REVIEW ARTICLE

# Stem Cell Transplantation for Treatment of Primary Immunodeficiency Disorders

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## ABSTRACT

Primary Immunodeficiencies constitute a group of highly complex congenital disorders most of which are characterized by a very poor prognosis. Allogeneic hematopoietic stem cell transplantation (HSCT) has become an established curative treatment approach in many of these disorders, which may be permanently corrected. In this presentation basic and practical aspects of HSCT are presented, with an emphasis on its application in lymphocyte disorders such as severe combined immunodeficiency (SCID). Optimal results and outcome of HSCT are highly dependant on early and correct diagnosis of these rare disorders, and HSCT should usually be applied early in the course of the disease in order to prevent irreversible complications from infections. Clinical results will be summarized based on recent analysis performed in large patient cohorts, which have shown steady improvements and have led to a marked change in the prognosis of patients with primary immunodeficiencies.

**Keywords:** Immunologic Deficiency Syndromes; Severe Combined Immunodeficiency; Stem Cell Transplantation

## INTRODUCTION

Primary immunodeficiency disorders (PID) constitute a group of hereditary diseases characterized by abnormalities of host defense mechanisms. The prognosis in affected patients usually is very poor. Allogeneic bone marrow transplantation (BMT) and hematopoietic stem cell transplantation (HSCT), respectively offers the chance to establish a new, donor derived immune system, therefore reversing this poor prognosis. Since the initial successful application in 1968 in two patients with SCID,[1,2] transplantation has gained an increasingly fundamental role in the management of these rare disorders.

Results can now be analyzed on the basis of larger patient cohorts, and have shown continuous improvement of the outcome, with long-term follow-up indicating permanent correction of the diseases.[3-5]

Importantly, this curative treatment can be applied for a broader spectrum of patients with less restricted donor selection, including unrelated and HLA-mismatched family donors. In this article, several aspects of HSCT in the treatment of primary immunodeficiencies are presented, with an emphasis on the outcome in patients with severe combined immunodeficiency diseases (SCID) and the mechanism of immune reconstitution.

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### The Spectrum of Primary Immunodeficiencies Treated by HSCT

Primary immunodeficiency disorders that are correctable by HSCT are shown in Table 1. A major group is due to deficient development and differentiation of lymphocytes, resulting in combined immunodeficiencies for both T and B cells, for which the term "severe combined immunodeficiency, SCID" is used. A second group of diseases comprises functional defects of mature effector cells involved in immune responses, including phagocyte and cytotoxic functions. Diseases caused by defects of lymphocyte homeostasis and immunoregulation, which manifest as autoimmune and as lymphoproliferative disorders, constitute the third group.

**Table 1. Immunodeficiencies treated by stem cell transplantation.**

**Defects of lymphocyte development/differentiation**

- SCID $B^{(+)}$ *(γc, JAK-3, IL-7Rα)**
- SCID $B^{(-)}$ *(RAG-1, RAG-2, Artemis)*
- SCID with enzyme deficiencies *(ADA, PNP)*
- SCID with ZAP-70 deficiency *(ZAP-70)*
- MHC-class-II-expression defects *(RFXAP, CIITA, RFX5, RFXANK)*
- SCID with agranulocytosis (Reticular Dysgenesis) *(?)*

**Defects of effector cell functions**

*migration / adhesion*

- Wiskott-Aldrich-Syndrome *(WASP)*
  Leukocyte adhesion defect *(CD18/ β2 Integrin)*

*intracellular pathogen killing*

- Chronic Granulomatous Disease *($GP91^{phox}$, $p22^{phox}$, $p47^{phox}$, $p67^{phox}$)*
- IFN-γ/ IL-12 signal blockage *(IFN-γR1, IFN-γR2, IL-12P40, IL-12Rβ1, Stat1*

*cytotoxicity / cytolysis*

- Lymphohistiocytosis *(Perforin)*
- Chediak-Higashi-Syndrome *(Lyst)*
- Griscelli-Syndrome *(RAB 27°)*
- XLP (Purtilo Syndrome)*(SAP)*

