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Long term outcomes of severe combined immunodeficiency: therapy implications

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Abstract

Introduction—Newborn screening has led to a better understanding of the prevalence of Severe Combined Immunodeficiency (SCID) overall and in terms of specific genotypes. Survival has improved following hematopoietic stem cell transplantation (HCT) with the best outcomes seen following use of a matched sibling donor. However, questions remain regarding the optimal alternative donor source, appropriate use of conditioning and the impact of these decisions on immune reconstitution and other late morbidities.

Areas covered—The currently available literature reporting late effects after HCT for SCID and use of alternative therapies including enzyme replacement, alternative donors and gene therapy are reviewed. A literature search was performed on Pubmed and ClinicalTrials.gov using key words 'Severe Combined Immunodeficiency', 'SCID', 'hematopoietic stem cell transplant', 'conditioning', 'gene therapy', 'SCID newborn screening', 'TREC' and 'late effects'.

Expert commentary—Newborn screening has dramatically changed the clinical presentation of newborn SCID. While the majority of patients with SCID survive HCT, data regarding late effects in these patients is limited and additional studies focused on genotype specific late effects are needed. Prospective studies aimed at minimizing the use of alkylating agents and reducing late effects beyond survival are needed. Gene therapy is being developed and will likely become a more commonly used treatment that will require separate consideration of survival and late effects.

Keywords

Severe Combined Immunodeficiency (SCID); Hematopoietic Stem Cell Transplant (HCT); TREC; Newborn Screening (NBS); conditioning; gene therapy; RAG SCID; XSCID; Radiosensitive SCID (RS-SCID); late effects

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Declaration of interest

MJ Cowan is on the Scientific Advisory Board of Homology Medicine with stock options, the Scientific Advisory Board of Exogen Bio with stock options and the Data Safety Monitoring Committee for Bluebird Bio. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

1. Introduction

Severe combined immunodeficiency (SCID) is the most severe form of primary immunodeficiency (PID), with patients who have the typical form of the disease presenting with a near absence of T cell numbers and function in the first months of life, or following a positive newborn screen [1]. Affected babies typically succumb to overwhelming infection in the first year of life without hematopoietic stem cell transplantation (HCT), gene therapy, or enzyme replacement therapy (ERT) [2]. In the last 10 years, the diagnosis of leaky SCID characterized by the presence of some T cells with limited function and no evidence of maternal engraftment also has been better defined [1]. Leaky SCID also is associated with a significant risk of severe infections and high rates of autoimmunity, but the hypomorphic mutations in SCID-associated genes allow for at least some T cells to develop, resulting in many of these patients presenting later in life [1,3]. Newborn screening (NBS) for SCID utilizing T cell receptor excision circle (TREC) PCR-based methods to identify infants with T cell lymphopenia at birth, is now utilized in most of the USA [4]. Based on patients currently followed by the NIH-funded Primary Immune Deficiency Treatment Consortium (PIDTC) prospective study of SCID, NBS is the more common method of diagnosing infants with SCID in the USA compared to clinical presentation (J Heimall, Philadelphia, personal communication). This has led to a significant decrease in the age at diagnosis and treatment for both typical and leaky SCID [5,6]. TREC-based SCID NBS has also allowed a better understanding of the true prevalence of SCID and a change in the demographics of this disease. Prior to the advent of TREC NBS, the prevalence of SCID was estimated at 1/100,000 live newborns. It is now known to be closer to 1/50,000–60,000 [5]. In addition, the demographics of those affected have become clearer. Previously, SCID was most commonly thought to be due to mutations in IL2RG, causing X-linked SCID which affected about 50% of all SCID babies in most prior retrospective reports. For those affected by autosomal recessive disease, adenosine deaminase (ADA)-deficient SCID was thought to be the most common form. In a study of the experience of SCID NBS in the first 11 states from 2010 to 2014, it was found that while still common, IL2RG SCID comprised only 19% of the babies diagnosed with SCID, and ADA-SCID represented only 10% of the autosomal form while RAG1 SCID accounted for 15% [5]. In the following discussion, we will review outcomes including survival, immune reconstitution, engraftment, graft failure, graft vs. host disease (GVHD) and late effects, focusing on important factors such as donor source, conditioning, SCID phenotype and genotype.

2. Survival

SCID was first treated successfully with allogeneic HCT nearly 50 years ago. Over time, the 5-year overall survival has improved from 56% in patients treated prior to 1995, to currently greater than 70% and depending on donor and age at diagnosis, better than 90% [7,8]. Among the most important factors in predicting long-term survival are early transplant, good clinical condition of the child at the time of allogeneic HCT (i.e. absence of active infection), and SCID phenotype/genotype [7–13]. Five-year survival is 80–95% for patients who are transplanted prior to onset of infection and under 3.5 months of age regardless of donor or conditioning [7,8,10–12,14,15]. It has been demonstrated that patients with typical

SCID who receive an HCT at <3.5 months of age have improved survival [7,9]. It appears that this age benefit is partially related to a lower relative risk of contracting an infection prior to transplant since even patients older than 3.5 months at the time of HCT do very well if they do not have an active infection [7]. Conversely, it is clear that age at transplant is also important independent of infection with infected patients under 3.5 months of age at the time of HCT having a significantly better survival than infected patients over 3.5 months of age [16]. While the number of large studies examining late outcomes following HCT for SCID are limited, they consistently demonstrate that the majority of deaths occur within the first 2–5 years following HCT, and that infections are the most common underlying trigger for death, particularly infections present at the time of transplant [7,9,17,18]. In addition to affecting survival, the presence of active infection at the time of HCT is associated with poor T cell recovery [7].

