Review Article

New Insights in the Treatment of Sickle Cell Disease in Childhood

Abstract

Sickle cell disease encompasses diseases that are pathophysiologically caused by hemoglobin S. The HbS component of total hemoglobin 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 at an outward-facing position in the hemoglobin molecule, explaining the reduced water solubility and altered molecular organization of HbS compared to normal hemoglobin. 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 hemoglobin variants (SCD-S/D, SCD-S/OArab, SCD-S/Lepore). The carrier status for the sickle cell mutationgenerally has no clinical significance except in extreme situations (e.g., eye trauma or surgeries involving cardiopulmonary bypass). 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 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 manuscript focus on new targets to treat sickle cell anemia in children.

Keywords

Sickle cell-children-treatment-insights

Introduction

Sickle cell disease or drepanocytosis is an inherited disorder of red blood cells. It belongs to the group of hemoglobinopathies and leads to corpuscular hemolytic anemia. The affected individuals have a mutation in the β chain of hemoglobin. Either all β chains can be affected or only a part (milder, heterozygous form).

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. It is still associated with high mortality in developing countries. 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 anemia was first used by Verne R. Mason in 1922. Affected individuals produce abnormal hemoglobin (sickle cell hemoglobin), which tends to form fibrils in low oxygen conditions. The red blood cells deform into sickle-shaped structures due to the fibers contained within them, clump together, and block small blood vessels, leading to inflammation. The clumping and vessel blockage can cause acute painful, sometimes life-threatening circulatory disorders, sickle cell crises, in homozygous individuals, which can lead to venous thrombosis, among other complications. Heterozygous carriers, with only one of the two hemoglobin genes altered, are protected from severe forms of malaria. This makes the mutated hemoglobin gene relatively common in malaria-endemic areas. The destruction of red blood cells results in severe chronic anemia. Due to the tendency of hemoglobin S to polymerize and deform the erythrocytes into a sickle shape, there are blockages in small arteries leading to recurrent circulatory disorders. This causes severe pain and damage in multiple organ systems: brain, spleen infarction, lungs (pneumonia, pulmonary hypertension), eye, heart and kidney failure, muscles, bones, or priapism. Life expectancy is reduced. Glomerulopathy with hyperfiltration occurs in up to a third of patients with the homozygous phenotype in childhood. Damage in the renal medulla leads to papillary necrosis, loss of kidney concentration ability, and macrohematuria. Damage in the glomeruli leads to increased protein excretion in the urine like micro- and macroalbuminuria and nephrotic syndrome. 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 percent progress to end-stage renal failure. Only homozygous carriers of the sickle cell gene exhibit this severe manifestation of the disease, where all hemoglobin is abnormal sickle cell hemoglobin. In heterozygous carriers, only about one percent of all erythrocytes are deformed. Symptoms worsen significantly when patients are physically active or at high altitudes. This is because the sickle shape of erythrocytes forms at low oxygen partial pressure, as under these conditions, hemoglobin precipitates into fibers (the solubility of hemoglobin in sickle cell anemia is 25 times lower than that of normal hemoglobin).

Symptoms may first appear around the sixth month of life, when fetal hemoglobin breakdown is well advanced. They typically manifest as a sickle cell crisis: External factors such as exertion lead to a decrease in blood oxygen partial pressure, causing hemolytic sickling of the sickle cells. Due to a point mutation in the HBB gene (c.20A>T) on chromosome 11, in sickle cell anemia, the amino acid glutamic acid is replaced by valine at position six of the β-globin protein subunit of hemoglobin. 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. Hemolysis releases hemoglobin, arginase, and free oxygen radicals. Free hemoglobin binds nitric oxide about 1000 times more strongly than intracellularly, and 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 hemoglobin is referred to

as HbS, in contrast to HbA, the normal hemoglobin of adult humans. Heterozygous carriers of the trait produce sufficient HbA alongside HbS to maintain the function of erythrocytes in these individuals.

