New Horizons in the Management of Sickle Cell Disease (SCD):

What Managed Care Needs to Know About Novel Therapies in an Evolving Treatment Paradigm

A CME/CNE Approved Activity

JOURNAL of MANAGED CARE MEDICINE

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Instructions for CME/CNE: Activity is valid from April 1, 2019 to March 31, 2021.

A score of 70% must be achieved on the post-test to receive continuing education credits.
Read the monograph, answer the post-test, complete the evaluation form, and send the completed post-test and evaluation to:

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Learning Objectives:
1. Discuss the pathophysiology, physical manifestations, economic burden, clinical course, and impact on patient quality of life of sickle cell disease (SCD).
2. Examine the safety and efficacy of emerging therapies that manage acute vaso-occlusive pain events in SCD.
3. Assess approaches currently utilized by third-party payers to manage costs associated with the care of patients with SCD.
4. Explore strategies to manage treatment-related adverse events of emerging therapies in the management of SCD.
5. Discuss the managed care considerations of novel therapies by exploring where these agents may fit into current SCD management paradigm.

Faculty Disclosure:
Dr. Owens has no relevant financial relationships to disclose.

All material has been peer reviewed for bias.

Planning Committee Disclosure
Bill Williams, MD; Jacqueline Cole, RN, CPHQ, CMCN; and Jeremy Williams have no relevant financial relationships to disclose.

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Post-Test Questions

1. Which of the following groups account for 90% of sickle cell disease cases in U.S.?
   a. Hispanics **b.** Indian immigrants
   c. African-Americans **d.** Central American immigrants
2. Sickle cell disease (SCD) is caused by mutations in the gene, which encodes for the _____.
   a. Hemoglobin subunit β **b.** Hemoglobin subunit α
   c. Beta thalassemia **d.** Alpha thalassemia
3. When both parents carry a sickle cell gene (sickle cell trait), their child has a _____ chance of having sickle cell disease.
   a. 15% **b.** 25% **c.** 35% **d.** 50%
4. Which of the following leads to hemolysis in sickle cell disease?
   a. Puncture of cell membrane by sickle hemoglobin polymers
   b. Impaired potassium and sodium channels
   c. Autoimmune reaction to sickle hemoglobin
   d. Repeated cycles of sickling
5. Which of the following accounts for the majority of chronic vascular damage in sickle cell disease?
   a. Red cell hemolysis **b.** Vaso-occlusion
   c. Autoimmune inflammatrion **d.** Endothelial dysfunction
6. Which type of organism are those with sickle cell disease and functional asplenia most likely to be infected by?
   a. Fungi **b.** Enterococcus
   c. Streptococcus pneumoniae **d.** Hepatitis C
7. Which of the following is NOT a demonstrated benefit of hydroxyurea?
   a. Reduced rate of complications
   b. Reduced frequency of acute sickle cell pain and acute chest syndrome
   c. Reduced need for blood transfusions
   d. Reduced need for hospitalizations
8. Which of the following is the proposed mechanism of action of L-glutamine?
   a. Increased production of nitric acid
   b. Decreased selectin levels
   c. Antioxidant
   d. Increased production of fetal hemoglobin
9. Which of the following is an accurate statement about the investigational anti-P-selectin antibody, crizanlizumab?
   a. It lowered rates of vaso-occlusive crisis compared to placebo.
   b. Approximately 20% more patients had no vaso-occlusive crisis on crizanlizumab compared to placebo.
   c. It appears to be associated with a low rate of adverse effects.
   d. Hydroxyurea should be discontinued when it is started
10. Which of the following is being investigated for the management of acute vaso-occlusive crisis?
    a. Olinciguat **b.** Voxelotor
    c. Rivipansel **d.** L-glutamine infusion

Activity Evaluation and Improvement Process

Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor

1. Based on the content presented, I am better able to:

   Discuss the pathophysiology, physical manifestations, economic burden, clinical course, and impact on patient quality of life of sickle cell disease (SCD).

