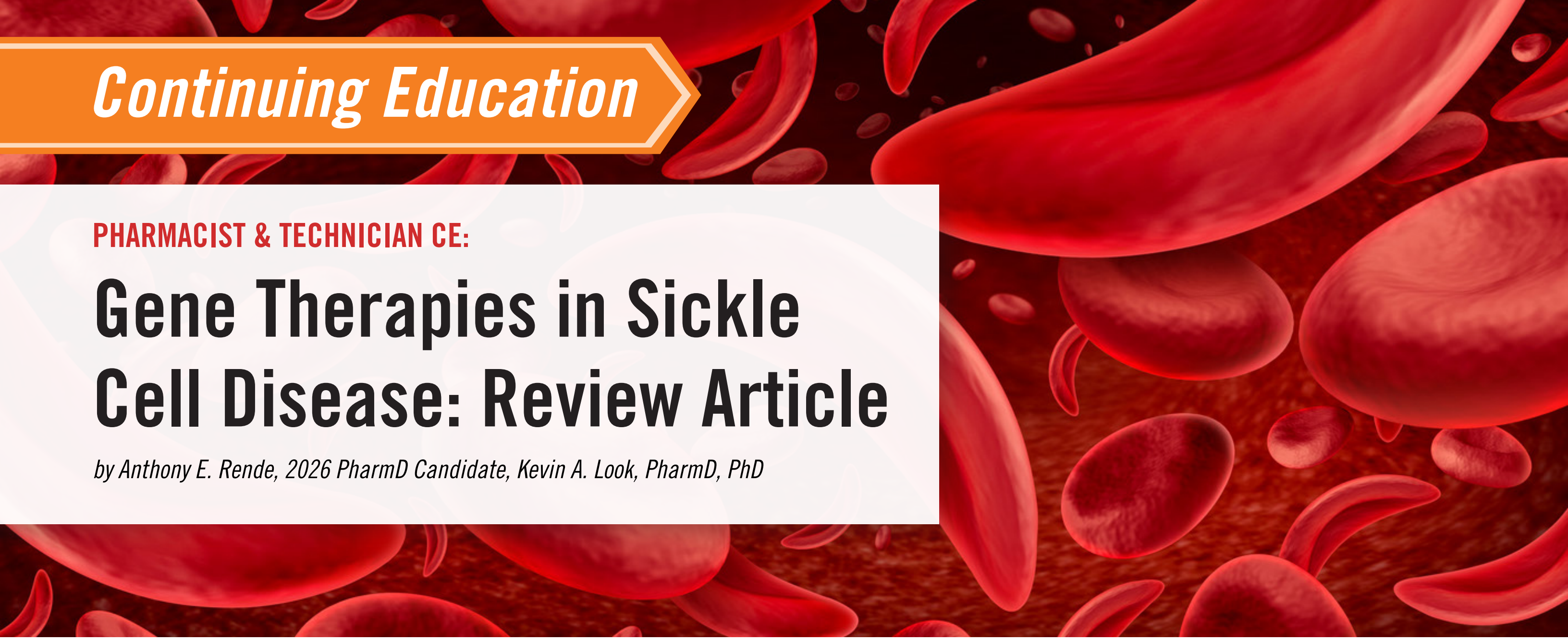

Continuing Education

PHARMACIST & TECHNICIAN CE:

Gene Therapies in Sickle Cell Disease: Review Article

by Anthony E. Rende, 2026 PharmD Candidate, Kevin A. Look, PharmD, PhD

Abstract

This article reviews sickle cell disease treatments with an emphasis on newly approved gene therapies. It examines the patient journey to achieving a potential cure with gene therapy while addressing its barriers. Additionally, it explores pharmacoeconomic considerations and the payer landscape, both of which play a large role in patients' access to these groundbreaking therapies.

Existing Treatments for Sickle Cell Disease

Approximately 100,000 people with sickle cell disease (SCD) live in the United States. Of those, over 90% affected identify as African American.[1] Individuals carrying this condition have a life expectancy that is 20 years shorter than the national average. SCD is a genetic disorder where red blood cells become sickle shaped and clump together, which can lead to blockages in blood flow, also known as vaso-occlusive crises. Vaso-occlusive crises are episodes that can cause severe pain or possible organ damage, as well as other serious complications due to a lack of oxygen-rich blood reaching the tissues. These complications can include leg ulcers, priapism, stroke, tissue death, kidney disease, and more.[2] Pain management can include the use of opioids, prescription pain medications, over-the-counter analgesics, and anti-inflammatory medications to help alleviate symptoms.

