FDA Approves First CRISPR Gene Therapy for Sickle Cell Disease

Two new gene-editing therapies may offer a functional cure, but cost and access issues could limit their use.

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On December 8, the Food and Drug Administration (FDA) approved the first-ever CRISPR gene-editing therapy to treat sickle cell disease, a blood disorder that mainly affects Black people. The agency also approved a second gene therapy that works in a different way. These treatments are potentially life-changing—and CRISPR is also being studied for many other conditions, including cancer and HIV—but they are not without risk, and their high cost could limit access.

"Sickle cell disease is a rare, debilitating and life-threatening blood disorder with significant unmet need," Nicole Verdun, MD, of the FDA's Office of Therapeutic Products, said in a news release. "Gene therapy holds the promise of delivering more targeted and effective treatments, especially for individuals with rare diseases where the current treatment options are limited."

Sickle cell disease is an inherited condition in which a mutated gene produces abnormal hemoglobin, the protein that carries oxygen throughout the body. This results in crescent-shaped red blood cells that can clump together and get stuck in small blood vessels, impeding the flow of blood and the delivery of oxygen. The condition can lead to vaso-occlusive events—blood vessel blockages, known as crises, that can cause severe pain—as well as fatigue, organ damage, strokes and early death. Some people can be treated with stem cell transplants, but most don't have compatible donors.

"The approval of the first gene therapies for sickle cell disease represents a tremendous step forward for the sickle cell disease community, which has been historically overlooked and underfunded," American Society of Hematology (ASH) president Robert Brodsky, MD, said in a statement. "While these new gene therapies are potentially life-changing for individuals living with sickle cell disease, they must be accessible to be effective."

Two New Gene Therapies

Casgevy (exagamglogene autotemcel, or exa-cel), from Vertex Pharmaceuticals and CRISPR Technologies, uses CRISPR-Cas9 technology, which acts as "molecular scissors" to edit blood-

forming hematopoietic stem cells. The edit turns off a gene that suppresses production of fetal hemoglobin (HbF), a form of the protein that is usually not present past infancy. The modified stem cells produce red blood cells that contain HbF, substituting for the abnormal adult protein.

Casgevy was approved in the United Kingdom last month for both sickle cell disease and beta thalassemia, a condition in which the body doesn't produce enough of a hemoglobin building block, necessitating frequent blood transfusions; an FDA decision on approval for beta thalassemia is expected in March 2024. [Update: This approval came earlier than expected on January 16.]

Casgevy was evaluated in the CLIMB-121 trial (NCT03745287), which enrolled 44 adolescents and young adults (ages 12 to 35) with sickle cell disease. They had experienced at least two severe vaso-occlusive events annually for the past two years. Among the 31 treated patients with adequate follow-up data, all but two (94%) did not experience further crises for at least 12 months. It is not yet known how long the benefits will last, but the first woman treated in the trial has been free of severe pain episodes for more than four years.

At the recent ASH annual meeting, researchers presented follow-up data from 96 patients (44 with sickle cell disease and 52 with beta thalassemia), showing durable responses at four years. People with both conditions reported improvements in their quality of life.

The second therapy, Bluebird Bio's Lyfgenia (lovotibeglogene autotemcel, or lovo-cel), modifies hematopoietic stem cells by using a lentivirus vector—essentially a disabled form of HIV—to deliver a functional gene that produces a novel type of hemoglobin (HbA^{T87Q}) with anti-sickling properties that works like the normal protein. Last year, the FDA approved Bluebird's Zynteglo (betibeglogene autotemcel, or beti-cel), which uses the same gene-editing technology to treat beta thalassemia.

Lyfgenia was evaluated in the HGB-206 trial (NCT02140554), which enrolled people ages 12 to 50 with sickle cell disease and a history of vaso-occlusive events. Of the 32 evaluable patients, all but four (88%) did not have any more events between six and 18 months after treatment administration, and 94% did not experience severe crises.

Further data presented at the ASH meeting showed that responses were durable for up to five years, and treatment led to improved quality of life. People who did experience events reported reduced pain and spent less time in a hospital.

Treatment with the new therapies involves an intensive and potentially risky process. Both are made from a patient's own stem cells, and the engineered cells are readministered as part of a stem cell transplant—a procedure similar to CAR-T therapy for cancer. To make room for the new modified cells, patients undergo strong chemotherapy (known as myeloablative conditioning) to kill off their existing stem cells. This destroys all types of blood cells, including immune system white blood cells, leaving recipients prone to infections and other complications.

