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B Cell Function in Severe Combined Immunodeficiency after Stem Cell or Gene Therapy: A Review

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Abstract

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

Introduction

Severe combined immunodeficiency (SCID) is a fatal syndrome of diverse genetic cause characterized by profound deficiencies of T and B cell function and, in some types, also of NK cells and function.¹ This condition is uniformly fatal in the first two years of life unless immune reconstitution can be accomplished.^{1–5} SCID is currently known to be caused by mutations in at least 13 different genes. X-linked SCID is caused by defects in the common gamma chain (γ c)(Table 1).⁶ Mutations in the genes encoding adenosine deaminase (ADA),⁷ Janus kinase 3 (Jak3),⁸ the α chain of the IL-7 receptor (IL7R α),⁹ recombinase activating genes 1 or 2 (RAG1 or RAG2),¹⁰ CD45,¹¹ 12 the Artemis gene,¹³ ligase IV,¹⁴ DNA protein kinase catalytic subunit (DNA-PKcs),¹⁵ CD3 δ ,¹⁶ CD3 ϵ ,¹⁷ or CD3 ζ ¹⁸ also result in SCID and are inherited as autosomal recessive traits (Table 1).

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

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

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

B Cell Chimerism, B Cell Function and Immunoglobulin Replacement After Bone Marrow Transplantation

Table 2 lists the studies discussed below. It should be noted that: 1) Most reports are from Europe; it has been the policy in European centers for many years to use pre-transplant chemotherapeutic conditioning and post-transplantation GVHD prophylactic immunosuppressive drugs for most SCIDs who do not have an HLA-identical donor. By contrast, the author's Center has never used pre-transplant conditioning or post-transplantation GVHD prophylaxis for SCID, and the Baylor and UCSF teams have performed some SCID transplants with and some without conditioning. 2) The European Centers generally have a higher percentage of HLA identical transplants (38%)²⁴ than the US Centers (21% at Baylor, 6% at Duke).^{1,5,30,31} 3) Some of the studies reported outcomes according to the lymphocyte phenotype (i.e., T-B- or T-B+),^{23,24,32} whereas most of the recent studies listed in Table 2 reported the outcomes by molecular type (when known).^{2,4,5,26-31,33-35} It has been suggested for a number of years now that the need for post-transplantation IG replacement is due to a lack of donor B cell engraftment, and this in

turn has been attributed to a lack of pre-transplant chemoablative conditioning, although data to support this premise have been far from clear.

Single Center Studies

University of California, San Francisco Reports—Among the earliest SCID transplant outcome studies in the past 2 decades was the report by Dror et al²³ who examined immune function in 14 surviving SCIDs from a total of 24 (58% survival rate) who had received T cell-depleted haploidentical parental bone marrow transplants from 1982–1991 at UCSF. Seventeen of the 24 had received pre-transplant conditioning. Two of 11 survivors were found to have B cell chimerism, 10 of 14 had B cell function and 7 of 14 (50%) were receiving IG replacement therapy. Thus, from this small series, it appeared that B cell chimerism did not occur often in SCID recipients of haploidentical bone marrow transplants, although 71% of the recipients had received pre-transplant chemotherapy.

O'Marcaigh et al³⁶ subsequently reported this group's experience in transplanting 16 infants with Athabascan SCID between 1984 and 1999. All but 3 received pre-transplant conditioning of various types. Twelve children (75%) survived with T cell reconstitution at a median follow-up of 7 years. However, only 3 had donor B cells and B cell function, one of whom did not receive pre-transplant conditioning. Nine of the 12 survivors were receiving IVIG replacement therapy. It is of note that only 1 of 6 of the SCIDs who received genotypically identical marrow developed B cell function and that infant did not receive pre-transplant conditioning. The authors also point out that Athabascan SCID infants are highly susceptible to the toxic effects of radiation and chemotherapy. The 4 who died had received myeloablative conditioning with either radiation or busulfan, and 2 of 8 who had received cytotoxic chemotherapy failed to develop secondary teeth.

