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Management of Older Adults with Sickle Cell Disease: Considerations for current and emerging therapies

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Abstract

People with sickle cell disease (SCD) are living longer than ever before, with a median survival increasing from age 14 years in 1973, beyond age 40 in the 1990s, and as high as 61 years in recent cohorts from academic centers. Improvements in survival have been attributed to initiatives such as newborn screening, penicillin prophylaxis, vaccination against encapsulated organisms, better detection and treatment of splenic sequestration, and improved transfusion support. There are an estimated 100,000 people living with SCD in the United States and millions of people with SCD globally. Given that the number of older adults with SCD will likely continue to increase as survival improves, better evidence on how to manage this population is needed. When managing older adults with SCD (defined herein as age ≥ 40 years), healthcare providers should consider the potential pitfalls of extrapolating evidence from existing studies on current and emerging therapies that have typically been conducted with participants at mean ages far below 40. Older adults with SCD have historically had little to no representation in clinical trials; therefore, more guidance is needed on how to use current and emerging therapies in this population. This article summarizes the available evidence for managing older adults with SCD and discusses potential challenges to using approved and emerging drugs in this population.

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Authors' contributions

We certify that all authors have made substantial contributions to all aspects of the work including conception and planning of the work that led to the manuscript, drafting and/or critical revision of the manuscript, and approval of the final version of the manuscript.

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1. Introduction

Sickle cell disease (SCD) is the most common severe inherited blood disorder in the United States (U.S.). In SCD, a point mutation in the β globin gene causes replacement of glutamic acid by valine at the 6th position of the β globin chain and leads to polymerization of deoxygenated hemoglobin.[1] Polymerization of hemoglobin decreases red blood cells (RBCs) deformability and causes RBCs to become sickle-shaped and rigid, this contributes to occlusion of small vessels.[2] Multiple other RBC changes, including dehydration, oxidative damage to the cell membrane and contents, and exposure of phosphatidylserine at the cell surface also promote abnormal RBC circulatory behavior and vaso-occlusion. Vaso-occlusion further exacerbates hemoglobin deoxygenation and hemolysis while also causing tissue hypoxia and painful episodes, which are the hallmarks of SCD. SCD causes organ dysfunction by several mechanisms, including recurrent episodes of sickling and vaso-occlusion, inflammation, hemolysis, and increased cell adhesion.[3] There is significant phenotypic variability in complications, even among individuals with the same β globin mutation. Individuals may experience retinopathy, cutaneous ulceration, avascular necrosis, infections from encapsulated organisms, acute and chronic cardiopulmonary complications, kidney injury, strokes, and premature death.[1] People with sickle cell anemia [homozygous for hemoglobin S (HbSS) or with hemoglobin SBeta^0-thalassemia (HbSβ^0)], have more hemolysis, are more anemic, and have a shorter life expectancy compared to compound heterozygotes with hemoglobin SC (HbSC) or SBeta$^+$-thalassemia (HbSβ$^+$).[3,4]

1.1 Comorbidities in the Older Adult with SCD

There are several similarities between conditions acquired by middle age in adults with SCD and in non-SCD geriatric populations (Figure 1).[5] Both populations have inflammation, progressive anemia, joint damage, an increased prevalence of vision and hearing loss, and increased risk of hematologic malignancies.[5] More data are needed to better distinguish sickle cell-related versus age-related changes that occur in older adults with SCD.

There are unique SCD-related changes that occur as people with SCD advance in age. Serjeant et al. showed that Jamaican adults with SCD aged ≥ 60 years were more likely to be female, have a higher fetal hemoglobin, experience fewer painful crises with age, and have declining hemoglobin and renal function.[6] It is important to note that the majority of individuals (51%) in that cohort who were tested for α-thalassemia had at least 1 α-globin gene deletion, which is higher than the ~30% prevalence of alpha thalassemia seen in Blacks in the United States, and may have attenuated the severity of SCD.[6–8] We previously published the largest multicenter study of older adults with SCD.[9] We found that older adults (age ≥ 50 years) were more likely to have a lower hemoglobin after controlling for sex, SCD genotype, and hydroxyurea (HU) usage [9.8 g/dL for older adults vs. 10.3 g/dL for younger adults (18-49.99 years); p=0.008], leg ulcers, SCD-related eye complications, avascular necrosis, hip replacement, heart failure, and pulmonary hypertension (defined as tricuspid regurgitant jet velocity ≥ 2.5 meters/second or having evidence of pulmonary HTN on echocardiogram interpretation).[9] Older adults had a lower mean eGFR (82 mL/min/1.73 m^2 compared to 133 mL/min/1.73 m^2 in younger adults; p<0.0001), higher baseline creatinine (mean 1.3 mg/dL versus 0.9 mg/dL; p<0.0001), and increased odds ratio (2.93,

p<0.0001) of proteinuria (≥ 1+ on urine dipstick).[9] The higher disease burden in older adults with SCD may be partially related to the lack of disease-modifying therapies available during their younger years.

We demonstrated that both younger adults (age 18-49) and older adults with SCD (age ≥ 50 years) also experienced accelerated functional decline, with a physical performance similar to individuals 20-30 years older than their chronological age.[10] A review by Idris et al. summarized evidence of accelerated aging in SCD such as shorter telomere lengths associated with more severe disease, dysfunction of the ubiquitin–proteasome system leading to accumulation of low quality proteins, bone disease such as osteoporosis, and earlier onset end-organ dysfunction in people with SCD compared to individuals without SCD.[11] This means that providers should consider geriatric conditions and syndromes such as frailty and falls in adults with SCD at an earlier age compared to the general population. Therefore, herein we define older adults as age ≥ 40 years, which is consistent with the definition commonly used in studies of aging in people with SCD.[12–15]

1.2 Potentially Inappropriate Medications and Polypharmacy

As people age, they experience changes in body composition and develop multiple chronic diseases that can lead to changes in pharmacokinetics and pharmacodynamics of medications.[16] Older adults in the general population often benefit from efforts to reduce risk of medication-related adverse outcomes, such as avoiding combinations of psychoactive medications that increase risk of falls, deprescribing unnecessary medications to reduce polypharmacy, and renally dosing medications to account for changes in eGFR.[17,18] It is unclear at what age older adults with SCD start to experiencing age-related changes also affect drug pharmacodynamics.[19,20] In a multicenter study of older adults with SCD, 60.8% of individuals aged ≥ 50 years reported taking opioids daily, which was similar to the proportion of young adults with SCD with daily opioid use.[9] This suggests that SCD patients may not change their opioid use patterns as they age, despite the risk associated with taking opioid receptor agonists and sedatives at an older age. Typically, providers are encouraged to avoid or minimize administration of medications that are potentially inappropriate for use in older adults based on the Beers Criteria. The Beers Criteria are guidelines published by the American Geriatrics Society to improve the safety of prescribing medications for adults 65 years and older and include an evidence-based list of potentially inappropriate medications.[17] Examples of medications associated with significant adverse events in older patients include anticholinergics, NSAIDS, anti-depressants, benzodiazepines, and opioid receptor agonists.[17]

