Sickle Cell Disease

Presented By
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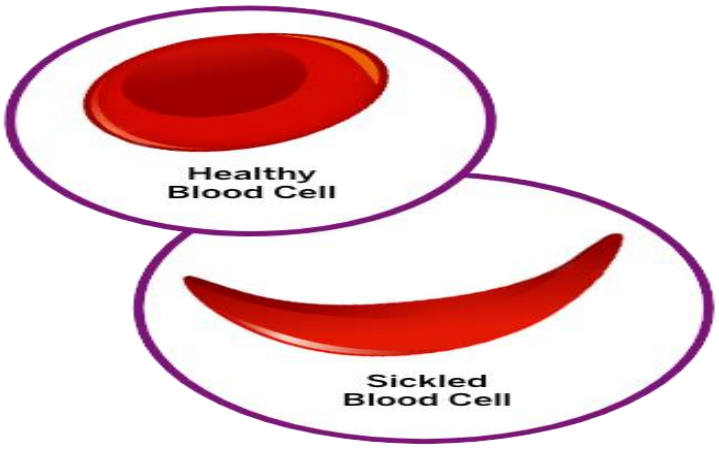
Introduction

Sickle cell disease (SCD) is a red blood cell disorder where hemoglobin, a protein that carries oxygen, is abnormal and causes red blood cells to be C-shaped instead of circular. In a healthy individual, red blood cells are round, and hemoglobin will carry oxygen throughout the body. The “sickled cells” die early, cause a shortage of red blood cells, and lead to blood flow blockage. SCD is genetically inherited when a child gains 2 genes (one from each parent) that code for abnormal hemoglobin. The disease can cause pain for the individual and other life-threatening complications.

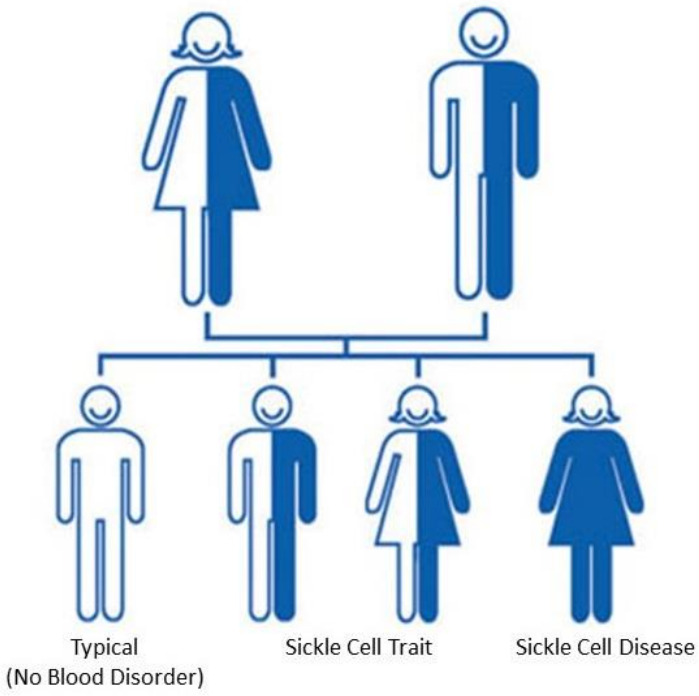


Types of Sickle Cell Disease

Sickle cell syndromes can be split into sickle cell trait (SCT) and sickle cell disease. SCT occurs when there is a heterozygous inheritance of one normal β-globin gene producing hemoglobin A (HbA) and one sickle gene producing sickle cell hemoglobin (HbS). People who have SCT inherit a hemoglobin “S” gene from one parent and a normal gene that codes for hemoglobin “A” from the other parent. People with SCT usually present without symptoms; However, in rare cases, individuals with SCT may develop health problems. Problems may occur when there are other stresses on the body, such as strenuous exercise or dehydration. Individuals who have SCT can pass the abnormal hemoglobin “S” gene on to their children and are referred to as carriers.

- If both parents have SCT, there is a 50% chance that any child of theirs also will have SCT, if the child inherits the sickle cell gene from one of the parents. The children may not have symptoms of SCD, but they can pass SCT on to their children.

- If both parents have SCT, there is a 25% chance that any child of theirs will have SCD. There is the same 25% chance that the child will not have SCD or SCT.