   4 3 2 1

   Examine the safety and efficacy of emerging therapies that manage acute vaso-occlusive pain events in SCD.

   4 3 2 1

   Assess approaches currently utilized by third-party payers to manage costs associated with the care of patients with SCD.

   4 3 2 1

   Explore strategies to manage treatment-related adverse events of emerging therapies in the management of SCD.

   4 3 2 1

   Discuss the managed care considerations of novel therapies by exploring where these agents may fit into current SCD management paradigm.

   4 3 2 1

2. The activity and presenters were free of bias.

   4 3 2 1

3. The activity was applicable to my position.

   4 3 2 1

4. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

5. Do you plan to change management strategies or patient care in your organization or practice based on the content presented?

   ☐ Yes ☐ No

6. If yes, what changes do you plan to implement in management strategies or patient care in your organization or practice?

   _____

   _____

   _____

   _____

7. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

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Sickle Cell Disease Monograph

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New Horizons in the Management of Sickle Cell Disease (SCD):

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Gary M. Owens, MD

Introduction

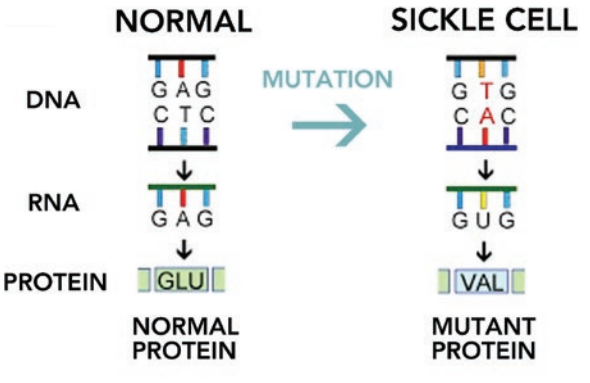
Sickle cell disease (SCD) was first described by a Chicago physician named James Herrick in 1910. Sickle cell disease describes multiple inherited hemoglobinopathies, including sickle cell anemia, sickle-hemoglobin C disease, and beta-thalassemia.

Epidemiology

Roughly two million Americans are carriers of the sickle cell trait, approximately 100,000 have SCD, and 72,000 suffer from sickle cell anemia.[1,2] Individuals of African, Mediterranean, Middle Eastern, Indian, Caribbean, and South and Central American ancestry have the highest rates for the sickle cell trait.[3] In the United States (U.S.), African Americans comprise more than 90 percent of the population with SCD. SCD occurs among one out of every 365 African American births and approximately one out of every 16,300 Hispanic American births.[4] Worldwide, sub-Saharan Africa accounts for approximately 75 percent of births with SCD.[5]

In 1973, the average life expectancy of a patient with SCD was 14 years. Secondary to advances in ongoing disease-management, therapy, and a comprehensive care model, the average lifespan of a patient with sickle cell extended to 50 years by the year 2000.[4]

Exhibit 1: Genetics of Sickle Cell Disease



Genetics of SCD

Sickle cell disease is caused by mutations in the HBB gene, which encodes for the hemoglobin subunit β. SCD is the result of a point mutation on chromosome 11, resulting in a single protein substitution in the hemoglobin molecule which makes the resultant molecule less soluble and prone to deforming (Exhibit 1).

Sickle cell trait is passed between generations in an autosomal recessive process. Those individuals who are heterozygous for this trait are considered carriers and normally will not show any clinical manifestations of the disease. Those that are homozygous for the trait have sickle cell anemia. When both parents carry a sickle cell gene (sickle cell trait), but are not sick themselves, their child has a 25 percent chance of having sickle cell disease (Exhibit 2). When one parent has SCD and the other carries only one of the abnormal genes, such as hemoglobin S, their child has a 50 percent chance of having SCD.