Polypharmacy, defined as being on 5 or more regular prescribed medications, also is associated with falls, hospitalizations, and mortality in older adults.[21–23] The prevalence of polypharmacy in older adults with SCD is unknown. More data are needed on the prevalence and potential associated adverse effects of polypharmacy in older adults with SCD to help providers determine how they should approach modifying and/or deprescribing medications in adults with SCD as they advance in age. For older adults in the general population, every patient interaction is an opportunity to deprescribe medications with an emphasis placed on those who are frail.[24] For older adults with SCD, we recommend that after age 40,

medications and doses should be reviewed at each clinic visit, during transfers between care settings, and when considering prescribing new medications. We also advise that a formal medication assessment be done annually. The focus of deprescribing is to determine if dose adjustments can be made, if medications that are no longer clinically indicated can be discontinued, and if potentially inappropriate medications can be safely discontinued without compromising patents' quality of life.[24,25]

2 Current Therapies

The current management strategy for SCD includes hydroxyurea as the cornerstone of therapy for individuals with HbSS/Sβ^0 to reduce complications of SCD. More recently approved SCD therapies—L-glutamine, voxelotor, and crizanlizumab—are usually added to hydroxyurea rather than used as monotherapy. The use of multiagent therapy employing medications with different mechanisms of action is desirable, allowing one to target different pathologic pathways. (Table 1)

2.1 Hydroxyurea

Hydroxyurea (HU) was the first U.S. Food and Drug Administration (FDA)-approved medication for management of SCD.[39] HU increases fetal hemoglobin, which reduces polymerization of HbS, decrease leukocytes, and lowers the number of adherent reticulocytes.[40,41] It was initially approved in 1998 for patients with HbSS and frequent severe pain episodes on the basis of the Multicenter Study of Hydroxyurea (MSH). [39,42] This double-blind randomized placebo-controlled trial (RCT) demonstrated that HU reduced the incidence of painful episodes and acute chest syndrome in adults with SCD by almost 50%, leading to termination of the study before the planned end date.[26,40] The mean age of participants in the MSH was 30.5 years, with only 10% of the 299 participants in the study aged ≥ 40 years.[40,42] A 9-year follow up observational study of MSH patients showed that HU reduced mortality by 40%.[41] It is currently the only approved SCD medication shown to improve survival.

There are no studies focused on the efficacy and safety HU in older adults with SCD. In our multicenter study, we found that 31.4% of older adults (aged ≥ 50) years and 42.1% of younger adults were taking HU. There was no significant difference in baseline hemoglobin between younger and older adults taking HU.[9,43] Older adults not taking HU did have a lower hemoglobin compared to younger adults not taking HU.[9] Older adults on HU also had a lower leukocyte count and platelet count compared to younger adults on HU, which was expected as HU-associated myelosuppression may compound age-associated cell count reduction.[9,44,45]

The effects of HU on the bone marrow remain unclear, considering that SCD itself has long-term negative effects on bone marrow health.[46] Likely mechanisms include bone marrow ischemia from vaso-occlusion, pathologic angiogenesis within the bone marrow microenvironment, and bone marrow hyperplasia stimulated by anemia and tissue hypoxia, leading to increased osteoclasts and bone loss.[46–48] Pathologic bone marrow changes and the blunted erythropoietin response of older individuals with SCD can impair hematopoiesis.[49,50]

In addition, there may be an increase in clonal hematopoiesis of indeterminate potential (CHIP) in adults with SCD, as is seen in older adults in the general population; however, the data on CHIP in adults with SCD is limited. In a study using whole-exome sequencing data from individuals with SCD from 5 U.S. and international cohorts compared to African American controls without SCD, CHIP was more prevalent in individuals with SCD and started at a younger age (age 17 in the SCD group vs age 34 in the non-SCD group).[51] The study was not powered to determine the impact of HU on CHIP. In another study of CHIP using specimens from the National Heart, Lung, and Blood Institute (NHLBI) Trans-Omics for Precision Medicine (TOPMed) consortium, there was no increase in CHIP among individuals with as compared to without SCD.[52] HU also did not have an impact on the prevalence of CHIP.[52] However, a population-based study in California showed that there was a 72% increase in risk of hematologic malignancies in individuals with SCD compared to the general California population, but no increase in risk of leukemia after HU was approved in 1998.[53] A national retrospective study in England also demonstrated an increase in risk of lymphoma, multiple myeloma, and leukemia in individuals with SCD compared to those without SCD.[54] These studies emphasize the need for better data to determine the impact, if any, of HU on the risk of CHIP and hematologic malignancies in SCD.

There are also concerns that HU may induce leg ulcers in 1 to 2% of older adults with myeloproliferative disorders.[55] In the general population, hard-to-heal venous leg ulcers are more common in older individuals.[56] Cutaneous leg ulcers in SCD typically are caused by vasculopathy from chronic hemolysis, and are associated with vaso-occlusion, lower hemoglobin, and lower fetal hemoglobin[57,58] A recent study of HU use in 769 patients with SCD (mean age 38 ± 16) showed that the incidence of leg ulcers in SCD was independent of HU use.[59] Although more data are needed on management of older adults on HU with leg ulcers, experts recommend that providers carefully consider the risk and benefit of discontinuing HU, since stopping HU may lead to exacerbation of SCD complications.[59]

As individuals both with and without SCD age, there is a decline in eGFR which requires reassessment of medication doses.[9,60,61] The elimination of HU includes both liver metabolism and renal excretion; therefore, individuals with SCD and renal insufficiency may experience elevated plasma levels.[62] In patients with SCD with creatinine clearance < 60 mL/min, the starting dose of HU should be reduced by 50% (7.5 mg/kg/day instead of 15 mg/kg/day).[62]

Recommendation: HU remains the backbone of therapy for management of SCD. For older adults with SCD it is important to routinely assess their renal and hepatic function and closely monitor for toxicity such as neutropenia, thrombocytopenia, or reticulocytopenia. The NHLBI 2014 Evidence-Based Management of Sickle Cell Disease guidelines, recommend a complete blood count with differential and reticulocyte count every 4 weeks when the HU dose is being adjusted and then every 2-3 months when on a stable dose.[63] HU should be held for moderate to severe neutropenia or thrombocytopenia and then restarted after counts recover. When renal function declines, the care provider should consider reducing their HU dose. If cytopenias are severe and do not improve with holding or

reducing the dose of HU, further evaluation for nutritional deficiencies, aplastic anemia, or hematologic malignancy may be indicated, since risk of these increases with age.

