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Unresolved issues in hematopoietic stem cell transplantation for severe combined immunodeficiency: Need for safer conditioning and reduced late effects

Biljana Horn, MD and **Morton J. Cowan, MD**

Division of Allergy, Immunology, and Blood and Marrow Transplantation, Benioff Children's Hospital, University of California, San Francisco

Abstract

In this review we discuss recent outcomes of hematopoietic cell transplantation (HCT) for patients with severe combined immunodeficiency (SCID), including survival, T- and B-cell reconstitution, and late effects, particularly those related to genotype, use of conditioning regimen, and use of alternative donors. We identify the following issues that require additional data, which can be obtained through cooperative studies: outcomes of patients with SCID who did not receive conditioning before alternative donor HCT; outcomes of patients with SCID who did not receive graft-versus-host disease prophylaxis after T cell–replete HCT; late effects of HCT for patients with SCID, including neurocognitive outcomes, growth, and development; and their relationship to genotype and use of alkylating agents for conditioning. Careful follow-up of outcomes of all newborns receiving diagnoses based on newborn screening programs for SCID is essential because data are scarce on the effects of conditioning regimens in very young patients. A consensus on the definition of T- and B-cell recovery, criteria for additional "boosts," pharmacokinetic data of chemotherapy agents used in young children, and uniformity of the use of various chemotherapy agents are needed to compare results among institutions. Finally, development of new nontoxic conditioning regimens for HCT that can be safely used in very young children is required.

Keywords

Severe combined immunodeficiency; T cell-depleted stem cell transplantation; alternative donors; immune reconstitution; late effects of transplantation

Severe combined immunodeficiency (SCID) is a life-threatening disease of infants caused by a heterogeneous group of genetic defects characterized by profound deficiencies in T- and B-lymphocyte function and, in some cases, natural killer (NK) cell function.

The first successful allogeneic HCT was performed in 1968 at the University of Minnesota in a boy with SCID. Although other therapies have been developed, such as enzyme replacement therapy for adenosine deaminase (ADA) deficiency and gene therapy for ADA

Corresponding author: Biljana Horn, MD, Benioff Children's Hospital, UCSF, 505 Parnassus Ave, Suite M-659, San Francisco, CA 94143-1278, hornb@peds.ucsf.edu.

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and X-linked SCID, allogeneic HCT remains the mainstay of therapy for the majority of patients with SCID. Results of transplantation have significantly improved over the last 40 years because of advances in HLA typing, development of reduced toxicity conditioning regimens, more sensitive assays for the detection of viral infections, and newer antiviral and antifungal agents, and other improvements in supportive care during transplantation. However, there remain significant challenges related to transplantation for these disorders.

Hematopoietic Stem Cell Transplantation for Patients with SCID: Challenges

The main challenge of performing transplantations in patients with SCID is that this category of disorders encompasses a large number of heterogeneous genetic defects. Table I [1–10] summarizes SCID subtypes that are more commonly encountered by transplant physicians. Full classification of SCID and other primary immunodeficiency diseases can be found in a recently published classification article.[11] For each genotype, Table I outlines data, such as the need for conditioning to achieve T-cell reconstitution, the frequency of B-cell reconstitution after transplantation, and genotype-specific long-term complications. Understanding the exact genetic defect before transplantation is essential in guiding the decision about donor type and conditioning regimen. For example, for patients with $T^{-}B^{-}NK^{+}$ SCID associated with Artemis deficiency, conditioning with alkylating agents should be minimized or avoided entirely, if possible, because of the radiosensitive DNA repair defect associated with Artemis deficiency.[1,2] Although they have the same immune phenotype, recombination-activating gene (RAG) 1/2– deficient patients do not have DNA repair defects and chemotherapy sensitivity; however, patients with both genotypes have resistance to engraftment with mismatched donor cells and poor B-cell reconstitution after nonconditioned HCT.[2,3] Patients with IL-7 receptor α chain (IL-7Rα) defects are likely to reconstitute B-cell immunity, even if only T-cell engraftment occurs after HCT without conditioning.[3] The molecular defect does not affect B-cell function, and therefore host B cells are functional if T cells are restored. The large number and heterogeneity of conditions with relatively small patient numbers and institutionally defined approaches to selection of donors and conditioning have hampered cooperative prospective randomized therapeutic trials. Current literature in this field consists of primarily retrospective institutional or registry studies reporting outcomes that span decades of transplantations and include a large number of different genetic defects, often combining outcomes of patients with SCID with those of patients with other primary immunodeficiency syndromes. Furthermore, each report uses different criteria to evaluate immune reconstitution and success of transplantation, making it difficult to meaningfully compare the reported treatment outcomes among different institutions.

