetically different because they are derived from another individual of the same species who is not an identical twin.

CHEMOTHERAPY: The treatment of cancer with specific chemical agents or drugs that help destroy malignant cells and tissues.

CHIMERISM: A condition that occurs as a result of engraftment of cells, organs, or tissues from another person or from a different species.

GRAFT-VERSUS-HOST DISEASE: A complication of bone marrow transplantation in which T cells present in the transplanted marrow or cord blood recognize the recipient as "foreign" and mount an immunologic attack. The condition can also develop from the T cells present in a blood or platelet transfusion if they are given to a T cell–deficient recipient.

HAPLOIDENTICAL: The condition of sharing the same haplotype or having the same alleles at a set of closely linked genes on one chromosome. This generally occurs with genes of the *HLA* locus on chromosome 6, which contains closely linked genes that are usually inherited *en bloc*.

IMMUNOGLOBULIN: Proteins with antibody activity produced by plasma cells of the immune system. These proteins are comprised of heavy and light chains with constant and variable regions that determine antigen specificity. There are 5 known human immunoglobulin isotypes.

INTRAVENOUS IMMUNOGLOBULIN: Purified IgG prepared from a pool of plasma from approximately 60,000 normal donors. It contains antibodies to a wide spectrum of antigens and is administered every 3 to 4 weeks to immunodeficient patients who have impaired antibody production.

ISOHEMAGGLUTININS: Natural antibodies to red blood cell antigens.

LYMPHOCYTE: An immune cell derived from a hematopoietic stem cell through a process called lymphopoiesis and thymopoiesis. The 2 main types of lymphocytes are B lymphocytes, which develop into plasma cells that produce antibodies, and T lymphocytes, which serve as the central type of cell in the immune response. T cells provide help to B cells, and they have several different subsets with different functions.

MALIGNANT: Cells or tumors that replicate progressively, usually resulting in death unless treatment is given. Malignant tumors spread to adjacent tissues through a process called metastasis.

MYELOID: A hemopoietic cell in the bone marrow that develops into neutrophils, eosinophils, basophils, monocytes, and dendritic cells.

ONCOGENESIS: The process of malignant transformation leading to the formation of a cancer or tumor (tumorigenesis).

PROPHYLACTIC: Refers to treatment or measures taken to prevent onset of a disease or condition. Patients are often treated prophylactically with immunosuppressive drugs to prevent graft-versus-host disease after they have undergone bone marrow or cord blood transplantation.

SEVERE COMBINED IMMUNODEFICIENCY: A syndrome caused by mutations in at least 13 different genes. It is characterized by an absence of T cells, a lack of B-cell function, and variable numbers of natural killer cells. Patients with severe combined immunodeficiency are vulnerable to all types of infectious diseases and usually die from infection in infancy unless they receive a successful bone marrow transplant or gene therapy.

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TABLE I. Thirteen abnormal genes in patients with SCID

	Lymphocyte phenotype
Cytokine receptor genes	
IL2RG	$T^-B^+NK^-$
JAK3	$T^-B^+NK^-$
IL7RA	$T^-B^+NK^+$
Antigen receptor genes	
RAG1	$T^-B^-NK^+$
RAG2	$T^-B^-NK^+$
Artemis	$T^-B^-NK^+$
Ligase 4	$T^-B^-NK^+$
DNA-PKcs	$T^-B^-NK^+$
CD3δ	$T^-B^+NK^+$
CD3E	$T^-B^+NK^+$
CD3ζ	$T^-B^+NK^+$
Other genes	
ADA	$T^-B^-NK^-$
CD45	$T^-B^+NK^+$

DNA-PKcs, DNA protein kinase catalytic subunit; *IL7RA*, IL-7 receptor α chain; *NK*, natural killer.

covers information relevant to the latter subject published in the last 2 decades.

