

REVIEW

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Recent progress in the treatment of sickle cell disease: an up-to-date review

Biswajeet Acharya¹, Durga Prasad Mishra^{1*}, Binapani Barik¹, Ranjan K. Mohapatra² and Ashish K. Sarangi^{3*} 

Abstract

Background Sickle cell disease is a fatal systemic condition characterized by acute painful episodes, persistent anemia, ongoing organ damage, organ infarction, and a markedly shorter average lifetime. It first appeared in the tropics' malarial zones, where carriers benefit from an evolutionary advantage by being shielded from malaria death. Due to demographic shifts, this crisis now affects people all over the world. In higher-income areas, such as vast swaths of Europe and North and South America, more children are born with the syndrome.

Main body Over the last 10 years, a clearer knowledge of the change from fetal to adult hemoglobin has evolved. Further investigation into chimerism, genomics, mixed gene editing, and therapeutic reactivation of fetal hemoglobin has produced very promising findings. Between 2017 and 2019, three innovative medications for sickle cell disease were approved by the FDA thanks to previous advances, while many more treatments are now under development.

Short conclusion To improve patient outcomes, various innovative medications that were created in the late 1990s and utilized to treat sickle cell disease are examined in this study. In our appraisal, we'll also focus on the most important developments of the decade.

Keywords Anemia, Hemoglobin, Hematological disorder, Sickle cell disease

1 Background

RBCs are distorted and broken down as a result of the abnormalities that make up sickle cell disease (SCD). Millions of individuals are impacted by this monogenic illness worldwide [1]. Hemolytic anemia, severe vas occlusion, and persistent organ destruction are all symptoms of this multisystem, autosomal recessive illness [2]. Each year, 3.2 lakhs newborn newborns throughout the globe are afflicted. This is not only a problem for young

children; it also affects adults. Due to the lack of neonatal screening, infant mortality is higher, ranging from 50 to 90% before diagnosis [3]. Although it is widespread worldwide, WHO found that in west Africa it is responsible for 9–16% of child deaths. Sub-Saharan Africa, India, Nigeria, and the Democratic Republic of the Congo have the highest patient rates for SCD. When oxygen is carried by blood cells, deformed hemoglobin polymerizes into fibers that change RBC, obstruct blood flow, and produce excruciating agony known as sickle cell crisis [4]. Multiple genetic variations may potentially be the source of SCD. Concerning SCD occurs, homozygous HbSS variant interpretation excludes mortality and morbidity caused by HbSC variations or thalassemia [5–8]. Hemoglobin analysis with or without the inclusion of the globin chain variation utilizing methods including HPLC, Hb electrophoresis, and isoelectric focusing may detect HbS (less than 50%) to help diagnose SCD [9–11]. The signs and symptoms of SCD might vary from person to person and from kid to child; however, some typical

*Correspondence:

Durga Prasad Mishra
dpm0149@gmail.com

Ashish K. Sarangi
ashishsbp_2008@yahoo.com

¹ School of Pharmacy, Centurion University of Technology and Management, Balangir, Odisha, India

² Department of Chemistry, Government College of Engineering, Keonjhar, Odisha, India

³ Department of Chemistry, School of Applied Sciences, Centurion University of Technology and Management, Balangir, Odisha, India



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signs and symptoms include anemia, yellowing of the skin, eyes, and mouth, pneumonia, severe dehydration-related coughing, acute chest syndrome, toe swelling, and discomfort in the fingers and arms [12]. The body cannot make enough blood cells after SCD recovery, and you may feel exceedingly exhausted and your pulse will be quicker. A youngster would likely have severe bacterial infections in addition to fevers, and the upper limit for temperature is 101°F [13]. SCD is more likely to harm the body in men since it lasts so long in them. Additionally, it has been shown that SCD patients often have spleen enlargement, stomach discomfort, headaches, and unconsciousness [14]. Kidney problems, gallstones, eye damage, bone or joint injury, and slow development are risk factors. SCD causes greater deaths in children under the age of five. Currently, an estimated 3.5 million neonates are born every year with the condition; more than 80% of them are born in Africa. Recent population movements have led to an increase in SCD cases in countries like the USA where malaria has never been prevalent [15]. About 100,000 Americans are thought to be affected by SCD, and the majority of them are of African descent. The number of those affected by SCD is projected to increase exponentially; it is estimated that 14,242,000 babies will be affected by SCD between 2010 and 2050; the movement of people and growing globalization will further spread SCD across the globe in the ensuing decades [16]. While almost all newborns with SCD may now be expected to survive to adulthood in medium- to well-resourced countries, 75% or more of neonates with SCD die before they turn five in Sub-Saharan Africa. However, the survival rate still lags behind that of a non-SCD person by 20–30 years. Despite these estimates of the global frequency of SCD and the fact that it is by far the most serious hemoglobinopathy concerning public health, the WHO did not classify SCD as a major public health problem until 2006 [17–19]. When Linus Pauling discovered in 1949 that SCD was made possible by a defective protein (hemoglobin S, HbS), it became the first molecular illness. The extensive scientific and clinical study was sparked by this revelation. SCD has been used as proof because of its genetic accessibility of concept for the polymerase chain reaction (PCR), which we now recognize as normal, and to demonstrate several breakthroughs in genetic analysis, such as identifying a DNA mutation by restriction fragment enzymatic analysis [20, 21]. Sickle cell disease (SCD) manifests itself throughout the first year of life, generally around the age of five months. Massive advances in the treatment and prevention of SCD problems have increased life expectancy. Now, approximately 95% of those born with SCD in the USA live to be 18 years old; nonetheless, individuals with the most severe types of SCD live 20–30 years

less than people without SCD [22]. Amazing progress has been made in the previous 50 years to comprehend the pathobiological and pathological challenges of SCD, but the progressive therapies have been unacceptably sluggish and ill-defined. The therapeutic action of SCD will vary in the next 30 years due to advancements in genetics and genomics and increased awareness on the part of the funding agencies NIH, USA. Since two to three clinical studies have been completed in the previous ten years, we are now fully contemplating advanced therapy for SCD from a pathophysiological standpoint [23, 24]. Figure 1 illustrates the history of advancements in SCD medical therapy graphically. This review, which might provide a fresh glimmer of hope for medical technology, primarily focused on many unique and common treatment techniques for SCD in this context.

2 Main text

2.1 Pathophysiology of SCD

The graphic (Fig. 1) [25–29] presents some of the pathophysiologic components of the condition in a more simplified manner. In-depth descriptions of the illness' pathogenesis can be found in numerous studies. After red blood cells undergo deoxygenation and assume the pathognomonic sickle cell shape, it is no longer accurate to state that only sickle cells may cause vascular obstruction or vaso-occlusion [30]. SCD is brought on by a single gene mutation that results in complex physiologic abnormalities, while vaso-occlusion is essential to understanding the condition and may induce local hypoxia and inflammation [31]. These changes lead to the disease's clinical symptoms. In addition to vaso-occlusion, anemia, and hemolysis, SCD is now understood to be a condition that also involves increased inflammation, oxidative stress, hypercoagulability, and issues with arginine metabolism [32]. SCD is a vasculopathy that causes the patient damage due to several dietary and nutritional deficiencies. Sickling is caused by sickle hemoglobin, which after deoxygenation becomes insoluble and starts to polymerize and agglomerate into tubulin fibers [33]. The cells' hard structure makes them prone to get caught in the microcirculation, which causes ischemia damage or even death by blocking oxygenated blood from reaching regions downstream. Damage from reperfusion or tissue injury results from a lack of blood flow [34]. Sickle cells are sensitive to hypoxia due to abnormalities in the Gardos channel. These cells produce less nitric oxide and adenosine triphosphate and have abnormal intracellular signaling pathways active. Additionally, the antioxidant capacity of these cells is decreased [35]. As a consequence, different biological components may sustain oxidative damage. The formation of microscopic