2.2 L-glutamine

L-glutamine is the second SCD disease-modifying medication approved by the FDA in 2017. L-glutamine is an essential amino acid required to produce nicotinamide adenine dinucleotide (NAD^+). The proposed mechanism is by reducing erythrocyte oxidative stress and adhesion. In a phase 3 RCT, L-glutamine treatment for 1 year reduced the median number of vaso-occlusive events (VOEs) to 3 versus 4 in the placebo group (25% reduction) and the median number of hospitalizations to 2 versus 3 in the placebo group, a 33% reduction.[27] Two-thirds of participants were also on HU. There were 2 deaths in the phase 3 trial, and both were sudden cardiac death in individuals on L-glutamine in their 40s.[27] These 2 occurrences of sudden cardiac death represented 1% of participants in the treatment group. Sudden cardiac death is responsible for ~30% of deaths in adults with SCD.[64,65] In addition, patients with renal and hepatic impairment were excluded from the clinical trial. Thus, it is unclear if there is an increased risk of adverse effects from L-glutamine in older adults with SCD.

Recommendation: It is reasonable to consider treating older adults with SCD with L-glutamine in combination with HU, as L-glutamine may be helpful in reducing VOEs and is best used in combination with HU rather than as monotherapy. However, L-glutamine must be used with caution in older adults with liver disease, since L-glutamine is metabolized into glutamate and ammonia by the liver.

2.3 Voxelotor

Voxelotor is an inhibitor of HbS polymerization designed to increase the oxygen affinity of hemoglobin and thereby reduce sickling of RBCs.[28] Voxelotor reversibly binds to hemoglobin to stabilize it in an oxygenated state. Voxelotor reduces HbS polymerization and blood viscosity, which improves RBC deformability, reduces hemolysis, and extends RBC survival. Voxelotor was FDA approved in 2019 based on the HOPE Trial, a phase 3, multicenter, double-blind RCT demonstrating an increase in hemoglobin level by at least 1 g/dL in 51% of participants on 1500mg daily compared to 7% in the control group.[28] There was also decreased hemolysis with a reduction in indirect bilirubin and reticulocyte count.

Safety, tolerability, and pharmacokinetics of voxelotor were assessed in 8 older adults (mean age 62.5 ± 7.1) with severe renal impairment (eGFR < 30 ml/min/1.73 m^2) compared to healthy controls, investigators found no difference in the excretion of a single dose of 900mg.[66] The standard dose (1500mg) or multiple doses were not tested in participants with severe renal impairment. It is unclear if it voxelotor is safe in patients with end-stage renal disease.

In the same study, investigators also evaluated the pharmacokinetics of voxelotor in 7 adults (mean age 55.4 ± 6.9) with SCD with hepatic impairment at various severity levels. Investigators found that a single dose of 1500mg was well-tolerated in participants with mild to moderate hepatic impairment.[66] The mean concentration of voxelotor was 90% higher in

individuals with severe hepatic impairment (Child-Pugh C) and investigators recommended a lower dose of voxelotor at 1000 mg in patients with severe hepatic impairment.[66]

Recommendation: Voxelotor is a promising treatment for older adults with SCD and moderate to severe anemia. It has the potential to reduce the need for transfusion by increasing the steady-state hemoglobin, thereby reducing the risk of symptomatic anemia due to chronic hemolysis. However, patients on chronic transfusion therapy for stroke prophylaxis likely would not benefit from voxelotor, since they are already increasing their hemoglobin with monthly transfusions providing normal RBCs, whereas voxelotor only increases the number of circulating HbS RBCs. It is also preferred that voxelotor be used in combination with HU, since HU increases HbF, which confers an additional anti-sickling effect, reduces acute complications, and may decrease mortality. Voxelotor should be used with caution in patients with hepatic impairment. More studies are needed on safety of voxelotor in older adults with SCD and to determine if increasing hemoglobin with voxelotor provides physical and cognitive benefits for older adults.

2.4 Crizanlizumab

Crizanlizumab is a monoclonal antibody targeting P-selectin expressed on the surface of the endothelium and platelets to block adhesion of leukocytes and thus reduce VOEs. Crizanlizumab was approved in 2019 for people with SCD age ≥ 16 years and is administered by intravenous infusion every 2 week for two doses and then every 4 weeks.

The SUSTAIN trial, a phase 2 multicenter, double-blind RCT, demonstrated that treatment with crizanlizumab (5 mg per kilogram) resulted in a 45% reduction in rate of VOEs (1.63 crises/year in 5 mg/kg crizanlizumab group compared to 2.98 crises/year in placebo group, p=0.01).[29] Crizanlizumab also resulted in a longer median time to the first VOE compared to placebo (4.07 month in the 5 mg/kg crizanlizumab group versus 1.38 months in the placebo group, p=0.001). There also was a longer median time to the second VOE (10.3 vs. 5.1 months, p=0.02) with crizanlizumab therapy. Serious adverse events in the treatment group included pyrexia in 2 participants, pneumonia in 5 participants, and influenza in 3 particpants.[29] The effect of renal and hepatic impairment on the pharmacokinetics of crizanlizumab is unknown.[67]

There currently are ongoing clinical trials to determine the efficacy of crizanlizumab to reduce recurrent priapism and proteinuria in people with SCD.

Recommendation: Crizanlizumab is an effective treatment for adults with SCD with at least 2 VOEs per year. It is unclear if there is a difference in efficacy or safety in older adults, since the effect of renal and hepatic impairment is unknown. There were a few participants who experienced pyrexia and infections as severe adverse events; therefore, crizanlizumab should be used with caution in older adults with a history of frequent infections.

2.5 Opioids

Acute Pain Management—Opioids are a mainstay of therapy for VOEs in individuals with SCD. Oral opioids are commonly prescribed for VOEs that can be managed at home.

