

Accelerating Drug Development for Sickle Cell Disease

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Discussion Guide

Background

Sickle cell disease (SCD) is a complex genetic disorder that affects over 100,000 Americans and millions of individuals worldwide. The disease impacts multiple systems within the body, causing a wide range of debilitating symptoms that can ultimately shorten life expectancy. The sickle-shaped red blood cells that are the hallmark of the disease were first described in 1910, and since then the understanding of the disease's underlying biology and pathophysiology has evolved significantly. However, there continue to be significant challenges in designing and executing randomized clinical trials for sickle cell disease. There are also very few effective treatments for the disease. The majority of available treatments manage symptoms rather than treat the underlying disease process. The U.S. Food and Drug Administration (FDA) is working with academia, industry, and patient stakeholders to accelerate the development of new drugs to treat sickle cell disease (SCD).

Definition and Origins

Sickle cell disease includes a group of inherited blood disorders that are characterized by the production of abnormal hemoglobin (Hemoglobin S). Hemoglobin S impacts the shape and functioning of red blood cells, turning them into rigid, crescent-shaped structures, which have a significantly shorter lifespan relative to healthy red blood cells. The disease manifests in several forms. The most common and often the most severe version of the disease, sickle cell anemia, is the result of a child inheriting the sickle cell gene from both parents. The mutation can also occur in several heterozygous forms, whereby one sickle cell gene and one gene from another abnormal hemoglobin type are inherited.

Symptoms and Disease Consequences

People with SCD experience a number of both chronic and acute symptoms, including painful vaso-occlusive crises (VOC) and acute chest syndrome, which contribute to most SCD-related hospitalizations. VOCs occur when the sickled cells begin sticking to the endothelium, obstructing blood flow through the body and causing significant pain and tissue injury. Acute chest syndrome is the most common cause of death in patients with the disease, and can be caused by a number of factors, including infection, fat emboli, or infarction with aggregations of sickled cells within the pulmonary system.¹ Additional consequences of sickle cell disease can include pulmonary hypertension, gallstones, strokes, splenic dysfunction, and kidney problems. The range of symptoms varies throughout the patient's life, and can present as early as infancy. Children with sickle cell disease are also at significant risk of bacterial infections, strokes, dactylitis (inflammation and pain in the fingers or toes, and cognitive as well as growth impairment. In the first five years of life, children are also at risk of). Later symptoms include enuresis (inability to control urination), leg sores and ulcers, priapism (painful and prolonged erections), renal failure and other cardiac issues.²

Patient and Population Burden

In the United States, approximately 100,000 people are affected by the disease, and about 1,800 to 2,000 infants are born with SCD every year.³ The disease predominately impacts people of African and Hispanic descent, occurring in approximately 1 in 500 African-Americans and 1 in 36,000 Hispanic-Americans. The incidence of sickle cell trait is approximately 1 in 12 African-Americans.⁴ Globally, the disease is even more common, particularly in sub-Saharan Africa, and affects millions of individuals worldwide.

Even in the U.S., where patients have better access to modern forms of preventive care and treatment, SCD can reduce life expectancy by an average of 25-30 years, and results in thousands of hospitalizations annually.⁵ Depending on the severity of an individual's condition, hospital encounters and emergency department visits can range from 0 to over 10 times per year. Both utilization and hospitalization are highest for the 18-30 year old demographic, with an average utilization rate of 3.61 encounters a year and a re-hospitalization rate of 41.1%.⁶

Current Treatment Options

Currently, there is no widely available cure for sickle cell disease. Bone marrow transplants are potentially curative, but their use is limited due to the high cost of the procedure, the difficulty of locating appropriate donors, and the level of risk associated with the procedure.⁷ It is typically performed in children, though recent research has shown that it may be appropriate for adult patients as well.⁸

In the absence of a widely available cure, medical treatment for patients with sickle cell disease focuses on disease management, acute episodic care during sickling crisis, and symptomatic treatment for complications. Regular blood transfusions are sometimes used as a preventive measure; however, they can lead to abnormally high levels of iron in the blood which can cause long-term organ damage.⁹