Currently, approximately one third of the US population is covered by statewide newborn screening programs for SCID measuring T-cell receptor excision circle (TREC) numbers in newborn blood. By 2013, it is anticipated that 60% of the US population will be covered by newborn screening programs. Transplantation centers practicing in states where screening is performed are treating very young but otherwise healthy patients with SCID, whereas in centers where there is no screening, patients with SCID present with multiple infections,

chronic diarrhea, and/or failure to thrive. The approach to donor selection and conditioning might be different depending on the patient's age, SCID genotype/phenotype, and comorbidities. Historical outcomes have been inferior in older patients with SCID and those with the evidence of pre-existing viral infections, respiratory impairment, or septicemia.[12] Because more newborns are diagnosed with SCID rather than presenting later in life with infectious complications, the issues of the use of alkylating agents for conditioning, pharmacokinetics and pharmacodynamics of these agents when used, as well as the potential early and late effects of these agents, have become more critical to resolve.

Donor Selection, Need for Conditioning, and Graft-Versus-Host Disease Prophylaxis for Patients with SCID

If a matched sibling donor is available, unconditioned T cell–replete HCT is the least controversial choice for treatment. A large retrospective study from Europe indicated that the use of conditioning in MSD hematopoietic stem cell transplantation for SCID decreased over time.[12] Before 1995, 24% of patients with SCID receiving matched sibling donor transplants also received some conditioning regimen. That percentage decreased to 12% during 2000-2005. The outcomes of this group of patients improved over time, and survival reached 90% for the later period.[12] However, the majority of patients do not have a matched sibling donor available, and the selection of alternative donors is typically based on institutional experience and availability of T-cell depletion. We will summarize the results from recent studies describing outcomes of alternative donor transplantations for SCID.

A recent publication from Duke University described the long-term clinical outcomes of a cohort of 161 patients with SCID undergoing transplantation between 1982 and 2008 without any conditioning or pharmacologic forms of *in vivo* graft-versus-host disease (GVHD) prophylaxis.[3] Ninety percent of patients received T cell–depleted (TCD) transplants from mismatched related/haplocompatible donors (MMRDs), and 10% received genotypically matched related donor (MRD) bone marrow transplants.[3] An earlier publication from the same institution indicated that 5 of 12 of the HLA-identical bone marrow transplants were TCD transplants.[13] Long-term survival was significantly better in patients undergoing transplantation in the first 3.5 months of life (94%) compared with those undergoing transplantation after 3.5 months of life (70%, $P = .002$). However, approximately one quarter of surviving patients required subsequent “booster” transplants to achieve T-cell immunity, and 58% of evaluable patients required long-term immunoglobulin therapy.[3] Booster transplants were required in 5 of 6 patients with RAG1/2 deficiency, 12 of 53 patients with γ chain (γc) deficiency, 3 of 15 patients with IL-7Rα deficiency, and 2 of 6 patients with Janus kinase 3 (Jak3) deficiency.[3]

