Revolutionizing genetic disease treatment: The case of exagamglogene autotemcel

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Recent approval of exagamglogene autotemcel (exa-cel) on November 16, 2023, in the United Kingdom, developed by Vertex Pharmaceuticals and CRISPR Therapeutics, represents the first cell-based therapy for treatment of sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs) or transfusion-dependent β-thalassemia (TDT) in patients aged 12 and above. Following suit, the US Food and Drug Administration authorized exa-cel for the same indications on December 8, 2023. Exa-cel represents the first commercially approved CRISPR-based gene therapy, offering hope to approximately 25,000 eligible patients in the US and Europe. The significance of exa-cel extends beyond revolutionizing therapeutic intervention in genetic medicine; it also raises profound ethical considerations and societal implications related to genome manipulation.

HOW DOES EXA-CEL WORK?

SCD is an autosomal recessive hereditary disorder caused by a point mutation in the HBB gene that encodes adult β-globin.[1] Healthy individuals have a hemoglobin complex consisting of two α-globin and two β-globin proteins. In contrast, patients with SCD exhibit an altered hemoglobin complex due to polymerization of mutated sickle β-globin under low oxygen levels, leading to the formation of crescent or sickle-shaped red blood cells. These abnormal cells have a shorter lifespan compared to healthy ones and are prone to adhering to capillary walls, resulting in acute VOCs that can be life-threatening and require immediate blood transfusion.

β-Thalassemia is attributable to different mutations in HBB, resulting in a decrease in β-globin production and an excess of α-globin. This leads to the formation of insoluble α-globin chain aggregates and subsequent intramedullary hemolysis.[2] The symptoms of β-thalassemia vary depending on the amount of functional β-globin produced by red blood cells. Patients with severe cases (known as TDT) rely on regular blood transfusions for survival.

Exa-cel utilizes CRISPR-Cas9 technology to suppress the expression of *BCL11A* by disrupting an erythroid-specific enhancer of *BCL11A* (Figure 1).[3] By inhibiting the expression of *BCL11A*, which serves as a repressor for fetal hemoglobin (also known as γ-globin) production, exa-cel enables the resurgence of fetal hemoglobin synthesis (Figure 1). Fetal hemoglobin can then compensate for the defective β-globin and restore functional tetrameric hemoglobin complexes along with α-globin in individuals with SCD or β-thalassemia (Figure 1).

As exa-cel permanently modifies the DNA of a patient's hematopoietic stem cells (HSCs), therapeutic effects are expected to be long-lasting, potentially lasting for many years or even a lifetime in the cases of SCD and TDT. Despite being classified as a one-time treatment, exa-cel involves a complex and multi-step therapeutic process that spans several months to a full year. This treatment begins with mobilization and collection of HSCs from the patient's peripheral blood. Once an adequate quantity of HSCs is obtained, they are sent to a manufacturing facility for precise genetic editing. Prior to reinfusion of these modified HSCs back into the patient, busulfan-based myeloablative conditioning is administered to prepare the bone marrow adequately for accepting and engrafting the modified

