REPORT

Sickle Cell Disease: Current Treatment and Emerging Therapies

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Background

Sickle cell disease (SCD) is a common, severe disorder that includes congenital hemolytic anemias caused by inherited point mutations in the β-globin gene.[1] These mutations result in abnormal hemoglobin polymerization, which leads to a cascade of physiologic consequences, including erythrocyte rigidity, vaso-occlusion, chronic anemia, hemolysis, and vasculopathy.[1] This change in the behavior of hemoglobin has profound clinical consequences, including recurrent pain episodes (known as sickle cell–related pain crises or vaso-occlusive crises), hemolytic anemia, multiorgan dysfunction, and premature death.[1] Newborn screening, early immunization, and prophylactic penicillin treatment in infants and children, as well as comprehensive management for pain and disease complications, have improved outcomes in these patients; however, the average life expectancy of a patient with SCD remains only about 40 to 50 years.[2,3]

Globally, it is expected that approximately 306,000 people are born every year with SCD; an estimated 79% of these births occur in sub-Saharan Africa. In the United States, approximately 100,000 people are living with SCD, including approximately 1 in 365 African Americans and 1 in 16,300 Hispanic Americans.[4,5]

The impact of SCD on patient quality of life (QOL) has been estimated to be greater than that of cystic fibrosis and similar to that of patients undergoing hemodialysis, which is widely recognized as having a severe impact on QOL.[6] Impairments are seen across functional and QOL domains and are particularly profound in terms of pain, fatigue, and physical function.[7,8]

Management of SCD can be intensive, time-consuming, and costly, particularly in patients with recurrent acute pain episodes. On average, patients with SCD experience approximately 3 vaso-occlusive crises each year, of which at least 1 requires inpatient treatment and 1 requires emergency department management without admission.[9] Among patients who require admission, the median length of stay is approximately 6 days.[9] More than 90% of acute hospital admissions for patients with SCD are due to severe and unpredictable pain crises, and these crises are responsible for 85% of all acute medical care for these patients.[10] Estimates of the

ABSTRACT

Sickle cell disease (SCD) is among the most common genetic diseases in the United States, affecting approximately 100,000 people. In the United States, SCD is characterized by a shortened life expectancy of only about 50 years in severe subtypes, significant quality-of-life impairments, and increased healthcare utilization and spending. SCD is characterized by chronic hemolytic anemia, vaso-occlusion, and progressive vascular injury affecting multiple organ systems. The pathophysiology is directly related to polymerization of deoxygenated hemoglobin, leading to a cascade of pathologic events including erythrocyte sickling, vaso-occlusion, tissue ischemia, and reperfusion injury as well as hemolysis, abnormal activation of inflammatory and oxidative pathways, endothelial dysfunction, increased oxidative stress, and activation of coagulation pathways. These multifactorial abnormalities have both acute and chronic clinical consequences across multiple organ systems, including acute pain episodes, chronic pain syndromes, acute chest syndrome, anemia, stroke and silent cerebral infarcts, cognitive dysfunction, pulmonary hypertension, and a wide range of other clinical consequences. Hydroxyurea was the only approved treatment for SCD for nearly 2 decades; in 2017, L-glutamine oral powder was approved for the prevention of the acute complications of SCD. During the last several years there has been a dramatic increase in research into treatments that address distinct elements of SCD pathophysiology and even new curative approaches that provide new hope to patients and physicians for a clinically consequential disease that has long been neglected.

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lifetime care costs for SCD vary dramatically based on underlying assumptions, from approximately $500,000 to nearly $9 million.[11,12]

Few options are currently available for the management of SCD. Hydroxyurea, which until recently was the only FDA-approved drug for adults with severe SCD genotypes (and is also used off-label for adults with less severe genotypes and children ages 9 months to 2 years), improves the course of SCD and results in substantial cost savings.[13,14] Unfortunately, hydroxyurea is underutilized and treatment adherence is poor for a variety of reasons.[15] Recently, L-glutamine became the second drug approved for SCD in the United States.[16]

Red blood cell (RBC) transfusion is common in patients with SCD for the management of acute complications, and regular or chronic transfusion regimens are used for stroke prevention in at-risk patients. Despite being effective for the management of both acute and chronic complications of SCD,[1] transfusion is associated with annual costs exceeding $60,000; it requires routine, costly iron chelation therapy to prevent liver and other organ damage as a result of iron overload; and it is associated with the risk of alloimmunization.[12,17] Stem cell transplantation, while potentially curative, is limited by a scarcity of matched donors and the risks for adverse events (AEs) and death.[18] Currently under investigation are novel gene therapies that offer considerable hope for a more broadly applicable curative therapy.

