Gene Therapy for Hemoglobinopathies

The State of the Field and the Future

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KEYWORDS

• Hemoglobinopathy • Thalassemia • Sickle cell disease • Gene therapy

KEY POINTS

- Hemoglobinopathies are the most common genetic defects worldwide. Hematopoietic stem cell (HSC) transplant, although curative, is limited by the availability of matched donors.
- Genetic modification of autologous HSC overcomes the availability of donors (every patient is their own donor) and immunological side effects (graft versus host disease/graft rejection).
- Critical determinants unique to gene therapy for hemoglobinopathies are erythroid-lineage and developmental stage-specific high levels of transgene expression and pretransplant conditioning that will allow 10%–20% gene-modified HSC chimerism.
- Scientific insights into regulation of the globin gene locus and improvements in gene transfer technology have led to development of β-/γ-globin based additive gene therapy a clinical reality.
- Clinical trials with β-/γ-globin lentivirus vectors are now open at multiple sites and transfusion independence following gene therapy has been reported in 1 patient with β-thalassemia.
- Promising new technologies such as induced pluripotent stem cells and genome editing can usher in a new era in the field of gene therapy.

Conflict of Interest: None.

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INTRODUCTION

Over the last 2 decades significant advances have been made in gene therapy for hemoglobinopathies. Gene therapy has exploited the ability of retrovirus (RV) vectors, which are equipped with the machinery to reverse transcribe their RNA into complementary DNA (cDNA) and integrate this cDNA into the host cell genome to deliver therapeutic genes into cells. Inherited hematopoietic disorders are potentially targetable, because hematopoietic stem cells (HSC) can be readily isolated from bone marrow or mobilized peripheral blood, manipulated ex vivo, and transplanted back using current tools and knowledge of bone marrow transplant technology. The initial vectors used for gene therapy were derived from the murine Moloney leukemia virus (MLV), a simple retrovirus belonging to the γ-retrovirus family, and were termed RV vectors. Despite initial successes in several immunodeficiency disorders, limitations of the RV include their inability to infect the quiescent nondividing HSC, hematopoietic malignancies from inadvertent integration of these vectors near cellular proto-oncogenes, and their activation by the viral promoter enhancer in the vector long terminal repeat (LTR) regions. For hemoglobinopathies, an additional limitation is their inability to carry the large cargo of the globin gene and its regulatory elements, required for high-level expression. These limitations prompted the development of human immunodeficiency virus (HIV)–based vectors. HIV belongs to the lentivirus (LV) family of retroviruses and hence these vectors are termed LV vectors. LV have several advantages for gene therapy for hemoglobinopathies. They differ from RV in their ability to enter an intact nucleus and integrate into nondividing cells, and hence they transduce HSC efficiently. Their self-inactivating (SIN) design, which removes all viral transcriptional machinery, and their ability to carry a large cargo makes them ideally suited for gene therapy for hemoglobinopathies. Since the first use of gene therapy for adenosine deaminase (ADA) deficiency in 1990, generational changes have made the vector design more effective and safe, advanced molecular tools have made it easier to study the insertional effects of gene transfer. Gene therapy has been shown to be effective in correction of many immunodeficiency disorders such as X-linked severe combined immunodeficiency (X-SCID), Wiskott-Aldrich syndrome (WAS), and chronic granulomatous disease (CGD). However, gene therapy for hemoglobinopathies has a unique set of challenges.

Hemoglobinopathies have the additional challenge of requiring high levels of expression of β-/γ-globin genes for therapeutic correction. Identification of critical regulatory elements needed for high expression of β-globin transgene has made gene therapy for β-hemoglobinopathies (sickle cell disease [SCD] and β-thalassemia) a feasible option. More recently, encouraging results from the first successful gene therapy for a patient with hemoglobin E-β-thalassemia in a French trial has opened up gene therapy as a potential definitive treatment option for patients with β-hemoglobinopathies. Trials with different iterations of the β-globin and γ-globin genes in SIN LV to treat thalassemia or SCD are beginning in Italy and 4 centers in the United States (New York, Memphis, TN; Cincinnati, OH; and Los Angeles, CA).

Because expression of increased levels of fetal hemoglobin (HbF) significantly ameliorates the phenotype of both SCD and β-thalassemia, critical elements involved in γ-globin repression in postnatal life have been identified, which has opened up new gene therapy approaches to increase endogenous γ-globin production without the need to add the globin genes and the large locus control region regulatory elements.

Even more promising is the development of gene editing approaches. The design of zinc finger nuclease (ZFN)–mediated repair was the first such approach. This approach was soon superseded by transcription activator–like effector nucleases