CONNECTICUT MEDICAL ASSISTANCE PROGRAM
DEPARTMENT OF SOCIAL SERVICES
&
ACENTRA HEALTH
QUARTERLY NEWSLETTER

The Contours of Sickle Cell Disease (SCD) and Configuration of Treatment Options

Sickle Cell Disease (SCD) is a group of red blood cell disorders that affect the formation of hemoglobin (Hb), the protein in red blood cells (RBCs) that carries oxygen throughout the body. HbA is normal adult hemoglobin, whereas HbS is an abnormal form of hemoglobin that causes RBCs to become stiff, brittle, sticky, and deformed (sickle shape) causing a disruption in normal blood flow through small blood vessels resulting in vaso-occlusion.[1] HbA is converted to HbS via a single point mutation in the beta-globulin chain of hemoglobin and is theorized to originate as a protective mechanism against malaria.[1,2] In addition to HbS, other mutated forms of hemoglobin can include HbC, Hb-beta thalassemia, HbD, HbE, and HbO.[3]

SCD is autosomal recessive, meaning both parents must provide their offspring with a copy of the mutated Hb gene for disease to develop.[1] HbSS is the most common and most severe form of SCD and occurs when both parents provide a copy of the HbS gene to their offspring. Other genotypes of SCD include HbSC, HbS-beta thalassemia, HbSD, HbSE, etc.[3] Sickle Cell Trait (SCT) occurs when one parent supplies a normal HbA gene and the other parent supplies an HbS gene, resulting in HbAS. Patients with SCT are carriers of the HbS gene which can be passed to offspring but does not typically present as overt disease.[3]

SCD is more common in certain ethnic groups including African, Hispanic, Mediterranean, Middle Eastern, and South Asian .[1,4,5,6] 25 million patients worldwide and 100,000 patients in the U.S. have SCD, with more than half of U.S. patients covered under Medicaid.[7] Disproportionately affecting Americans of African descent, 1 in 365 Black infants are born with SCD and about 1 in 13 will carry SCT.[3] During the previous year, 814 (533 adult and 281 pediatric patients) Connecticut Medical Assistance Program patients received a diagnosis of SCD (HbSS).

The extent of HbS polymerization determines the severity of disease.[2] Complications are a direct result of sickling and aggregation of RBCs which leads to anemia, ischemia, vaso-occlusive crises (VOCs), and vaso-occlusive events (VOEs). Symptoms can include dizziness, fatigue, inflammation, acute and chronic pain, risk of infection, ocular complications, priapism, stroke, cognitive dysfunction, osteonecrosis, and organ damage (Table 1).[2,4] Children with SCD often experience growth delays and are prone to higher rates of stroke compared to adults.[2] 10% of children with severe SCD have documented strokes and 20-35% have experienced silent stroke.[2] Anemia is a hallmark of disease and is attributed to the short half-life of sickled RBCs. Organ damage such as kidney failure, splenic sequestration, gall bladder disease, and Acute Chest Syndrome (ACS) can occur. ACS presents as chest pain, fever, cough, and shortness of breath stemming from SCD induced infection or pulmonary embolism. ACS is the most common cause of hospitalization and is responsible for 25% of SCD deaths.[1,2] Health complications and pain crises contribute to anxiety and depression, absence from school and work, increased hospitalizations, negative quality of life, and a reduced life expectancy.[4] SCD patients in the U.S. live about 20 years less than the average life expectancy and 50% will die within the 5th decade of life.[2] In low income countries, 90% of children diagnosed with SCD do not survive into adulthood.[2]

