IJBPAS, May, 2026, 15(5): 2293-2307

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)
'A Bridge Between Laboratory and Reader'
www.ijbpas.com

RECENT ADVANCES IN THE TREATMENT OF SICKLE CELL ANAEMIA

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Received 6th April 2025; Revised 5th May 2025; Accepted 24th July 2025; Available online 1st May 2026

https://doi.org/10.31032/IJBPAS/2026/15.5.10159

ABSTRACT

Sickle cell anaemia belongs to homozygous HbS (HbSS) type. This arises from a single point substitution of value for glutamine at position 6 in the beta globin chain. This reduces or lessens the red blood cells solubility, which causes polymerization and vaso-occlusion in the vasculature. The beta globin gene is located on the chromosomes short arm 11. Hemoglobin S (HbS) is created when two mutant beta globin subunits bind together. The lack of a polar amino acid at position 6 of the beta globin chain facilitates the non-covalent polymerization of Hemoglobin in low-oxygen environments, causing red blood cells to assume a sickle shape and losing their flexibility. Low oxygen tension in sickle cell disease causes red blood cells to sickle, and recurrent sickling episodes weaken the flexibility of the cell and harm the cell membrane. When the normal oxygen tension is restored, these cells are unable to revert to their original shape. Because of their rigidity, these blood cells cannot flex when passing through small capillaries, which causes ischemia and vascular obstruction. The illness's true anaemia is brought on by haemolysis, or the spleen's red cell destruction. People who have this disease have chronic anaemia, and those who have a normal adult haemoglobin genotype will not survive due to the malformation of their cells, which destroys the splenic cells.

Keywords: Sickle cell disease; genetics; inheritance; etiology; pathophysiology; symptoms; diagnosis; complications; treatment; transplantation

INTRODUCTION:

A lifelong blood condition known as sickle cell disease, sickle cell anaemia, or depanocytosis is typified by red blood cells that take on an unusual, stiff, sickle form.

Sickle cell disease is typified by haemolytic anaemia, a heightened vulnerability to infection, and vaso-occlusion, which happens in nearly all arterial beds and causes ischemic tissue damage, organ failure, and premature death. Sickling increases the risk of several problems and reduces the elasticity of the cells. A mutation in the haemoglobin gene is the cause of sickling. For men and women, the life expectancy is 42 and 48 years, respectively. This disease, which typically manifests in childhood, is more common in individuals from tropical and subtropical locations where malaria is endemic because sideling the infected cells stop the malaria plasmodium from spreading. The sickle cell gene is inherited in two copies by those who have the illness, one from each parent **[1]**.

People with families from Africa, South or Central America (particularly Panama), the Caribbean islands, and India are most likely to have sickle cell disease. The many sorts of erythrocytes-Normal, sickle, or with other deformities- can be counted and observed using a variety of techniques. Using a microscope to prepare a slide of the patient's blood, the manual counting is carried out. This method is less expensive, but it is laborious, time-consuming, needs a lot of concentration, and is more error-prone. The cells that overlap are not counted precisely. The majority of haematology analysers that are sold commercially operate on the expensive electrical resistance theory. These processes aren't automated. Therefore, the ideal solution to this issue is to use Matrix Laboratory (MATLAB) for image processing. With the use of this tool, numerous techniques with diverse properties have emerged. In order to determine the percentage of sickle cell anemia, we segment the sickle- shaped red blood cells for shape analysis using the Fractional Dimension Technique. Anticipated outcomes demonstrate the technique's potential since it can surpass conventional approaches for shape recognition and analysis available in many literatures. The suggested approach necessitates meticulous algorithm design, programming, and implementation **(Figure 1)**.

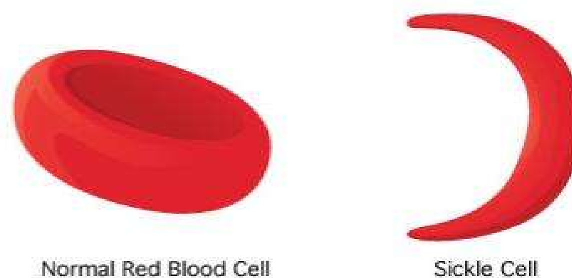


Figure 1: Difference between a Normal Blood Cell and a Sickle Cell

History:

Before the 1904 explanation of the sickle cells by Chicago cardiologist and professor James B. Herrick (1861-1954), whose 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, who was admitted to the Chicago Presbyterian Hospital in December 1904 due to anaemia, this collection of clinical findings was unknown. Over the course of the following three years, Noel experienced multiple readmissions due to "muscular rheumatism" and "bilious attack". After completing his education, Noel went back to Grenada's capital to start a dental practise. He is interred in the Catholic cemetery and passed away from pneumonia in 1906.

