Advances in the Treatment of Pediatric Sickle Cell Disease

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Abstract

Sickle cell disease (SCD) is a hereditary haematological disorder associated with significant morbidity and mortality, characterised by a wide spectrum of clinical complications that vary across age groups. The disease predominantly affects individuals from sub-Saharan Africa and their descendants, but it is also prevalent in parts of the Mediterranean, the Middle East, and India, with global distribution influenced by migration patterns. SCD encompasses a group of disorders caused by the presence of haemoglobin S. The HbS component of total haemoglobin in SCD is normally over 50%. HbS is based on an amino acid substitution at position 6 of the β-globin chain, where glutamic acid is replaced by valine. This substitution replaces a hydrophilic amino acid with a hydrophobic amino acid, explaining the reduced water solubility and altered molecular organisation of HbS compared to normal haemoglobin. Diseases caused by HbS include homozygous SCD, where both alleles are affected by the sickle cell mutation (SCD-S/S), HbSC disease, where one allele is affected by the sickle cell mutation and the other by the HbC mutation (SCD-S/C), and sickle cell β-thalassemia with mixed heterozygosity for the sickle cell mutation and a β-thalassemia mutation (SCD-S/β-thalassemia). In SCD-S/β-thalassemia, forms are distinguished where the β-thalassemia mutation completely inactivates the affected gene (SCD-S/β0-thalassemia) and forms where the allele with the thalassemia mutation still has residual activity (SCD-S/β+-thalassemia). Rarely, the sickle cell mutation can also be combined with other haemoglobin variants (SCD-S/D, SCD-S/OArab, SCD-S/Lepore). Carriers have a normal life expectancy. However, there are individual reports of complications in heterozygous carriers of the sickle cell mutation under common circumstances such as pregnancy, mountain sports, intense physical activity, or air travel. It is also unclear whether the

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carrier status is associated with an increased rate of kidney complications. Nevertheless, it is not appropriate to indicate specific medical care needs based on these individual case reports, given the frequency of carrier status. However, the familial risk of developing SCD should be considered in adult carriers. This review aims to summarise and critically evaluate recent advances in the treatment of sickle cell disease in children, with a particular focus on novel pharmacological agents, gene-based therapies, and targets for increasing fetal haemoglobin levels. Recent developments in treatment include agents such as voxelotor, hydroxyurea, and crizanlizumab, as well as innovative approaches like CRISPR/Cas9 gene editing and HbF induction therapies. These strategies offer promising improvements in disease management and patient outcomes. The overall clinical burden of SCD remains substantial, underscoring the importance of continued research to improve therapeutic strategies and patient outcomes.

Keywords: *Sickle cell disease; haemoglobin S; anaemia; hydroxyurea; voxelotor; gene therapy; CRISPR/Cas9.*

1. Introduction

Sickle cell disease (SCD) is an inherited disorder of red blood cells. It belongs to the group of haemoglobinopathies and leads to corpuscular haemolytic anaemia (Rees et al., 2010). Affected individuals have a mutation in the β chain of haemoglobin (Rees et al., 2010; Ware et al., 2017; Matte et al., 2020). Either all β chains can be affected or only a part (milder, heterozygous form) (Jacob et al., 2023; Steinberg, 1996). SCD has evolved in regions with high prevalence of *Plasmodium falciparum* malaria, as the heterozygous state confers a selective protective advantage (Colombatti et al., 2026). Sickle cell carriers are typically asymptomatic but may experience vaso-occlusive crises when extremely hypoxic (Conway et al., 2022; Hanna et al., 2026).