3. Donor source

3.1. Matched sibling donor (MSD)

The use of an HLA genotype identical MSD is associated with the highest survival rates and the lowest risk of morbidity and GVHD [7,8,19,20]. The use of MSDs also generally is associated with an improved likelihood of B cell reconstitution even without the use of conditioning and irrespective of the underlying genotype [7,11,15,21]. Unfortunately, <20% of SCID patients have an MSD available, thus most require the use of an alternative donor source: mismatched (haplocompatible) related donor (MMRD), phenotypic matched unrelated donor (MUD) or publically banked unrelated umbilical cord blood (UCB). Some patients will also have a matched related, but non-sibling donor available (MRD); this type of donor source is sometimes classified as a phenotypic-related donor (PRD) or other related donor (ORD). PRD and ORD are not genetically identical and therefore are not always associated with the same outcomes as MSD.

3.2. Mismatched related donor

Haplocompatible MMRDs have historically been the most commonly used alternative donor type for SCID, thus there are more adult SCID survivors post-MMRD HCT available for study than those of other sources [11,17,18,22]. MMRD transplants are performed at centers with graft processing capability for T cell depletion to avoid GVHD but there are differences in T cell depletion protocols that have introduced center-based effects upon outcomes. In one European study, patients treated at centers with greater experience in MMRD transplantation demonstrated higher survival (57%) than those treated at less experienced centers (43%; $p = 0.009$) [14]. These techniques have improved over time and likely contributed to improvement in survival from about 50% in the era prior to 1995 to a survival rate of about 70% in those treated since 1995 based on a multicenter European cohort [8]. In a retrospective study conducted by the PIDTC of patients treated between 2000 and 2009 in North America, it was found that in patients with typical SCID and an active infection at the time of transplant, survival was highest with the use of a MSD (93%). However, in the absence of an available MSD and presence of an infection, use of an MMRD without pretransplant conditioning was associated with better survival (65%) than UCB, other donors (MUD and MRD) or MMRD with conditioning ($p < 0.001$) [7]. Conversely, when

infections were not present, there was no significant difference in survival between the alternative donor groups. In light of these data, it is somewhat surprising that studies of kinetics have shown that normal T cell function does not develop until 3–4 months post-HCT in T-cell-depleted grafts for SCID patients [10,23], which confers a greater window of vulnerability for infectious complications than would be seen in a T replete graft. Thus, the need for T cell depletion with its attendant delay in T cell reconstitution in addition to the prolonged immunosuppression associated with use of conditioning, may explain why those patients with infection at the time of HCT who did receive conditioning with an MMRD transplant had worse survival than those who received an MMRD transplant without conditioning. Recently, the use of TCRα/β–CD19 depletion from MMRD grafts to decrease the risk of GVHD while potentially resulting in earlier T cell reconstitution compared to other approaches for T cell depletion, was described in a series of 37 PID patients, only 5 of whom had SCID. Of the SCID patients reported, all survived (although follow up remains short) and 2/5 experienced aGVHD, 1/5 experienced extensive cGVHD indicating that GVHD is not eliminated with this approach. Overall, T cell recovery was very good with most patients demonstrating presence of T cells by day 30 and T cells >500 by day 120 [24] comparable to what has been reported in SCID patients receiving CD34-selected haploidentical grafts [23]. The risk of GVHD with this approach is further emphasized in a large study of 182 children in which clinically significant aGVHD occurred in 40% of malignant and 27% of nonmalignant recipients of TCRα/β CD19-depleted haplocompatible-related or -unrelated donor grafts [25]. It must be noted that no direct comparison between TCRα/β CD19 depletion and other forms of T cell depletion has been made to date.

3.3. Adult MUD

While an adult MUD may be used without T depletion, there is a delay in time to transplant compared to other donor sources while the donor is identified and scheduled [26]. In addition to the frequent use of conditioning for MUD transplants, this delay in access to the donor source may be another factor in the poorer survival seen in this cohort compared to MSD and in some circumstances MMRD recipients. However, long-term survival is similar to [7], and in some reports [17,19] better than, that of other alternative donor sources. In the PIDTC study of typical SCID patients treated with HCT for SCID in North America between 2000 and 2009, it was found that in the absence of infection for patients treated at any age, 5-year survival following either MRD or MUD transplant (93%) was similar to that for an MMRD transplant with conditioning (91%), an MMRD transplant without conditioning (81%), and UCB (77%, $p = 0.16$). When age at transplant was considered, patients transplanted at less than 3.5 months of age also had similar survival across alternative donor groups [7]. In contrast, a single center study of 58 SCID patients treated between 1991 and 2002, found overall survival following an MUD transplant of 83% versus an MMRD transplant of 61% (*p* value not provided). It should be noted that most MMRD recipients in this study received myeloablative conditioning (MAC) and infection status and age at HCT were not addressed [17]. In a study of 94 patients with SCID treated with MRD, MMRD or MUD from 1990 to 2004, survival was highest in the recipients of an identical related donor transplant (presumably MSD) (92%), followed by MUD (80.5%) and MMRD (52.5%) [19]; however, presence of infection at the time of HCT was not addressed. In another multicenter retrospective study comparing outcomes from MSD versus MUD/UCB

transplants without conditioning for SCID, when serotherapy (ATG or alemtuzumab) was used for MUD recipients, the estimated 5-year survival following MUD HCT was comparable to that of MSD (227). Of note, compared to the MSD recipients, the MUD recipients had significantly more acute grade II–IV GVHD (MUD 50% vs. MSD 22%), chronic GVHD (MUD 39% vs. MSD 5%), and a greater number remained IVIG dependent (MUD 72% vs. MSD 17%). There was no significant difference in T cell reconstitution between MUD vs. MSD recipients [27]. Finally, in a single institution retrospective study, although autoimmunity and need for nutritional support was higher in recipients of MMRD or MUD/ORD HCT compared to MSD, there were no significant differences in the rates of these complications between the 2 alternative donor types [18].