The relationship between a molecule defect and a disease was first demonstrated in the case of sickle cell anemia in a famous study by Linus Pauling, Harvey Itano, and Seymour Jonathan

Singer in 1949. The difference in hemoglobin 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. Sickle cell anemia is an autosomal codominant genetic disorder. The genetic makeup of a healthy individual contains two incomplete dominant alleles for hemoglobin 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 hemoglobin S. Their red blood cells contain HbA and HbS in a 1:1 ratio. 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. 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, there is a significant deformation of the red blood cells. They lose their elasticity and easily clump together, leading to capillary blockages. Under normal conditions, hemoglobin in red blood cells is finely distributed. As the pH and oxygen content of the blood decrease, HbS molecules clump together into rod-shaped crystalline structures. This causes the erythrocyte to deform into a sickle shape and lose its elasticity. The diagnosis of sickle cell anemia is initially based on medical history, including family history and other cases of the disease in the family. It is then confirmed clinically based on symptoms and finally in the laboratory, where a hemolytic anemia may appear in a blood test, and examination of the blood under a microscope may reveal the typical sickle-shaped cells - especially if the blood has been stored under oxygen deprivation for 24 hours (sickle cell test). Additionally, hemoglobin electrophoresis can identify the altered molecules conclusively. Finally, the gene segment for hemoglobin can be examined in a restriction analysis to show the point mutation at the DNA level.

New targets for the treatment of sickle cell disease

Voxelotor (Oxbryta)

Voxelotor is a medication used to treat anemia (hemolytic anemia) 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 polymerization of sickle cell hemoglobin and the occurrence of hemolytic anemia. 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 polymerization inhibitor for hemoglobin S (HbS). In vitro studies have shown that the compound binds to the N-terminal alpha chain of hemoglobin, increasing HbS affinity for oxygen in a dose-dependent manner. This delays HbS polymerization 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 hemoglobin 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 hemoglobin 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, diarrhea, abdominal pain, nausea, fatigue, rash, and fever.

Hydroxycarbamide (Hydroxyurea)

Hydroxycarbamide (INN), also known as hydroxyurea, is a cytostatic drug used primarily in the treatment of malignant blood disorders such as leukemias 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 center composed of two Fe3+ ions. Hydroxyurea complexes with iron and reduces it to Fe2+, 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 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 molecule size, hydroxycarbamide diffuses well into various body compartments. At higher blood levels, it crosses the blood-brain barrier and enters the cerebrospinal fluid. The substance also penetrates into ascites, pleural effusions, and breast milk. The mechanism of biotransformation or metabolism is not precisely understood, and it is primarily excreted unchanged through the kidneys. Hydroxycarbamide is used for cytoreductive therapy in myeloproliferative disorders such as chronic myeloid leukemia (CML), polycythemia vera, essential thrombocythemia, and osteomyelofibrosis. Its use in CML has decreased significantly with the introduction of imatinib (Gleevec), but in certain situations, hydroxycarbamide may still be beneficial. In polycythemia vera, regular phlebotomy is usually the preferred treatment, but hydroxycarbamide may be useful in cases of significantly elevated leukocyte or platelet counts. Its use has also declined since the approval of ruxolitinib (Jakavi) in 2012. Hydroxycarbamide competes with anagrelide (Xagrid) in essential thrombocythemia, and it is commonly used in osteomyelofibrosis. The European Medicines Agency has approved

hydroxycarbamide for the treatment of sickle cell disease. It increases the synthesis of fetal hemoglobin (HbF), which helps prevent the aggregation of sickle cell hemoglobin (HbS) during vaso-occlusive crises. Clinical studies have demonstrated its effectiveness in managing these crises. Several clinical studies have investigated the combination of hydroxycarbamide with antiretroviral drugs for HIV treatment, with varying results. Its use should be limited to controlled clinical trials, as it is not approved for HIV treatment. Hydroxycarbamide may be used off-label for chronic myelomonocytic leukemia (CMML) under certain circumstances. Possible side effects include dizziness, nausea, vomiting (rare), diarrhea, constipation, stomatitis (rare), loss of appetite, hair loss, rash, transient liver function abnormalities, and myelosuppression. The most significant side effect is myelosuppression, which limits the dosage that can be administered. 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. Hydroxycarbamide has shown genotoxic and embryotoxic effects in animal studies. Women planning pregnancy should discontinue hydroxycarbamide after consulting their healthcare provider.

