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Current Knowledge and Priorities for Future Research in Late Effects after Hematopoietic Stem Cell Transplantation (HCT) for Severe Combined Immunodeficiency (SCID) Patients: a Consensus Statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT

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Abstract

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Severe Combined Immunodeficiency (SCID) is one of the most common indications for pediatric hematopoietic cell transplantation (HCT) in patients with primary immunodeficiency (PID). Historically, SCID was diagnosed in infants who presented with opportunistic infections within the first year of life. With newborn screening (NBS) for SCID in most of the U.S., the majority of infants with SCID are now diagnosed and treated in the first 3.5 months of life, although in the rest of the world, the lack of NBS means that most infants with SCID still present with infections. The average survival for transplanted SCID patients currently is >70% at 3 years post-transplant, although this can vary significantly based on multiple factors including age and infection status at the time of transplantation, type of donor source utilized, manipulation of graft prior to transplant, GVHD prophylaxis, type of conditioning (if any) utilized and underlying genotype of SCID. In at least one study of SCID patients who received no conditioning, long-term survival was 77% at 8.7 years (range out to 26 years) post-transplantation. While a majority of patients with SCID will engraft T cells without any conditioning therapy, depending on genotype, donor source, HLA match and presence of circulating maternal cells a sizable percentage of these will fail to achieve full immune reconstitution. Without conditioning, T cell reconstitution typically occurs, although not always fully, while B cell engraftment does not—leaving some molecular types of SCID patients with intrinsically defective B cells in most cases dependent on regular infusions of immunoglobulin. Because of this, many centers have used conditioning with alkylating agents including busulfan or melphalan known to open marrow niches in attempts to achieve B cell reconstitution. Thus, it is imperative that we understand the potential late effects of these agents in this patient population. There are also non-immunologic risks associated with HCT for SCID that appear to be dependent upon the genotype of the patient. In this report we have evaluated the published data on late effects and attempted to summarize the known risks associated with conditioning and alternative donor sources. These data, while informative, are also a clear demonstration that there is still much to be learned from the SCID population in terms of their post-HCT outcomes. This paper will summarize current findings and recommend further research in areas considered high priority. Specific guidelines regarding a recommended approach to long-term follow up, including laboratory and clinical monitoring will be forthcoming in a subsequent paper.

Keywords

Late effects; pediatric allogeneic bone marrow transplant; severe combined immunodeficiency

Introduction

SCID was among the first PID treated successfully with allogeneic HCT nearly 50 years ago, and it continues to be the most common PID treated with HCT. With survival rates following HCT greater than 70% and depending on donor and age at diagnosis, better than 90%, a majority of these patients are living long-term (1–6). The age at diagnosis and treatment for both typical and leaky SCID has significantly decreased in the USA with the introduction of newborn screening (NBS) for SCID (7,8), although most other countries have yet to adopt this practice. Since most patients with SCID are treated before 6–9 months of age and in the setting of NBS or prenatal diagnosis before 3.5 months of age, the use of chemotherapy conditioning in order to achieve full immune reconstitution raises concern

regarding the attendant risk of significant late effects associated with these drugs (7,9). We will present below the features that are known about overall survival, the long term risks and benefits of various alternative donor sources, the risks and benefits of utilizing (or not) pre-HCT conditioning particularly with regard to the differences between reduced intensity (RIC) and myeloablative (MAC) conditioning and the use (or not) of conditioning in certain SCID subgroups. We also review what is known to date about the kinetics of early T and B cell reconstitution, which biomarkers are useful in predicting long term immune reconstitution, and certain non-immunologic late effects that are known to be associated with certain SCID phenotypes or genotypes. The summary and research priorities we present are the product of a working group established for an international consensus conference sponsored by the Pediatric Blood and Marrow Transplant Consortium (PBMTC), the Primary Immune Deficiency Treatment Consortium (PIDTC) and the Inborn Errors Working Party (IEWP) of the European Society for Blood and Marrow Transplantation (EBMT).

Overall Survival and Morbidities (TABLE 1)

Early diagnosis, good clinical condition of the child at the time of allogeneic HCT (i.e., absence of active infection) and SCID phenotype/genotype are important predictors of survival (2,4–6,10–12). Since 1968, when the first child with SCID successfully underwent HCT, the overall survival rate of patients with SCID after HCT has improved not only for patients transplanted with a graft from a matched, related donor but also for those receiving a graft from alternative donors, with an overall 5 year survival of 70–80% (1,4–6, 13). This level of overall survival has been stable for patients transplanted since 1996. Five year survival is 80–95% for patients who are transplanted prior to onset of infection and early in life (under 3.5 months of age) regardless of donor or conditioning (4–6, 10,11,13, 14).