B-CELL CHIMERISM, B-CELL FUNCTION, AND IMMUNOGLOBULIN REPLACEMENT AFTER BONE MARROW TRANSPLANTATION

Table II[2-5,23,24,26-37] lists the studies discussed below. It should be noted first that most reports are from Europe. It has been the policy in European centers for many years to use pretransplantation chemotherapeutic conditioning and posttransplantation GHVD ***prophylactic*** immunosuppressive drugs for most patients with SCID who do not have an HLA-identical donor. By contrast, the author's center has never used pretransplantation conditioning or posttransplantation GVHD prophylaxis for SCID, and the Baylor and University of California, San Francisco (UCSF) teams have performed some SCID transplantations with and some without conditioning. Second, the European centers generally have a higher percentage of HLA-identical transplants (38%)[24] than the US centers (21% at Baylor and 10% at Duke).[1,5,30,31] Third, some of the studies reported outcomes according to the ***lymphocyte*** phenotype (ie, T^-B^- or T^-B^+),[23,24,38] whereas most of the recent studies listed in Table II reported the outcomes by molecular type (when known).[2,4,5,26-34] It has been suggested for a number of years now that the need for posttransplantation ***immunoglobulin*** replacement is due to a lack of donor B-cell engraftment, and this in turn has been attributed to a lack of pretransplantation chemoablative conditioning, although data to support this premise have been far from clear.

Single-center studies

UCSF reports. Among the earliest SCID transplant outcome studies in the past 2 decades was the report by Dror et al,[23] who examined immune function in 14 surviving patients with SCID from a total of 24 (58% survival rate) who had received T cell–depleted haploidentical parental bone marrow transplants from 1982 to 1991 at UCSF. Seventeen of the 24 had received pretransplantation conditioning. Two of 11 survivors were found to have B-cell ***chimerism***, 10 of 14 had B-cell function, and 7 (50%) of 14 were receiving immunoglobulin replacement therapy. Thus from this small series, it appeared that B-cell chimerism did not occur often in patients with SCID receiving haploidentical bone marrow transplants, although 71% of the recipients had received pretransplantation ***chemotherapy***.

O'Marcaigh et al[35] subsequently reported this group's experience in performing transplantations in 16 infants with Athabascan SCID between 1984 and 1999. All but 3 received pretransplantation conditioning of various types. Twelve (75%) children survived with T-cell reconstitution at a median follow-up of 7 years. However, only 3 had donor B cells and B-cell function, one of whom did not receive pretransplantation conditioning. Nine of the 12 survivors were receiving ***intravenous immunoglobulin*** (IVIG) replacement therapy. It is of note that only 1 of 6 of the patients with SCID who received genotypically identical marrow had B-cell function, and that infant did not receive pretransplantation conditioning. The authors also point out that infants with Athabascan SCID are highly susceptible to the toxic effects of radiation and chemotherapy. The 4 who died had received myeloablative conditioning with either radiation or busulfan, and 2 of 8 who received cytotoxic chemotherapy did not develop secondary teeth.

More recently, this group reported the results of transplanting megadoses of $CD34^+$ haplocompatible stem cells into 15 infants with SCID who had received nonmyeloablative pretransplantation conditioning.[33] The overall survival rate was 13 (87%) of 15, with a median follow-up of 39 months. Although T-cell reconstitution occurred in all, B-cell chimerism developed in only 4 recipients, B-cell function developed in only 5 (33%) recipients, and 7 were receiving immunoglobulin therapy. The authors concluded that this approach was useful for ensuring T-cell engraftment and function but was of no value for improving B-cell reconstitution.

Leiden University report. In 1994, van Leeuwen et al[37] reported on the outcome of bone marrow transplantations performed in 31 infants with SCID from 1968 to 1992 in The Netherlands. All but 2 had received pretransplantation conditioning. Ten had HLA-identical donors, and the rest received either haploidentical parental marrow or, in 2 cases, marrow from a closely matched unrelated donor. The overall survival rate was 15 (48%) of 31. All 15 survivors had donor T-cell chimerism, but only 10 (67%) of the 15 had B-cell chimerism. Nevertheless, the 14 whose B-cell function was evaluated were all said to have function. There was no statement about whether any were receiving immunoglobulin replacement.

Los Angeles Children's Hospital report. Smogorzewska et al[36] reported on the results of marrow transplantation in 37 infants with SCID receiving T cell–depleted haploidentical bone marrow transplants at Los Angeles Children's Hospital from 1984 to 1997. All received pretransplantation conditioning. Seventeen (46%) of the 37 were surviving, and all had T-cell function. Data on B-cell chimerism and function were not reported, but 5 (29%) of the 17 were receiving IVIG.