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 anemia. 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. Vaso-occlusive crises are painful complications of sickle cell disease caused by the obstruction of blood circulation by sickled red blood cells. 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 sickle cell disease history of 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.

CRISP Cas-9 Technology

The CRISPR/Cas method is a molecular biology technique used to precisely cut and modify DNA (genome editing). Genes can be inserted, removed, or disabled using this system, and nucleotides within a gene can be altered. 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. 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 defense mechanism known as CRISPR, allowing for precise DNA cutting at a specific DNA sequence. 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.

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 a 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.

Targets to increase HbF concentration

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 (36). This trial aimed to identify minimal effective doses of oral decitabine without cytotoxicity in SCD adults at risk of early death. Patients were randomized to THU-decitabine or placebo in 5 cohorts, treated 2X/week for 8 weeks (36). The primary endpoint was ≥ grade 3 non-hematologic toxicity, which was not triggered. At the decitabine 0.16 mg/kg dose, DNMT1 protein depletion, CpG methylation reduction, and HbF increase were observed. Hemoglobin and F-cells also increased, with improvements in hemolysis, thrombophilia, and inflammation markers. Platelets increased, and neutrophils decreased without treatment holds. Limitations of this early phase study include small patient numbers and limited evaluation of clinical benefits (36).

Arginin-Butyrat

Arginine Butyrate is a compound that combines the short-chain fatty acid butyrate with the amino acid arginine (36-43). 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 tumor cell growth arrest and apoptosis (36-43). Butyrate stimulates fetal-globin-gene expression in sickle cell disease (36-43).

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. A prerequisite for these measures is the newborn screening for sickle cell disease, which has been available in Germany since November 2020. 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 hemoglobin S. It leads to increased production of HbF, the "baby hemoglobin," 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 hemoglobin," is formed, or, in sickle cell patients, the diseased HbS. The more HbF, baby hemoglobin, 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 had less or no pain or lung problems when they received this medication. Since 2014, HC has been recommended for all HbSS, HbSß°-Thal, HbSD, and HbSOArab patients from the age of 2. Like all medications, hydroxyurea has side effects: suppressed bone marrow production of blood cells, dry skin, possible reduction of sperm in men, abdominal pain, discolored fingernails, very rarely severe infections due to suppressed immune system. It is not proven that hydroxyurea (HC) harms the unborn baby if the mother takes HC. In animal experiments, mice and hamsters given an extremely high dose of HC had deformed offspring. So far, no birth defects have been observed in any woman who took HC at the time of conception or during pregnancy. It is therefore justifiable to continue taking hydroxyurea during pregnancy. Breastfeeding while taking HC is also allowed. The suspicion that HC could lead to malignant diseases due to the constantly suppressed immune system has not been confirmed. For several years, it has been known that children with very fast blood flow in the brain vessels (occurs in about 10-12% of examined children) are at risk of a stroke. It is also known that most of these strokes can be prevented if these children receive regular blood transfusions over many years.

The speed of blood flow can be measured through the skull bones using a special ultrasound method. This examination is called Transcranial Doppler Sonography (TCDS). Since some hospitals in Germany have only 1-2 sickle cell patients, TCDS is only performed at hospitals with many patients. Patients from smaller hospitals are sent to these larger centers. It is recommended to perform TCDS annually for