People with SCD would ideally be cared for by hematologists, but they are commonly seen by generalists, emergency nurses, and hospitalists who generally lack the expertise needed to handle this complex condition. Studies also suggest that healthcare providers may have more negative attitudes and increased frustration towards patients with SCD. Another survey found that only 20% of family physicians felt confident treating SCD.[3]

Available treatments to date are scarce, and until 2017, only a single medication—hydroxyurea—was available as a disease-modifying option. Hydroxyurea reduces red blood cell sickling and increases fetal hemoglobin. This drug is the first-line therapy and most prescribed medication for SCD. The main treatment effect involves lowering the number of vaso-occlusive crises. Despite the benefits of this medication, it is significantly underprescribed in eligible children and adults, partly due to societal factors such as mistrust in healthcare, stemming from historical and ongoing disparities.[2]

Other treatments include crizanlizumab and L-glutamine. Both of these medications are often reserved as second-line therapies or as adjunct for those not adequately responding to hydroxyurea alone. Crizanlizumab, approved in 2019, works against p-selectin, which may be involved in causing pain crises. L-glutamine, approved in 2017, is an amino acid supplement that can lower the amount of clumping and sickling of red blood cells.[2] Voxelotor was recently withdrawn from the market by Pfizer after almost 5 years, with the manufacturer stating that the "overall benefit no longer outweighs the risk." The decision was based on data suggesting an imbalance between vaso-occlusive crises and fatal events.[4] The high cost of these therapies also presents a challenge, with estimated annual net costs of $96,354 for crizanlizumab, $92,584 for voxelotor, and $30,046 for L-glutamine, according to a 2020 Institute for Clinical and Economic Review (ICER) report.[5] This in turn leaves even fewer options for SCD patients, highlighting the need for innovative therapies.

For very severe forms of SCD, blood transfusions can be utilized as needed. However, transfusions come with notable

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Learning Objectives

- Identify the current available treatment options for sickle cell disease and their limitations
- Describe the patient journey for receiving gene therapy for sickle cell disease
- Explain pharmacoeconomic and payer landscape challenges affecting access to gene therapies for sickle cell disease

risks, such as iron overload, and necessitate hospitalizations. SCD-related hospital admissions have increased over time. Patients with SCD frequently require inpatient care, and the total estimated costs of SCD are around $2.98 billion per year in the US.[2,3,6]

Before the arrival of gene therapies, the only possible cure was a hematopoietic stem cell transplant (HSCT). The main issue with an HSCT is finding an optimal donor. It is estimated that, at best, someone with SCD has a 25% chance of matching with a donor. For ethnic minorities, the chances are even lower—only between 6%and 10% of finding someone through a U.S. registry. Additionally, HSCT introduces the risk of graft-versus-host disease where the donor's immune cells attack the recipient's body. These findings emphasize the importance of developing alternatives.[2,7]

TABLE 1. Comparative Overview of Sickle Cell Disease Treatments

Treatment	*Type*	*Key Benefits*	*Key Limitations/Challenges*
Hydroxyurea	Oral Medication	Reduces frequency of pain crises and hospitalization	Underused, Requires ongoing administration
L-glutamine	Amino acid supplement	Reduces frequency of pain crises	Requires ongoing administration
Crizanlizumab	Monoclonal antibody	Reduces frequency of pain crises	Requires ongoing administration
Bone Marrow Transplant	Stem cell transplant	Potentially curative	Requires matching donor, significant risks of toxicity
Exagamglogene autotemcel	Gene therapy (CRISPR/Cas9)	Potentially curative	High cost, long-term efficacy unknown, intensive treatment, limited availability, requires extensive evaluation and support system
Lovotibeglogene autotemcel	Gene therapy (lentiviral vector)	Potentially curative	High cost, long-term efficacy unknown, intensive treatment, limited availability, requires extensive evaluation and support system

CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats, Cas9: CRISPR-associated protein 9

Emerging Treatments for Sickle Cell Disease

While traditional treatments have helped with managing SCD, they fall short of offering a cure. However, recent significant advancements have been made in curing SCD through gene therapies, specifically with two new Food and Drug Administration (FDA)-approved treatments: exagamglogene autotemcel (Casgevy®) and lovotibeglogene autotemcel (Lyfgenia®).[8,9]

