INTRODUCTION

Sickle cell disease (SCD) is a worldwide health concern. Despite improvements in outcomes since its discovery, the life expectancy for patients with SCD is decreased by about 25 to 30 years. Globally, as many as 25 million people are estimated to have homozygous sickle cell, with more than 300,000 babies born annually with this genotype. SCD commonly occurs in areas with a high prevalence of malaria, such as sub-Saharan Africa, the Middle East, and India. However, because of migration patterns, SCD and sickle cell genes have been disseminated into areas where the occurrence of malaria is not prevalent. Approximately 8% of African-Americans are carriers of sickle cell genes. Within the United States, population estimates report that approximately 100,000 Americans live with SCD.

SCD is an inherited genetic condition distinguished by the presence of structurally abnormal hemoglobin caused by a substitution in the sixth amino acid of the beta polypeptide chain of glutamic acid with valine. Causes of this abnormality are attributed to the homozygous inheritance of the sickle cell gene (Hbs), which results in the anomalous structure of hemoglobin SS (Hbs/S) or by heterozygous inheritance of Hbs coupled with other globin chain abnormalities. Usually these malformations are hemoglobin C (Hbs/C), which is caused by the replacement of glutamic acid with lysine, beta-thalassemia (Hbs/β-thalassemia), or beta-thalassemia (Hbs/β-thalassemia). Whereas Hbs/β-thalassemia patients have no normal hemoglobin (Hba), patients with Hbs/β-thalassemia have detectable levels of Hba that mitigates the severity of the disease. Generally, Hbs/C and Hbs/β-thalassemia produce less-severe clinical manifestations of SCD. However, there is a noted increased prevalence of proliferative sickle retinopathy with Hbs/C. Clinical presentations of SCD in patients with Hbs/S and Hbs/β-thalassemia genotypes vary among individuals but are usually severe in nature.

A major cause of hospitalizations among patients with SCD is the intense, recurrent ischemic pain related to the condition. These acute, severely painful episodes are commonly referred to as vaso-occlusive episodes (VOEs) and are a distinguishing feature of SCD. Though the mechanism by which these events occur is complex, factors related to the occurrence of these episodes are erythrocyte microvascular occlusion, chronic inflammation, impaired oxygen supply, and infarction-reperfusion injury. In addition to vaso-occlusive factors, painful episodes can be associated with chronic bone joint pain secondary to avascular necrosis. Pain related to SCD can vary in intensity, frequency, and quality.

patients age and SCD progresses, complications due to SCD and increased frequency of VOEs have shown a correlation to increased mortality.

Currently, universal treatment approaches for SCD revolve around infection prevention through the use of antibiotics, vaccines, and education; blood transfusions for prevention of stroke and silent cerebral infarctions; and hydroxyurea. Historically, use of hydroxyurea for adults with SCD was the only oral treatment option approved by the Food and Drug Administration (FDA) for the reduction of pain episodes, acute complications, and need for blood transfusions that decreased mortality. Multiple research findings agree that there is significant underutilization of hydroxyurea in practice for varying reasons. Therefore, the emergence of other medications to treat SCD may provide better utilization and outcomes. In 2017, the FDA approved L-glutamine to reduce acute complications of SCD in patients 5 years of age and older. In addition, studies of crizanlizumab (investigational, Novartis), a human monoclonal antibody, have reported favorable results in decreasing acute SCD pain episodes. This paper will review clinical data concerning the uses of hydroxyurea, L-glutamine, and crizanlizumab in treating associated SCD pain episodes.

HYDROXYUREA

In 1998, hydroxyurea was approved by the FDA for the treatment of adults with SCD. Clinical trial results from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) demonstrated its effectiveness in decreasing VOEs and acute chest syndrome (ACS) in addition to increasing levels of fetal hemoglobin (Hbf). The randomized, double-blind, placebo-controlled MSH trial enrolled 299 patients who were at least 18 years of age with sickle cell anemia who reported a minimum of three crisis events during the year prior to the start of the study. Patients with Hbs/β-thalassemia and Hbs/β-thalassemia were excluded. Enrolled patients were randomized to receive either hydroxyurea (152 participants) or placebo (147 participants).