HbSS, HbSß°-Thal, HbSD, and HbSOArab sickle cell patients between 2-16 years of age. If it is found that the blood flows too fast, a follow-up examination is done a few weeks later. If the flow rate is still too high, a transfusion program must be started to prevent a stroke. Triggers for pain crises can be hypothermia not drinking enough fluids, alcohol, infections. Such triggers should be avoided if possible. In some girls and women, menstruation can trigger a pain crisis. When a pain crisis occurs, pain medication should be taken immediately. Waiting until the pain is very severe makes it difficult to control the pain with simple means.
For mild pain, Stage I medications (Paracetamol, Novalgin, Ibuprofen) are sufficient; for stronger pain, a Stage II medication (Tramal) must be taken in addition. Every sickle cell patient should always have a Stage I and Stage II medication at home. If the combination of both medications is not enough to reduce the pain, the hospital must be visited, as a Stage III medication (Morphine, Dipidolor), given intravenously, becomes necessary. In addition to a Stage III pain medication, a Stage I medication (usually Novalgin intravenously) must always be given. Morphine or similar strong pain medications have unpleasant side effects: shallow breathing, nausea, vomiting, constipation, itching, urinary retention. Therefore, if these problems occur, additional medications may need to be used to reduce these side effects. If a patient receives morphine intravenously, it must always be ensured that the lungs are well ventilated. Therefore, all patients receiving morphine as an infusion should be given a small device (spirometer) every 2 hours, into which they should blow forcefully 10 times against resistance. Alternatively, a balloon can be inflated.
Those who need morphine because of severe pain are no morphine-dependent. Dependency has completely different reasons.

When during an infection with parvovirus B19, the bone marrow does not produce any red blood cells for several days. Doctors then speak of an aplastic episode. When in splenic sequestration, almost all red blood cells are held in the spleen, and only clear fluid flows through the blood vessels. A transfusion is then life-saving. When, for example, during an infection, hemolysis (blood breakdown) is increased to the point where the patient has symptoms of severe anemia (weakness, shortness of breath, very rapid pulse).
When during pregnancy, the Hb level drops so low that the mother can no longer manage her household.There is a lung complication of sickle cell disease called Acute Chest Syndrome. The patient has chest pain, breathes rapidly and laboriously, requires oxygen, and has a fever. X-rays show dense white spots, lung areas where no oxygen reaches. The treatment of Acute Chest Syndrome includes transfusion, and sometimes, if this lung complication develops very rapidly, an exchange transfusion may be necessary. In an exchange transfusion, blood is taken from the patient and replaced with the same amount of healthy blood. Such an exchange transfusion is necessary when red blood cells with their disease-causing properties (clogging of vessels, sticking to the inside of blood vessels) need to be rapidly exchanged for blood cells that do not have these properties. An exchange transfusion may be necessary in Acute Chest Syndrome, severe bacterial infections, intestinal vessel occlusion, and other life-threatening complications. The third type of transfusion is called a chronic transfusion program. In a chronic transfusion program, the aim is to prevent the patient's bone marrow from producing sickle blood over a long period, sometimes years.
Patients who do not experience improvement from taking hydroxyurea over a long period.

Patients who are transfused over a long period accumulate too much iron in the body. Each blood transfusion contains about 250 mg of iron. The iron from 2 blood transfusions is enough, for example, to supply a healthy 6-year-old child with iron for a whole year. Knowing that a 6-year-old child on a chronic transfusion program needs about 12-15 blood transfusions a year, one can imagine how much excess iron enters the body. Our body is designed to absorb iron from food (through the intestines) but does not get rid of it once it is in the body. Excess iron is very harmful to many organs, especially the hormone-producing glands and the heart muscle. All patients who receive blood transfusions over a long period, regardless of whether they have sickle cell disease, thalassemia, or another condition, must take medications that remove iron from the body through urine or stool. These medications used to be available only as infusions, but now fortunately come in tablet form, although they must be taken regularly. Transfusions can save lives, but they can also be life-threatening if given at the wrong time and in the wrong amount. If sickle cell patients, who have their usual Hb values (e.g., Hb 7.5 g/dl) and feel well, receive a blood transfusion because a doctor believes the very low value needs to be raised, e.g., during a pain crisis, severe complications can occur. Sickle cell patients or their parents should, when a transfusion is planned, ask the doctor to explain exactly why this transfusion is necessary. They can also ask the doctor to check www.sicklecellanemia.com to see if there is a real need for a transfusion.

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. A 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 is ancuring therapy option since 2019 focussing by a study investigation 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 curing treatment in one-time approach.