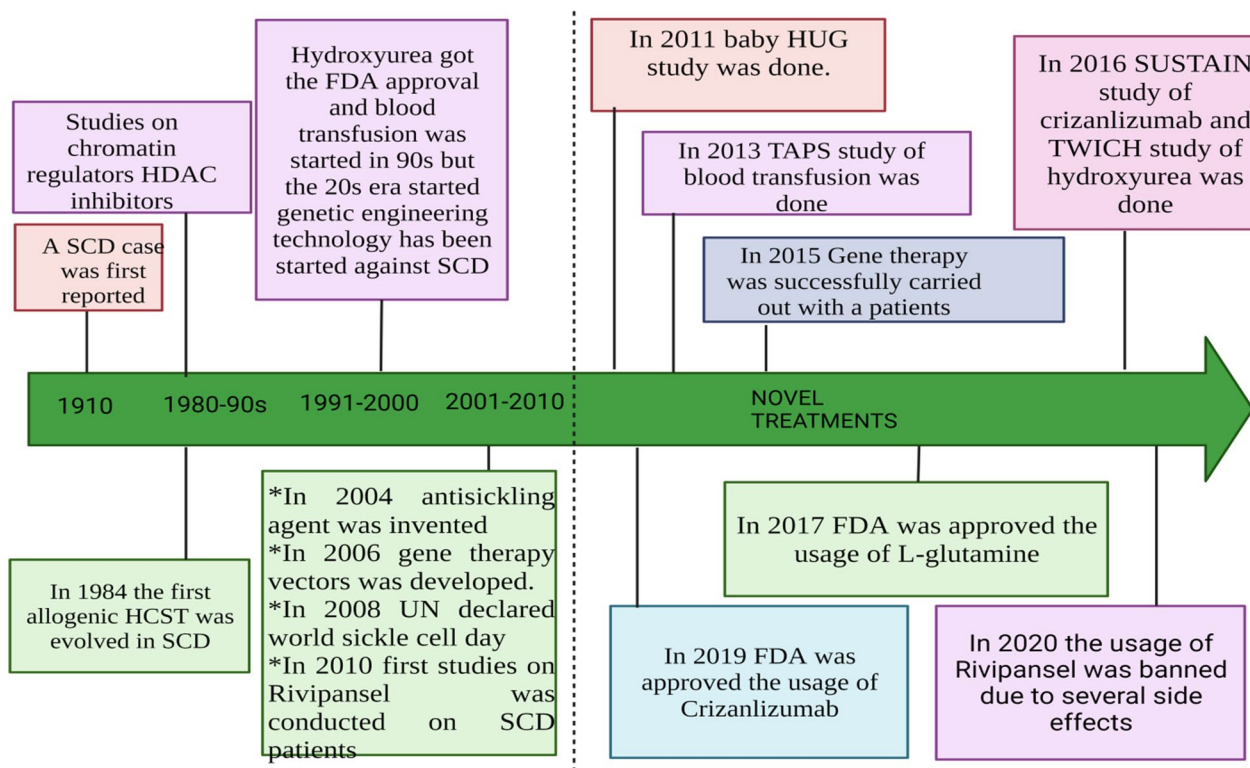


Fig. 1 A timeline representing the invention of therapeutic strategies protocols from the 90 s to now onwards (Created with BioRender.com)

particles and an increase in phosphatidylserine exposure are the results of intracellular abnormalities at the red cell membrane, which may be brought on by protein aggregation along the inner side of the cytoplasmic membrane and oxidative damage to cellular membrane proteins [36]. During hemolysis, free hemoglobin is discharged into the plasma and acts as a nitric oxide scavenger. Since sickle cells have lower levels of arginase-1 activity than normal red blood cells do, nitric oxide cannot be created from scratch, especially in those who hemolyze often [37]. The pictorial presentation on arginine dysregulation in a blood vessel is given in Fig. 2. Reactive oxygen species are created as a byproduct of hemolysis via processes involving free hemoglobin. In sickle cells, microRNAs are dysregulated, short non-coding RNAs work to silence RNA, and post-transcriptional transcription takes place [38]. As a consequence, erythropoiesis's gene expression is abnormal. The abnormally sticky properties of sickle erythrocytes may activate adhesion receptors like those for intercellular adhesion molecule-4 [39]. Similar to this, the transmembrane adhesion molecule glycoprotein basal cell adhesion molecule (Lutheran blood group) and its particular integrin- α 4- β 1 mediate the attachment of sickle cells to the endothelium [40]. Leukocytes, red blood cells, endothelium, platelets, and components of

the extracellular matrix consequently interact abnormally with one another. A continual process of adherent contact caused by abnormal cell-cell connections causes endothelial cells to produce procoagulant substances [41]. Sickle red cells have enhanced adhesion because the upstream kinase MEK 12 and the mitogen-activated protein kinase ERK 12, which is necessary for its beginning, are both constitutively active. E-selectin and P-selectin, which promote adhesion, are increased in SCD, and the level of red cell adhesion is linked with pathogenicity [42]. Sickle hemoglobin-containing red blood cells are tougher than regular red blood cells in circulation, in contrast to these alterations. Even after the cell has taken on an apparent normal ovoid shape, aberrant deformability still exists. Sickle hemoglobin-containing healthy erythrocytes are morphologically comparable to chronically sickled cells in their susceptibility to attachment [43]. Additionally required for the beginning of vas obstruction is inflammation. Platelets and leukocytes are activated even in a steady state, and inflammatory symptoms are prevalent. Significant amounts of IL-4, macrophage-inflammatory protein, IL-10, and tumor necrosis factor-alpha are present even at baseline. Higher levels of leukotriene are associated with more frequent painful episodes because, in the steady state, the leukotriene synthesis enzyme

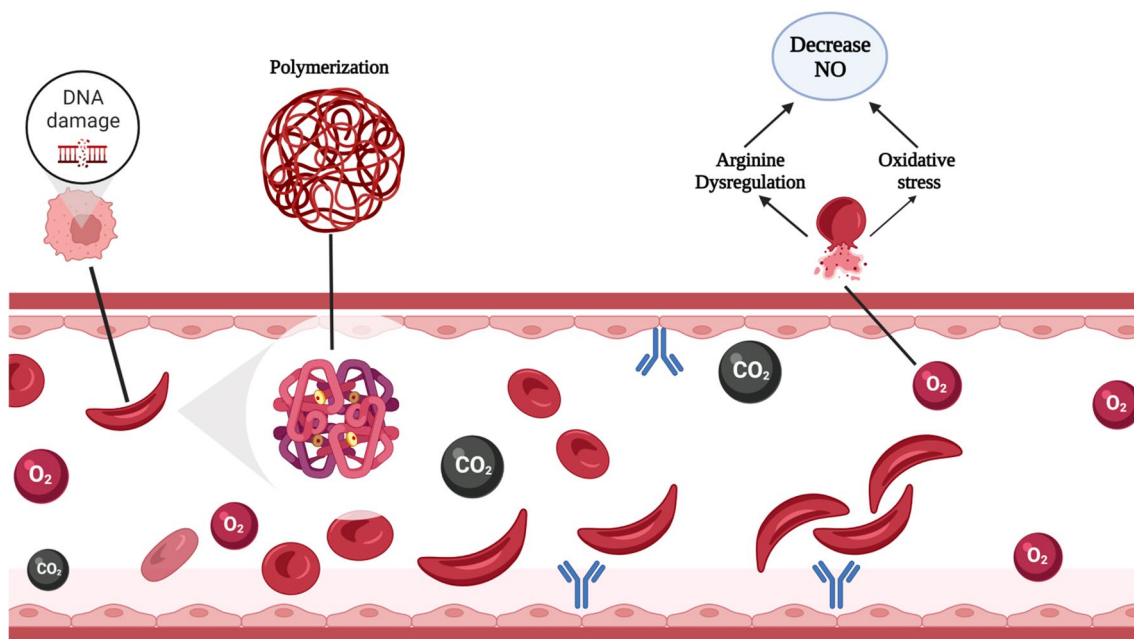


Fig. 2 A representation of arginine dysregulation in blood vessel of SCD patient (Created with BioRender.com)

5-lipoxygenase activates endothelial and monocytic cells [44]. Additionally activated and more prevalent are invariant natural killer T cells. As a sign of their importance, they could be involved in the pathophysiology of ischemia damage in SCD [45]. All of these alterations show how the condition is a complex patchwork of underlying problems that are fascinating to research but make creating an all-encompassing treatment strategy difficult. Figure 3 shows sickle-shaped blood cells and the regular flow of blood components within blood

arteries. Figure 4 illustrates the effect on the disease’s continuous course as well as its repercussions.