In a prospective single-institution study from the University of California, San Francisco, investigators used megadoses (>20 × 10^6/kg) of $CD34^+$ cells with a fixed dose of CD3 (3 × 10^4/kg) from TCD MMRD transplants to improve engraftment. Fludarabine (125 mg/m^2 over 5 days) was used only in the first 2 patients with NK^+ SCID and in 2 patients with maternal engraftment and evidence of GVHD (90 mg/m^2). Genetic defects included RAG1/2 deficiency (4 patients), γc deficiency (7 patients), Artemis deficiency (1 patient), and an

unknown genetic defect (3 patients). Eleven (73%) of 15 patients had engraftment. Nine of them did not receive any chemotherapy before engraftment. All patients with prior maternal chimerism and all patients with γc deficiency engrafted. The 4 patients without engraftment initially (2 with RAG and 2 with unknown mutations) were salvaged with a second myeloablative or nonmyeloablative conditioned transplantation, resulting in 87% overall long-term survival. B-cell function recovered in 6 (40%) of 15 patients, including 3 of 9 evaluable patients whose cells engrafted without any conditioning; in 2 of 4 patients who received conditioning for a second transplantation; and in 1 patient who received fludarabine because of maternal GVHD.[4]

Patel et al[14] reported the long-term outcomes of 20 children with SCID treated with TCD MMRD transplants at Texas Children's Hospital between 1981 and 1995. In this study only 60% of patients who received MMRD transplants without conditioning achieved engraftment, and 50% survived long-term, as opposed to 100% of patients who received matched related donor transplants.[14]

Two recent retrospective studies from the European Group for Blood and Marrow Transplantation compared outcomes of alternative donor transplantations in patients with SCID.[12,15] In the study published by Gennery et al,[12] there was no difference in long-term survival between patients with SCID receiving TCD MMRD transplants (66%) or unrelated donor matched at A, B, C, DrB1, and DQ loci by high resolution (MUD) transplants (69%) for patients undergoing transplantation during the 2000-2005 period. Conditioning was used in 94% of MUD transplant recipients and in 61% of TCD MMRD recipients.[12] Also, in the entire cohort comprising patients between 1968 and 2005, the use of a conditioning regimen did not significantly affect survival; 280 patients who received chemotherapy had 61% survival, and 399 patients who did not receive chemotherapy had 63% survival.[12]

Fernandes et al[15] compared the outcomes of patients with SCID receiving TCD MMRD transplants with those receiving unrelated umbilical cord blood (UCB) transplants. Five-year overall survival was 62% ± 4% after MMRD transplants and 57% ± 6% after UCB transplants, which was not a statistically significant difference. Patients from the UCB transplant group received myeloablative conditioning more often than patients in the MMRD transplant group; however, only 17% of patients in the MMRD and 10% of patients in the UCB transplant categories did not receive any conditioning regimen. There was no significant difference in immune recovery between recipients of MMRD and UCB transplants. Fifty-five percent of UCB transplant recipients and 70% of MMRD transplant recipients were still receiving gammaglobulin replacement therapy at 3 years after transplantation.[15] In this study a second transplantation for nonengraftment was significantly more frequent in TCD MMRD transplant recipients than in UCB transplant recipients (28% vs 9.5%, respectively; $P = .002$).[15] Unfortunately, approximately 40% of patients in this study did not have a characterized genetic defect, and the authors comment only on relatively low survival in patients with Omenn syndrome as opposed to patients with other SCIDs.[15]

In summary, if an MRD transplant is not available, alternative donors, including those providing MUD, TCD MMRD, and unrelated UCB transplants, have been used with similar

survival rates in patients with SCID.[4,12-15] The robustness of long-term T-cell reconstitution in patients receiving unconditioned TCD MMRD transplants might not be the same for all genetic forms of SCID and appears to be lower in patients with RAG and possibly other forms with VDJ recombination defects.[3,4] Data on omitting conditioning in patients receiving MUD and UCB transplants are sparse.

One question that will need to be addressed in future studies is whether conditioning can be eliminated for well-matched MUD and cord blood transplants for patients with SCID, whose cells historically have engrafted after an MRD HCT. Another question is whether a minimal dose of conditioning therapy can be identified that achieves T- and B-cell reconstitution in patients with SCID who are unlikely to reject even a mismatched donor graft, such as those with γc or Jak3 defects.