3.4. Unrelated UCB

The most recently added alternative donor source for HCT is UCB, which was first used in 1987. Public cord blood banks are a readily available source of HSC. However, a significant limitation of their use in HCT for SCID is the inability to obtain more donor cells for a second transplant or donor lymphocyte infusion. Also, this graft source is associated with the longest window of potential infection risk owing both to a prolonged period for recovery of neutrophils and a slower rate of T cell immune reconstitution than T-replete bone marrow or peripheral blood HSC grafts. In a multicenter, multinational study comparing UCB to MMRD donor sources in 249 patients with SCID, overall survival was similar and the most common cause of death in both groups was infection [28]. Of note, the degree of HLA matching had a significant impact on long-term survival: UCB transplants with a 6/6 HLA match had a 76% survival, 5/6 HLA match 62% survival, and 4/6 HLA match 35% survival. In this cohort, UCB recipients were more likely to have been treated with MAC and serotherapy compared to recipients of an MMRD. At 5-year posttransplant, UCB patients were more likely to be free of IVIG and this was associated with use of a myeloblative conditioning regimen ($p = 0.003$); however, there was no significant difference in CD3 or CD4 recovery between the 2 groups. In the 2000–2009 retrospective PIDTC study of 240 patients with SCID, while not statistically significant, there did appear to be a lower survival in the recipients of UCB vs. other alternative sources and MRD [7].

4. Graft vs. host disease

Post-HCT, one of the most significant and well-described adverse events is the development of GVHD. Unlike patients with a malignancy undergoing allogeneic HCT where relapse can be a major problem, no degree of GVHD is beneficial for patients with SCID. It is troubling then that in the PIDTC study of 240 patients with typical SCID transplanted between 2000 and 2009, 20% experienced grade 2–4 acute GVHD by 100 days posttransplant, and the incidence of chronic GVHD at 2 years was 15% [7]. Interestingly, donor source was not associated with the risk of developing GVHD. In a retrospective single institution European cohort specifically aimed at examining late effects of HCT in 90 patients with SCID, the incidence of chronic GVHD was similar to the PIDTC study with 11% of patients affected; 3 of the 10 patients with cGVHD died underscoring the severity of this complication [18]. In those patients with low T cells at 1–2 years post-HCT, there were higher rates of cGVHD

and autoimmunity. In a study specifically designed to compare outcomes of MMRD and UCB HCT recipients in SCID, chronic GVHD was more common in UCB recipients [28].

5. Graft failure/rejection

Another area of concern in terms of long-term outcomes for SCID patients following HCT is the risk of rejection or developing graft failure requiring a second transplant, in particular, when no conditioning is used. This is much less of an issue when an MRD is available. However, recipients of an MMRD without conditioning have a higher risk of rejection than MRD recipients and the delay in immune reconstitution may be associated with an increased risk of infection; also, second transplants have a renewed risk of GVHD. Both delayed immune reconstitution and GVHD may increase mortality. In those patients treated with an MUD who have graft failure or rejection, the donor may not be readily available for a second transplant, and for unrelated UCB transplants, the donors are never available. In the PIDTC 2000–2009 study, 18% of the overall cohort required a second transplant, with the risk lowest amongst those who received an MRD HCT; there was no significant difference in the rate of graft failure when comparing MMRD, MUD, and UCB donor sources. Survival following a second transplant was 56% [7]. In a single center study of 171 patients originally treated with MMRD HCT, 29% required a subsequent transplant or a boost, with a 63% survival rate [29]. In this cohort, older age at initial HCT was associated both with increased chance of needing an additional transplant/boost and increased risk of death, and chronic viral infections were the most common cause of death.

6. Immune reconstitution

Satisfactory T cell numbers, evidence of thymic activity via the presence of naïve T cells and/or detectable TRECs, and T cell response to PHA within the first 1–2 years post-HCT appear to be linked to durable (10–20 years post-HCT) T cell reconstitution [18,30,31]. However, donor origin appears to have no effect on T cell counts beyond 1–2 years posttransplant [17,32]. B cell reconstitution is the next most commonly reported immunologic outcome in available studies reporting post-HCT immune reconstitution in patients with SCID and independence from IVIG is the most common end point. Achieving B cell reconstitution requires a longer interval than T cell reconstitution with a median time of 1–2 years or more posttransplant [11,13,16,33] and normal B cell function typically is dependent on restoration of T cell function [13]. While IL2RG/JAK3 SCID and B-negative SCID require donor B cell engraftment for normal B cell reconstitution, for most other SCID genotypes host B cells can cooperate with donor T cells and function normally, including IL7Rα-deficiency, CD3 chain deficiencies and ADA-SCID, and some autosomal recessive SCIDs of unknown molecular type [22,34]. Overall, poor B cell reconstitution defined by continued IVIG dependence is seen in 15–58% of patients with IL2RG/JAK3 and RAG forms of SCID [17,18,34]. In patients who are independent of IVIG, most are able to mount appropriate vaccine responses [18] although this has not been studied in detail in most reports. In one single-institution retrospective study, continued immunoglobulin dependence was associated with more GVHD, infections, autoimmunity, and need for nutritional support [18]. Although some patients without a conditioning regimen and without myeloid engraftment may have normal B cell function, use of conditioning and some degree of donor

myeloid and B cell engraftment are associated with a higher likelihood of B cell reconstitution [7,17,18,20]. The issue is that it is highly likely that full donor chimerism is not needed to correct T and B cell immunity in patients with SCID and may be as little as 5–10%. This raises the important question at to what intensity of conditioning is actually needed for patients with SCID and whether the use of MAC or even reduced-intensity conditioning (RIC) is too much; in fact, could a non-myeloablative (NMA) regimen of low-dose busulfan be sufficient? This question remains to be answered.