There are a limited number of large studies (1–3,6) of late outcomes following HCT for SCID (Table 1). 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% of patients and cGVHD in up to 15% of patients. In one study all of the deaths occurring greater than 2 years from transplant occurred in patients with either cGVHD, persistent need for nutritional support, autoimmunity/auto-inflammation or some combination of these 3 clinical features (3). 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 (1–3). From a neurocognitive standpoint, the majority of patients were enrolled in school and had normal school performance with only 3–7.5% requiring extra classroom support. In one study, attention-deficit/hyperactivity disorder (ADHD) was diagnosed in 21% of the patients, the majority of whom had ADA-SCID (2).

RESEARCH PRIORITIES: SURVIVAL AND LONG-TERM MORBIDITIES

- Prospective studies of long term survival, immune reconstitution including thymopoiesis and late effects in children with SCID and leaky SCID (including Omenn Syndrome) treated without or with alkylating agents extending to at least 10 years post-HCT.
- Assessment of the impact of newborn screening on survival, including as a distinct group those with leaky SCID and Omenn syndrome.
- Focused studies on the long term outcomes and quality of life for all SCID patients beyond the first 5 years after HCT, particularly with regard to cGVHD, autoimmunity, infections, neurodevelopmental and growth impairment with stratification by phenotype (as defined by T, B and NK cell populations at diagnosis) and genotype but also donor source and match as well as pre-transplant conditioning.

Alternative Donor Sources: Risks and Benefits

The majority of transplants for SCID worldwide have been performed using either a matched related donor (MRD) or mismatched related donor (MMRD) following T cell depletion by a variety of methods. MRDs confer the highest survival rates, with lowest risk of morbidity and lowest risk of GVHD (4,6, 16,17). In addition, with an MRD, the likelihood of B cell reconstitution is high regardless of genotype or conditioning although more than 20% of long-term survivors remain on immunoglobulin replacement therapy (6,10,14,19). However, since <20% of SCID patients have a MRD available, most require the use of an alternative donor source: MMRD, phenotypic matched unrelated donor (MUD) or publically banked unrelated umbilical cord blood (UCB).

A MMRD is typically a parent of the patient and, therefore, has the advantage of being readily available both for an expedient transplant and for boosts (infusion of additional hematopoietic stem cells from the same donor without conditioning) if needed following the transplant to enhance immune recovery. Since early transplant is associated with better survival, an MMRD was initially the most commonly used alternative donor source; there are more surviving adult SCID patients who were recipients of an MMRD than any other alternative donor source (1,3,10,15). 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) (13). In the last 50 years, there has been significant improvement in survival following an MMRD HCT, with survival at 10 years similar to that of MUD HCT in patients transplanted since the mid-1990's (4,13). This may be attributed to improvement in T cell depletion techniques as well as supportive care. In patients treated between 2000–2009 in North America (6) with active infections at the time of transplant and without an available MRD regardless of age, use of a MMRD without pre-transplant conditioning was associated with better survival (65%) than UCB, MUD or MMRD with conditioning (39–40%;

p=0.006). In this same study when infections were not present, there was no significant difference in survival between the alternative donor groups. The rate of second transplant in those receiving a MMRD was 24% (6). In a single center study of 171 patients originally treated with a MMRD HCT without conditioning, 28.7% required a subsequent transplant/boost, with a 63% survival rate after the 2nd transplant/boost (20). In this cohort, later age at initial HCT was associated both with increased chance of needing an additional transplant/boost and increased risk of death with subsequent transplants; chronic viral infections were the most common cause of death. Of note, outcomes of a MMRD transplant for ADA-SCID were poor in one study (15) but excellent in others (5,10) in the absence of conditioning.