More recently, this group reported the results of transplanting megadoses of CD34+ haplocompatible stem cells into 15 infants with SCID who had received non-myeloablative pre-transplant conditioning.³⁴ The overall survival rate was 13 of 15 or 87% with a median follow-up of 39 months. While T cell reconstitution occurred in all, B cell chimerism developed in only 4 recipients, B cell function developed in only 5 (33%) and 7 were receiving IG therapy. The authors concluded that this approach was useful for ensuring T cell engraftment and function but was of no value for improving B cell reconstitution.

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

Los Angeles Children's Hospital Report—Smogorzewska et al³⁷ reported on the results of marrow transplantation in 37 SCID infants given T cell-depleted haploidentical bone marrow transplants at LA Children's Hospital from 1984–1997. All received pre-transplant conditioning. Seventeen of the 37 (46%) were surviving and all had T cell function. Data on B cell chimerism and function were not reported, but 5 of the 17 (29%) were receiving IVIG.

Hopital Necker Reports—One of the first studies to examine factors that contribute to development of B cell function post-transplantation was that of Haddad et al³³ from the

Hopital Necker, Paris, France, who reported on 22 B+ SCID patients (14 X-linked, 4 Jak3 deficient and 4 of unknown molecular type), 5 of whom had received HLA-identical bone marrow transplants and 17 of whom had received T cell-depleted haploidentical bone marrow transplants between 1976 and 1995. Only 4 of the 22 (18%) patients had donor B cells, yet 12/22 (55%) were reported to have normal B cell function and 11 (50%) were receiving IgG replacement, including 2/5 (40%) of the HLA-identical marrow recipients. Nine of the 17 haploidentical recipients received pre-transplant conditioning with 8 mg/kg busulfan and 200 mg/kg cyclophosphamide, but the authors found that use of the conditioning regimen neither promoted B cell engraftment nor affected B cell function. Three of the four with donor B cell chimerism had received conditioning. The authors concluded that, in some transplanted patients, host B cells can cooperate with donor T cells to fully mature into immunoglobulin producing cells.

Cavazzana-Calvo et al²⁶ in their report on longterm T cell reconstitution in patients with T cell immunodeficiency disorders who had received bone marrow transplants between 1971 and 1991 at the Hopital Necker, did not provide data on B cell chimerism or B cell function. However, they reported that 13 of the 31 (42%) SCID patients who were more than 10 years post-transplantation required IgG replacement therapy. Six of the 13 requiring IVIG had received pre-depleted transplant conditioning. The authors also noted that the presence (or not) of good thymic output did not correlate with whether there was B cell reconstitution.

Neven et al's³⁵ most recent report from that group covered all 149 SCID patients transplanted at the Hopital Necker between 1972–2004. While myeloid chimerism results were presented, no data were provided for B cell chimerism. Fifty-four of the 82 survivors (67%) were reported to have good B cell function and 17/82 (21%) were said to be receiving IG replacement therapy. However, the overall survival rate was 58%, and eight of the 67 deaths occurred late.

Brescia, Italy Report—Mazzolari et al²⁷ studied 40 patients with severe T cell deficiency transplanted between 1991 and 2003 who were surviving more than 5 years post-transplantation. All had received pre-transplant conditioning except for 5 who received HLA-identical sibling transplants and 3 who received T cell-depleted haploidentical in utero transplants. Twenty-seven of the 40 (68%) had B cell chimerism and 33 of the 40 (83%) had B cell function. Only 5 were receiving IgG replacement: 2 who had received in utero transplants, 1 who had received pre-transplant conditioning with busulfan, cytoxan and thiotepa, 1 who had received ATG and cytoxan, and 1 who had received ATG alone. One of the infants with IL7R alpha chain deficient SCID who received an in utero T cell-depleted haploidentical transplant did not have donor B cells but developed normal B cell function and did not require IG replacement.³⁸ Endocrine and severe neurologic abnormalities were observed in 17.5% and 10%, respectively.