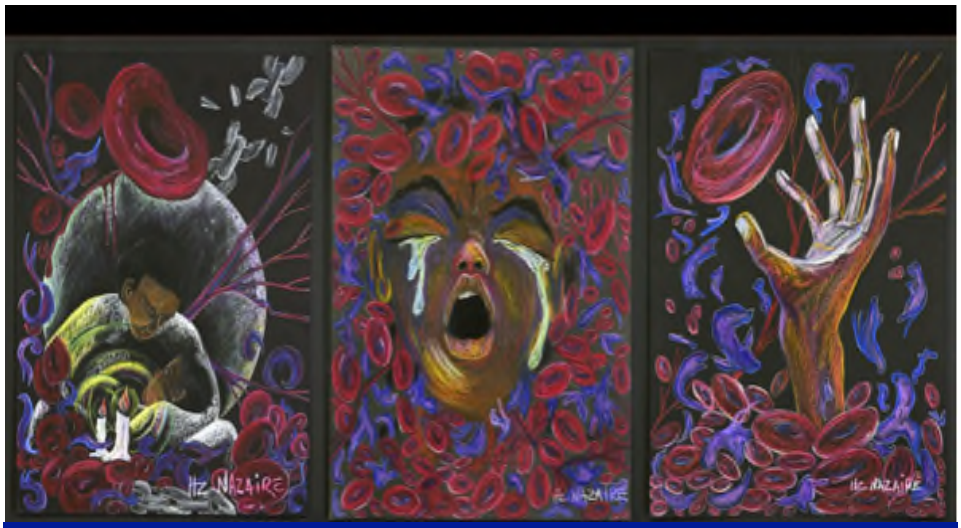

Image 1. During 2016 Bridgeport, Connecticut artist Hertz Nazaire used his paintings (above) to raise awareness about SCD, a disease Nazaire himself struggled with until 2021 when he succumbed to complications of the illness.[37,38,39]

Preventing genetic disorders is difficult, however, clinical laboratory and genetic testing can be used to screen for and diagnose SCD and SCT. All newborns in the US are screened for SCD.[1] If a diagnosis of SCD is made, prevention of symptoms becomes the mainstay of treatment. Barriers to screening, prevention, and treatment include systemic racism, gaps and inequality in healthcare, and lack of funding for research and development of this disease.[8] Addressing barriers while educating and informing patients and families regarding preventative measures is key.

Supportive care is an important component of preventing SCD VOCs and VOEs. Blood trans-

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fusions provide healthy RBCs with normal hemoglobin to patients, diluting the sickled cells which in turn promotes better oxygen delivery, decreased occlusion, and helps to prevents stroke. Approximately 90% of patients with SCD will receive at least 1 transfusion in their lifetime.[9] Adequate hydration, both oral and intravenous, aids in proper blood flow and prevents sickling. Medications such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and opioids help to manage acute and chronic pain, and antibiotics can be used to prevent infections. Screening patients to identify those who are at an increased risk of stroke is also an important preventative measure.[10]

Hydroxyurea is first line therapy for treatment of SCD. Originally approved in the 1960s as an antineoplastic medication, hydroxyurea gained FDA approval in the late 1980s to reduce pain events associated with SCD in adults, and more recently for use in children with SCD as young as 2.[11,12,13] It is thought to work by increasing the production of fetal hemoglobin (HbF), the main form of hemoglobin produced during fetal development and into the first 6 months of life.[13] Normally, production of HbF is suppressed after 6 months of age and is replaced by production of HbA, or HbS in SCD. Hydroxyurea works by turning production of HbF back on which increases the number of RBCs carrying HbF that do not sickle. Outcomes of treatment include reduction of anemia, VOCs, VOEs, and pain events associated with SCD.[1] Hydroxyurea is given orally once per day, with a max dose of 35 mg/kg/day, with recommended reduced dosing in renal impairment. Two black box warnings exist for this medication: myelosuppression and risk of malignancy. Common side effects include nausea and vomiting, neutropenia, and increased liver function tests (LFTs). Monitoring recommendations include LFTs and complete blood counts (CBCs). Prior to beginning therapy, patients and families should be made aware of the potential risk of infertility which may be irreversible. Hydroxyurea should not be used during pregnancy or breastfeeding.[9] Despite its efficacy, hydroxyurea is commonly underused.[14] The average cost of therapy for an adult weighing 70 kg is $23 per month.[15]

More recently, three new medications have received approval for use in SCD.

Endari (L-glutamine) was approved in 2017 to reduce acute complications of SCD in adults and pediatric patients 5 years of age and older.[16] The amino acid l-glutamine is a building block of nicotinamide adenine dinucleotide (NAD+) and ultimately NADH (NAD+hydrogen) which acts as an antioxidant of RBCs and is thought to reduce sickling and lysis.[9] In clinical trials, l-glutamine reduced VOCs by 25% and hospitalizations by 33%.[17] L-glutamine is supplied as an oral powder to be mixed with soft foods or dissolved in liquid and dosed twice per day based on weight. Common side effects include constipation, nausea, headache, and abdominal pain.[16] The average cost of therapy for an adult weighing 70 kg is $3,600 per month.[18]