2.2 Signs and symptoms

2.2.1 Vaso-occlusive crisis (VOC)

This is how SCD is often manifested. Inflammatory mediators are released together with tissue and vascular damage and inflammation as a result of microvascular occlusion, which is the primary pathophysiological cause of acute pain. These events activate nociceptors. The discomfort and

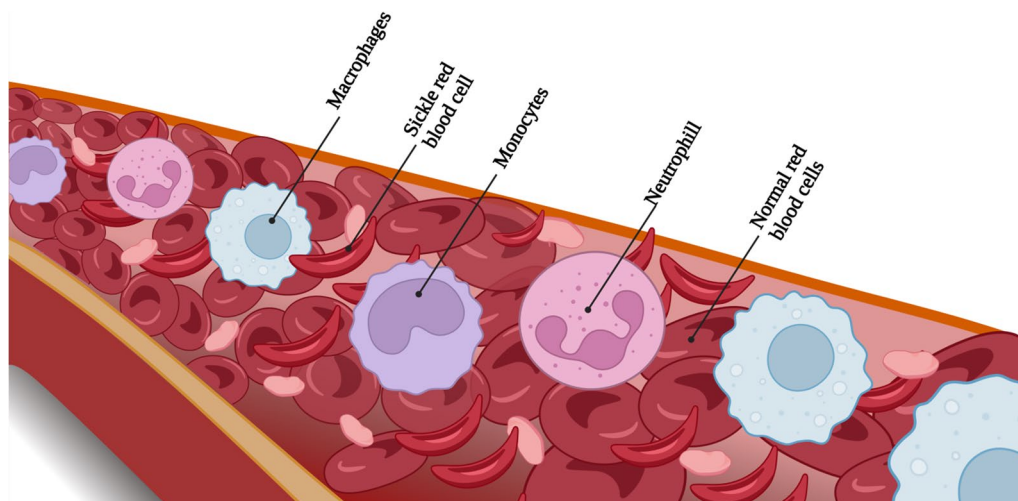


Fig. 3 Flow of normal blood and sickle shape of blood along with its all components in blood vessels (Created with BioRender.com)

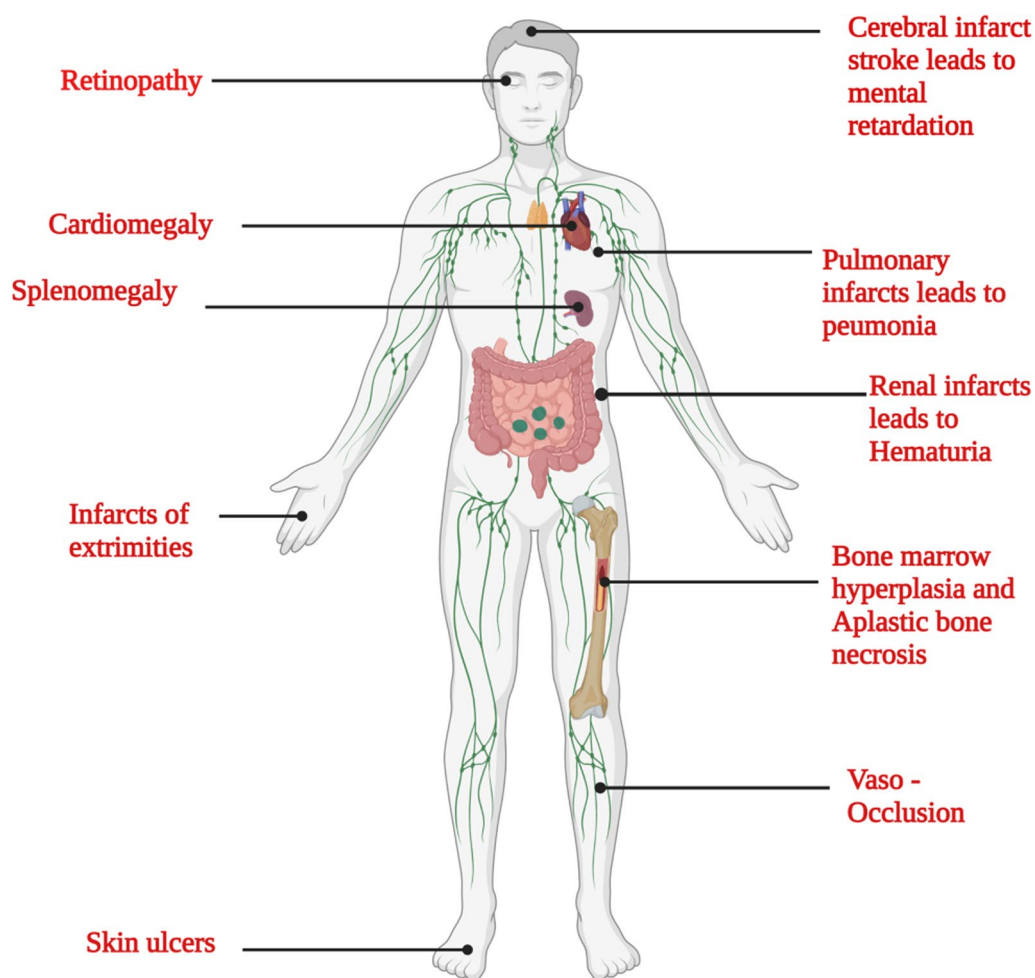


Fig. 4 Complications associated with SCD (Created with BioRender.com)

resulting inflammation are made worse by reperfusion. In any area of the body, patients report excruciating, incapacitating pain, although the long bones, back, pelvis, chest, and abdomen are the most often mentioned. Pain and swelling in the hands and feet may appear as early as six months of age (dactylitis). Most of the time, there are no accurate symptoms or tests to determine whether or not there is VOC-related discomfort [46].

2.2.2 Acute chest syndrome (ACS)

A new pulmonary infiltration on chest radiography that is accompanied by a fever and respiratory symptoms such as a cough, tachypnea, and chest pain is referred to be ACS. ACS is thought to be caused by hypoxia and an increase in pulmonary microvasculature adhesion to sickled erythrocytes brought on by inflammatory mediators. Nitric oxide (NO), which typically would counterbalance this activity, is also decreased as a result of this mechanism. Fever, coughing, chest discomfort, and dyspnea are the most typical symptoms of ACS in patients. A

lung exam may also reveal restricted air entry, rales, and occasionally wheezing. If ACS is not treated right away, it can quickly develop into hypoxemia and respiratory failure. Chlamydia, Streptococcus pneumonia, and Mycoplasma predominate when infectious organisms can be identified [47].

2.2.3 Infections

Due to their functional asplenia and functional immunocompromised status, patients with SCD are more vulnerable to infections with encapsulated organisms (increased bone marrow turnover and altered complement activation). Significant progress has been made in lowering the prevalence of bacterial infections and sepsis thanks to the widespread use of the pneumococcal vaccine and the prophylaxis of penicillin in children [48].

2.2.4 Pulmonary hypertension (PHTN)

PHTN has a 6–10% incidence and a 2–5% mortality. Changes in medial smooth muscle and endothelial cells

are thought to play a significant role in the development of PHTN. Reduced exercise capacity is the main clinical finding (45% of patients are New York Heart Association class III or IV). Increased levels of the neurotransmitter N-terminal pro-brain natriuretic peptide (NT-proBNP), increased regurgitated jet velocity of the tricuspid valve on echocardiography, and elevated pulmonary pressures on right cardiac catheterization are among the diagnostic findings [49].

2.2.5 Cerebrovascular accidents (CVA)/stroke

Children as young as two years old can experience CVA, and 11% of people with SCD will experience a stroke by the time they are 20. Silent cerebral infarcts (SCI), which are linked to small-vessel disease, are more frequent than obvious strokes; by the age of 14, 34% of SCD patients had SCI. Transcranial Doppler is a useful screening procedure that can be used to determine SCD patients who are at a higher risk of CVA starting at age two [50].

2.2.6 Pulmonary embolism (PE)

Patients with SCD have a greater incidence of PE. The annual incidence of SCD in patients is 50–100 times higher than that of individuals without SCD [51].