Hôpital Necker reports. One of the first studies to examine factors that contribute to the development of B-cell function after transplantaton was that of Haddad et al[32] from the Hôpital Necker, Paris, France, who reported on 22 B^+ patients with SCID (14 X-linked, 4 Janus kinase 3 deficient, and 4 of unknown molecular type), 5 of whom had received HLA-identical bone marrow transplants and 17 of whom had received T cell–depleted haploidentical bone marrow transplants between 1976 and 1995. Only 4 (18%) of the 22 patients had donor B cells, yet 12 (55%) of 22 were reported to have normal B-cell function and 11 (50%)

TABLE II. Reports of posttransplantation survival and B cell function

Center and reference	Chemoablation used in nonidentical transplants	Overall survival	Donor B cells present	B-Cell function	No. (%) receiving immunoglobulin
Antoine et al,[24] Europe (1968-1999)	Yes	475 patients with SCID; 77% in 181 HLA-identical, 54% in 294 nonidentical	Not reported	Not reported	12% of the HLA-identical group; 34% of the HLA-nonidentical group
Cavazzana-Calvo et al,[26] Paris, France (1971-1995)	Yes	55/88 (63%); 31 studied, 11 HLA-identical, 20 nonidentical	Not reported	Not reported	13/31 (42%)
Dvorak et al,[33] UCSF (2001-2007)	Yes, nonmyeloablative	13/15 (87%), all nonidentical	4/15 (27%)	5/15 (33%)	7/15 (47%)
Dror et al,[23] UCSF (1982-1991)	Yes in 17/24 (71%)	14/24 (58%); 14 studied, all nonidentical	2/11 (18%)	10/14 (71%)	7/14 (50%)
Friedrich et al,[28] Ulm, Germany (1982-1995)	Yes	50/82 (61%); 31 studied, 6 HLA-identical, 25 haploidentical	19/31 (61%)	Not reported	10/31 (32%)
Haddad et al,[32] Paris, France (1976-1995)	Yes	22; 5 HLA-identical, 17 nonidentical	4/22 (18%)	12/22 (55%)	11/22 (50%)
Mazzolari et al,[27] Brescia, Italy (1991-2003)	Yes	42/58 (73%); 40 studied, 10 HLA-identical, 20 nonidentical, 10 MUDs	(27/40) 68%	33/40 (83%)	5/40 (13%)
Neven et al,[34] Paris, France (1972-2004)	Yes	86/149 (58%); 90 studied, 37 HLA-identical, 51 nonidentical, 2 MUDs; 8 died late	Not reported	54/82 (67%)	17/82 (21%)
O'Marcaigh et al,[35] UCSF (1984-1999)	Yes	12/16 (75%); 7 HLA-identical, 9 nonidentical	3/12 (25%)	3/12 (25%)	9/12 (75%)
Patel et al,[31] Baylor (1998-2007)	Yes (mostly)	18/23 (78%); 5 HLA-identical, 10 nonidentical, 6 MUDs, 1 MMUD, 1 MUD cord	11/18 (61%)	11/17 (65%)	6/18 (33%)
Slatter et al,[29] United Kingdom (1987-1994)	Yes	36; all haploidentical	19/36 (53%)	25/36 (69%)	11/36 (31%)
Smogorzewska et al,[36] Los Angeles Children's Hospital (1984-1997)	Yes	17/37 (46%); all haploidentical	Not reported	Not reported	5/17 (29%)
van Leeuwen et al,[37] The Netherlands (1968-1992)	Yes	15/31 (48%); 10 HLA-identical, 19 haploidentical, and 2 MUDs	10/15 (67%)	14/15 (93%)	Not reported
Buckley et al,[2] Duke University (1982-1998)	No	72/89 (81%); 12 HLA-identical, 77 haploidentical	26/72 (36%)	33/72 (46%) had isohemagglutinins	45/72 (63%)
Myers et al,[3] Duke University (1982-2001)	No	20/21 (95%); 2 HLA-identical, 19 haploidentical	9/20 (45%)	9/20 (45%)	13/20 (65%)
Patel et al,[30] Baylor (1981-1995)	No	15/25 (60%); 5 HLA-identical, 20 haploidentical	4/8 (50%)	7/15 (53%)	7/15 (47%)
Railey et al,[5] Duke University (1982-2008)	No	124/161 (77%); 111 studied, 15 HLA-identical, 96 haploidentical	Not reported	Not reported	64/111 (58%)
Sarzotti-Kelsoe et al,[4] Duke University (1982-2007)	No	123/158 (78%) plus 5 transplanted elsewhere; 16 HLA-identical, 112 haploidentical	41/128 (32%)	Not reported	70/128 (55%)