The various types of SCD that are caused by different mutations are shown in Exhibit 3.[6,7] In addition to sickle cell hemoglobin (HgS), there are other abnormal forms of hemoglobin which can be inherited, including HgC, HgD, HgE, and HgO. Only HgC is relatively common in the U.S. People can also inherit a gene which leads to low production of hemoglobin (beta thalassemia). SCD results when someone inherits two genes for abnormal hemoglobin, whether it is two sickle genes, or one sickle gene and beta thalassemia, or one sickle gene and one HgC gene.

Pathophysiology

Hemoglobin is the main ingredient in red blood cells, helping them carry oxygen from the lungs to other parts of the body. Normal hemoglobin (HbA) is composed of two alpha and two beta globin chains. Sickle hemoglobin (HbS) varies from HbA by a single amino acid mutation substitution between valine and glutamic acid in the sixth position on the beta globin chains, resulting in changes in structure and function (Exhibit 4).

Exhibit 2: Autosomal Recessive Pattern of Inheritance

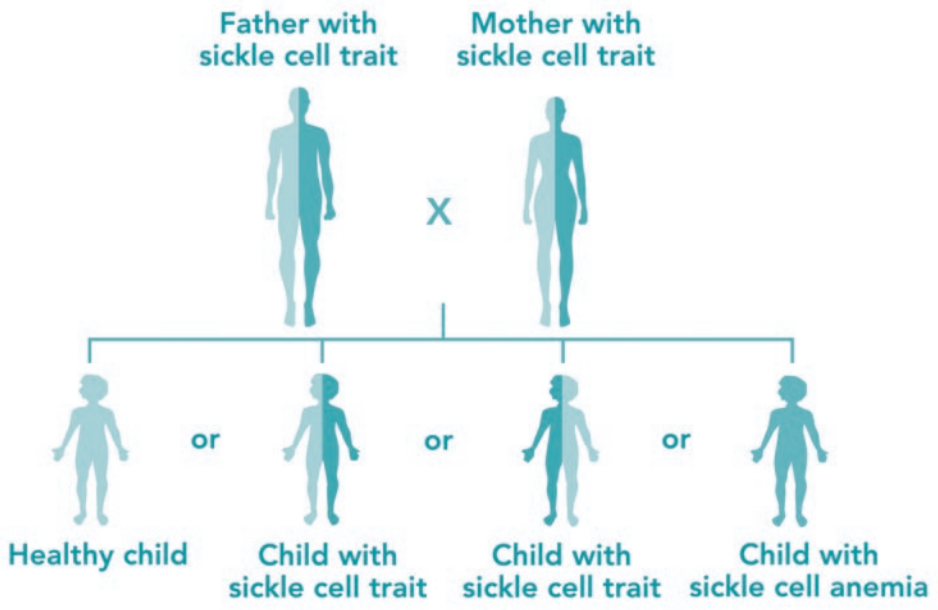


Exhibit 3: Types of Sickle Cell Disease[6,7]

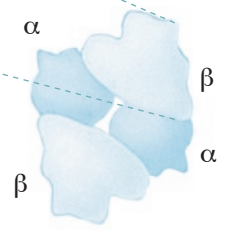
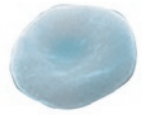
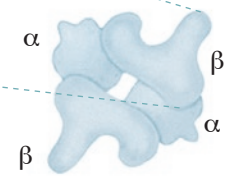
Type	Name	Genetics	Severity
HbSS	Sickle cell anemia	One sickle cell gene (*S*) from each parent	Typically the most severe
HbSC	Sickle cell hemoglobin C disease	Sickle cell gene (*S*) from one parent and an abnormal Hb (C) from the other parent.	Milder form
HbS β-thalassemia	β-thalassemia anemia	Sickle cell gene (*S*) from one parent and one gene for β-thalassemia from the other parent.	Severe form
HbS β-thalassemia			Milder form
HbSD, HbSE, HbSO	Other sickle disease	Sickle cell gene (*S*) from one parent and one abnormal Hb (*D, E, or O*) from the other parent.	Varies
HbAS	Sickle cell trait	One normal gene (*A*) from one parent and one sickle cell gene (*S*) from the other parent	*

