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Genetic Therapy for Primary Immunodeficiency Disease; SCID as an Example

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Abstract

Primary Immunodeficiency Diseases (PIDs) are rare hereditary and congenital disorders of the immune system. Lack of awareness amongst physicians of these rare diseases results in a long delay in their diagnosis and treatment. This delay can amount to approximately six years for primary antibody deficiency disease, and by the time patients are diagnosed, they are already suffering from complications such as bronchiectasis and chronic sinusitis. These complications can be avoided, in the majority of patients, by early diagnosis and adequate treatment with immunoglobulin replacement therapy. Bone Marrow Transplantation (BMT) now offers the chance for curative treatment for some of these diseases but is limited by the shortage of suitable matching donors, and by complications that arise from engraftment of donor cells. For these reasons, BMT is applicable to only a proportion of cases. Somatic gene therapy allows the transplantation of new genes into the patients' own bone marrow to directly complement the genetic mutation, and restore full function to the white blood cells.

Keywords: Severe combined immunodeficiency; Immunoglobulin replacement therapy; Gene therapy; Primary immunodeficiency diseases; Interleukin-2 receptor

Background and Diagnosis of SCID

Severe Combined Immunodeficiency (SCID) is a syndrome resulting from a group of a heterogeneous group of X-linked and Autosomal Recessive Disorders T. In SCID patients, generalized lymphadenopathy with splenomegaly can be seen. SCID patients present within the first few months of life with severe and persistent viral and opportunistic respiratory infections, persistent diarrhea (enteroviral infection, rotavirus, small round structured virus), failure to thrive, persistent oral and genital thrush, and failure to clear live vaccines (oral polio, BCG). These infections result from opportunistic infections (*Aspergillus*, *Candida*) and viral infections (Enteroviruses, Rotavirus, Adenovirus, Cytomegalovirus (CMV), Human Herpes Viruses, Respiratory Syncytial Virus (RSV), Para-Influenza Virus and Epstein-Barr virus (EBV).

Diagnosis of SCID relay on the infectious clinical picture, absence of tonsils, lymph nodes and thymic shadow, together with the laboratory finding of low lymphocyte count and absent T cell function. The result of antibody investigation would vary depending on when investigated.

A physical examination would reveal the absence of lymphoid organs, while radiology would show the absence of thymus shadow. In some patients, a physical examination may reveal lymphadenopathy, hepatosplenomegaly, eczema/erythroderma and alopecia. Initial laboratory investigation would show, in the majority of cases, low lymphocyte counts (2×10^9/L<; normal), various combinations of T, B and NK lymphopenia and absent T cell proliferation responses to mitogens (e.g. PHA) and antigens (e.g. tetanus toxoid). Absent T cell response occurs in all SCID.

PHSC Gene Therapy for Severe Combined Immunodeficiency (SCID)

The primary immunodeficiency diseases form a heterogeneous group of single-gene disorders of the immune system. Although rare, PIDs are optimal candidates for the development of a curative treatment based on the transfer of therapeutic genetic material to hematopoietic stem cells.

PIDs are a group of rare disorders in which the development, homeostasis or effector function of immune cells is comprised of an inherited genetic mutation. Severe Combined Immunodeficiency (SCIDs) is characterized by a profound reduction or absence of T lymphocyte function. They are becoming significantly distributed in the KSA and in the region and ME countries [1-4].

The resulting defects in both cell-mediated and humoral immune responses invariably lead to premature mortality in the absence of hematopoietic stem cell transplantation. The X-linked form of the disease, X-SCID, accounts for about 60% of all cases and is often distinguishable from other forms by its characteristic pattern of inheritance and the observation that affected boys usually have normal or elevated levels of B cells and reduced or absent NK (T-B+NK-SCID). X-SCID is caused by

defects in the common cytokine receptor γ chain (γc) gene originally identified as a component of the high and intermediate affinity Interleukin-2 Receptor (IL-2R), and is now known to be expressed constitutively in many haematolymphoid cells (including Short-Term Self-Renewing (STHSC), Common Lymphoid Progenitor cells (CLP), lymphoid cells and mature myeloid cells) and to be a component of additional cytokines receptors (IL-4R, IL-7R, IL-9R and IL-15R) [5]. γc signaling activity is dependent on heterodimerization with other components of individual receptors, which in lymphoid cells results in translocation from intracellular stores to the cell membrane [6,7]. γc-deficient mice generated by gene targeting exhibit severe lymphopenia, and are very similar immunophenotypically to mice with specific IL-7/IL-7Rα and JAK1/JAK3 gene mutations [8] **(Table 1)**.

