Journal of Blood Medicine

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REVIEW

Newer Modalities and Updates in the Management of Sickle Cell Disease: A Systematic Review

Zeel Vishnubhai Patel[1], Priyadarshi Prajjwal[2], Lakshmi Deepak Bethineedi[3], Divyakshi J Patel[4], Kaarvi Khullar[5], Hinal Patel[6], Kanishka Khatri[2], Mohammed Dheyaa Marsool Marsool[7], Srikanth Gadam[8], Soumya Aleti[9], Omniat Amir[10]

[1]Internal Medicine, Medical College Baroda, Baroda, Gujarat, India; [2]Internal Medicine, Bharati Vidyapeeth University Medical College, Pune, India; [3]Internal Medicine, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India; [4]Internal Medicine, Smt. NHL Municipal Medical College, Ahmedabad, India; [5]Internal Medicine, Maharashtra University of Health Sciences, Government Medical College, Gondia, India; [6]Internal Medicine, GMERS Medical College and Hospital Sola, Ahmedabad, India; [7]Internal Medicine, University of Baghdad, Al-Kindy College of Medicine, Baghdad, Iraq; [8]Internal Medicine, NYC Health+ Hospitals, New York, NYC, USA; [9]Internal Medicine, Berkshire Medical Center, Pittsfield, MA, USA; [10]Internal Medicine, Al Manhal Academy of Science, Sudan

Correspondence: Omniat Amir, Internal Medicine, Al Manhal Academy of Science, Khartoum, 1442, Sudan, Email omniatamir123@gmail.com

Abstract: Sickle cell disease (SCD), the most common autosomal recessive genetic disorder, affects the hemoglobin (Hb) chains in human red blood cells. It is caused by mutations in the β-globin genes, leading to the production of hemoglobin S, which results in the formation of sickle-shaped red blood cells (RBCs). These abnormal cells cause hemolysis, endothelial damage, and small vessel occlusion, leading to both acute and long-term complications. According to the World Health Organization's 2008 estimates, SCD affects approximately 2.28 per 1000 individuals globally. Despite this high prevalence, therapeutic advancements have been slow. For many years, the only FDA-approved medications for managing SCD complications were hydroxyurea and deferiprone. However, recent years have seen the approval of several new therapies, including L-glutamine (2017), voxelotor and crizanlizumab (2019), as well as exagamglogene autotemcel (Casgevy) and lovotibeglogene autotemcel (Lyfgenia) (2023). These treatments have proven effective in managing both the acute and chronic effects of SCD, including hemolytic anemia, chronic pain, stroke, vaso-occlusive crises, and multiple organ damage syndromes. This review explores the mechanisms of action, practical considerations, and side effects of these emerging therapies, drawing from a comprehensive search of databases such as PubMed, Medline, and Cochrane.

Keywords: sickle cell disease, L-Glutamine, Voxelotor, Crizanlizumab, Casgevy, Lyfgenia

Introduction

Sickle cell disease (SCD) mainly affects people of African, Mediterranean, Middle Eastern, and South Asian descent, while it can strike any ethnic group.[1,2]

Because of the autosomal recessive inheritance pattern, the disease requires two copies of the faulty gene, one from each parent, to appear. Genetic tests or neonatal screening are usually used to diagnose it.

The primary intervention for anemia is blood transfusion, which increases the oxygen-carrying capacity of the blood and reduces the percentage of sickled cells. However, for vaso-occlusive crises (VOCs), the interventions include pain relief (typically with analgesics), hydration (to reduce blood viscosity), and, in some cases, blood transfusions to reduce the concentration of sickle cells and prevent further sickling.[2]

While gene editing and bone marrow transplantation (BMT) represent significant advancements in the treatment of SCD, they are not universally accessible or without significant risks. The availability of these treatments is limited by various factors, including cost, healthcare infrastructure, and patient eligibility. Moreover, while these treatments offer the potential for a cure, they come with substantial risks of morbidity and mortality, particularly in the context of BMT.[2]

Received: 4 June 2024
Accepted: 2 September 2024
Published: 12 September 2024

Pathophysiology of Sickle Cell Disease

(SCD) occurs due to a mutation in the hemoglobin-producing gene. Thus Hemoglobin S, an abnormal form of hemoglobin, is produced as a consequence of this mutation due to which RBCs take sickle shape when they become deoxygenated due to the polymerization of HbS molecules.[3,4] These sickled cells can induce tissue damage, occlusions in small blood vessels, and blood flow obstruction due to their stiffness and clotting tendency. Anemia results from sickled red blood cells' reduced lifespan compared to healthy red blood cells.[4]

The blockages and reduced oxygen delivery result in episodes of acute pain, tissue ischemia, and organ damage. Further, repeated sickling and unsickling cycles damage the cell membrane, contributing to chronic inflammation and endothelial dysfunction. The various consequences of SCD, such as acute chest syndrome, stroke, pain crises, and multi-organ damage, are caused by the combined effects of these processes.[4]

Past Treatment Modalities

Moderate but steady progress has been made in the development of SCD therapy techniques. Previously, care focused on symptomatic alleviation and reducing complications because there was no curative treatment available (Figure 1).[5–7] Early methods for treating anemia and vaso-occlusive crises included blood transfusions, pain relief, and hydration. Hydroxyurea became a significant medication, showing promise in lowering the frequency and intensity of the situation by increasing the fetal hemoglobin levels. However, worries about its long-term safety and some patients' poor reactivity highlighted the need for different approaches.[6]