This review will first examine our current understanding of the pathogenesis of SCD and explore the broad range of clinical manifestations of this disease. It will then focus on the relatively limited current therapeutic options, recent clinical trials, and near-term therapies for the chronic and acute management of the disease.

The Pathogenesis of SCD

SCD is not a single disorder. Rather, it is a clinical entity that includes a number of heritable hemolytic anemias with widely variable clinical severity and life expectancy. All involve point mutations in the β-globin gene, resulting in an abnormal hemoglobin referred to as hemoglobin S (HbS).[19] In the most common forms of SCD, which are also the most severe, the patient inherits the sickling gene from both parents and produces HbS exclusively.[19] The compound heterozygous forms of SCD are defined by the production of HbS and another abnormal β-globin protein.[19]

The point mutation in the β-globin gene results in the substitution of glutamic acid in position 6 with valine in the resulting protein.[1] This small change in the amino acid sequence of hemoglobin has profound structural and functional consequences, because under low oxygen conditions, it produces a hydrophobic region in deoxygenated HbS that promotes binding between the β1 and β2 chains of 2 hemoglobin molecules, ultimately resulting in HbS polymerization into rod-shaped structures.

The polymerization of HbS changes both the shape and physical properties of RBCs, resulting in red cell dehydration, increased rigidity, and a variety of deleterious structural abnormalities, including the characteristic sickled RBCs from which the disease gets its name.[20] The rigidity of deoxygenated RBCs contributes to vaso-occlusion by impeding their passage through the microcirculation.[1] Repeated cycles of tissue hypoxia and reperfusion damage elicits upregulation of adhesion molecules, such as P-selectin and E-selectin, on the vascular endothelium. This promotes adherence of RBCs, white blood cells (WBCs), and platelets, further contributing to a propensity for vaso-occlusive events and a chronic inflammatory state.[1,20,21]

Hemolytic anemia is an important driver of the pathophysiology of SCD. The average RBC in homozygous SCD survives only approximately 10 to 20 days, compared with 120 days for normal RBCs.[22] Destruction and release of the contents of RBCs into the circulation results in progressive endothelial dysfunction and proliferation, which may in part be due to scavenging of nitric oxide (a key regulator of vascular tone) by extracellular hemoglobin.[20,23-25] The end result is an impaired vasodilatory response, chronic activation of endothelial cells and platelets, and an ongoing inflammatory state. Exposure of phosphatidylserine, which is normally only found on the inner surface of the RBC membrane, also occurs, and this predisposes cells to premature lysis and promotes the activation of coagulation pathways.[26,27] Excess levels of adenosine, often related to stress, are also seen in SCD. Adenosine signaling contributes to the pathophysiology of SCD by stimulating the production of erythrocyte 2,3-bisphosphoglycerate, an intracellular signal that decreases oxygen binding to hemoglobin.[28]

Clinical Consequences of SCD

SCD is associated with a broad range of acute and chronic complications that have a profound impact on patients, their families, and society. As noted previously, patients with SCD can present with a broad range of manifestations and disease severities depending upon the underlying genetics of their disease; the discussion below primarily refers to the most common homozygous form of the disease.

Acute pain events affect approximately 60% of patients with SCD in any given year.[29-31] Such events can begin as early as 6 months of age and may recur throughout the patient's life. Acute pain events are responsible for more than three-quarters of hospitalizations in patients with SCD,[32] and from the perspective of the patient, they are often considered the most important and disabling consequence of the disease.[32,33] Many such events can be managed at home with oral analgesics, hydration, and rest; however, in some cases, patients must be administered opioids in the emergency department or hospital setting to achieve adequate pain control.[34] Acute pain events are major contributors to the high healthcare utilization of many patients with SCD.[32]

Stroke is the most common, and most concerning, long-term risk of homozygous SCD. The risk for stroke in children with SCD is approximately 300 times higher than for children without SCD,

and approximately 25% of adults with SCA will have a stroke.[20,35] Silent cerebral infarcts occur in 27% of patients by age 6 years and in 37% by age 14 years; the prevalence of silent cerebral infarct in adults is less well defined, although it is likely that progressive injury occurs as patients age.[36] Cognitive impairment is seen in 5 to 9 times as many patients with SCD as compared with patients without SCD, likely due to silent repetitive ischemic brain injury.[29] The use of transcranial Doppler or MRI to screen patients can help to identify patients who would benefit from additional measures to decrease the frequency and severity of stroke.[20]

