A Scientific Renaissance
Novel Drugs in Sickle Cell Disease

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KEYWORDS

• Sickle cell disease • Therapeutic targets • Pathophysiology
• Induction of fetal hemoglobin • Antiadhesion molecules

KEY POINTS

- We have entered an era of exploding interest in therapeutics for sickle cell disease.
- The expansion in our understanding of sickle cell disease pathophysiology has enhanced the range of potential therapeutic targets.
- From induction of fetal hemoglobin to antiadhesion molecules, we are potentially on the cusp of making life-altering modifications for individuals with sickle cell disease.
- This disease population cannot afford to let the current momentum wane.
- Studies exploring combinations of therapies affecting multiple steps in the pathophysiology and exploring novel and clinically relevant outcomes are incumbent.

INTRODUCTION

It has been 2 decades since hydroxyurea was approved by the US Food and Drug Administration (FDA) for the treatment of sickle cell disease (SCD) in adults, and until recently it remained the only approved medication for this disease. Up until the last 5 years, there has been minimal progress in drug development to improve the survival and quality of life of children with SCD (**Fig. 1**).

The eruption of recent activity in drug development for this population can be linked to changes in legislation promoting pharmaceutical research in orphan diseases and children, and the evolution of our understanding of the pathophysiology of SCD. Over the past few decades, investigators have identified novel pathways in the complex pathophysiology of this disease.[1] Although the polymerization of deoxygenated hemoglobin S (HbS) remains the initiating event in the pathophysiology of SCD, our understanding of how cellular adhesion (leukocytes, platelets, and endothelial cells), oxidative damage, vascular reactivity, nitric oxide (NO), inflammation, and the coagulation system contribute to vasoocclusion and the broader phenotype of the disease

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Pediatr Clin N Am 65 (2018) 445–464
https://doi.org/10.1016/j.pcl.2018.01.006
pediatric.theclinics.com

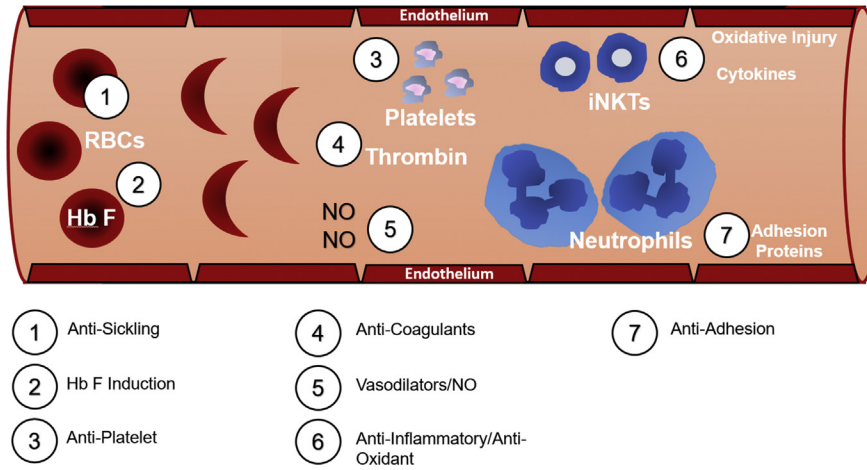

Fig. 1. Various targets of new drugs in sickle cell disease. iNKTs, invariant natural killer T cells; NO, nitric oxide; RBCs, red blood cells.

have provided novel targets whose exploration is providing hope for more disease modifying treatments. The investigation and recent FDA approval of L-glutamine, only the second drug labeled for SCD, was the result of thinking beyond hemoglobin and red blood cells.

Although significant strides are being made in drug development, the conduct of clinical trials in SCD remains challenging with respect to choice of meaningful clinical endpoints and rate of enrollment that may require more centers and costs. Many recent trials have developed novel endpoints, and have included enrollment in regions of the world with a high disease burden. In this review, we aim to discuss the current state of drug development in SCD. Owing to the expansive nature of current research in SCD, we highlight some drugs within the text of the article, but have included tables with a complete list of compounds under investigation.

THERAPEUTIC STRATEGIES FOR SICKLE CELL DISEASE

Agents That Induce Fetal Hemoglobin or Modulate Hemoglobin

The polymerization of deoxygenated HbS can be interfered with through a variety of mechanisms. Recognition that naturally occurring high levels of fetal hemoglobin (HbF) improve mortality in SCD,[2] increasing the proportion of HbF is a clear therapeutic opportunity to improve SCD phenotypes. Deoxygenation of HbS reveals the substituted hydrophobic valine residue that participates in HbS polymerization. Therefore, efforts to increase HbS oxygen affinity or interfere with polymerization directly have also drawn interest. Finally, epigenetic mechanisms such as histone deacetylation and DNA methylation do play an important role in the silencing of the gamma globin genes, and provide yet another pathway being targeted by investigators. There are several drugs that are being actively studied for their ability to increase the proportion of HbF or modulate hemoglobin to prevent sickling (**Table 1**).

Hemoglobin-Modifying Agents

GBT440

Global Blood Therapeutics is developing a novel oral small molecule hemoglobin modifier for SCD that binds to alpha globin and increases hemoglobin oxygen affinity.