In the past, blood transfusion has played a crucial role in sickle cell disease treatment plans by assisting in the management of the disease's numerous clinical symptoms. Transfusions, particularly those containing erythrocytes with hemoglobin A, have been shown to increase hemoglobin levels, lower the risk of anemia, and reduce the incidence of stroke. Transfusion methods such as red blood cell exchange, simple transfusion, and chronic transfusion have been employed to tailor therapy regimens to individual patient requirements.[7]

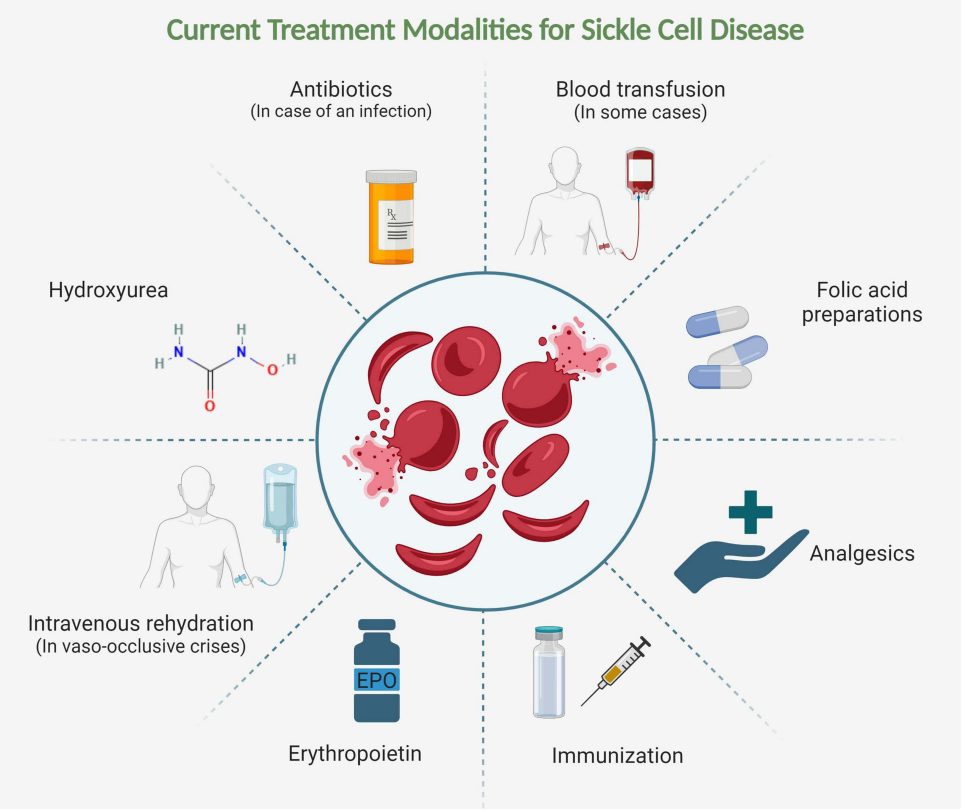

Figure 1 Current and past treatment modalities for patients diagnosed with Sickle Cell Disease.

Even though previous treatment modalities have helped SCD patients live better lives and achieve better outcomes, more work is needed to address the problems that still exist, such as disparities in treatment availability, access to care, and the search for curative interventions to lessen the disease's significant burden.

Limitations of Previous Treatment and Need for New Treatment Modalities

Regarding the development of new frontline treatments for SCD, it has historically grappled with significant limitations. Thus, there has been a pressing need for novel treatment modalities. Previous treatments like fluid replacement, pain relief, and blood transfusions attempted to relieve symptoms, but they frequently failed to address the disease's underlying pathophysiology. Hydroxyurea has proven to be an effective treatment for SCD due to its ability to increase fetal hemoglobin levels, thereby reducing vaso-occlusive crises.[8] However, its inconsistent response rates and worries about long-term safety and adherence brought to light ongoing gaps in available treatments. For some people, hydroxyurea therapy does not produce sufficient results. For these patients, the disease may continue to progress despite treatment, requiring new or different therapeutic modalities. Moreover, hydroxyurea alone might not be sufficient to prevent or treat all SCD complications, including cerebral vasculopathy.[8] L-glutamine was introduced in the following years as an oral preparation, which acts via a novel mechanism of action by lowering oxidative stress and promoting cellular detoxification. A hemoglobin polymerization inhibitor, namely Voxelotor, recently got approval, which was considered a major step because it gave people with hemoglobinopathies a targeted treatment option. The development of new molecules such as Voxelotor and Crizanlizumab, as well as advancements in gene therapy, offer promise as good treatment options. Voxelotor's development as an inhibitor of hemoglobin polymerization represents a breakthrough that provides targeted treatment for people with hemoglobinopathies.[9] Ongoing assessment is necessary, though it has shown promising results for its long-term safety profile and effectiveness in larger populations. A comprehensive strategy addressing both immediate complications and long-term effects, such as organ damage and reduced quality of life, is necessary due to the complex nature of sickle cell disease.[8,10] To improve outcomes and quality of life for affected individuals, it has been urgently necessary to develop novel treatment modalities that not only address the intricate interactions between clinical manifestations but also target the underlying cause of SCD.

Methodology

Literature Search Method

For the conduction of a comprehensive review, we adhered to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines" (Figure 2).