Acute chest syndrome is a common and potentially fatal complication that is particular to SCD[1,20]; it is formally defined as a new radiodensity on chest radiograph accompanied by fever and/or respiratory symptoms.[37] Acute chest syndrome is often triggered by infection, an embolic event, and/or occlusion of the pulmonary vasculature. Although the incidence is highest in children aged 2 to 4 years,[37] the severity of acute chest syndrome increases with age; in adults, more than 10% of cases result in death or severe complications.[20] The greater disease severity seen in adults may be related to a higher incidence of emboli in bone marrow or fat.[38]

Pulmonary hypertension has been considered a common complication of SCD; however, the true incidence of pulmonary hypertension in patients with SCD remains an open question. Early studies estimated the rate to be as high as 32%; in a more recent study in which patients underwent right heart catheterization, the incidence of pulmonary hypertension was estimated to be approximately 6%.[23,39,40] The risk for pulmonary hypertension may be linked to the rate of hemolysis.[41]

SCD is accompanied by severe functional asplenia in the vast majority of patients, which may result in impaired clearance of blood-borne bacteria and an increased risk for infection, particularly among young children.[20]

Acute anemic events occur in up to half of patients with SCD; they can be fatal.[20] Acute splenic sequestration is also a potentially fatal complication of SCD; splenic enlargement is accompanied by hypovolemia and a rapid fall in hemoglobin levels. Acute splenic sequestration is common in infants and children.[42] Other anemic events that may occur in patients with SCD include aplastic crisis (a temporary absence of RBC production, often associated with an acute viral illness such as parvovirus) and hyperhemolysis.[43,44] Hemolysis seen in patients with SCD can result in cholelithiasis, with about 20% of patients presenting with acute pain that often require surgical removal of the gallbladder.[45]

Venous thromboembolism (VTE), which includes both deep vein thrombosis and pulmonary embolism, is increasingly recognized as an important complication of SCD that occurs as a result of the hypercoagulable state that is elicited by the disease. By age 30 years, up to 25% of patients with SCD have experienced ≥1 episode of VTE.[46] The risk for VTE is approximately 1.75-fold higher among patients with compound heterozygous disease as compared with homozygous disease.[46]

The kidney is at particular risk in SCD.[47] In fact, nephropathy begins as early as infancy, with impaired urine-concentrating ability and impaired glomerular hyperfiltration. Up to 60% of patients with SCD develop chronic kidney disease, and at least 18% progress to end-stage renal disease and require dialysis or renal transplantation; these patients are at increased risk for death.[48-50]

Other common clinical sequelae of SCD include avascular necrosis and priapism. Avascular necrosis of the bone is seen in 25% to 50% of adults as a result of vaso-occlusion, tissue hypoxia, and subsequent localized osteonecrosis.[51] Approximately 20% of adults with SCD develop leg ulcers, primarily in areas with less subcutaneous fat or thin skin, as a result of arteriovenous shunting that deprives the skin of oxygen, often combined with local insult to the tissues as a result of trauma; patients with higher rates of hemolysis are at increased risk for leg ulcers.[52] Up to 35% of men with SCD experience ischemic priapism as a result of obstruction of venous drainage, with the potential for permanent erectile dysfunction.[53]

Beyond these commonly seen long-term consequences of SCD, a number of other clinical sequelae are clinically important but less frequently observed. Between 15% and 20% of patients develop retinopathy as a result of retinal artery occlusion and ischemia; if left untreated, it can result in loss of visual acuity.[54] For reasons that are poorly understood, patients with compound heterozygous disease are more likely to be affected by retinopathy than those with homozygous disease.[55] SCD is also associated with a range of maternal and perinatal complications during pregnancy, such as preeclampsia, preterm labor, intrauterine growth restriction, and spontaneous abortions.[56] The physiological changes of pregnancy, such as increased metabolic demand, increased blood viscosity, and hypercoagulability, all increase risk of SCD complications. Vaso-occlusion can also occur in the placenta, causing impaired uteroplacental circulation that leads to chronic fetal hypoxia and adverse fetal outcomes.[56]

The most common and clinically concerning complications of SCD are summarized in **Table 1**.[20,23,29-32,35-37,39,40,45,46,48-51,53,55,56]