MMUD, Mismatched unrelated donor; *MUD*, matched unrelated donor.

were receiving IgG replacement, including 2 (40%) of 5 of the HLA-identical marrow recipients. Nine of the 17 haploidentical recipients received pretransplantation conditioning with 8 mg/kg busulfan and 200 mg/kg cyclophosphamide, but the authors found that use of the conditioning regimen neither promoted B-cell engraftment nor affected B-cell function. Three of the 4 with donor B-cell chimerism had received conditioning. The authors concluded that host B cells can cooperate with donor T cells

to fully mature into immunoglobulin-producing cells in some patients undergoing transplantation.

Cavazzana-Calvo et al,[26] in their report on long-term T-cell reconstitution in patients with T-cell immunodeficiency disorders who had received bone marrow transplants between 1971 and 1991 at the Hôpital Necker, did not provide data on B-cell chimerism or B-cell function. However, they reported that 13 (42%) of the 31 patients with SCID who were more than 10 years after transplantation required IgG replacement therapy. Six of the 13 requiring IVIG had received pretransplantation conditioning. The authors also noted that the presence (or not) of good thymic output did not correlate with whether there was B-cell reconstitution.

Neven et al's[34] most recent report from that group covered all 149 patients with SCID undergoing transplantation at the Hôpital Necker between 1972 and 2004. Although ***myeloid*** chimerism results were presented, no data were provided for B-cell chimerism. Fifty-four (67%) of the 82 survivors were reported to have good B-cell function, and 17 (21%) of 82 were said to be receiving immunoglobulin replacement therapy. However, the overall survival rate was 58%, and 8 of the 67 deaths occurred late.

Brescia, Italy, report. Mazzolari et al[27] studied 40 patients with severe T-cell deficiency undergoing transplantations between 1991 and 2003 who were surviving more than 5 years after transplantation. All had received pretransplantation conditioning except for 5 who received HLA-identical sibling transplants and 3 who received T cell–depleted haploidentical *in utero* transplants. Twenty-seven (68%) of the 40 had B-cell chimerism, and 33 (83%) of the 40 had B-cell function. Only 5 were receiving IgG replacement: 2 who had received *in utero* transplants; 1 who had received pretransplantation conditioning with busulfan, cyclophosphamide, and thiotepa; 1 who had received antithymocyte globulin and cyclophosphamide; and 1 who had received antithymocyte globulin alone. One of the infants with IL-7 receptor α chain–deficient SCID who received an *in utero* T cell–depleted haploidentical transplant did not have donor B cells but had normal B-cell function and did not require immunoglobulin replacement.[39] Endocrine and severe neurologic abnormalities were observed in 17.5% and 10%, respectively.

Newcastle upon Tyne, England, report. Slatter et al[29] studied 36 patients who had received maternal, paternal, or unrelated bone marrow depleted of T cells with anti-CD52 (n = 19) or were given positively selected $CD34^+$ cells (n = 19). All but 2 of the patients had received pretransplantation conditioning. Nineteen (53%) of the 36 had B-cell chimerism, 25 (69%) had B-cell function, and 11 (31%) were requiring IgG replacement therapy. Thus pretransplantation conditioning did not ensure that B-cell chimerism or B-cell function would occur uniformly. There was no difference in donor B-lymphocyte chimerism with the type of marrow received, but significantly more patients given anti-CD52–treated marrow had class-switched memory B lymphocytes ($P = .024$), normal IgG levels, and normal antibody responses to tetanus and *Haemophilus influenzae* type B vaccination. More patients with common γ chain–or Janus kinase 3–deficient SCID given anti-CD52–treated marrow had donor B lymphocytes. The authors concluded that the results imply more incomplete donor chimerism and less B-lymphocyte function in patients given positively selected $CD34^+$ marrow cells than in those who received anti-CD52–treated marrow. The question arises as to whether some other types of cells (eg, dendritic cells or $CD34^-$ stem cells) in the anti-CD52 T cell–depleted marrow promoted B-cell development. Those cell types would all be missing from $CD34^+$ selected cells. Because the overall number of transplantations performed at that center was not provided, the mortality rate is unknown.