A thorough search was carried out on electronic databases such as Pubmed, Medline and Cochrane and search strategy was developed using a combination of keywords and Medical Subject Headings (MeSH) terms such as "sickle cell disease", "sickle cell anemia", "sickle cell crisis", "L-Glutamine", "Endari", "Crizanlizumab", "P-Selectin inhibitor", "Voxelotor", "Oxbryta", "hemoglobin S polymerization inhibitor", "Exagamglogene autotemcel", "Casgevy", "Lovotibeglogene autotemcel", "Lyfgenia", "CRISPR/CAS9", "lentiviral gene therapy" and related terms.

Inclusion Criteria

Randomized controlled trials and clinical trials that were relevant to treatment outcomes and adverse effects of the above drugs for the management of SCD were included in the review. Only the articles in the English language were considered.

Exclusion Criteria

We excluded review articles, letter-to-editor, abstracts, and studies that were not directly related to recently approved drugs.

Results

We included 23 articles in total which were relevant to new drugs and the patient treatment outcome. In our paper, we discussed L-Glutamine, a potent antioxidant agent and Voxelotor, an anti-sickling drug that had shown promising results in pain reduction and improving haematological profile in all age groups of people including paediatrics, Crizanlizumab,

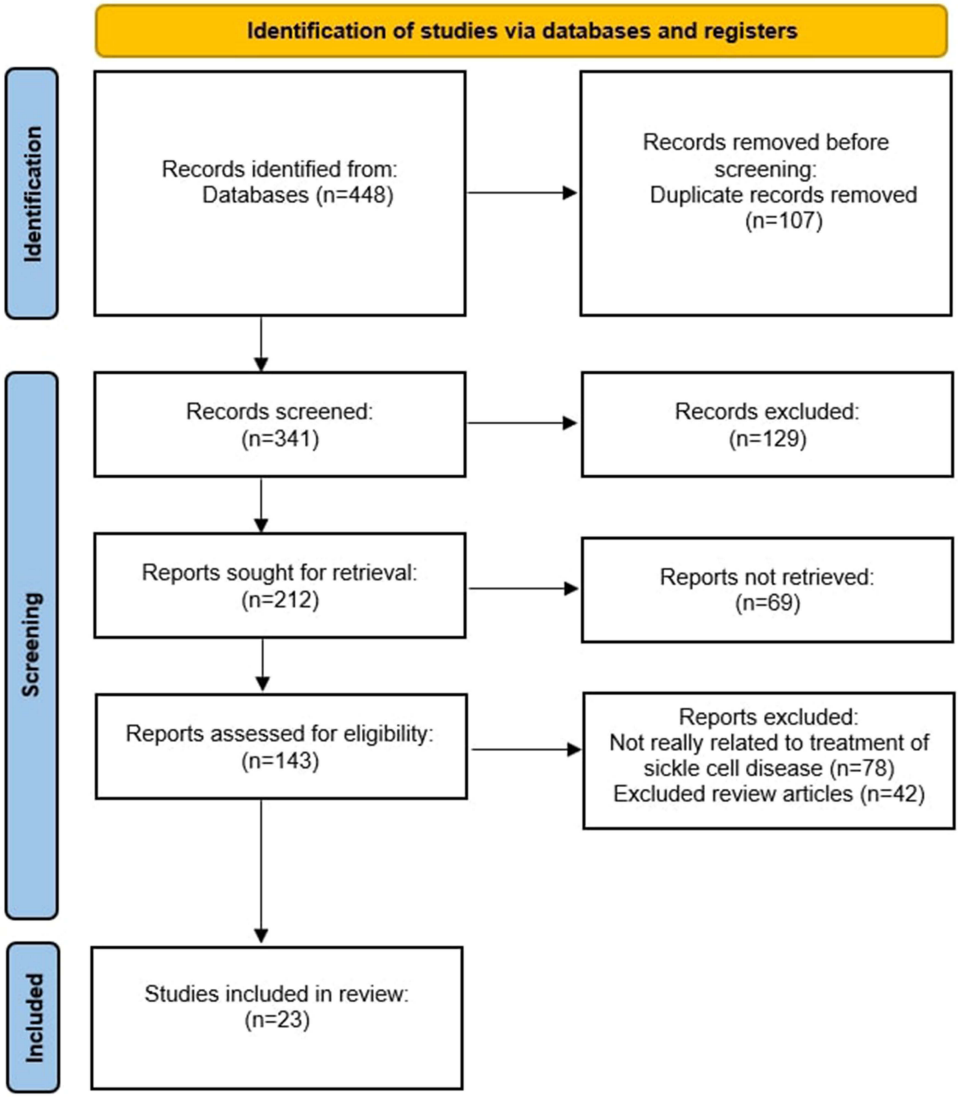

Figure 2 Prisma Flow Diagram.

a P-Selectin inhibitor which alleviates vaso-occlusive crisis and evolving gene therapies like Exagamglogene autotemcel-(Casgevy) and Lovotibeglogene autotemcel (Lyfgenia). Casgevy and Lyfgenia are CRISPR/Cas 9-based groundbreaking therapies to treat SCD from its origin.

The summary of included text is given below in table (Table 1).

Table 1 Shows Summary of the Included Studies

Author's last name-year	Type of study	Objective	Conclusion
Gotesman et al 2022[11]	Retrospective cohort study	To find out if a healthy diet and L-glutamine (Gln) could reduce the severity of sickle cell anemia	Younger, healthier, and better-hydrated patients typically have more favorable clinical outcomes. The severity of the sickness was highest among teenagers who did not follow proper diet and hygiene habits. L-glutamine along with pre-albumin monitoring should be considered for additional evaluation in pediatric SCD.