The conditioning chemotherapy can cause typical side effects, such as nausea, mouth sores and

hair loss. What's more, it can lead to infertility. Procedures can be done ahead of time to preserve eggs and sperm, coupled with later assisted reproductive technology, but these are expensive and may not be accessible.

Gene therapy comes with other risks as well. CRISPR could potentially cut DNA at unintended sites in the genome, leading to so-called off-target effects. Prior to Casgevy's approval, an FDA advisory committee met in late October to discuss this concern and how to evaluate the risk, ultimately deciding that the treatment is safe enough to use.

Lyfgenia could potentially trigger the development of new blood cancers. Its product label includes a "black box" warning to this effect—and some experts think Casgevy should carry the warning too. Because Lyfgenia uses a modified HIV vector, people undergoing treatment should not take antiretroviral drugs for HIV prevention (the prescribing information doesn't mention HIV treatment), and it can lead to a false-positive HIV PCR test.

The FDA has asked Vertex and Bluebird to follow trial participants for 15 years to monitor long-term safety outcomes.

Cost and Availability

Both new treatments are approved for people ages 12 and up who experience vaso-occlusive events. (Click here for full prescribing information for Casgevy and Lyfgenia.) Approximately 100,000 people in the United States are living with sickle cell disease, most of whom are African American or Latino. About 16,000 may be eligible for Casgevy, according to Vertex.

But adoption of the new treatments is expected to be slow, and they likely will not be accessible to a majority of people living with severe sickle cell disease in the United States, not to mention the millions in Africa, where the condition is most common.

Vertex and CRISPR Technologies set the cost of Casgevy at $2.2 million for the one-time treatment, while Bluebird priced Lyfgenia at $3.1 million. This puts them among the most expensive medications on the market. The current record holder is Hemgenix (etranacogene dezaparvovec), a gene therapy for hemophilia B, at $3.5 million. Bluebird holds two other positions in the top 10 for its beta thalassemia treatment Zynteglo and Skysona (elivaldogene autotemcel) for cerebral adrenoleukodystrophy.

The companies argue that the price is worthwhile, as the lifetime cost of managing severe sickle cell disease can reach $4 to $6 million. The Institute for Clinical and Economic Review (ICER), an independent nonprofit that conducts evidence reviews to determine fair pricing, estimates that Casgeny and Lyfgenia would be cost effective at a price between $1,350,000 and $2,050,000.

Recognizing that cost is a barrier, Bluebird has devised an outcomes-based pricing scheme that ties payment to clinical benefits, and the company has made agreements with state Medicaid programs. It is estimated that around half of sickle cell patients eligible for the new treatments are covered by Medicaid.

Beyond the cost of the therapies themselves, patients must spend weeks or months in a hospital, and parents or other caregivers may need to relocate temporarily to provide support.

But cost is not the only issue. Because they require specialized experience in stem cell transplantation, Casgeny and Lyfgenia will be available through a limited network of around three dozen authorized treatment centers, with more expected to come online later. Most are in major cities, largely in the Northeast, the upper Midwest, on the West Coast or in Texas. More than 20 states currently have no centers, including most of the Southeast, where the Black population is large and sickle cell disease is more prevalent.

Moreover, people with sickle cell disease may be hesitant about receiving the new gene therapies and feel they're being treated like "guinea pigs." Sickle cell disease has long been neglected and underfunded, and being on the cutting edge of a treatment revolution is a novel experience for the Black population, which has more often been left behind.

"I worry that the celebration around this approval is ignoring a significant barrier: a historic legacy of medical mistrust," Jennifer Fields, who has lived with sickle cell disease for 39 years, wrote for STAT. "Transparent communication about the safeguards in gene therapy research can help dispel fears rooted in historical injustices and empower individuals to make informed decisions about their health care."

Despite these challenges, the new therapies can be life-changing. Jimi Olaghere, who testified at the Casgevy FDA advisory committee meeting, hasn't experienced a sickle cell crisis since receiving the treatment in a clinical trial, and he can do things that previously seemed unimaginable.

"After I received [Casgevy], I started to experience things I had only dreamt of," he wrote for MIT Technology Review. "Most significantly, I gained the confidence that sickle cell disease won't take me away from my family, and a sense of control over my own destiny."

"Even though I benefited greatly from gene editing, I worry that not enough others will have that opportunity," he continued. "Denying access to such a powerful and transformative treatment based on someone's ability to pay, or where they happen to live, strikes me as unethical. I believe patients and health-care providers everywhere deserve to know that the treatment will be available to those who need it."

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