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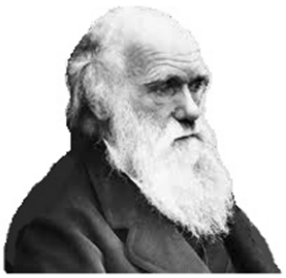

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# Current trends in the treatment of sickle cell anemia

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**ABSTRACT**

Sickle cell disease is a set of illnesses characterized by the misshaping and breakdown of red blood cells. Red blood cells twist into a sickle shape in sickle cell disease, an inherited set of illnesses. The cells die early, resulting in a lack of healthy red blood cells (sickle cell anemia), and they might impede blood flow, causing pain (sickle cell crisis). Vernon Mason coined the term "sickle cell anemia" in 1922. SCD is thought to have killed approximately 114,800 individuals worldwide, and it is more common among people whose ancestors lived in tropical and subtropical sub-Saharan Africa, where malaria is or was prevalent. There are several types of SCD, including homozygous HbS and HbS/HbC co-inheritance (usually called HbSC). A genetic mutation causes the condition, which disrupts the iron-rich molecule essential for making blood red and transporting oxygen. SCD has been treated using a variety of approaches. The use of hydroxycarbamide and L-glutamine, blood transfusions, bone marrow transplants, gene therapy, and nutritional supplementation are just a few of them. Gene therapy is the most effective treatment option on the list. The method relies on modifying and reprogramming cells from the patient's own blood cells, as well as genetic engineering, to fix the inborn genetic defect. hydroxyurea, on the other hand, has been shown to change the course of the disease. Finally, if utilized correctly, a combination of available therapeutic medications could greatly improve the disease.

***Keywords*:** Sickle cell anemia, hydroxycarbamide, gene therapy

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## 1. INTRODUCTION

Sickle cell anemia (SCA) is hemolytic anemia marked by irregularly shaped (sickled) red blood cells (RBCs) that are removed from circulation and destroyed at an elevated rate, resulting in anemia. The sickled RBCs produce vascular blockage, which leads to tissue ischemia and infarction, which is of greater clinical consequence. The presence of aberrant sickle cell hemoglobin (HbS), which becomes highly insoluble when deoxygenated and forms aggregates with other hemoglobin molecules inside the RBC, is the underlying abnormality in the RBC of SCA. These aggregates form lengthy chains, distorting the RBC into a sickled shape and obstructing blood flow via arteries. Furthermore, malformed RBCs are more likely to cling to the endothelium, exacerbating vascular obstruction, ischemia, and the risk of tissue infarction. The vaso-occlusive consequences of SCA are significantly more clinically bothersome for the great majority of SCA patients than the anemia, which is frequently well tolerated [9]. SCA is also a chronic blood condition in which red blood cells take on an unnatural, hard sickle form. Sickling reduces the elasticity of the cells, increasing the likelihood of problems. Because of a mutation in the hemoglobin gene, sickling occurs. Male and female life expectancies are 42 and 48 years, respectively [47]. Sickle cell disease, which usually manifests in childhood, is more common in people from tropical and subtropical locations where malaria is prevalent since the malaria Plasmodium's infestation is interrupted by the sideling of the cells infects. Medical improvements in the treatment of sickle cell anemia have resulted in a significant rise in the life expectancy of this patient group. Improved public health, neonatal screening, parental and patient education, breakthroughs in red cell transfusion medicine, iron chelation therapy, children's penicillin prophylaxis, pneumococcal immunization, and hydroxyurea therapy are all likely to have contributed to this influence on longevity [10].

## 2. HISTORICAL BACKGROUND OF SICKLE CELL ANEMIA

This collection of clinical findings was unknown until 1904 when Chicago cardiologist and professor of medicine James B. Herrick (1861-1954) and his intern Ernest Edward Irons (1877-1959) discovered "peculiar elongated and sickle-shaped" cells in the blood of Walter Clement Noel, a 20-year-old first-year dental student from Canada after Noel was admitted to the Chicago Presbyterian Hospital suffering from anemia. Over the next three years, Noel was readmitted multiple times for "muscular rheumatism" and "bilious attack." Noel finished his education and went back to Grenada's capital to practice dentistry. In 1906, he died of illness and was buried in the catholic cemetery of Sauteurs in Grenada's northwestern region. Vernon Mason coined the term "sickle cell anemia" in 1922.