There is no consensus about the use of GVHD prophylaxis in patients with SCID receiving a matched sibling transplant. Although the European transplant physicians and the investigators from Duke recommend not using GVHD prophylaxis in cases involving unmanipulated MRD bone marrow transplants, many others routinely use GVHD prophylaxis for these patients. The incidence of GVHD in a cohort of 12 patients receiving MRD bone marrow transplants without pharmacologic forms of *in vivo* GVHD prophylaxis but with *in vitro* T-cell depletion in 5 of 12 patients was 50%.[13] Unfortunately, the reported data are limited. A retrospective study of a larger number of patients with SCID receiving an MRD transplant with and without GVHD prophylaxis might resolve this issue.

Long-Term T- and B-Cell Function in Patients with SCID

A few older studies of long-term T-cell reconstitution of patients with SCID point to a possible decrease in TREC numbers over time in children receiving nonmyeloablative or unconditioned transplants after their peak at 1 to 2 years after transplantation.[16,17] It was postulated that low TREC numbers and oligoclonality of the T-cell repertoire might be caused by either loss of T-cell progenitors in the absence of donor stem cell engraftment or thymic dysfunction caused by damage from infections, chemotherapy, or GVHD. However, subsequent studies have shown that if good T-cell function is achieved within 1 to 2 years after transplantation, T-cell function, thymic output, and T-cell clonal diversity are maintained long-term, decreasing at a rate of normal control values.[2,18] Myeloid donor engraftment was identified as the main predictor of T-cell reconstitution, stable thymic output, and recovery of B-cell function.[2,19] However, in patients with γc defects, myeloid chimerism might not be necessary for the development of $TREC^+$ T cells after transplantation.[19]

In a large long-term study of patients with SCID from France, use of conditioning was correlated with higher $CD4^+$ counts at all time points and good B-cell reconstitution. In this study 80% of patients who received conditioning did not require long-term gammaglobulin support, as opposed to only 42% in patients who had not received conditioning.[2] The rate of B-cell function recovery in patients with SCID has been well summarized in a recent review by Buckley[20] and varies from 25% to 80%.

Based on the French and Duke data,[2,3] one might speculate that if good T-cell reconstitution, including normal TREC numbers, are not achieved by 1 to 2 years after transplantation, an additional boost or conditioned transplantation should be considered. However, more data addressing the durability of immunity over time are needed before this recommendation can be made.

Late Effects of Transplantation in Patients with SCID

A recent report from the Center for International Blood and Marrow Transplant Research points to a high rate (7%) of late deaths (>2 years after HCT) in patients with SCID.[21] The main causes of late mortality in patients with SCID in this study were infection, organ failure, and chronic GVHD.[21] Late mortality risk did not differ between patients with B^- SCID and those with B^+ SCID.[21] The cumulative incidence of second malignancies, including lymphoproliferative disorders, was 2% in patients with SCID at 5 and 10 years after transplantation and 3% at 15 years after transplantation.[22] When lymphoproliferative disorders and lymphomas were excluded, only 2 of 1050 patients with SCID followed long-term had a solid tumor: 1 brain tumor and another desmoplastic squamous cell carcinoma of the foot.[22]

A single-institution study from France describing the long-term outcomes of 90 patients with SCID reported that 9% died more than 2 years after HCT.[2] Other late morbidities described in this study included chronic GVHD persisting for more than 2 years after transplantation, as seen in 10% of patients with SCID, and late autoimmune and inflammatory complications, as seen in 13% of patients with SCID.[2] This study also reported that 20% of patients with SCID required long-term nutritional support caused by digestive symptoms, and 25% had chronic human papilloma virus cutaneous infection.[2] Human papilloma virus infection was seen very late and only in patients with γc-, Jak3-, and IL-7Rα–defective genotypes. This latter complication was not believed by the authors to be related to NKor B-cell function but likely to be related to abnormal γc/Jak3-dependent signaling in keratinocytes.[2] Patients with Artemis deficiency had a significantly higher frequency of complications and much lower event-free survival than other genotypes, which was attributed to a known DNA repair defect, making them more prone to tissue damage caused by infections, chemotherapy, and GVHD.[2] All complications, except for papilloma virus infection, were more common in alternative donor transplant recipients, patients with lower $CD4^+$ cell counts, and patients with the Artemis genotype.[2] In a recently completed retrospective study of 69 patients with Artemis-deficient SCID compared with 76 patients with RAG deficiency, it was found in multivariate analysis that patients with Artemis deficiency who were treated with alkylator therapy were significantly more likely to have short stature, abnormal dental development, and endocrinopathies greater than 2 years after HCT compared with similarly treated patients with RAG deficiency in whom there is no DNA repair defect (personal communication, M. Cowan, manuscript in review).