Newcastle upon Tyne, England Report—Slatter et al²⁹ studied 36 patients who had been transplanted with maternal, paternal or unrelated bone marrow depleted of T cells with anti-CD52 (N=19) or were given positively selected CD34+ cells (N=19). All but two of the patients had received pre-transplant conditioning. Nineteen of the 36 (53%) had B cell chimerism, 25 of the 36 (69%) had B cell function and 11 of the 36 (31%) were requiring IgG replacement therapy. Thus, pre-transplant conditioning did not ensure that B cell chimerism or B cell function would occur uniformly. There was no difference in donor B-lymphocyte chimerism with the type of marrow received, but significantly more patients given anti-CD52–treated marrow had class-switched memory B lymphocytes (P = .024), normal IgG levels, and normal antibody responses to tetanus and Haemophilus influenzae type B vaccination. More patients with common γ chain or Jak-3 deficient SCID given anti-CD52–treated marrow had donor B lymphocytes. The authors concluded that the results

imply more incomplete donor chimerism and less B-lymphocyte function in patients given positively selected CD34+ marrow cells than in those who received anti-CD52-treated marrow. The question arises as to whether some other types of cells (dendritic cells, CD34 negative stem cells, etc.) in the anti-CD52 T cell-depleted marrow promoted B cell development. Those cell types would all be missing from CD34+ selected cells. Since the overall number of transplants performed at that center was not provided, the mortality rate is unknown.

University of Ulm, Germany Report—Friedrich et al²⁸ studied 31 SCID children out of 50 surviving recipients (from a total of 82, survival rate 61%) given bone marrow transplants between 1982 and 1995 at their institution. They compared three groups: the first was an HLA-identical marrow recipient group (n=6), the second was a non-conditioned haploidentical group (n=12) and the third was a conditioned haploidentical group (n=13). There were differences among the three groups with regard to B cell chimerism: all of the HLA-identical recipients and all but two of the conditioned haploidentical marrow recipients had donor B cells, whereas only two of the non-conditioned haploidentical marrow recipients had donor B cells. The authors also reported on CD34 bone marrow chimerism in 24 of the 31 patients: 1 of 4 HLA identical marrow recipients, 1 of 9 non-conditioned recipients of haploidentical marrow and 9 of 11 conditioned haploidentical recipients had donor CD34+ cells in their bone marrow. The authors noted a strong correlation between the presence of CD34 marrow chimerism and the persistence of B cell immunity. However, data on B cell function were not presented. Ten of the 31 patients (32%) were receiving IVIG; eight of the latter patients were from the non-conditioned group.

Baylor University Reports—More recently, Patel et al³⁰ reported on the longterm status of 20 infants with SCID who were given anti-CD6 T cell-depleted marrow from a parent and of 5 more who had received unfractionated HLA-identical sibling marrow between 1981 and 1995. None of the patients received pre-transplantation chemotherapy or GVHD prophylaxis. Ten of the 20 patients (50%) who received haploidentical marrow were surviving, as were all 5 of those who received HLA identical marrow. Chimerism was analyzed in 8 patients and 4 (50%) were found to have donor B cells, 3 of whom had received T cell-depleted haploidentical marrow and 1 of whom had received HLA-identical unfractionated marrow. Seven of the 15 (47%) survivors were reported to have normal antibody responses to vaccines, 5 of whom had received T cell-depleted haploidentical marrow and 2 of whom had received unfractionated HLA-identical marrow. Seven of the 15 (47%) were receiving IG replacement, including two who had received HLA-identical marrow.