Table 1: SCID disorders.

Disorder	%	Inheritance	Gene defect	Location
$T^- B^+ NK^-$	50-60	X-linked	γc	Xq13-13.3
$T^- B^- NK^+$	20-30	AR	RAG-1/2	11p13
		AR	ARTMIS	10p13
$T^- B^+ NK^+$	5	AR	IL-7Rα	5p13
	Rare	AR	IL-7	
	Rare	AR	CD3ε	
	Rare	AR	CD3δ	
	Rare	AR	CD45	
Omen syndrome		AR	RAG-1/2	11p13

AR: Autosomal Recessive; γc: common IL-2 gamma; ADA: Adenosine Deaminase; RAG: Recombinant Activation Gene; CD: Cluster of Differentiation; IL: Interleukin

An incomplete block in thymic T cell development is common to all these models, indicating that other γc-dependent cytokines are redundant at this stage of development, and is consistent with the hypothesis that the molecular pathogenesis of X-SCID results primarily from a failure of γc-mediated signaling through IL-7R [5].

SCID patients usually have normal or elevated numbers of B cells. However, studies showing that IL-2 and IL-15 fail to induce class-switching in vitro, and that signaling molecules downstream of the IL-4R receptor (JAK3 and STAT6) are not activated after ligand binding point to significant intrinsic abnormalities in this population [9].

Currently, the cure rate for all forms of SCID (measured by functional T cell reconstitution) using sibling donor transplantation is over 90%. However, for only 30% of patients does such a donor exist (this is true for all PID patients), and for T-cell depleted haploidentical parental grafts, success rate falls to 50% [10]. Complications primarily relate to toxicity arising from the conditioning regimen, pre-existing infection, and to delayed reconstitution of immune function post-transplant. In cases of X-SCID where genotypically matched sibling donor is available, most toxicity is obviated because containing is unnecessary for T cell engraftment. Clearly, there is a finite risk of GvHD which may compromise both maternal and fetal health, and the procedure is limited to those families with previously affected children **(Table 2)**.

Table 2: Patients to be investigated for SCID.

Sr No.	Patients to be investigated for SCID
1.	Recurrent upper and lower respiratory tract infections
2.	Two or more severe infections (e.g. pneumonia, septicemia)
3.	Chronic or recurrent diarrhea/malabsorption
4.	Vaccine complications (e.g. BCG)
5.	Patients with chronic obstructive lung disease
6.	Neonate with low lymphocyte counts
7.	Infants with liver abscesses

The alternative strategy, somatic gene therapy, is dependent on efficient gene transfer to Pluripotent Hematopoietic Stem Cells (PHSCs), or possibly in the case of SCID, long-lived common lymphoid progenitor cells, and for the reasons outlined above, constitutive gene expression in dysfunctional cells. This primary immunodeficiency has advantages over many other hematological and immunological disorders for this type of therapy as corrected lymphoid cells will have significant growth and differentiation advantage, the immune response to the transgene are less likely to be initiated.

In one atypical SCID patient, a spontaneous revision of the genetic defect in early T cell precursors led to partial reconstitution of the T (but not B or NK) cell compartment [11]. It is, therefore, possible that low efficiency of gene transfer to PHSCs or even common lymphoid progenitors will have a therapeutic benefit.

For X-SCID, any BMT reconstitution will be measured by analysis of γc expression (in null mutants) on engrafted $CD45^+$, $CD45^+CD2^+$, $CD45^+CD13^+$, and $CD45^+CD19^+$ cells. Ongoing experiments in canine and murine models of X-SCID, phase-I clinical trials are being planned in Europe and the United States.

Conclusion

In conclusion, locally, we hope that with securing a long-term core funding for gene therapy research here in KSA will be able to develop the resources and techniques for the successful transfection of genes into human hematopoietic stem cells and to obtain long-term expression of functional proteins in their descendent cell populations. Additionally, this will allow us for a broader approach in the design of therapeutic strategies and attract high caliber research staff for genetic and non-cancer hematological diseases.

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