*Sickle cell trait is not considered a sickle cell disease but those with trait can rarely develop vaso-occlusive crisis under extreme environmental circumstances

Erythrocytes undergo cycles of oxygenation and de-oxygenation in circulation during which HbS molecules repeatedly form hard polymers, which damage the membrane of the erythrocyte. The red blood cells (RBCs) becomes elongated, rigid, and curved on the ends, resembling a sickle shape.[6] Abnormalities within the red blood cells are not limited to the hemoglobin – intracellular potassium is rapidly decreased, abnormalities exist in cellular membrane phosphorylation, and calcium pump abnormalities are also seen. These abnormalities can lead to dehydration within the cell and increased membrane calcium levels, leaving the cell in an irreversible sickle shape.[8]

Healthy RBCs are round and move smoothly through blood vessels, whereas sickle cells are overly adhesive, abnormally shaped, and do not move smoothly. In SCD, two interlinked mechanisms

Exhibit 4:Pathophysiology of Sickle Cell Disease

	Beta Subunit	Quaternary Structure	Function	Red Blood Cell Shape
Normal hemoglobin		Normal hemoglobin 	Molecules do not associate with one another; each carries oxygen.	
Sickle-cell hemoglobin	Exposed hydrophobic region 	Sickle-cell hemoglobin 	Molecules crystallize into a fiber; capacity to carry oxygen is reduced.	

contribute to the clinical picture. Repeated cycles of red blood cell sickling leads to hemolysis, anemia and a multicellular adhesion process involves red blood cells, white blood cells, and platelets that aggregate and adhere to endothelial cells of the vessel wall.[9, 10] As a result, this process promotes vaso-occlusion that leads to chronic vascular damage, which begins early in childhood. The chronic nature of SCD is the result of a self-perpetuating cycle of inflammation, cell activation, multicellular adhesion, vaso-occlusion, and tissue damage.

Consequences of Sickle Cell Disease

Hemolysis and episodic vaso-occlusive crises are the classic manifestations of SCD. The sickle red blood cell has a decreased lifespan of four to 20 days because of hemolysis, which results in a chronic hemolytic anemia. Vaso-occlusion leads to chronic organ damage (Exhibit 5).

Silent, ongoing vaso-occlusion driving the chronic nature of the disease is caused by multicellular adhesion among endothelial cells, red blood cells, white blood cells, and platelets. This multicellular adhesion occurs as a result of endothelial damage and inflammation, which cause chronic upregulation of specific adhesion mediators, including selectins.[11,12] Ongoing vaso-occlusion can culminate in vaso-occlusive crises (VOCs, sickle cell crisis) – the clinical hallmark of sickle cell disease – which can be extremely painful events that typically result in medical intervention.[13,14] Pain with crisis results from tissue ischemia and most often occurs in the arms, legs, chest, and abdomen. Vaso-occlusive crises result from interactions between the endothelium, plasma factors, leukocytes, and sickle cells, resulting in tissue hypoxia, tissue death, and pain. Vaso-occlusive crises are associated with decreased quality of life and increased risk of organ damage and death.[15-16] By age 50 nearly half of patients with SCA are diagnosed with at least one chronic organ failure syndrome.[17]

Most people with sickle cell trait (SCT) do not have any symptoms of SCD, although, in rare cases, people with SCT might experience complications of SCD, such as pain crises with extreme changes in environment.[18] Environmental conditions that can provoke crisis include increased pressure in the

Exhibit 5: Consequences of Sickle Cell Disease	
System	**Complication**
Cardiovascular	Cardiomegaly
Genitourinary	Renal dysfunction, priapism
Hematologic	Chronic hemolytic anemia
Hepatobiliary	Cholelithiasis, hepatic fibrosis
Immune	Splenic sequestration, Functional asplenia
Neurologic	Ischemic and hemorrhagic stroke; Chronic pain
Ocular	Proliferative retinopathy; Rentinal detachment
Other	Delayed puberty and reduced growth
Pulmonary	Acute chest syndrome; Pulmonary hypertension
Skeletal	Dactylitis, aseptic necorsis
Skin	Chronic leg ulcers