7. Conditioning

Another significant factor in terms of both survival and long-term immune reconstitution for patients with SCID treated with HCT is the use of chemotherapy-based conditioning when an alternative donor source is necessary. There is significant debate in the SCID treatment community about the necessity for chemotherapy prior to alternative donor HCT and its use varies based on the presenting genotype/phenotype, donor source, presence of infection and individual center experience. In addition, there is debate regarding the degree of myeloablation (fully myeloablative (MAC), reduced intensity (RIC) or nonmyeloablative (NMA)) that confers the most advantageous risk to benefit ratio. Descriptions of commonly used MAC, RIC, and NMA conditioning regimens are summarized in Table 1 [36,37]. There are few studies specifically looking at the long-term effects of conditioning toxicities in patients with SCID, and there are significant concerns in the SCID community about the risks of conditioning, but also the converse risk of not achieving adequate long-term immune function (particularly thymopoiesis and B cell function) in the absence of conditioning [38]. This issue is of particular importance with the use of NBS resulting in the majority of patients diagnosed and treated under 3 months of age. In all forms of SCID, it appears that the use of busulfan-based conditioning is associated with a greater likelihood of B cell reconstitution [7,17,20,39,40]. While some but not all studies have found use of a conditioning regimen to be associated with better T cell reconstitution, the amount of chemotherapy, RIC versus MAC versus NMA, needed to achieve optimal T cell reconstitution has varied significantly between studies. At least one study [7] demonstrated a benefit for both MAC or RIC and another [38] found that only the use of MAC was associated with a higher thymic output. In both the PIDTC 2000–2009 study and the larger retrospective analysis of over 700 patients treated since 1968 [7,16], the use of RIC or MAC (vs. none/IS) was associated with significantly better T cell reconstitution although RIC was not compared to MAC. It has also been shown that donor myeloid engraftment was associated with better T cell function and better thymic output [17,18,34]. In contrast, in a single-center study of 128 patients treated with unconditioned MRD or MMRD HCT and followed for at least 10 years, sustained T cell reconstitution (including TRECs, TCR spectratyping, and proliferation to PHA) was seen in 83% of the patients [30]. However, in at least one other study, overall survival was better in patients who received RIC (94%) compared to MAC (53%) [41]. In the PIDTC 2000–2009 retrospective study of typical SCID, deaths associated with pulmonary complications were more common in patients receiving MAC than any other group [7]. Use of alkylator-based conditioning agents, such as busulfan, melphalan, cyclophosphamide, and thiotepa, has several well-described adverse effects. One of the most severe early effects of myeloablative dosing with busulfan is hepatic

veno-occlusive disease (VOD) [42]. In addition, use of alkylating agents has been implicated in late adverse effects, including thyroid dysfunction [43] irrespective of underlying genotype in the SCID population and late effects unique to the Artemis SCID population including dental abnormalities affecting secondary dentition [44] and growth failure [45]. Puberty may be delayed in patients receiving busulfan-containing regimens compared to those containing fludarabine/ melphalan, with females affected more than males [46]. None of these have been evaluated in detail in SCID populations in multi-center studies. Most of the reported studies evaluating the impact of conditioning are retrospective and from single centers with limited numbers of patients.

Treosulfan is an alkylating pre-HCT conditioning agent that compared to busulfan may require less monitoring of drug levels and is associated with a lower risk of complications, particularly VOD although no head-to-head comparisons between the two drugs have ever been done. Availability in the USA is limited to clinical trials. In a European study utilizing treosulfan for pediatric nonmalignant diseases in 316 patients, survival was 83% and event-free survival 76%; 95 of these patients were under 1 year of age. In that younger cohort, there was no significant difference in overall or event-free survival compared to older children but there was an increased risk of respiratory toxicity [47]. In a report focused on the use of treosulfan in the UK for 70 children with PID, including 26 SCID infants, overall survival was 81% and in those patients transplanted under 1 year of age it was 83% [48]. In this study, treosulfan was used in combination with either fludaribine ($n = 40$) or cyclophosphamide ($n = 30$); the 2 observed cases of VOD occurred in patients who received treosulfan/ cyclophosphamide combination therapy. Grade 2–4 GVHD was seen in 18 patients, there were 3 deaths associated with GVHD and 4 patients had limited chronic GVHD of the skin. Although the median follow up in the cohort was limited to 19 months, chimerism at 1 year was reported for 42 of the 70 children in the study. In the SCID patients (exact number not reported), mixed chimerism was significant with 90% having 100% donor T cells, slightly greater than 60% having 100% donor B cells and 50% having 100% donor myeloid cells. Late effects and more detailed evaluation of immune reconstitution in this cohort were not reported. Further long-term studies are needed to determine the late effects and durability of immune reconstitution in SCID patients treated with treosulfan prior to HCT.

The use of targeted biologic therapy for host stem cell depletion has the potential to eliminate or greatly reduce the need for alkylator based therapies. By targeting both c-kit, a molecule critical to homing, proliferation, adhesion, and maintenance of stem cells, and CD47, a cell surface marker on many cell types including stem cells that protects against antibody-dependent cell-mediated cytotoxicity, it was demonstrated in a mouse model that host stem cells were sufficiently eliminated to allow for significant donor stem cell engraftment [49]. Anti-CD45 monoclonal antibody coupled with saporin was shown to be an effective immunotoxin to deplete stem cells and allow for donor cell engraftment in another mouse model [50]. A clinical trial utilizing anti-c-kit monoclonal antibody prior to HCT in SCID patients is currently recruiting, but no results are available yet (**ClinicalTrials.gov**: NCT02963064)

8. Phenotype

Several studies have examined survival and long-term outcomes based on the presenting phenotype. In a large European retrospective study including patients transplanted from 1968 to 2005, a B+ phenotype (most commonly associated with IL2RG, JAK3 or IL7Rα genotypes) was associated with a 70% 10-year survival compared to 51% 10-year survival in those presenting with a B-phenotype (mostly RAG and DCLRE1C (Artemis) genotypes) [8]. However, in the PIDTC study of North American patients with typical SCID transplanted between 2000 and 2009 this effect was not seen [7]. In addition to survival, improved T cell reconstitution has been shown [6,7,13,17,29] when comparing B+ vs. B− phenotypic forms of SCID. With regard to the effect of the presence or absence of NK cells at the time of HCT, CD4 and naïve CD4 counts were lower at 2–20 years post-HCT in NK+ SCID patients [7,13,18,31,38], many of whom were also B− forms of SCID such as RAG1/RAG2. We will now discuss some features that have been described to be uniquely associated with certain genotypes.