**Defects of immune regulation**

- ALPS ***(TNFR, FASL, Caspase-10)***
- IPEX Syndrome *(FoxP3)*

* indicates genes involved in the disorder

* SCID severe combined immunodeficiency; JAK Janus Activated Kinase; IL-7Rα Interleukin 7 receptor α chain; RAG 1 /2 Recombination Activation Gene 1/ 2; ADA adenosine deaminase; PNP purine nucleosid phosphorylase; ZAP 70 Zeta associated protein 70; CD3γ/CD3ε γ/ε chain of the CD3–complex; MHC major histocompatibility complex; XLP X-linked lymphoproliferative; ALPS autoimmune lymhoproliferative syndrome; IPEX immunodysregulation, polyendocrinopathy, enteropathy, x-linked

Most congenital immunodeficiencies are due to monogenetic defects, and in the majority the molecular basis has been clarified during recent years.[6,7] Understanding of the molecular mechanisms has many implications, in particular for more precise classification and diagnosis, including prenatal diagnosis. It also has opened possibilities of novel treatment strategies by gene manipulation.[8-10]

SCID constitutes the most serious immuno-deficiency and is characterized predominantly by complete lack of specific immune functions.[11-13] The diagnosis is considered a medical emergency because of the extreme threat of patients to rapidly develop fatal infections, which can not be overcome without effective immune functions. SCID is not a single disorder but rather a group of genetically distinct entities. Prior to the identification of the underlying genetic abnormalities, the various SCID forms were distinguished on the basis of differences in phenotype and function of circulating lymphocytes, differences in inheritance, which may be autosomal recessive or X-linked recessive, as well as presence or absence of accompanying enzyme deficiencies. By immuno-phenotyping of blood lymphocytes, two main forms are delineated: one with an autosomal recessive inheritance characterized by the absence of T and B lymphocytes but the presence of normal natural killer (NK) cells [B(-)SCID]; a second, associated both with an X-linked or an autosomal recessive mode of inheritance, which is characterized by the absence of T cells but the presence of nonfunctional B cells [B(+)SCID]. In 1993, two groups independently demonstrated the association of X-linked SCID, the most common variant, with mutations of the gene encoding the common gamma chain, a molecule associated with multiple cytokine receptors, including those for IL-2, IL-4, IL-7, IL-9 and IL-15.[14,15] The molecular basis of autosomal recessive forms of B(+) SCID include mutations in the gene encoding JAK3, a signaling molecule associated with the common gamma chain, and mutations in the IL7R α gene.[16-18] Defects in genes involved in V(D)J recombination during T-cell receptor and immunoglobulin synthesis cause B(-) SCID, and include the recombinant-

activating genes (RAG) 1 and 2, and the more recently described Artemis gene.[19,20]

An unusual feature in SCID patients, which may contribute significantly to phenotypic variation and also can misguide definition of the patient`s HLA haplotypes and thus donor selection, is the presence of transplacentally derived maternal T cells.[21] These maternal T cells can be detected in the blood in over 50% of the patients and may initiate characteristic complications of graft versus host disease (GVHD). [22]

**Specific Aspects of HSCT in SCID**

For the treatment of SCID patients by HSCT, several specific aspects have to be considered. One is the application of transplantation without the use of preparative conditioning, which is based on the absent or low capacity of SCID patients to reject foreign cells. Another is the use of HLA-nonidentical family donors, an approach, which has become almost standard in SCID patients since its introduction 20 years ago. [23,24]

In contrast to grafts from HLA-nonidentical family-donors, marrow grafts from HLA-identical siblings are infused without prior manipulation and contain both mature donor T and B cells. Specifically T-cells can markedly expand in the recipient and are responsible for an effective early immunological reconstitution after transplantation, independent of the thymus. It is important to note that in SCID, transplanted from matched siblings, the rate of complicating GVHD is low and immunosuppressive GVHD prophylaxis is usually omitted, thus additionally favoring a rapid immunological recovery. Patients commonly show a prompt clinical improvement within a few weeks after transplantation and susceptibility to develop serious infections is resolved.