Study results for the primary outcome reported a median rate of 2.5 VOEs per year in the hydroxyurea group compared with 4.5 VOEs per year in the placebo group (P = 0.001). Additional results evaluating VOEs severe enough to require hospitalization reported annual median rates in the hydroxyurea group compared with placebo as 1.0 and 2.4, respectively (P < 0.001). ACS occurred in 49% fewer patients in the hydroxyurea group compared with the placebo group (P < 0.001). At the end of the study, it was noted that Hbf levels were higher in the hydroxyurea group versus the placebo group, which peaked around week 40 of the study.

Disclosures: The authors report no commercial or financial interests in regard to this article.
A meta-analysis that reviewed one randomized controlled trial, three case reports, and 22 observational studies reported a 5% to 20% increase in HbF and a 56% to 87% decrease in hospitalization rates in patients treated with hydroxyurea.18 While the complete mechanism by which hydroxyurea induces HbF levels is unknown, other mechanisms have been documented that contribute to this action.19 Hydroxyurea is a myelosuppressive agent that exerts cytotoxic activity by inhibiting ribonucleotide reductase, altering the kinetics of cell division in rapidly dividing precursors. This may be responsible for creating a shift in hemoglobin production to increase the level of HbF red blood cells (RBCs).20 Other cytotoxic effects that have been identified are suppression of bone marrow and decreased production of neutrophils, reticulocytes, and platelets, which may provide benefit.19,20 By lowering white blood cell counts, this may improve outcomes for patients with SCD because elevated white blood cell counts have historically been associated with increased morbidity and mortality.21

In a follow-up involving patients enrolled in the MSH study, results suggested that mortality correlates with HbF concentration and the rates of acute pain crisis and ACS. Enrolled patients who received hydroxyurea therapy for one year experienced a 40% reduction in mortality.16 In an extension of the MSH trial, patients were retrospectively evaluated to determine all-cause mortality and classification of death over a 17.5-year period. Study results reported a reduction in all-cause mortality in patients with cumulative hydroxyurea exposure of more than 15 years in comparison to patients who had never used hydroxyurea. Furthermore, the study reported no increases in serious complications due to prolonged exposure to hydroxyurea and improved survival without the occurrence of serious adverse events.16

The use of hydroxyurea in children remains a subject of discussion. Given the potential effects SCD may have on patient quality of life, additional clinical data have continued to support hydroxyurea usage in the pediatric population. The BABY-HUG trial, a randomized, double-blind, placebo-controlled trial, studied patients 9–18 months of age treated with either hydroxyurea or placebo for two years.21 Though the study failed to determine differences in its primary endpoints of splenic and renal function, reported results found a decreased incidence of pain (177 events versus 375 events) and dactylitis (24 events versus 123 events) in patients treated with hydroxyurea compared with placebo. The trial also confirmed an increase in HbF and a decrease in white blood cell counts in patients treated with hydroxyurea. Additional results showed a decrease in ACS (eight events versus 27 events), hospitalization for any cause (232 events versus 324 events), and gastroenteritis (26 events versus 70 events).21 The study recorded significant toxicity exhibited as mild neutropenia, which was defined as an absolute neutrophil count of 500–1,250 mm³.19,23 A post-trial analysis regarding cost for patients enrolled in the BABY-HUG trial revealed a 21% decrease in total estimated annual cost ($11,072 versus $13,962), contributing to the discussion that hydroxyurea has the potential to be safe and efficacious in children as well as reducing burdens of health care cost for affected families.25 An observational follow-up study of the BABY-HUG trial and the Long-Term Effects of Hydroxyurea Therapy in Children With Sickle Cell Disease are ongoing. Results of these studies could potentially provide insight into the hydroxyurea mortality benefit in the pediatric population and possibly impact future indications for hydroxyurea.23,24