9. Genotype

9.1. IL2RG/JAK3

IL2RG remains the most common gene associated with typical SCID and usually presents with a T-B+NK- phenotype. JAK3 SCID has a similar presenting phenotype to IL2RG, likely because JAK3 normally functions as a component of the intra-cellular signaling cascade used by IL2RG. Both IL2RG and JAK3 SCID are associated with a higher risk of IVIG dependence in the absence of B cell lineage chimerism. Severe cutaneous infections with HPV presenting years after HCT are commonly seen in IL2RG and JAK3 forms of SCID with a median time of onset of about 7 years post HCT [9,17,18].

In addition to HCT, gene therapy is being evaluated as a definitive treatment for several forms of SCID (Table 2). Gene therapy was first attempted for IL2RG SCID utilizing a murine γ-retroviral vector in the early 2000's [51,52]. Twenty of the initial 21 patients demonstrated good T cell immune reconstitution. However, 5 of these patients developed T cell acute lymphoblastic leukemia within 5 years of treatment due to insertional site mutagenesis that allowed transactivation of the LMO2 or CCND2 protooncogenes [53,54]. A more recent trial has used a self-inactivating (SIN) γ retroviral vector that did not contain the powerful enhancer regions that drove the LMO or CCND2 activity [55]. This vector demonstrated efficacy in 7 of 8 treated patients in terms of T cell immune reconstitution but no B cell reconstitution (no conditioning). In addition, in an analysis reported at 12–39 months posttreatment, there was no evidence of integration site clustering near lymphoid oncogenes and there were no patients with clonal malignancies identified [56]. In a single-center study comparing patients treated from 2000 to 2013 with either of these 2 γ-retroviral vectors to patients treated in the same time frame with an MMRD, there were significant differences in the rate of T cell reconstitution. In the gene therapy-treated group, a normal T cell count for age was achieved by 6 months in 78%, compared to 26% in the MMRD group; this difference was not seen by 5-year posttreatment. In addition, thymic output of CD4 +/CD31+/CD45RA+ cells was higher in the gene therapy group and this difference persisted to 5-year posttreatment. Naïve CD8 Cells (CCR7+/CD45RA+/CD8+) were also present in

higher numbers in the gene therapy group at 5-year posttreatment [57]. There are also ongoing trials utilizing an SIN lentiviral vector generated by Brian Sorrentino at St Jude Hospital for correction of IL2RG SCID. One of these trials being conducted at NIAID-NIH (**ClinicalTrials.gov**: NCT01306019) is focused on older patients with IL2RG SCID who have evidence of poor immune reconstitution following a prior allogeneic HCT. In a report of the first 5 patients enrolled in this study, all had previously received an MMRD and 3 had also received DLI [58]. They ranged in age from 7 to 23 years, and were IVIG dependent with chronic nor-ovirus infections; 4 had bronchiectasis and 2 had significant cutaneous viral infections. Early data from that trial, which utilizes low-dose busulfan prior to transplant, have demonstrated clinical improvement in severe warts and molluscum contagiosum as well as chronic norovirus infection [58]. One patient with severe bronchiectasis and irreversible lung damage developed a pulmonary bleed more than 2 years after gene therapy and did not survive. In addition, gene marking has been seen in myeloid, T, B, and NK cell lineages, which indicates stem cell correction. This is in contrast to all prior trials using γ-retroviral vectors without any conditioning that demonstrated T cell reconstitution only. It should be noted that despite these promising results, this is a small study and the follow-up time for some subjects was limited to 3 months. A second trial using the St Jude vector at St. Jude, UCSF and Seattle is enrolling newly diagnosed babies with IL2RG SCID and includes conditioning with low-dose exposure targeted busulfan (**ClinicalTrials.gov**: NCT01512888). The third trial being conducted at Boston Children's Hospital, Cincinnati Children's Hospital and UCLA uses an SIN γ-retroviral vector to treat newly diagnosed IL2RG SCID patients with busulfan-based conditioning (**ClinicalTrials.gov**: NCT01129544).

9.2. ADA

ADA deficiency causes SCID as well as nonimmune manifestations secondary to the accumulation of toxic metabolites affecting multiple organ systems. It is also important to note that ADA SCID can be a progressive disease and milder forms may be missed by TREC-based NBS. ADA ERT is an option and is often used as a bridge to definitive treatment, either allogeneic HCT or gene therapy. However, ERT is not universally available, it is costly, it requires weekly to biweekly intramuscular injections and its effect on immune function in terms of sustaining lymphocyte counts often decreases over time. This is thought to be due to the development of anti-ADA antibodies in the immune dysregulated host [59]. In a study of 106 patients with ADA-SCID treated with HCT, overall survival was 67% with a median follow up of 6.5 years [22]. Survival was highest in recipients of MSD (86%), followed by MUD (67%), and poorest in MMRD (43%). The type of conditioning also influenced survival with 78% survival for unconditioned transplants compared to 56% survival following MAC-HCT ($p = 0.009$). HCT using RIC had a survival rate of 67%, which was not significantly different than unconditioned transplant outcomes. The majority of unconditioned HCT procedures occurred in patients receiving a MSD HCT. There was no difference in survival between patients who were or were not given PEG-ADA pre-HCT. Of note, a single-center study that did not use conditioning prior to haplocompatible MMRD transplant for 13 ADA-SCID patients reported 85% survival [10,11]. Neurocognitive impairment, attention-deficit hyperactivity disorder (ADHD) and other learning challenges are more common in patients with ADA SCID than in other SCID genotypes irrespective of

the use of conditioning prior to HCT. In a study of neurocognitive outcomes in patients treated with HCT between 1979 and 2003 for PID in which there were 43 SCID patients of varying phenotypes/ genotypes including 13 ADA SCID, mean IQ scores were highest in those with IL2RG, IL7R, JAK3, RAG1/2 (mean IQ = 96), compared to those with ADA SCID (mean IQ = 65) [60]. There was no difference in IQ by use of MAC vs. RIC vs. no conditioning, however, this was a small study with a limited number of patients with SCID, and reflects patients treated several decades ago. Hearing loss is common in ADA SCID [61] and a patient with ADA SCID was reported to develop hearing loss even after a successful unconditioned HCT [62]. Patients with ADA also have a higher rate of multicentric dermatofibrosarcoma protuberans (a rare form of skin tumor) than the general population even after HCT [63].