University of Ulm, Germany, report. Friedrich et al[28] studied 31 children with SCID of 50 surviving recipients (from a total of 82; survival rate, 61%) receiving bone marrow transplants between 1982 and 1995 at their institution. They compared 3 groups: the first was an HLA-identical marrow recipient group (n = 6), the second was a nonconditioned haploidentical group (n = 12), and the third was a conditioned haploidentical group (n = 13). There were differences among the 3 groups with regard to B-cell chimerism: all of the HLA-identical recipients and all but 2 of the conditioned haploidentical marrow recipients had donor B cells, whereas only 2 of the nonconditioned haploidentical marrow recipients had donor B cells. The authors also reported on CD34 bone marrow chimerism in 24 of the 31 patients: 1 of 4 HLA-identical marrow recipients, 1 of 9 nonconditioned recipients of haploidentical marrow, and 9 of 11 conditioned haploidentical recipients had donor $CD34^+$ cells in their bone marrow. The authors noted a strong correlation between the presence of CD34 marrow chimerism and the persistence of B-cell immunity. However, data on B-cell function were not presented. Ten (32%) of the 31 patients were receiving IVIG; 8 of the latter patients were from the nonconditioned group.

Baylor University reports. More recently, Patel et al[30] reported on the long-term status of 20 infants with SCID who were given anti-CD6 T cell–depleted marrow from a parent and 5 more who had received unfractionated HLA-identical sibling marrow between 1981 and 1995. None of the patients received pretransplantation chemotherapy or GVHD prophylaxis. Ten (50%) of the 20 patients who received haploidentical marrow were surviving, as were all 5 of those who received HLA-identical marrow. Chimerism was analyzed in 8 patients, and 4 (50%) were found to have donor B cells, 3 of whom had received T cell–depleted haploidentical marrow and 1 of whom had received HLA-identical unfractionated marrow. Seven (47%) of the 15 survivors were reported to have normal antibody responses to vaccines, 5 of whom had received T cell–depleted haploidentical marrow and 2 of whom had received unfractionated HLA-identical marrow. Seven (47%) of the 15 were receiving immunoglobulin replacement, including 2 who had received HLA-identical marrow.

In a more recent article from the same center, Patel et al[31] reported on the 9-year outcome of 23 additional patients with SCID who had received bone marrow transplants from 1998 to 2007, 18 of whom had received either anti-CD6, anti-CD8, and anti-CD20 T cell–depleted marrow or $CD34^+$ cell–selected haploidentical related marrow stem cells (n = 10); matched or mismatched unrelated donor marrow (n = 7); or $CD34^+$ cell–selected unrelated marrow stem cells (n = 1). Seventeen of the 18 had received pretransplantation conditioning. Thirteen (72%) of the 18 who received the mismatched transplants survived, as did all 5 of those receiving HLA-identical marrow. B-cell chimerism was reported in 11 of the 18 survivors, B-cell function was deemed normal in 11 (65%) of the 17 studied, and 6 (33%) of the 18 were receiving immunoglobulin replacement. In this article the authors compared the patients in this and in the first report discussed above[30] for multiple outcome variables. The 3 groups compared were the 17 patients with SCID who had been given pretransplantation conditioning for their mismatched transplants, the 21 who had received no pretransplantation

conditioning for their mismatched transplants, and the 10 patients who had received unfractionated HLA-identical sibling marrow. There was a difference in overall survival, with 100% of the patients who received HLA-identical sibling marrow surviving and 70% of the mismatched conditioned patients and 62% of the nonconditioned mismatched group surviving. There was a statistically significant survival difference ($P = .04$) for the matched related donor recipient group when compared with each of the last 2 groups but not when the last 2 groups' survival rates were compared with each other. More importantly, the authors found no significant differences in the rates of donor B-cell engraftment or development of B-cell function or in the numbers of patients receiving immunoglobulin replacement among the 3 groups. They concluded that pretransplantation conditioning did not reduce dependence on IVIG infusions for haploidentical recipients.

Duke University reports. The first report of the long-term outcome of SCID bone marrow transplantation at the author's center was published in 1999 and included all transplantations performed from 1982 to 1998.[2] Eighty-nine patients had undergone transplantation at that time, and 72 (81%) were surviving. Only 12 (13%) of the 89 had HLA-identical related donors; the other 77 (87%) received rigorously T cell–depleted haploidentical parental marrow. None of the patients had been given pretransplantation chemotherapy or posttransplantation GVHD immunosuppressive drugs. Twenty-six (36%) of the 72 had donor B cells, 33 (46%) had ***isohemagglutinins***, and 45 (63%) were receiving IVIG.