Parenteral opioids are used for severe VOEs managed in the emergency department (ED), sickle cell day hospital, and inpatient settings.

Multiple studies have shown that older adults with SCD have less healthcare utilization compared to younger adults, but the data is conflicting on whether older adults with SCD experience less pain.[68–70] Older adults (aged ≥ 37 years) in the Pain in Sickle Cell Epidemiology Study (PiSCES) had higher proportion of pain and pain crisis days, increased mean number of body parts that hurt, and higher proportion of home pain days on opioids compared to the transition group (age 16-25 years). However, older adults had a 50% lower ED reliance for health care compared to the transition group and younger adults aged 26-36 years. All groups had similar pain intensity, proportion of days in the hospital, and fetal hemoglobin levels (%). We also showed a similar proportion of younger and older adults with SCD with daily short-acting and long-acting opioid use, but older adults had fewer hospitalizations.[69] These findings of similar pain but less utilization may be due to older adults having better home self-management strategies compared to younger adults. On the contrary, a Jamaican cohort of older adults with SCD age ≥ 60 years reported that pain improved with age and had a higher fetal hemoglobin, which may be explained by survival bias and the higher prevalence of alpha thalassemia in this cohort.[6]

Older adults in the general population (age ≥ 65 years) experience increased rates of social, medical, and psychological adverse effects related to opioid use.[71] Older adults are at higher risk of developing adverse effects such as constipation, falls, sedation, respiratory depression, delirium, and cognitive impairment.[71]

The American Society of Hematology (ASH) 2020 guidelines for SCD suggest adding non-pharmacologic therapies such as massage, yoga, and audiovisual relaxation for management of acute pain.[31]

Chronic Pain Management—Chronic pain is a common and debilitating complication in adults with SCD with over half of adults in the United States meeting criteria for chronic pain.[72] The etiology of chronic pain can be related to both SCD and non-SCD causes and is often managed with short-acting and/or long-acting opioids.[73] Chronic pain, depression, and multiple co-morbidities are risk factors for opioid-related adverse effects in older adults.[71] These conditions are common in older adults with SCD; however, more data are needed on whether they have similar risk of adverse effects from opioids compared to older adults in the general population.[9,74]

Data on chronic opioid therapy in adults with SCD suggest worse symptom burden, poor functional outcomes, and higher healthcare utilization compared to adults with SCD not on chronic opioids.[75] Older age and pre-transplant use of long-acting opioids have been associated with persistent pain after curative therapy with hematopoietic stem cell transplant in adults with SCD.[76] In a qualitative study, adults with SCD reported an interest in non-opioid options for pain management, but expressed concerns about access and costs of alternative therapies.[77] The ASH guidelines suggest including strategies such as non-opiate medications (serotonin and norepinephrine reuptake inhibitor [medications, gabapentinoids,

tricyclic antidepressants and non-pharmacologic therapies (cognitive behavior therapy and acupuncture for management of chronic pain).[31]

Recommendation: Older adults in general are more sensitive to the effects of opioids. As people with SCD age, it is important to review their outpatient and inpatient opioid analgesic regimens to determine if dose reductions are indicated. As their renal function and lean body mass decline with age, they may become more susceptible to adverse events. Data on weaning full agonist opioids and transitioning to buprenorphine has demonstrated safety and efficacy in reducing acute visit in adults with SCD.[78] It is advisable to incorporate more non-opioid and non-pharmacologic strategies, such as cognitive behavioral therapy, massage, yoga, and acupuncture to reduce pain and the risk of medication-related side effects in older adults with SCD.[31,79] More data are needed to determine the most effective and safe pain management strategies for older adults with SCD.

2.6 Transfusion

Throughout the lifetime of a person with SCD, there are many scenarios where RBC transfusions are indicated. They may experience symptomatic anemia due to an acute hemolytic episode or an aplastic crisis.[80] Simple transfusion or red cell exchange (RCE) may also be used to manage moderate or severe acute chest syndrome, treat an acute stroke, or to reduce the risk of complications in the perioperative setting.[80,81] Many individuals receive chronic simple RBC transfusions or RCE for primary or secondary stroke prophylaxis, recurrent acute chest syndrome, or cardiopulmonary disease with severe anemia. The SCD-CARRE trial (NCT04084080) is an ongoing multi-center phase 3 RCT to determine the efficacy of RCE vs standard care in high mortality risk adults (age ≥ 18 years with significant cardiopulmonary or renal disease) with SCD to reduce total number of episodes of clinical worsening of SCD requiring acute health care encounters or death over 12 months.

Blood transfusions are common in older adults in the general U.S. population. Older adults are more likely to experience transfusion-related complications such as transfusion-associated circulatory overload (TACO) and alloimmunization.[82,83] There is mixed data on the benefit of liberal vs restrictive transfusion strategies in adults in the general population. A systematic review and meta-analysis that included studies in adults aged ≥ 65 years demonstrated a higher mortality rate in those who followed restrictive transfusion strategies compared to a liberal transfusion strategies.[84]

Since older adults with SCD have a lower hemoglobin, more comorbidities, and are more likely to undergo hip surgery compared to younger adults, they are more likely to encounter scenarios where transfusions are warranted.[9] There are few high-quality studies to guide transfusion for adults with SCD undergoing surgery.[85] A RCT comparing conservative transfusion (increasing hemoglobin to 10 g/dL with simple transfusion) to aggressive transfusion (RCE with goal HbS < 30%) demonstrated no difference in perioperative complications between the 2 groups.[33] The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study was another RCT that demonstrated a benefit to preoperative transfusion compared to no transfusion in individuals with HbSS or HbSβ^0 undergoing low or moderate risk surgery.[34] The transfused group had fewer clinically significant

complications compared to the non-transfused group (15% vs 39%, respectively).[34] There are no dedicated transfusion guidelines for older adults with SCD. Studies demonstrating the benefits of transfusion for primary and secondary stroke prevention in individuals with SCD were performed in children.[86,87] Existing studies on transfusions in SCD have not had adequate representation from older adults (age ≥ 40 years) and people with severe end-organ damage due to conservative inclusion and exclusion criteria that do not reflect real-world experience.

