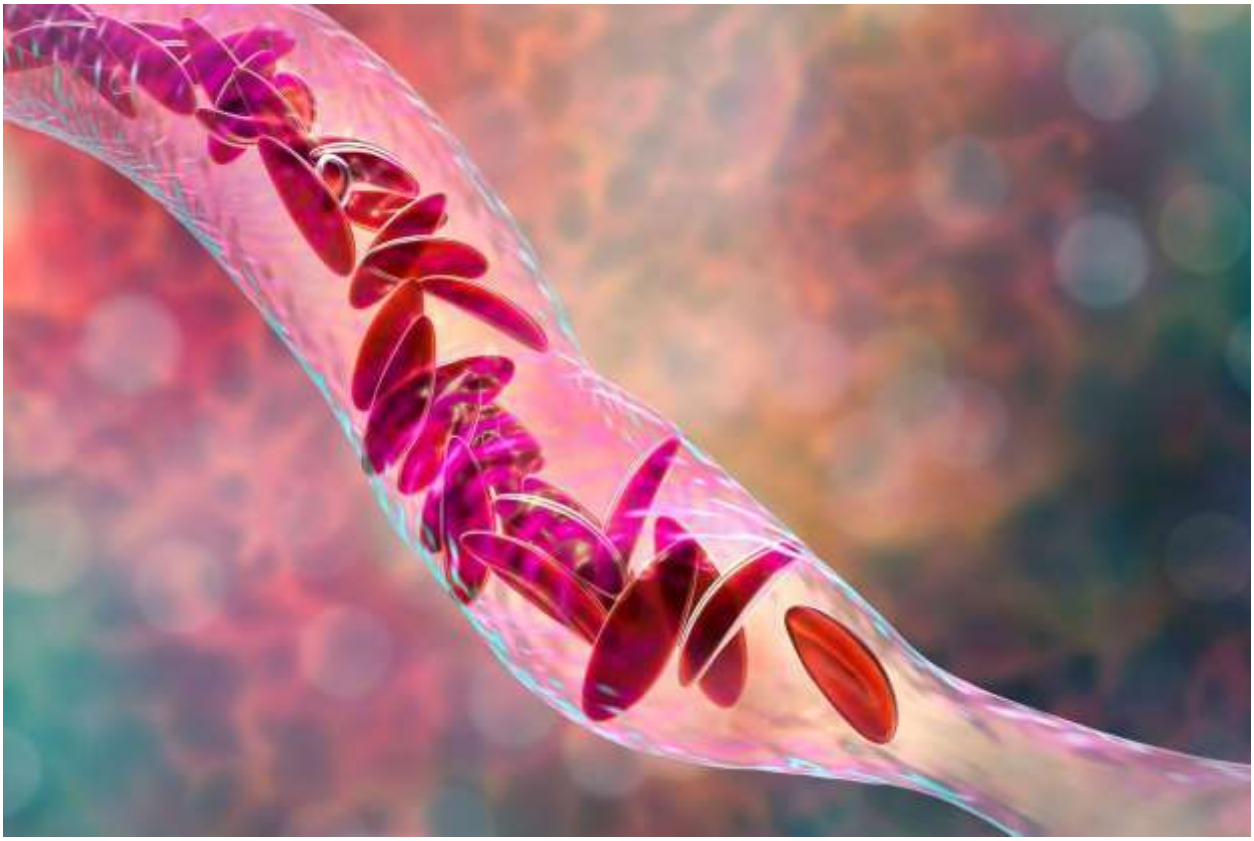
FDA Approved the First CRISPR Treatment - Potential Cure for People with Sickle Cell Disease



Victoria Gray was diagnosed with sickle cell disease (SCD) when she was just three months old; since then, episodes of pain and frequent hospitalizations have been a part of her life. Many of her dreams seemed like far-off impossibilities when the smallest things, like changing weather, would put her in the hospital. Every four to six weeks, she would go to the hospital to have a catheter pull out four to five units of her blood and receive replacement blood to keep her healthy. Then, in 2019, when she was 33, the mother and Walmart associate became the first person with SCD to be treated with a new therapy called Casgevy. Within eight months, she was no longer going to the hospital or emergency room, and her symptoms had vanished.

In December, the U.S. Food and Drug Administration approved Casgevy and Lyfgenia, two treatments expected to be game changers in treating sickle cell disease (SCD) in patients 12 years and older. Casgevy and Lyfgenia are the first cell-based gene therapies for the condition, and Casgevy is the first FDA-approved treatment using CRISPR technology. Both therapies represent a potential cure for the hereditary disease.

Until recently, the only possible cure for the inherited blood disorder was a bone marrow transplant, which came with challenges, including finding a match and graft-versus-host-disease. Many patients with SCD can't even undergo a bone marrow transplant because only

about 15% of patients have a matched sibling and unrelated donors are typically found for only 10% to 12%, meaning only 25% of those with the disease are being helped, explained Lakshmanan Krishnamurti, MD, chief of Yale Medicine Pediatric Hematology & Oncology.