The use of HLA-nonidentical donors for HSCT requires depletion of T cells from the graft in order to prevent an otherwise fatal GVHD. A markedly different kinetics and quality of immune reconstitution is observed, being delayed for several months. This delay reflects the absence of expandable mature lymphocytes in the graft and the time required for effective intrathymic T cell maturation. Patients undergo an extended period of profound and continued immunological incompetence after transplantation. Furthermore, donor cell development usually remains restricted to the T cell system and the majority of patients remain without effective B cell immunity even after extended observation times, necessitating regular immunoglobulin substitution.

In these cases an unusual and unique pattern of chimerism results. Donor cell engraftment usually remains restricted to lymphoid cells: the patient's blood group remains unchanged and, except T cells and rarely B cells and NK cells, all other white blood cells remain of recipient origin. An analysis of cells in the bone marrow of non-conditioned patients has failed to show donor type CD34+ precursor cells.[25] This lack of precursor cell engraftment in the marrow raises the obvious question as to the mechanism of the observed immune reconstitution. In our own studies, naïve donor T cells appear for the first time in the blood at 3 to 4 months after transplantation and subsequently normalize in numbers. At this time also an increase in size of the initially extremely small thymus in SCID is detectable.[25] These findings provide strong evidence that donor T cells develop intrathymically, as confirmed similarly by others.[26] A relevant question in this scenario, however, pertains to the source of these intrathymic donor cells. On the presumption that donor precursor cells fail to engraft in the marrow, at least on a permanent basis, a physiological, continued immigration of donor progenitor T-cells derived from pluripotent precursor cells in the marrow is not conceivable. It is very likely that donor lymphoid precursor cells seed the thymus directly, possibly during a narrow time window following transplantation. Does this unusual pattern of thymic reconstitution in SCID reveal any consequences? In a recent study, immune reconstitution was evaluated in long-term surviving SCID patients transplanted without conditioning.[27] This study also included a longitudinal evaluation of thymic functions. The authors observed a decrease of previously normal thymic functions in patients beyond 10 years after BMT, as based on a skewed T cell receptor (TCR) repertoire, as well as a decrease of TCR excision circles (TREC) and of the number of naïve T cells. As one of the several possible explanations, one could speculate that thymic functions in non-conditioned patients declined due to absence of engrafted donor lymphoid precursor cells in the marrow, and as a consequence, the lack of continued repopulation of the thymus. To clarify this important issue, more studies are needed in long-term surviving SCID patients.

Immune reconstitution following HLA-nonidentical, T cell-depleted transplantation in SCID may also completely fail. This has been observed in SCID for adenosine deaminase (ADA) deficiency and particularly in SCID variants characterized by the presence of residual autologous T cells.[13,28] There is some controversy regarding the role of NK cells, which are

preserved in some SCID variants. Graft failure has also been commonly observed after matched unrelated donor (MUD) transplantation when performed without conditioning.[29] These transplants were not T cell-depleted, but comparable to HLA-identical sibling transplants, and the reason for this graft failure after MUD transplants in SCID remains poorly understood.

Graft failure in SCID is preventable by using cytoreductive conditioning prior to transplantation. The largest experience has been gained with the use of busulfan, a primarily myelo-suppressive agent, combined with cyclophosphamide, which is mainly immunosuppressive. It is interesting that the latter drug, when used alone, was repeatedly found to be ineffective in enhancing marrow cell engraftment.[31] In our experience, a delayed partial or complete recovery of autologous hematological functions may be observed in conditioned patients, reflecting the use of a comparatively low dosage of busulfan, which fails to permanently eradicate the recipient's hematopoietic cell compartment. The resulting split or mixed chimerism, however, has not been accompanied by the loss or decrease of immune functions in these patients.

**Results of HSCT**

Although PID are rare and transplant frequencies low compared to acquired haematological diseases, significant experience has accumulated during the last three decades. Close collaborations between transplant groups have allowed regular analysis of comparable cohorts of patients and a continuous flow of important multicenter studies has been reported.[3,30-32] In a study published in 2003, results of HSCT in immunodeficient patients transplanted in Europe between 1968 and 1999 were analyzed.[3] A total of 919 patients was studied, 444 of whom suffered from SCID and 512 from other immunodeficiencies, including Wiskott-Aldrich syndrome ($n$=103), phagocytic-cell disorders ($n$=48) and hemophagocytic syndromes ($n$=90). Marrow was used as a source of HSC in 88%, peripheral stem cells in 12% and cord blood in 0.7% of the patients. Conditioning was not applied in 118 HLA-identical and 87 HLA-mismatched HSCT for SCID. In the other 239 SCID patients, the conditioning regimen consisted of busulfan (8 mg/kg) and cyclophosphamide (200 mg/kg) in most cases. In non-SCID patients, all but 10 received conditioning consisting of busulfan (16–20 mg/kg) and cyclophosphamide (200 mg/kg). T cell depletion was used in 91% of HLA-mismatched and in 41% of unrelated marrow samples, using E-rosetting, soybean agglutination, monoclonal antibodies or, more recently, positive selection of CD34+ cells.