(*Continued*)

Table 1 (Continued).

Author's last name-year	Type of study	Objective	Conclusion
Elenga et al 2023[12]	Prospective cohort study	To evaluate the overall effect of L-glutamine therapy on kidney function in patients with sickle cell disease.	According to the study, L-glutamine therapy improved therapeutic outcomes and decreased hemolysis. Throughout 48 to 120 weeks of treatment, it was found that L-glutamine improved kidney function in patients with sickle cell disease.
Vichinsky et al 2019[13]	Phase 3 Randomized control trial	To evaluate voxelotor in people suffering from SCD	Voxelotor significantly increased hemoglobin levels in SCD patients while lowering the risk of hemolysis and exacerbating their anemia. Following voxelotor treatment, hematologic improvements were noted, and concurrent HU treatment may have an added benefit.
Muschick et al 2022[14]	Retrospective cohort study	To examine general quality-of-life outcomes and the hematologic response in patients receiving voxelotor treatment.	Following voxelotor treatment, hematologic improvements were noted, and concurrent HU treatment may have an added benefit.
Estepp et al 2022[15]	Phase 2a clinical trial	Evaluate the voxelotor's effectiveness and safety in pediatric SCD patients (4–11 years old).	Voxelotor significantly improved hemolytic markers and Hb levels, demonstrating efficacy consistent with adult and juvenile SCD patients. The safety profile was good, with few unfavorable situations that required stopping. Dispersible pill dosing based on weight was well tolerated.
Shah et al 2022[16]	Retrospective analysis of the database	Evaluate the efficacy of Sickle cell disease Voxelotor in treating sickle cell disease in the United States.	Based on the evidence of improved hemoglobin levels, lower transfusion rates, shorter hospital stays and VOC-related hospitalizations, among other outcomes, the study proposes that V, oxelotor may reduce transfusion and vaso-occlusive crisis (VOC) rates in clinical practice.
Hutchaleelaha et al 2019[17]	Phase 1/2 Randomised clinical trial	To assess Voxelotor's (GBT440) pharmacokinetics and pharmacodynamics in sickle cell disease patients and healthy adults.	With a once-daily dosage, Voxelotor (GBT440) exhibited prolonged pharmacodynamic effects due to its high binding specificity for hemoglobin and linear pharmacokinetics across the investigated dose range. The study demonstrated that Voxelotor was well tolerated in both sickle cell disease patients and healthy volunteers, and it offered evidence of a mechanism for boosting Hb-oxygen affinity.
Howard et al 2019[18]	Phase 1/2 Randomised clinical trial	To evaluate Sickle cell disease Voxelotor's pharmacokinetic and pharmacodynamic characteristics in sickle cell disease patients.	In sickle cell disease patients, Voxelotor had encouraging pharmacokinetic and pharmacodynamic profiles, indicating the drug's potential as a therapy alternative.
Phan et al 2023[19]	Clinical trial	Examine how voxelotor affects cardiopulmonary testing in young people with	In 9 out of 10 young SCA patients already on HU with reasonably high Hgb F, Voxelotor therapy did not increase peak VO2. As anticipated, Voxelotor increased hemoglobin levels, but it also changed the hemoglobin oxygen dissociation curve. The lack of improvement in exercise was likely caused by limitations in oxygen delivery.

(*Continued*)

Table 1 (Continued).

Author's last name-year	Type of study	Objective	Conclusion
Alshurafa et al 2022[20]	Case report	Voxelotor safety and effectiveness in a patient with stage IV chronic renal disease and sickle cell disease	In summary, based on the available data, this case report suggests that voxelotor is safe and tolerated in patients with sickle cell disease (SCD) and severe renal impairment. However, more research is needed to corroborate this result.
Strader et al 2019[21]	Case report	To assess the selectivity and stoichiometry of GBT440-HbS adducts in a hemolysate from a patient with sickle cell disease.	The hemolysate of SS patients contains GBT440-HbS adducts that are unique to the α subunit and occur in a 1:1 stoichiometry, which helps with dose optimization and therapy monitoring.
Kanter et al 2023[22]	Phase 2 open-label clinical trial	Examine crizanlizumab's safety, PK/PD, and effectiveness in patients with sickle cell disease (SCD) to gauge leukocyte adherence to P-selectin and the drug's inhibitory effect.	Crizanlizumab reduces VOC frequency effectively and has a good safety profile at 5.0 mg/kg. PK/PD profiles that are in line with earlier research.
Man et al 2020[23]	Short communication review article	To assess actual Crizanlizumab data in SCD	The assay for standardized microfluidic biochip whole blood adhesion showed that leukocytes adhered heterogeneously to immobilized P-selectin and that this adherence was inhibited in a dose-dependent manner after pre-exposure to crizanlizumab. Crucially, Crizanlizumab therapy induced rolling leukocyte dissociation but did not firmly adhere to leukocytes after attachment to P-selectin. It is proposed that the microfluidic Biochip technology is a promising in vitro assay for SCD patient screening, treatment response monitoring, and guiding the development of new and existing anti-adhesive medicines.
Cheplowitz et al 2023[24]	Retrospective analysis of the database	To look at DMT use in SCD patients from 2014 to 2021 and assess patterns and traits	Crizanlizumab may reduce the number of acute care visits, especially for heavy users; nonetheless, the high rate of discontinuation suggests that more research is required.
Newman et al 2023[25]	Cross-sectional study	Evidence to date about the profile of crizanlizumab and its potential to prevent pain crises in sickle cell disease	The study discovered a gradual rise in the usage of DMT, especially with more recent treatments like crizanlizumab and voxelotor. Still, there is a significant unmet need in the SCD community as seen by the low total DMT use.
Riley et al 2019[26]	Review article	To assess LentiGlobin's effectiveness and safety in sickle cell disease patients	According to phase 2 studies, crizanlizumab has a favorable safety profile and may help people with sickle cell disease have fewer vaso-occlusive crises.