One of the more concerning late effects in patients with SCID undergoing HCT is the finding of cognitive difficulties, which are also related to emotional and behavioral problems. The average IQ of 75 patients with primary immunodeficiency undergoing transplantation for SCID (43 patients), ADA deficiency (13 patients), and unspecified

combined immunodeficiency (19 patients) was significantly lower ($P = .006$) than the IQ of unaffected siblings or a population control. The lower IQ seemed to be related to consanguinity, diagnoses of ADA SCID, and a severe clinical course requiring intensive care unit admission.[5] However, use of conditioning did not affect IQ scores significantly.[5] It is now clear that patients with ADA SCID have an increased risk of cognitive difficulties and behavioral issues independent of HCT that is not corrected by enzyme replacement therapy and is possibly related to adenosine receptors and increased central nervous system adenosine levels.[5,6]

In summary, patients with SCID have a number of late effects, some of which are transplantation related, whereas others might be related to genotype. Additional late-effect studies, including studies of neurocognitive development and growth, are needed, in particular in very young children undergoing HCT who are exposed to alkylating agents.

Conclusions and Suggestions for Future Work

1. SCID comprises a large number of heterogeneous genetic defects. Understanding the relationship between the genetic defect, clinical status, resistance to engraftment, sensitivity to conditioning, and degree of chimerism necessary for phenotype correction are essential when making a decision about conditioning and donor type. Further collaborative data correlating genotype and outcomes are needed. Genotyping of all patients with SCID should be adopted as standard clinical practice.

2. MRD transplantation without conditioning is the gold standard for transplantation in patients with newly diagnosed SCID. There is no consensus on the use of GVHD prophylaxis in this patient group.

3. If an MRD transplant is not available, one of 3 alternative donor types (TCD MMRD, MUD, and UCB transplants) can be used. Data are sparse on omitting conditioning in well-matched MUD and cord blood transplants in patients with SCID. The robustness of long-term T-cell reconstitution in patients receiving unconditioned TCD MMRD transplants might not be the same for all genetic forms of SCID and appears to be lower in patients with RAG and possibly other forms of VDJ recombination defects. Prospective multicenter studies are needed to fully determine the optimal conditioning regimen for patients with SCID receiving alternative donor transplants.

4. Some degree of myeloid donor engraftment is thought to be required for durable T-cell function, stable thymic output, and B-cell engraftment and reconstitution after HCT for many types of SCID. If good T-cell function, including TREC numbers, is not achieved by 1 to 2 years after transplantation, additional cell boosts or transplants with conditioning can be considered, although this needs to be studied in more detail. Prospective multicenter studies are needed to define the minimum dose of chemotherapy necessary to achieve sufficient donor myeloid chimerism that results in durable T- and B-cell immune reconstitution with minimal toxicity. In addition, adoption of a common definition for T- and B-

cell function recovery and indication for a posttransplantation boost with or without conditioning is needed. Finally, for patients with Artemis-deficient SCID (and other more rare SCIDs with radiation sensitivity), alkylators should be avoided, if possible, and when used, a careful and complete discussion with the parents of the pros and cons of conditioning with alkylating therapy is essential as part of the therapeutic decision-making process.

5. Patients undergoing transplantation for SCID experience a number of late effects after transplantation. Better studies of late effects, including pretransplantation and posttransplantation neurocognitive testing, are required to differentiate disease-related from transplantation-related neurocognitive deficits. Decreasing transplantation-related insults is critical to achieve better long-term quality of life in these patients. This is particularly relevant for patients diagnosed and treated at a very young age.