One of the observations from the above study was that patients with SCID undergoing transplantation in the first 3½ months of life had a much higher survival rate than those undergoing transplantation after that time. In a report published in 2002, Myers et al[3] studied immune reconstitution in the 21 patients with SCID who had been given nonablated HLA-identical (n = 2) or rigorously T cell–depleted haploidentical parental marrow transplants (n = 19) in the neonatal period at this center from 1982 to 2001 to seek an explanation for the better survival rate. Although a remarkably superior survival rate (95%), earlier and higher T-cell reconstitution, and greater thymic output were found in the patients with SCID undergoing neonatal transplantation compared with those undergoing transplantation after that age, there was no difference in the attainment of B-cell reconstitution. Donor B-cell chimerism was found in 9 (45%) of the 20 survivors, normal IgA levels were found in 9 (45%), and 13 (65%) were receiving immunoglobulin replacement therapy.

In one of 2 recent long-term (>26 years) studies from this center, 41 (32%) of 128 survivors (5 of whom had undergone transplantation at other institutions) had B-cell chimerism.[4] None of the patients had been given pretransplantation chemotherapy or posttransplantation GVHD immunosuppressive drugs. However, donor B-cell engraftment was present in approximately one third of the patients with X-linked SCID despite the lack of conditioning.[4] Only 16 of the patients had received HLA-identical related marrow, and all the rest had received T cell–depleted haploidentical marrow. B-cell function was not reported in that article, which focused on long-term T-cell reconstitution and thymic output, but 70 (55%) of the 128 were receiving immunoglobulin replacement therapy. In our most recent long-term report[5] of SCID transplantations at this center from 1982 to 2008, there were 124 (77%) survivors of 161 patients undergoing transplantation. Although B-cell function and chimerism were not reported in that article, 64 (58%) of the 111 recipients contacted for long-term clinical outcome characteristics were receiving immunoglobulin replacement therapy. However, the percentage requiring immunoglobulin varied based on the molecular defect. Only 27% of the IL-7 receptor α chain–deficient patients required immunoglobulin, whereas 83% of RAG-deficient patients and 72% of patients with X-linked SCID required replacement. Thus the molecular type of SCID appears to be an important determinant of B-cell development after transplantation, irrespective of whether there is B-cell chimerism.

Multicenter studies

Bertrand et al[38] reported on the results of 214 T cell–depleted haploidentical bone marrow transplants given to 178 infants with SCID undergoing transplantation in 18 centers in Europe between 1981 and 1995. The disease-free survival was significantly better for B^+ patients with SCID (60%) than for B^- patients with SCID (35%, $P = .002$), with median follow-up periods of 57 and 52 months, respectively. Pretransplantation conditioning was given for 66% and 75% of the patients in the 2 groups, respectively. However, no information on B-cell reconstitution was presented in that report.

Antoine et al[24] reported on the outcomes of stem cell transplantations performed in 475 patients with SCID at 37 centers in 18 countries in Europe between 1968 and 1999. The overall survival rate in the 181 who received HLA-identical marrow was 77%, but the overall survival rate in 294 recipients of nonidentical stem cells was only 54%. Pretransplantation conditioning was used for all but 107 HLA-identical related donor transplants, 87 mismatched transplants, and 11 unrelated donor transplants. No data were reported on B-cell chimerism or B-cell function, but 12% of the recipients of HLA-identical marrow and 34% of the recipients of nonidentical marrow were receiving immunoglobulin replacement therapy.

B-cell function and immunoglobulin replacement after gene therapy

Over the past decade, significant progress was made toward gene therapy for patients with X-linked and ADA-deficient SCID. Investigators at the Hôpital Necker in Paris, France, treated 11 patients with X-linked SCID with gene-corrected autologous bone marrow cells.[40] Nine infants had normal T- and B-cell functions after the treatments. The 9 patients who acquired normal immune function did not require IVIG infusions and were at home without any medication.[41] Subsequently, investigators in London reported success with a similar gene therapy protocol for X-linked SCID.[42] However, 4 of the 10 patients treated in London have poor B-cell reconstitution and are dependent on immunoglobulin supplementation. Unfortunately, serious adverse events with this therapy occurred in 4 patients treated at the Hôpital Necker and in 1 patient treated in London.[43] These patients had leukemias or lymphomas caused by a process called insertional ***oncogenesis***. Four of these patients responded to conventional chemotherapy regimens and are presently in remission. Before these cases, ***malignant*** changes had not been seen in any human subjects given retroviral vectors for gene transfer. Considering the success of bone marrow transplantation for recipients of HLA-matched related donor grafts and for those who are treated in early infancy, new gene therapy trials for X-linked SCID are now being developed with the objective of reducing their oncogenic potential.[44]