Gene therapies aim to offer a one-time cure by fixing the genetic defect at the root, unlike traditional therapies, which are used to manage symptoms. Despite their promising outcome, gene therapies have disadvantages. They are expensive, difficult to access, and don't have well-established safety profiles.[10,11]

Exagamglogene autotemcel, developed by Vertex Pharmaceuticals, became the first FDA-approved gene therapy for SCD in late 2023. Exagamglogene autotemcel uses CRISPR/Cas9 gene editing to increase hemoglobin in stem cells. This is accomplished by editing and inactivating the BCL11A gene. In a phase 3, single-group, open-label trial, 30 patients aged 12 to 35 received the therapy and were followed for at least 16 months after infusion. Baseline characteristics included 53% male and 87% Black participants. Of the 30 patients evaluated, 29 remained free from vaso-occlusive crisis-related hospitalizations ($P<0.001$). The safety profile was comparable to myeloablative conditioning, with most common adverse events including stomatitis (55%) and febrile neutropenia (48%) and no cases of cancer or graft failure.[8]

Lovotibeglogene autotemcel was later developed by Bluebird Bio. It uses a lentiviral vector to insert a functional hemoglobin gene into stem cells, which increases hemoglobin levels. In a phase 1–2 study, 35 patients received therapy with a median follow-up of 17.3 months. Baseline characteristics included a median age of 24 years old, 37% female, and 97% Black. For all 25 evaluated patients, there was complete resolution of severe vaso-occlusive events. The safety profile was also consistent with myeloablative conditioning. The two most common adverse events were stomatitis (69%) and thrombocytopenia (66%). No cases of hematologic cancer were noted.[9]

Both SCD gene therapies take different approaches but share the same goal of offering a one-time cure. The long-term risks remain uncertain, and it will take years of monitoring to truly understand the safety and effectiveness beyond clinical trial data.[12]

Patient Experience and Barriers to Accessibility

Patients seeking SCD gene therapy may experience a complex and demanding journey. Both therapies are approved for patients 12 years and older with SCD. Lovotibeglogene autotemcel is indicated for those with a history of vaso-occlusive events, and exagamglogene autotemcel is specifically approved for patients with recurrent vaso-occlusive crises.[13,14]

Patients eligible for either gene therapy follow a process including screening, stem cell collection, chemotherapy, infusion, and post-treatment monitoring. Before collection, patients receive red blood cell transfusions to reduce sickled hemoglobin levels. For exagamglogene autotemcel, stem cells are collected over 2 to 3 days, while lovotibeglogene autotemcel requires bone marrow harvesting under anesthesia. Both therapies utilize a four-day myeloablative conditioning course to eliminate existing bone marrow cells. The modified cells are then infused after chemotherapy. Patients remain hospitalized for approximately 1 month for engraftment monitoring and supportive care.[8,9]

Access to SCD gene therapies is a major challenge. They are limited to specialized medical centers because of the expertise and resources required for procedures. Additionally, the process requires a strong support system for the physical and emotional challenges patients face. It also demands significant financial resources due to inpatient and outpatient costs.[15,16]

Payer Landscape and Pharmacoeconomics

Gene therapies for sickle cell disease can be prohibitively expensive, with exagamglogene autotemcel estimated to cost $2.2 million and lovotibeglogene autotemcel at $3.1 million per patient.[17] This does not include the cost of chemotherapy, hospital admissions, and medications that need to be taken after transfusion. The question of whether commercial insurance will cover these treatments has not yet been determined.[12] This uncertainty may stem from the concern for patients changing insurance plans. Payers who cover a one-time treatment with high upfront costs might not see any downstream cost savings if a patient switches plans. This issue makes commercial payers less likely to commit to treatment coverage, as they have a high potential to miss out financially on the long-term savings of this treatment. Even if the treatment is deemed cost effective, insurance agencies may still decide to opt out due to prioritizing short-term budgeting.[18]

ICER assumed that lovotibeglogene autotemcel and exagamglogene autotemcel would be equally effective based on the small number of patients studied so far. ICER generates a Health Benefit Price Benchmark (HBPB), a value representing the estimated cost of a treatment when taking its health benefits into account. This benchmark helps determine whether the treatment price accurately reflects its health improvements. ICER's HBPB for either therapy ranges between $1,350,000 and $2,050,000. Although actual prices for these treatments have not been determined, estimates suggest that the HBPB may be lower than the cost of the treatment. This indicates that the estimated price could exceed the value the therapy delivers in health outcomes, suggesting potential overpricing by manufacturers.[3]