2.2.7 Renal complications

Renal complications are extremely common in SCD, with 30% of adults developing chronic renal failure. This is due to the low partial pressure of oxygen, low pH, and high osmolality in the renal medulla which contribute to erythrocyte dehydration and vaso-occlusion. Microalbuminuria and proteinuria are common diagnostic findings [52].

2.2.8 Eye complications

The most frequent ophthalmologic consequence of SCD is proliferative retinopathy, which develops when the peripheral retinal vasculature is blocked (up to 70% more frequently in HbSC) [53].

2.2.9 Splenic sequestration

Splenic sequestration, a potentially fatal SCD consequence, is characterized by an abrupt drop in hemoglobin levels. This condition is more common in children, especially those with HbSS anemia, and it can cause severe stomach discomfort and circulatory collapse. This is because the splenic auto-infarction happened at the age of six. However, people with HbSC and other hemoglobinopathies can exhibit this [54].

2.2.10 Priapism

The low-flow type of priapism connected to stasis, hypoxia, and ischemia is typical of SCD [55].

2.2.11 Cholelithiasis

Chronic hemolysis and increased bilirubin turnover lead to the development of cholelithiasis and biliary sludge [56].

2.2.12 Osteonecrosis

Osteonecrosis frequently affects the femoral and humeral heads and is brought on by increasing erythrocyte marrow pressure or vascular blockage. Sometimes surgical intervention is necessary [57].

2.2.13 Aplastic crisis

Interruption of erythropoiesis brought on by parvovirus B19 can produce severe anemia and cardiovascular decompensation. The normal duration of this self-limited infection is 7–10 days, and it can be fatal [58].

3 Diagnosis of disease

Some of the diagnostic techniques include the peripheral smear, solubility testing, DNA testing (prenatal diagnosis), and hemoglobin electrophoresis (or thin-layer isoelectric focusing). The patient's age determines the kind of tests that are conducted [59]. DNA testing may be utilized for prenatal diagnosis or to confirm sickle cell genotype identification. Neonatal screening, which includes hemoglobin electrophoresis, is offered by the majority of states in the US. Hemoglobin solubility tests, hemoglobin electrophoresis, and peripheral smear examination are all utilized in the diagnosis and screening of both adults and children [60].

3.1 Prenatal screening

The accuracy of prenatal diagnoses has considerably increased with the development of polymerase chain reaction technology. It is labeled for families at risk for SCD [61]. At 10–12 weeks of pregnancy, chorionic villus sampling may be used to collect DNA samples. Amniotic fluid may be checked at 14–16 weeks. A diagnosis is required for genetic counseling.

3.2 Newborn screening

Currently, nationwide testing is advised, and a battery of newborn screening tests often includes it. Methods that have been authorized to distinguish between hemoglobin (Hb) S, A, F, and C include hemoglobin electrophoresis using acid citrate agar and cellulose acetate, thin-layer isoelectric focusing, and hemoglobin fractionation by HPLC [62]. Verification testing may be necessary between the ages of three and six months.

Solubility testing for HbS during the first several months of life is unreliable.

3.3 Diagnosis and screening of children and adults

By using peripheral smear, hemoglobin electrophoresis, and hemoglobin solubility tests, a patient's SCD must be noted with their family history. Unaccounted-for hematuria, excruciating and unexplainable bone pain, slow development, and aseptic necrosis of the femoral head indicate the patient's illness is difficult to treat [63]. Hemoglobin electrophoresis, red blood cell analysis, and hemolytic anemia screenings are required for black individuals with normocytic anemia. If SCD persists, the RBC count will be 2–3 million/ μmL and the hemoglobin ratio will be lower [64]. Nucleated RBCs often develop in peripheral blood and account for 10% of reticulocytosis. Dry stained smears that have extended or pointed ends and crescent-shaped shapes may be used to identify sickled RBCs. By showing HbS with a changeable amount of HbF, the homozygous condition is separated from sickle hemoglobinopathies by electrophoresis [65]. HbA is more prevalent on electrophoresis, which may distinguish heterozygotes, than HbS. By using an electrophoretic pattern to screen pathognomonic RBC shape, HbS may be identified from other hemoglobins. Testing of the bone marrow is not necessary for diagnosis [66]. The completion of differentiation with other anemias results in bone marrow destruction during severe infection and hyperplasia. Uneven density. Long bones may be used to demonstrate cortical thinning and the creation of new bone in the medullary canal. If the patients are not diagnosed with SCD, then unexplained hematuria should be taken into consideration as a sign of SCD [67].

3.4 Evaluation of exacerbations

A complete blood count and reticulocyte count should be done in individuals with SCD who have acute exacerbations and exhibit symptoms such as infections, fevers, aplastic crises, etc. [68]. Reticulocyte count increases as hemoglobin levels drop and suggests an aplastic crisis when it is more than 1%. If a painful crisis does not accompany aplasia during bacterial infection, the WBC count will rise. Acute chest syndrome will result in a higher platelet count. When urobilinogen is present in urine as shown by measurement and confirmation, serum bilirubin is often high. Chest X-rays and pulse oximetry help identify patients with acute chest syndrome, chest discomfort, and breathing issues [69]. It is essential since acute chest syndrome kills SCD patients, necessitating early detection and preventative measures.

4 Major novel treatment protocol for SCD

According to the National Institutes of Health, effective care for people with sickle cell disease (SCD), including preventative care, is best achieved through therapy in SCD-specific clinics. All individuals with SCD should have a primary health care practitioner who is either a hematologist or regularly consults with one. When the severity of the episode is determined, self-treatment at home with bed rest, oral analgesics, and fluids are possible. Individuals with SCD frequently present to the emergency department (ED) when self-care fails. A diagrammatical representation of detailed treatment strategies with their mechanism of action is depicted in Fig. 5.

4.1 Voxelotor

The drug voxelotor is utilized as a polymerization inhibitor for the HbS protein, which binds to certain regions of the hemoglobin chain and limits the capacity of oxygen. By limiting RBC oxygenation and preventing Hb polymerization, the destruction and sickling of RBCs are avoided [70]. According to some theories, voxelotor's ability to lessen RBC sickling enhances RBC conformation and lengthens RBC half-life, which in turn reduces whole-blood stiffness, hemolysis, and ultimately anemia [71]. Only three FDA-approved medications could treat SCD before 2021. On November 25, 2019, voxelotor was approved for treating SCD patients over 12 years old. Oral Voxelotor (Oxbryta[®]) inhibits HbS polymerization. Voxelotor binds reversibly and covalently to the N-terminal valine of Hb alpha chains. Within 2 weeks of its first dose, Hb levels rose by 1 g/dl and hemolytic events stopped. It reduces RBC sickling by reducing hypoxemic events, which reduces hemolysis and vaso-occlusive infarction in SCD patients. In a clinical trial, voxelotor was well-tolerated up to 2800 mg, but 1500 mg once daily was recommended for SCD patients without comorbidities. Once absorbed in plasma, the drug is quickly distributed to RBCs, according to Hutchaleelaha et al. In healthy volunteers, its half-life is 65–85 h and in SCD patients, 50 h. Patients with hepatic dysfunction should take lower doses of voxelotor (1000 mg). Patients with renal impairments can safely take the drug with minimal renal excretion. This novel drug reduced anemia and hemolytic markers like hyperbilirubinemia and lactate dehydrogenase without affecting blood viscosity. Voxelotor does not increase erythropoietin or reticulocytosis like previous Hb modifiers. In a clinical study of voxelotor on SCD patients, diarrhea, headache, abdominal pain, nausea, vomiting, and maculopapular rash were observed. Headache and diarrhea were common. Most trial participants had mild or moderate symptoms, and only 4 out of 81 had fatal adverse events (pulmonary sepsis, sickle cell anemia with crisis, and acute sickle hepatic