For MUDs there can be a delay in time to transplant when compared to other donor sources while the donor is identified and scheduled. It is possible that this delay in access to the donor source may contribute to poorer survival in this cohort compared to MRD recipients. However, long-term survival is at least similar to that of other alternative donor sources (1,6). In one retrospective study of 94 SCID patients treated with MRD, MMRD or MUD from 1990–2004, survival was highest in the recipients of an MRD (92%), followed by MUD (80.5%) and MMRD (52.5%) (Grunebaum, 2006). In a comparison of unconditioned MUD to MRD transplants, estimated 5 year survival was 71% with MUD vs 92% with MRD ($p<0.01$) (18). However, in that multicenter retrospective study when serotherapy (ATG or alemtuzumab) was used for the MUD recipients, the estimated 5-year survival following MUD HCT was comparable to that of MRD; however, compared to the MRD recipients the MUD recipients had significantly more cGVHD (39% vs 5%) and IVIG dependency (72% vs 17%). There was no significant difference in rates of GVHD when comparing bone marrow vs cord blood vs peripheral stem cells in the URD group and there was no significant difference in T cell reconstitution between MUD vs MRD transplants (18). In a large retrospective study of recipients of HCT for SCID between 2000–2009 in North America, 15% of patients who initially received a MUD transplant required a 2nd transplant (6). Finally, in another single institution retrospective study, although autoimmunity and need for nutritional support was higher in recipients of MMRD or MUD HCT compared to MRD, there were no significant differences in the rates of these complications between the 2 alternative donor types (3).

UCB from infants without known health risks was first used in 1987 for HCT and public banks are a readily available source of HSC. However, once an UCB unit is used, there is no ability to contact the donor for an additional transplant or donor lymphocyte infusion. Also, there is a prolonged period post HCT for recovery of neutrophils and platelets resulting in an increased risk of infection. In addition, the infused cells are functionally naïve and therefore have a slower rate of immune reconstitution than T-replete bone marrow or peripheral blood HSC preparations, further adding to the longer window of increased risk for infection post-transplant. In a study comparing UCB to MMRD donor sources in 249 SCID patients, overall survival was similar and the most common cause of death in both groups was infection (21). In the UCB transplant cohort, there was a strong correlation of survival with degree of HLA matching: those with a 6/6 HLA match had 76% survival, 5/6 HLA match 62% survival and 4/6 HLA match 35% survival. In this cohort UCB patients were more likely to have been treated with myeloablative conditioning and serotherapy. Chronic GVHD was more common in UCB recipients. At 5 years post transplant, 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 SCID patients, 14% who initially received an UCB transplant required a 2nd transplant. In addition, while not statistically significant there did appear to be a lower survival in the recipients of UCB vs other alternative sources and MRD (6).

RESEARCH PRIORITIES: ALTERNATIVE DONOR SOURCES

- Prospective assessment of survival, need for boost or second transplant and rates of GVHD associated with the various alternative donor groups particularly in terms of comparing efficacy and complications, e.g., GVHD with UCB donors to other alternative donor sources
- Assessment of the role of genotype/phenotype in outcomes from alternative sources, in particular, engraftment and need for boost or second transplants.
- Assessment of durability of immune reconstitution following the use of various alternative donor sources and role that genotype might play.

Conditioning: Risks and Benefits

The use of conditioning prior to HCT for SCID with alternative donor sources remains controversial. The decision to use conditioning, and the degree of myeloablation (fully myeloablative (MAC) or reduced intensity (RIC)) varies by transplant center, donor type, clinical presentation of the patient (particularly with regard to the presence of an active infection) and SCID phenotype/genotype.

The risks of conditioning include drug-associated toxicities, particularly veno-occlusive disease (VOD), organ damage (renal, liver and lung), neurocognitive effects, abnormal growth and development and gonadal dysfunction. There are few studies specifically looking at the long term effects of conditioning toxicities in SCID patients, 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 (24) and B cell function) in the absence of conditioning.

Overall, the use of conditioning, in particular busulfan, is associated with a greater likelihood of B cell reconstitution (6,19). This has been reported in all forms of SCID (1,6,22,23). However, in at least one study, overall survival was better in patients who received RIC (94%) compared to MAC (53%) (25); and, deaths associated with pulmonary complications were more common in patients receiving MAC than any other group (6). One of the most severe early effects of myeloablative dosing of busulfan is hepatic VOD (26). In addition, use of busulfan has been implicated in a number of late adverse effects, including dental anomalies affecting secondary dentition (27), thyroid dysfunction (28), and growth failure in radiosensitive SCID (29). In addition, puberty may be delayed in patients receiving busulfan-containing regimens compared to those containing fludarabine/melphalan, with females affected more than males (30).