SCD disproportionately affects non-Hispanic Black and African Americans with roughly 50% to 60% relying on Medicaid for their healthcare coverage. As a result, it is crucial to consider whether government programs, such as Medicaid and the Children's Health Insurance Program, will cover treatments, as extremely high costs could restrict access to therapy and result in worse health outcomes.[19]

The government is currently taking steps to make gene therapies more accessible and affordable through the Cell and Gene Therapy (CGT) Access Model. The CGT Access Model is a form of value-based contracting designed to simplify the Medicaid coverage of gene therapies by using outcome-based agreements to control costs. In value-based contracting, drug prices are tied to their real-world performance. The Centers for Medicare & Medicaid Services will negotiate terms with pharmaceutical companies, including pricing and outcomes measures. States can choose whether to enter into these agreements and voluntarily participate in this model starting January 2025.[20,21] These discussions will have significant effects on coverage, access, and cost management, but continued efforts will be needed to ensure the individuals who need these therapies the most can obtain them.

Although the CGT Access Model doesn't provide funds for gene therapy, it creates a framework that supports states to cover these treatments by negotiating better prices and managing costs through outcome-based agreements. The model's ultimate aim is to help Medicaid programs afford cutting-edge gene therapies. Medicaid will not benefit from the long-term savings of the cured condition if a patient switches to commercial or private insurance.[14]

Other Limitations

In addition to high costs and insurance coverage limiting accessibility, as mentioned earlier, many patients with SCD are not regularly managed by hematologists, making it difficult to ensure access to treatment. Beyond this, one major concern is the potential for serious adverse events such as cancer. For patients less than 12, parents may be hesitant to take advantage of gene therapy because of these risks. Additionally, the treatment process itself requires a long period of hospitalization, which can lead to more problems. Increasing the availability of the treatment to meet demand remains a significant challenge, and initial uptake of these therapies is expected to be slow due to accessibility barriers.[3]

Conclusion

As summarized in Table 1, treatment options for SCD range from disease-modifying therapies to recently approved gene therapies, each with its own set of benefits and limitations. Gene therapies mark a major breakthrough in the treatment of SCD. They offer hope for a cure to a condition that causes chronic pain, poorer quality of life, and shorter life spans. These treatments could drastically change the lives of people living with SCD. However, barriers such as limited production, restricted insurance coverage, and location-based administration constraints must be overcome to make these therapies available to all patients who need them. As we continue to monitor the therapies' long-term effectiveness and safety, it will be essential to address these barriers, especially those related to insurance coverage and healthcare costs. With continued progress, a cure for SCD may be reached.

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Assessment Questions

1. Which of the following is considered a first-line disease-modifying treatment for sickle cell disease?
   a. Crizanlizumab
   b. L-glutamine
   c. Hydroxyurea
   d. Exagamglogene autotemcel

2. Which of the following is a major limitation of bone marrow transplants for sickle cell disease?
   a. Iron overload
   b. High cost
   c. Underprescribed in children
   d. Difficulty finding suitable donors

3. Which of the following treatments were recently withdrawn from the market?
   a. Voxelotor
   b. L-glutamine
   c. Lovotibeglogene autotemcel
   d. Crizanlizumab

4. Before receiving the newly treated cells, the patient must first:
   a. Undergo bone marrow transplant
   b. Receive chemotherapy
   c. Take hydroxyurea for at least 12 months
   d. Fail treatment with exagamglogene autotemcel

5. **True or False:** Patients undergoing treatment with either lovotibeglogene autotemcel or exagamglogene autotemcel must undergo a four-day myeloablative conditioning regimen before receiving their modified stem cells.
   a. True
   b. False

6. What is the estimated cost of exagamglogene autotemcel for a single patient?
   a. $500,000
   b. $1.2 million
   c. $2.2 million
   d. $3.1 million

7. What could be a reason why insurance payers are hesitant to cover gene therapy for SCD?
   a. Gene therapies have a high failure rate
   b. Patients may switch insurance plans
   c. Medicaid will never allow coverage for gene therapies
   d. Special handling including shipping and storage

8. **True or False:** The Cell and Gene Therapy (CGT) Access Model is a funding program designed to pay for gene therapy in Medicaid patients.
   a. True
   b. False

9. The Institute for Clinical and Economic Review (ICER) estimated the Health Benefit Price Benchmark (HBPB) for gene therapies for SCD at:
   a. $500,000 - $1,000,000
   b. $1,350,000 - $2,050,000
   c. $2,500,000 - $3,500,000
   d. $4,000,000+

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