Adakveo (crizanlizumab), a monoclonal antibody P-selectin inhibitor, was approved in 2019 to decrease VOEs in patients 16 years of age and older with SCD.[19] Administered as a once monthly IV infusion, crizanlizumab was shown to decrease the occurrence of pain crises, VOCs, hospitalizations, and enhance patient quality of life.[9,19] Monitoring for infusion related reactions is recommended and crizanlizumab should not be used during pregnancy or breastfeeding. Common side effects include nausea, arthralgia, abdominal and back pain.[19] The average cost of therapy for an adult weighing 70 kg is approximately $10,000 per month.[20]

Oxbryta (voxelotor), a hemoglobin S polymerization inhibitor, was approved in 2019 for the treatment of SCD in patients 4 years of age and older.[21] In clinical trials voxelotor was shown to increase hemoglobin levels by 1g/dL in approximately 50% of patients which contributed to a reduction in anemia, VOCs, and VOEs.[9,22] Administered orally as a tablet or suspension, dosing for pediatric patients less than 12 years of age is weight based, dosing for patients 12 years of age and older is 1,500 mg per day as a single daily dose. There are no contraindications and common adverse events include headache, nausea, abdominal pain, and diarrhea.[21] The average cost of therapy for an adult weighing 70 kg is approximately 12,000 per month.[23]

Hydroxyurea remains first line therapy for reduction of pain events associated with SCD, however, newer agents l-glutamine, crizanlizumab, and voxelotor are also effective at reducing SCD related complications and can be used concurrently with hydroxyurea or in place of hydroxyurea in patients who are intolerable.[14] While these therapies treat symptoms associated with SCD, they do not provide a cure.

Hematopoietic stem cell transplantation (HSCT), or bone marrow transplant (BMT), is a curative procedure where defective stems cells are destroyed and replaced by healthy stem cells to cure disease.[24] HSCT was first used to cure SCD in 1984 and is indicated in patients with severe disease who have experienced stroke, hospitalization, ACS, and in patients with 3 or more VOEs per year.[9] Since the 1980s, approximately 1,200 patients have undergone HSCT in the U.S. for SCD resulting in > 90% cure rate.[25] The procedure is more commonly used in children and adolescents due to a higher rate of mortality in adults.[24,26] Risks include graft versus host disease (GVHD), infection, organ injury, and increased risk of mortality. Patients who undergo HSCT must receive ablative chemotherapy to remove defective stem cells prior to infusion of the replacement stem cells. Risks associated with chemotherapy include infertility, toxicity, and chemotherapy related malignancies. Once chemotherapy is complete healthy stems cells from a donor (allogenic) or a patient's own genetically modified cells (autologous) are infused.[24] Human

Table 1: Sickle Cell Disease Complications and Manifestations[2]

Complications	Manifestations
Acute and chronic pain	Opioid addiction, negative quality of life
Splenic sequestration	Anemia, abdominal pain, infection
Acute Chest Syndrome (ACS)	Fever, pain, shortness of breath, pulmonary embolism
Stroke	Weakness, paralysis, cognitive and memory dysfunction
Retinopathy	Vision loss and blindness
Priapism	Irreversible erectile dysfunction, Peyronie's disease
Chronic Kidney Disease	Anemia, albuminuria, compromised elimination of certain medications, end stage renal disease
Skin Ulcers	Chronic wounds, thrombosis, gangrene, amputation
Osteonecrosis	Limping, fractures, arthritis

Leukocyte Antigen (HLA) HSCT is the most common form of allogenic HSCT and uses a matched donor, typically a sibling of the patient. However, only about 15% of siblings match as a donor.[2] Haploidentical (Haplo) HSCT is a less common type of allogenic HSCT that does not require a matched donor, however, is associated with a higher risk of rejection by the patient. Autologous HSCT for SCD is a new and groundbreaking treatment/ procedure/cure. This process uses a patient's own genetically modified stem cell to cure disease. Autologous HSCT does not require a matched donor and avoids rejection by the patient since the donated stem cells are the patient's own cells.[26]

Two new gene therapies using this technique were recently approved by the FDA in December 2023, Casgevy and Lyfgenia. The process is difficult and time-consuming, spanning over 8-12 months. Both therapies require about 2 months of outpatient blood transfusions, followed by apheresis, a procedure similar to dialysis where a patient's stem cells are extracted. Once collected, the stem cells are sent to a processing facility where they are genetically modified, which can take approximately 4 -6 months.[4,27,28] Patients will then receive treatment with chemotherapy to kill their defective stem cells. [4,27,28] After chemotherapy is complete, the modified stem cells are infused back into the patient followed by a month-long hospital stay to ensure efficacy. [27,28]