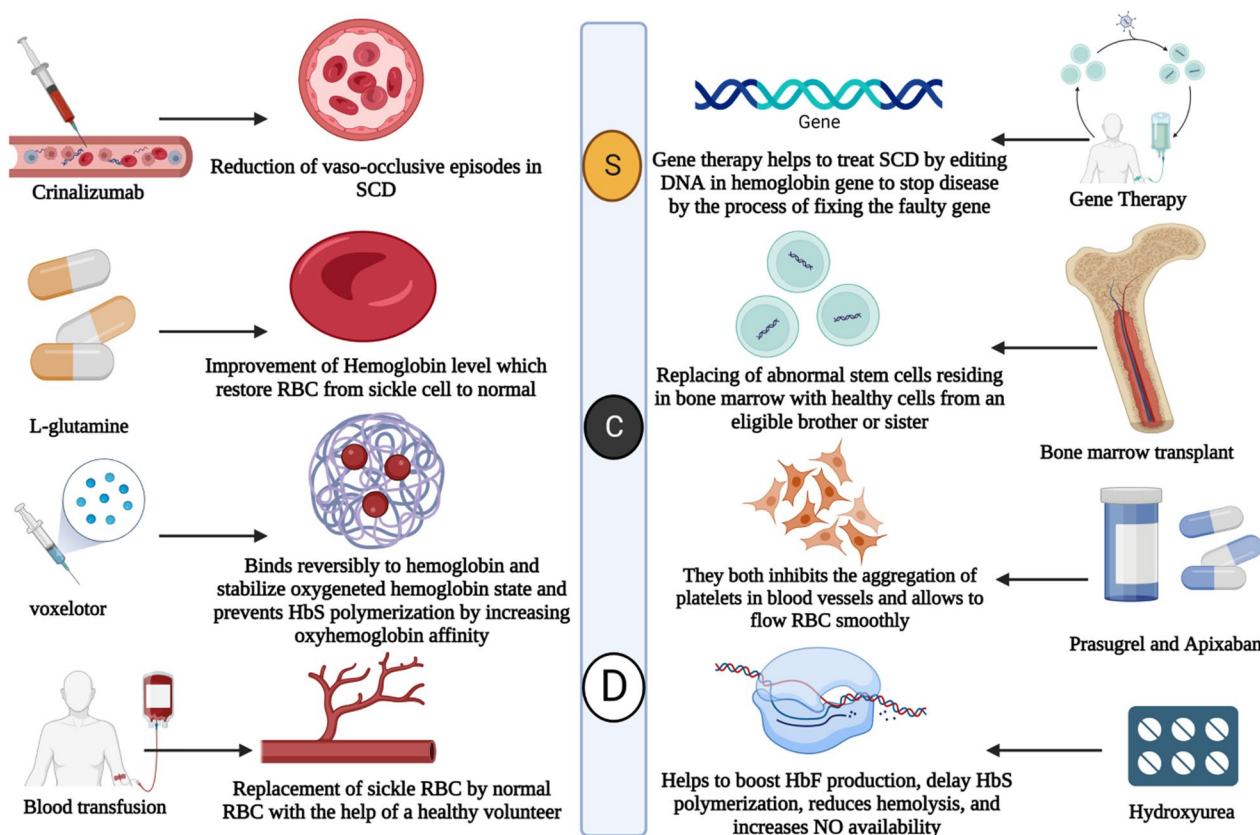


Fig. 5 Treatment protocol of SCD with their proper mechanism of action and pharmacological action (Created with BioRender.com)

crisis). Voxelotor is contraindicated in patients with a history of severe drug hypersensitivity or those taking fluconazole, ketoconazole, or rifampin. CYP3A4 inhibitors like fluconazole can increase voxelotor’s toxicity. Voxelotor interfered with HPLC measurements of Hb subtypes (HbA, HbS, and HbF). Clinically, voxelotor should only be used during pregnancy if the benefits outweigh the risks, as the drug could harm both the fetus and the mother. Breastfeeding should be stopped during treatment and for 2 weeks after the last dose due to the risk of adverse effects in breastfed children [72–74].

4.1.1 Pharmacokinetics and pharmacodynamics

Voxelotor was available at all times. As combined with a high, elevated lunch, total blood area under the curve (AUC) and Cmax rose by 42 and 45%, respectively, when compared to fasting circumstances [75]. A single 400-mg dosage of voxelotor was given after just a low-fat meal, yet relative bioavailability was shown to be 108% higher than when the patient was famished. Between 6 and 18 h are needed to travel the same distance to reach the mean saturated solution of the voxelotor in RBCs. Voxelotor is highly protein that binds in vitro (99.8%), and it has a comparatively large volume of flow in the central (338 L

and peripheral (72.2 L) compartments of plasma. Voxelotor’s pharmacokinetics are linear and dose-dependent; they reach a steady state after 8 days of continuous treatment. The whole half-life lasts 35.5 h [76–81]. Voxelotor undergoes considerable phase I and phases II metabolism. It is a strong CYP3A4 substrate as well as a modest CYP2C9, CYP2B6, and CYP2C19 substrate. The majority of voxelotor is eliminated in the urine (35.5%) and feces (62.6%). Voxelotor reduces oxygen levels in a dose-dependent manner; steady-state Hb oxygen saturation is 20%. (p20). In individuals taking 1500 mg per day, the mean proportion of Hb bound by voxelotor is 26.5%. Since patients who are HbS heterozygous and have around 30% circulating fetal hemoglobin seldom have the severe clinical course linked to SCD, this is expected to be effective [81–84].

4.1.2 Case reports

Before the results of the most recent clinical studies are revealed, case reports provide further information on the effectiveness of voxelotor in certain patient groups. Voxelotor did not significantly increase Hb in a case study of a 38-year-old woman with SCD and severe anemia who did not respond well to infusions because she had RBC

autoimmunity, presumably because she quickly replaced her RBCs despite having autoimmune cell lysis. Voxelotor significantly improved Hb levels in patients with a variety of comorbidities, including serious renal failure, oxidative stress, and severe anemia with initial Hb values in the range of 5.2 g/dl in a case series of 7 SCD patients [85–89]. Patients' perceptions of their general health, pain levels, and depressive symptoms all improved. A case study of a 27-year-old male participant in phase 2 GBT440-001 research who described how voxelotor improved his overall quality of life, gave him more energy, and reduced his discomfort also showed subjective improvement in psychological well-being [90–93].

4.1.3 Safety and warnings

The voxelotor garnered generally positive reviews. In both the voxelotor 1500 mg/d and placebo groups, the rates of severe treatment adverse events (TEAEs) were comparable, although significantly more patients in the voxelotor group (9.1% vs. 4.4%) discontinued medication owing to TEAEs [94–96]. Because one person experienced severe hypersensitivity reactions during clinical testing, Voxelotor acts as a caution. Although there are theoretical concerns about the possibility of hypoxemia with voxelotor therapy, cardiopulmonary exercise tests in 12 patients in the phase 1/2 GBT440-001 investigation who received voxelotor for 90 days showed no significant differences from baseline compared to the control. Numerous clinical investigations are being carried out to evaluate the long-term security of voxelotor in patients, both adults, and children [80, 81, 97, 98].

4.1.4 Drug interactions

Fluconazole or strong CYP3A4 inhibitors may increase the plasma concentration of voxelotor and cause noticeable side effects. Fluconazole is a moderate CYP3A4 and CYP2C9 blocker as well as a strong CYP2C19 blocker. When voxelotor and fluconazole are used together, pharmacokinetic simulations indicate that the AUC will rise by 40% to 116% [99]. Strong or moderate CYP3A4 elicitors can reduce the plasma levels of voxelotor, which can reduce its effectiveness. Fluconazole, potent or intermediate CYP3A4 stimulators, and potent or intermediate CYP3A4 blockers should be used separately, if at all possible, according to the manufacturer [98]. The voxelotor dose should be changed if concurrent use is required. It has been demonstrated that Voxelotor interacts with cation exchange high-performance liquid chromatography, a technique used to estimate the proportion of systemic HbS before replenishing transfusion. This disturbance is believed to be caused by voxelotor-Hb aggregates, which occur in voxelotor patients [85, 92, 100]. A similar disruption can occur during capillary zone electrophoresis,

another frequently used HbS diagnostic technique. FDA labeling suggests that chromatography be conducted while the user is not using voxelotor until more details on how to interpret chromatography results in the context of this disruption and the potential need for alternate quantification procedures are available [85].