Treosulfan, a structural analogue to busulfan, has shown some promise in European studies. Treosulfan has an immunosuppressive effect in addition to opening marrow niches with low extramedullary toxicity, particularly with regard to the risk of developing VOD. It is being used increasingly for SCID HCT in very young infants and appears to have less short tern toxicities than busulfan, but the late effects are unknown, the number of infants studied relatively small and limited pharmacokinetic data available (31, 32).

With NBS for SCID becoming increasingly available, more patients are being treated with HCT in early infancy, at a time when drug metabolism for many alkylators can be highly variable from one infant to another (33,34). This increases the likelihood of exposing young infants to amounts of alkylating agents that may result in both short and long term toxic effects. Unfortunately, there are few studies that focus on the potential side effects of conditioning in infants <3.5 months of age. In a recently reported study of MAC with busulfan-containing regimens in 102 infants under 1 year of age (median age 0.1 y) who received UCB-HCT for a diverse mix of indications including malignancies and inborn errors of metabolism as well as 17 PID patients, the overall survival was 93% at 10 years post transplant with a median follow up time of 13.8 years. In this study limited by the diverse mix of patients reported, late effects were seen in 98% of the cohort. In the non-metabolic disease cohort the most common late effects included dental problems (82%), short stature (27%), and moderate cognitive problems (25%) although the median performance on Lansky/Karnofsky scales was 100%. In the overall cohort 72% had normal puberty, 17.6% had abnormal thyroid function and 18.6% had pulmonary dysfunction. After 5 years post-HCT, 17.6 % had persistent cGVHD and more than half of these continued to require either systemic steroid or other immunosuppression (9). The enhanced likelihood of full T and B cell immune reconstitution associated with MAC must be balanced with the potential toxicities and their effects on survival and overall bodily function and quality of life. For babies with SCID who need conditioning, the goal must be to use the least toxic regimen that permits durable immune reconstitution.

In radiosensitive forms of SCID (Artemis, DNA Ligase IV, DNA-PKcs, Cernunnos (XLF or /NHEJ1 deficiency) and Nijmegen Breakage Syndrome(NBS1) the use of alkylator-based conditioning at doses that are myeloablative in non-radiosensitive individuals appears to be associated with significant morbidity and mortality (29,35,36). This risk appears to be higher for LIG4-, NHEJ1- and NBS1- SCID patients compared to PRKDC- or DCLRE1C- SCID patients. 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 (35); there were 2 patients who received no conditioning, and both survived. In a single center study of Artemis-SCID patients, the 4 reported deaths all occurred in patients receiving MMRD with MAC (36). In a large study comparing outcomes in patients with Artemis SCID to those with RAG SCID, overall survival was similar between the two cohorts regardless of conditioning while late effects beyond two years were significantly greater in the Artemis group compared to the RAG patients especially when receiving alkylating chemotherapy (29). The dilemma is that in order to optimize the likelihood of achieving both T and B cell reconstitution it appears that at least some conditioning with alkylating therapy to open marrow niches may be necessary in these (and other) genotypes.

RESEARCH PRIORITIES: CONDITIONING

- Evaluations of pharmacokinetics and pharmacodynamics of all conditioning agents used in HCT for all infants and children, including fludarabine, busulfan, melphalan, treosulfan (still under clinical investigation) and thiotepa.
- Prospective controlled multicenter studies of limiting dose exposures of busulfan, treosulfan and other marrow niche-opening agents with long term follow up of late toxicities.
- Development and use of non-alkylating agents when at all possible especially in the radiosensitive-SCID patient population and approaches such as the use of gene-corrected autologous HCT which will minimize the need for alkylators should be encouraged.
- Prospective, multicenter studies of late toxicity focused on radiosensitive SCID patients
- Development of non-chemotherapy agents that safely and effectively open marrow niches