Mortality Associated With SCD

While some progress has been made toward improvement in health outcomes, patients with homozygous SCD still have a dramatically shortened lifespan compared with the overall population. In a study that evaluated all deaths from SCD in the United States between 1979 and 2014, the average age at death increased from just 28 years to 43 years.[3] The primary causes of death among patients with SCD have shifted over time: Between 1979 and 1989, acute cardiac and infection complications were the most common underlying causes of death in this population; by 2010 to 2014, chronic cardiac complications were most commonly identified as the underlying cause

of death. Causes of death in this patient population are summarized in the **Figure**.[3]

Comorbidities

In addition to the complications that are driven directly by the pathophysiology of SCD, patients are also at an increased risk for other health issues that add considerably to the burden of disease. Study results showed that depression and anxiety were seen in 27.6% and 6.5% of patients with SCD, respectively; depressed subjects had pain on significantly more days (71.1%) than nondepressed subjects (49.6%), as well as higher ratings for pain severity, distress caused by pain, and interference caused by pain.[57] Asthma is common, occurring in approximately 25% of patients with SCD. In children, asthma is associated with an increase in acute pain crises, acute chest syndrome, and premature mortality.[20] Of note, some observational data suggest that SCD is associated with an increased rate of autoimmune disease that often goes unrecognized due to overlapping symptoms.[58]

The Management of SCD: Present and Future

Treatment options for SCD have historically been limited. An increased understanding of the molecular underpinnings of the disease, along with the encouragement by regulatory authorities, has led to an expansion of newly studied therapies, which aim to address the disease from the proximal HbS polymerization event to more distal pathologic processes, such as RBC and SBC adhesion to the vascular endothelium. Early research also suggests that gene therapy may offer the potential for curative treatment.

TABLE 1. Acute and Chronic Complications of Sickle Cell Disease[20,23,29-32,35-37,39,40,45,46,48-51,53,55,56]

Acute anemia	• Occurs in up to 50% of patients with SCD • May be fatal
Acute chest syndrome	• Incidence highest in children aged 2 to 4 years • Severity increases with age; in adults, >10% of cases result in death or serious complications
Acute pain events	• Affect ~60% of patients with SCD in any given year • Responsible for up to 75% of SCD-related hospitalizations
Cholelithiasis	• Occurs in approximately 20% of patients • Often requires surgical removal of the gallbladder
Functional asplenia	• Seen in majority of patients with SCD • Associated with increased risk for infection
Ischemic priapism	• Occurs in up to 35% of men with SCD
Nephropathy	• Overt kidney disease develops in up to 60% of patients • 18% progress to end-stage renal disease
Osteonecrosis	• Occurs in 25%-50% of adults with SCD
Pulmonary hypertension	• Most recent estimates suggest incidence of 6%
Retinopathy	• Occurs in 15%-20% of patients with SCD • May be more common in patients with compound heterozygous disease
Risks in pregnancy	• Associated with increased risk for preeclampsia, preterm labor, intrauterine growth restriction, spontaneous abortion
Stroke	• Risk is elevated by 300-fold in children with SCD vs children without • Approximately 25% of adults with SCD have stroke • Silent cerebral infarcts occur in 37% of patients by age 14 years • Cognitive impairment is observed in 5 to 9 times as many individuals with SCD as those without
Venous thromboembolism	• Occurs in up to 25% of patients with SCD by age 30 years • Risk higher in patients with compound heterozygous disease

SCD indicates sickle cell disease.

Established Treatments

Hydroxyurea was approved by the FDA in 1998 to reduce the frequency of painful crises and to reduce the need for blood transfusions in adults with homozygous SCD who have recurrent moderate to severe painful crises.[13] Hydroxyurea is a ribonucleoside diphosphate reductase inhibitor that was first used in myeloproliferative disease[19] and its mechanism in SCD is multifactorial, but it primarily involves increasing production of fetal hemoglobin (HbF); the absence of the mutated β chain in HbF means that it is unaffected by the sickle mutation.[59] While the properties of HbF are somewhat different than those of normal adult hemoglobin, incorporation of HbF into normal adult RBCs is not associated with functional impairment.[60] Some patients with SCD who have naturally high levels of HbF have milder, although not asymptomatic, disease.[60]

The efficacy and safety of hydroxyurea for the treatment of SCD in adults was evaluated in a double-blind, randomized clinical trial. Patients who had historically had ≥3 pain crises per year were randomly allocated to hydroxyurea (n = 152) or placebo (n = 147).[61] The trial was halted after 21 months; at this time, patients who had received hydroxyurea experienced 2.5 crises per year compared with 4.5 per year among those who had received placebo (P <.001). Among patients assigned to hydroxyurea, both times to first crisis (3.0 vs 1.5 months; P = .01) and second crisis (8.8 vs 4.6 months; P <.001) were longer, and fewer

patients who received hydroxyurea required transfusion ($P = .001$). A long-term analysis conducted in adult patients who had received up to 9 years of treatment found that hydroxyurea was associated with a significant (40%) reduction in mortality.[62]