The disease mainly affects individuals from sub-Saharan Africa and their descendants, but also occurs in parts of the Mediterranean region, the Middle East, and India, and has been globally spread through migration (Rees et al., 2010; Gravitz & Pincock, 2014; Sheth et al., 2013). It is still associated with high mortality in developing countries (Esrick & Bauer, 2018; Ross et al., 2002). The history of sickle cell disease is profoundly intertwined with the evolution of modern medicine and integrates medical discovery with cultural and geographic heritage, particularly in Africa, where the disease is most prevalent (Sahu et al., 2023; Almarghalani et al., 2024). The disease was first described in 1910 by James Herrick and Ernest E. Irons in a patient from the Caribbean, and the term sickle cell anaemia was first used by Verne R. Mason in 1922 (Rees et al., 2010; Pace et al., 2021; Gravitz & Pincock, 2014). Affected individuals produce abnormal haemoglobin (sickle cell haemoglobin), which tends to form fibrils in low oxygen conditions. The red blood cells deform into sickle-shaped structures due to the fibres contained within them, clump together, and block small blood vessels, leading to occlusive episodes and inflammation. blockage causes acute, painful, sometimes life-threatening circulatory events, known as sickle cell crises, in homozygous individuals, which can lead to venous thrombosis, among other complications (Esrick & Bauer, 2018; Sher & Olivieri, 1994). Heterozygous carriers, with only one of the two haemoglobin genes altered, are protected from severe forms of malaria. This might be a reason the mutated haemoglobin gene is relatively common in malaria-endemic areas as a protective

mechanism by nature. Due to the tendency of haemoglobin S to polymerise and deform the erythrocytes into a sickle shape, there are blockages in small arteries leading to recurrent circulatory disorders. This affects multiple organ systems: brain, spleen infarction, lungs (pneumonia, pulmonary hypertension), eye, heart and kidney failure, muscles, bones, or priapism, which leads to decreased life expectancy) (Rees et al., 2010; Fertrin & Costa, 2010; Lovett et al., 2017; Sheth et al., 2013; Adams-Graves & Bronte-Jordan, 2016). Glomerulopathy with hyperfiltration occurs in up to a third of patients with the homozygous phenotype in childhood (Crossley et al., 2022; Matte et al., 2020). Damage in the renal medulla leads to papillary necrosis, loss of kidney concentration ability, and macrohematuria (Carrara et al., 2023; Lovett et al., 2017). Damage in the glomeruli leads to increased protein excretion in the urine, like micro- and macroalbuminuria and nephrotic syndrome (Osunkwo et al., 2021). Focal segmental glomerulosclerosis is the predominant glomerular damage seen in histological examination. Up to a third of patients develop proteinuria in the first few decades of life, and five per cent progress to end-stage renal failure (Inusa et al., 2023). Only homozygous carriers of the sickle cell gene exhibit this severe manifestation of the disease, where all haemoglobin is abnormal sickle cell haemoglobin. In heterozygous carriers, only about one per cent of all erythrocytes are deformed (Piel et al., 2023). Symptoms worsen significantly when patients are physically active or at high altitudes (Inusa et al., 2020). This is because the sickle shape of erythrocytes forms at low oxygen partial pressure, as under these conditions, haemoglobin precipitates into fibres (the solubility of haemoglobin in sickle cell anaemia is 25 times lower than that of normal haemoglobin) (Chawla et al., 2013; Lee, 2022).

Symptoms may first appear around the sixth month of life, when fetal haemoglobin breakdown is well advanced (Antwi-Boasiako et al., 2020; Ross et al., 2002). They typically manifest as a sickle cell crisis. Due to a point mutation in the HBB gene (c.20A>T) on chromosome 11, in sickle cell anaemia, the amino acid glutamic acid is replaced by valine at position six of the β-globin protein subunit of haemoglobin. This variant is officially designated as HBB-p.E6V. The affected erythrocytes deform into a sickle shape under decreasing oxygen partial pressure, easily getting trapped in capillaries and lysing rapidly (Esrick & Bauer, 2018; Dover et al., 1994). Hemolysis releases haemoglobin, arginase, and free oxygen radicals. This arginase converts nitric oxide to nitrite and nitrate. Nitric oxide is the most important vasodilator, and its decrease leads to vasoconstriction and circulatory disorders. Sickle cell haemoglobin is referred to as HbS. Heterozygous carriers of the trait produce sufficient HbA alongside HbS to maintain the function of erythrocytes (Zhang et al., 2019; Zempsky et al., 2010; Ross et al., 2002).