Casgevy (exagamglogene autotemcel (exacel)) modifies stem cells using CRISPER/Cas9 genome editing technology.[27] This treatment excises the defective portion of the beta globulin gene that produce HbS and also excises the portion of the gene that suppresses production of HbF. The modified stem cells are infused back into the patient's body where they engraft in the bone marrow, multiply, and produce HbF - ultimately resulting in healthy and regular shaped RBCs that no longer sickle.[6,8,27,29] Made by Vertex Pharmaceuticals and CRISPER Therapeutics, this gene therapy is approved for use in patients 12 years of age and older and is intended to be a one-time treatment. The safety and efficacy of Casgevy was studied in a single arm, multi-center trial in adults and adolescents with SCD and at least 2 prior severe VOCs in the previous 2 years.[27] 94%, 29 of the 31 patients followed up on, met the primary end point of no pain episodes for at least one year during a two-year follow-up.[27] The most common side effects were neutropenia, thrombocytopenia, nausea and vomiting, stomatitis, and muscle pain.[27] There were no reported instances of rejection of therapy.[4,6]

Lyfgenia (lovotibeglogene autotemcel (lovocel)) works by inserting copies of an altered beta globulin gene via lentivirus viral envelope into patient stem cells.[28] The modified stem cells are infused back into the patient where they engraft in the bone marrow to multiply and produce HbA^{T87Q}. HbA^{T87Q} is a genetically modified form of adult hemoglobin, similar to endogenous HbA, that promotes healthy/ regular shaped RBCs that no longer sickle.[8,28,29] Made by Bluebird Bio, this gene therapy is approved for use in patients 12 years of age and older with a history of VOEs and is intended to be a one-time treatment.[28] The safety and efficacy of Lyfgenia was studied in a single arm, multi-center trial in adults and adolescents with SCD and history of at least 4 VOCs in the previous 2 years.[28] 88%, 28 of the 32 patients followed up on, met the primary end point of complete resolution of VOEs between 6-18 months after treatment.[28] The most common side effects were neutropenia, thrombocytopenia, and stomatitis.[28] Two patients developed hematologic malignancy prompting a black box warning regarding the risk with a recommendation of lifetime monitoring for blood cancer in patients who receive treatment.[4,6,28] Determining if patients have any risk factors for the development of hematological malignancy prior to initiating treatment may be beneficial.

While Casgevy and Lyfgenia show promising results, questions remain such as where this technology fits into therapy, will there be any off-target effects from genetic modification, and what the long-term safety and efficacy outcomes are. Financial impact of these agents is also a major concern. The mean cost per year of SCD in the United States is $10k for a pediatric patient and $34k for an adult patient.[30] The cost of gene therapy for SCD can be upwards of $2-3 million per patient and precedence has not yet been set as to how these therapies will be covered.[4,31] These concerns are not unique to SCD as healthcare evolves and more Cell and Gene Therapy (CGT) products come to market.

In response to these concerns, The Centers for Medicare and Medicaid Services (CMS) has created the CGT Access Model, using SCD as their initial focus.[7] Under this voluntary model, states and manufacturers of CGT products enter outcomes-based agreements (OBAs) that allow CMS to negotiate collectively on behalf of the participating Medicaid programs for better pricing and rebates, increasing overall buying power. It is important to note that states will be responsible for the cost of CGT but will receive discounted prices negotiated by CMS, which are tied to specific outcomes. This model will expand access to CGT products for Medicaid patients and improve outcomes for rare and severe diseases. These new therapies may also reduce overall healthcare costs by curing diseases that are costly to treat.

While CGT may provide an opportunity to cure SCD, it is not for everyone. As with many diseases, the decision to treat and selection of therapeutic options should be made between the provider and patient. Consideration of risks and benefits, overall health of the patient, and severity of disease are important factors. Patients with severe SCD may opt for CGT, weighing the benefit of treatment more heavily over the associated risks of therapy. Patients with mild SCD may opt for traditional pharmacotherapy, choosing to live with the disease rather than enduring the difficult process of stem cell transplant. The cost and coverage of therapeutic options adds another variable to the equation. Regardless of treatment selection, SCD remains a difficult to treat disease with devastating outcomes. Affected patients experience race-based health disparities, poor outcomes, and shortened life expectancy.[11] Managing this disease with prevention and screening tools, conventional and novel therapeutics, and the newly minted CMS CGT Access Model ensures advancement in the treatment of SCD.

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