Reference www.CDC.gov

Knowledge Test

What is the chance of a child having SCT if both parents have SCT?

a. 100%
b. 75%
c. 50%
d. 25%

SCD can be from heterozygous or homozygous inheritance.

Homozygous HbS (HbSS)

Individuals who have this form of SCD inherit two genes, one from each parent, that code for hemoglobin "S." Hemoglobin S is an abnormal form of hemoglobin that causes the red cells to become rigid and sickle shaped. This type is commonly referred to as *sickle cell anemia* and is usually the most severe form of the disease.

HbSC

Heterozygous inheritance of HbS can result in sickle cell hemoglobin C (HbSC). Individuals who have this form of SCD inherit a hemoglobin "S" gene from one parent and a gene for a different type of abnormal hemoglobin called "C" from the other parent. This is usually a milder form of SCD.

HbS beta thalassemia

Individuals who have this form of SCD inherit a hemoglobin "S" gene from one parent and a beta thalassemia gene from the other parent. Beta thalassemia is another type of abnormal hemoglobin. The two types of beta thalassemia are: "zero" (HbS beta^0) and "plus" (HbS beta$^+$). Those with HbS beta^0-thalassemia usually have a severe form of SCD. Individuals with HbS beta$^+$-thalassemia tend to have a milder form of SCD, sickle cell β-thalassemia (HbS β+thal and HbS β0thal), and other rare phenotypes.

Knowledge Test

Which form of sickle cell is the most severe?

a. HbS beta^0-thalassemia
b. HbS beta$^+$-thalassemia
c. sickle cell hemoglobin C
d. sickle cell anemia

Epidemiology/Etiology

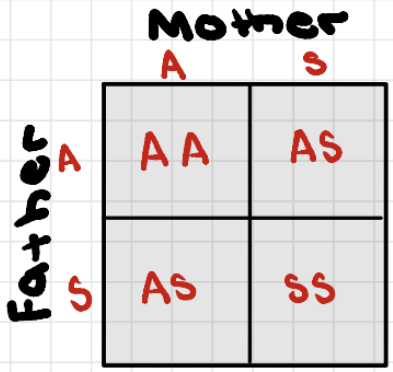
Millions of people worldwide are affected by SCD. This disease most commonly affects African-Americans and Hispanics. In the United States, SCD affects almost 100,000 Americans, occurs in about 1 out of every 365 Black or African-American births, occurs in about 1 out of every 16,300 Hispanic-American births, and about 1 in 13 Black or African-American babies are born with SCT. In areas of the world where malaria is common, it is seen that SCD is prevalent as well. Individuals with SCT are more likely to survive an acute malaria illness because the red blood cells that are carrying the abnormal sickle hemoglobin prevent the normal growth and development of *Plasmodium falciparum* within red blood cells.

Normal hemoglobin (HbA) is composed of two α-chains and two β-chains(α2β2). Sickle cell hemoglobin (HbS) develops when glutamic acid is substituted for valine as the sixth amino acid in the β-polypeptide chain. Hemoglobin C (HbSC) is another abnormal hemoglobin that results when glutamic acid is substituted for lysine as the sixth amino acid in the β-chain. The most common form of SCD, sickle cell anemia or homozygous HbSS, occurs when an individual inherits both β-globin alleles that code for HbS from both the mother and the father. The figures below show the different probabilities of inheritance with each pregnancy with parents that have HbA, SCT, HbSS.

Knowledge Test

Sickle cell disease most commonly affects:

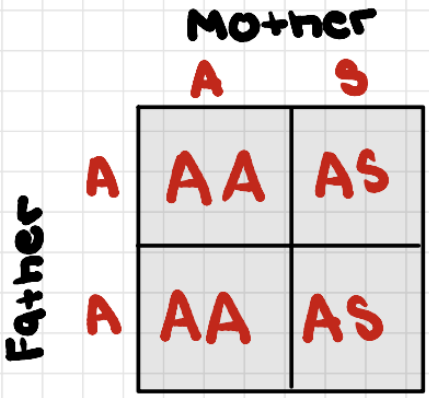
a. African Americans
b. Asians
c. Hispanics
d. A and C



Sickle cell gene for both parents with sickle cell trait

- 25% normal (AA)
- 50% SCT (AS)
- 25% SCA (SS)

