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Casgevy (exagamglogene autotemcel) and Lyfgenia (lovotibeglogene autotemcel) for individuals 12 years and older with sickle cell disease (SCD) and recurrent vaso-occlusive crises (VOC): A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

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Background

Sickle cell disease (SCD) is an autosomal recessive form of congenital anemia due to a missense pathogenic variant in the gene encoding Hemoglobin Subunit Beta (*HBB*). A substitution of valine for glutamic acid at the sixth codon of *HBB* creates abnormal hemoglobin (HbS), which polymerizes under deoxygenated conditions, inducing sickling of the red cells and eventually stasis of microvascular blood flow and endothelial damage.[1] Approximately 100,000 individuals are affected by SCD in the United States.[1-3] SCD

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is characterized by chronic hemolytic anemia, recurrent vaso-occlusive crises (VOCs), and progressive vasculopathy, leading to various end-organ damages.[1,2] Individuals with SCD have shortened lifespans due to multiple comorbidities, including strokes, nephropathy, retinopathy, and cardiomyopathy.[1,2]

Management and treatment

Supportive and palliative care have been central to the management of SCD.[1,4] Chronic blood transfusion with iron chelation therapy, optimal pain management during VOCs, and hydroxyurea are the first-line treatments.[1,5] Other disease-modifying agents, such as L-glutamine, crizanlizumab, and voxelotor, have been recently approved by the US Food and Drug Administration (FDA) as adjunctive or second-line treatments.[5-7] Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only curative treatment option for SCD.[8] However, the limited donor pools, potential adverse events from graft-versus-host disease, graft failure, and the increased risk of transplantation-related mortality are barriers to offering this treatment.[8,9]

Newly approved therapy

Indication and approved treatment population

Both Casgevy (exagamglogene autotemcel) and Lyfgenia (lovotibeglogene autotemcel) are autologous hematopoietic stem cell-based gene therapies.[10-12] On December 8, 2023, under Priority Review and Fast Track designation, each therapy received FDA approval for individuals aged 12 years and older with SCD who experience recurrent VOCs.[10] Additionally, on January 16, 2024, Casgevy received FDA approval for individuals aged 12 years and older who have transfusion-dependent β-thalassemia.[13]

Mechanism of action

The products reduce red blood cell sickling by different mechanisms. Casgevy utilizes CRISPR/Cas9 technology for gene editing to downregulate *BCL11A*, which inhibits the transition from fetal hemoglobin (HbF) to adult hemoglobin.[11,12] HbF has a higher affinity for oxygen than HbS and inhibits the polymerization of HbS.[11,12]

In contrast, Lyfgenia is a lentiviral vector that expresses a novel HbA^{T87Q} variant of hemoglobin, which functions similarly to normal adult hemoglobin (HbA).[10,14]

Outcomes and efficacy

In the ongoing clinical trial (NCT03745287), the interim efficacy of Casgevy was evaluated. Out of the 44 participants who received Casgevy, 30 had at least 12 consecutive months of follow-up, with 29 individuals (97%) achieving freedom from severe VOCs.[10,11] Notably, all treated individuals experienced successful engraftment without any cases of graft failure or rejection.[10,11]

As per the interim analysis from the Phase 1/2 HGB-206 clinical trial (NCT02140554), 28 out of 32 (87.5%) participants who received Lyfgenia achieved freedom from VOCs during follow-up, which ranged from 6 to 18 months after treatment.[10,15]

Adverse effects and toxicity

Common adverse effects of Casgevy include leukopenia, thrombocytopenia, neutropenic fever, mouth sores, nausea, vomiting, abdominal pain, musculoskeletal pain, headache, and itching.[10] Similarly, common adverse effects of Lyfgenia include stomatitis, leukopenia, anemia, thrombocytopenia,

Table 1 Comparisons of the 2 gene therapies for sickle cell disease

Feature	Casgevy (Exagamglogene Autotemcel)	Lyfgenia (Lovotibeglogene Autotemcel)
Mechanisms	A cell-based gene therapy using CRISPR/Cas9	A cell-based gene therapy utilizing a lentiviral vector as a gene delivery vehicle for genetic modification
Effects	By silencing erythroid-specific *BCL11A* enhancer, the goal is to increase the production of HbF	By delivering engineered hemoglobin containing missense HBB 87T>Q variant which has anti-sickling properties similar to HbF
Common grounds	Individuals' hematopoietic stem cells are collected and genetically modified to prepare them for treatment. These stem cells are reinfused after high-dose chemotherapy.	
Adverse effects	Leukopenia, thrombocytopenia, neutropenic fever, mouth sores, nausea, vomiting, abdominal pain, musculoskeletal pain, headache, and itching	Stomatitis, leukopenia, anemia, thrombocytopenia, and febrile neutropenia. One individual developed acute myeloid leukemia after treatment.
Comments	The first FDA-approved gene therapy utilizing CRISPR/Cas9, a type of genome editing technology. This approval marked the integration of CRISPR/Cas9 into clinical practice.	Individuals who receive Lyfgenia may be at risk of developing hematologic malignancies. Therefore, it is recommended that these patients undergo lifelong monitoring.

FDA, Food and Drug Administration; *HbF*, fetal hemoglobin.

and febrile neutropenia.[10] These adverse effects were generally consistent with the use of myeloablative busulfan conditioning and autologous HSCT. Acute myeloid leukemia has occurred in individuals treated with Lyfgenia, and the FDA has added a boxed warning on the label with information regarding this risk.[10,16] Casgevy does not contain any boxed warnings for prescribers.

Table 1 summarizes the comparison between Casgevy and Lyfgenia.

Additional considerations

The safety and efficacy of Casgevy (exagamglogene autotemcel) and Lyfgenia (lovotibeglogene autotemcel) need to be further evaluated in long-term follow-up studies. Although short-term adverse events were reportedly comparable to other autologous HSCT, ex vivo genomic manipulation coupled with a myeloablative conditioning regimen could potentially accelerate the risk of developing hematologic malignancies. A few individuals who developed myelodysplastic syndrome and acute myeloid leukemia after Lyfgenia have been reported, although extensive investigations ruled out insertional oncogenesis driving this process.[16,17] It is postulated that the increased risk for therapy-related myeloid neoplasm after gene therapy is related to accelerated clonal hematopoiesis in this population; thus, prescreening individuals with SCD for preleukemic progenitors before gene therapy has been recommended.[18]

There are other ongoing studies, both at preclinical and clinical stages, investigating other genomic manipulation strategies, such as induction of HbF promoter, direct base editing, and RNA therapeutics.[19-21] There have been multiple studies that demonstrated promising results of novel approaches for allogeneic HSCT in SCD, including the use of nonmyeloablative conditioning regimen and posttransplant cyclophosphamide in haploidentical HSCT.

Conflict of Interest

The authors declare no conflicts of interest.

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