As shown in Figure 1, in SCID patients the observed overall survival rate after HLA-identical HSCT was 77% compared to 54% after HLA-mismatched HSCT ($P$=0.002). Importantly, in the latter group of patients, significant improvements in survival rates were noted when comparing results obtained during the initial study period until 1990 and those obtained thereafter, increasing from about 50% to 80% (Figure 2). The variants of SCID were found to have an impact on survival after HLA-mismatched HSCT, since B(-) SCID had a poorer prognosis than B(+) SCID (36% vs. 64%). In the former group, the use of conditioning prior to HLA non-identical HSCT led to a trend towards better survival. For patients presenting with ADA deficiency, the 3-year survival was 81% after HLA-matched and 29% after HLA-mismatched HSCT; for reticular dysgenesis, a 3-year survival of 75% and 29%, respectively, was observed.

In the 512 non-SCID patients, survival with sustained engraftment and control of the immunodeficiency ranged between 42% and 71%, depending on the donors used. As in SCID, survival was better after HLA-matched than after HLA-mismatched HSCT (Table 2). No difference was observed in survival rates between genotypically HLA-identical and unrelated donor HSCT. A significant difference in the rate of sustained engraftment was noted after HLA-identical HSCT compared to HLA-mismatched HSCT, which was 99% and 75% ($P$=0.001), indicating an increased risk of graft failure of HLA-mismatched donor cells.

Wiskott-Aldrich syndrome (WAS) represents another disorder with extensive experience for HSCT.[29] Patients affected by this X-linked recessive disorder suffer from immunological abnormalities, mainly progressive T cell deficiency, from bleeding complications due to severe thrombocytopenia, severe eczema and autoimmune complications.[33] An increased risk for developing malignant lymphomas has also been observed. A series of reports document the potential of HSCT to permanently and completely overcome all immunological and hematological abnormalities, including the risk for malignancies.[34-36]

In a collaborative multicenter study in 176 WAS patients treated by HSCT between 1968 and 1996, the impact of donor origin on the outcome of HSCT was analyzed.[5] The 5-year probability of survival for all subjects was 70% and differed according to donor type, being 87% with HLA-sibling donors, 52% with