However, both Casgevy — made by Vertex Pharmaceuticals and CRISPR Therapeutics — and Lyfgenia — by Bluebird Bio — use the patient's own blood stem cells and are intended to be a one-time fix or cure, although this requires years of follow-up to be confirmed.

"These approvals represent an important medical advance with the use of innovative cell-based gene therapies to target potentially devastating diseases and improve public health," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research. "Today's actions follow rigorous evaluations of the scientific and clinical data needed to support approval, reflecting the FDA's commitment to facilitating the development of safe and effective treatments for conditions with severe impacts on human health."

Before both treatments, the patients must undergo high-dose chemotherapy to kill the faulty bone marrow cells so they can be replaced with the new modified cells in Casgevy and Lyfgenia. The time-intensive and grueling process takes about eight to 12 months from start to finish.

"I didn't want to wait," Gray says. "There was an urgency for me because my life was hard. My kids began to have a fear of me dying. Their behaviors had changed in school. I knew I had to do something."

A hammer and chisel on the bones: what is sickle cell disease, and why it's painful

Sickle cell disease is a rare, debilitating disorder affecting approximately 100,000 Americans and is most prevalent in African Americans. The inherited disease is caused by a mutation in the hemoglobin protein found in red blood cells responsible for delivering oxygen to the body's tissues. The mutation causes red blood cells to adopt a hard, brittle, sticky, crescent (sickle) shape that scratches and gets stuck within vessels, causing inflammation and restricting oxygen delivery to tissues.

"Sickle cell disease impacts every organ. Children are having strokes, and young adults—people in their 30s—are experiencing kidney failure—all because of sickle cell disease," says Dr. Calhoun.

Chronic pain, organ damage, anemia, fatigue, dizziness, and a shortened life expectancy are common for those with the disease. When the cells start to clog blood vessels, it can cause vaso-occlusive crises (VOCs), which patients say feel like someone is stabbing or taking a hammer and chisel to their bones. Medications and blood transfusions can be used to manage such complications, but doctors say it is often not enough for many patients with the debilitating disease.

All newborns in the U.S. are screened for the disease via a blood test, and when family members have a history of SCD, babies can be diagnosed in utero.

Casgevy: switching the Fetal hemoglobin back on

It's been a little over a decade since the landmark paper on editing DNA in test tubes with CRISPR was published, and now the first-ever CRISPR-based therapy has been approved. The treatment works by making a specific cut in the *BCL11A* gene responsible for telling the body to make less fetal and more adult hemoglobin. The therapy eliminates the need for a donor by using the patient's own blood stem cells. Once the patients' modified cells are re-transplanted, they engraft within the bone marrow and stimulate the production of fetal hemoglobin (HbF) — the healthy, oxygen-carrying form of hemoglobin that's produced during fetal development but typically turns off after birth. The increased levels of HbF prevent the sickling of red blood cells in patients with the disease. Previously, researchers found a protective genetic mutation that causes fetal hemoglobin to persist into adulthood; when this happens to individuals with the disease, their symptoms are milder.

The treatment is infused only once, but the therapy isn't easy or fast to receive. Gray says the start of the treatment was hard and came with chemotherapy side effects like body aches. "I didn't feel an immediate change. It was about eight months before I felt a real difference."

Because the chemotherapy side effects can cause low levels of infection-fighting white blood cells, patients must be hospitalized in sterile conditions and remain there until their immune system recovers and the risk of serious infection subsides. This generally takes 4-6 weeks but can vary based upon the individual.

Data Supporting Casgevy: absence of painful VOCs and successful engraftment

The safety and efficacy of Casgevy were evaluated in an ongoing trial of 44 adult and adolescent patients with SCD. Two years before screening, patients had a history of at least two severe vaso-occlusive crises (VOCs). The primary efficacy outcome was an absence of severe VOC episodes for at least 12 consecutive months during the 24-month follow-up period. Of the 31 patients that remained in the study long enough for data to be collected, 29 (93.5%) achieved this outcome, and all treated patients had successful engraftment free of any graft failure or rejection. For the 29 people who didn't have a severe VOC for 12 months, so far, the average length of time without a severe VOC has been 22.2 months.

There were no notable safety concerns. The most common side effects included low levels of platelets and white blood cells, mouth sores, nausea, musculoskeletal pain, abdominal pain, vomiting, fever, headache, and itching. However, Dr. Cece Calhoun, a Yale Medicine hematologist-oncologist, says the side effects are from the chemotherapy and not the gene therapies.

Lyfgenia: using a virus to drop off a functional hemoglobin gene

Lyfgenia uses a lentiviral vector to deliver a genetically modified version of a functional hemoglobin-producing gene. The patient's blood stem cells are modified to produce HbA^{T87Q}, a gene-therapy-derived hemoglobin that operates similarly to the normal adult hemoglobin A produced in people without sickle cell disease. Red blood cells with HbA^{T87Q} have a lower risk of sickling and impeding blood flow. The modified stem cells are then delivered to the patient.