Hydroxyurea is currently the only FDA-approved drug that treats the underlying causes of sickle cell disease. Approved by FDA in 1998, the drug stimulates the production of fetal hemoglobin in some patients with sickle cell disease. The exact mechanism of action of the drug in sickle cell disease is not fully understood, but hydroxyurea has been shown to reduce the frequency of sickle cell disease-related complications. However, there are several limitations of the drug that inhibit its widespread use and underscore the need for further development of alternative agents.

Challenges in Drug Research and Development

A number of barriers contribute to the lack of treatment options for sickle cell patients. Sickle cell disease is complex and affects multiple systems in the body, which complicates efforts to successfully translate basic scientific findings into new therapeutics. Existing therapies used to manage symptoms of the disease often only treat one aspect of the disease and do not address the larger network of interactions that cause VOCs and other ailments.¹⁰ Since the disease causes damage to a number of different systems, endpoint selection can be particularly challenging.

Sickle cell disease is also subject to many of the same research barriers as any rare disease—the patient population is relatively small, and designing clinical trials that can enroll adequate numbers of patients to sufficiently power a trial is challenging. Sickle cell disease has several sub-types that have differing clinical manifestations, which can further complicate trial design. In response, many researchers have called for new approaches to clinical trial design that can ensure sufficient enrollment, redefine appropriate study endpoints, and account for the heterogeneity of the patient population.¹¹

The largest funder of basic, translational, and clinical care research on sickle cell disease are the National Institutes of Health, which provide roughly \$90 million in annual funding.¹² However, there is also an increased interest in the development of drugs to treat sickle cell disease by industry, and the FDA is interested in facilitating this drug development.

Regulatory Efforts to Facilitate Drug Development for Rare Diseases

The FDA has taken a number of steps to encourage drug developers to target rare conditions such as sickle cell disease. These include incentive programs for orphan drugs and rare pediatric diseases, the development of expedited approval pathways, and initiatives aimed at incorporating the patient voice into the drug development and approval process.

Incentive programs

FDA has created several incentive programs to encourage drug manufacturers to develop therapeutic products for rare diseases. Under the Orphan Drug Designation program, a drug or biologic may be granted orphan status if it is intended to treat, diagnose, or prevent a disease that affects fewer than 200,000 people in the US, or is not expected to recover the cost of its development. Once designated, orphan drug products are exempt from the user fee that manufacturers are generally required to pay for a pre-market approval application, and the sponsor is also granted tax incentives for clinical testing of the product. The agency also maintains an Orphan Products Grants program, which directly funds clinical research on drugs, biologics, devices, and medical foods for rare diseases. Since these programs were created in 1983, 3,000 drugs have been granted orphan drug designation, more than 500 clinical studies have been funded, and more than 460 drugs for rare diseases have been approved for marketing.¹³

Expedited Review and Approval Pathways

FDA has also established a number of pathways designed to expedite the review and approval process for drugs that target serious conditions. These include the above-mentioned priority review designation, through which the FDA commits to review a drug within six months following submission, rather than the typical 10-month timeframe. Fast-track designation, which can be granted based on either preclinical or clinical data, allows the manufacturer to meet earlier and more frequently with FDA to discuss the drug under development, and to submit its marketing application on a rolling basis rather than all at once. Under the accelerated approval program, the FDA may provide conditional approval for a drug based on a surrogate or intermediate endpoint, provided that the manufacturer conducts post-approval trials to confirm the drug's benefit. The newest of these expedited review programs is breakthrough therapy designation, which is reserved for drugs that show early clinical evidence of a substantial improvement over existing products for a particular disease.¹⁴ Under this designation, the sponsor is eligible for the same benefits afforded under fast-track designation, and the FDA commits to working particularly closely with the sponsor to help inform and facilitate the development process. These designations can be used in conjunction with each other to further reduce the time to market. In 2012 alone, more than half of the drugs approved by the FDA were reviewed under at least one of these pathways.¹⁵