(*Continued*)

Table 1 (Continued).

Author's last name-year	Type of study	Objective	Conclusion
Kanter et al 2022[27]	Phase 1–2 clinical trial	To assess LentiGlobin's effectiveness and safety in sickle cell disease patients	After receiving LentiGlobin for a single treatment, antisickling hemoglobin was produced continuously, which resolved the severe vaso-occlusive episodes and produced a safety profile in line with the known hazards associated with autologous stem-cell transplantation. There were no documented cases of cancer or stroke, and the demographics were typical of the larger sickle cell disease population in the US. A small sample size, a brief follow-up period, and the absence of a control group are among the limitations. Sustained monitoring is required to evaluate long-term safety and efficacy.
Kanter, Thompson et al 2022[28]	Phase 1/2 open-label Clinical Trial	To assess the development of lovo-cel gene therapy as a treatment and its results for sickle cell disease	The study shows how the course of treatment has changed and how the HGB-206 trial groups have fared well.
Drakopoulou et al 2022[29]	Cohort study	The goal of the study was to ascertain whether sickle cell disease (SCD) CD34+ cells could be cultured in vitro to produce higher amounts of fetal hemoglobin (HbF) and lower levels of sickle hemoglobin (HbS) using the GGHI-mB-3D lentiviral vector.	In SCD, the use of CD34+ cells cultured in the GGHI-mB-3D lentiviral vector has been shown to increase HBF levels and decrease HBS levels, suggesting its use as a therapeutic intervention for SCD.
Morgan et al 2020[30]	Lab-based experiment	To assess a new lentiviral vector design for sickle cell disease (SCD) gene therapy.	The use of CoreGA-AS3-FB in a mouse model of SCD showed better infectivity and therapeutic efficacy as a therapeutic intervention for SCD.
Weber et al 2020[31]	Lab-based experiment	To repair the sickle cell disease phenotype and restore fetal hemoglobin synthesis by editing a binding site of γ-globin repressor.	The study demonstrated that the phenotype of SCD can be corrected and HBF synthesis can be restored by editing the γ-globin repressor binding site, suggesting a role of gene editing as a treatment option for SCD patients.
Koniali et al 2023[32]	Lab-based experiment	Testing the safety and effectiveness of gene therapy for sickle cell disease utilizing a GLOBE1 lentiviral vector-transduced autologous CD34+ enriched cell fraction.	The study demonstrated the positive effectiveness and safety of gene therapy (GLOBE1 lentiviral vector) as a treatment of SCD.
Galactéros et al 2023[33]	Meta-analysis	To determine the effect of voxelotor on the burden of sickle cell disease using a modelling technique in France and considering the device's expected acceptance and dispersal over the next five years.	Voxelotor may benefit public health by enhancing haemoglobin levels in SCD patients when used as a treatment choice and lessening the toll of SCD on individuals and the medical system.

Discussion

Novel approaches to treating sickle cell disease can target different pathophysiological pathways. The dysregulation of the von Willebrand factor (VWF) - ADAMTS13 axis is a key component of the pathophysiology of sickle cell disease and plays a significant role in its pathogenesis.[34] Examining the effects of oxidative stress and chronic hemolysis, which aggravate organ damage and endothelial dysfunction, is another area of research. Through the reduction of hemolysis,

oxidative stress, and inflammation, these treatments seek to slow down the course of the disease. Furthermore, the goal of therapies targeting sickle cell adhesion to the vascular endothelium and endothelial dysfunction is to avoid tissue ischemia and vaso-occlusion.[35] Another important pathophysiological event in sickle cell disease is the polymerization of hemoglobin under deoxygenation, which causes red blood cell sickling and other complications. As a result, it has become a key objective to stop sickle hemoglobin (HbS) from polymerizing, which will stop sickle-shaped red blood cells from forming and lower the risk of vaso-occlusive crises. Furthermore, methods to enhance the synthesis of fetal hemoglobin (HbF) have attracted interest because HbF prevents HbS polymerization and lessens the symptoms of SCD.[36] Since inflammation is essential to both chronic organ damage and vaso-occlusive crises, it also presents a target for intervention. It is possible that treating inflammation and its consequences will help SCD patients' live better lives.[36]

L-glutamine aims to lower the burdens associated with this disease by acting through various pathways. L-glutamine operates by replenishing cellular antioxidants. Thus by enhancing the antioxidant defenses within cells, it helps to overcome damaging effects of reactive oxygen species. L-glutamine also enhances the production of nitric oxide, a pivotal molecule involved in vasodilation.[11] Gotesman et al[11] in a retrospective cohort study, found that younger, healthier, and better-hydrated patients had more favorable clinical outcomes. The study suggests that L-glutamine, along with pre-albumin monitoring, should be considered for additional evaluation in pediatric SCD patients. In addition, Elenga et al[12] prospective cohort study concluded that L-glutamine therapy improved therapeutic outcomes and decreased hemolysis, particularly enhancing kidney function over 48 to 120 weeks of treatment in SCD patients. By facilitating vasodilation, L-glutamine contributes to improving vascular tone and ameliorating complications associated with impaired blood circulation. It also exhibits modulatory effects on inflammatory pathways by dampening inflammatory responses, it helps mitigate the systemic inflammation characteristic of the disease.[11,12]