4.1.5 Cost and access

The average wholesale price for 500 mg of Voxelotor is \$138.89. The cost per year ranges from \$101 389 to \$253 474 with FDA-approved daily dosages of 1000 mg to 2500 mg [84]. In comparison to best-practice standard care, the Institution for Clinical and Economic Review (ICER) produced a report on the evidence and cost analyses for recently permitted SCD medicines, including voxelotor [101]. The estimated lifetime cost of SCD patients (from the age of 24) managed with the best standard care is \$1.2 million in this study. Likewise, the overall cost of pharmaceutical therapy is anticipated to be close to \$1.1 million with voxelotor's forecasted annual net price of \$92,580 [102]. The study also discovered that managing with voxelotor compared to optimum standard care alone starting at age 24 would cost \$55,000 per life year gained and \$1,000,000 per adjusted life year (QALY) gained. Based on these results, the cost-effectiveness threshold of \$1,50,000 per QALY gained is considerably exceeded by voxelotor. Voxelotor's annual cost would have to be \$12,630 or less, according to ICER, to be considered an expense under the \$1,50,000 QALY threshold [103–105].

4.2 Hydroxyurea seems to be the gold standard for sickle cell disease therapy

The main SCD treatment method accepted by the FDA and the European Medical Agency is hydroxyurea (HU) (EMA). All SCD patients, from children to adults, should receive HU, according to US and European recommendations. In SCD, HU has a multimodal effect that aids in enhancing HbF production, delaying HbS polymerization, which also lessens hemolysis, increasing NO availability, thereby aiming at cGMP production, and aiding in the regulation of endothelial activation and neutrophil accumulation, thereby reducing inflammatory processes. Long-term use of HU reduces mortality rates in both children and adults with SCD and is safe and effective in larger samples of adults and children with SCD [106]. HU lowers the risk of hospitalization as well as the development of Vaso-occlusive Crisis (VOC). In a subpopulation of SCD patients, such as SCD children who are developing cerebrovascular illness, HU may be administered in conjunction with a transfusion operation in the absence of an antigen-matched related donor. The transcranial Doppler scan (TCD), which is used to screen for cerebrovascular disease in pediatric patients,

has a history of abnormalities in SCD children with a history of transfusion dependency, and new research suggests that HU is a viable alternative to a continuous transfusion regimen in these cases. Every three months, a TCD scan is necessary, with the possibility of restarting the continuous transfusion procedure if aberrant transcranial velocity is discovered once more. In SCD juvenile patients, both an elevated reticulocyte count before HU therapy and a high leukocyte count thereafter have been identified as risk factors for reverting to insufficient TCD velocities [107–110]. Inflammation and vasculopathy, therefore, seem to be important indicators of severe chronic outcomes in SCD. While all SCD patients should have access to HU, the biggest obstacle is adult SCD patients' low adherence to HU therapy. Studies have found that several factors, such as treatment chronicity, financial concerns, and adhesion hurdles related to the change from the pediatric to the adult healthcare system, affect SCD patients' poor adherence to HU [5, 111–113]. Particularly in Sub-Saharan Africa and other developing nations with a high prevalence of SCD, HU use is widespread. African children receiving HU at a dosage of 20 mg/kg/d in Uganda, a nation with a high malaria incidence, are safe to Opoka et al. (NOHARM study, NCT01976416). This discovery supports the use of HU as a first-line therapy for SCD patients globally. Low-dose HU (10 mg/Kg/d) has been shown to have positive benefits on SCD acute clinical symptoms in Nigerians living in remote locations without access to routine hematologic testing, according to research by *Toya et al.* [114–117]. Up until 2017, the only approved SCD treatment was hydroxyurea, despite the disease's high frequency and low survival rates. By blocking ribonucleotide reductase, hydroxyurea raises fetal hemoglobin levels. Minimizing ischemia and infarction episodes lessens pain crises. In SCD patients, hydroxyurea replaces high-risk blood transfusions and is safe for long-term use. The myelo-suppressive effects of this medication necessitate close observation. Marrow suppression brought on by infections might worsen, leading to an aplastic crisis and compromised immune system. Concerns have been expressed over the long-term consequences of hydroxyurea on fertility, teratogenicity hazards during pregnancy, and recipients' higher chance of developing cancer. Animal studies recommend stopping the medication during pregnancy; however, it is unknown how hydroxyurea may affect the growing fetus and the pregnancy [118, 119].

4.3 Other effective treatment protocols

4.3.1 L-Glutamine

Constitutionally essential amino acid L-glutamine is necessary for the synthesis of pyridines for nucleotides including nicotinamide adenine dinucleotide

(NAD), glutathione, and glutamate, and its importance increases in response to oxidative stress [119]. The availability of glutamine is crucial in SCD because the NADH:[NAD + + NADH] (redox) ratio in sickle red blood cells (RBCs) is less than it is in healthy RBCs, indicating oxidative stress. In one of the SCD experiments, it was discovered that the ratio of glutamine to glutamate was adversely related to the pace of the tricuspid regurgitant flow. In modest studies with SCD patients, oral L-glutamine was associated with a rise in NADH and a decrease in RBC endothelium adhesion. In a model using sickle mice, glutamate concentrations were found to be related to cerebral blood flow [120]. Phase II and III randomized, double-blind, controlled studies comparing L-glutamine 0.6 g/kg/day to placebo in adults and children with SCD and two episodes of pain in the previous year provide evidence that L-glutamine is helpful and linked to a decrease in painful episodes and hospitalization. Only two-thirds of patients who tolerated L-glutamine, anemia, and hemolysis persisted, and there is little information on organ damage and death. Future research should examine other total protein and amino acid consumption [121]. L-glutamine was authorized for elderly SCD patients in 2017. Hospitalizations, persistent pain, and vaso-occlusion are all decreased by L-glutamine. The medication has a slightly annoying effect. 5 out of 151 patients in the L-glutamine group, according to *Niihara et al.* [7], stopped taking the medication because of hypersplenism, gastrointestinal pain, dyspepsia, a burning sensation in the feet, and hot flashes. Due to its brief duration of usage and lack of research on its safety in pregnant patients, L-glutamine has not demonstrated any advantages in the treatment of other SCD-related problems [122].

4.3.2 Blood transfusion

The goal of blood transfusion in SCD patients is to raise blood oxygen load capacity while lowering the risk of vaso-occlusion-related complications. Each strategy has advantages and disadvantages, which suggests that it can be used in a variety of situations [123]. Both straightforward manual transfer and automatic exchange can reduce both acute and recurring SCD issues. A blood transfusion (simple or exchange) is given to keep the HbS level below 30%. (STOP 1 and 2 trials). A more realistic goal for HbS in patients receiving routine replacement transfusions who have a history of stroke, intolerance to hydroxyurea, or who have had a negative reaction to it is 25% to prevent an increase in HbS of more than 30% after four weeks if the patient does not receive replacement transfusions [5].

4.3.3 Bone marrow transplantation (BMT)

The only treatment for SCD is BMT, a very new therapeutic approach. The researchers discovered a death rate of less than 5% and an event-free survival rate of 91%. A prominent risk of BMT is graft-versus-host disease, which develops when freshly formed bone marrow leucocytes attack destination tissue cells [124]. Vomiting, weight loss, and jaundice are symptoms, and damage to the skin, liver, intestines, and eyes is also present. Graft versus host disease (GVHD) is rare when the donors and the recipient are related and have compatible HLA types [125]. The likelihood of GVHD is increased when the donor and recipient are unrelated or have different HLA types; nonetheless, efforts for wise immunosuppression after transplant can reduce the risk of GVHD. The risks of BMT include strokes, fatal infections, organ failure, and fits. BMT thus demands specialized facilities with highly skilled personnel and cutting-edge technology. Typically, a bone marrow transplant is only recommended if the symptoms and effects of SCD are severe enough to warrant the risks of BMT [126]. In September 2018,

the NHLBI (National Heart, Lung, and Blood Institute) introduced the Cure Sickle Cell Initiative. New gene therapy preclinical and clinical experiments have produced encouraging outcomes. To create anti-sickling cells, this new approach will involve removing stem cells from the patient’s bone marrow and then injecting a therapeutic gene into those cells. Not all sickle cell patients are eligible for hematopoietic stem cell transplantation due to the severe associated toxicity (HSCT). Only people with severe sickle cell disease who also have comorbidities such as priapism, acute chest syndrome, nephropathy, retinopathy, osteonecrosis of multiple joints, and exchange transfusions are eligible for hematopoietic stem cell transplants. Only when the advantages outweigh the risks is transplantation carried out [127, 128] (Table 1).