Vernon Mason coined the term "Sickle Cell Anaemia" for the illness in 1922. Nonetheless, several aspects of the illness have been identified sooner: A report published in the Southern journal of medical pharmacology in 1846 detailed how a fugitive slave's autopsy revealed no spleen. Due to the extremely high infant mortality rate caused by this illness, it was locally known as "Children who come and go" (ogbanjes) when it was first documented in African medical literature in the 1870s. A genealogy of the ailment traced back to 1670 in a single Ghanaian family.

The first one to show that an anomaly in the haemoglobin molecule is the cause of sickle cell disease was Linus Pauling and associated in 1949. This was documented in their work "Sickle Cell Anaemia a molecular disease" and marked a turning point in the history of molecular biology as the first hereditary disease connected to a mutation of a particular protein.

It was first believed that the mutation that gave rise to the sickle cell gene originated in the Arabian Peninsula and spread to Asia and Africa. Evaluation of chromosomal structures has revealed that at least four independent mutational events occurred, three of which have occurred in Africa and the fourth in either Saudi Arabia or central India. These independent events took place between 70-150,000 years ago, or between 3,000 and 6,000 generations ago.

GENETICS:

Single point mutations are the cause of sickle cell disease and its variations, which are genetic illnesses. The illness is one of the most prevalent severe monogenic illnesses worldwide. The autosomal recessive illness homozygous haemoglobin S disease (HbSS) is the most common severe type of sickle cell disease (SCD) in North America.

The adult haemoglobin (HbA) genes beta-globin chain gene has a single base pair mutation that causes haemoglobin S. The beta-s allele of sickle haemoglobin (HbS) is a haemoglobin subunit beta allele in which

valine has replaced glutamic acid at position 6 in the beta-globin chain due to an adenine-thymine substitution in the beta- globin's sixth codon **[2]**.

Fibres are formed by a single amino acid alteration in the haemoglobin protein. The results of restriction endo nuclease study indicate that the mutation in the sickle cell gene most likely developed spontaneously in geographical locations. These variations go by the names Saudi-Asians, Cameroon, Senegal and Benin. Their clinical significance stems from the fact that some of them, such as the Senegalese and Saudi-Asian variations, have milder symptoms and are linked to greater HbF levels **[3]**.

Since the normal allele can produce more than 50% of the haemoglobin, polymerization issues are not as severe in individuals who are heterozygous for HbS. Long-chain HbS Polymers cause red blood cells in homozygous individuals to change from having a smooth, dount-like form to being ragged and spike-filled, which makes them brittle and prone to shattering inside capillaries. Carrier's only show symptoms when they are severely dehydrated or oxygen-deprived. Normally, a patient had these excruciating crises 0.8 times a year. When valine replaces glutamic acid, the seventh amino acid (if we include the first methionine), the structure and function of the body are altered, leading to S-CD. The p-globin gene's single nucleotide (A to T) is known to have undergone a mutation that causes valine to replace glutamate at position 6 in the gene deficiency. This mutation results in haemoglobin S, which is referred to as HbS rather than the typical adult HbA. The GAG to GTG codon mutation, which is the cause of the genetic condition, is a single nucleotide mutation. Usually, this mutation is benign and has no discernible impact on the secondary, tertiary, or quaternary structure of haemoglobin. On the other hand, it does permit the polymerization of the HbS itself under low oxygen environments. Between the E and F helices of the protein, there is a hydrophobic region that is visible in the deoxy form of haemoglobin. Haemoglobin "S" molecules can combine and form fibrous precipitates when the hydrophobic residues of the valine at position 6 of the beta chain in haemoglobin connect with the hydrophobic patch.