The relationship between a molecular defect and a disease was first demonstrated in the case of sickle cell anaemia in a famous study by Linus Pauling, Harvey Itano, and Seymour Jonathan Singer in 1949. The difference in haemoglobin of both red blood cells was revealed in gel electrophoresis conducted by Itano. The authors already suspected differences in amino acids, which Vernon Ingram confirmed in 1956, showing that the difference involved the exchange of a single amino acid. The inheritance patterns of the disease were also elucidated by James V. Neel in 1949. The genetic makeup of a healthy individual contains two incomplete dominant alleles for haemoglobin A (AA). Their red blood cells are always elastic. A carrier with the genotype AS (heterozygous) contains both the A allele and the mutated S allele, which causes the altered haemoglobin S. Their

red blood cells contain HbA and HbS in a 1:1 ratio (Osunkwo et al., 2022; Ross et al., 2002; Sher & Olivieri, 1994). Under normal conditions, the red blood cells show no changes, and the disease does not manifest. Only under severe oxygen deficiency do the red blood cells deform into sickle-shaped structures, affecting organ circulation (Zhang et al., 2017). A carrier with the genotype SS (homozygous) produces only the altered HbS. Even under physiological oxygen deficiency, such as in the capillaries of oxygen-consuming organs, causes significant deformation of the red blood cells. They lose their elasticity and easily clump together, leading to capillary blockages. It is then confirmed by HPLC **(**High-Performance Liquid Chromatography) (Bittmann et al., 2024)**.**

2. New Targets for the Treatment of Sickle Cell Disease

2.1 Voxelotor (Oxbryta)

Voxelotor is a medication used to treat anaemia (haemolytic anaemia) caused by sickle cell disease. It was approved in the USA in November 2019 and in the EU in February 2022 under the trade name Oxbryta (manufactured by Global Blood Therapeutics). Voxelotor is administered orally. Voxelotor suppresses the polymerisation of sickle cell haemoglobin and the occurrence of haemolytic anaemia. It is the first drug with this mechanism of action (first-in-class medication). Voxelotor is a white to yellowish to beige, non-hygroscopic substance. It is highly soluble in organic solvents such as acetone and toluene but insoluble in water. Due to its low water solubility and high in vitro permeability, it is classified as a Class II substance according to the Biopharmaceutics Classification System (BCS). Pharmacologically, Voxelotor acts as a polymerisation inhibitor for haemoglobin S (HbS). In vitro studies have shown that the compound binds to the N-terminal alpha chain of haemoglobin, increasing HbS affinity for oxygen in a dose-dependent manner. This delays HbS polymerisation and prevents sickling of erythrocytes. In a mouse model of sickle cell disease, Voxelotor extended the half-life of erythrocytes, reduced the number of reticulocytes, and prevented sickling of erythrocytes ex vivo. The substance preferentially distributes into erythrocytes. Non-clinical studies also suggest that Voxelotor can improve erythrocyte deformability and reduce whole blood viscosity.

Voxelotor is approved in the USA for patients aged 12 and older, and since December 2021, also for children aged 4 to 11. In the EU, the approval granted in February 2022 applies to patients aged 12 and older. The US approval was granted through an Accelerated Approval process, while Oxbryta in the EU was supported by the European Medicines Agency's Priority Medicines Program (PRIME). The approval was based on data from the Phase 3 HOPE study involving 274 patients aged 12 and older with sickle cell disease. Treatment with Voxelotor showed clinically significant improvements in haemoglobin levels and a reduction in red blood cell destruction (hemolysis). After 24 weeks of treatment, 51.1% of patients receiving Voxelotor had an increase in haemoglobin of more than 1 g/100 mL compared to 6.5% of those receiving a placebo. Significant improvements in hemolysis markers such as "indirect bilirubin" and "reticulocyte count" were observed.

The most common side effects observed in the study were headaches, diarrhoea, abdominal pain, nausea, fatigue, rash, and fever.

