Gene Therapy for Adenosine Deaminase (ADA)-Deficient Severe Combined Immune Deficiency

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Inherited deficiency of adenosine deaminase (ADA), an enzyme of purine metabolism, is the cause of 10-15% of human Severe Combined Immune Deficiency (SCID). Transplantation of hematopoietic stem cells (HSC) from a healthy donor can be curative of SCID. But, there are risks from graft versus host disease caused by an immune reaction by the donor's cells against the patient. Transplantation using the patient's own (autologous) HSC that are treated to add a normal copy of the ADA gene (gene therapy) may have similar benefits as a transplant from a donor, without the immunologic risks. From initial studies to insert a normal ADA gene into T cells that began in the early 1990's, gene therapy for ADA-SCID has been developed to be a highly effective and safe therapy. Use of reduced intensity conditioning with busulfan to "make space" in the hematopoietic niche is essential to achieve engraftment of sufficient gene-modified HSC. Initial metabolic detoxification using ADA enzyme replacement therapy for several months allows the gene therapy transplant to be done when the patient is clinically well and without infections. Murine retroviral vectors were used for initial studies at several centers and led to consistent immune restoration in the majority of patients. The first of these, developed in the TIGET Institute in Milan, has been brought to licensure in the European Union by GSK. Currently, our groups in Los Angeles and London are performing trials of gene therapy for ADA SCID with HSC using a lentiviral vector and reduced intensity conditioning. The lentiviral vector achieved higher levels of ADA gene transfer and expression than did a murine retroviral used in our preceding clinical trial, and more consistent and robust immune reconstitution. Efforts are underway to advance this therapeutic to licensure to make it widely available for ADA SCID patients. Over 25 years, gene therapy for ADA SCID has advanced from early investigations to becoming potentially a standard of care.