Sickle cell anaemia is caused by an autosomal recessive allele located on the short arm of chromosome 11. The condition develops in those who acquire the faulty gene from both their mother and father; carriers, or those who receive one defective allele and one healthy allele, are known to be carriers but stay healthy. When a child is born to two carriers, there is a one in four chance that the child will get the disease and a one in two chance that the child will only be a carrier due to incomplete gene reception. Carriers can produce a small amount of sickled red blood

cells, not enough to cause symptoms but enough to confer resistance against malaria. Heterozygotes are therefore more fit than either of the homozygotes **[4]**.

The disease persists because of the Heterozygotes adaptive benefit, particularly in individuals with recent ancestry from malaria-affected regions including Africa, the Mediterranean, India, and the Middle East. Although malaria was once endemic throughout Southern Europe, it was proclaimed extinct in the middle of the 20th century, with the exception of an occasional, unusual instance.

A portion of the malaria parasite's intricate life cycle is spent inside the red blood cells. When the malaria parasite is present in a carrier, the red blood cells with faulty haemoglobin burst early, preventing the plasmodium from reproducing. Additionally, the polymerization of Hb influences the parasite's initial capacity to consume Hb. Thus, carrying the sickle cell trait actually increases a person's chances of survival in locations where malaria is a concern.

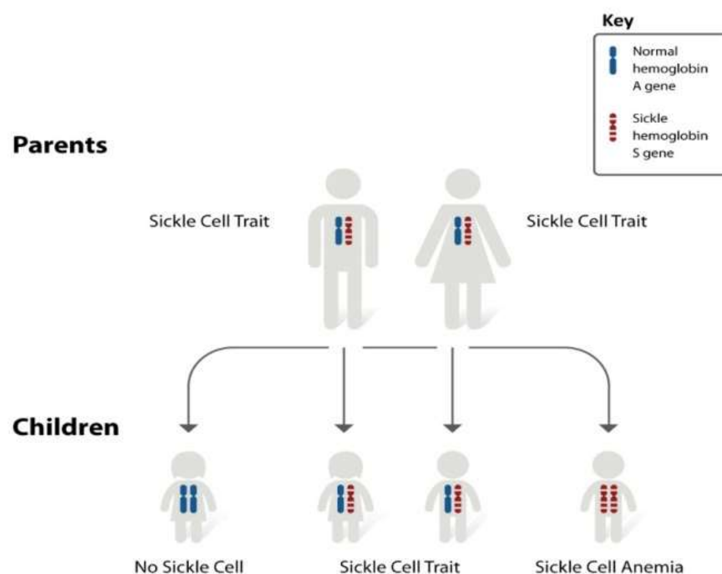
Black people in the United States have a declining incidence of sickle-cell anaemia (approximately 0.25%) compared to West Africa (about 4.0%), where endemic malaria is not present. In the absence of African endemic malaria, the illness is entirely detrimental and tends to drive out those who are afflicted. The lack of cultural predispositions towards polygamy in North America is another factor impeding the dissemination of sickle-cell genes **[5]**.

INHERITANCE:

The same physical characteristics as blood type, eye colour, hair texture, and colour are inherited from parents along with sickle cell anaemia. The haemoglobin genes that an individual inherits from his parents determine the type of haemoglobin that individual produces in red blood cells.

1. A child has a 50% probability of having sickle cell disease (SS) and a 50% chance of having sickle cell trait (AS) if one parent has sickle cell anaemia (SS) and the other has sickle cell trait (AS).
2. A child has a 25% probability of having sickle cell disease (SS) if both parents have sickle cell trait (AS).

ETIOLOGY: Sickle cell anaemia patients receive two defective haemoglobin genes-haemoglobin S – from each parent **[6]**.



PATHOPHSIOLOGY:

The haemoglobin molecule polymerizes as a result of the genetic mutation mentioned, changing the shape and deformability of erythrocytes. Increase erythrocyte adherence is followed by the development of heterocellular aggregates, which physically obstruct tiny blood vessels and produce local hypoxia. Increased HbS production, the release of inflammatory mediators, and the release of free radicals are all set off by this process and contribute to reperfusion injury. Additionally, haemoglobin releases oxygen when it binds to nitric oxide (NO) a strong vasodilator. When erythrocytes are dehydrated, they are more prone to sickle and stiffen. Changes in cation homeostasis, notably elevated potassium and water efflux mediated by potassium-chloride co-transport and Gardos channels (calcium-dependent potassium channel) are mostly responsible for this process. Enhanced nitric oxide binding, hypercoagulability, enhanced platelet activation, and neutrophil adhesiveness are other pathological processes that are linked to this condition.

