Gene Therapy and Genome Editing

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KEYWORDS

• Thalassemia • Gene transfer • Gene editing • Lentivirus • CRISPR/Cas9

KEY POINTS

- The β-thalassemias are inherited blood disorders that result from the insufficient production of the β-chain of hemoglobin. β-thalassemia major is characterized by transfusion-dependence.
- The only means to cure severe β-thalassemia is to provide patients with hematopoietic stem cells that harbor functional globin genes.
- Successful allogeneic hematopoietic stem cell transplantation is potentially curative, but this option is not available to most patients with thalassemia because a suitably matched donor cannot be found.
- Globin gene therapy offers the promise of a curative autologous stem cell transplantation without incurring the risks of the immunologic complications of allogeneic transplantation.
- Future directions of gene therapy include the enhancement of the lentiviral vector-based approaches, fine tuning of the conditioning regimen, and the design of safer vectors.

INTRODUCTION

Of course, a gene therapy cure is still some time away and when it comes will be expensive; in the meantime, I believe that the richer countries should do all they can through developing partnerships with the poorer countries to try to help them establish some kind of services for the control and management of thalassemia.

—Sir David Weatherall (Interview with the Cooley's Anemia Foundation December 3, 2009)

The β-thalassemias are among the most common inherited blood disorders worldwide. They are recessive genetic disorders that are caused by mutations in, or near, the β-globin gene. More than 200 mutations have been described that reduce or abolish the synthesis

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of the β-globin chain of adult hemoglobin (HbA, $\alpha_2\beta_2$).[1] Homozygotes and compound heterozygotes may develop thalassemia intermedia or β-thalassemia major. Absent β-globin chains (β^0/β^0) or profound decrease in the synthesis of β-globin (β^0/β^E or β^0/β^+) trigger the precipitation of unpaired α-globin chains in erythroid cell precursors, resulting in intramedullary hemolysis, dyserythropoiesis with increased expansion of erythroid cell precursors but decreased production of mature red cells, and increased production of erythropoietin.[2]

The standard of care treatment modalities for β-thalassemia major consist of palliative care with transfusion of red blood cells and chelation of the iron overload, or curative treatment with allogeneic hematopoietic stem cell transplantation when an HLA-matched related donor is available.[3] Despite the considerable improvement in the life expectancy of transfusion-dependent individuals in the last decades,[4–6] the risk of serious complications arising over the long term from viral infections, iron toxicity, and liver cirrhosis remain.[7]

Hematopoietic stem cell transplantation has been performed in more than 1 thousand patients from matched related donors worldwide with very good results. At our center, we have performed allogeneic stem cell transplantation in 32 patients with β-thalassemia major from HLA-matched related donors, with an overall 95% survival and 91% disease-free survival (Boulad F, unpublished results, 2017). A number of trials of allogeneic hematopoietic stem cell transplantation from matched unrelated or mismatched related donors have occurred or are in progress.[8,9] However, there remains to date an increased risk for complications, including graft rejection, graft-versus-host disease, and mortality.[8–12]

For patients lacking a matched related donor, globin gene therapy offers the promise of a curative autologous stem cell transplantation without incurring the risks of graft-versus-host disease.[3]

RATIONALE FOR GLOBIN GENE TRANSFER TO CURE β-THALASSEMIA

Since the foundational report by May and colleagues[13] in 2000, which opened a path for therapeutic globin gene transfer by demonstrating erythroid-specific expression of the human β-globin gene at therapeutic levels in thalassemic bone marrow (BM) transplanted recipient mice, several studies have confirmed the efficacy of lentiviral-mediated globin gene transfer and extended these results to additional mouse models of β-thalassemia, paving the way for the clinical application of globin gene transfer.

The goal of globin gene transfer is to restore the capacity of the hematopoietic stem cells of the patient with thalassemia to generate red blood cells with a normal hemoglobin content[14,15]

Only transduced HSCs can provide long-term clinical benefits through productive erythropoiesis based on a normalized α/β globin chain synthesis ratio. The goal of curative therapy for thalassemia is to achieve transfusion independence without exposing patients to the risks of HSCT from a suboptimally matched donor. For patients who lack an HLA-matched donor and thus have a higher risk of mortality after allogeneic HSCT, globin gene transfer in autologous stem cells offers the prospect of a curative stem cell-based therapy.[3]

GLOBIN GENE TRANSFER

How It All Started: The First 10 Years (–2000): Preclinical Proof-of-Principle and Safety Studies

The human β-globin gene (*HBB*), which spans less than 5 Kb on the short arm of chromosome 11, contains 3 exons and 2 introns, one of which at least is required