Immune Reconstitution

Inextricably entwined with survival is the quality and degree of immune reconstitution following HCT for SCID patients. In addition to early survival, good immune reconstitution is also a major contributor to long-term quality of life. Most severe complications such as opportunistic infections, chronic GVHD and autoimmunity are associated with poor immune reconstitution, and contribute to late deaths post HCT. Therefore, assessing the immune reconstitution in a comprehensive and systemic manner so that values can be monitored over time is absolutely crucial, however, there is no single set of accepted assessments that are obtained at specific post-HCT intervals across institutions. Measures of immune reconstitution commonly utilized in clinical practice include assessment of T cell populations, including CD3, CD4, CD8 cells as well as naïve (CD45RA+) and memory (CD45RO+) T cells, but further assessment of thymic output via TRECs or recent thymic emigrants, T cell function (via proliferation studies), diversity of T cell reconstitution (via spectratyping) and determination of T cell subsets (Tregs, iNKT, MAIT cells) may be able to serve an important role in both short and long-term assessment of graft function. B cell reconstitution is also clearly an important facet to examine, and consideration should be given to the underlying genotype since those with IL2RG/JAK3 genotypes have intrinsically dysfunctional B cells, but the autologous B cells of patients with CD3/IL7Ra/ADA SCID genotypes function normally with donor T cells (37). Post-transplant evaluation of B cell function includes presence of CD19 and CD20 B cells and a lack of continued reliance on immunoglobulin replacement therapy, but the ability of the immune system to demonstrate appropriate development of switched memory CD19+/CD27/IgD- cells, normal total immunoglobulins with appropriate responses that are sustained over time to both protein and polysaccharide based vaccine challenges also warrants assessment (37,38). NK cell development and function are also important to assess, and NK cells are often prominent in the first wave of lymphoid regeneration of donor origin post-transplant. There are little data

published on the current status of long term NK cell reconstitution in patients with SCID (5,39). However, lack of NK cell reconstitution post HCT for SCID when seen in patients with IL2RG and JAK3 SCID was not associated with increased risk of infections including HPV (3,39,40). Finally, lineage specific chimerism studies can certainly provide a clearer picture of the duration of donor cells and longevity of the graft.

In all forms of typical SCID, T cells are absent and a primary objective in most reported studies examining immune reconstitution post HCT for SCID has been the quality of the T cell compartment. A number of retrospective and prospective studies have examined the long-term immune status of SCID patients treated with HCT (1, 3, 5, 6, 10–12, 24,29, 41–43) The overall conclusion of these various studies is that successful T cell engraftment is seen in the majority of SCID patients treated with HCT, and that B+ SCID is associated with a better outcome than B- SCID. However, there remain a number of issues that are less well defined including the impact of specific genotype, donor type, age at transplantation, and use of conditioning in the ultimate outcome. In any HCT, there are potentially two waves of T-lymphocyte engraftment. The first occurs due to expansion in the periphery of mature donor T-lymphocytes given in a T-replete allograft, a phase which may not occur in T-depleted transplants. The second wave occurs at approximately 120 days post-transplant as newly developed T-lymphocytes from donor precursor cells emerge from the thymus, having undergone ‘education’ within the recipient thymus (42). The presence of active infection at the time of HCT is associated with poor T cell recovery (6). 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 (5, 43) and that the median time to achieve normal T cell function is 9 months to 1 year (12, 42,44,45). Although initial studies demonstrated a decrease of thymic output over time (46), subsequent studies showed stable T cell reconstitution and thymic output for the majority of patients (1,24,41, 47). There is an overall consensus that 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 are all linked to durable (10–20 years post HCT) T cell reconstitution (3,41,48). Donor origin appears to have no effect on T cell counts beyond 1–2 years post transplant (1, 42). In those patients with low T cells at 1–2 years post HCT, there were higher rates of cGVHD and autoimmunity (3).

The role of conditioning for T cell reconstitution remains controversial. While some but not all studies have found use of a conditioning regimen to be associated with a better T cell reconstitution, the amount of ablative therapy-RIC versus MAC- needed to achieve better T cell reconstitution has varied significantly between studies, with some (6) demonstrating a benefit for both MAC or RIC and others (24) finding that only high doses of busulfan were associated with a higher thymic output. It was also shown that donor myeloid engraftment was associated with better T cell function and better thymic output (1,3, 24). In contrast, in a large population of 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 population (48).

The assessment of B cell reconstitution is the next most commonly reported immunologic outcome in available studies reporting post-HCT immune function in SCID patients with

independence from IVIG being the most common endpoint. Achieving B cell reconstitution requires a longer interval than T cell reconstitution with a median time 1–2 years or more (10,12,49) and B cell function depends on acquisition of T cell function (12). While IL2RG/JAK3 SCID and of course B-SCID requires donor B cell engraftment for normal B cell reconstitution, host B cells can cooperate with donor T cells and function normally in IL7R alpha-deficiency, CD3 chain deficiency and ADA-SCID, and some autosomal recessive SCIDs of unknown molecular type (37). Overall, poor B cell reconstitution defined by continued IVIG dependence is seen rather commonly (Table 1; 15–58%), particularly in IL2RG/JAK3 and RAG forms of SCID (1, 3, 37). In patients who are independent of IVIG, most are able to mount appropriate vaccine responses (3) although this has not be studied in detail in most reports.