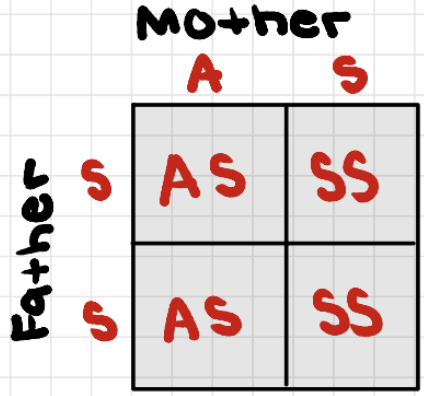
(A, normal hemoglobin; S, sickle cell hemoglobin)



Sickle cell gene for one parent with sickle cell trait and one parent with no sickle cell gene

- 50% normal (AA)
- 50% SCT (AS)

(A, normal hemoglobin; S, sickle cell hemoglobin)



Sickle cell gene for one parent with sickle cell trait and one parent with sickle cell anemia

- 50% SCT (AS)
- 50% SCA (SS)

(A, normal hemoglobin; S, sickle cell hemoglobin)

Risk Factors

SCD is most common in groups that include individuals with ancestors from sub-Saharan Africa, India, Saudi Arabia, Mediterranean countries and in the Hispanic population.

Diagnosis

In the United States, all babies are tested for the disease during routine newborn screening at the hospital. Tests may also be performed while the baby is in the womb by testing a sample of amniotic fluid or tissue from the placenta. If an infant's screening results test positive, a second test is to be performed before 2 months of age to confirm the diagnosis. An early diagnosis is very important as sickle cell symptoms can begin at four months of age. Children may be at an increased risk of infections and other health problems.

Clinical Presentation

Individuals with SCT are usually asymptomatic unless they are under extreme conditions. This can cause red blood cell sickling and result in painless hematuria (blood in the urine) and dehydration. Most individuals with SCD will experience vaso-occlusive pain episodes, swelling of the hands and feet, frequent infections, and visual problems. Common clinical signs associated with HbSS include fever, arthralgia, abdominal pain, hematuria, enlargement of the spleen, liver, and heart. Complications of SCD include stroke, acute chest syndrome, splenic sequestration, blindness, priapism, deep vein thrombosis to name a few.

Complications of Sickle Cell Disease

Sickle cell disease may lead to various acute and chronic complications. Patients with SCD often experience ‘sickle cell crisis’ which are several independent acute conditions which last from hours to days, but some of the most common ones are below.

Acute Chest Syndrome

Acute Chest Syndrome (ACS) is a pulmonary infiltrate that is associated with fever, chest pain, and/or respiratory problems. It is the second most common cause of hospitalization and the leading cause of death in individuals with SCD. ACS is caused by pulmonary vascular occlusions and infections. Fat emboli from bone marrow, VTE, or adhesion of RBCs can be the cause of vascular occlusions. Pathogens like *M. pneumonia, C. pneumoniae, Staph. Aureus, and Strep. Pneumoniae* can cause infections that result in ACS. Risk factors and recurrence for ACS include young age, low HbF, high leukocytes, asthma, smoking history, or a recent stroke. Although ACS is more common in children, it is more severe in adult cases. It is important to recognize ACS swiftly and manage it accordingly.

Aplastic Crisis

Aplastic crisis consists of acute worsening of the patient's baseline anemia. Patients have a pale appearance, rapid heart rate and fatigue. The crisis occurs from parvovirus B19, which directly affects red blood cell production by destroying them. Parvovirus B19 infections inhibits red blood cell production for two to three days. As a result, patients will experience significant decrease in reticulocyte counts and hemoglobin. Most patients will require a blood transfusion to manage the crisis.

Avascular Necrosis

Sickled cells can block blood flow in blood vessels that provide blood to bones in the body. When the bone does not get enough oxygen, the bone tissue can die and lead to a complication known as avascular necrosis (AVN). When there is not enough blood reaching the bone, the joint can narrow, and the bone can collapse. AVN can affect single joints or multiple joints at the same time. The most common location of an AVN occurring is the hip joint, but it can also occur in other areas of the body. AVN can occur without any symptoms, but as AVN progresses, it can result in mild to severe joint pain in the affected area.