In a more recent paper from the same center, Patel et al³¹ reported on the 9 year outcome of 23 additional SCID patients who had received bone marrow transplants from 1998–2007, 18 of whom had received either anti-CD6, anti-CD8 and anti-CD20 T cell depleted marrow or CD34+ cell-selected haploidentical related marrow stem cells (n=10), matched or mismatched unrelated donor marrow (n=7) or CD34+ cell selected unrelated marrow stem cells (n=1). Seventeen of the 18 had received pre-transplant conditioning. Thirteen of the 18 (72%) who received the mismatched transplants survived, as did all 5 of those receiving HLA identical marrow. B cell chimerism was reported in 11 of the 18 survivors, B cell function was deemed normal in 11 of the 17 (65%) studied and of the 18 (33%) were receiving IG replacement. In this paper, the authors compared the patients in this and in the first report discussed above³⁰ for multiple outcome variables. The three groups compared were the 17 SCID patients who had been given pre-transplant conditioning for their mismatched transplants, the 21 who had received no pre-transplant conditioning for their mismatched transplants and the 10 patients who had received unfractionated HLA-identical sibling marrow. There was a difference in overall survival, with 100 % of the patients who

received HLA-identical sibling marrow surviving, 70% of the mismatched conditioned patients and 62% of the non-conditioned mismatched group surviving. There was a statistically significant survival difference ($p=.04$) for the matched related donor recipient group when compared to each of the last two groups, but not when the last two groups' survival rates were compared with each other. More importantly, the authors found no significant differences in the rates of donor B cell engraftment, development of B cell function or in the numbers of patients receiving IG replacement among the 3 groups. They concluded that pre-transplant conditioning did not reduce dependence on IVIG infusions for haploidentical recipients.

Duke University Reports—The first report of the long term outcome of SCID bone marrow transplantation at the author's center was published in 1999 and included all transplants performed from 1982–1998.² Eighty-nine patients had been transplanted at that time, and 72 (81%) were surviving. Only 12 (13%) of the 89 had HLA-identical related donors; the other 77 (87%) received rigorously T cell-depleted haploidentical parental marrow. None of the patients had been given pre-transplantation chemotherapy or post-transplantation GVHD immunosuppressive drugs. Twenty-six of the 72 (36%) had donor B cells, 33 (46%) had isohemagglutinins and 45 of the 72 (63%) were receiving IVIG.

One of the observations from the above study was that SCIDs transplanted in the first three and one half months of life had a much higher survival rate than those transplanted after that time. In a report published in 2002, Myers et al³ studied immune reconstitution in the 21 SCIDs who had been given non-ablated HLA-identical ($n=2$) or rigorously T cell-depleted haploidentical parental marrow transplants ($n=19$) in the neonatal period at this center from 1982 to 2001 to seek an explanation for the better survival rate. While a remarkably superior survival rate (95%), earlier and higher T cell reconstitution and greater thymic output were found in the neonatally transplanted SCIDs as compared to those transplanted after that age, there was no difference in the attainment of B cell reconstitution. Donor B cell chimerism was found in 9 of the 20 (45%) survivors, normal IgA was found in 9 (45%) and 13 of the 20 (65%) were receiving IG replacement therapy.

In one of two recent longterm (>26 years) studies from this center, 41 of 128 (32%) survivors (5 of whom had been transplanted at other institutions) had B cell chimerism.⁴ None of the patients had been given pre-transplantation chemotherapy or post-transplantation GVHD immunosuppressive drugs. However, donor B cell engraftment was present in approximately one third of the X-linked SCIDs despite the lack of conditioning.⁴ Only 16 of the patients had received HLA-identical related marrow, all of the rest had received T cell-depleted haploidentical marrow. B cell function was not reported in that paper, which focused on longterm T cell reconstitution and thymic output, but 70 of the 128 (55%) were receiving IG replacement therapy. In our most recent longterm report⁵ of SCID transplants at this center from 1982–2008, there were 124 survivors out of 161 transplanted (77%). While B cell function and chimerism were not reported in that paper, 64 of the 111 (58%) recipients contacted for longterm clinical outcome characteristics were receiving IG replacement therapy. However, the percentage requiring IG varied based on molecular defect. Only 27% of the IL-7 receptor alpha chain deficient patients required IG, while 83% of RAG deficient patients and 72% of X-linked SCID patients required replacement. Thus, the molecular type of SCID appears to be an important determinant of B cell development post-transplantation, whether or not there is B cell chimerism.