2.2 Hydroxycarbamide (Hydroxyurea)

Hydroxycarbamide (INN), also known as hydroxyurea, is a cytostatic drug used primarily in the treatment of malignant blood disorders such as leukaemias and myeloproliferative neoplasms. It is also approved for the treatment of sickle cell disease. The substance works by inhibiting the enzyme ribonucleotide reductase, which reduces ribose to deoxyribose. This process involves a radical mechanism that requires the formation of a tyrosine radical in the enzyme's active site. The stable tyrosine radical is generated by a nearby iron centre composed of two Fe^{3+} ions. Hydroxyurea complexes with iron and reduces it to Fe^{2+}, significantly limiting the DNA synthesis capacity of the cell. After oral administration, hydroxycarbamide is rapidly absorbed from the gastrointestinal tract. The exact bioavailability is not known, but it appears to be high (no significant difference in levels between oral and intravenous administration). Peak serum concentration is reached approximately 2 hours after ingestion. Due to its small molecular size, hydroxycarbamide diffuses well into various body compartments. At higher blood levels, it crosses the blood-brain barrier and enters the cerebrospinal fluid. It also penetrates ascitic fluid, pleural effusions, and breast milk. The mechanism of biotransformation or metabolism is not precisely understood, and it is primarily excreted unchanged through the kidneys.

It increases the synthesis of fetal haemoglobin (HbF), which helps prevent the aggregation of sickle cell haemoglobin (HbS) during vaso-occlusive crises. Clinical studies have demonstrated its effectiveness in managing these crises.

The side effects include dizziness, nausea, vomiting (rare), diarrhoea, constipation, stomatitis (rare), loss of appetite, hair loss, rash, transient liver function abnormalities, and myelosuppression. The most significant side effect is myelosuppression. Hydroxycarbamide can also increase blood uric acid levels, potentially leading to kidney function deterioration or gout attacks. The leukemogenic potential of hydroxycarbamide is debated, with a low risk likely. Isolated cases of skin squamous cell carcinomas have been reported after hydroxycarbamide therapy (Bittmann et al., 2024).

2.3 Crizanlizumab

Crizanlizumab (Adakveo) is a monoclonal antibody that targets P-selectin and is used to reduce vaso-occlusive crises in individuals aged 16 and above with sickle cell anaemia. It is administered via intravenous injection and common side effects include joint pain, nausea, back pain, fever, and abdominal pain. Approved by the FDA in November 2019, it is considered a first-in-class medication. Crizanlizumab can be used in combination with hydroxyurea/ hydroxycarbamide or as a standalone therapy for patients who cannot use or do not respond to hydroxyurea/hydroxycarbamide. P-selectin molecules on activated platelets and vascular endothelial cells are associated with these crises. The FDA approval was based on a clinical trial involving 132 participants with a history of sickle cell disease and vaso-occlusive crises. The European Medicines Agency recommended withdrawing Adakveo due to insufficient benefits compared to risks, as shown in the STAND phase III study.

2.4 Arginin-Butyrat

Arginine Butyrate is a compound that combines the short-chain fatty acid butyrate with the amino acid arginine (Molokie et al., 2017; McMahon et al., 2010; Martí-Carvajal et al., 2012; Starlard-Davenport et al., 2022; Sher & Olivieri, 1994). It has the potential to induce the Epstein-Barr virus thymidine kinase gene (EBV-TK). When administered, arginine butyrate triggers the expression of thymidine kinase (TK), which activates an antiviral like ganciclovir, leading to the destruction of EBV-infected cancer cells. Additionally, butyrate inhibits histone deacetylase (HDAC), resulting in hyperacetylation of histones H3 and H4. Acetylated histones have a reduced affinity for chromatin, potentially allowing for chromosomal unfolding and enhancing the expression of genes involved in tumour cell growth arrest and apoptosis. Butyrate stimulates fetal-globin-gene expression in sickle cell disease (Perrine & Faller, 1993; Dover et al., 1994; Reid et al., 2014).