Dactylitis

Dactylitis is painful swelling in the hands and feet and usually the first sign/symptom of SCD in infants and toddlers. The swelling, often accompanied with a fever, is caused by the sickled cells getting stuck in the blood vessels and blocking blood flow in the small bones of the hands and feet.

Pain

Pain is the most common complication of SCD, and the main reason that patients with SCD visit the emergency department. Sickled cells traveling through small blood vessels can get stuck and block blood flow throughout the body, causing pain. A pain crisis (vaso-occlusive episode or VOE) can begin suddenly, range from mild to severe, and can last for any length of time. Pain can occur in any part of the body, but commonly occurs in the hands, feet, chest, and back.

Pain that comes suddenly and lasts for a short time is referred to as acute pain. Chronic pain is daily, on-going pain lasting more than 6 months. People with SCD can experience acute pain, chronic pain, and/or both.

Priapism

Priapism is defined as painful and persistent erection of the penis. Sickling of RBCs within the sinusoids of the corpora cavernosa and stasis is the usual cause of priapism. Priapism lasting more than 4 hours should be considered an emergency. Thirty percent of boys/men with SCD will experience at least one episode of priapism in their lifetime, first episode commonly occurring in childhood.

Splenic Sequestration

Splenic sequestration is the sudden enlargement of the spleen due to sequestration of sickle RBCs in the splenic parenchyma. Signs and symptoms include sudden fatigue, dyspnea, distended abdomen, rapid decrease in Hb and Hct with increased reticulocyte, splenomegaly, abdominal pain, hypotension, shock, and vomiting. The most common symptom is pain on the left side of the abdomen. This is more commonly seen in infants and children because their spleens are functioning and

intact. Parents of a child with SCD can learn how to feel and measure the size of their child's spleen and seek medical attention if the spleen is enlarged. Sequestration crises are considered an emergency as patients may die within one to two hours due to circulatory failure if not treated.

Stroke

A stroke occurs when sickled cells become trapped in a blood vessel and block blood flow to the brain. As a result, the brain does not receive the oxygen it needs to properly function. About 10% of children with SCD will have a symptomatic stroke. A stroke is more common among people with sickle cell anemia. It is recommended that children with sickle cell anemia get a special type of exam called a Transcranial Doppler ultrasound (TCD) every year starting at 2 years old until they are 16 years old. A TCD can identify children who are at high risk of a stroke.

Some signs or symptoms of a stroke include:

- Sudden numbness or weakness, especially on one side of the body
- Sudden confusion or difficulty understanding speech
- Sudden trouble seeing in one or both eyes
- Sudden trouble walking, dizziness, loss of balance, or lack of coordination
- Sudden severe headaches with no known cause

A silent stroke is a stroke that occurs without any signs or symptoms. Patients who experience a silent stroke may not be aware of their stroke and can only be detected using a magnetic resonance imaging (MRI). A silent stroke can lead to brain injury.

Venous Thromboembolism

Patients with SCD are at a higher risk for developing VTE due to impaired blood flow, endothelial dysfunction, and hypercoagulable state. Restricted blood flow to organs lead to ischemia, pain, necrosis, and organ damage. Frequent hospitalization, decreased mobility, and central venous access are additional risks of VTE. Elevated D-dimer is seen in about 90% of SCD patients, therefore D-dimer tests cannot be used in

these patients to detect deep vein thrombosis. It is essential to be aware of VTE when managing SCD patients presenting with SCA vaso-occlusive episodes.

Knowledge Test

Sickled cells can block blood flow in blood vessels that provide blood to bones in the body. When the bone does not get enough oxygen, the bone tissue can die and lead to which complication?

a. Venous thromboembolism

b. Stroke

c. Priapism

d. Avascular necrosis

Therapeutic Management

In SCD, the goal of treatment is to improve quality of life, reduce hospitalizations and mortality. Prevention strategies should include lifestyle modifications as well as screenings and interventions to prevent SCD complications.

Lifestyle Modifications

A few simple steps that patients with SCD can do to help prevent and reduce the occurrence of pain crises including the following:

- Avoid high altitudes
- Avoid being too hot or too cold.
- Avoid places or situations with exposure to low oxygen levels
- Drink plenty of water

Simple steps that patients with SCD can do to prevent harmful infections include the following:

- Wash hands often. Washing hands with soap and clean water many times each day is one of the best ways patients, their family members, and other caregivers can help prevent an infection.
- Prepare food safely. Bacteria can be especially harmful to children with SCD.