Multi-Center Studies

Bertrand et al³² reported on the results of 214 T cell-depleted haploidentical bone marrow transplants given to 178 SCID infants transplanted in 18 centers in Europe between 1981

and 1995. The disease-free survival was significantly better for B+ SCID patients (60%) than for B- SCID patients (35%, $p=.002$), with median follow-ups of 57 and 52 months, respectively. Pre-transplant conditioning was given for 66% and 75% of patients in the two groups, respectively. However, no information on B cell reconstitution was presented in that report.

Antoine et al²⁴ reported on the outcomes of stem cell transplants performed in 475 SCID patients at 37 centers in 18 countries in Europe between 1968 and 1999. The overall survival rate in the 181 who received HLA-identical marrow was 77%, but the overall survival rate in 294 recipients of non-identical stem cells was only 54%. Pre-transplant conditioning was used for all but 107 HLA-identical related donor transplants, 87 mismatched transplants and 11 unrelated donor transplants. No data were reported on B cell chimerism or B cell function, but 12% of the recipients of HLA-identical marrow and 34% of the recipients of non-identical marrow were receiving IG replacement therapy.

B Cell Function and Immunoglobulin Replacement After Gene Therapy

Over the past decade, significant progress was made toward gene therapy for X-linked and ADA-deficient SCID. Investigators at the Hôpital Necker in Paris, France treated 11 patients with X-linked SCID with gene-corrected autologous bone marrow cells.³⁹ Nine infants developed normal T and B-cell functions after the treatments. The nine patients who acquired normal immune function did not require intravenous immunoglobulin infusions and were at home without any medication.⁴⁰ Subsequently, investigators in London reported success with a similar gene therapy protocol for X-linked SCID.⁴¹ However, four of the 10 patients treated in London have poor B cell reconstitution and are dependent on immunoglobulin supplementation. Unfortunately, serious adverse events with this therapy occurred in four patients treated at the Hôpital Necker and in one patient treated in London.⁴² These patients developed leukemias or lymphomas due to a process called insertional oncogenesis. Four of these patients responded to conventional chemotherapy regimens and are presently in remission. Before these cases, malignant changes had not been seen in any human beings given retroviral vectors for gene transfer. Considering the success of bone marrow transplantation for recipients of HLA-matched related donor grafts and for those who are treated in early infancy, new gene therapy trials for X-linked SCID are now being developed with the objective of reducing their oncogenic potential.⁴³

Gene therapy trials for ADA deficiency were initiated in the early 1990's, with only modest success. Recently, two European research groups reported gene therapy trials for ADA deficiency using low dose busulfan pre-therapy without PEG-ADA or (in those patients who were on it) withdrawing the enzyme for a few weeks before infusion of the gene-modified cells.⁴⁴⁻⁴⁵ Eleven of the 15 patients treated with this approach (10 in Italy and 5 in London) showed good immune reconstitution. In the Italian series, IG replacement was discontinued in 5 patients and all 5 were able to produce antibodies normally to their vaccine antigens. Of note, there have not been cases of leukemia or lymphoma in the ADA-deficient SCIDs who have been corrected by gene therapy, although insertions of gene vectors near oncogenes similar to the X-linked SCID trials have been observed.