However, several aspects of the condition had previously been identified: The absence of a spleen' in the autopsy of a fugitive slave was noted in a study published in the southern journal of medical pharmacology in 1846. Because of the high infant death rate caused by this illness, it was known locally as Ogbanjes ("Children who come and go") in the 1870s, according to African medical literature. The condition's history can be traced back to 1670 in one Ghanian family [31,18]. In 1949, Linus Pauling and colleagues were the first to show that sickle cell disease is caused by a mutation in the hemoglobin molecule. This was the first time a hereditary disease was connected to a protein mutation, a watershed moment in molecular biology, and it

was described in their publication "Sickle Cell Anemia, a Molecular Disease." The origin of the sickle cell gene mutation was assumed to be in the Arabian Peninsula, before moving to Asia and Africa. Based on the analysis of chromosome architecture, at least four independent mutational events have occurred, three in Africa and one in either Saudi Arabia or central India. Between 3,000 and 6,000 generations ago, or roughly 70-150,000 years ago, these distinct events occurred [18].

### 2. 1. Epidemiology of Sickle Cell Anemia

Tropical locations, particularly Sub-Saharan Africa, India's tribal regions, and the Middle East, have the highest prevalence of sickle cell disease [62,63]. Significant population migration from high-prevalence areas to low-prevalence countries in Europe has increased substantially in recent decades, and sickle cell disease has now surpassed more common genetic disorders such as hemophilia and cystic fibrosis in some European countries [51]. It claimed the lives of approximately 114,800 people in 2015 [22]. People whose ancestors lived in tropical and subtropical sub-Saharan Africa, where malaria is or was common, are more likely to develop sickle cell disease. Carrying a single sickle-cell allele (trait) gives a heterozygote advantage in areas where malaria is frequent; persons with one of the two sickle cell disease alleles display less severe symptoms when infected with malaria [64]. This disease is autosomal recessive, which means both copies of the gene in each cell have mutations. The parents both have one copy of the faulty gene, but they usually don't display any indications or symptoms of the disease [39].

#### 2. 1. 1. Africa

Africa accounts for three-quarters of all sickle cell cases. According to a recent WHO research, sickle cell anemia affects roughly 2% of infants in Nigeria, resulting in a total of 150,000 afflicted children born each year in the country. The carrier frequency varies between 10% and 40% in equatorial Africa, down to 1–2% on the North African coast and 1% in South Africa [66]. Because of the sickle cell trait, studies in Africa reveal a considerable reduction in newborn death rates between the ages of 2 and 16 months. This occurred in locations where malaria was prevalent [1]. Uganda has Africa's fifth-highest rate of sickle cell disease [60]. According to one study, 20,000 newborns are born with sickle cell illness each year, with the sickle cell trait accounting for 133% and the disease accounting for 7% [41].

#### 2. 1. 2. United State of America

In the United States, around one in every 5,000 persons has the condition, which primarily affects Americans of Sub-Saharan African origin [40]. Sickle cell anemia affects roughly one in every 365 African-American children and one in every 16,300 Hispanic-American children in the United States [13]. The condition affects an estimated 100,000 people in the United States [13]. Men with SCD have a life expectancy of 42 years, whereas women have a life expectancy of six years longer [13]. Routine newborn screening detects the majority of infants with SCD born in the United States. As of 2016, all 50 states now incorporate sickle cell disease screening as part of their newborn screening. A hee-prick is used to take a sample of the newborn's blood, which is then submitted to a lab for testing. Before doing the heel-prick test, the baby must have eaten for at least 24 hours. Some states also demand a second blood test after the baby is two weeks old to guarantee the accuracy of the results (www.stanfordchildrens.org).

### 2. 2. Pathophysiology of Sickle Cell Anemia

The pathogenesis of sickle cell disease revolves around the loss of red blood cell flexibility. Normal red blood cells are pliable and have a biconcave disc shape, allowing them to flex and flow through capillaries [11]. Low oxygen tension increases red blood cell sickling in sickle cell disease, and repeated episodes of sickling damage the cell membrane and reduce the cell's flexibility.