SYMPTOMS:

Sickle cell anaemia typically manifests as signs and symptoms around six months of age. They differ from person to person and are subject to change. Among the symptoms and indicators are:

- **ANAEMIA:** Sickle cells are brittle and eventually perish. Normally red blood cells require replacement after 120 days of use. However Sickle cells usually expire

within 10 to 20 days, resulting in anaemia, or a lack of red blood cells. Fatigue results from the body not getting enough oxygen if there are insufficient red blood cells.

- **OCCURRENCES OF PAIN:** Agony crises, which are recurring episodes of excruciating agony, are one of the main signs of sickle cell anaemia. When red blood cells with a sickle shape obstruct blood flow to your chest, belly, and joints, pain results.

  The discomfort might last anywhere from a few hours to many days, depending upon its strength. Some people experience few to no pain crises annually. Some people have twelve or more in a year. A hospital stay is necessary for a serious pain crisis. Along with persistent pain, some adults and adolescents with sickle cell anaemia also experience ulcers, bone and joint degeneration, and other conditions.

- **SWELLING IN THE FEET AND HANDS:** Red blood cells with a sickle shape that obstruct blood flow to the hands and feet are the source of the oedema.
- **FREQUENT INFECTIONS:** The spleen may sustain damage from sickle cells, making it more susceptible to infections. Vaccinations and antibiotics are frequently administered to infants and children with sickle cell anaemia in order to prevent potentially fatal illness like pneumonia.
- **DELAYED PUBERTY OR DEVELOPMENT:** The body gets its oxygen and nutrition from red blood cells, which are essential for growth. In young children, a deficiency of healthy red blood cells can cause growth retardation; in teenagers, it can postpone puberty.
- **ISSUES WITH VISION:** Sickle cells can clog the tiny blood arteries supplying the eyes. Vision issues may result from thus injury to the retina, which is the area of the eye that interprets visual images **(Figure 2)**.

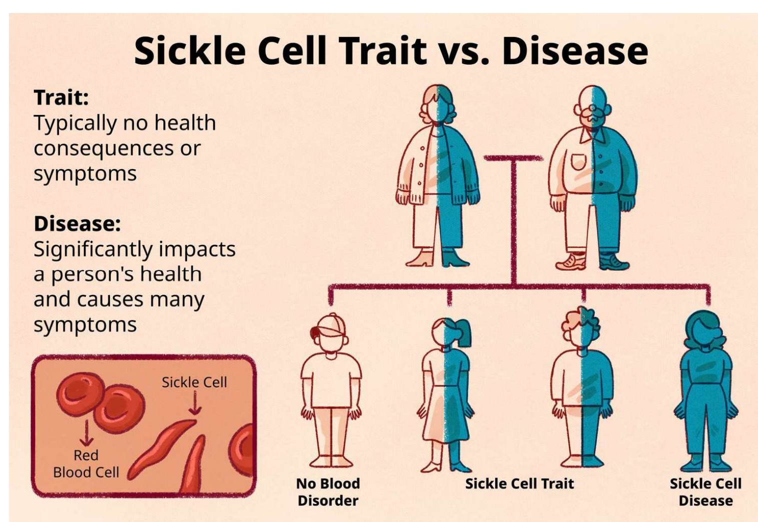


Figure 2: Sickle Cell Trait and its Disease

DIAGNOSIS:

Fall blood counts (FBC) in patients with haemoglobin-storing disease (HbSS) show values of 6-8 g/dl of haemoglobin and a high reticulocyte count. Hb levels are typically greater in sickle cell diseases other than the one described. Target cells and Howell-Jolly bodies are two signs of hyposplenism that can be seen on a blood film.

Sodium metabisulfite can be used to cause sickling of the red blood cells on a blood film. The "Sickle solubility test" can also be used to show that sickle haemoglobin is present. Whereas regular haemoglobin produces a clear solution, a combination of haemoglobins (HbS) in a reducing solution such as (sodium dithionite) appears muddy. On haemoglobin electrophoresis, a type of gel electrophoresis where the different types of haemoglobin move at different speeds, abnormal haemoglobin form can be identified. Here HbSS and HbSC can be distinguished.

