Genetic Therapies for Sickle Cell Disease

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KEYWORDS

• Sickle cell anemia • Viral vectors • Gene therapy • HSC gene editing

KEY POINTS

- Gene therapy has the potential for curing hemoglobinopathies such as sickle cell anemia permanently.
- Lentivirus vectors have revolutionized genetic correction, with several patients with thalassemia and one with sickle cell anemia cured of their disease.
- The actual correction of the sickle mutation or permanent reactivation of fetal hemoglobin with gene editing may be possible in the near future.

INTRODUCTION

Historically, sickle shaped red blood cells (RBCs) were first described in a patient with sickle cell anemia (SCA) by James Herrick.[1] It was not until almost two decades later that the RBC sickling phenomenon was shown to be dependent on oxygen concentration.[2,3] In 1949, Linus Pauling was the first to show that the hemoglobin (Hb) in sickle RBC differed in structure from normal Hb.[4] That same year, Janet Watson predicted the importance of fetal Hb (HbF) by showing paucity of sickled RBC in newborns compared with adults with SCA.[5] By 1955, Ingram and Hunt showed that glutamic acid at position 6 of the beta-globin gene was replaced by a valine, which resulted in SCA,[6] which made SCA the first genetic disorder whose molecular basis was discovered. However, it took more than one-half of a century thereafter before the globin genes were cloned and sequenced, the organization of the globin gene clusters was characterized, and a great deal of insight was provided into the mechanisms of their regulated expression.[7]

Human Hb, the protein that carries oxygen from the lungs to the tissues, is a tetrameric molecule that consists of 2 pairs of identical polypeptide subunits (2 α-like globin peptides and 2 β-like globin peptides). The human α-like globin gene cluster (ζ, α_1, and

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Pediatr Clin N Am 65 (2018) 465–480
https://doi.org/10.1016/j.pcl.2018.01.008
pediatric.theclinics.com

α_2) is located on chromosome 16, and the β-like globin gene cluster (ε, Gγ, Aγ, δ, and β) is located on chromosome 11. Interestingly, the globin genes present on both these clusters are in the same order in which they are expressed during development.[8] During fetal life, the predominant Hb produced is HbF ($\alpha_2\gamma_2$), which is gradually replaced postnatally by HbA ($\alpha_2\beta_2$) when the γ-globin gene gets silenced. Upon this switch from HbF to HbA, β-globinopathies, such as sickle cell disease (SCD) and β-thalassemia manifest clinically.[5] This important observation, and natural mutations resulting in hereditary persistence of fetal hemoglobin with no clinical consequence led into an understanding of the process of switching from γ- to β-globin, and has formed the basis behind designing genetic therapies that reactivate γ-globin or similar antisickling globins.

SCA is caused by a homozygous point mutation (A-T) in the sixth codon of the β-globin/*HBB* gene. The dimerization of the mutant β-globin (β^S) chains with α-globin results in the formation of sickle Hb S (HbS, $\alpha_2\beta^S{}_2$). Various other β-globin mutations, like β-thalassemia, HbC, HbD, and HbE, when coinherited in compound heterozygosity with β^S mutations, also result in a sickle cell phenotype, and are grouped broadly as SCD, with patients that only make β^S-globin ($\beta^S\beta^S$ and $\beta^S/\beta^{0-\text{thalassemia}}$) termed as having SCA. SCD is among the most common monogenic diseases, with 330,000 affected births per year worldwide.[9] The sickle mutation was selected for in areas affected by malaria, because it conferred protection from severe forms of malaria in heterozygous individuals (HbAS), who are largely asymptomatic.[10,11]

MEDICAL MANAGEMENT OF SICKLE CELL DISEASE

The first breakthrough occurred when the use of pneumococcal vaccine with penicillin prophylaxis was found to be effective in preventing death from pneumococcal sepsis in children with SCD.[12] Next, hydroxyurea was shown to increase HbF and reduce the frequency of pain episodes,[13] and was approved by the US Food and Drug Administration in 1998 for adults with SCD. Chronic blood transfusions were also shown to reduce the risk of stroke by 90%.[14,15] Acute sickle events are managed with supportive care. Together, these are the cornerstones of preventive and symptomatic management in SCD that have prolonged survival in this disease. However, disease-modifying therapies, such as hydroxyurea, are not equally effective in all patients, often owing to poor compliance of life-long administration. Therefore, there remains significant morbidity and shortened life span in patients with SCD with the median age of death being 42 years for men and 48 years for women.[16] Current medical management of SCD are reviewed in Emily Riehm Meier's article, "Treatment Options for Sickle Cell Disease," and Ahmar U. Zaidi and Matthew M. Heeney's article, "A Scientific Renaissance: Novel Drugs in Sickle Cell Disease (SCD)," in this issue.

CURATIVE OPTIONS

The first cure of SCD occurred by serendipity in 1984, when a bone marrow transplant was performed to treat acute leukemia in a child with SCD and it eradicated both the leukemia and SCD,[11] setting the precedence for hematopoietic stem cell transplant (HSCT) as a curative modality. At present, allogeneic HSCT is the only definitive cure, with a disease-free survival of greater than 80% with HLA-matched sibling donor transplants.[17] However, most patients lack matched sibling donors. The use of unrelated donors increases the mortality and morbidity associated from transplant and its immune side effects, such as graft-versus-host disease and graft rejection/failure, thus limiting allogeneic HSCT as the major treatment option.[18] Only about 1200 HSCT have been performed so far for SCD, a disproportionately small number compared to the huge global burden of this disease.[19]