When normal oxygen tension is restored, these cells do not revert to their original shape. As a result, as these hard blood cells move through tiny capillaries, they are unable to soften, resulting in artery obstruction and ischemia. Because of their form, hemolysis, or the breakdown of red cells, is the actual cause of the illness's anemia. The bone marrow tries to compensate by producing new red cells, but it can't keep up with the pace of destruction. Healthy red blood cells endure 90–120 days on average, but sickled cells only last 10–20 days (Emergency Medicine, 2010).

### 2. 3. Classification of Sickle Cell Anemia

The most common form of SCD is homozygous HbS, also known as sickle cell anemia (SCA), the proportion of which varies depending on the place of origin [63,62]; American Society of Haematology, 2015). The co-inheritance of HbS and HbC, also known as HbSC, is the second most frequent form of SCD. It is most common in Western Africa, particularly Burkina Faso and Mali, as well as coastal countries such as Ghana, Benin, and Western Nigeria [63;46].

The sickle-thalassemia genotype (HbS/o or HbS/+) is the result of co-inheritance with -thalassemia; depending on the genetic lesion on the thalassemia component, the clinical presentation may be moderate or as severe as homozygous SCD (HbS/HbS) [57]. Those with HbS/o-thalassemia have a more severe course of disease, similar to homozygous SS patients, but those with HbS/+-thalassemia have a varied phenotypic ranging from mild to severe phenotypes SCD, depending on the -globin mutation [27,17].

### 2. 4. Causes of Sickle Cell Anemia

A mutation in the gene that signals your body to generate the iron-rich compound that makes blood red and allows red blood cells to transmit oxygen from your lungs throughout your body causes sickle cell anemia (hemoglobin). The defective hemoglobin in sickle cell anemia causes red blood cells to become hard, sticky, and malformed. For a kid to be impacted, the faulty form of the gene must be passed down from both parents. If only one parent carries the sickle cell gene to their child, the youngster will inherit the characteristic. People with the sickle cell trait produce both normal and sickle cell hemoglobin because they have one normal and one faulty hemoglobin gene.

They may have sickle cells in their blood, but they are usually asymptomatic. They are, nonetheless, disease carriers, meaning they can pass the gene on to their children (Mayo Clinic Health Book, 2020).

### 2. 5. Signs and Symptoms of Sickle Cell Anemia

Sickle cell disease symptoms commonly appear in early childhood. Symptoms can vary in severity from individual to person [39]. Sickle cell disease can cause a variety of acute and chronic consequences, some of which are fatal [69].

### 2. 5. 1. Sickle cell crisis

The names "sickle cell crisis" and "sickling crisis" can refer to a number of distinct acute illnesses that occur in SCD patients and result in anemia and crises of various types, such as the vaso-occlusive crisis, aplastic crisis, splenic sequestration crisis, hemolytic crisis, and others. The majority of sickle cell crises last five to seven days. Infection, dehydration, and acidosis (all of which favor sickling) can all be triggers, although in most cases, no underlying factor is found [32].

### 2. 5. 2. Vaso-occlusive crisis

Ischemia, discomfort, necrosis, and often organ damage are all symptoms of a vaso-occlusive crisis, which is produced by sickle-shaped red blood cells obstructing capillaries and restricting blood flow to an organ. These crises vary greatly in terms of occurrence, severity, and duration. Hydration, analgesics, and blood transfusions are used to treat painful crises; pain treatment needs opioid drug delivery at regular intervals until the crisis has passed. A subset of people controls milder crises with non-steroidal anti-inflammatory medicines like diclofenac or naproxen. Most patients require in-patient treatment for intravenous opioids in more acute crises; patient-controlled analgesia devices are frequently employed in this situation. Vaso-occlusive crises involving organs like the penis [43] or the lungs are treated with red blood cell transfusions as an emergency. The use of incentive spirometry, a technique for encouraging deep breathing and preventing telectasis, is recommended [21].