Summary

From the above studies it can be seen that pre-transplant conditioning of SCID infants who do not have a matched sibling donor does not always result in B-cell function. Data on B cell function and chimerism were lacking in many studies, so it will be important to detail these more completely in future reports. The question arises as to why infants who do not have a matched sibling donor should be treated differently than SCIDs who do have an HLA-identical related donor. The latter are usually not given pre-transplant conditioning yet

often achieve good immune reconstitution, frequently without donor B cells and usually without donor myeloid cell chimerism. The reason for the difference in success in achieving B cell immune reconstitution in the matched versus mismatched transplants is not known. It also appears that the molecular type of SCID has an important influence on whether B cell function develops after transplantation. What other factors might have an impact are not clear. It is possible that the development of some degree of GVHD favors development of donor B cell chimerism and function. Whether intercurrent infection at the time of transplantation has a negative influence on emergence of B cell function is unknown.

The principal causes of death in SCID infants are viral infections for which there is no effective antibiotic. When one administers conditioning agents that damage the innate immune system of SCID infants who present with one or more such viral infections, the expectation is that this would increase the mortality rate. As seen in Table 2, the mortality rates are highest at those centers where pre-transplant chemotherapeutic conditioning is usually administered, with or without post-transplantation GVHD prophylactic immunosuppressive drugs. Thus, when one is considering whether to use pre-transplantation chemoablation, the associated risks may not justify giving these drugs to attempt B cell reconstitution, and the same goes for post-transplantation immunosuppressive agents that interfere with immune reconstitution. In addition to removing innate immune components and increasing susceptibility to infection, there are also longterm toxicities from conditioning agents, including neutropenia, red cell and platelet transfusion-dependency, mucositis, veno-occlusive disease, busulfan lung disease, growth suppression, endocrine abnormalities, sterility and a 15% risk of later malignancy.⁴⁶ As noted above, in SCIDs with mutations that cause radiation sensitivity, the side effects of pre-transplant conditioning are even more devastating.³⁶ Finally, now that newborn screening for SCID has been recommended, it will be particularly important to avoid these toxic agents when transplants are performed in the very early months of life.

Key Concepts and Therapeutic Implications

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

Key Words and Abbreviations

SCID	Severe combined immunodeficiency
ADA deficiency	Adenosine deaminase deficiency
Jak3 deficiency	Janus kinase 3 deficiency

RAG1, RAG2 deficiencies	Recombinase activating genes 1 and 2 deficiencies
IL7R α deficiency	IL-7 receptor alpha chain deficiency
DNA-PKcs	DNA protein kinase catalytic subunit
GVHD	Graft-versus-host disease
HSCT	Hematopoietic stem cell transplantation
IG therapy	Immunoglobulin
MUDs	Matched unrelated donors
BMT	Bone Marrow Transplant
TRECs	T cell receptor recombination excision circles

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Table1**Thirteen Abnormal Genes in SCID**

• Cytokine Receptor Genes	Lymphocyte Phenotype
– <i>IL2RG</i>	T-B+NK–
– <i>JAK3</i>	T-B+NK–
– <i>IL7Rα</i>	T-B+NK+
• Antigen Receptor Genes	
– <i>RAG1</i>	T-B–NK+
– <i>RAG2</i>	T-B–NK+
– <i>Artemis</i>	T-B–NK+
– <i>Ligase 4</i>	T-B–NK+
– <i>DNA-PKcs</i>	T-B–NK+
– <i>CD3δ</i>	T-B+NK+
– <i>CD3ϵ</i>	T-B+NK+
– <i>CD3ζ</i>	T-B+NK+
• Other Genes	
– <i>ADA</i>	T-B–NK–
– <i>CD45</i>	T-B+NK+