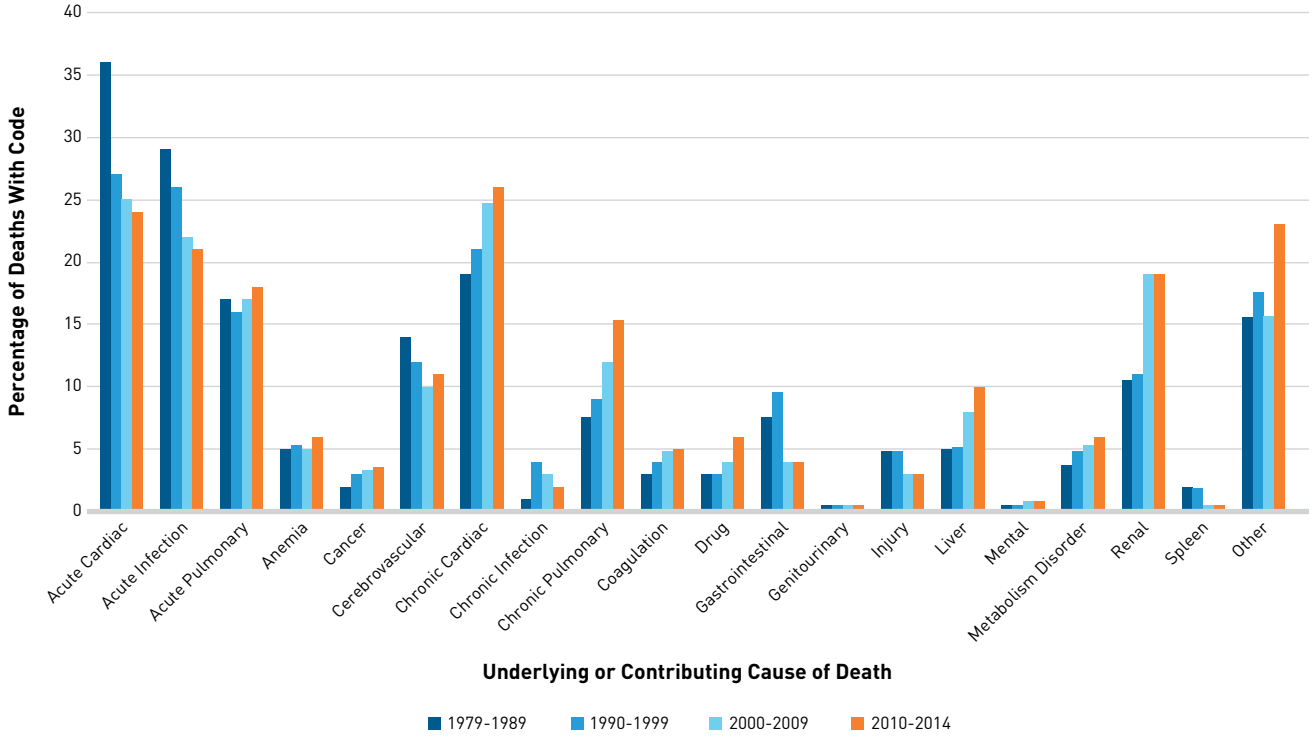
Evidence supporting the use of hydroxyurea in children came from the BABY HUG and ESCORT-HU studies. In the placebo-controlled BABY HUG trial, hydroxyurea was associated with a statistically significant reduction in the rates of initial and recurrent episodes of pain, dactylitis, acute chest syndrome, and hospitalization.[63] In the ESCORT-HU study, the rate of vaso-occlusive episodes was reduced from 2 in the 12 months prior to enrollment to 0 after 12 months of treatment, and the number of hospitalizations was reduced from 2 to 0 during the same time frame.[64] These data supported the approval of hydroxyurea for pediatric patients in late 2017.[65]

The evidence that hydroxyurea therapy benefits children and adults with homozygous SCD is overwhelming. Unfortunately, multiple barriers exist to its use in patients with SCD, and studies have found that adherence to hydroxyurea is often poor.[66-68] AEs—which include alopecia, rash, nail discoloration, headache, nausea, and weight gain,[13] as well as the need for frequent blood draws—have a negative impact on initiation of and long-term adherence to treatment. Hydroxyurea is potentially carcinogenic, although no increased risk for malignancy has been seen in patients with SCD, and may also have effects on fertility.[59]