Treatment with L-glutamine has shown positive outcomes in the control of SCD. According to studies, giving L-glutamine therapy results in a lesser number of hospital admissions, fewer red blood cell transfusions, a lesser number of pain crises, and longer intervals between first and second crises. It has also been found that L-glutamine significantly reduces the need for vaso-occlusive crises (VOCs), acute chest syndrome (ACS), hospital stays, and blood transfusions. Additionally, it has been shown that L-glutamine treatment improves clinical outcomes through a decrease in hemolysis markers, an increase in hemoglobin levels, and a reduction in hospital admissions, days of stay, and VOCs.[37,38]

In an article recently published by Narcisse, Elenga, Gylna, Loko et. al[37] on real-life data for L-glutamine therapy, Glutamine has shown remarkable efficacy in alleviating various clinical manifestations of SCD, as proved by several key findings from the study evaluating its impact. Treatment with L-glutamine resulted in an observable reduction in the number of pain crises, hospitalizations, days of hospitalization, and blood transfusions among patients with SCD at 24, 48, and 72 weeks following initiation of therapy.

The mechanism of action of Voxelotor involves blocking the polymerisation of haemoglobin.[19] This is achieved by binding to sickle haemoglobin (HbS) and stabilising it in the oxygenated state leading to an overall decrease in the formation of HbS polymer, thereby reducing sickling of red blood cells (Figure 3). Furthermore, the reduced viscosity and lesser deformability of the red blood cells improves blood flow and it results in fewer incidences of vaso-occlusive crises.[17] The inhibition of HbS polymerization may also lessen hemolysis, oxidative stress, and endothelial dysfunction. These factors combined together further enhance the overall outcomes of Voxelotor use in SCD.[18,20]

Vichinsky et al[13] in a phase 3 randomized control trial, voxelotor was shown to significantly increase hemoglobin levels in SCD patients while lowering the risk of hemolysis and exacerbating anemia. The study highlighted hematologic improvements with possible additive benefits when used with hydroxyurea (HU). In addition, Shah et al[16] in their retrospective analysis, highlighted voxelotor's potential to reduce transfusion rates, hospital stays, and VOC-related hospitalizations in clinical practice. Also, Hutchaleelaha et al[17] A phase 1/2 trial showed voxelotor's prolonged pharmacodynamic effects due to its high binding specificity for hemoglobin, with a good tolerance profile.

OxbrytaTM, commonly known as voxelotor, is a game-changer in the treatment of sickle cell disease. Its distinct process entails attaching to hemoglobin, maintaining its oxygenated form, and preventing HbS polymerization, which holds great promise for individuals suffering from this painful sickness.[40,41] With once-daily oral administration, it unleashes a barrage of benefits, from reducing red-cell sickling and improving blood viscosity to enhancing red-cell deformability.[18,42] Moreover, its knack for extending red-cell half-life and curbing anemia in vivo underscores its