### 2. 5. 3. Splenic sequestration crisis

The spleen is frequently impacted due to its narrow arteries and function in removing faulty red blood cells [4]. In people with sickle cell anemia, it is frequently infarcted before the end of childhood. This spleen impairment raises the chance of infection from encapsulated organisms [45,68]; for people who don't have a healthy spleen, antibiotics and immunizations are suggested. Splenic sequestration crises are sudden, painful splenic enlargements induced by intrasplenic red cell entrapment, resulting in a rapid drop in hemoglobin levels and the risk of hypovolemic shock. Sequestration crises are treated as emergency situations. Patients may die within 1–2 hours if they are not treated for circulatory failure. Management is supportive, with blood transfusions being used on occasion. These crises are brief; they last 3–4 hours and can persist up to a day [30].

### 2. 5. 4. Acute chest syndrome

At least two of the following signs or symptoms characterize acute chest syndrome: chest discomfort, fever, pulmonary infiltration or localized abnormalities, respiratory symptoms, or hypoxemia [21]. It is the second most prevalent complication, accounting for around 25% of all fatalities among SCD patients. The majority of patients begin with vaso-occlusive crises and progress to acute chest syndrome [35,44]. Despite this, around 80% of persons experience vaso-occlusive crises during acute chest syndrome.

### 2. 5. 5. Aplastic crisis

Aplastic crises are characterized by an acute exacerbation of a patient's baseline anemia, resulting in a pale look, a rapid heart rate, and weariness. This crisis is usually driven by the

parvovirus B19, which directly impacts red blood cell synthesis by infiltrating and proliferating red cell precursors [32]. For two to three days, parvovirus infection almost entirely stops red blood cell synthesis. In healthy people, this is of no importance, but in SCD patients, the shorter red cell life causes an immediate and life-threatening condition. The condition causes a severe decline in reticulocyte numbers (reticulocytopenia), and the quick turnover of red cells causes a drop in hemoglobin. It takes 4 to 7 days for this crisis to pass. The majority of patients may be handled with supportive care; however, some will require blood transfusions [55]

### 2. 5. 6. Hemolytic crisis

Hemolytic crises are characterized by rapid and severe reductions in hemoglobin levels. The red blood cells degrade more quickly. This is more common in persons who also have a G6PD deficiency [8]. Management is supportive, with blood transfusions being used on occasion (Glassberg, 2011).

## 2. 6. Clinical Complications of SCA

Despite the fact that SCA is caused by an RBC defect, it is essentially a multi-system condition that affects practically every organ system in the body, as depicted. Hemolysis and hematological problems, vaso-occlusion, infection, and organ failure are the four types of clinical repercussions. The following are examples of SCA complications:

The lack of functioning spleen tissue increases the risk of serious bacterial infections (and comparable to the risk of infections after having the spleen removed surgically). Encapsulated organisms like Streptococcus pneumoniae and Haemophilus influenzae are commonly responsible for these illnesses. The most typical treatment during childhood is daily penicillin prophylaxis, with some hematologists prescribing it permanently. Vaccination against S. pneumoniae is now routinely administered to patients [29].

A stroke is caused by a gradual constriction of blood vessels in the brain, which stops oxygen from reaching the brain. In children, cerebral infarction occurs, while in adults, cerebral hemorrhage occurs.

Salmonella (especially the atypical serotypes Salmonella typhimurium, Salmonella enteritidis, Salmonella choleraesuis, and Salmonella paratyphi B) is the most common cause of osteomyelitis in SCD, followed by Staphylococcus aureus and Gram-negative enteric bacilli, possibly because intravascular sickling of the bowel leads to patchy ischemic infarction [2].

Shortness of breath, poor exercise tolerance, and episodes of syncope are common signs of pulmonary hypertension (increased pressure in the pulmonary artery), which can put a strain on the right ventricle and increase the risk of heart failure. When evaluated, 21% of children and 30% of adults have indications of pulmonary hypertension, which is linked to decreased walking distance and increased mortality [12].

Hypertension, protein loss in the urine, red blood cell loss in urine, and worsening anemia are all symptoms of chronic kidney failure caused by sickle-cell nephropathy. It has a bad prognosis if it advances to end-stage renal failure [48].