2.5 Alpha-Glutamin

Glutamine is a non-essential α-amino acid that serves as the γ-monoamide of L-glutamic acid. It is coded as Gln in the three-letter code and Q in the one-letter code. L-Glutamine acts as a universal amino group donor in metabolism and constitutes 20% of the free amino acid pool in blood plasma. Severe glutamine depletion is observed in hypercatabolic and hypermetabolic conditions such as post-surgery, severe injuries, burns, and infections. The one-letter code Q for glutamine was assigned after N for asparagine due to their structural similarity. Glutamine is encoded by the base triplet CAG or CAA in mRNA. The mnemonic "Qlutamine" was suggested for easy recall. Glutamine has two enantiomers, with L-glutamine being the predominant form in proteins. D-glutamine is the mirror image of L-glutamine and is not found in proteins. Racemic DL-glutamine has limited significance. Glutamine is present at an average of 3.9% in proteins and is a central metabolite in the metabolism of all living organisms (Bittmann et al., 2024).

3. Targets to Increase HBF Concentration

3.1 Decitabine and Tetrahydrouridine (THU)

In the first human clinical trial (NCT01685515) to pharmacologically re-induce HbF by inhibiting DNMT1, two small molecules were combined: decitabine to deplete DNMT1 and tetrahydrouridine (THU) to inhibit cytidine deaminase (CDA), which rapidly inactivates decitabine (Molokie et al., 2017). The decitabine 0.16 mg/kg dose, DNMT1 protein depletion, CpG methylation reduction, and HbF increase were observed. Limitations of this early phase study include small patient numbers and limited evaluation of clinical benefits (Molokie et al., 2017).

3.2 Gene Therapy: CRISPR Cas-9 Technology

The CRISPR/Cas method is a molecular biology technique used to precisely cut and modify DNA (genome editing) (Ma et al., 2023; Boisson et al., 2021; Esrick & Bauer, 2018; Jayavaradhan & Malik, 2018; Leonard & Tisdale, 2023). Genes can be inserted,

removed, or disabled using this system, and nucleotides within a gene can be altered (Leonard et al., 2022; Ma et al., 2023). Despite its simplicity, scalability, and cost-effectiveness, the CRISPR/Cas method still faces challenges with specificity due to off-target effects. The foundation for the development of the CRISPR/Cas method was laid through the discovery and exploration of CRISPR sequences and the associated CRISPR/Cas system in the immune systems of various bacteria and archaea. The method was first documented in 2012 by a research group led by Emmanuelle Charpentier and Jennifer Doudna (Leonard & Tisdale, 2023). The scientific journal Science declared the CRISPR method as the Breakthrough of the Year in 2015. Both scientists were awarded the Nobel Prize in Chemistry in 2020 for their work on the CRISPR/Cas method.

The CRISPR/Cas method is based on a bacterial adaptive antiviral defence mechanism known as CRISPR, allowing for precise DNA cutting at a specific DNA sequence (Ma et al., 2023; Boisson et al., 2021; Esrick & Bauer, 2018; Jayavaradhan & Malik, 2018; Leonard & Tisdale, 2023). The DNA-cutting enzyme Cas binds to a specific RNA sequence, facilitating the cutting process. The system's components, including Cas proteins and RNA sequences, enable targeted DNA manipulation through double-strand breaks. Alternative systems like CRISPR/Cpf1 and CRISPR/Cas12b offer similar capabilities for genetic manipulation. Other methods like TALENs and ZFNs require more complex protein design for specificity adjustments compared to the CRISPR/Cas system (Leonard & Tisdale, 2023).