In December 2017, the FDA approved use of hydroxyurea in patients 2 years of age and older based on clinical data that analyzed the frequency of adverse events reported from another active study, the European Sickle Cell Disease Cohort (ESCORT HU).25

L-GLUTAMINE

Glutamine, a conditionally essential amino acid, is considered one of the more pervasive amino acids in the human body.26 Glutamine was originally isolated by scientists in the late 19th century; its importance in maintaining cell function and supporting normal physiology has been identified.27 Historically, glutamine has been used in both enteral and parenteral nutrition supplementation to aid in restoring gut mucosal cellularity, reduce intestinal permeability, and enhance nutrient absorption in patients with short bowel syndrome.27 In addition to this indication, studies involving oral supplementation of glutamine in patients with SCD have shown promise in adults and children. While the mechanism of action in SCD remains unknown, it may involve increased availability of reduced glutathione, but other pathways are likely involved.14

The most serious and incapacitating complications of SCD are generally due to severe anemia and frequent vaso-occlusive processes leading to tissue damage, including stroke. A longer transit time through the microvasculature is a key predictor of intracellular sickling and resulting significant blockage and accumulation of deoxygenated sickle RBCs. Niibara and colleagues conducted a two-part experiment with the blood samples of five adult SCD patients who were receiving 30 g a day of L-glutamine therapy for at least four weeks compared with patients in a control group. The results showed significant reductions in the mean adhesion of sickle RBCs to human umbilical vein endothelial cells, suggesting positive physiological effects of L-glutamine in SCD.28

In July 2017, the FDA approved the use of oral L-glutamine for the treatment of acute complications of SCD in patients 5 years of age or older. This approval was based primarily on two clinical trials. The first was a phase 2, randomized, double-blind, placebo-controlled, parallel-group study conducted across multiple U.S. centers. Patients were included if they were at least 5 years of age, diagnosed with HbS/S or sickle HbS/β-thalassemia, and had at least two episodes of painful crises within 12 months of screening. Patients were excluded if they suffered any significant medical condition requiring hospitalization (other than painful sickle crises) within two months of screening, diabetes mellitus with untreated fasting blood glucose greater than 115 mg/dL, prothrombin time international normalized ratio greater than 2.0, serum albumin less than 3.0 g/dL, or the receipt of blood products within three weeks of the screening visit.29

Patients were randomized in a 1:1 ratio to receive treatment with oral L-glutamine at 0.3 g/kg or oral placebo twice daily for 48 weeks. The primary endpoint was the impact of oral L-glutamine on the frequency of painful sickle cell crises (SCC). Secondary endpoints included effects on frequency of hospitalizations for sickle cell pain, frequency of emergency
CRIZANLIZUMAB

Crizanlizumab is a monoclonal antibody that inhibits the interaction of P-selectin glycoprotein ligand 1 by binding to P-selectin. The activation by specific biological response modifiers such as thrombin is required to express P-selectin on endothelial cells and platelets. The role of endothelial cells in vaso-occlusion were evaluated in an ex vivo animal study that injected rats with normal and sickle human cells. Results of this study indicated increased adherence of sickle cells to venules compared with little or no adherence of normal cells. Another study assessed the effect of a P-selectin–blocking monoclonal antibody, 9E1, on adherence of nonsickle and sickle cells treated or untreated with thrombin.

Findings of this study reported a statistically significant reduction in sickle cell adherence of 30% (P = 0.002) to untreated endothelium and 76% (P = 0.038) to thrombin-treated endothelium. These results imply that treatments that inhibit P-selectin have the potential to target associated sickle cell VOEs.

In a randomized, double-blind, placebo-controlled phase 2 study, the safety and efficacy of crizanlizumab were evaluated in 198 patients with SCD between 16 and 65 years of age over 52 weeks. Patients had a history of two to 10 SCCs within the 12 months prior to enrollment in the study. Patients taking hydroxyurea prior to initiation of the study could continue therapy if there was an established minimum treatment history of six months or longer. In addition, these patients were required to be on a stable hydroxyurea dosing regimen at least three months prior to the start of the study. Though utilization of hydroxyurea did not prohibit patients from participating in the study, the number of patients receiving hydroxyurea was limited to 65% of the total enrollment. Patients not receiving hydroxyurea therapy prior to the start of the study were not allowed to start hydroxyurea during the study period.