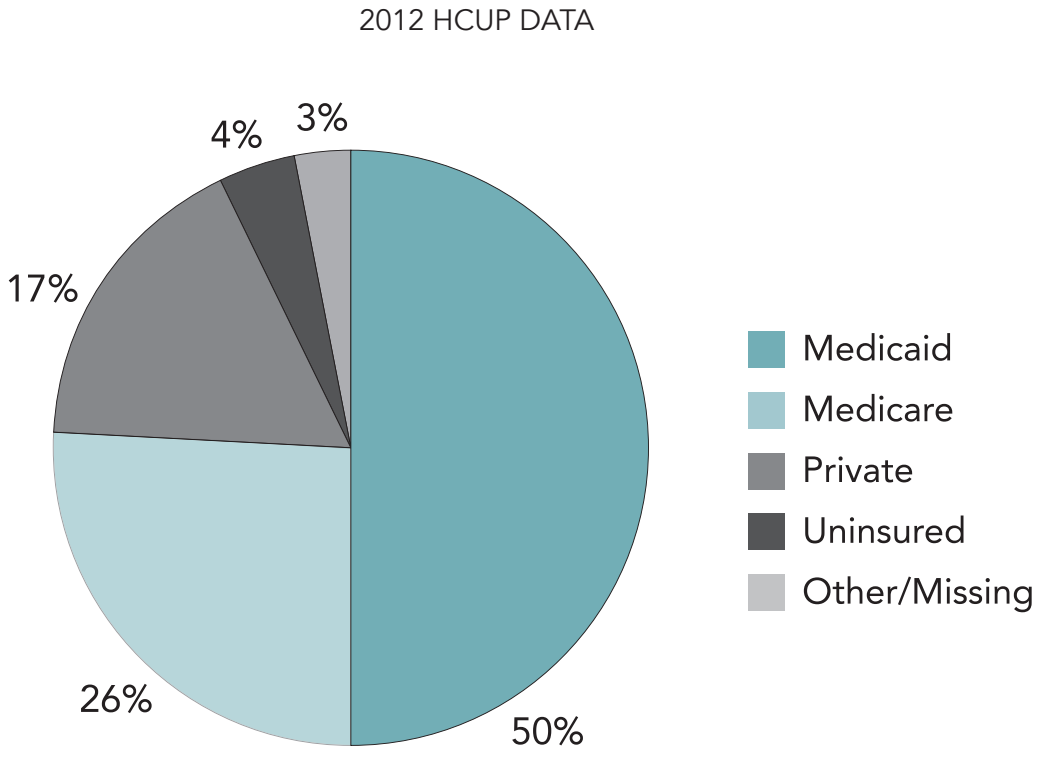
atmosphere (e.g., scuba diving), low oxygen levels in the air (e.g., mountain climbing, extreme exercise, or training for an athletic competition), dehydration, high altitudes (e.g., flying, mountain climbing, or visiting a city at a high altitude), and dramatic changes in temperature (e.g., vasoconstriction with extreme cold, dehydration from fever).

Some patients have sickle cell with hereditary persistence of fetal hemoglobin (S-HPFH). The persistent fetal hemoglobin reduces the severity of the consequences of the sickle cell disease, thereby, reducing the degree of cellular deformity, or sickling.