Conclusion

Sickle cell anemia typically manifests from the 3rd to 4th month of life with pallor and jaundice and is characterized by two symptom complexes:The particularly increased tendency of hemoglobin molecules to aggregate under conditions of oxygen deprivation leads to the characteristic sickle shape of erythrocytes and, through the associated disturbance of microcirculation, to vascular occlusive disease. 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 crises, and kidney damage). Due to the sickle shape, erythrocytes lose their flexibility and are sequestered in the liver and spleen (chronic hemolytic anemia), leading to the accumulation of large amounts of blood in the spleen and shock-like conditions. Repeated infarction of the spleen leads to functional asplenia and subsequently to severe bacterial infections. Individuals with sickle cell anemia have very high HbS levels in hemoglobin electrophoresis. Compensatorily, HbF can be formed, which mitigates the symptoms.Sickle cell anemia 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 aheterozygous HbS mutation is combined with other mutations in the ß-globin gene or other hemoglobinopathies, a variable spectrum of symptoms emerges. Sole heterozygosity for HbS has no clinical significance.

References

1. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010 Dec 11;376(9757):2018-31. doi: 10.1016/S0140-6736(10)61029-X. Epub 2010 Dec 3. PMID: 21131035.
2. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet. 2017 Jul 15;390(10091):311-323. doi: 10.1016/S0140-6736(17)30193-9. Epub 2017 Feb 1. PMID: 28159390.
3. Pace BS, Starlard-Davenport A, Kutlar A. Sickle cell disease: progress towards combination drug therapy. Br J Haematol. 2021 Jul;194(2):240-251. doi: 10.1111/bjh.17312. Epub 2021 Jan 20. PMID: 33471938; PMCID: PMC8282668.
4. Jacob SA, Talati R, Kanter J. The evolving treatment landscape for children with sickle cell disease. Lancet Child Adolesc Health. 2023 Nov;7(11):797-808. doi: 10.1016/S2352-4642(23)00201-8. PMID: 37858508.
5. Leonard A, Tisdale JF, Bonner M. Gene Therapy for Hemoglobinopathies: Beta-Thalassemia, Sickle Cell Disease. Hematol Oncol Clin North Am. 2022 Aug;36(4):769-795. doi: 10.1016/j.hoc.2022.03.008. Epub 2022 Jun 27. PMID: 35773052.
6. Gravitz L, Pincock S. Sickle-cell disease. Nature. 2014 Nov 13;515(7526):S1. doi: 10.1038/515S1a. PMID: 25390134.
7. Ma L, Yang S, Peng Q, Zhang J, Zhang J. CRISPR/Cas9-based gene-editing technology for sickle cell disease. Gene. 2023 Jul 20;874:147480. doi: 10.1016/j.gene.2023.147480. Epub 2023 May 12. PMID: 37182559.