The Food and Drug Administration Safety and Innovation Act of 2012

Most recently, the Food and Drug Administration Safety and Innovation Act of 2012 directed the FDA to convene a public meeting on ways to accelerate drug development for rare pediatric diseases, as well as develop a strategic plan for encouraging this development. Under a separate provision of this legislation—the Prescription Drug User Fee Act (PDUFA) Reauthorization—the FDA also committed to hold a public meeting to discuss complex issues in developing new drugs and biologics for rare diseases. Following a three-day public workshop that combined these two overlapping subjects, the agency published its Strategic Plan to Accelerate the Development of Rare Disease Therapies for Children. The Plan outlines FDA's approach to supporting basic and translational science for pediatric rare diseases, enhancing collaboration between the agency and key stakeholders, aiding clinical trial design and performance, and strengthening its regulatory review process.

As part of a separate commitment under the PDUFA reauthorization, the agency is implementing the Patient-Focused Drug Development Initiative, the aim of which is to better incorporate the patient voice into the agency's regulatory process, including its assessments of treatment risks and benefits. Between 2012 and 2017, FDA will host 20 disease-specific public meetings focused on obtaining patient perspectives on their

disease.¹⁶ On February 7, 2014, the agency held a meeting focused on sickle cell disease, which included a discussion of patient perspectives on the available treatments for the disease, the decision to participate in clinical trials, and the outcomes of greatest interest to sickle cell patients.

Following this work under the PFDD, and in line with its broader efforts to accelerate drug development for rare diseases, the FDA is also working with researchers in the field to address issues related to endpoint selection and clinical trial design, which may help facilitate the development of new therapeutics for sickle cell patients. Under a cooperative agreement with the FDA, the Engelberg Center on Health Care Reform at the Brookings Institution is convening an expert workshop that brings together industry, academia, government, and patient representatives for the purpose of discussing these issues and identifying strategies for moving forward.

Accelerating Drug Development for Sickle Cell Disease: Workshop Agenda and Discussion Questions

Session I: Clinical Trial Endpoint Selection: Drug Development for Chronic Prevention versus Acute Management

Topics will include:

- What primary endpoints should be considered for drugs being developed for:
 - Chronic prevention
 - Acute management
- What additional secondary efficacy endpoints would be considered meaningful and supportive?
- Taking into account current clinical practice, is hospitalization use still a relevant endpoint for consideration?
- What endpoints correlate best with clinical benefit?

Session II: Clinical Trial Design—Special Considerations for Adult Clinical Trials

Topics will include:

- What is considered the ideal trial design for adult patients with sickle cell disease?
- For chronic prevention, what is the baseline level of disease severity which should be considered to show a meaningful change in the disease? Are there other considerations for the study population? Are there certain stratification factors which are considered important?
- Define further clinical benefit in the adult sickle cell patient
- What are the specific considerations for trial design and monitoring for adult patients with sickle cell disease?
- Are there any specific thoughts on the use of hydroxyurea during clinical trials that are studying a novel agent? Challenges and benefits?

Session III: Clinical Trial Design—Special Considerations for Pediatric Clinical Trials

Topics will include:

- What is considered the ideal trial design for pediatric patients with sickle cell disease?
- Are there certain stratification factors which are considered important in the pediatric patient (relevant age cohorts)?
- Are there specific considerations for the adolescent patient?
- Define further clinical benefit in the pediatric population.
- What are the specific considerations for trial design and monitoring for pediatric patients with sickle cell disease?

Session IV: Development of Patient-Reported Outcomes

A global discussion on the development of PROs, challenges, and how to facilitate the use of more PROs in sickle cell disease investigations.

Session V: Identifying Next Steps

Participants will identify the day's major themes that warrant future attention and analysis. What is discussed will also inform the agency's next steps.

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