## 2. 7. Diagnostic of Sickle Cell Anemia

The complete blood count in HbS reveals hemoglobin levels in the 6–8 g/dl range, as well as a high reticulocyte count (as the bone marrow compensates for the destruction of sickled cells by producing more red blood cells). Hb levels are usually higher in other types of sickle

cell disease. Hyposplenism may be visible on a blood film (target cells and Howell-Jolly bodies). The addition of sodium metabisulfite to a blood film can cause the sickling of red blood cells. The "sickle solubility test" can also be used to show the existence of sickle hemoglobin. In a reducing solution (such as sodium dithionite), a mixture of hemoglobin S (HbS) produces a murky solution, whereas regular Hb produces a clear solution.

Hemoglobin electrophoresis, a sort of gel electrophoresis in which different types of hemoglobin flow at different speeds, can detect abnormal hemoglobin forms. From there, the two most frequent kinds of sickle cell hemoglobin (HbS) and sickle cell hemoglobin C with sickling (HbSC) may be distinguished. High-performance liquid chromatography can be used to confirm the diagnosis. Other investigations for HbS and HbC are highly specific, thus genetic testing is rarely used [14]. Infection is a common cause of acute sickle cell crisis. As a result, a urinalysis for detecting an occult urinary tract infection and a chest X-ray for detecting occult pneumonia should be conducted on a regular basis [33].

Before having children, those who are known carriers of the disease often seek genetic counseling. A blood sample from the fetus or a sample of amniotic fluid is used in a test to detect if an unborn kid has the condition. The latter test is frequently utilized since collecting a blood sample from a fetus carries more hazards. Neonatal screening allows for the identification of groups of people who carry the sickle cell trait, as well as a technique of early detection for persons with sickle cell disease [33].

### 2. 8. Mechanism of Sickle Cell Anemia

Under low oxygen conditions, a point mutation in a specific gene that forms the -globin chain of hemoglobin causes the hydrophilic amino acid glutamic acid to be replaced by the hydrophobic amino acid valine at the sixth position from the short arm of chromosome11, resulting in two mutant -globin associations that form hemoglobinS (HbS) [56]. Polymerization of HbS: Sickle cell morphologies are caused by HbS molecules polymerizing inside red blood cells, resulting in produced bundles of fibers aligned along the axis. Each fiber is made up of 14 pairs of filaments. In contrast to regular red blood cells, which are highly elastic and easily move through blood capillaries, HbS are less flexible and tougher [49,54]. This polymerization leads RBC membranes to become aberrant, shortening their life span to 10-20 days instead of 120 days, causing them to become caught in small blood arteries and occluding them, a condition known as sickle cell crisis [34].

### 2. 9. Genetics of Sickle Cell Anemia

Humans' bodies normally include hemoglobin A, which has two alpha and two beta chains, hemoglobin A 2, which has two alpha and two delta chains, and hemoglobin F, which has two alpha and two gamma chains. Hemoglobin F is the most common of the three kinds until about 6 weeks of age. After that, hemoglobin A takes over for the rest of your life [52]. At least one of the-globin subunits in hemoglobin A is replaced by what is known as hemoglobin S in persons with sickle cell disease. Hemoglobin S replaces both-globin subunits in the hemoglobin in sickle cell anemia, a typical type of sickle cell disease [39].

Sickle cell disease is inherited from parents in an autosomal recessive way [38]. The hemoglobin types a person produces in red blood cells are determined by the hemoglobin genes she or he inherits from her or his parents. If one parent has sickle cell anemia and the other has sickle cell trait, the child will have a 50% risk of developing sickle cell illness and a 50% chance

of developing sickle cell trait. A kid has a 25% probability of developing sickle cell disease if both parents have the trait; 25% do not have any sickle cell alleles, and 50% have the heterozygous condition (Genetics Home Reference, 2016).

Restriction endonuclease study suggests that the sickle cell gene mutation evolved spontaneously in distinct geographic locations. Cameroon, Senegal, Benin, Bantu, and Saudi-Asian are the names given to these varieties. Their clinical significance stems from the fact that certain, such as Senegal and Saudi-Asian variations, are linked to higher HbF levels and have a milder illness [23]. The gene defect is a single nucleotide polymorphism (SNP; GAG codon shifting to GTG) in the -globin gene, which causes glutamic acid (E/Glu) to be replaced by valine (V/Val) at position 6 (E6V substitution) (Suzanne, 2008). In contrast to the normal adult HbA, hemoglobin S with this mutation is referred to as HbS. In situations of normal oxygen concentration, this is a benign mutation that has no effect on the secondary, tertiary, or quaternary structures of hemoglobin. Because the deoxy form of hemoglobin exposes a hydrophobic patch on the protein between the E and F helices (Phe 85, Leu 88), HbS polymerizes and produces fibrous precipitates at low oxygen concentrations [65].