Gene therapy trials for ADA deficiency were initiated in the early 1990s with only modest success. Recently, 2 European research groups reported gene therapy trials for ADA deficiency using low-dose busulfan pretherapy without PEG-ADA or (in those patients who were receiving it) withdrawing the enzyme for a few weeks before infusion of the gene-modified cells.[45,46] Eleven of the 15 patients treated with this approach (10 in Italy and 5 in London) showed good immune reconstitution. In the Italian series immunoglobulin replacement was discontinued in 5 patients, and all 5 were able to produce antibodies normally to their vaccine antigens. Of note, there have not been cases of leukemia or lymphoma in the ADA-deficient patients with SCID whose conditions have been corrected by means of gene therapy, although insertions of gene vectors near oncogenes similar to the X-linked SCID trials have been observed.

SUMMARY

From the studies described above, it can be seen that pretransplantation conditioning of infants with SCID who do not have a matched sibling donor does not always result in B-cell function. Data on B-cell function and chimerism were lacking in many studies, and therefore it will be important to detail these more completely in future reports. The question arises as to why infants who do not have a matched sibling donor should be treated differently than patients with SCID who do have an HLA-identical related donor. The latter are usually not given pretransplantation conditioning yet often achieve good immune reconstitution, frequently without donor B cells and usually without donor myeloid cell chimerism. The reason for the difference in success in achieving B-cell immune reconstitution in the matched versus mismatched transplants is not known. It also appears that the molecular type of SCID has an important influence on whether B-cell function develops after transplantation. What other factors might have an effect is not clear. It is possible that the development of some degree of GVHD favors development of donor B-cell chimerism and function. Whether intercurrent infection at the time of transplantation has a negative influence on the emergence of B-cell function is unknown.

The principal causes of death in infants with SCID are viral infections for which there are no effective antibiotics. When one administers conditioning agents that damage the innate immune systems of infants with SCID who present with 1 or more such viral infections, the expectation is that this would increase the mortality rate. As seen in Table II, the mortality rates are highest at those centers where pretransplantation chemotherapeutic conditioning is usually administered, with or without posttransplantation GVHD prophylactic immunosuppressive drugs. Thus when one is considering whether to use pretransplantation chemoablation, the associated risks might not justify giving these drugs to attempt B-cell reconstitution, and the same goes for posttransplantation immunosuppressive agents that interfere with immune reconstitution.

In addition to removing innate immune components and increasing susceptibility to infection, there are also long-term toxicities from conditioning agents, including neutropenia, red cell and platelet transfusion dependency, mucositis, veno-occlusive disease, busulfan lung disease, growth suppression, endocrine abnormalities, sterility, and a 15% risk of later malignancy.[47] As noted above, in patients with SCID with mutations that cause radiation sensitivity, the side effects of pretransplantation conditioning are even more devastating.[35] Finally, now that newborn screening for SCID has been recommended, it will be particularly important to avoid these toxic agents when transplantations are performed in the very early months of life.

Key concepts and therapeutic implications

- **Neither bone marrow transplantation nor gene therapy guarantees that B-cell immune reconstitution will occur, although both are highly capable of providing T-cell immune reconstitution.**
- **The use of pretransplantation chemoablation results in a higher percentage of B-cell chimerism and function than seen after transplantation without conditioning. However, there is still a significant percentage of patients in both groups who require immunoglobulin replacement. Thus pretransplantation conditioning does not guarantee B-cell reconstitution.**
- **Considering that most infants with SCID present with serious infections or will be given diagnoses in the neonatal period, one must decide whether there is a justification for using agents that compromise innate immunity and have intrinsic toxicities to gain B-cell immune reconstitution. The mortality rates at centers that use pretransplantation conditioning are higher than those at centers where it is not used.**

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