Recommendation: When considering transfusion in older adults with SCD it is important to take an individualized approach. Consider the indications for acute transfusions and chronic transfusion therapy.[80,85] Review their medical history for renal failure and cardiopulmonary issues that may put them at risk for TACO. Older adults often require a slower rate of transfusion and may benefit from diuretics or isovolemic RCE. Review their history for prior transfusion reactions, alloantibodies, and iron overload. If they are on chronic transfusion therapy, weigh the risk and benefit of continuing chronic transfusion as they age. New and emerging therapies such as anti-sickling agents and pyruvate kinase activators increase hemoglobin in some individuals with SCD. These agents show promise as a potential way to reduce transfusion in adults with SCD. In addition, the use of erythropoiesis-stimulating agents may also reduce the need for transfusion in adults with SCD, especially in individuals with anemia of CKD.[88,89]

2.7 Iron chelation

Transfusional iron overload is a common and undertreated condition in adults with SCD. The duration and severity of iron overload increases the risk of iron toxicity and damage to multiple organs, which contributes to liver disease, diabetes, hypogonadism, malignancy, ineffective erythropoiesis, cardiomyopathy, and mortality.[90] Iron toxicity can be especially problematic in older adults with SCD who already have organ damage and multiple transfusions over the course of their lives.[90] In a study on screening and management of iron overload in 1223 adults with SCD in the Globin Research Network for Data and Discovery (GRNDaD) registry, out of the 69 individuals with a liver iron concentration (LIC) ≥ 5 mg/g dry weight, 20.3% were aged 35-49 years and 17.4% were ≥ 50 years.[91]

Iron chelation is recommended in patients with iron overload with LIC > 3 mg/g dry weight or serum ferritin > 1000 μg/l.[90] The three approved iron chelators are deferoxamine, deferiprone, and deferasirox. Deferoxamine must be administered by continuous subcutaneous or intravenous infusion due to its short half-life and poor oral bioavailability. Deferiprone is administered as a tablet two or three times a day. Deferasirox is available in 2 formulations (dispersible tablet for oral suspension and a film-coated tablet), but the film-coated tablet is better tolerated and has better adherence.[92] One of the major concerns about using deferasirox in older adults with SCD is nephrotoxicity.[93] As adults with SCD and iron overload develop worsening renal function, they may have to switch to deferiprone or deferoxamine, since these can be used in patients with renal disease. Another concern is that deferoxamine can cause hearing loss and impaired vision, two conditions that are already of concern as individuals with SCD age.[5,90]

Recommendation: There is limited data on iron chelation therapy in older adults with SCD; therefore, more studies are required to better understand safety in this population. For older adults with SCD and iron overload, we recommend use of iron chelation agents to reduce the risk of organ damage and mortality associated with iron toxicity. When selecting an iron chelator, consider the patient's comorbidities. Adults with SCD are at higher risk of sensorineural hearing loss compared to the general population.[94] When considering starting deferoxamine, refer the patient for audiology and vision exams to establish a baseline.[95] Deferasirox should be used with caution in patients with renal impairment and discontinued if their eGFR < 40 mL/minute/1.73m^2.[38] Older adults with SCD are at higher risk for cytopenias; therefore, patients on deferiprone should have their absolute neutrophil count monitored closely (weekly for 6 months and then every 2 weeks) given the risk of medication-induced agranulocytosis.[96]

3 Emerging therapies under investigation

There are multiple investigational therapies for the management of SCD (Table 2). However, it is unclear how these new treatments will benefit older adults with SCD since clinical trials are often not powered to assess efficacy in this sub-population.

3.1 Pyruvate kinase activators

Etavopivat is an oral RBC pyruvate kinase-R (PKR) activator that decreases in 2,3-diphosphoglycerate (2,3-DPG) in RBCs, which in turn increases hemoglobin oxygen affinity.[97] Increasing hemoglobin oxygen affinity then reduces HbS polymerization and RBC sickling.

Etavopivat was shown to decrease 2,3-DPG and increase adenosine triphosphate (ATP) in non-human primates and in healthy subjects.[97] In an ex-vivo study of whole blood of individuals with SCD, treatment with etavopivat resulted in increased hemoglobin oxygen affinity and improved sickle RBC function.[97] A phase 1 study was recently completed (NCT03815695), showing that most patients treated with etavopivat achieved a total hemoglobin increase of 1 g/dL or more (manuscript in preparation). There is currently a phase 2/3 trial evaluating the safety and efficacy of etavopivat (HIBISCUS; NCT04624659).

Mitapivat is another oral PKR activator under investigation for management of anemia and VOEs in SCD. In a phase 1 dose-escalation clinical trial (NCT04000165), mitapivat was shown to increase hemoglobin by a mean of 1.2 g/dL at the 50 mg dose, and 56.3% (9/16) of participants (mean age 39 years) achieved a hemoglobin response of ≥ 1 g/dL compared to baseline.[49] There were also reductions in hemolytic markers. Four VOEs (23.5%) were documented as severe adverse events, 2 of which occurred while the dose was being tapered.[49]

3.2 Anti-sickling therapies

GBT021601 is a second generation HbS polymerization inhibitor. In SCD mouse models, investigators noted a dose-dependent reduction in p50 (partial pressure at which hemoglobin is 50% saturated), increased hemoglobin and reduced hemolysis.[98] GBT021601 is more potent than voxelotor, which may allow for lower dosing and a lower pill burden. Phase 1

studies in 63 healthy volunteers (NCT05036512) and 6 adults with SCD (NCT04983264) demonstrated a higher % hemoglobin occupancy compared to voxelotor in healthy controls, it was well tolerated, and there was no evidence of tissue hypoxia.[99] The phase 2/3 trial for GBT021601 in individuals aged 6 months to 65 years is ongoing (NCT05431088).

3.3 Anti-adhesion therapies

Inclacumab is a humanized IgG4 monoclonal antibody that competitively inhibits the interaction between P-selectin with its ligand P-selectin glycoprotein ligand 1 (PSGL-1) to reduce adhesion of sickle RBCs by inhibiting platelet-leukocyte aggregate formation.[100,101] It differs from crizanlizumab in that the inhibition with inclacumab is directly in the PSGL-1 binding region on P-selectin rather than at a distant epitope, as with crizanlizumab.[102] In a study using blood samples from healthy controls and from people with SCD, inclacumab demonstrated greater maximal inhibition of platelet-leukocyte cell adhesion compared to crizanlizumab.[102]

Preliminary results of the phase 1 study in 15 healthy adults (median age 42 years (range 22-52) receiving a single dose of inclacumab at 20 mg/kg (n=6) or 40 mg/kg (n=9) demonstrated no treatment-emergent adverse events greater than grade 1.[103] Platelet-leukocyte aggregate formation decreased from 33-39% at baseline to 9-14% at 2 hours following end of infusion and was sustained for at least 12 weeks.[103]

The phase 3 trial of inclacumab in individuals with SCD age ≥ 12 years is ongoing (NCT04935879).

