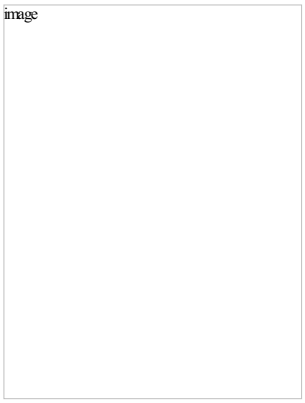

Genetic therapies for sickle cell disease

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Genetic therapies for sickle cell disease

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ABSTRACT

After decades with few novel therapeutic options for sickle cell disease (SCD), autologous hematopoietic stem cell (HSC) based genetic therapies including lentiviral gene therapy (GT) and genome editing (GE) now appear imminent. Lentiviral GT has advanced considerably in the past decade with promising clinical trial results in multiple disorders. For β-hemoglobinopathies, GT strategies of gene addition and fetal hemoglobin (HbF) induction through BCL11A regulation are both being evaluated in open clinical trials. GE techniques offer the possibility of a non-viral curative approach, either through sickle hemoglobin (HbS) mutation repair or HbF elevation. Although GE currently remains at the preclinical stage, multiple clinical trials will likely open soon. In addition to reviewing current strategies for GT and GE, this review highlights important next steps toward optimization of these therapies. All autologous cell-based genetic therapies rely on safely obtaining an adequate yield of autologous HSCs for genetic modification and transplantation. HSC collection is uniquely challenging in SCD. Peripheral mobilization with plerixafor has recently emerged as a promising approach. The acute and long-term toxicities associated with myeloablative conditioning are risks that may not be acceptable to a significant number of SCD patients, highlighting the need for novel conditioning regimens. Finally, increasing availability of autologous genetic therapies will require comprehensive and collaborative discussions regarding cost and access for SCD patients, at individual centers and worldwide.

OVERVIEW

Sickle cell disease (SCD) is one of the most common genetic diseases in the world. In North America, an estimated 2600 babies are born with SCD each year(1), and approximately 70,000 to 100,000 individuals of all ages are affected in the United States(2). This is only a small proportion of the global SCD burden, more than 230,000 affected children are estimated to be born yearly in sub-Saharan Africa(1). Currently allogeneic hematopoietic stem cell transplant (HSCT) can provide curative therapy for some patients with SCD resulting in the remission of vaso-occlusive crises and the stabilization or improvements of neurologic and pulmonary abnormalities(3,4). The best outcomes and least toxicity are achieved after matched sibling transplant(5,6), but unfortunately fewer than 20% of SCD patients in the United States have such a donor available, and in most studies grade III/IV graft versus host disease (GVHD) still occurs in 5-10% of children with a matched sibling donor(4). For SCD patients without a fully matched sibling, finding an unrelated matched donor is possible for less than 1/3 of patients(7) and outcomes include high rates of transplant-related toxicities. For example, in a multicenter phase II (Sickle Cell UnRelated Transplant, SCURT) trial testing HSCT outcomes with unrelated donor and reduced intensity conditioning, the cohort with matched cryopreserved umbilical cord units was closed early due to an unacceptable incidence of graft failure(8), and the cohort of 30 subjects with matched unrelated marrow donors (8/8 loci) suffered high rates of chronic GVHD including GVHD-related mortality in 6 patients(9).