Economic Costs

Sickle cell disease is costly to treat. The annual cost of medical care in the U.S. for those with SCD exceeds $1.1 billion. Public payers bear a disproportionate share of the costs (Exhibit 6). Emergency department (ED) visits and inpatient hospital stays account for the majority of these costs. The most common SCD complications associated with ED visits are VOCs with pain, infection, and pneumonia. More than 230,000 ED visits occur annually related to SCD.[20] The annual hospitalization rate for SCD in those less than 18 years old is approximately 30,000 and

Exhibit 6: Payer Mix for Sickle Cell Disease[19]



for those over 18 is approximately 80, 000.[21] In one analysis of Florida Medicaid data, 80.5 percent of the SCD-related costs were from hospitalization.[22]

Diagnosis

Although the disease does not present clinically until four or five months after birth, because of the large percentage of fetal hemoglobin (HbF) present, the HbS is present in the blood stream at birth. Umbilical cord blood samples can undergo electrophoresis for diagnosis of SCD. Currently, all 50 states require SCD screening for all newborns. For those who were not diagnosed as children, SCD and SCT can be diagnosed with hemoglobin electrophoresis, high performance liquid chromatography (HPLC), or DNA testing.

Treatment

Relatively few interventions for SCD have a strong evidence base. Those that do include penicillin prophylaxis in children, primary stroke prevention with the use of transcranial Doppler screening and blood transfusion, regular blood transfusions to prevent the progression of silent cerebral infarction, hydroxyurea to prevent acute pain and acute chest syndrome as well as primary stroke, and L-glutamine to reduce the frequency of acute pain and hospitalizations.[16,23,24]

A common complication of SCD is abnormal function of the spleen. Tissue hypoxia in the spleen is so common that by age 8 the spleen shrinks in size secondary to scarring (autosplenectomy, asplenia).[25] This results in an increased risk of infection particularly from encapsulated organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenza*. Infection prophylaxis with penicillin V is recommended for children up to 5 years of age. Vaccinations, particularly those for encapsulated organisms, are also recommended for those with SCD. The current vaccination guidelines from the Centers for Disease Control and Prevention (CDC) should be consulted for specific recommendations for children, adolescents, and adults (www.cdc.gov/vaccines/schedules/index.html).

Acute pain secondary to VOCs can be difficult to manage. People with SCD are not affected equally by pain. Only 20 percent will have frequent pain episodes. Mild to moderate pain is often treated at home with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen and heating pads. If pain continues, a narcotic may be needed. The narcotic may be used alone or with NSAIDs or acetaminophen. Severe pain may require hospitalization and treatment with narcotic pain relievers and fluids to prevent dehydration, which worsens sickling. Drug dependency or addiction is rare when pain medications are used as prescribed. Pain management has improved with the advances of day centers for pain crises and a better understanding of the disease process.

The use of hydroxyurea is a mainstay in the overall management of individuals with SCD. It is used to help reduce cell sickling, as well as many of the major complications of SCD, with a primary mechanism of action of fetal hemoglobin induction. Treatment benefits include reduced frequency of acute sickle cell pain and acute chest syndrome, reduced need for blood transfusions and hospitalizations, and possibly improved survival.[26] Hydroxyurea is a once-daily oral medication. Adverse effects of hydroxyurea include neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, and anorexia. This agent is also teratogenic, carcinogenic and increases risk for skin cancer and leukemia.

L-glutamine, an amino acid precursor of the antioxidant glutathione, is an oral medication approved in 2017 to reduce acute complications in children greater than 5 years of age and adults with SCD. The mechanism of action is unknown, but it is thought to involve an antioxidant effect. Oral therapy with pharmaceutical-grade L-glutamine increases the proportion of the reduced form of nicotinamide adenine dinucleotides in sickle cell erythrocytes, which probably reduces oxidative stress. The FDA-approved formulation is an oral powder (Endari®), which costs approximately $40,000 annually. In the trial used for FDA approval, patients in the L-glutamine group had significantly fewer pain crises than those in the placebo group ($P = 0.005$), with a median of 3.0 in the L-glutamine group and 4.0 in the placebo group over the 48-week trial.[27] Fewer hospitalizations occurred in the L-glutamine group than in the placebo group ($P = 0.005$), with a median of 2.0 in the L-glutamine group and 3.0 in the placebo group. There was also a decrease in cumulative in-hospital days (6.5 versus 11.0) and an increase in the median time to first crisis (84 versus 54 days). Two-thirds of the patients in both trial groups received concomitant hydroxyurea. The adverse effects of L-glutamine are relatively benign and were similar to the placebo. L-glutamine is not indicated for patients with renal failure, uncontrolled liver disease, pregnancy, lactation, or recent transfusions because these conditions were associated with poor outcomes in earlier studies and were exclusionary criteria in the current trials. Hydroxyurea, if currently being used, should be continued with the L-glutamine. Further experience will be required to identify patients likely to benefit from L-glutamine. Decreasing the rate of VOCs with L-glutamine may be cost effective; however, no data

on this have been published.