3.4 Antioxidants and anti-inflammatory agents

There are several studies that demonstrate that inflammation and complement activation play important roles in pathologic manifestations of SCD.[104,105] A study of the role of C5 in the pathophysiology of SCD demonstrated that C5a and the membrane attack complex (C5b-9) were mediators of ischemia-reperfusion injury and that C5a given to SS mice induced vasoocclusion.[106]

Crovalimab is a C5 inhibitor evaluated in the phase 1 CROSSWALK clinical trial, in individuals age 12-55 for management of acute uncomplicated VOEs (NCT04912869).[107] The current phase 2 trial is to assess the prevention of VOEs in individuals with SCD (NCT05075824). Crovalimab was also previously studied in an open-label phase 1/2 trial for management of paroxysmal nocturnal hemoglobinuria (PNH) using escalating intravenous doses up to 1500mg followed by 170mg - 680mg administered subcutaneously up to every 4 weeks (COMPOSER trial NCT03157635).[108] Crovalimab differs from approved C-5 inhibitors (eculizumab and ravilizumab) in that it is highly soluble, allowing subcutaneous self-administration of small volumes.[108] It also may have a lower risk of breakthrough symptoms in patients with PNH, where it was shown to decrease hemolytic activity.[108] There were no serious treatment-related adverse effects.

Rifaximin is an antibiotic under investigation for use in SCD for its ability to modulate the intestinal microbiome and reduce inflammation.[109] Activated and aged neutrophils may increase risk of sickle RBC adherence to the endothelium.[109] Individuals with SCD have

high levels of activated neutrophils and circulating aged neutrophils. Intestinal microbial composition, such as intestinal bacterial overgrowth, may increase neutrophil activation and VOEs in individuals with SCD. In a Phase 2 clinical trial with 11 adults with HbSS, oral rifaximin 550mg twice daily significantly reduced circulating aged neutrophils by a median 12.7% (range 6.1-40.1] after 2-4 weeks of therapy.[110] There were no *Clostridium difficile* infections or adverse effects.[110] In the same trial, treatment with rifaximin in 12 patients reduced median number of VOEs from 2.25 (range 1-6.5) per 6 months to 1 per 6 months (range 0-4) (P =.003).[109] The mean self-reported medication adherence was 86% (range 50-100). There was no significant change in white blood cell count, hemoglobin, and hemolysis labs.[109]

3.5 Novel Development in gene therapy and gene editing

Curative therapies such as hematopoietic stem cell transplantation (HCST), including matched sibling and alternative donors, and gene therapy (gene addition and editing) will likely continue to improve the treatment of people with SCD. However, multiple challenges have limited the availability of these therapies, especially for older adults. Currently, matched sibling HCST is recommended for people with severe SCD as defined by prior stroke or abnormal TCD, frequent pain or recurrent acute chest syndrome despite disease modifying medications. HSCT outcomes (including better disease-free survival and less graft versus host disease) are good for those < 16 years old.[111] Availability and experience in adults is more limited. A recent meta-analysis of HSCT for SCD identified 33 studies with 2853 participants. Only 8 studies included participants over 40 years and only 3 studies, enrolling a total of 53 participants, had a median age of over 30 years.[112] HCST with reduced intensity conditioning and post-transplant cyclophosphamide permits the use of haploidentical donors, greatly expanding the proportion of people with SCD with donors. This approach is well tolerated in adults with SCD and has lower treatment related mortality compared to myeloablative approaches in older adults leading to increased availability of HSCT.[113]

Gene therapy is also in clinical trials, and some gene therapy studies include older ages. However, few older adults qualify for the current studies due to rigorous exclusion criteria designed to assure the safety of the required myeloablative preparative regimen generally with high-dose busulfan. The oldest patient in a published report to receive gene therapy is 38 years old.[114–116]

4 Considerations when using combination therapy in older adults

When combining different drugs in older adults with SCD it is important to consider the following:

1. Hydroxyurea is currently the only approved medication for SCD that has a mortality benefit in SCD; therefore, it should remain an integral part of treatment. Consider the patient's history of adherence to hydroxyurea and whether it has been optimized by titrating it to the maximum tolerated dose before adding an additional agent.

2. Consider the patient's underlying comorbidities, such as CKD or hepatic impairment, especially in patients with severe iron overload. More data are needed to determine the safety of new and emerging therapies in older frail patients and those with end organ damage.

3. As adults with SCD have new and emerging medications added to their regimen, this is expected to increase the complexity of their medication management and thus increase their risk of medication-related adverse events. Consider the patient's concerns about polypharmacy, pill burden, issues with swallowing, and visual issues that may make it difficult to read pill bottles. Inquire about their current system for keeping up with taking the right medications at the right time, such as use of a pill-organizer. Also, ask about their social support system at home and determine if they qualify for home health services to help with medication management.

5 Conclusion

There is a paucity of data to guide management of older adults with SCD, requiring extrapolation from SCD data in younger people and data on older adults in the general population. Using guidelines based on clinical trials performed in children and young adults may not be generalizable to older adults who have different physiology and comorbidities. It is also important to note that chronologic age often does not reflect physiologic age, so studies on safety and efficacy of SCD therapies should include frail individuals with advanced physiologic aging in addition to more robust older adults.[117]

5.1 Future Directions

SCD clinical trials have historically had little or no representation from older adults (age ≥ 40 years) and individuals with severe end organ damage or frailty. There is a need for clinical trials focused on older adults with SCD to determine how to safely prescribe disease-modifying therapies and other commonly used medications in this population. These trials should include the effects of physiologic changes and comorbid conditions that may occur earlier in adults with SCD and can increase the risk of adverse events. Until there is more data on current and emerging therapies in older adults with SCD, we recommend closer monitoring and reporting of adverse events. The most important areas of focus for future studies involving older adults with SCD include: 1) establishing the most clinically relevant and patient-important outcomes for older adults with SCD, such as improving function, and including these outcome measures in clinical trials;[74,118] 2) non-pharmacologic strategies to improve pain, extend healthspan (which is the length of time a person is healthy), and quality of life;[119] 3) real-world experience on effectiveness of disease-modifying therapies (monotherapy and combination therapy) in older adults with SCD, since they have historically been underrepresented in clinical trials; 4) pharmacokinetic and pharmacodynamic studies in older adults with SCD to determine optimal doses of medications to minimize risk of adverse events; and 5) transfusion guidelines for older adults with SCD.