### 2. 10. Treatment of Sickle Cell Anemia

#### 2. 10. 1. Disease-modifying and curative treatments

Currently, hydroxycarbamide and L-glutamine are the only disease-modifying medicines available for SCD. Both are taken on a daily basis to lower the risk of acute problems, although the outcomes differ from one individual to the next. Blood transfusion is another effective disease-modifying therapy for improving oxygenation in severe anemia and lowering the proportion of sickle hemoglobin (HbS percent). It can be given as a simple top-up blood transfusion or as an exchange transfusion (manual or automated).

#### 2. 10. 2. Hydroxy carbamide

Hydroxycarbamide is now widely used around the world [37]. Although it was first utilized as a cytoreductive drug by inhibiting ribonucleotide reductase, the main method by which hydroxycarbamide helps people with SCD is by raising total hemoglobin levels and HbF synthesis [61] Hydroxy carbamide also lowers the number of leucocytes in the blood and lowers the expression of surface adhesion molecules on neutrophils, red cells, and vascular endothelium, improving blood flow and lowering the risk of vaso-occlusion [37]. Long-term hydroxycarbamide usage has been demonstrated to reduce the severity and frequency of crisis in children with SCD in a variety of trials in adults and children [57].

#### 2. 10. 3. L-Glutamine

Glutamine is a conditionally necessary amino acid, which means that while the body regularly produces enough, the body's need for glutamine increases during times of stress, and it must rely on dietary glutamine to supply this demand. The Food and Drug Administration (FDA) in the United States has approved the use of pharmaceutical-grade L-glutamine in sickle cell patients aged five and up [42] This refined version of glutamine dramatically reduced the prevalence of acute SCD problems, according to formal clinical trials. The side effects appear to be mild and do not necessitate further testing [42,20]. The FDA granted clearance based on the findings of two randomized, double-blind, placebo-controlled trials that looked at the effects

of L-glutamine on clinical endpoints in adults and children over the age of five who had HbSS or HbS/o-thalassemia.

### 2. 10. 4. Blood Transfusion

Because of their persistent hemolysis, people with SCD have a baseline degree of anemia. There are no blood transfusions given to rectify this baseline anemia or to treat acute pain episodes. Instead, transfusions are used to treat acute severe anemia, which occurs when a person's hemoglobin falls drastically below his or her baseline, causing impairment in oxygen supply to bodily tissues, which would otherwise result in more sickling of deoxygenated Hb. Red cell aplasia produced by Parvovirus B19 infection, acute splenic sequestration, and hyper-hemolysis crises are all examples [16] Transfusion is also utilized in an acute environment to bridge periods of significant physiologic stress, such as major surgery or critical sickness, such as acute chest crises. Blood transfusion using HbS-negative blood lowers the fraction of circulating hemoglobin that can sickle, lowering vascular blockage and hemolysis from aberrant sickle RBCs.

### 2. 10. 5. Bone marrow transplantation (BMT)

The sole current cure for SCD is BMT, which is one of the more recent therapy options. The researchers discovered a 91 percent event-free survival rate and a death rate of less than 5% [40]. BMT poses a number of dangers, including the new bone marrow-producing leucocytes attacking the tissue cells of the recipient, a condition known as graft-versus-host disease (GVHD) [28]. The skin, liver, gastrointestinal tract, and eyes are all affected, and symptoms include nausea, weight loss, and jaundice. When the donor and receiver are related and HLA type matched, the likelihood of getting GVHD is low. When the donor and recipient are unrelated or have different HLA types, the risk of GVHD is higher; nevertheless, efforts for judicious immunosuppression following transplant can lower the risk of GVHD [67]. Strokes, deadly infections, organ damage, and fits are all dangers associated with BMT. As a result, BMT need specialised centers with highly skilled personnel and cutting-edge technology resources. Because of the present hazards, a bone marrow transplant is usually only advised if the symptoms and complications of SCD are severe enough to outweigh the risks of BMT [24].