Transfusion therapy is another option in the treatment of patients with SCA. Indications for transfusion therapy include acute chest syndrome, heart failure, multiorgan failure syndrome, and stroke.[28] Transfusions do have risks, most commonly iron overload, infection, transfusion reactions, and alloimmunization.

Stem cell transplant is the only FDA-approved therapy that is a potential cure for SCD. Even though bone marrow transplant is a cure for SCD, its use is limited because of the problems in finding a matched donor, and the complications associated with transplant. Stem cell transplant will likely be superseded by gene therapy and gene editing approaches.

Treatment Pipeline

Several agents are in Phase II and III studies for treatment of SCD which are attempting to target underlying pathophysiologic defects better than current therapies. Each of these agents has at least one designation from the FDA allowing for expedited approval (orphan drug, rare pediatric, breakthrough therapy, or fast track).

Crizanlizumab

Crizanlizumab is an anti-P-selectin antibody being developed as a potential treatment of sickle cell anemia. It is a monoclonal antibody that is given by monthly infusion, and it binds P-selectin, a protein that is found on the surface of endothelial cells and platelets. P-selectin is one of the major drivers of the vaso-occlusive process. The FDA granted crizanlizumab breakthrough therapy designation for the prevention of VOCs in patients of all genotypes with SCD in January 2019. In a Phase II clinical trial of crizanlizumab in 198 patients with sickle cell anemia and a history of two to 10 pain crises in the previous year, patients received either a low dose of crizanlizumab (2.5 mg per kilogram of body weight), a high dose of crizanlizumab (5 mg per kilogram of body weight), or a placebo, given as an intravenous injection 14 times over a period of 52 weeks. Patients using hydroxyurea at a stable dose could continue that treatment. Clinically meaningful lower rates of VOCs were observed with high-dose crizanlizumab than with the placebo, regardless of concomitant hydroxyurea use, or sickle cell disease genotype.[29] Crizanlizumab appeared to be associated with a low rate of adverse effects.

A post-hoc analysis of the previously discussed trial found that a considerable number of patients, across multiple subgroups treated with crizanlizumab, did not experience a VOC compared with those treated with the placebo. Of those with two to four events in the year prior to participating in the study, 40.5 percent treated with crizanlizumab had no VOC during the study compared to 24.4 percent in the placebo group.[30] For those with five to 10 events in the year prior, 28.0 percent treated with crizanlizumab had a VOC compared with 4.2 percent of the placebo group. It reduced the median annual rate of VOC by 45.3 percent. Reported adverse effects include arthralgia, diarrhea, pruritus, vomiting, and chest pain.

Olinciguat

Olinciguat is an oral investigational therapy that stimulates soluble guanylate cyclase (sGC), known to play a key role in the production of nitric oxide. The stimulation of sGC can restore the bioavailability of nitric oxide in the blood to increase blood flow, which may stop the destruction of blood cells and help address disease symptoms in SCD. Olinciguat is currently being evaluated in the Phase II, STRONG-SCD clinical trial, enrolling a planned 88 patients, aged 16 to 70, at five U.S. sites.