Although some patients without a conditioning regimen and without myeloid engraftment may have normal B cell function, use of conditioning and degree of donor myeloid and B cell engraftment are associated with higher likelihood of B cell reconstitution (1,3,6,19). Continued immunoglobulin dependence was associated with more GVHD, infections, autoimmunity, and need for nutritional support (3).

RESEARCH PRIORITIES: IMMUNE RECONSTITUTION

- Identify the most crucial early biomarkers for eventual T, B and NK cell reconstitution and evaluate late biomarkers such as degree of T cell exhaustion or telomere length as well as level of lineage specific chimerism as predictors for long term T and B function, freedom from infection or other long-term morbidities and good quality of life; determine when is the earliest date and what are the correct intervals to use these biomarkers.
- Identify to what degree GVHD prophylaxis slows the rate of immune reconstitution and determine if this has a lasting effect on immune function
- Identify the effect of acute and chronic GVHD on immune reconstitution.
- Define the specific B cell lineage markers, BCR diversity and degree of antibody responses to T cell dependent and independent antigens that predict full B cell reconstitution and ability to discontinue immunoglobulin replacement post HCT.
- Compare immune reconstitution post HCT vs post gene therapy.
- Study prospectively the management of SCID patients who have poor immune reconstitution at varying intervals post HCT to improve outcomes.

Phenotype and Genotype Impact on Late Effects (TABLE 2)

There are a few broad categories of SCID that have been compared in several retrospective long term studies, including the so-called B+ SCID, which include IL2RG, JAK3, IL7Ra, CD3 and CD45 SCID genotypes and the B- SCID, including ADA, RAG1, RAG2, Artemis (DCLRE1C), DNA Ligase IV (LIG4), DNA-PKcs (PRKDC), Cernunnos-XLF deficiency (NHEJ1) and Nijmegen Breakage Syndrome (NBS1) forms of SCID. Within the B- negative group, the latter 5 genotypes are associated with radiosensitivity. SCID forms associated

with defects in purine metabolism, particularly ADA deficiency also warrant separate discussion of their attendant late morbidities. Reticular dysgenesis [due to *AK2* mutations] is generally considered separately given the associated neutropenia in addition to lymphopenia, increased risk of myelodysplastic transformation and sensorineural deafness (50). While many of these differences have already been addressed, here we discuss additional important issues associated with genotype.

Although some studies have shown superior overall survival (4, 46) in B+ vs B- phenotypes of SCID, improved T cell reconstitution in the B+ vs the B- phenotypes has been shown more consistently (3, 4,6,12, 46). 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 (3,6, 12, 24, 41), many of whom will also be B- forms of SCID such as RAG1/RAG2. Some studies also demonstrate improved ability to achieve immunoglobulin independence for ADA, IL7Ra and CD3 deficient forms of SCID in the absence of conditioning (15, 37).

There are certain non-immunologic late effects that are more commonly seen in specific genotypes of SCID which we will review. In particular there have been focused reports on late effects seen in IL2-RG, JAK3, IL-7R, RAG, ADA and Artemis forms of SCID. Severe cutaneous infections with HPV presenting years after HCT are commonly seen in IL-2RG, JAK3 (1,2,3) and some RAG and IL-7R SCID patients (1,3).

ADA deficiency causes SCID but also non-immunologic manifestations secondary to the accumulation of toxic metabolites affecting multiple organ systems. 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 (15); overall survival was stable at 73% in the period from 1991–2000 compared to 2001–2009. Survival was highest in recipients of MRD (83–86%), 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). RIC-HCT had a survival rate of 67% which was not significantly different than unconditioned transplant outcomes. There was no difference in survival between patients who were or were not given PEG-ADA pre-HCT. Neurocognitive impairment, ADHD and other learning challenges are more common in ADA patients irrespective of the use of conditioning prior to HCT. In a study of neurocognitive outcomes in patients treated between 1979–2003 for PID with HCT, including 43 SCID patients of varying phenotype/genotype and 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). There was no difference in IQ with use of MAC vs RIC vs no conditioning, however, this was a small study with a limited number of SCID patients, and reflects patients treated several decades ago (51). Hearing loss is common in ADA SCID (52) and an ADA patient was reported to develop hearing loss even after a successful unconditioned HCT (53). Finally, ADA patients have a higher rate of multicentric dermatofibrosarcoma protuberans (a rare form of skin tumors) than the general population even after HCT (54).