- Avoid those who are sick

Prevention Strategies for SCD Complications

Prevention of Infections

- Vaccines can protect against harmful infections. It is important that children with SCD receive their scheduled childhood vaccines. It is highly recommended for children and adults to receive the flu vaccine each year, as well as the pneumococcal vaccine and any others recommended by their physician.
- Penicillin greatly reduces the risk of infections in people with HbSS and has been shown to be even more effective when it started early. It is important for young children with HbSS to take penicillin (or other antibiotic prescribed by physician) daily until at least age 5 years to decrease the risk of infection. Daily penicillin is usually not prescribed for children with other types of SCD unless the severity of the disease is similar to that of HbSS, such as HbS beta^{0}-thalassemia.

Prevention of Vision Loss

- Yearly visits to an eye doctor to check for damage to the retina are important to avoid vision loss. If possible, it is ideal to see an eye doctor who specializes in diseases of the retina.
- If the retina is damaged by excessive blood vessel growth, laser treatment often can prevent further vision loss.

Prevention of Stroke

- Children who are at risk for stroke can be identified using a special type of exam called transcranial Doppler ultrasound (TCD). If the child is found to have an abnormal TCD, a physician may recommend frequent blood transfusions to help prevent a stroke.
- Patients who have frequent blood transfusions are usually monitored closely due to serious side effects. Transfusions can lead to a condition called iron overload,

in which too much iron builds up in the body. Iron overload can cause life-threatening damage to the liver, heart, and other organs. It is important for SCD patients receiving regular blood transfusions to also receive treatment to reduce excess iron in the body. This type of treatment is known as iron chelation therapy.

Prevention of Severe Anemia

- Blood transfusions may be used to treat severe anemia. A sudden worsening of anemia resulting from infection or enlargement of the spleen is a common reason for a transfusion.
- As with stroke prevention, frequent blood transfusions can cause iron overload, and iron chelation therapy may be needed to reduce excess iron in the body.

Therapeutic Management

Penicillin

Penicillin is recommended as prophylaxis against invasive pneumococcal infections in children with SCD HbSS or HbSβ0-thal until at least 5 years of age, even if they have received PCV13 or PPSV23 immunization. Penicillin V potassium should be administered at 125 mg orally twice daily until 3 years of age, then 250 mg twice daily until 5 years of age. Erythromycin 20 mg/kg/day may be used instead if patient is allergic to penicillin.

Hydroxyurea

Studies have shown that patients with higher levels of HbF are associated with decreased red blood cell sickling and adhesion, and a lower severity of SCD. Hydroxyurea stimulates Hbf synthesis and will increase the number of reticulocytes that have HbF and the intracellular HbF. Hydroxyurea can be used in individuals who are 2 years of age or older with recurrent moderate-to-severe pain crises to reduce the

frequency of the pain and their need for blood transfusions. Bone marrow suppression that results in neutropenia, thrombocytopenia, and decreased reticulocyte count is the most common adverse drug reaction of hydroxyurea. The reactions usually recover within 2 weeks of therapy discontinuation. In adults, the starting dose is 15 mg/kg/day rounded to the nearest 500 mg as a single daily dose or a dose of 5 to 10 mg/kg/day if the patient has chronic kidney disease. In children, it is recommended to start with a dose of 20 mg/kg/day and can be increased by 5 mg/kg/day up to 35 mg/kg/day in 8-week intervals if the patient has not shown adverse drug reactions and blood counts are stable. It takes about 3-6 months to see improvements. Patients on hydroxyurea should be closely monitored for toxicity, blood counts should be taken every 2 weeks during dose titration and every 4-8 weeks after.

L-Glutamine

Sickled red blood cells can be subjected to oxidative damage, leading to vaso-occlusion and hemolysis. Glutamine is an important amino acid that is a precursor of nicotinamide adenine dinucleotide (NAD+) synthesis. The uptake of glutamine is increased by sickled red blood cells to produce NAD+. Children with SCD have a low glutamine level, and an increase in NAD+ can restore balance in the oxidative stressed red blood cells. L-glutamine is indicated for patients 5 years and older to reduce the acute complications of SCD. L-glutamine is available in 5 gram packets and should be combined with 8 ounces (240ml) of liquid or 4-6 ounces (110-170g) of food. Dosing is based on weight: 5 g twice a week for patients less than 30 kg, 10 g twice a day for patients 30 to 65 kg, and 15 g twice a day for patients greater than 65 kg. Constipation, abdominal pain and nausea are the most common adverse drug reactions of L-glutamine.