8. Sheth S, Licursi M, Bhatia M. Sickle cell disease: time for a closer look at treatment options? Br J Haematol. 2013 Aug;162(4):455-64. doi: 10.1111/bjh.12413. Epub 2013 Jun 15. PMID: 23772687.
9. Matte A, Cappellini MD, Iolascon A, Enrica F, De Franceschi L. Emerging drugs in randomized controlled trials for sickle cell disease: are we on the brink of a new era in research and treatment? Expert Opin Investig Drugs. 2020 Jan;29(1):23-31. doi: 10.1080/13543784.2020.1703947. Epub 2019 Dec 25. PMID: 31847604.
10. Steinberg MH. Review: sickle cell disease: present and future treatment. Am J Med Sci. 1996 Oct;312(4):166-74. doi: 10.1097/00000441-199610000-00004. PMID: 8853065.
11. Boisson C, Rab MAE, Nader E, Renoux C, Kanne C, Bos J, van Oirschot BA, Joly P, Fort R, Gauthier A, Stauffer E, Poutrel S, Kebaili K, Cannas G, Garnier N, Renard C, Hequet O, Hot A, Bertrand Y, van Wijk R, Sheehan VA, van Beers EJ, Connes P. Effects of Genotypes and Treatment on Oxygenscan Parameters in Sickle Cell Disease. Cells. 2021 Apr 5;10(4):811. doi: 10.3390/cells10040811. PMID: 33916502; PMCID: PMC8067408.
12. Fertrin KY, Costa FF. Genomic polymorphisms in sickle cell disease: implications for clinical diversity and treatment. Expert Rev Hematol. 2010 Aug;3(4):443-58. doi: 10.1586/ehm.10.44. PMID: 21083035.
13. Esrick EB, Bauer DE. Genetic therapies for sickle cell disease. Semin Hematol. 2018 Apr;55(2):76-86. doi: 10.1053/j.seminhematol.2018.04.014. Epub 2018 May 7. PMID: 29958563.
14. Lovett PB, Sule HP, Lopez BL. Sickle Cell Disease in the Emergency Department. Hematol Oncol Clin North Am. 2017 Dec;31(6):1061-1079. doi: 10.1016/j.hoc.2017.08.009. PMID: 29078924.
15. Crossley M, Christakopoulos GE, Weiss MJ. Effective therapies for sickle cell disease: are we there yet? Trends Genet. 2022 Dec;38(12):1284-1298. doi: 10.1016/j.tig.2022.07.003. Epub 2022 Aug 4. PMID: 35934593; PMCID: PMC9837857.
16. Sheth S, Licursi M, Bhatia M. Sickle cell disease: time for a closer look at treatment options? Br J Haematol. 2013 Aug;162(4):455-64. doi: 10.1111/bjh.12413. Epub 2013 Jun 15. PMID: 23772687.
17. Matte A, Cappellini MD, Iolascon A, Enrica F, De Franceschi L. Emerging drugs in randomized controlled trials for sickle cell disease: are we on the brink of a new era in research and treatment? Expert Opin Investig Drugs. 2020 Jan;29(1):23-31. doi: 10.1080/13543784.2020.1703947. Epub 2019 Dec 25. PMID: 31847604.
18. Adams-Graves P, Bronte-Jordan L. Recent treatment guidelines for managing adult patients with sickle cell disease: challenges in access to care, social issues, and adherence. Expert Rev Hematol. 2016 Jun;9(6):541-52. doi: 10.1080/17474086.2016.1180242. Epub 2016 May 24. PMID: 27098013.
19. Jayavaradhan R, Malik P. Genetic Therapies for Sickle Cell Disease. Pediatr Clin North Am. 2018 Jun;65(3):465-480. doi: 10.1016/j.pcl.2018.01.008. PMID: 29803277.