Gene therapy was initially attempted for ADA SCID patients in the early 1990s [35] utilizing transduced peripheral blood lymphocytes that were reinfused while the patients continued to receive ERT and pretreatment conditioning was not used. While there was some initial benefit to this therapy in terms of T cell recovery, the effects only lasted about 5 years before gene marking declined. In addition, because peripheral blood lymphocytes were used there was some skewing of the T cell repertoire and there was no ability of the corrected cells to respond to unique antigen challenges with highly specific T cells. In addition, the level of correction was not adequate to affect the systemic metabolic disease associated with ADA deficiency. Another trial utilizing a γ-retroviral vector, in auto-logous hematopoietic stem cells but without conditioning and with continuation of ERT was also unsuccessful [35]. The lack of success in these trials was attributed to the lack of selective advantage for the gene corrected cells due to the use of ERT although we now know that this was probably not the case, and lack of effective use of pretreatment conditioning contributed to the failure of this therapy. Subsequently, a study of 18 patients receiving autologous γ-retroviral vector-transduced autologous bone marrow CD34+ stem cells following conditioning with low-dose busulfan was reported [64]. There were 3 patients who restarted ERT due to failure of the gene therapy and 2 of these subsequently received an allogeneic HCT. For those patients with successful improvement in immune function with gene therapy, after 1 year the modified cells represented 70% of the peripheral blood CD3 population. At a median of 7-year posttreatment, all of the patients have survived. The event-free survival of 83% and defined as lack of restarting ERT or needing an allogeneic HCT, is similar to that of patients with ADA SCID treated with an alternative donor source HCT. In addition, the patients with successful gene therapy treatment also demonstrated a good level of systemic metabolic correction, although as expected, previously present CNS abnormalities were not improved [64]. A recent study demonstrated correlation between busulfan dose and TCR diversity, again highlighting the importance of using conditioning prior to administration of the genetically corrected stem cells [65]. Gene therapy for ADA SCID is now being explored in a commercially prepared SIN γ-retroviral vector product (STRIMVELIS) in Europe [66]. In the USA, a lentiviral ADA vector, OTL-101 from Orchard Therapeutics, has recently obtained Rare Pediatric Disease Designation in addition to Orphan Drug and Breakthrough Therapy designations from the FDA all of which should accelerate its ultimate approval for use in patients (Table 2). Interestingly, ERT is being continued through the

therapy and does not appear to interfere with engraftment and reconstitution (D. Kohn, UCLA, personal communication)

9.3. Radiation sensitive (RS) – SCID

When considering the effects of chemotherapy-based conditioning in light of specific genotypes, the use of myeloablative alkylator-based conditioning has been shown to have a negative effect on survival in the RS forms of SCID (Artemis, DNA Ligase IV, DNA-PKcs, Cernunnos (XLF or/NHEJ1 deficiency) and Nijmegen Breakage Syndrome (NBS1) [67,68]. This risk appears to be higher for LIG4-, NHEJ1- and NBS1-SCID patients compared to DNA-PKcs or Artemis SCID patients although a direct comparison has never been made. In a publication summarizing the data for 22 LIG4-, NHEJ1- and NBS1-SCID patients, 5/7 patients who received MAC-HCT and 1/13 patients who were treated with RIC-HCT died [67]; there were 2 patients who received no conditioning, and both survived. In a single-center study of patients with Artemis-deficient SCID, the 4 reported deaths all occurred in patients receiving an MMRD with MAC [68].

Both Artemis and RAG1/RAG2 SCID genotypes typically lack T and B cells but have relatively normal NK cells at diagnosis, while only Artemis-deficient patients have a DNA repair defect and increased susceptibility to alkylating agents and ionizing radiation. In a study comparing survival and late effects in 69 patients with Artemis SCID to 76 patients with RAG1/RAG2 SCID with a median follow up of 8.5 years, patients with either genotype demonstrated 85% surviving beyond 2 years following an MRD HCT without conditioning and 67% surviving beyond 2 years after an MMRD HCT with high-dose busulfan and cyclophosphamide/fludarabine conditioning [45]. The majority of MMRD recipients with no or immunosuppressive conditioning alone rejected the grafts and required retrans-plant with busulfan containing regimens. Although survival in the two genetic groups was comparable, late effects were seen in 70% of patients with Artemis SCID compared to 24% of patients with RAG1/RAG2 defects. Amongst the patients with Artemis mutations compared to the RAG1/RAG2-deficient patients, there were higher percentages with poor growth at less than the 3rd percentile (49% vs. 9%), severe or recurrent infections (34% vs. 13%), cGVHD/autoimmunity (30% vs. 18%), need for nutritional support (21% vs. 4%), death occurring greater than 2-year post-HCT (10.5% vs. 4.5) and sequelae of pre-HCT morbidity (8.5% vs. 4.5%); p values for these differences were not reported. In addition, there was a group of late effects that were uniquely observed in the patients with Artemis deficiency and significantly linked to exposure to alkylators: dental abnormalities (21%), and other late complications including growth hormone deficiency, central hypothyroidism, type 1 diabetes (IDDM), renal tubulopathy, exocrine pancreatic insufficiency or pulmonary fibrosis were seen in 15% of the patients ($p < 0.001$). Among the Artemis-deficient patients, exposure to alkylators was associated with significantly lower height ($p < 0.03$ girls, $p < 0.001$ boys). There were no malignancies in any of the patients reported over a mean follow up of 10 years. Immunoglobulin replacement was required in 47% of survivors. Factors associated with an increased risk of need for immunoglobulin replacement included Artemis genotype, poor T cell reconstitution, requirement for additional transplant, absence of alkylator therapy and MMRD donor source.