4.3.4 Nutritional supplements

Omega-3 fatty acids from fish oil have been purified and investigated for their potential to have antithrombotic, antioxidant, and anti-inflammatory effects. In the therapeutic trials, numerous doses, amounts, and types of

Table 1 Types of SCD and their nature [27, 34, 43, 56, 93]

<i>Severe sickle cell disease</i>	
$\beta 6\text{Glu} > \text{Val}/\beta 6\text{Glu} > \text{Val}$ (HbS/S)	The most prominent SCD is the common form
Thalassemia (HbS/ β^0)	This is widely seen in the eastern Mediterranean region and India mostly
Thalassemia (Severe HbS/ β^+)	This is widely seen in the eastern Mediterranean region and India mostly(1% to 5%)
$\beta 6\text{Glu} > \text{Val}/\beta 121\text{Glu} > \text{Lys}$ (HbS/OArab)	The Balkans, the Middle East, and North Africa are mostly seen; very rare
$\beta 6\text{Glu} > \text{Val}/\beta 121\text{Glu} > \text{Gln}$ (HbS/D Punjab)	It occurs worldwide but in northern India it is principal
$\beta 6\text{Glu} > \text{Val}/\beta 6\text{Glu} > \text{Val}/\beta, \beta 73\text{Asp} > \text{Asn}$ (HbS/C Harlem)	It is clinically severe but looks like HbSC electrophoretically; β -globin gene with double mutation; usually very rare
$\beta 6\text{Glu} > \text{Lys}/\beta 6\text{Glu} > \text{Val}, \beta 23\text{Val-Ile}$ (HbC/S Antilles)	β -globin gene is double mutated which results in severe SCD with co-inhabitation with HbC; usually very rare
$\beta 6\text{Glu} > \text{Val}/\beta 87\text{Thr} > \text{Ile}$ (HbS/Quebec-CHORI)	Only two number of cases have been described with this form
<i>Moderate sickle cell disease</i>	
$\beta 6\text{Glu} > \text{Val}/\beta 6\text{Glu} > \text{Lys}$ (HbS/C)	Mostly 25–30% of cases of the sickle cell disease are found in African populations
Moderate thalassemia (HbS/ β^+)	Mostly found in the region of eastern Mediterranean
$\beta A/\beta 6\text{Glu} > \text{Val}, \beta 121\text{Glu} > \text{Lys}$ (HbA/S Oman)	It is The most dominant form of the sickle cell disease which is caused by a duple mutation in the β -globin gene
<i>Mild sickle cell disease</i>	
Mild HbS/ β^{++} thalassemia	Mostly prominent in African populations
$\beta 6\text{Glu} > \text{Val}/\beta 26\text{Glu} > \text{Lys}$ (HbS/E)	HbE dominates in the southeast region of Asia and so HbSEis uncommon, and frequency is usually increasing with migration of population
$\beta A/\beta 6\text{Glu} > \text{Val}, \beta 68\text{Leu}/\text{Phe}$ (HbA/Jamaica Plain)	The very dominant form of the sickle cell disease; double mutation causes low oxygen affinity carrying Hb
<i>Very mild sickle cell disease</i>	
HPFH/ HbS/	This group of disorders is generally caused by deletions of the larger β -globin complex of gene and found typically in fetal Hemoglobin at a concentration of 30%
other Hb variants	Here HbS is usually co-inherited with so many other variants of Hb

There is a list of genotypes that have been linked to sickle cell disease. At a minimum, one copy of the S allele is present in all of them, along with one or even more mutations in the globin gene. Hb = hemoglobin, haemoglobin variant HbA A, sickle hemoglobin (HbS) haemoglobin variant HbE

omega-3 fatty acids were used [125]. People with SCD who received large daily doses of fish oil capsules as compared to adults who took large daily doses of olive oil capsules as a placebo experienced much reduced discomfort and platelet activation. In a large-scale study conducted in Sudan, children with SCD who took fish oil had much lower rates of missed school days than those who received a placebo [129]. According to the notion that increased erythropoiesis increases the risk of folic acid shortage, folic acid is frequently advised for SCD patients [98]. The only double-blind non-randomized clinical trial conducted in the 1980s was the subject of a Cochrane Systematic Review, which found inconsistent results regarding its benefits for children and no evidence of effectiveness in adults. The Cochrane reviewers call for more studies, but they also point out that there won't be any more folic acid studies in SCD [125]. Niprisan, a herbal medicine used to treat SCD in Nigeria, showed excellent preclinical results, but it's expected to have side effects due to its significant inhibition of cytochrome CYP3A4 activity. Niprisan was classified as an "Orphan

Drug" by the FDA. However, budgetary restrictions forced the suspension of development, and clinical trials for Niprisan have not yet begun [130]. Table 2 contains a list of the few additional natural treatments for SCD that have been recommended.

4.3.5 Cell adhesion inhibitors with activated microvascular endothelium: rivipansel, crizanlizumab, heparins, and heparin-derived molecules)

Crizanlizumab, a monoclonal antibody that has been humanized, is one treatment option. As was already mentioned, a crucial aspect of the pathophysiology of SCD is platelet attachment to red blood cells, monocytes, and neutrophils. The degree of red cell adhesion correlates with the severity of the sickness [131]. P-selectin in particular, which is elevated in SCD, is crucial for the sickle red cells' static adhesion to the artery wall and the subsequent vascular occlusion seen in emergencies or inflammatory conditions. Therefore, efforts have been undertaken to develop methods to block the P-selectin function [132]. It hinders cell-cell adhesion by targeting

Table 2 Natural therapies associated with sickle cell disease

Serial no.	Biological Source	Family	Major chemical constituents	Inducer	Pharmacological effects	References
1	<i>Angelica arcangelica</i>	Apiaceae	α-pinene, myrcene, camphene, β-limonene, phellandrene, caryophyllene, carvone, borneol, and others	Angelicin	Erythroid differentiation and HbF induction	[114]
2	<i>Aegle marmelos</i>	Rutaceae	Furocoumarins like methyl ester of alloimperatorin, xanthoxol with several flavonoids, rutin, and marmesin	Bergaptene	Erythroid differentiation of K562 cells and HbF induction	[115]
3	<i>Citrus bergamia</i>	Rutaceae	Naringin, neoeriocitrin, ponceritin, neohesperidin, mitrocin, melitidin, brutieridin, miriflin, and bergamottin	Citropten and bergapten	Erythroid differentiation and HbF production	[116]
4	<i>Trichosanthes kirilowii</i>	Cucurbitaceae	5-hydroxymethyl-2-furfural, Trichosanthin, vanillic acid, chrysoeriol, 4'-hydroxyscutellarin, and alpha-spinasterol	Cucurbitacin D	HbF production and Erythroid differentiation of K562 cells	[117]
5	<i>Terminalia catappa</i>	Combretaceae	Magnesium, manganese, iron, calcium, and zinc	Distilled water active fraction	Erythropoiesis, cell proliferation, and transcription	[118]
6	<i>Vitis vinifera</i>	Vitaceae	Catechin, Resveratol, gallic acid, epicatechin and quercetin,	Resveratrol	HbF induction	[119]
7	<i>Streptomyces hygroscopicus</i>	Streptomycetaceae	Ascomycin and rapamycin	Rapamycin	HbF induction	[119]
8	<i>Streptomyces species</i>	Streptomycetaceae	Daptomycin, Chloramphenicol, and Mithramycin	Mithramycin	HbF production	[116]

P-selectin [133]. In a randomized, double-blind phase 2 study, 198 participants received either high- or low-dose crizanlizumab or a placebo. Patients receiving the higher dose of the medication observed a drop in their yearly median crisis rate of 45.3%, compared to patients receiving the lower dose, who had a reduction of 32.6% [134]. 18% of the study participants experienced no crises at all during the therapy phase. The drug's 30-day half-life was identified after it was administered intravenously. On the other hand, the fact that the medication is administered via intravenous infusion may not be advantageous. Additionally, the lack of youngsters hampered the study's impact and significance [135]. Heparins can bind selectins, which might be why they can reduce sickle cell adhesion to functional endothelium. Using tinzaparin, a low-molecular-weight heparin, reduced the duration of painful emergency and hospital admission by a statistically significant amount when compared to supportive care alone among 253 SCD patients who were admitted with an acute painful crisis [136]. Sevuparin is a novel heparin-derived compound that retains selectin-binding abilities but lacks the anticoagulant qualities of heparins [137]. The FDA-approved Crizanlizumab on November 15, 2019, after approving it as a breakthrough treatment for vaso-occlusive crises in January 2019. An anti-P-selectin antibody that has been humanized blocks the binding of glycoprotein ligand 1 to substrate. Inhibiting P-selectin reduces sickle erythrocyte and leukocyte adhesion to endothelial cells, improving microvascular blood flow. Because recipients of crizanlizumab are susceptible to infection, this must be considered in post-marketing pharmacovigilance. Headache, back pain, arthralgia, diarrhea, vomiting, and pyrexia are typical adverse effects. Crizanlizumab can have single-occurrence life-threatening adverse effects, such as anemia and brain hemorrhage. Crizanlizumab failed to stop the SCD hemolysis. Ataga et al. found no discernible differences between the active therapy and placebo group in the event of a hemolytic crisis. Crizanlizumab and L-glutamine were unable to increase participants' hemoglobin levels during studies [138, 139].