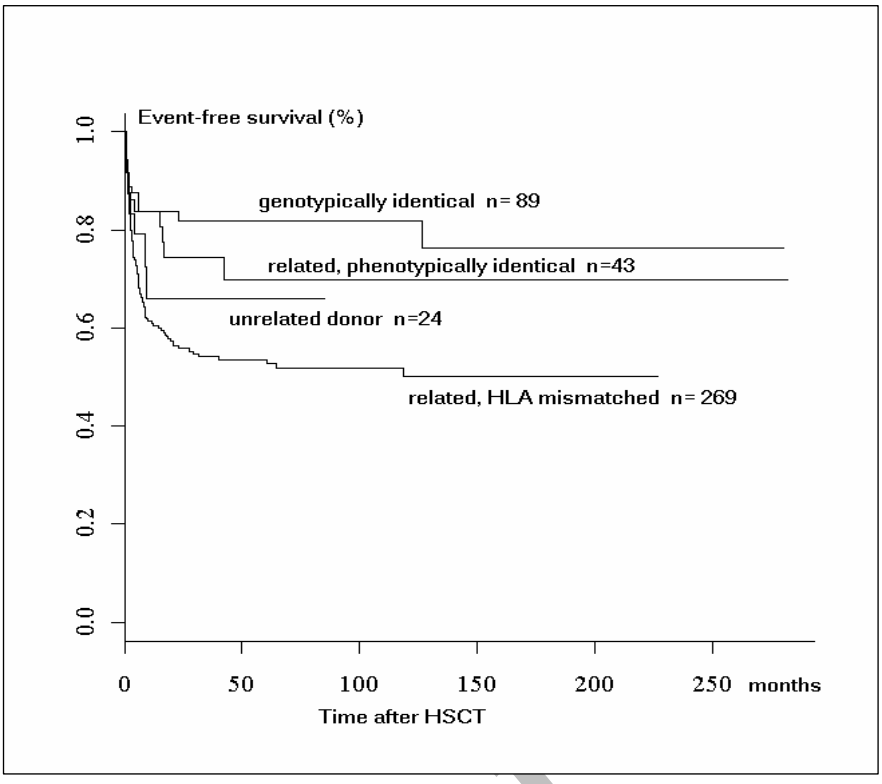


**Figure 1. Cumulative survival rates in SCID patients after HSCT according to stem cell donor (HLA genotypically identical n=104, HLA phenotypically identical related n=49, unrelated n=28, HLA-nonidentical related n=294) (EBMT/SCETIDE registry, Antoine C. et al, Lancet 2003).[3]**

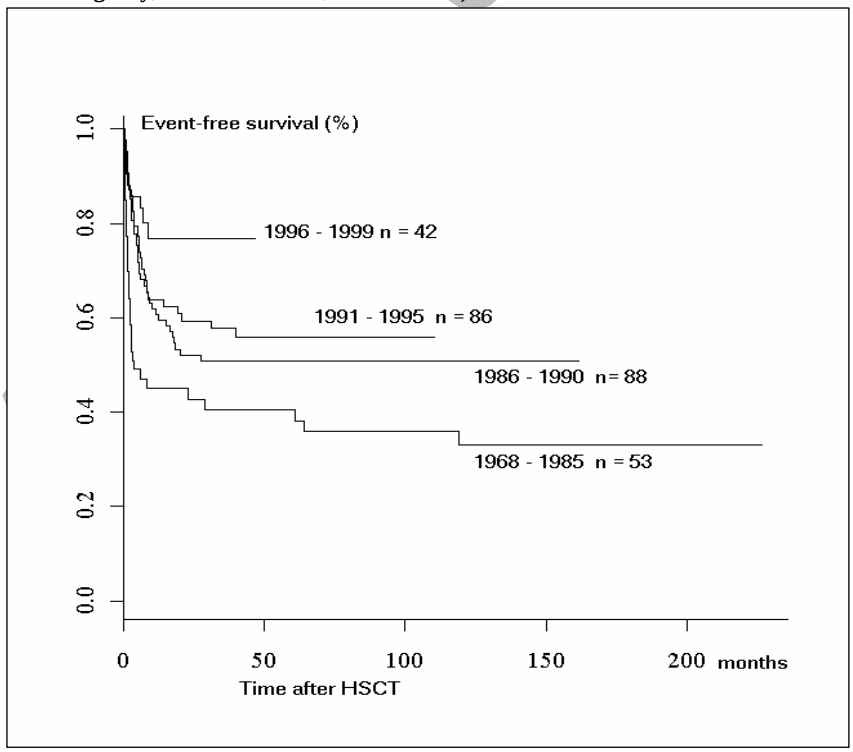


**Figure 2. Cumulative survival rates in SCID patients after HSCT from HLA-nonidentical related donors according to year of transplant (1968-1985 n=56, 1986-1990 n=91, 1991-1995 n=98, 1996-1999 n=49). (EBMT/SCETIDE registry, Antoine C. et al, Lancet 2003).[3]**

**Table 2. Three-year survival rates in non-SCID patients according to primary disease and donor-recipient compatibility (EBMT/SCETIDE registry, from Antoine C. et al, Lancet 2003).[3]**

| Disorders and Syndromes | HLA-Identical Sibling Donors | | HLA-Nonidentical Donors | |
|---|---|---|---|---|
| | Number of Patients | Survival Rate (%) | Number of Patients | Survival Rate (%) |
| **Phagocytic Cell Disorders** | 23 | 70% | 14 | 69% |
| **Wiskott-Aldrich Syndrome** | 32 | 81% | 43 | 45% |
| **Hemophagocytic Syndromes** | 32 | 68% | 28 | 49% |
| **Non SCID T cell Disorders** | 47 | 63% | 72 | 35% |

other related family (mostly HLA-mismatched donors), and 72% with matched unrelated donors. Age was found to be an important variable for successful matched unrelated donor transplants, with an outcome comparable to sibling transplants when performed at young age.