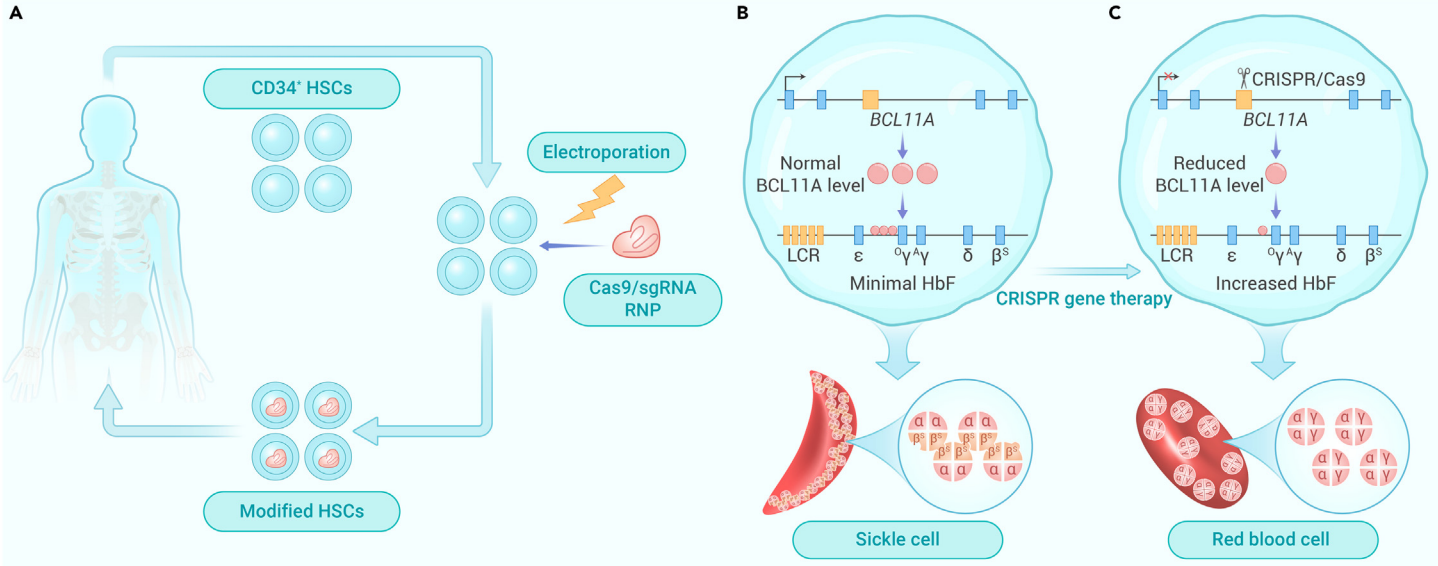

Figure 1. *Ex vivo* genome editing for the treatment of SCD (A) Workflow of *ex vivo* gene therapy based on hematopoietic stem and progenitor cells (HSPCs). The *ex vivo* gene therapy involves isolating HSPCs from patients, performing CRISPR gene editing, and subsequently infusing the modified cellular product back to patients after a conditioning regimen. (B) Genetic mechanisms underlying SCD. Normal hemoglobin A (HbA) consists of two α-globin subunits and two β-globin subunits encoded by HBB. The sickle Hb allele (HbS, also called β^S) is an HBB allele where an adenine-to-thymine substitution leads to the replacement of glutamic acid with valine at position 6 in the mature β-globin chain. Under conditions of deoxygenation, tetramers containing two HbS subunits can polymerize and cause erythrocytes to assume a crescent or sickled shape, giving rise to the name of disease. (C) Targeted genome editing within the *BCL11A* erythroid enhancer would reduce *BCL11A* expression in erythroid cells, thereby promoting high-level expression of γ-globin. γ-Globin can substitute for the defective HbS subunit, thus restoring functional tetrameric hemoglobin complexes with α-globin in individuals with SCD.

HSCs. Following administration, these genetically edited HSCs undergo differentiation into erythrocytes capable of producing therapeutic levels of fetal hemoglobin, commencing a critical transformation toward improved health and quality of life. During this intricate process, patients may require at least 1 month hospital stay to monitor both engraftment progression of the edited HSCs and stable onset of hemoglobin synthesis.

The two international clinical trials CLIMB-121 and CLIMB-131 have successfully achieved their respective primary endpoints in evaluating exa-cel as a therapeutic intervention for SCD and TDT.[4,5] Specifically, 29 out of 31 evaluable SCD participants (93.5%) achieved freedom from severe VOCs, while 32 out of 35 evaluable TDT participants (91.4%) attained transfusion independence. Both outcomes were sustained for at least 12 consecutive months during the 24-month follow-up period, providing support for the use of exa-cel in managing these hemoglobinopathies.

SAFETY CONSIDERATION

The authorization of exa-cel has introduced complex challenges in assessing its safety and therapeutic implications. The most frequently observed adverse events in the two clinical trials primarily relate to busulfan-based myeloablative conditioning, including nausea, vomiting, low blood cell counts, and organ toxicities. These side effects are more prevalent among older patients or those with pre-existing organ impairment due to SCD. Notably, there is a significant concern regarding potential infertility resulting from the busulfan-based conditioning regimen for individuals who plan to conceive in the future.

Another safety issue pertains to the possibility of unintended off-target genetic alterations that may pose health risks for patients. Currently, only a limited number of patients have received treatment with exa-cel, and only a small subset underwent specific testing for off-target changes. Given that SCD primarily affects individuals of African heritage, it is challenging to conclusively assess the long-term safety of exa-cel across diverse populations using reference genomes that may not fully capture the genetic heterogeneity. As part of a post-approval study for exa-cel, Vertex is initiating a comprehensive 15-year follow-up study focusing on malignancies, mortality, and other health outcomes to monitor the safety profile of exa-cel. Balancing medical innovation promotion with public health protection continues to present an ongoing challenge for regulatory agencies, particularly as CRISPR-based gene therapies continue to evolve.

ACCESSIBILITY AND AFFORDABILITY OF EXA-CEL

The authorization of exa-cel also highlights concerns regarding accessibility and affordability. The high cost associated with this treatment—$2.2 million per patient—raises significant questions about its availability to a broader population and whether it will remain accessible solely to affluent individuals. Furthermore, establishing the necessary infrastructure for HSC collection, *ex vivo* therapeutic editing, and reinfusion may be beyond the means of low-income nations, potentially exacerbating global health disparities. As CRISPR-based gene therapies increasingly become part of clinical practice, addressing these inequalities becomes imperative in order to ensure equitable access to advanced treatments.

ETHICAL CONSIDERATIONS

The ethical implications of exa-cel's approval extend beyond its medical application for SCD and TDT, sparking a debate on the broader consequences of gene editing. The potential for unintended effects on human genetics raises concerns among bioethicists regarding the prospect of eugenics and genetic enhancement, igniting controversy over the extent to which genetic modification should be pursued. The infamous case of Jiankui He's unethical application of CRISPR technology in editing the *CCR5* gene in embryonic stem cells 5 years ago serves as a stark reminder of the necessity for stringent ethical standards and oversight in gene therapy. The subsequent reinforcement of regulatory processes underscores the global commitment to responsible innovation that prioritizes individual and societal welfare.

In conclusion, the commercial availability of exa-cel represents a pivotal moment at the intersection of scientific progress, medical treatment, and ethical responsibility. The transition from laboratory research to regulatory approval is an extraordinary achievement; however, it necessitates careful consideration of the profound responsibilities inherent in altering life's genetic fabric.

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DECLARATION OF INTERESTS

The authors declare no competing interests.