Study participants were grouped using a block design according to pain crisis event history and usage of hydroxyurea. Of the 198 enrolled patients, 67 were randomized to high-dose crizanlizumab (5 mg/kg), 66 were randomized to low-dose crizanlizumab (2.5 mg/kg), and 65 were assigned to placebo. As determined by treatment-group assignments, each patient received one 30-minute intravenous infusion of 2.5 mg/kg crizanlizumab, 5 mg/kg crizanlizumab, or placebo on study day 1 and day 15 as loading doses. All subsequent doses were administered at four-week intervals, with the final dose administered at week 50. Collection of patient data occurred at every injection meeting, week 52, and week 58, which was six weeks after the end of the study.

The primary efficacy outcome was the number of SCCs experienced by every patient in each treatment arm over the course of the study period. The results showed a statistically significant lower annual median crisis rate in the high-dose group compared with placebo (1.63 events versus 2.98 events, respectively; P = 0.01). In addition, 24 patients in the high-dose group reported zero crisis events compared with 11 patients in the placebo group. Data for the low-dose treatment arm, though not statistically significant, reported an annual median crisis rate of 2.01, which was fewer than the 2.98 events in the placebo arm (P = 0.18). In addition, 12 patients in the low-dose group reported zero crisis events over the study period.

Subgroup analysis evaluated 42 patients in the high-dose group, 41 patients in the low-dose group, and 40 patients in the placebo group who received hydroxyurea over the course of the study. The annual median crisis rate among the three groups was 2.43 for the high dose, 2.0 for the low dose, and 3.58 for placebo. Analysis of patients who did not also receive hydroxyurea reported a median crisis rate of 1.97 episodes versus 5.32 episodes, respectively. Patients with a baseline of two to four annual crises enrolled in the high-
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Table 1 Cost of FDA-Approved Sickle Cell Disease Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Available Dosage Form (Strength) (Package Size)</th>
<th>Average Wholesale Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea</td>
<td>Adult</td>
<td>500-mg capsules (100)</td>
<td>$102</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>100-mg tablets (60)</td>
<td>Not yet available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,000-mg triple-score tablets (30)</td>
<td>(FDA approval December 2017)</td>
</tr>
<tr>
<td>L-glutamine</td>
<td>5 years of age or older</td>
<td>4,000 mg/5 mL powder for suspension (240 g)</td>
<td>$14</td>
</tr>
<tr>
<td></td>
<td>&lt; 30 kg:</td>
<td>500-mg tablets (100)</td>
<td>$11</td>
</tr>
<tr>
<td></td>
<td>30–65 kg:</td>
<td>750-mg capsules (90)</td>
<td>$8</td>
</tr>
<tr>
<td></td>
<td>10 g twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 65 kg:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION

SCD remains a debilitating condition despite advances in the treatment of acute crises. Acute ischemic painful episodes of VOE occur in more than 90% of patients with SCD, and more than 50% suffer from ACS. In addition to these complications, patients commonly suffer from stroke, crippling and painful osteonecrosis, proliferative retinopathy, splenic infarction, leg ulcers, infection, and significantly increased morbidity and mortality. Unfortunately, there has been only one oral medication option available, hydroxyurea, that reduces mortality in SCD. Other available treatment options are directed toward the control of symptoms and complications of SCD. A cost comparison of available treatments appears in Table 1.

Several clinical trials of therapies, including selectin inhibitors, vaso-occlusive agents, antisickling agents, and adhesion inhibitors, are ongoing for SCD (Table 2). While the introduction and use of hydroxyurea have had a significant impact on patients suffering from SCD, hospitalization rates have either increased or remained the same; the cost for inpatient treatment has increased.