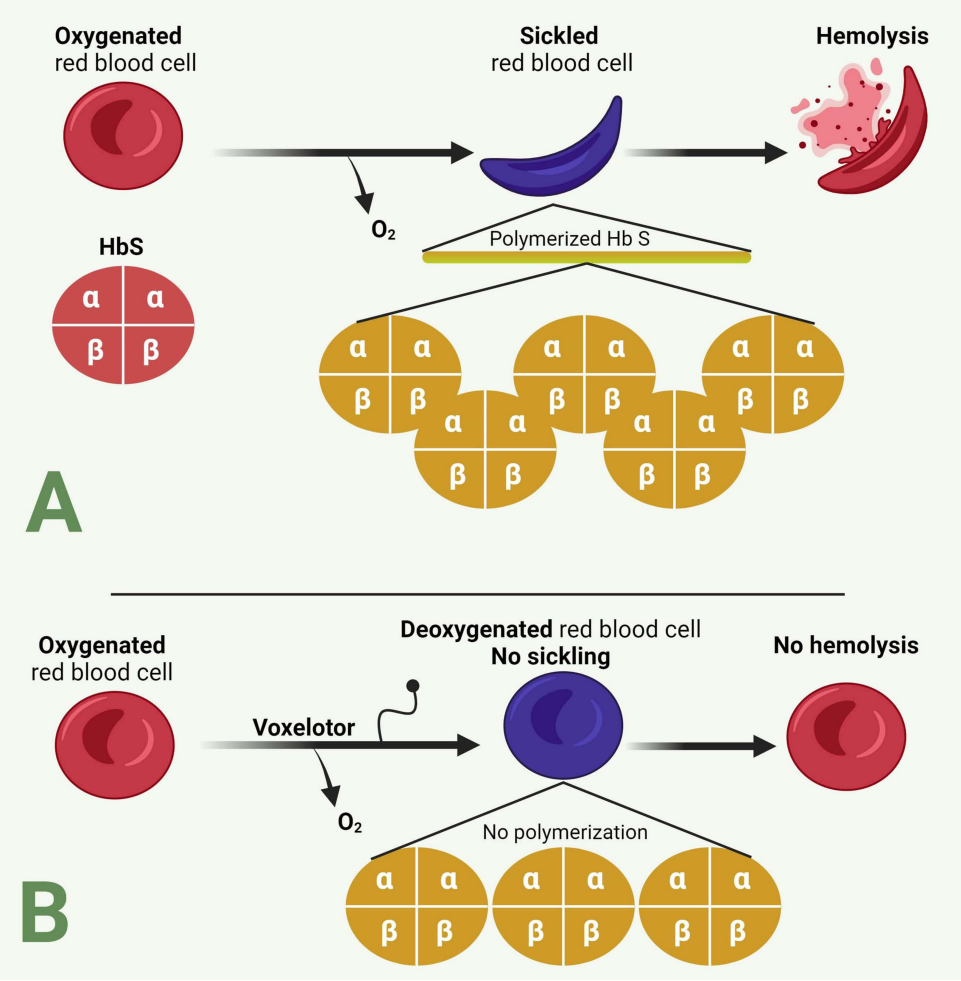

Figure 3 The mechanism underlying sickle cell disease and the therapeutic action of Voxelotor in preventing the sickling of red blood cells (RBCs).
Notes: (**A**) The process begins with an oxygenated red blood cell, where hemoglobin is in its normal soluble form. As the cell becomes deoxygenated, the abnormal hemoglobin S (HbS) molecules polymerize, forming long, rigid chains that distort the cell into a sickle shape. This sickling of RBCs makes them less flexible and more prone to hemolysis. (**B**) Voxelotor exhibits preferential binding to hemoglobin, enhancing its affinity for oxygen, hence maintaining it in the oxygenated state and inhibiting sickling. Data from Engel ER, Howard AL, Ankus EJ, Rico JF. Advances in Sickle Cell Disease Management. Adv Pediatr. 2020 Aug;67:57-71. doi: 10.1016/j.yapd.2020.03.001. Epub 2020 May 14. PMID: 32591064.[39]

potential to revolutionize sickle cell disease management.[13,43] Although concerns initially loomed over potential oxygen delivery compromises, preclinical findings put those worries to rest, emphasizing voxelotor's knack for maintaining tissue oxygenation without compromising organ function.[41,44,45] Furthermore, voxelotor emerges as a ray of hope for people living with sickle cell disease, providing not just alleviation but also a fresh sense of hope, because of clinical studies such as the phase 3 HOPE trial that are highlighting it.[42] Subjects using oxelotor during trials reported few major or severe side effects after 6 months of treatment.[46] More than 10% of cases were of diarrhea, nausea, vomiting, stomach discomfort, fever, rash, headache and were the most frequently reported adverse effects while less than 1% of people experienced anaphylaxis, making it an uncommon occurrence.[47–49] No adverse effects specific to cardiovascular or respiratory function were identified.[50] Trials conducted thus far have been small in size and have not included individuals with other significant comorbid health conditions. Additional adverse effects may be reported as more individuals gain access to voxelotor and postmarketing data are available. Voxelotor may affect laboratory measurements, interfering with high-performance liquid chromatography readings of hemoglobin variants (HbA, HbS, HbF).[43] Individuals and providers can temporarily discontinue voxelotor for accurate subtype readings, as its effect is not permanent. The medication is contraindicated only in cases of documented hypersensitivity.[17] Limited data exist regarding voxelotor's use in pregnant women and breastfeeding mothers, with caution advised due to potential adverse effects on infant hematopoiesis.[13] Adolescents aged 12 and older can take voxelotor, but data on its use in individuals aged 65 and older are lacking.[51]

Nurses should counsel women with SCD on contraception options, considering the risks of SCD during pregnancy.[52,53] In a single-center study of Kathryn Muschick et al[14] Voxelotor treatment showed favorable hematologic responses in patients with SCD like increased hemoglobin (Hb) levels, decreased reticulocyte percentage, and reduced total bilirubin. The study included 77 patients, mostly female (62%) with homozygous HbSS genotype (86%) and concomitant hydroxyurea (82%). Voxelotor demonstrated potential additive benefits when used with hydroxyurea, enhancing hematologic improvements. Adverse events were rare, mild, and resolved with dose modification. Quality-of-life outcomes improved, assessed via patient and clinician global impression questionnaires, with higher scores in patients using hydroxyurea. This retrospective review, although limited by its observational nature and single-center design, provides valuable real-world insights into the efficacy of voxelotor in treating SCD.[54]

Crizanlizumab works as a P-selectin inhibitor, targeting important mechanisms of vaso-occlusive events. P-selectin is an adhesion molecule found on endothelial cells and platelets, it is responsible for the adhesion of red blood cells to the vascular endothelium.[22,23] P-selectin then facilitates the RBCs' subsequent entrapment and occlusion within the microvasculature. Crizanlizumab binds to P-selectin and covers its active site thereby preventing the interaction between RBCs, platelets and endothelial cells. This effectively lowers the frequency and severity of vaso-occlusive crises.[23,25] Crizanlizumab's therapeutic benefits also involve an additional mechanism that works by reducing inflammation and endothelial activation. Kanter et al[22] a phase 2 open-label clinical trial found that crizanlizumab effectively reduced VOC frequency with a good safety profile. A cross-sectional study by Newman et al[25] showed a gradual rise in crizanlizumab usage, highlighting its potential in preventing pain crises in SCD, though unmet needs remain in the SCD community.