20. Leonard A, Tisdale JF. Gene therapy for sickle cell disease. Hematology Am Soc Hematol Educ Program. 2023 Dec 8;2023(1):542-547. doi: 10.1182/hematology.2023000487. PMID: 38066927; PMCID: PMC10727030.
21. Carrara J, Habibi A, Benachi A, Cheminet G. Sickle cell disease and pregnancy. Presse Med. 2023 Dec;52(4):104203. doi: 10.1016/j.lpm.2023.104203. Epub 2023 Nov 7. PMID: 37939877.
22. Lovett PB, Sule HP, Lopez BL. Sickle Cell Disease in the Emergency Department. Hematol Oncol Clin North Am. 2017 Dec;31(6):1061-1079. doi: 10.1016/j.hoc.2017.08.009. PMID: 29078924.
23. Esrick EB, Bauer DE. Genetic therapies for sickle cell disease. Semin Hematol. 2018 Apr;55(2):76-86. doi: 10.1053/j.seminhematol.2018.04.014. Epub 2018 May 7. PMID: 29958563.
24. Osunkwo I, Andemariam B, Minniti CP, Inusa BPD, El Rassi F, Francis-Gibson B, Nero A, Trimnell C, Abboud MR, Arlet JB, Colombatti R, de Montalembert M, Jain S, Jastaniah W, Nur E, Pita M, DeBonnett L, Ramscar N, Bailey T, Rajkovic-Hooley O, James J. Impact of sickle cell disease on patients' daily lives, symptoms reported, and disease management strategies: Results from the international Sickle Cell World Assessment Survey (SWAY). Am J Hematol. 2021 Apr 1;96(4):404-417. doi: 10.1002/ajh.26063. Epub 2021 Feb 25. PMID: 33264445; PMCID: PMC8248107.
25. Inusa BP, Atoyebi W, Andemariam B, Hourani JN, Omert L. Global burden of transfusion in sickle cell disease. Transfus Apher Sci. 2023 Oct;62(5):103764. doi: 10.1016/j.transci.2023.103764. Epub 2023 Jul 17. PMID: 37541800.
26. Piel FB, Rees DC, DeBaun MR, Nnodu O, Ranque B, Thompson AA, Ware RE, Abboud MR, Abraham A, Ambrose EE, Andemariam B, Colah R, Colombatti R, Conran N, Costa FF, Cronin RM, de Montalembert M, Elion J, Esrick E, Greenway AL, Idris IM, Issom DZ, Jain D, Jordan LC, Kaplan ZS, King AA, Lloyd-Puryear M, Oppong SA, Sharma A, Sung L, Tshilolo L, Wilkie DJ, Ohene-Frempong K. Defining global strategies to improve outcomes in sickle cell disease: a Lancet Haematology Commission. Lancet Haematol. 2023 Aug;10(8):e633-e686. doi: 10.1016/S2352-3026(23)00096-0. Epub 2023 Jul 11. PMID: 37451304.
27. Inusa BPD, Stewart CE, Mathurin-Charles S, Porter J, Hsu LL, Atoyebi W, De Montalembert M, Diaku-Akinwumi I, Akinola NO, Andemariam B, Abboud MR, Treadwell M. Paediatric to adult transition care for patients with sickle cell disease: a global perspective. Lancet Haematol. 2020 Apr;7(4):e329-e341. doi: 10.1016/S2352-3026(20)30036-3. PMID: 32220342.
28. Chawla A, Sprinz PG, Welch J, Heeney M, Usmani N, Pashankar F, Kavanagh P. Weight status of children with sickle cell disease. Pediatrics. 2013 Apr;131(4):e1168-73. doi: 10.1542/peds.2012-2225. Epub 2013 Mar 4. PMID: 23460681.
29. Lee C. Should Intravenous Fluids Be Administered During Hospitalizations for Sickle-Cell Disease? NEJM Evid. 2022 Oct;1(10):EVIDtt2200159. doi: 10.1056/EVIDtt2200159. Epub 2022 Sep 27. PMID: 38319834.
30. Osunkwo I, James J, El-Rassi F, Nero A, Minniti CP, Trimnell C, Paulose J, Ramscar N, Bailey T, Rajkovic-Hooley O, Andemariam B. Burden of disease, treatment utilization, and the impact on education and employment in patients with sickle cell disease: A comparative analysis of high- and low- to middle-income countries for the

international Sickle Cell World Assessment Survey. Am J Hematol. 2022 Aug;97(8):1055-1064. doi: 10.1002/ajh.26576. Epub 2022 Jun 20. PMID: 35472249; PMCID: PMC9540420.