Crizanlizumab

Vascular obstruction in SCD occurs when erythrocytes and leukocytes adhere to the endothelium and increase the severity of the disease. Crizanlizumab is a monoclonal antibody that is FDA indicated to reduce the frequency of vaso-occlusion. Patients 16 years and older may receive this drug at a dose of 5mg/kg once every 2

weeks for the first two doses and then 5 mg/kg once every 4 weeks via intravenous (IV) route of administration. The most common adverse reactions are chest pain, vomiting, pruritus, diarrhea, and arthralgia.

Voxelotor

The process of which erythrocytes sickle and unsickle is due to HbS polymerization and will cause damage to the cell membrane resulting in hemolysis. Hemolysis will cause SCD complications like anemia, pulmonary hypertension, priapism, chronic kidney disease, and leg ulcers. Voxelotor will inhibit the polymerization of HbS. It is FDA approved to be given in patients 4 years and older at a dose of 1,500 mg taken once daily by mouth. The dose may be adjusted to 1,000 mg once daily in severe hepatic impairment (Child Pugh Class C). Strong CYP3A4 inhibitors should be avoided while taking this drug.

Iron Chelation

Many patients receive chronic blood transfusions for their SCD which can cause iron overload, leading to damage of the liver, heart, and other organs. Chelation therapy is used to remove excess iron from the body to avoid damage. Deferasirox at 20 mg/kg/day and Defriprone at 75 mg/kg/day given in three divided doses are oral chelating drugs that are most commonly used. Common adverse drug reactions include rashes and gastrointestinal symptoms, and more serious reactions include neutropenia and agranulocytosis.

Pain Management

The primary clinical feature of sickle cell is pain. Sickle cell patients experience excruciating pain that is characterized as unrelenting discomfort that can occur in any part of the body. Painful episodes are often abrupt and will disrupt daily life activities. Home comfort measures may include heating blankets, massages, pain medications. When pain crises occur, clinical management may include the following:

- Intravenous fluids
- Pain-reducing medicine (opioids)
- Hospitalization for severe pain crises

Bone Marrow/Stem Cell Transplant

The only cure for patients with SCD is Allogeneic Hematopoietic Stem Cell Transplantation (Allogeneic HSCT). The overall and disease-free survival rate for children and young adults with human leukocyte antigen (HLA)-matched sibling donors has been reported to be 95-98% and 87-92% respectively. Patients with severe SCD (HbSS and HbSβ0) prior to onset of SCD symptoms are the most ideal candidates for this transplantation. In addition, SCD patients with a history that includes stroke, recurrent ACS, recurrent pain, pulmonary hypertension, and sickle neuropathy can be considered for transplantation. Screening for an HLA-matched donor is recommended to be done during the first year of life. Transplantation has a mortality risk of 5-10% and graft rejection of about 10%. Risks must be considered carefully. Other risks associated with transplantation include secondary malignancies. Cyclosporine and Tacrolimus should be used with caution as it may cause increased risk of reversible encephalopathy syndrome.

Another source for transplantation can be hematopoietic stem cells from the umbilical cord blood. Umbilical cord blood stem cells are hematopoietic stem cells that are recovered from the blood of the umbilical cord and placenta after birth. Umbilical cord blood is rich in cells that express the CD34 molecule, a surface protein that identifies cells as stem cells. Umbilical cord blood stem cells are proving to be a promising alternative for several reasons. First, these cells are readily available and have a low cost of acquisition. Umbilical cords are plentiful and are often discarded as a byproduct of birth. Second, these cells seem not to trigger significant immune responses, which allows for more flexible matching. Since these cells have not yet fully developed, it is presumed that they are equipped with an immature immune response and are not yet programmed to attack specific antigens, which prevents rejection by the body. Third, there is less chance of graft vs. host infection (GVHI), which is very important.