VOCs are a major cause of morbidity and mortality in individuals with SCD and often lead to hospitalizations and decreased quality of life. The landmark SUSTAIN trial demonstrated the efficacy of crizanlizumab in reducing the frequency of VOCs among patients with SCD. Crizanlizumab causes sickle cells, endothelial cells as well as leukocytes to not adhere to one another by selectively inhibiting P selectin. In contrast to volatile organic molecules, this lessens the inflammatory reaction and microvascular obstruction.[55] The pathophysiology of SCD is consistent with this method of action as the tissue damage and organ dysfunction are caused by ischemia reperfusion injury and vaso-occlusion.

Moreover crizanlizumab ability to prevent VOCs extends beyond symptom management to address the underlying pathophysiology of SCD. P selectin mediated platelet activation and endothelial cell adhesion play critical roles in the initiation and propagation of VOCs. Crizanlizumab disrupts these processes and thereby reduce the incidence and severity of VOCs. This targeted approach offers a novel therapeutic strategy for individuals with SCD and potentially minimizes the need for opioid analgesics and hospitalizations associated with VOCs.[56] The safety and tolerability profile of Crizanlizumab observed in clinical trials further support its potential as a disease modifying therapy for SCD.

In addition to its effects on VOCs, Crizanlizumab may also have broader implications for other SCD related complications. ACS, a severe pulmonary complication of SCD, shares common pathogenic mechanisms with VOCs including inflammation and endothelial activation and and microvascular occlusion. Preclinical studies have shown that P selectin blockade can attenuate lung injury and improve outcomes in mouse models of ACS, suggesting a potential role for Crizanlizumab in preventing or mitigating this complication in individuals with SCD.[57] Furthermore, the antithrombotic properties of Crizanlizumab may reduce the risk of thrombotic events in patients with SCD who are predisposed to both venous and arterial thrombosis.[58] By targeting P selectin, Crizanlizumab offers a multifaceted approach to managing SCD and addressing both acute and chronic complications associated with the disease.

Autologous HSCT refers to when stem cells are obtained from the patient's marrow or blood. These can then be altered in laboratory settings so that they lack any genetic abnormalities found therein before being reintroduced back into the donor's body system again. Although this method eliminates compatibility issues with donors, it does not necessarily work for all diseases. Morgan et al[30] in their lab-based experiment, showed that the CoreGA-AS3-FB lentiviral vector improved therapeutic efficacy in a mouse model of SCD, offering a promising gene therapy approach. Gene editing is a novel technique that allows scientists to alter an organism's nucleotide sequence directly at a highly specific point. This offers hope in finding treatment for sickle cell disease, which is also a genetic disorder. Weber et al[31] which is another lab-based experiment demonstrated the correction of the SCD phenotype and restoration of HbF synthesis through gene editing, highlighting the potential of gene therapy for SCD patients.

Challenges and Further Perspectives

Even with the introduction of disease-modifying medications such as L-glutamine oral powder, Voxelotor, and Crizanlizumab and the use of stem cell transplantation in certain situations, issues like restricted availability, related hazards, and insufficient effectiveness highlighted the necessity for more thorough and easily accessible therapeutic methods.

L-glutamine treatment has been associated with side effects such as abdominal pain, nausea, vomiting and serious side effects such as spleen enlargement, indigestion, and hot flashes.[59]

Patients receiving voxelotor have common side effects due to medication, such as pyrexia, diarrhea, vomiting, headaches, and back discomfort.[60] Also, adverse effects like the pulmonary crisis were reported by Vichinsky et al which was stated "may be unrelated" to Voxelotor the author.[13]

The major side effects that were observed after the therapeutic use of crizanlizumab were pyrexia, influenza, and pneumonia along with some occasionally reported side effects like headache, nausea, back pain, chest discomfort, and arthralgia.

Gene therapy and stem cell transplantation are considered promising approaches for treating SCD. However, its implementation on a large scale is still limited due to several reasons. First of all, finding compatible donors for allogeneic hematopoietic stem cell transplants can be difficult for many patients, making the very first step a significant challenge, Furthermore, the high expense of gene therapy and stem cell transplantation overburdens patient pocket expenditure. The limitation to access such therapies is also a significant barrier to people, especially for those living in resource-constrained environments.

Even when it comes to treating pediatric populations with SCD, stem cell transplantation has become the standard of excellence, but its use is limited by the risks involved and the availability of suitable donors.

Moreover, considering gene therapy and gene editing techniques are still in their early stages of development, concerns about safety and efficacy are yet to be tested. Further research and rigorous clinical trials are necessary to establish the safety and effectiveness of these innovative approaches before they are widely implemented as standard treatments for SCD.

Limitations

Although this systemic review was carried out with utmost precision, there might be a deficiency in data due to limited trials and studies available. Furthermore, the data is available for a limited population which might hinder the quality of information available. The papers included in our study were in English language only, so the possibility is there that we might have missed important papers.

Conclusion

Over the past ten years, advancements in sickle cell disease have given doctors more alternatives and opened the gateway for more studies. The pathophysiology of disease advancement and the therapies that regulate its progression are now more understood. There has been rapid advancement in the discovery of variable solutions available that have the potential to treat the underlying cause of the symptoms and alleviate them.

The FDA approval of Exagamglogene autotemcel and lovotibeglogene autotemcel, which treat diseases at their base, would undoubtedly change the game. Additionally, a sizable number of individuals from nations with both abundant and scarce resources who are unable to pay for stem-cell therapy would benefit from L-glutamine, Voxelotor, and Crizanlizumab.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article.

Funding

There is no funding to report.

Disclosure

The authors declare no conflicts of interest, financial or otherwise.

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