Long-term RBC transfusion therapy is commonly given to patients with SCD for the management of both acute and chronic complications.[1] Transfusion has a number of beneficial effects in SCD, including correcting anemia and suppressing endogenous RBC production.[1] However, chronic, long-term use of transfusions can cause iron overload; parenteral or oral iron chelation therapy is used to prevent iron loading in the liver.[19] Chronic exchange transfusion (erythrocytapheresis) sometimes overcomes iron overload, but it typically requires a central venous catheter and access to specialized facilities that can perform this procedure.[69] Alloimmunization, in which the transfused patient develops an immune response to donor RBC antigens, is a risk associated with chronic transfusions that is more common in adults.[20] Such reactions complicate between 4% to 11% of transfusions for SCD.[70,71]

Nearly 2 decades after the approval of hydroxyurea, L-glutamine was approved by the FDA in 2017 to reduce acute complications of homozygous SCD in adult and pediatric patients aged ≥5 years.[16] L-glutamine has a complex, indirect mechanism of action that may be related to decreasing the susceptibility of sickle erythrocytes to oxidative damage.[72] The approval of L-glutamine was based on a study of 230 patients who were randomized to L-glutamine or placebo; approximately 66% of patients in both groups were taking concomitant hydroxyurea. Treatment with L-glutamine was associated with a reduction in pain crises from 4.0 in the placebo

FIGURE. Percentages of Underlying and Contributing Causes Among Sickle Cell Disease–Related US Deaths by Time Period, 1979-2014[3]



group to 3.0 in the L-glutamine group ($P = .005$) and a reduction in hospitalizations from 3.0 to 2.0, respectively.[73] AEs of L-glutamine consisted of low-grade nausea, noncardiac chest pain, fatigue, and musculoskeletal pain. Adherence to L-glutamine therapy may prove challenging for many patients because it is formulated as a powder and requires twice-daily administration in quantities of up to 15 grams. L-glutamine's long-term efficacy and safety remain to be determined; further, the cost of this therapy (approximately $3000 per month for adults) may prove to be a barrier.[74]

Currently, hematopoietic stem cell transplant (HSCT) is the only established curative therapy available for patients with SCD.[19,20] Commonly used for hematopoietic malignancies, HSCT is a time-intensive, rigorous, potentially high-risk procedure; it is only used when the benefits of a cure outweigh the considerable risks of the procedure, and only when a suitable donor is available. However, ≥2000 patients with SCD have undergone this procedure and survival has exceeded 90%.[75,76] The procedure relies on the identification of a suitable donor; only about 10% to 20% of patients in the United States have matched related donors, although the pool of potential candidates for HSCT has expanded with new approaches that utilize matched unrelated donors and haploidentical donors.[19] Children tolerate transplant relatively well, and some argue that all children with a matched sibling should be offered this therapy. However, many adults are not able to endure the required myeloablative regimens.[19,77,78]

Investigative Treatments for SCD

Novel therapies for SCD approach the disease from a number of directions.[19] Comprehensive reviews of the broad range of therapies currently in the pipeline for SCD have been published recently (see Kapoor et al)[19]; this section will focus on several therapies in later-stage development that, if successful, will enter the therapeutic paradigm for SCD in the relatively near term.

Crizanlizumab is a humanized monoclonal antibody that binds to P-selectin, blocking its interaction with P-selectin glycoprotein ligand and inhibiting WBC and RBC adhesion to the vascular endothelium.[19] It was evaluated both alone and in combination with hydroxyurea therapy for the prevention of sickle cell–related crises in patients with SCD.[79] In this double-blind, randomized, placebo-controlled phase 2 trial, participants who were receiving concomitant hydroxyurea, as well as patients who were not receiving hydroxyurea, were randomly allocated to treatment with crizanlizumab 2.5 mg/kg, crizanlizumab 5.0 mg/kg, or placebo, all administered intravenously 14 times over the course of a year. The primary endpoint was the annual rate of sickle cell–related pain crises among participants receiving high-dose therapy versus placebo.