Voxelotor

Voxelotor is an orally bioavailable modulator and stabilizer of HbS being investigated as a treatment of SCD. Voxelotor targets and covalently binds to the N-terminal valine of the alpha chain of HbS which stabilizes it and thereby improves oxygen binding affinity. The binding of voxelotor to HbS prevents HbS polymerization, reduces sickling, decreases red blood cell damage and increases the half-life of red blood cells. It may improve blood flow and decrease hemolytic anemia. Sixty-five percent of patients treated with 1,500 mg per day of voxelotor and 33 percent of patients treated with 900 mg experienced an increase in hemoglobin of more than 1 g/dL at 24 weeks compared with 10 percent of patients in the placebo arm. Improvements in hemoglobin were seen as early as two weeks and maintained through 24 weeks. [31] Improvements in hemoglobin among patients treated with voxelotor were comparable, regardless of background treatment with hydroxyurea. Improvements in reticulocytes and bilirubin were also observed in both groups receiving voxelotor.

Sevuparin

Sevuparin was developed through a chemical depolymerization of heparin, with the aim to optimize its anti-adhesive and anti-inflammatory effects, while increasing the therapeutic window by removal of the anti-thrombin binding sites. Preclinical studies with sevuparin have shown that the broad anti-adhesive

and thus anti-inflammatory effects are retained from heparin, however, with a substantially reduced effect on anti-coagulation. It is currently in a Phase II trial for the management of acute VOCs in the hospital.

Rivipansel

Rivipansel is a pan-selectin inhibitor. The Phase III RESET clinical trial is currently assessing the effectiveness and safety of this agent for the management of acute VOCs in hospitalized SCD patients. This study expects to include about 350 patients, ages 6 and older, who will receive placebo or rivipansel through intravenous administration every 12 hours, up to a maximum of 15 doses.

Gene Therapy

Gene therapy is the future cure of SCD. Currently, there are two different strategies being investigated to cure sickle cell anemia with gene therapy. Both of these strategies involve genetically altering the patient's own hematopoietic stem cells. Four trials are testing the efficacy and safety of gene therapy to replace the mutated HBB gene with a healthy HBB gene. These Phase II trials are recruiting both children and adults in the U.S. and Jamaica. The LentiGlobin BB305 lentiviral vector trial reported promising results at a recent American Society of Hematology meeting. Substantial advances in genome engineering tools, particularly CRISPR/Cas9, have raised the possibility of genetic correction in induced pluripotent stem cells, as well as patient-derived hematopoietic stem and progenitor cells.

Current Payer Management

Payer management of SCD is mostly focused on case management of those individuals with complications or who are frequent users of resources. Medications used in the past have been relatively inexpensive and thus have not been a focus of management. Chronic narcotic use has been one area of focus.

Challenges in managing SCD are numerous for payers. Primary care physicians are often not trained to manage SCD well and, at the same time, access to specialists may be limited. Some "super users" use the hospital and ED as their primary source of care. Sickle cell day hospitals (dedicated infusion centers where patients can get intravenous treatment for VOC) have been shown to reduce hospitalizations and the length of crises, and yet fewer than a dozen such centers exist in the U.S.[32] Because the disproportionate share of the burden is on public payers, often the funding to do proper care coordination is lacking.

Management will change with the introduction of new specialty therapeutics for the treatment of SCD. Payers will need to develop the expertise to evaluate a growing number of new therapeutic options for SCD that will target VOC for prevention or treatment. Case management of patients will no longer be adequate in a new era of treatments. However, proper use of coming therapies has the potential to offset inpatient and ED costs in this population. Gene therapy offers a potential cure, but there are many unanswered questions, including how it will be covered financially.

Conclusion

SCDs are genetically transmitted hemoglobin disorders that can affect virtually all organ systems. SCD was once considered fatal; however, in the past several decades, it has been transformed into a chronic disease by early detection, preventive measures, and disease-modifying therapies (e.g., hydroxyurea, L-glutamine, and chronic transfusions). Current therapeutic approaches are targeted to managing the symptoms and complications of the disease. Newer therapies are targeting different aspects of the pathophysiology of SCD. Expensive targeted medications will become increasingly important in the management of SCD, resulting in possible cost offsets by decreasing emergency department and hospital utilization. Payer strategies will need to evolve to meet this changing landscape in SCD.

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Notes