4. Discussion

The most important prophylaxis to prevent life-threatening infections caused by pneumococci in infants is the pneumococcal vaccination in the 2nd month of life and penicillin administration from the 3rd month of life until the 5th birthday. Prophylaxis also includes treatment with hydroxyurea (HC) (=Litalir, Hydrea, Siklos), as this medication is not given to treat pain but to prevent it. Hydroxyurea is a cytostatic agent, meaning a substance that destroys cells and is also used to treat some malignant diseases. It has different effects on red blood cells: it helps them retain more fluid inside, thereby diluting the haemoglobin S. It leads to increased production of HbF, the "baby haemoglobin," in most patients. HbF is the red blood pigment that children predominantly have before birth and does not cause sickling of red blood cells; in fact, it can even prevent it. At birth, the proportion of HbF is still about 60-70%. Therefore, newborns with sickle cell disease do not show signs of the disease. After birth, almost only HbA, the "adult haemoglobin," is formed, or, in sickle cell patients, the diseased HbS. The more HbF, baby haemoglobin, a sickle cell patient has, the less HbS he has, and the less the cells can sickle and get stuck in the vessels. Hydroxyurea also reduces the stickiness of the surface of red blood cells – they no longer stick as easily to the inside of blood vessels. Since 1995, we have known that about 70% of sickle cell patients who suffer from frequent and severe pain crises or who have had more than 2 acute chest syndromes have had less or no pain or lung problems when they received this medication. Like all medications, hydroxyurea has side effects: suppressed bone marrow production of blood cells, dry skin, possible reduction of sperm in men, abdominal pain, discoloured fingernails, and, very rarely, severe infections due to a suppressed immune system.

Patients who do not experience improvement from taking hydroxyurea for a long period.

Treatment that can lead to a cure by stem cell transplantation (SCT). Stem cells are cells in the bone marrow that are capable of producing all blood cells, namely red and white blood cells and platelets. Without stem cells in the bone marrow, one is not viable. In an SCT, a patient whose bone marrow produces diseased blood cells has this disease-causing bone marrow destroyed by very strong medications or radiation. For the patient to survive without their previous illness, healthy stem cells must now be given to them. In sickle cell patients, these healthy stem cells must be from an HLA-identical donor in the family (either a sibling, very rarely a parent). HLA-identical unrelated donors are also possible. HLA-identical means that the donor has inherited the same surface characteristics of their lymphocytes. The new healthy stem cells will then form healthy blood cells if the patient survives the difficult period immediately after the transplantation, i.e., the patient is cured. An SCT should be offered to all HbSS and HbSß°-Thal patients who have an HLA-identical family donor. For all sickle cell patients on a chronic transfusion program who do not have an HLA-identical family donor, a matched unrelated donor should be sought. The so-called haplo-identical SCT from a parent or sibling who is only half-identical is still experimental. An SCT is not without risk for the patient. Even under optimal conditions, 10% of transplanted patients die from complications after an SCT. Among the patients who are cured by the SCT, late or chronic damage can occur.

Gene Therapy has been a curative therapy option since 2019, with a study investigating whether gene therapy can achieve a permanent cure for sickle cell disease. There is only limited experience with individual patients so far, and this possible cure in a one-time approach (Bittmann et al., 2024).

5. Conclusion

Sickle cell anaemia typically manifests from the 3rd to 4th month of life with pallor and jaundice, and is characterised by two symptom complexes: Episodic vascular occlusive crises manifest as severe pain and swelling in the affected body regions (hand-foot syndrome, bones and joints, abdominal crises, lung infarctions, CNS crisis, and kidney damage). Due to the sickle shape, erythrocytes lose their flexibility and are sequestered in the liver and spleen (chronic hemolytic anaemia), leading to the accumulation of large amounts of blood in the spleen and shock-like conditions due to sequestration crisis. Repeated infarction of the spleen leads to functional asplenia and subsequently to severe bacterial infections. Individuals with sickle cell anaemia have very high HbS levels in haemoglobin electrophoresis. Consequently, HbF can be formed, which mitigates the symptoms. Sickle cell anaemia is inherited in an autosomal recessive manner and is caused by a mutation in the HBB gene on chromosome 11p15.5. This involves a point mutation in codon 6 of the HBB gene, resulting in the substitution of the amino acid glutamine with valine. Most often, there is homozygosity for this point mutation. A compound heterozygosity with the above mutation and another amino acid substitution at the same position (Glu -> Lys) typically shows a slightly milder symptomatology. When a heterozygous HbS mutation is combined with other mutations in the ß-globin gene or other haemoglobinopathies, a variable spectrum of symptoms emerges. Sole heterozygosity for HbS has no clinical significance.

Consent and Ethical Approval

It is not applicable.

Disclaimer (Artificial Intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

Competing Interests

Authors have declared that no competing interests exist.

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