Through the use of High-performance liquid chromatography (HPLC) the diagnosis can be verified. Since other studies are very specific for HbS and HbC, genetic testing is rarely done. An infection frequently sets off an acute cell crisis. Consequently, it is recommended to routinely do a urinalysis to look for occult pneumonia and to detect an occult UTI.

COMPLICATIONS:

Numerous issues can result from sickle cell anaemia, such as:

- **STROKE:** Blood flow to a portion of the brain might be obstructed by sickle cells. Seizures, numbness or paralysis in the arms and legs, abrupt speech problems, and loss of consciousness are all indicators of a stroke. A stroke may be lethal.
- **SYMPTOMS OF THE ACUTE CHEST:** This potentially fatal consequence can be brought on by a lung infection or sickle cell disease that obstructs lung blood vessels, causing breathing difficulties, fever, and chest pain. It may need immediate medical attention.
- **HYPERTENSION IN THE LUNGS:** Individuals who have sickle cell anaemia may experience elevated blood pressure in their lungs. It is typically an adult complication. Fatigue and dyspnoea are frequent signs of this potentially lethal illness.
- **ORGAN IMPAIRMENT:** The afflicted organs are deprived of blood and oxygen when sickle cells obstruct blood flow to them. The blood's oxygen content is also consistently low in sickle cell anaemia. This deficiency in oxygen-rich blood can be lethal and cause damage to the kidney, liver, and spleen, among other organs and nerves.

- **SPLEEN CRISIS:** The spleen can grow and could cause left side abdominal pain if a high number of sickle cells become stuck in it. This might endanger life. It's important for parents of sickle cell anaemia children to periodically check for spleen in their child.
- **BLINDNESS:** Tiny blood arteries that supply the eyes might be blocked by sickle cells. This may eventually result in blindness.
- **LEG SORES:** Leg open sores can be quite painful if you have sickle cell anaemia.
- **GALLSTONES:** Bilirubin is a chemical that is produced when red blood cells breakdown. Gallstones may result from the body having an excessive amount of Bilirubin.
- **PRIAPISM:** Men with sickle cell anaemia may experience excruciating, protracted erections as a result of this illness. The blood vessels in the penis might become blocked by sickle cells, which over time can cause impotence.
- **STROKE IN THE DEEP VEINS:** Red cell sickling can result in blood clots, which raises the possibility that a clot will lodge in a lung (pulmonary embolism) or deep vein (deep vein thrombosis). Either one has the potential to be fatal or seriously ill.
- **COMPLICATIONS THROUGHOUT PREGNANCY:** Pregnancy-related high blood pressure and blood clots can be made more likely by sickle cell anaemia. Additionally, it may raise the chance of miscarriage, early delivery, and low birth weight children.

TREATMENT/MANAGEMENT:

The two approaches to managing sickle cell anaemia are maintenance of health and management of complications. Screening for and identifying risk factors and early warning indicators of complications is the aim of health maintenance. There is a proof that the administration of penicillin prophylaxis from early infancy until at least age five, the pneumococcal immunization, and education regarding fever treatment have significantly decreased the death and morbidity caused by invasive infections. Children with sickle cell disease may not always have access to routine Transcranial Doppler (TCD) scanning of big cerebral blood arteries, which may forecast the risk of stroke. Furthermore, in many impoverished countries, the course of treatment-chronic transfusion therapy-is not practical.

The way sickle cell problems managed varies depending on the kind of issue. Quick assessment of pain, prompt administration of analgesic medication, maintenance of this analgesia (PCA pump), and hydration are the

components of VOC management. These steps must be followed until symptoms subside.