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Conflicts of Interest

C.I.O. has received research funds from the NIA (NIH).

K.L.H. declares that they have no conflict of interest.

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Availability of data and material

No datasets were generated or analyzed during the current study.

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Key Points

Clinical trials for current and emerging therapies for sickle cell disease have historically had little or no representation from older adults (age ≥ 40 years) and individuals with severe end organ damage or frailty; therefore, more real-world data are needed to determine safety and effectiveness of sickle cell therapies in older adults.

Management of older adults with sickle cell disease should focus on both disease and age-related conditions using pharmacologic and non-pharmacologic strategies with special consideration for the impact of physiological changes that occur age, such as a decline in renal and hepatic function and increased sensitivity to psychoactive medications.

Hydroxyurea should remain the cornerstone of disease-modifying therapy for sickle cell disease since it is currently the only approved medication shown to improve survival in sickle cell disease; the addition of other novel therapies with complementary mechanisms of action should be considered in those with inadequate disease control.

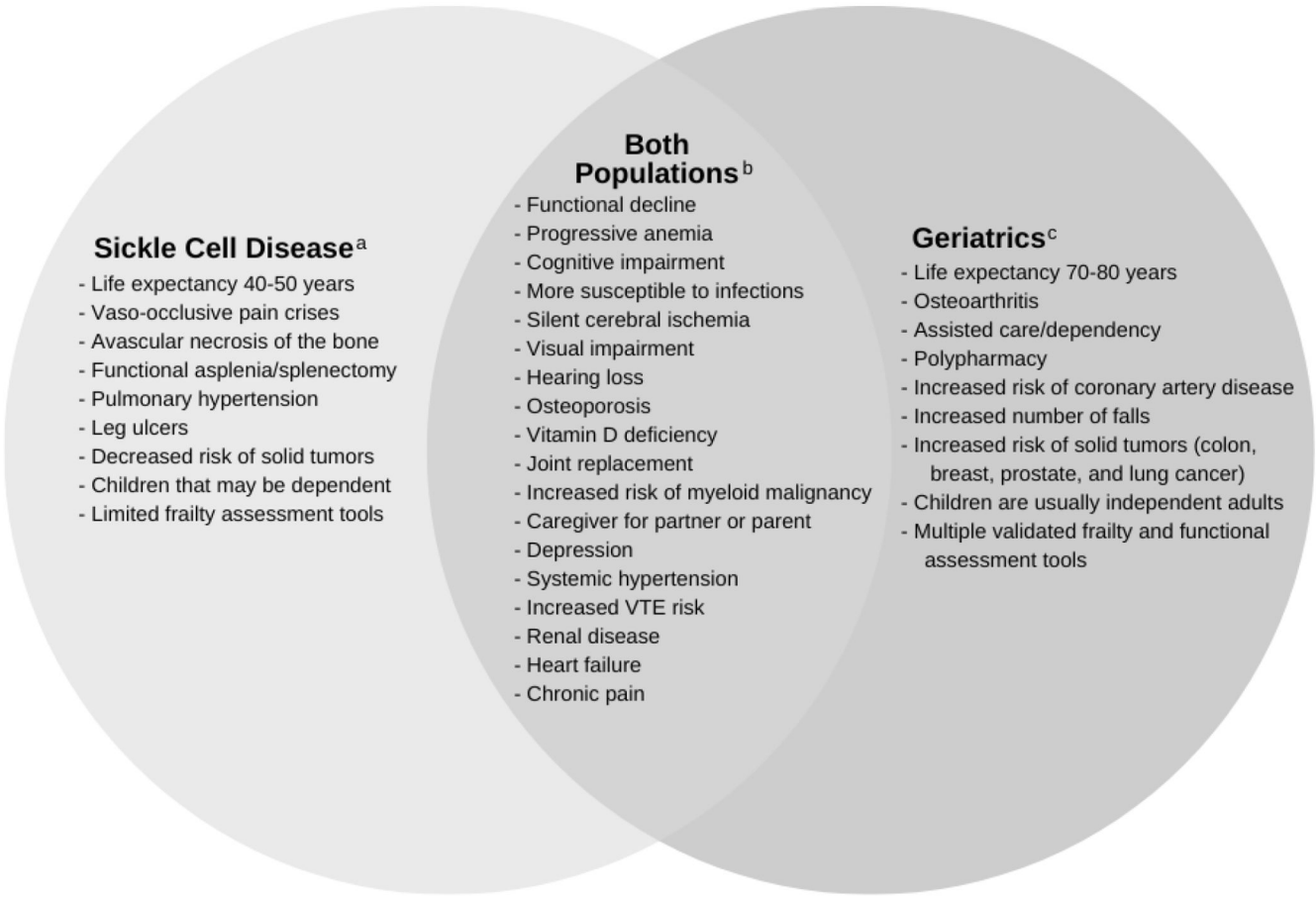

Fig. 1.

Venn diagram describing characteristics and complications at the intersection of sickle cell disease and geriatrics

a. Individuals with SCD have a shorter life expectancy [4,120], vaso-occlusive pain crises [69,121], avascular necrosis of the bone [122], asplenic/splenectomy [69], increased pulmonary hypertension [123], leg ulcers [69], lower risk of solid tumors [53], more likely to have younger children that are still dependents, and there are few validated frailty and functional assessment tools for this population[74].

b. Both geriatric populations and individuals with SCD have functional decline/ disability[74], worsening anemia[9,45], cognitive impairment [124,125], increased susceptibility to infections[13,112], silent cerebral ischemia [125,126], vision impairment [127,128], hearing loss [128,129], osteoporosis [122,130], vitamin D deficiency [122,130], joint replacement [69], a higher risk of myeloid malignancies compared to the general population [53,131], may be a caregiver for their partner or parents. renal disease [69,132], high rates of depression [133,134], systemic hypertension, increased venous thromboembolism (VTE) risk [135,136] heart failure [121,123], and chronic pain [69,137].

c. Geriatric populations life expectancy 70-80 years [138], osteoarthritis [139], institutionalization, polypharmacy [140], , coronary artery disease [121], experience falls [141], increased risk of solid tumors [142], have older children (non-dependents), and multiple functional assessment tools [143].

Figure adapted from Oyedeji CI, Hall K, Luciano A, Morey MC, Strouse JJ. Geriatric assessment for older adults with sickle cell disease: protocol for a prospective cohort pilot study. *Pilot Feasibility Stud*. 2020 Sep 17;6:131. doi: 10.1186/s40814-020-00673-3.