The study enrolled a total of 198 patients at multiple sites.[72] Among patients who received high-dose crizanlizumab, the median rate of crises per year was 45.3% lower, falling from 2.98 per year with placebo to 1.63 per year with crizanlizumab. High-dose crizanlizumab also significantly increased the median time to first crisis to 4.07 months from 1.38 months ($P = .001$), as well as the median time to second crisis (10.32 months vs 5.09 months). Of note, crisis rates were reduced both among those receiving hydroxyurea (32.1%) and those who were not receiving hydroxyurea (50.0%). Serious AEs were reported at the same rate in the high-dose crizanlizumab and placebo groups; AEs that occurred in ≥10% of participants in either active-treatment group and at a 2-fold or greater frequency than placebo included arthralgia, diarrhea, pruritus, vomiting, and chest pain. Next-generation agents that block P-selectin, designed to improve safety and duration of action, are in clinical development.

Another novel treatment, voxelotor, directly targets HbS polymerization by forming a reversible covalent bond with the N-terminal valine of the α chain of hemoglobin. This changes the conformation of hemoglobin in a manner that increases its affinity for oxygen, reducing the amount of deoxygenated HbS available for polymerization.[80] Preclinical studies suggested that voxelotor improved RBC deformability and increased blood viscosity in vitro.[81]

The efficacy of voxelotor was assessed in a phase 1/2, randomized, double-blind, placebo-controlled, ascending-dose trial in adult healthy volunteers and in patients with SCD, followed by a single-arm, open-label extension study.[82] A total of 38 subjects with SCD received voxelotor at dosages of 500, 700, or 1000 mg/day, or placebo, for 28 days; and 16 subjects received voxelotor at 700 or 900 mg/day, or placebo, for 90 days. No sickle cell crises occurred during treatment and improvements in surrogate markers were observed, including increased hemoglobin, reduced hemolysis, and a decline in the percentage of sickled red cells.

After 2 weeks of treatment, all doses of voxelotor were associated with increases in median hemoglobin levels and/or a reduction in clinical laboratory markers of hemolysis.[82] These improvements persisted through 6 months of treatment, with a median increase in hemoglobin of approximately 1 g/dL, with >50% of patients achieving an increase in hemoglobin of ≥1 g/dL from baseline, regardless of hydroxyurea use.

On the basis of these results, a phase 3 trial of voxelotor was initiated in patients with SCD. In the Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) trial, 274 patients aged ≥12 years with hemoglobin levels from ≥5.5 to ≤10.5 g/dL, with 1 to 10 vaso-occlusive crises in the previous year, were randomly allocated to voxelotor 1500 mg, voxelotor 900 mg, or placebo. Approximately two-thirds of patients were taking concomitant hydroxyurea. The primary endpoint was the proportion of patients with increases in hemoglobin of >1 g/dL.[83]

In the intent-to-treat analysis, a hemoglobin response was seen in 51% of patients in the voxelotor 1500-mg group (95% CI, 41%-61%), 33% of the voxelotor 900-mg group (95% CI, 23%-42%), and 7% of the placebo group at week 24 (95% CI, 1%-12%) ($P < .001$

for voxelotor 1500 mg vs placebo).[83] Per protocol, the percentage of participants who had a hemoglobin response was 59% in the 1500-mg voxelotor group, 38% in the 900-mg voxelotor group, and 9% in the placebo group. A trend was seen toward decreased vaso-occlusive crises in both voxelotor groups, from 3.19 crises per person per year in the placebo group to 2.77 and 2.76 crises in the 1500-mg and 900-mg groups, respectively. The annualized incidence rates of acute anemic episodes (defined as a decrease in hemoglobin level of >2.0 g/dL from baseline at any time) were 3-fold lower in the voxelotor 1500-mg group (0.06 episodes/year) and 4.5-fold lower in the voxelotor 900-mg group (0.04) as compared with placebo (0.18). The adjusted mean change in hemoglobin from baseline to week 24 in the intent-to-treat group was 1.1 g/dL (95% CI, 0.9-1.4; P <.001) in the 1500-mg group, 0.6 g/dL in the 900-mg group (95% CI, 0.3-0.8), and −0.1 g/dL (95% CI, −0.3 to 0.2) in the placebo group. Of note, significant reductions in markers of hemolysis were observed in patients treated with voxelotor 1500 mg, including indirect bilirubin levels and the percentage of reticulocytes; other markers, including absolute reticulocyte count and lactate dehydrogenase level, showed numerical, but nonsignificant, decreases from baseline to week 24.

The rate of AEs was similar across groups. AEs of grade 3 or greater were observed in 26%, 23%, and 26% of the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively. Most AEs were unrelated to the trial drug or placebo.[83] Clinical trials are ongoing to determine longer-term safety, including in subpopulations for which elevated blood viscosity might exacerbate AEs.