31. Antwi-Boasiako C, Andemariam B, Colombatti R, Asare EV, Strunk C, Piccone CM, Manwani D, Boruchov D, Farooq F, Urbonya R, Wilson S, Boatemaa GD, Perrotta S, Sainati L, Rivers A, Rao S, Zempsky W, Ekem I, Sey F, Segbefia C, Inusa B, Tartaglione I, Campbell AD. A study of the geographic distribution and associated risk factors of leg ulcers within an international cohort of sickle cell disease patients: the CASiRe group analysis. Ann Hematol. 2020 Sep;99(9):2073-2079. doi: 10.1007/s00277-020-04057-8. Epub 2020 May 6. PMID: 32377816; PMCID: PMC7430152.
32. Zhang J, Jones SM, Lykotrafitis G, Andemariam B. Valsartan impedes epinephrine-induced ICAM-4 activation on normal, sickle cell trait and sickle cell disease red blood cells. PLoS One. 2019 May 13;14(5):e0216467. doi: 10.1371/journal.pone.0216467. PMID: 31083675; PMCID: PMC6513067.
33. Zempsky WT, Loiselle KA, McKay K, Lee BH, Hagstrom JN, Schechter NL. Do children with sickle cell disease receive disparate care for pain in the emergency department? J Emerg Med. 2010 Nov;39(5):691-5. doi: 10.1016/j.jemermed.2009.06.003. Epub 2009 Aug 22. PMID: 19703740.
34. Ross AS, Graeme-Cook F, Cosimi AB, Chung RT. Combined liver and kidney transplantation in a patient with sickle cell disease. Transplantation. 2002 Feb 27;73(4):605-8. doi: 10.1097/00007890-200202270-00022. PMID: 11889439.
35. Zhang J, Abiraman K, Jones SM, Lykotrafitis G, Andemariam B. Regulation of Active ICAM-4 on Normal and Sickle Cell Disease RBCs via AKAPs Is Revealed by AFM. Biophys J. 2017 Jan 10;112(1):143-152. doi: 10.1016/j.bpj.2016.11.3204. PMID: 28076805; PMCID: PMC5232864.
36. Molokie R, Lavelle D, Gowhari M, Pacini M, Krauz L, Hassan J, Ibanez V, Ruiz MA, Ng KP, Woost P, Radivoyevitch T, Pacelli D, Fada S, Rump M, Hsieh M, Tisdale JF, Jacobberger J, Phelps M, Engel JD, Saraf S, Hsu LL, Gordeuk V, DeSimone J, Saunthararajah Y. Oral tetrahydrouridine and decitabine for non-cytotoxic epigenetic gene regulation in sickle cell disease: A randomized phase 1 study. PLoS Med. 2017 Sep 7;14(9):e1002382. doi: 10.1371/journal.pmed.1002382. PMID: 28880867; PMCID: PMC5589090.
37. McMahon L, Tamary H, Askin M, Adams-Graves P, Eberhardt RT, Sutton M, Wright EC, Castaneda SA, Faller DV, Perrine SP. A randomized phase II trial of Arginine Butyrate with standard local therapy in refractory sickle cell leg ulcers. Br J Haematol. 2010 Dec;151(5):516-24. doi: 10.1111/j.1365-2141.2010.08395.x. Epub 2010 Oct 19. PMID: 20955402.
38. Martí-Carvajal AJ, Knight-Madden JM, Martinez-Zapata MJ. Interventions for treating leg ulcers in people with sickle cell disease. Cochrane Database Syst Rev. 2012 Nov 14;11:CD008394. doi: 10.1002/14651858.CD008394.pub2. Update in: Cochrane Database Syst Rev. 2014;12:CD008394. PMID: 23152256.
39. Starlard-Davenport A, Gu Q, Pace BS. Targeting Genetic Modifiers of HBG Gene Expression in Sickle Cell Disease: The miRNA Option. Mol Diagn Ther. 2022

Sep;26(5):497-509. doi: 10.1007/s40291-022-00589-z. Epub 2022 May 12. PMID: 35553407; PMCID: PMC9098152.

40. Sher GD, Olivieri NF. Rapid healing of chronic leg ulcers during arginine butyrate therapy in patients with sickle cell disease and thalassemia. Blood. 1994 Oct 1;84(7):2378-80. PMID: 7919358.
41. Perrine SP, Faller DV. Butyrate-induced reactivation of the fetal globin genes: a molecular treatment for the beta-hemoglobinopathies. Experientia. 1993 Feb 15;49(2):133-7. doi: 10.1007/BF01989417. PMID: 7680003.
42. Dover GJ, Brusilow S, Charache S. Induction of fetal hemoglobin production in subjects with sickle cell anemia by oral sodium phenylbutyrate. Blood. 1994 Jul 1;84(1):339-43. PMID: 7517215.
43. Reid ME, El Beshlawy A, Inati A, Kutlar A, Abboud MR, Haynes J Jr, Ward R, Sharon B, Taher AT, Smith W, Manwani D, Ghalie RG. A double-blind, placebo-controlled phase II study of the efficacy and safety of 2,2-dimethylbutyrate (HQK-1001), an oral fetal globin inducer, in sickle cell disease. Am J Hematol. 2014 Jul;89(7):709-13. doi: 10.1002/ajh.23725. Epub 2014 Apr 15. PMID: 24677033.