6. Development of effective, nontoxic, non–alkylator-based conditioning regimens, which will allow durable myeloid engraftment while reducing or eliminating early and late toxicities, is essential for a successful transplantation and good quality of life for all patients with SCID.

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Abbreviations used

ADA	Adenosine deaminase
γc	γ Chain
GVHD	Graft-versus-host disease
HCT	Hematopoietic cell transplantation or hematopoietic stem cell transplantation
IL-7Rα	IL-7 receptor α chainl

Jak3	Janus kinase 3
MMRD	Mismatched related/haplocompatible donor
MRD	Genotypically matched related donor
MUD	Unrelated donor matched at A, B, C, DrB1, and DQ loci by high resolution
NK	Natural killer
RAG	Recombination-activating gene
SCID	Severe combined immunodeficiency
TCD	T cell depleted
TREC	T-cell receptor excision circle
UCB	Umbilical cord blood

Table I
SCID subtypes and transplantation-related characteristics

Phenotype/syndrome	Genetic defect	Characteristics related to transplantation
$T^-B^-NK^-$	ADA deficiency	ERT or gene therapy (on a research study) might be available and considered if MRD transplants are not available for HCT. ERT should be held before nonconditioned transplantation. Fifty percent of patients have marked neurologic and cognitive abnormalities after transplantation or with ERT.[5,6] B-cell function is usually recovered after unconditioned MRD transplantation.[7]
$T^-B^-NK^+$	RAG1 or RAG2 mutation	There is increased risk of nonengraftment and graft rejection in nonconditioned mismatched HCT.[3,4] No radiation sensitivity is present. B-cell function recovers in a minority (17%) of nonconditioned patients.[3] There is a frequent need for boost transplants in nonconditioned HCT (83%).[3]
	Artemis deficiency (*DCLRE1C*)	DNA repair defects are seen (alkylating agents and radiation sensitivity). There are frequent late effects after transplantation with alkylating agents.[2] Reconstitution of B-cell function is rare (<20%) in patients receiving MSD transplants without myeloablation.[1]
	Ligase IV deficiency	A DNA repair defect is seen. There are limited transplantation data.
$T^-B^+NK^-$	Common γc (IL-2Rγ, X-linked SCID)	There are no barriers to engraftment, even with mismatched donors.[3,4] Gene therapy is successful in correcting immune deficiency, but there is a high risk of malignant transformation in an early gene-therapy study.[8] Reconstitution of B-cell function develops in 30% to 40% of patients after nonconditioned transplantation with MMRD transplants.[3,4] There are few long-term problems except for cutaneous warts.[2]
	Jak3	There are no barriers to engraftment. There is reconstitution of B-cell function in up to 50% of nonconditioned patients with MMRD transplants.[3] Warts are seen late after transplantation.[2]
$T^-B^+NK^{+/-}$	CD45 deficiency	Limited data are available.
$T^-B^+NK^+$	IL-7Rα	There are good long-term outcomes and chance of B-cell function recovery without conditioning (70%).[3]
$T^-B^+NK^+$	CD3γ, CD3δ, CD3ε, CD3ζ	Limited data are available. The degree of immunodeficiency and need for transplantation depend on specific mutation.
ZAP-70 deficiency	ZAP-70	$CD8^-$ lymphopenia and high IgE levels are seen. A case report indicates that conditioning might not be needed in closely matched transplants.[9]
Omenn syndrome	Hypomorphic RAG1, RAG2, or other SCID mutations	Autoreactive T cells causing inflammatory and allergic symptoms are found.

Phenotype/syndrome	Genetic defect	Characteristics related to transplantation
		Conditioning was historically used even with MRD transplants, although there are no data to suggest that it should be treated differently than the underlying genetic defect.
Reticular dysgenesis AK2 deficiency	Defective maturation of lymphoid and myeloid cells (stem cell defect) defect in mitochondrial adenylate kinase 2	Limited transplantation data are available. Full myeloablative conditioning might be needed before mismatched transplantation.[10]

ERT, Enzyme replacement therapy; *ZAP-70*, ζ chain–associated protein of 70 kDa.