4.3.6 Anticoagulant agents and antiplatelet agent

4.3.6.1 Prasugrel Prasugrel prevents platelet aggregation brought on by ADP. A recent study found that after vaso-occlusive episodes, active platelets attach to the endothelium and draw leucocytes [140]. In a phase III study of 341 children with SCD, there was no difference in the number of vaso-occlusive events per person-year between those who took Prasugrel and those who got a placebo. Additionally, as reported in the diary, there was no discernible reduction in pain episodes [141].

4.3.6.2 Apixaban The active direct Factor Xa blocker apixaban prevents prothrombin from becoming thrombin [142]. In phase III randomized placebo-controlled study, the effectiveness of the preventive dose Apixaban in reducing daily average pain ratings in people with SCD is being examined [143–145].

4.3.7 Nitric oxide depletory restorer in the microvasculature: L-arginine, statins

Nitric oxide produced by the endothelium relaxes the smooth muscles in the arteries, causing vasodilation and an increase in blood flow. Additionally, it lessens the generation of procoagulant factors, intercellular adhesion on endothelium, and platelet aggregation [146]. Free hemoglobin is released into the patient's plasma by intravascular hemolysis. This operates as a nitric oxide scavenger. In addition, arginine, a substrate for the generation of endogenous nitric oxide, is degraded by arginase, which is formed from ruptured red blood cells. Nitric oxide levels are decreased as a result of both of these events [111]. Two drug classes that have been investigated for their potential to boost SCD nitric oxide reserves are statins and L-arginine. Statins inhibit Rho kinase, which then causes endothelial nitric oxide synthase to become active [147].

4.3.8 Gene therapy

Gene therapy is now being investigated as a potential treatment for SCD. Host stem cells are created in place of embryonic stem cells by reshaping and genetically altering blood cells from the participant to rectify an innate genetic anomaly [148]. Since the patient is the sole source of the stem cells, there is no requirement to find a matching donor, negating the possibility of GVHD [149]. The objective is to correct the defective gene and make the patient's blood cells pluripotent [142]. Following that, those cells will be induced to develop into hematopoietic cells, which can produce all varieties of red blood cells. As of this writing, three gene therapy clinical studies employing various lentiviral vectors have allegedly successfully treated a small number of patients with SCD. The future holds several innovative sickle cell treatment options, and combination treatment is no longer an impossibility. The optimum combinations, patient profiles, and availability for a sizeable part of patients must therefore be urgently discussed [127]. It is thus important to commission a review of newborn sickle cell screening, not just for European nations, which face the burden of immigration, but also for Africa and India [150–152]. Gene therapy can be curative, like a bone marrow transplant. After therapy, sickle cell disease won't cause health crises. Some stem cell transplant recipients must take immunosuppressive

drugs for life, which can have serious side effects. Receiving their stem cells shouldn't require this. These trials help determine treatment risks and side effects. If clinical trials show too many risks, the treatment won't be approved. Even if current clinical trials fail, another sickle cell gene therapy may be approved. Gene therapy may increase cancer risk [153–155]. Other gene therapies for medical conditions have shown a risk for this and other toxic side effects. These haven't been seen in sickle cell gene therapy studies. Some risks may be hard to predict because the technique is new. Many people worry about the chemotherapy required for sickle cell gene therapy. This may cause a lowered immunity, hair loss, and infertility. Bone marrow transplants include chemotherapy. Gene therapy worked well in sickle cell mouse models. Some have had successful treatment [156, 157].

5 Future prospects

Thanks to the development of highly relevant transgenic mouse models and improvements in clinical trial designs and implementation, new treatments for SCD may now be evaluated with greater objectivity and certainty than ever before. Since the majority of SCD patients live in less developed countries, efforts will need to be made to make these medications available there. These initiatives appear to be more viable than ever right now. However, the greatest number of SCD patients will benefit from improved awareness of SCD as a severe health problem in Africa and India, including the adoption of newborn screening programs and expanded access to even the most fundamental medical care. With the development of new technology, stem cell transplantation or gene therapy appears to be more widely applicable, with the use of pluripotent stem cells showing the most promise. Genome-wide prospective research should help in the discovery of additional intrinsic and unrelated factors to explain the phenotypic variation and allow for a better prognosis, potentially leading to the treatment of different diseases.

6 Conclusion

These illustrations of novel sickle cell disease treatments demonstrate some of the most cutting-edge approaches being used to control or treat the condition. SCD research has gained prominence, giving millions of people throughout the world hope. More clinical trials need to be launched, and those that have already been launched need to undergo thorough examination and discussion. 80 years ago, sickle cell disease was at the forefront of biomedical study as the first disease to be linked to a hereditary etiology. Although stem cell and gene therapies are becoming more common, the majority of SCD patients still cannot afford them. To address

health-related residual symptoms in the majority of SCD patients in the USA and around the world, it is crucial to maximize non-curative therapies, such as those that do not include stem cell or gene therapy but avoid or abort SCD effects. Innovative drugs that target several pathways connected to SCD pathogenesis have emerged as a consequence of collaboration between the government (National Institutes of Health), industry, and academia. As seen by their participation in multiple trials investigating new therapies, many SCD patients are anxious to learn more about the potential therapeutic benefits of these drugs. The best results to utilize in determining the beneficial impact these drugs could have on the clinical course and effects of SCD are unfortunately less evident. It's an exciting time, and in the future, it might be feasible to fully address correlation and causation in SCD by utilizing a multimodal approach involving a variety of medications, similar to cancer therapy regimens. L-glutamine and hydroxyurea, two drugs that support red cell health, may complement non-overlapping therapies like anti-selectin therapies, which reduce inflammatory adhesion during stressful situations. We must be vigilant but realistic in our assessments of the benefits and long-term safety of emerging medicines as members of the greater sickle cell community, relying on long-term, prospective evidence where available. To improve SCD care, we must get better at immediately identifying issues with all novel treatments. This will allow us to identify (inevitable) dangers and complications and manage them in light of how they affect the illness.

Abbreviations

SCD	Sickle cell diseases
RBC	Red blood cells
WHO	World Health Organization
HPLC	High-performance liquid chromatography
RNA	Ribonucleic acid
ERK12	Extracellular signal-regulated protein kinase
DNA	Deoxynucleic acid
WBC	White blood cells
AUC	Area under curve
Cmax	Maximum concentration
Hb	Hemoglobin
TEAEs	Treatment-emergent adverse event
FDA	Food and drug administration
ICER	Institution for clinical and economic review
HU	Hydroxyurea
EMA	European medical agency
cGMP	Cyclic GMP
VOC	Vaso-occlusive crisis
NAD	Nicotinamide adenine dinucleotide
BMT	Bone marrow transplant
GVHD	Graft versus host disease
HLA	Human leukocyte antigen
ADP	Adenosine diphosphate

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AKS contributed to conceptualization and idea for the article. AKS, RKM and BA contributed to literature search and design of the work. BA, DPM and BB performed data analysis and interpretation. AKS and BA performed writing—original draft preparation. BA, DPM, RKM and BB performed writing—review and editing. All authors have read and approved the final manuscript.

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