Gene Therapy

On December 8, 2023, The Food and Drug Administration approved two new gene therapies for sickle cell disease. The two milestone treatments, Casgevy and Lyfgenia, may be used for patients 12 years and older with the severe form of the disease. The first gene therapy is made by Vertex Pharmaceutical and CRISPR Therapeutics. The second gene therapy is made by Bluebird Bio.

Casgevy, is the first FDA-approved treatment to use a novel type genome editing technology, CRISPR/Cas9, signaling an innovative advancement in the field of gene therapy. Patients' hematopoietic (blood) stem cells are modified by genome editing using CRISPR/Cas9 technology. CRISPR/Cas9 can be directed to cut DNA in targeted areas, enabling the ability to accurately edit (remove, add, or replace) DNA where it was cut. The modified blood stem cells are transplanted back into the patient where they engraft (attach and multiply) within the bone marrow and increase the production of fetal hemoglobin (HbF), a type of hemoglobin that facilitates oxygen delivery. Increased levels of HbF prevent the sickling of red blood cells in patients with SCD.

Lyfgenia is a cell-based gene therapy and uses a lentiviral vector (gene delivery vehicle) for genetic modification. Lyfgenia is recommended for SCD patients who have a history of vaso-occlusive events. With Lyfgenia, the patient's blood stem cells are genetically modified to produce HbA^{T87Q}, a gene-therapy derived hemoglobin that functions similarly to hemoglobin A, which is the normal adult hemoglobin produced in persons not affected by sickle cell disease. Red blood cells containing HbA^{T87Q} have a lower risk of sickling and occluding blood flow. These modified stem cells are then transplanted to the patient.

Both products are made from the patients' own blood stem cells, which are modified, and returned as a one-time, single-dose infusion as part of a hematopoietic (blood) stem cell transplant. Prior to treatment, a patients' own stem cells are collected, and then the patient must undergo myeloablative conditioning (high-dose chemotherapy), a process that removes cells from the bone marrow so they can be replaced with the modified cells in Casgevy and Lyfgenia. Patients who received Casgevy or Lyfgenia will be followed in a long-term study to evaluate each product's safety and effectiveness.

Casgevy Supporting Data

The safety and effectiveness of Casgevy were evaluated in an ongoing single-arm, multi-center trial in adult and adolescent patients with SCD. Patients had a history of at least two protocol-defined severe VOCs during each of the two years prior to screening. The primary efficacy outcome was freedom from severe vaso-occlusive (VOC) episodes for at least 12 consecutive months during the 24-month follow-up period. A total of 44 patients were treated with Casgevy. Of the 31 patients with sufficient follow-up time to be evaluated, 29 (93.5%) achieved the outcome. All treated patients achieved successful engraftment without patients experiencing graft failure or graft rejection.

The most common side effects were low levels of platelets and white blood cells, mouth sores, nausea, musculoskeletal pain, abdominal pain, vomiting, febrile neutropenia (fever and low white blood cell count), headache and itching.

Lyfgenia Supporting Data

The safety and effectiveness of Lyfgenia is based on the analysis of data from a single-arm, 24-month multicenter study in patients with SCD and history of VOEs between the ages of 12- and 50- years old. Effectiveness was evaluated based on complete resolution of VOEs (VOE-CR) between 6 and 18 months after infusion with Lyfgenia. Twenty-eight (88%) of 32 patients achieved VOE-CR during the time period.

The most common side effects included stomatitis (mouth sores of the lips, mouth, and throat), low levels of platelets, white blood cells, and red blood cells, and febrile neutropenia, consistent with chemotherapy and underlying disease.

Hematologic malignancy (blood cancer) has occurred in patients treated with Lyfgenia. A black box warning is included in the label for Lyfgenia with information regarding this risk. Patients receiving this product should have lifelong monitoring for these malignancies.

Conclusion

Sickle cell disease is an inherited disorder that affects many organs, causes serious complications, and can lead to death. As healthcare providers, pharmacists can educate patients about the disease, share preventive strategies, as well as help each patient by managing overall health for optimal care. Pain is a hallmark feature and pain medications should never be withheld for SCD patients. Pharmacists may also encourage and empower their patients to be advocates for the debilitating and life-threatening disease. The addition of gene therapy allows more targeted and effective treatments which may lead to better quality of life.

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