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 Artemis SCID patients to 76 RAG1/RAG2 SCID patients with a median follow up of 8.5 years, the entire cohort demonstrated 85% 2-year survival in MRD HCT recipients who did not receive conditioning and 67% 2- year survival in MMRD HCT recipients who did receive conditioning (29). However, Artemis patients were more likely to have received MMRD donor origin HCT, and RAG1/RAG2 were more likely to have received MAC prior to HCT. Although survival in the two groups was comparable, late effects were seen in 70% of Artemis patients compared to 24% of RAG1/RAG2 patients. Late effects most commonly seen in RAG1/RAG2 patients included cGVHD or autoimmunity (AIHA/ITP/myositis) (18%), and severe or recurrent infections (12%). Less common but still notable in the RAG1/RAG2 group were growth less than the 3rd percentile (9%), need for nutritional support (4%), sequelae of pre-HCT morbidity (4.5%) and death occurring greater than 2 years post-HCT (4.5%). In contrast, amongst the Artemis patients there were higher percentages of patients affected by the same late effects seen in the RAG1/RAG2 group (growth less than the 3rd percentile (49%), severe or recurrent infections(34%), cGVHD/autoimmunity (30%), need for nutritional support (20%), death occurring greater than 2 years post-HCT (10.5%) and sequelae of pre-HCT morbidity (8.5%)). In addition, there was a group of late effects that were uniquely observed in the Artemis group: 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, and in particular, exclusively in Artemis patients who received alkylator-based conditioning. In addition, among the Artemis patients, exposure to alkylators was associated with significantly lower height ($p<0.03$ girls, $p<0.001$ boys). This is most likely linked to the DNA repair defect associated with Artemis-deficiency. There were no malignancies reported over a mean follow up of 10 years. Risk factors of developing any clinical late effect were Artemis genotype, viral infection prior to HCT, treatment with alkylator based conditioning, need for repeat HCT or boost, and need for IVIG. Immunoglobulin replacement was required in 47% of survivors, factors associated with increased risk of need for immunoglobulin included Artemis genotype, poor T cell reconstitution, requirement for additional transplant, absence of alkylator therapy and MMRD donor source.

RESEARCH PRIORITIES: LATE EFFECTS by SCID GENOTYPE

- Conduct prospective multicenter studies of survival and late effects beyond the first 5 years post HCT with sufficient numbers to be able to identify the effects of genotype and phenotype.
- Multicenter prospective natural history studies of ADA SCID patients post HCT with a focus on signs of non-immunologic manifestations of this metabolic disease
- Early diagnosis and recognition of patients with SCID defects associated with increased sensitivity to alkylating agents and ionizing radiation to promote more judicious use of alkylators in this subgroup

Conclusion

While HCT has been used to treat SCID since 1968, patients continue to receive their transplants at multiple centers in the US and Europe utilizing a variety of conditioning regiments varying from none to MAC, with MRD, MMRD, MUD and UCB as the primary donor sources. Improved T cell depletion and HLA typing techniques as well as supportive care have led to improved survival of SCID patients following HCT. Overall, long-term survival is high, particularly in patients transplanted prior to the onset of infection, but late morbidities are fairly common including growth retardation, cGVHD, autoimmune/autoinflammatory complications, and endocrinopathies, which correlate with the age at transplantation, donor type, use of conditioning, and possibly the quality of immune reconstitution, particularly T and B cell. As the ability to treat these patients improves and more patients are identified via newborn screening with both typical and hypomorphic SCID, it will be important for transplant physicians to have available the best data on long term outcomes for patients treated with the available approaches and stem cell sources so that optimal therapy can be individualized for any given patient. Research gaps and priority for future studies are outlined in this document to encourage development of programs to address critical questions and promote data sharing. In a follow up publication, we will specifically address recommendations for post-transplant care and evaluation that both optimize care of the patient and provide sufficient information about their immune status to allow us to understand how best to care for this unique and growing cohort of patients.