The use of matched unrelated donors, which has become increasingly feasible with large-sized volunteer donor registries, has gained broad acceptance as an alternative to related mismatched donor transplants in WAS and in other PID. In most of these disorders, the necessary delay of the transplant, which is due to the time needed for successful donor search, is acceptable. This is different in SCID, in whom there is usually significant urgency to perform a HSCT.

**The Use of Conditioning with Reduced Toxicity**

In a number of PID, specific risks for particular infections exist, such as hepatic cryptosporidial infections in CD40L deficiency, aspergillus infections in chronic septic granulomatosis and virus-induced lymphoproliferative disorders in defects of lympho-cyte cytotoxicity. If preventive measures are available and instituted, the patients may remain without complications for prolonged time periods, allowing HSCT to be postponed, in particular if a matched family donor is not available. Optimal timing of HSCT in this group of patients is of critical importance, requiring close patient monitoring and coordination of care takers. With advanced disease, risks associated with HSCT increase drastically, in particular due to the toxicity of the ablative conditioning. In patients who have developed chronic complications, the use of alternative, less intensive conditioning is attractive.

Several groups are exploring a conditioning regimen with reduced toxicity as successfully applied in elderly patients for malignant diseases. Success of this approach relies on the effect of donor T cells and immunomodulatory drugs to establish stable donor cell chimerism and to prevent recurrence of the disease or autologous reconstitution. Experience in PID has so far been published in two small series of patients at increased risk for transplant complications with encouraging results, but further evaluation of this approach is needed.[37,38]

**In Utero HSCT**

The use of in utero (IU) HSCT has been advocated for the treatment of congenital disorders of the lympho-hematopoietic system, many of which can be recognized now by prenatal diagnosis. Arguments and rationales in favor of considering IU HSCT as an alternative to postnatal treatment have included, beside the continuous sterile environment for the affected fetus while undergoing treatment, the immunological immaturity of the fetus with an expected tolerance to foreign cells, allowing transplantation without the need for immuno-suppression. Furthermore the possibility, that the fetal environment may be permissive under specific circumstances to an engraftment of HSC without requirement for myeloablation could argue pro IU HSCT. In clinical practice these promises unfortun-ately have not been held, and expectations that in utero transplantation of hematopoietic stem cells might offer significant biological advantages compared to postnatal HSCT, were not fulfilled. Lack of stem cell engraftment and failure to develop donor cell chimerism has been a uniform finding. The only exceptions to this observed absolute barrier for donor cell engraftment had been several SCID patients in whom isolated reconstitution of donor T-cells reflecting their selective growth advantage was observed.[39] Even in SCID patients, the benefit and advantage of IU HSCT have been questioned, since early postnatal HSCT prior to onset of clinical complications has been found to offer optimal chances of success and uneventful transplant courses.[40] In all other diseases, which in theory form candidates for prenatal therapy, in particular

hematological disorders, further progress will depend on successful approaches to endow donor cells with a necessary selective growth advantage.

## CONCLUSIONS

HSCT has become a firmly established treatment strategy and in fact is the treatment of choice for many congenital disorders of the immune system. However, this therapeutical modality remains associated with possible serious complications and, in many respects, HSCT still represents an experimental procedure, in particular if an HLA-nonidentical donor is used. Further progress depends on the development of alternative preparative conditioning regimens, allowing stable engraftment of donor precursor cells with minimal systemic toxic side effects. It will also depend on the development of strategies to enhance and to improve the development and reconstitution of immune functions, in particular when this development arises exclusively from early precursor cells, a situation in which ontogenesis of the lymphoid cell system is recapitulated. It is possible that gene therapy will widen the range of treatment options in the future for many of these genetic disorders. However, also here a basic challenge will depict the need for stable engraftment of genetically modified and corrected precursor cells.

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