9.4. RAG

Based on the study of NBS for SCID in the US mutations in RAG1 or −2 accounted for 17% of all patients with SCID [5]. Hypomorphic mutations in RAG1 are the most commonly seen genotype associated with leaky SCID. In these patients, the defect in V(D)J recombination allows for development of a lower than expected, but not absent, number of T and B cells. RAG1 and RAG2 mutations can present with a spectrum of disease, including typical SCID, leaky SCID, and Omenn Syndrome [69]. In patients with Omenn Syndrome, there is a high degree of autoinflammation and autoantibody production, which can increase the challenges of treating this group of patients. Unpublished data from the PIDTC (16 and J Heimall, Philadelphia, personal communication) suggest that survival for typical and leaky SCID are comparable. Further studies are needed to be able to comment on the specific differences in outcomes for these groups and to be able to better inform treatment decisions with regard to use of pre-transplant immunosuppression as well as conditioning.

10. Late effects

There are a limited number of large studies [7,9,17,18] primarily focused on late outcomes following HCT for SCID (Table 3). These studies consistently demonstrate that the majority of deaths occur within the first 2–5 years following HCT, but that other late morbidities are fairly common, particularly growth concerns (12.5–17.5%), chronic gastrointestinal issues such as diarrhea or poor oral feeding (20%), continued need for immunoglobulin replacement or antibiotic prophylaxis (15–58%), sinopulmonary infections/pneumonia (2–20%), and chronic HPV Infections (12–25%). Autoimmunity, most commonly autoimmune hemolytic anemia, has been seen in 1–12% and cGVHD in up to 15% of patients with SCID [9,17,18]. In one of the studies, all of the deaths that occurred more than 2 years posttransplant were in patients with either cGVHD, persistent need for nutritional support, autoimmunity/auto-inflammation or some combination of these 3 clinical features [18]. While the median age in most of the cohorts is too young to know the effects of HCT on reproductive health, the majority of patients reaching adolescence have been able to achieve age-appropriate puberty [9,17,18]. From a neurocognitive standpoint, in one study of 111 patients from a single center all treated without conditioning, 10% had developmental delay and 21% had ADHD. Of those with ADA SCID in this cohort, 50% had ADHD, compared to 15–20% of those with IL2RG, IL7R, JAK3 or RAG defects [9]. In a European single-center study of 90 patients with SCID, 93% of those over 10 years of age had normal school performance [18]. Careful long-term follow up of surviving patients that includes detailed developmental testing is critical to fully appreciate the potential late effects of HCT with or without conditioning in this patient population.

Consensus recommendations for screening of late effects following HCT for SCID were recently published [70]. These guidelines suggest a timetable for basic testing of immune function and engraftment along with recommendations for use of immunoglobulin replacement, antibiotic prophylaxis and vaccine administration. In addition, recommendations for monitoring nonimmune-mediated late effects are provided including close monitoring of growth and developmental milestones, neurocognitive testing, and health-related quality of life assessment, assessment of endocrinologic effects (thyroid

function, gonadal function, growth hormone sufficiency), assessment of pulmonary function, hearing, dental exams, and dermatology consultation for those patients who develop difficulty with warts. These guidelines are based on currently available data regarding late effects observed in SCID patients post-HCT. They provide a framework for continued care of these patients as survival continues to improve. Further study of late effects in more contemporarily transplanted SCID patients many of whom will be diagnosed by NBS and thus, treated early in life, is needed. As the data becomes more robust, these guidelines will need to be updated.

11. Expert commentary

Thanks to population-based NBS in many areas of North America, and hopefully growing use of NBS around the world, many SCID babies have the potential to be treated before developing infections. This will likely change the pattern of late effects observed after treatment with HCT, and in some cases gene therapy. Similarly, the growing use of whole-exome- and whole-genome-based technologies is likely to foster discovery of new underlying genetic defects in patients with SCID, which may be associated with their own predispositions to late effects-both those intrinsic to the defect itself and those secondary to use of alkylator-based therapy.

Based on the data presented, it is clear that there is much work that still needs to be done to understand the long-term outcomes for patients with SCID treated with HCT. In particular, prospective studies focused on long-term outcomes and quality of life for all SCID patients beyond the first 5 years after HCT are needed. In addition, focus needs to be on identification of bio-markers for early risk factors for GVHD, graft failure necessitating second transplant and survival. This might be accomplished via exploration of the association of early biomarkers of T cell development including lineage-specific chimerism, evidence of thymopoiesis, T cell receptor diversity as well as evaluation of late biomarkers such as degree of T cell exhaustion or telomere length as predictors for durable T cell reconstitution. Similarly, exploration of B cell lineage markers, B cell receptor (BCR) diversity and degree of antibody responses to T cell-dependent and -independent antigens that predict full B cell reconstitution with ability to discontinue immunoglobulin replacement post-HCT will be important to predict freedom from infection or other long-term morbidities and good quality of life. It will also be crucial to determine when is the earliest date and what are the correct intervals in which to measure these biomarkers. We must identify to what degree GVHD prophylaxis slows the rate of immune reconstitution and determine if this has a lasting effect on immune function and conversely identify the effect of acute and chronic GVHD on immune reconstitution. Recently, monoclonal antibody therapies have been used in various aspects of HCT for SCID, including preparative regimens, infection management, and GVHD treatment. Assessment of the impact of these and other emerging interventions on long-term immune reconstitution, morbidity, and mortality is also an area that requires both retrospective and prospective analysis. Finally, it will be critical to determine the minimum degree of chemotherapy necessary to fully and durably reconstitute T and B cell immunity as well as the potential late effects from this therapy.