“The lentivirus enters the blood-making stem cells, drops off the gene, and then the gene becomes part of the genome, and the virus goes away,” Dr. Krishnamurti says. “While Casgevy activates the native fetal hemoglobin, Lyfgenia uses an artificial gene. But both are trying to dilute the sickle hemoglobin that the body would otherwise continue to make.”

Data Supporting Lyfgenia: the majority of patients free of VOCs

The safety and efficacy of Lyfgenia were assessed via a 24-month study in adults and adolescents with sickle cell disease who had a history of vaso-occlusive crises or events (VOCs/VOEs). The drug was deemed effective if patients experienced a complete resolution of VOEs between six and 18 months after the infusion. Of the 32 patients, 28 (88%) were free from VOEs during this period.

The most common side effects included stomatitis, febrile neutropenia, and low platelet, white blood cell, and red blood cell levels, consistent with receiving chemotherapy and underlying disease. Additionally, a black box warning is included on the label for Lyfgenia, warning patients of the risk of developing blood cancer, which two patients treated with the drug developed. It's recommended that patients who have Lyfgenia should have lifelong monitoring.

It should also be noted that with both Lyfgenia and Casgevy, the required chemotherapy process can lead to infertility.

Beta thalassemia: condition causing mutation in hemoglobin chain

People with SCD are not the only ones that could benefit from the two new therapies. Beta thalassemia, a condition where a genetic mutation stops the body from producing enough of the beta chain component of hemoglobin — resulting in red blood cells that can't bind or carry iron — is also approved for the treatments.

Similar to SCD, most people with beta thalassemia require blood transfusions every few weeks for their entire lives. Unlike SCD, the transfusion can create further complications. Typically, the body takes iron from old red blood cells and recycles them into new red blood cells, but because people with beta thalassemia can't make new, working red blood cells and are receiving more iron via transfusion, iron begins to accumulate in organs like the heart and liver. However, this can be managed by medications that help the body excrete the excess iron.

Approval doesn't mean access: concerns of the sickle cell community

Despite the approval of the therapies tagged as advancing treatment of sickle cell anemia, the accessibility of the drugs may come with some barriers. Teonna Woolford, CEO of a sickle cell patient advocacy group, notes that approval does not mean access. Woolford also points out that the community wants to see far-reaching data following patients through the rest of their lives before companies start touting the drug as "curative."

Additionally, the potential of infertility from the chemotherapy makes Woolford question if egg and sperm freezing options will be available for patients. Even if it is, she notes that the price of in vitro fertilization also acts as a barrier. "What good does it do to have a bunch of eggs that you can't actually turn into a birth because you can't afford the IVF when you're ready to have a baby?" said Woolford.

Candidates for the therapies: risks versus benefits

There are many factors to consider, and patients will need to discuss their personal risks and potential benefits of the gene therapies with their primary hematologist. Objective factors like how their organs function, how they would handle the required chemotherapy, and if their disease is severe enough that the risks outweigh the benefits of the procedure will be assessed, Dr. Calhoun explains. "Then, there are more subjective factors. It takes a year; it's not an easy process. Do you have a support system? Who will help you navigate these challenging ups and downs?"

Vertex estimates there are approximately 25,000 people with sickle cell disease and 7,000 with beta thalassemia in the U.S. and European Union who may be good candidates for Casgevy.

Reimbursement and access: cost of the gene therapies

Two to three million dollars is the estimated cost per patient receiving either gene therapy. With insurance companies, including Medicaid, still determining if or how the treatments will be covered, the high prices could prevent many patients from accessing them.

Casgevy's price of $2.2 million is on par with other cell and gene therapies, and an independent drug-pricing watchdog group has said it's likely to be cost-effective when compared to the current high cost of care for someone with SCD over their lifetime. Vertex expects uptake to be slow due to the treatment's complexity and the need to sort out reimbursement and access.

In the coming weeks, the Biden administration will start negotiating with the Pharmaceutical companies to obtain discounts for state Medicaid plans under the Centers for Medicare & Medicaid Services' Cell and Gene Therapy Access Model, which aims to make expensive treatments more accessible. According to Centers for Disease Control and Prevention, between 50 and 60% of Americans with SCD are covered by Medicaid.

The future of Casgevy and Lyfgenia: a new beginning for those with SCD

On February 9th, Casgevy was approved by the European Commission for the treatment of sickle cell disease and beta thalassemia. The approval — which marks the first CRISPR-approved therapy in the European Union — could help approximately 8,000 European patients, 12 years and older, who have the diseases.

As candidates for the newly approved therapies begin the grueling first steps of treatment, Casgevy and Lyfgenia's promise of a future free of frequent hospitalizations is on the horizon. While potential cost barriers and certain side effects from the chemotherapy, including the possibility of infertility, may outweigh the benefits of the therapy for some, for many, the treatment could improve their quality of life. Victoria Gray no longer has to go to the hospital every month to keep her healthy. Her blood count has remained stable, and she no longer experiences pain from her SCD.

"It meant a new beginning," Gray said. "It is more than I ever dreamed of, for everything to be gone."