Table 2

Center	Chemoablation Used in Non-Identical Transplants	Overall Survival	Table	Donor B Cells Present	B Cell Function	Number (%) On Immunoglobulin
Antoine et al. ²⁴ Europe (1968–1999)	Yes	475 SCIDs 77% in 181 HLA Id, 54% in 294 non- Id		Not Reported	Not Reported	12% of the Identicals 34% of the non- Identicals
Cavazzana-Calvo et al. ²⁶ Paris, France, (1971–1995)	Yes	55/88 (63%) 31 studied, 11 HLA Id 20 non Id		Not Reported	Not Reported	13/31 (42%)
Dvoretz et al. ³⁴ UCSF (2001–2007)	Yes, non-myeloablative	13/15 (87%) All non-Id		4/15 (27%)	5/15 (33%)	7/15 (47%)
Dror et al. ²³ UCSF (1982–1991)	Yes in 17/24 (71%)	14/24 (58%) 14 studied All non-Id		2/11 (18%)	10/14 (71%)	7/14 (50%)
Friedrich et al. ²⁸ Ulm, Germany, (1982–1995)	Yes	50/82 (61%) 31 studied 6 HLA-Id, 25 haplo- id		19/31 (61%)	Not Reported	10/31 (32%)
Haddad et al. ³³ Paris, France (1976–1995)	Yes	22 5 HLA Id, 17 non-Id		4/22 (18%)	12/22 (55%)	11/22 (50%)
Mazzolari et al. ²⁷ Brescia, Italy (1991–2003)	Yes	42/58 (73%) 40 studied, 10 HLA-Id, 20 non-Id, 10 MUD		(27/40) 68%	33/40 (83%)	5/40 (13%)

Center	Chemoablation Used in Non-Identical Transplants	Overall Survival	Table	B Cell Function	Number (%) On Immunoglobulin
Neven et al ³⁵ Paris, France, (1972–2004)	Yes	86/149 (58%) 90 studied, 37 HLA-Id, 51 non-Id, 2 MUD 8 died late	Not Reported	54/82 (67%)	17/82 (21%)
O'Marcaigh et al ³⁶ CSF (1984–1999)	Yes	12/16 (75%) 7 HLA-Id, 9 non-Id	3/12 (25%)	3/12 (25%)	9/12 (75%)
Patel et al ³¹ (Baylor, USA, 1998–2007)	Yes (mostly)	18/23 (78%) 5 HLA-Id, 10 non-Id, 6 MUD, 1 IMMUD, 1 MUD Cord	11/18 (61%)	11/17 (65%)	6/18 (33%)
Slatter et al ²⁹ (UK, 1987–1994)	Yes	36 All Haplo-Id	19/36 (53%)	25/36 (69%)	11/36 (31%)
Smogorzewska et al ⁴⁶ Los Angeles Children's, 1984–1997)	Yes	17/37 (46%) All Haplo-Id	Not Reported	Not Reported	5/17 (29%)
Van Leeuwen et al ⁴⁷ (Netherlands, 1968–1992)	Yes	15/31 (48%) 10 HLA-Id, 19 haplo-Id, and 2 MUD	10/15 (67%)	14/15 (93%)	Not Reported
Buckley et al ² Duke University, USA (1982–1998)	No	72/89 (81%) 12 HLA-Id, 77 haplo-Id	26/72 (36%)	33/72 (46%) had iso-hemagglutinins	45/72 (63%)

Center	Chemoablation Used in Non-Identical Transplants	Overall Survival	Table	B Cell Function	Number (%) On Immunoglobulin
Myers et al ³ (Duke University, 1982–2001)	No	20/21 (95%) 2 HLA-Id, 19 haplo-Id	9/20 (45%)	9/20 (45%)	13/20 (65%)
Patel et al ³⁰ (Baylor, USA, 1981–1995)	No	15/25 (60%) 5 HLA-Id, 20 haplo-Id	4/8 (50%)	7/15 (53%)	7/15 (47%)
Railey et al ⁵ (Duke University, 1982–2008)	No	124/161 (77%) 111 studied, 15 HLA-Id, 96 haplo-Id	Not Reported	Not Reported	64/111 (58%)
Sarzotti-Kelsoe et al ⁴ (Duke University, 1982–2007)	No	123/158 (78%) plus 5 transplanted elsewhere, 16 HLA-Id, 112 haplo-Id	41/128 (32%)	Not Reported	70/128 (55%)