Acetaminophen or NSAIDs may be adequate for the majority of people with mild pain, but opiates, either with or without NSAIDs, are recommended for individuals with moderate to severe pain. In sub-dissociative doses, ketamine has been demonstrated more recently to decrease the usage of opiates. Upon onset of fever, patients should be evaluated promptly for potentially fatal infections. This includes doing complete blood counts (CBC) with differential, reticulocyte count, blood culture, and urine culture if UTI is suspected. If necessary, broad-spectrum antibiotic therapy should be started. Transfusion therapy, careful supportive care (oxygen, sparing fluid supply), and acute chest syndrome are required for the majority of additional problems, Including splenic sequestration and strokes. Hydroxyurea has been demonstrated to provide notable advantages for those experiencing severe and frequent problems. The transplantation of bone marrow containing hematopoietic stem cells holds considerable potential in treating sickle cell disease. Antihistamines (hydroxyzine and diphenhydramine) may lessen Opiate-induced itching and may even have some opioid-sparing properties. Empirical antibiotics (macrolide and cephalosporin), sufficient analgesics, oxygen supplementation, exchange or simple transfusion, beta-agonist inhalation, and incentive spirometry may be required for acute chest syndrome **[7, 8]**.

TRANSPLANTATION

The development of genetically modified autologous cells and gene editing has made it unnecessary to search for a genetically matched donor or undergo immunosuppressive therapy, and it also reduces the risk of GVHD and graft rejection. The ideal treatment for sickle cell disease (SCD) would involve either therapeutic reactivation of haemoglobin or preventing the conversion of foetal to adult's haemoglobin. Improved knowledge of transcriptional regulators, including BCL11A, offers genomic-based strategies to stop foetal haemoglobin synthesis from switching or reactivation Lentivral transfer of the beta (A(T87Q))-globin gene is one method in the treatment of beta-hemoglobinopathies using gene therapy **[9]**.

Currently, transplanting stem cells from an immunological matched sibling is the "Curative" treatment for sickle cell disease (SCD). Nevertheless, the paucity of matched sibling donors may be a limitation to this strategy. Transplantation is obviously expensive and associated with a number of acute and chronic consequences, such as morbidity, mortality, and graft versus host disease (GVHD) **[10]**.

CURRENT ADVANCES IN THERAPY MODIFYING THE PATIENT'S GENOTYPE

Modifying the patient's genotype via hemopoietic stem cell transplantation (HSCT) was first reported to be performed over 30 years ago in an 8-year-old child who had SCD (HbSS) with frequent VOCs; she subsequently developed acute myeloid leukaemia. The patient received HSCT for the acute myeloid leukaemia from an HLA-matched sister who was a carrier for HbS (HbAS). She was cured of her leukaemia and at the same time, her sickle cell complications also resolved **[11, 12]**. Until then, HSCT had not been considered as a therapeutic option for SCD. This successful HSCT demonstrated that reversal of SCD could be achieved without complete reversal of the haematological phenotype to HbAA, and paved the way for bone marrow transplant (BMT) as a curative option for children with severe SCD **[13]**.

The conclusion was that, as long as stable mixed hemopoietic chimerism after BMT can be achieved, patients can be cured of their SCD without complete replacement of their bone marrow **[14]**.

ALLOGENEIC BONE MARROW TRANSPLANT

Hematopoietic stem cell transplant (HSCT) has now become an important therapeutic option for patients with SCD. Currently there are about 35 clinical trials at ClinicalTrials.gov studying allogeneic BMT in patients with SCD. As described by Walters *et al* in 2010, HSCT can establish donor-derived erythropoiesis, but even more importantly, can stabilize or even restore function in affected organs of patients with SCD when performed in time.

Between 1986 and 2013, 1,000 patients received HLA-identical matched sibling donor (MSD) HSCTs. The outcomes for both children and adults were excellent, demonstrating 93% overall survival. Eighty seven percent of the patients received myeloablative chemotherapy (MAC) and the rest (13%) received reduced intensity chemotherapy (RIC). It is important to note that patients 16 years or older had worse overall survival (95% vs. 81% $p = 0.001$) and a higher probability of graft versus host disease (GVHD)-free survival (77% vs. 86% $p = 0.001$). These results should encourage physicians to provide early referrals to SCD patients for transplant evaluation so that the donor search can be started in a timely matter **[15]**.

Although myeloablative conditioning has achieved high rates of overall and event free survival, the conditioning is too toxic for adult patients with pre-existing organ dysfunction. Reversal of the sickle haematology without complete replacement of the patient's bone marrow led to the development of less intense conditioning regimens expanding allogeneic transplantation in adult patients, who

otherwise would not be able to tolerate the intense myeloablative conditioning. Donors could be HbAA or HbAS, and in order to reverse the sickle haematological genotype, the myeloid donor chimerism has to be >20% **[16]**.