Table 1

Current sickle cell therapies and potential issues in older adults

Therapy	Mechanism	Clinical trial in adults and age of treatment group	Potential issues in older adults
Hydroxyurea[26]	-Increases fetal hemoglobin, thereby reducing polymerization of HbS - Reduces leukocytes and number of adherent reticulocytes - Reduces frequency of vaso-occlusive events and acute chest syndrome	Multicenter Study of Hydroxyurea (MSH) Mean age 30.5, 10% over age 40	Renal clearance May cause: • Reversible, dose-dependent myelosuppression due to age-related decline in hematopoietic stem cells • Decreased drug clearance as eGFR declines, requiring dose reduction
L-Glutamine[27]	Leads to production of nicotinamide adenine dinucleotide (NAD^+) which reduces erythrocyte oxidative stress and adhesion	Trial of L-Glutamine in Sickle Cell Disease Median 19 (range 5-57)	Hepatic metabolism; metabolized to glutamate and ammonia by the liver May cause constipation
Voxelotor[28]	Binds to hemoglobin and shifts O_2 dissociation curve toward normal (i.e., leftward), thus reducing O_2 tension at which hemoglobin deoxygenates, thereby reducing sickling and hemolysis	Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) trial Median age 24 (range 12-59)	Hepatic metabolism Requires dose adjustment in patients with severe (Child-Pugh C) liver disease • Limited experience with advanced renal disease
Crizanlizumab[29,30]	Monoclonal antibody targeting P-selectin to block adhesion of red blood cells and leukocytes to reduce vaso-occlusive events	Sickle Cell Disease Patients with Pain Crises (SUSTAIN) trial Median age 29 (range 16-63)	Reticuloendothelial system clearance May cause: • Infusion reaction • Use with caution in patients with history of frequent severe infections • Unknown if it is safe in the setting of kidney and/or liver impairment
Opioids[31,32]	Agonist or mixed agonist/antagonists of Mu-opioid receptor	Weight-based vs patient-specific opioid dosing in acute setting Median age 27.0 (IQR 23.0-32.5)	Hepatic (first pass) and renal clearance May cause: • Excess sedation, confusion, respiratory depression • Opioid-induced constipation • Increased falls • Cognitive impairment • Decreased muscle strength • Osteoporosis • Hypogonadism • Dental Issues
Transfusion Therapy[33,34]	Increases total hemoglobin and reduces hemoglobin S%	The Preoperative Transfusion in Sickle Cell Disease Study 0-9 years 40% 10-19 years 35% ≥ 20 years 25% The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study Median age 13.4 (IQR 6.4-26.5)	Reticuloendothelial system clearance May cause: • Volume overload • Iron overload • Alloimmunization to minor red blood cell antigens
Iron Chelation Therapy Deferoxamine[35] Deferiprone[36] Deferasirox[37]	Removal of excess iron from tissues	Barriers to adherence to Deferoxamine Mean age 12.1 (range 5-17) Deferasirox in Sickle Cell Trial Median age 15 (range 3-54) Ferriprox in Patients with Iron Overload in Sickle Cell Disease Trial (FIRST) Mean age 16.9 ± 9.6 (range 3-59)	Deferoxamine • Urine and fecal excretion • May cause hearing loss, visual disturbances, and osteoporosis Deferiprone • Urine excretion • May cause agranulocytosis and arthropathy Deferasirox • Fecal excretion • Can be nephrotoxic so should be avoided when eGFR is < 40 mL/minute/1.73m[238] • May cause acute liver injury

Therapy	Mechanism	Clinical trial in adults and age of treatment group	Potential issues in older adults
			Deferoxamine and Deferiprone can be used in patients with decreased renal function; dialyzable

Table 2

Emerging therapies for management of sickle cell disease

Medication		Mechanism	Clinical Trial Information
Pyruvate Kinase Activator	Etavopivat	RBC pyruvate kinase-R (PKR) activator. Decreases 2,3-DPG in RBCs to increase Hb oxygen affinity. Increase ATP	Phase 2/3: NCT04624659 HIBISCUS Age 12-65 years Endpoints: • Increase in hemoglobin • Rate of VOEs.
	Mitapivat	RBC pyruvate kinase-R (PKR) activator. Decreases 2,3-DPG in RBCs to increase hemoglobin oxygen affinity. -Increase ATP	Phase 2 /3 NCT05031780 Age ≥ 16 years Endpoints: • % with a hemoglobin response by 12 weeks • % with treatment-emergent adverse events and treatment-emergent serious adverse events • % with a hemoglobin response by week 52 • Phase 3: Annual rate of sickle cell pain crises
Anti-sickling	GBT021601	Second generation HbS polymerization inhibitor. Binds to hemoglobin and shifts O_2 dissociation curve toward normal (i.e., leftward), thus reducing O_2 tension at which hemoglobin deoxygenates, thereby reducing sickling	Phase 2/3 NCT05431088 6 Months to 65 Years Endpoints: • Number of adults with change from baseline in hemoglobin through week 12 • Proportion of participants with an increase from baseline of >1 g/dL in hemoglobin at week 48 • Pharmacokinetics, while observing maximum concentration after a single dose. • Pharmacokinetics, at minimum concentration and maximum concentration after multiple dose administration
Anti-adhesion therapies	Inclacumab	IgG4 monoclonal antibody that selectively targets P-selectin	Phase 3 NCT04935879 Age ≥ 12 Endpoints: • Rate of VOEs during the 48-week treatment period Phase 3 NCT04927247 Age ≥ 12 years Endpoints: • Re-admission for a VOE within 90 days of randomization
Antioxidant/ Anti-inflammatory	Crovalimab	C-5 (complement) inhibitor to downregulate complement contribution to acute VOE	Phase 2 CROSSWALK-c (NCT05075824) Aged 12 - 55 years Endpoints: • Annual rate of medical facility VOEs
	Rifaximin	Oral antibiotic for intestinal microbial modulation (gut decontamination) to reduce translocation of intestinal bacteria and activated neutrophils	Phase 2 (NCT03719729) Median age 29 years (range 24-56). Endpoints: • Toxicity profile (incidence of nausea, vomiting, diarrhea, abdominal discomfort, worsening anemia)

DPG, diphosphoglycerate. RBC, red blood cell, ATP, adenosine triphosphate. VOE, vaso-occlusive events