Current therapies for SCD, as well as most that are in the pipeline (**Table 2**),[19,80] are directed at reducing the frequency of vaso-occlusive crises, leaving the management of acute crises to be purely symptomatic. Available treatments that shorten the duration of acute vaso-occlusive crises would also be desirable. To this end, a "pan-selectin" approach to the inhibition of adhesion molecules has also been explored, in this case for the acute treatment of vaso-occlusive crises. In a phase 2, randomized, placebo-controlled, double-blind study, 76 patients with vaso-occlusive crises related to their SCD were treated with rivipansel, a small molecule that binds to all 3 members of the selectin family (E-, P-, and L-selectin).[84] Participants were treated every 12 hours at a dosage of 20 mg/kg or placebo for up to 15 doses. The composite primary endpoint was the resolution of the vaso-occlusive crisis, which was defined as a sustained reduction in pain as measured by a visual analogue scale, transition to oral analgesia, or documentation that the patient was ready for discharge. While there was no difference between active treatment and placebo in time to reach the composite endpoint, rivipansel was associated with a clinically meaningful reduction in mean time to vaso-occlusive crisis of 41 hours (a 28% reduction vs placebo; P = .19). Mean cumulative intravenous opioid analgesic use was reduced significantly, by 83%, with rivipansel.[84]

While these results were promising, the results of the phase 3 placebo-controlled trial of the efficacy of rivipansel in the setting of hospitalization for acute pain crisis were recently released, and neither the primary endpoint of time to readiness for discharge nor the key secondary endpoints of time to discharge, cumulative intravenous (IV) opioid consumption, or time to discontinuation of IV opioids were met.[85] A fuller description of the results of this trial awaits publication or presentation in a peer-reviewed forum.

Gene Therapy for SCD

SCD may be amenable to gene therapy and gene editing technologies. Early observations suggest that the gene therapy approach is associated with less frequent treatment-related toxicities compared with HSCT.[86] In an early study, hematopoietic cells were transduced ex vivo with a lentiviral vector carrying a construct that suppresses production of BCL11A, which, ultimately, results in upregulation of the production of gamma globulin.[87] This treatment requires patients to undergo myeloablative therapy, after which the transduced hematopoietic cells are reinfused. In an initial proof-of-principle study, 1 patient had an absence of irreversibly sickled cells on peripheral smear with substantially reduced hemolysis. Further evaluation showed that nearly 25% of erythrocytes carried HbF. As a result of this upregulation, intracellular concentrations of HbF are increased, and levels of HbS are decreased, inhibiting polymerization. As of the time of this publication, at least 12 clinical trials of gene therapy for SCD are ongoing. However, gene therapy remains subject to considerable technological and regulatory challenges and is likely to be costly.

Conclusions

The pathophysiology of SCD is complex, with contributions from multiple pathways. No single pharmacologic therapy has been able

TABLE 2. The Near-term Pipeline for Sickle Cell Disease[19,80]

Drug	Target/Mechanism of Action	Phase
Crizanlizumab	Humanized monoclonal antibody directed against P-selectin; blocks interaction of PSGL-1, inhibiting leukocyte and erythrocyte adhesion to the vascular endothelium	3 (NCT01895361)
Voxelotor	Targets HbS polymerization by forming a reversible covalent bond with the N-terminal valine of the α chain of hemoglobin; changes the conformation of HbS, increasing affinity for oxygen and reducing the amount of deoxygenated HbS available for polymerization	3 (NCT03036813)

HbS indicates sickle hemoglobin; PSGL-1, P-selectin glycoprotein ligand.

to completely suppress the adverse outcomes of SCD, although several therapies, acting on different pathways, have shown the ability to provide varying degrees of improvement in outcomes in clinical practice and trials. While the optimal therapeutic strategy would be to replace the mutated β-globin gene altogether—either through gene therapy or stem cell transplant—both strategies are complex, costly, and associated with considerable risks.

Given the potential for the approval of a range of different drugs with varying mechanisms of action, it is possible that the treatment of SCD may be optimized for individual patients by using these therapies either alone or in combination. The clinical utility of multiagent therapy has now been demonstrated in clinical trials of new agents, in which subgroups of patients who were already receiving hydroxyurea nevertheless experienced substantial and statistically significant reductions in crisis rates. Such a "cocktail" approach is widely used in numerous other therapeutic areas, from cardiology to epilepsy and cancer, allowing treatment to be tailored to the individual patient.[88] ■

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