In a study that analyzed data from a statewide health service, the cost of care for adults with SCD after adjustments for inflation rose by 60% from 1995 to 2003. Nationwide, the average total cost of hospitalizations of patients admitted primarily for SCD in 2004 was $488 million, with 70% of these admissions originating from the ED.

The introduction of L-glutamine as an option for SCD provides an opportunity to reduce the occurrence of crises by approximately 17%, which could potentially lead to savings of approximately $83 million or more in annual hospitalization costs minus medication costs. A similar trend in the reduction and prevention of SCC was demonstrated in preliminary results for crizanlizumab, which could also translate to significant health care cost-savings in the future. Until the approval of other SCD-specific therapies, L-glutamine’s reduction of SCD complications, ED visits, and hospital admissions could potentially alleviate some of the financial burden for health systems impacted by frequent readmissions due to SCD and for patients in whom hydroxyurea is contraindicated.

REFERENCES

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Table 2 Selected Clinical Trials Targeting Selectin Inhibitors, Vaso-Occlusion, Antisickling, and Adhesion Inhibitors in Sickle Cell Disease

<table>
<thead>
<tr>
<th>Clinical Trial ID</th>
<th>Intervention</th>
<th>Study Phase</th>
<th>Enrollment</th>
<th>Endpoint Measure</th>
<th>Participant Age in Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02187003</td>
<td>Rivipansel (GMI 1070)</td>
<td>3</td>
<td>Recruiting participants</td>
<td>Safety, efficacy</td>
<td>≥ 6</td>
</tr>
<tr>
<td>NCT02433158</td>
<td>Rivipansel (GMI 1070)</td>
<td>3</td>
<td>Recruiting participants</td>
<td>Safety (open-label extension study)</td>
<td>≥ 6</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vaso-occlusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01895361</td>
<td>Crizanlizumab (SelG1)</td>
<td>2</td>
<td>Completed</td>
<td>Safety, efficacy</td>
<td>16–65</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Antisickling agents</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NCT02580773</td>
<td>Tinzaparin</td>
<td>3</td>
<td>Recruiting participants</td>
<td>Safety, efficacy</td>
<td>≥ 18</td>
</tr>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>Adhesion inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02127668</td>
<td>Rivaroxaban</td>
<td>2</td>
<td>Enrolling by invitation only</td>
<td>Efficacy</td>
<td>18–65</td>
</tr>
<tr>
<td>NCT01960413</td>
<td>Montelukast and hydroxyurea</td>
<td>2</td>
<td>Recruiting participants</td>
<td>Efficacy</td>
<td>16–70</td>
</tr>
<tr>
<td>NCT02580773</td>
<td>Tinzaparin</td>
<td>3</td>
<td>Recruiting participants</td>
<td>Efficacy</td>
<td>≥ 18</td>
</tr>
<tr>
<td>NCT02515838</td>
<td>Sevuparin</td>
<td>2</td>
<td>Recruiting participants</td>
<td>Safety, efficacy</td>
<td>12–50</td>
</tr>
</tbody>
</table>

Note: This list is not all-inclusive, but serves as a snapshot of targets of drug therapy for sickle cell disease.

15. NCT01895361 Crizanlizumab (SelG1) 2 Completed Safety, efficacy 16–65
33. NCT02850406 GBT 440 2 Recruiting participants Safety, efficacy 12–17
34. NCT03036813 GBT 440 3 Recruiting participants Safety, efficacy 12–65
35. NCT02127668 Rivaroxaban 2 Recruiting participants Safety, efficacy 12–65
36. NCT01960413 Montelukast and hydroxyurea 2 Recruiting participants Safety, efficacy 12–65
37. NCT02580773 Tinzaparin 3 Recruiting participants Safety, efficacy 12–65
38. NCT02515838 Sevuparin 2 Recruiting participants Safety, efficacy 12–50
39. Note: This list is not all-inclusive, but serves as a snapshot of targets of drug therapy for sickle cell disease.
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