In an international, multicentre study, 59 patients had MSD HSCT, of which 50 survived and were cured of SCD. Of the nine patients that had a negative outcome, five had graft rejection and four intracranial haemorrhages. Thirteen patients developed mixed chimerism. Of those patients that developed mixed chimerism, there was no GVHD or disease recurrence/graft rejection. Patients with stable mixed chimerism did not have worse outcomes related to complications of SCD. Hsieh *et al*. (2009) developed a protocol for non-myeloablative HSCT with low dose total body radiation, alemtuzumab, and sirolimus. In the initial 10 patients with SCD, nine had long-term, stable, mixed donor chimerism and reversal of their sickle cell phenotype **[17]**. An updated report showed that 87% of the 30 patients had long-term stable donor engraftment without acute or chronic graft-versus-host disease (Clinical trials [NCT00061568]) in the reports mentionewd by Walters *et al*., 2001 and Hsieh *et al*., 2014. More recent data reported at least 95% cure rate in 234 children and young adults (<30 years) with SCA after MSD with no increased mortality compared to SCA itself and better quality of life. The data also showed that myeloablative HSCT can be a safe option for patients <15 years old if a MSD is available unless there is a clear and strong recommendation not to undergo transplant **[18]**.

However, in the US, less than 15% of patients with SCD have HLA- matched siblings as donors, but a promising alternative donor source is haplo-identical family members. Studies are now underway in several centers to find a balance of conditioning regime that provides adequate immunosuppression without rejection and minimal GVHD **[19]**. Matched unrelated donors (MUD) have shown promising results in patients with thalassemia major and are currently being evaluated in patients with SCD as mentione by Fitzhugh *et al*., in 2014. One of the main limitations, unfortunately, is the low probability of finding suitable donors for African and African American populations as per the National Marrow Donor Program and so, not sufficient MUD transplants have been completed in patients with SCD. HLA-haploidentical HSCT following RIC has been reported to show promising results with prolonged and stable engraftment, but for both unrelated umbilical cord blood (UCB) and haploidentical HSCT, rejection remains a major obstacle in the context of RIC **[20]**.

Although encouraging options with promising results in clinical trials, acute and chronic GVHD remain major complications which can be life threatening and have severe effects

on quality of life. Multiple factors affect the development of GVHD in patients undergoing transplant, including the source of the stem cells, the intensity of immunosuppression in the conditioning regime (dose of anti-thymoglobulin) and the mismatch status of the donor to the recipient **[11, 12]**.

Acute GVHD remains a concern in patients receiving mismatched donor transplants but UCB continues to show reduced rates of chronic GVHD **[13]**. Reduced-intensity conditioning regimens have also been studied in related and unrelated HSCT, and while a suitable option for patients with a matched sibling, patients with unrelated donor should be made aware of the not-so-favourable short and long-term outcomes **[14-20]**.

As new transplant modalities emerge with less transplant related mortality, better immune-modulators to prevent GVHD are being developed and graft rejection has become less frequent and accepted indications for HSCT have become less restrictive. Nonetheless, clinicians continue to have reservation toward transplant and tend to delay the referral to a HSCT specialist because of concerns for GVHD, mortality/morbidity related to transplant itself and the risk of graft rejection, which has not been eliminated completely. An on-going clinical trial will compare 2-year overall survival and outcomes related to SCD in patients that undergo transplant compared with current standard of care as mentioned in ClinicalTrail.gov Identifier: NCT02766465

CONCLUSION

Considerable progress has been made in our understanding of the complicated pathophysiology, pathobiology, clinical manifestation, educational implications, psychological consequences, and complications of sickle cell disease since the condition was first described in 1910 and its hereditary origin was discovered in 1945. However, up until recently, sickle cell disease treatment advancement has only addressed and prevented the disease's acute episodes and consequences.

Given the notable progress achieved in gene therapy, sickle cell disease may one day be treated by a genetic modification that will permanently cure the condition and advert its major recognized consequences, long-term social and psychological impairments, and death from this hereditary ailment.

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