12. Five year view

Over the next 5–10 years, it will be important to address how NBS impacts the epidemiology, survival, and long-term outcome for SCID patients. In addition to early diagnosis, most patients now have the advantage of having their SCID genotype characterized. Over the next 5 years, it will be important to assess survival and late effects as a function of molecular subgroups, as well as the effect of donor source and conditioning on their outcomes. It would be beneficial to see prospective, controlled multicenter studies, such as the current prospective natural history of SCID study currently organized through the PIDTC. Studies specifically aimed at characterizing quality of life and neurocognitive outcomes in SCID patients have also been proposed as an aspect of this study and will likely be useful in gauging the true success of HCT beyond survival. There will also be prospective multicenter studies of limiting dose exposures of busulfan and other marrow niche-opening agents including monoclonal antibodies targeting the c-kit receptor and/or CD47, and immunotoxins targeting CD45 with long term follow up of efficacy and toxicity. Finally, as gene therapy becomes increasingly available for regular use in ADA and IL2RG SCID and hopefully for a broader array of SCID genotypes, close monitoring for quality of immune reconstitution and late effects following gene therapy will become critical.

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Key issues

- TREC NBS for SCID has led to earlier diagnosis of the disease and a better understanding of the epidemiology
- Five year survival for SCID is generally greater than 70% and for MRD HCT, approaches 90% with most deaths occurring within the 1st 2 years post transplant
- Survival after alternative donor sources for HCT is generally similar across all donor types
- About 20% of patients require a second transplant
- The role of conditioning is controversial, but some degree of alkylator base conditioning prior to HCT does appear to improve B cell reconstitution; the exact degree of conditioning needs to be determined and may vary with genotype/phenotype.
- Alkylator-based conditioning is associated with increased risk of death as well as poor growth in Artemis and other RS-SCID genotypes
- B+ SCID is associated with improved T cell reconstitution compared to B- SCID
- cGVHD is seen in up to 15% of patients with SCID and when present increases the risk of death; approaches that eliminate GVHD need to be developed.
- Poor nutritional status, autoimmunity and GVHD are risk factors for late death following HCT for SCID
- Gene therapy has shown promise in patients with IL2RG and ADA SCID and low dose chemotherapy or some other means of opening marrow niches appears essential to achieving full immune reconstitution.

Table 1

Summary of conditioning regimens used for HCT in SCID [35].

Level of intensity	Commonly used agents	Commonly used total dosage
Minimal Intensity (MIC)/Non-myeloablative (NMA)	1. Fludarabine	120–160 mg/m^2
	Cycophosphamide[a]	200 mg/kg
	2. Fludarabine	120–160 mg/m^2
	TBI[a]	2–300 cGy
Reduced intensity (RIC)	1. Alemtuzumab	1–3 mg/kg
	Fludaribine	150 mg/m^2
	Melphalan	140 mg/m^2
	2. Busulfan	8–12 mg/kg with pharmacokinetic monitoring
	Fludarabine	160–180 mg/m^2
	rATG (Thymoglobulin)	3.5–8 mg/kg
	3. Fluadarabine	150 mg/m^2
	Treosulfan	36 mg/m^2
Myleoablative (MAC)	1. Busulfan	14–16 mg/kg ± pharmacokinetic monitoring
	Cyclophosphamide[a]	120–200 mg/kg
	2. Treosulfan	42 mg/m^2
	Fludarabine	150 mg/m^2
	rATG (Thymoglobulin)	6 mg/kg

[a]Rarely used today for SCID.

HCT: hematopoietic stem cell transplantation; SCID: severe combined immunodeficiency.

Table 2

Summary of currently active gene therapy clinical trials for SCID.

Genotype	Vector	Clinical trial number	Clinical trial sites	Conditioning	Ages
IL2RG	SIN – Gamma-retrovirus-transfected autologous CD34+ cells	NCT01410019	Paris (France)	Unknown	Up to 12 months
	SIN – Lentivirus-transfected autologous CD34+ cells	NCT01512888	St Jude Research Hospital, Memphis, TN (USA); University of California, San Francisco, CA (USA); Seattle Children's Research Center; Seattle; WA (USA)	Busulfan (very low exposure) with targeted pharmacokinetics	Up to 12 months and newly diagnosed
	SIN – Gamma-retrovirus-transfected autologous CD34+ cells	NCT01129544	Children's Hospital Boston, MA (USA); Cincinnati Children's Medical Center, Cincinnati, OH (USA) University of California, Los Angeles, CA (USA)	Busulfan (low exposure) with targeted pharmacokinetics	Age unlimited
	SIN – Lentivirus-transfected autologous CD34+ cells	NCT01306019	National Institutes of Health; Bethesda, MD (USA)	Busulfan (moderate-low dose)	2–20 y and failed allogeneic HCT
ADA	Lentivirus-transfected autologous CD34+ cells	NCT02999984	University of California, Los Angeles, CA (USA)	Busulfan (low dose)	30 days–17y
	Lentivirus-transfected autologous CD34+ cells	NCT01380990	Great Ormond Street Hospital for Children; London (UK)	Busulfan (low dose)	Males up to 5 y/o
	Retrovirus-transfected autologous CD34+ cells	NCT00598481	Milan (Italy), Jerusalem (Israel)	Non-myeloablative Busulfan	Up to 17y

Table 3

Summary of reported survival and late effects in SCID patients following HCT.

Study	Number of patients	Years of HCT	Survival; Median follow up	Donor source (survival)	Conditioning	cGVHD	Infections	IVIG	Autoimmunity	Growth failure	Neurocognitive effects	Other
Mazzolari et al. [17]	58	1991–2002	72.4% at 5 years; 11y (5.6–16.3)	MRD 12 (90%) MMRD 33 (61%) MUD 10 (83%) UCB 0 (n/a) Other Related 3 (100%)	None 13 IS 2 MAC[a] 43	None	HPV 17.5% (most in *IL2RG/JAK3*) Bacterial PNA 7.5% Pneumocystis 2.5%	15%	12.5% (AIHA, hypothyroidism, hyperthyroidism)	Weight <3rd %tile 17.5% Height <3rd %tile 12.5%	In school 100% School support 7.5% Severe neurologic dysfunction 10%: • ADA SCID w/hypotonia/cognitive impairment • Artemis SCID w/ impairments secondary to post HCT encephalitis • JAK3 SCID w/ impairments secondary to pre-HCT anoxic brain damage associated with PNA • RAG Omenn SCID w/paraplegia	Dental Issues 7.5%