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TABLE 1

Summary of large single or multicenter studies comparing survival and morbidities in SCID following HCT

Study	**Mazzolari et al. JACI, 2007**	**Neven et al. Blood, 2009**	**Railey et al. J Pediatrics, 2009**	**Pai et al. NEJM, 2014**
Number of Patients	58 treated 40 in late analysis	149 treated 90 in late analysis	161 treated 111 in late analysis	240 treated and analyzed
Date of HCT, Single vs Multicenter	1991–2002 Single Center	1972–2004 Single Center	1982–2008 Single Center	2000–2009 North American multicenter
Donor Sources (Survival by Source)	MRD 12 (90%) MMRD 33 (61%) MUD 10 (83%) UCB 0 (n/a) Other Related 3 (100%)	MRD 22 (nr) MMRD 51 (nr) MUD 15 (nr) UCB 0 (nr) Other Related 15 (nr)	MRD 16 (100%) MMRD 145 (75%)	MRD 32 (97%) MMRD 138 (79% no conditioning; 66% w/ conditioning) MUD 19 (74%) UCB 43 (58%)
Conditioning Use	None 13 IS 2 MAC* 43	None 46 IS 5 RIC 22 MAC 17	None 161	None 120 IS 39 RIC 35 MAC 46
Median Follow up (range in years)	11y (5.6–16.3)	14 y (2–34)	8.7y (0.5–26)	nr
Overall survival (% at x years)	72.4% at 5 years	63% at 2 years; 9% late-mortality (> 2y post- HCT)	77% overall	74% at 5 years
Infectious Complications	HPV 17.5% Bacterial PNA 7.5% Pneumocystis 2.5%	HPV 25% Sinopulm 5.5% OI 3.3% PNA 2.2% Viral Encephalitis 1.1%	Sinopulm 20% HPV 12% PNA 8% Otitis Media 5%	nr
cGVHD	None	11%	Skin 3.6%	15% at 2y
Autoimmunity	12.5% (AIHA, hypothyroidism, hyperthyroidism)	AIHA 6.6% Fever/cytopenia 3.3% Myositis 2.2% Psoriasis/Alopecia/ Vitelligo 1.1% CD8 Granulomas 1.1%	AIHA 1.8%	nr
Neurocognitive Function	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	>10y/o and normal 93% Psychotherapy 3.3% Developmental Delay/Seizure 1.1% ADHA 1.1% Schizophrenia 1.1%	School Support 3% ADHD 21% CP 2% Seizure Disorder 2% 66% (10/15) College aged & attend college	nr
Growth	Weight <3rd %tile 17.5% Height <3rd %tile 12.5%	Growth Failure 17.7%	Growth Failure 12%	nr
Other Medical Issues	IVIG/Antibiotic PPX/both 15% Dental Issues 7.5%	IVIG 21% Diarrhea/Poor oral feeding 20% All patients >15y/o completed puberty –2 patients have children following unconditioned HCT –1 patient achieved pregnancy post RIC	IVIG 58% Antibiotic PPX 27% Chronic Diarrhea 14% Poor oral feeding 5% Rashes 25% Asthma 14%	nr

nr= not reported, IS= Immunosuppression, AIHA=Auto Immune Hemolytic Anemia, PNA= Pneumonia, OI= Opportunistic Infection, PPX=prophylaxis, CP= Cerebral Palsy

* MAC with Busulfan/Cytoxan

TABLE 2

Known data regarding late effect risks in specific genotypes and the impact on alkylator therapy on those risks

SCID Genotype	Late Effects Compounded by Conditioning Use (Busulfan/ Alkylator)	Late Effect Risks Lowered by Conditioning Use (Busulfan/ Alkylator)	No Known Conditioning effect on Late Complication
IL2-RG, JAK3		IVIG dependence (longterm)	Warts
IL-7R, CD3, CD45			Warts (IL-7R)
RAG1/RAG2		Durability of T cell reconstitution; IVIG dependence (longterm)	
Artemis/Other radiosensitive SCID *With regard to radiosensitive SCID (RS) genotypes: PRKDC, LIG4, NHEJ1, and NBS1 patients may be even more sensitive to alkylators than ART-SCID patients	Fertility Concerns, Skeletal Growth, Dental Complications (delayed/ absent eruption, abnormal shape, abnormal enamel) Hypothyroidism For RS-SCID, poorer survival with MAC vs RIC	Durability of T cell reconstitution; IVIG dependence (longterm)	
ADA	Decreased survival associated with intensity of conditioning		Neurocognitive Impairment (learning challenges, ADHD) Hearing Impariment
Others			Hearing impairment (AK2/Reticular Dysgenesis)