## 2. 11. New and emerging therapies for sickle cell disease

Researchers are looking into a variety of new and existing drugs for SCD to address various pathophysiological causes. Adhesion blockers, HbS polymerization blockers, antioxidants, inflammation and activation regulators, and nitric oxide promoters are among the candidates in clinical trials. Combination medicines to prevent and cure acute sickle cell problems could be created by identifying a variety of molecular targets.

## 2. 12. Treatments that Reduce HbS polymerization

GBT440 (Voxelotor) is an orally administered small chemical that increases HbS oxygen affinity by moving the oxy-HbS oxygen dissociation curve to the left [36]. It accomplishes this by reversibly interacting with the N-terminal valine of hemoglobin's alpha chain, modifying its conformational shape and stabilizing the molecule's oxygenation form. Deoxygenated HbS, the form of the molecule that polymerizes to cause the sickle phenotype, is reduced as a result of

this. Voxelotor was well tolerated in phase I/II research, with predictable pharmacodynamics and pharmacokinetics [36].

### 2. 12. 1. Nutritional supplements

Penicillin is advised daily from birth to five years of age due to the underdeveloped immune system that makes them more susceptible to early childhood diseases. The WHO had previously suggested folic acid supplementation in the diet. Due to a lack of medical data, a 2016 Cochrane review of its use concluded that "the efficacy of supplementation on anemia and any symptoms of anemia remains uncertain" [19]. Niprisan, a traditional herbal medication used to treat SCD in Nigeria, exhibited encouraging pre-clinical findings, despite its considerable suppression of cytochrome CYP3A 4 activity is likely to cause drug interactions. The FDA designated Niprisan as. However, production was halted due to financial constraints, and Niprisan has yet to enter clinical trials [15].

### 2. 12. 2. Agents that improve blood flow

Prasugrel prevents platelet aggregation caused by ADP. Activated platelets are thought to stick to the endothelium during vaso-occlusive events and recruit leucocytes, according to a previous study. In a phase III study of 341 children with SCD, there was no significant difference in the number of vaso-occlusive events per person-year between those who took Prasugrel and those who took a placebo. It also found no evidence of a substantial decrease in diary-reported pain episodes [25,26].

Apixaban is an oral direct Factor-Xa inhibitor that stops prothrombin from converting to thrombin. The effectiveness of preventive dosage Apixaban in lowering mean daily pain scores in adults with SCD is being investigated in phase III randomized placebo-controlled trial [59].

### 2. 12. 3. Gene Therapy

Gene therapy is now being researched as a potential cure for sickle cell anemia. Instead of embryonic stem cells, host stem cells are created by manipulating and reprogramming cells from the patient's own blood cells, with genetic engineering employed to rectify the inborn genetic defect. There is no need to identify another person to serve as a stem cell donor because the cells are donated by the patient, and there should be no risk of GVHD. The goal is to turn a patient's blood cells into pluripotent stem cells and replace the gene that is faulty. These cells will then be coaxed into becoming hematopoietic cells, which have the ability to regenerate all types of red blood cells. A small number of people have reportedly been cured of SCD in three gene therapy clinical studies using different lentiviral vectors as of this writing [50].

## 3. CONCLUSION

Drug intervention will remain the main therapeutic option for sickle cell disease unless dramatic advancements in gene therapy or bone marrow transplantation make these treatments available to a large number of patients. To achieve the best results, several agents will most likely be used alone or in combination. Only hydroxyurea has been shown to change the course of sickle cell disease; therefore, combination therapy is currently not a possibility. Many, if not all, of the agents under investigation will most likely fall short of investigators' expectations.

Drugs with different mechanisms of action should be included in the therapy regimens, ideally. For example, combining hydroxyurea with clotrimazole would combine a medicine that promotes fetal hemoglobin production (hydroxyurea) with one that prevents erythrocyte dehydration (clotrimazole) (clotrimazole). Neither medicine alone may be able to significantly alleviate sickle cell symptoms in a specific patient. The combination, on the other hand, has the potential to considerably improve the condition.

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