Review Article

Gene Editing with CRISPR: A New Era for Treating Beta Thalassemia

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ABSTRACT

Beta thalassemia is a serious genetic blood disorder that affects thousands of people around the world, especially in regions like the Mediterranean, the Middle East, South Asia, and parts of Africa. It happens when a person inherits mutations in the HBB gene, which is responsible for making hemoglobin, the protein in red blood cells that carries oxygen throughout the body. These mutations reduce or block the production of healthy hemoglobin, leading to chronic anemia, fatigue, organ complications, and in severe cases, lifelong dependence on blood transfusions. Despite the availability of supportive treatments like iron chelation therapy and stem cell transplants, most options only manage symptoms rather than cure the disease. This is where CRISPR-Cas9, a powerful tool that can directly modify the DNA responsible for the condition. Instead of treating symptoms over a lifetime, CRISPR offers the possibility of a one-time, long-lasting solution. Casgevy is a new CRISPR-based therapy developed by Vertex Pharmaceuticals and CRISPR Therapeutics, and is currently being used in clinical trials to help patients with transfusion-dependent beta thalassemia and sickle cell disease by reactivating fetal hemoglobin production. Early results are promising: patients who once needed frequent transfusions have been able to live transfusion-free for over a year. This paper explores beta thalassemia, the science behind CRISPR-Cas9 gene editing, the mechanism and outcomes of Casgevy, and the ethical and medical considerations of deploying such technologies.

Keywords: Beta Thalassemia; Gene Editing; CRISPR-Cas9; Clinical Trials; Hemoglobin

INTRODUCTION

Beta thalassemia is an inherited blood disorder, with a particularly high prevalence in the Mediterranean basin, the Middle East, South Asia, and sub-Saharan Africa. The disease results from mutations in the HBB gene, which encodes the β-globin subunit of hemoglobin. Hemoglobin, composed of two alpha and two beta chains, allows red blood cells to transport oxygen throughout the body. Mutations in *HBB* disrupt beta-chain production, causing an imbalance between alpha and beta chains. The resulting accumulation of free alpha chains damages red blood cells, leading to chronic anemia, bone deformities, and enlargement of the spleen and liver (1).

The most severe form, known as beta thalassemia major (or Cooley's anemia), requires lifelong regular blood transfusions. Due to the frequency of transfusions, patients often suffer from iron overload, which can damage vital organs such as the heart, liver, and endocrine glands unless treated with iron chelation

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therapy (2, 3). Hematopoietic stem cell transplantation remains the only established curative option but is limited by donor availability and risks of graft-versus-host disease.

CRISPR-Cas9 gene editing has emerged as a transformative platform, capable of correcting disease-causing mutations at their genetic source. Unlike traditional approaches, CRISPR enables targeted disruption of regulatory elements, such as the BCL11A erythroid enhancer, to reactivate fetal hemoglobin (HbF) production. This strategy has advanced rapidly from preclinical proof-of-concept to clinical application, culminating in Casgevy (exa-cel), the first FDA-approved CRISPR-based therapy for TDT and sickle cell disease.

While several reviews have broadly discussed gene therapy for hemoglobinopathies, few have focused specifically on CRISPR-Cas9, its mechanisms, the emerging results of clinical trials, and the broader ethical and societal implications of its use. This review aims to fill that gap by outlining the molecular basis of CRISPR-Cas9 editing for beta thalassemia, analyzing clinical outcomes of Casgevy trials, and evaluating unresolved technical and ethical challenges.

CRISPR-CAS9 AND THE CASGEVY TREATMENT

CRISPR-Cas9 is a gene-editing tool that enables scientists to cut and modify DNA at highly specific locations by using a single guide RNA (sgRNA) to direct the Cas9 endonuclease (protein) to a complementary sequence adjacent to a protospacer adjacent motif (PAM). Once bound, Cas9 introduces a double-strand break (DSB), which the cell attempts to repair through endogenous DNA repair mechanisms. Two major repair pathways can be activated: non-homologous end joining (NHEJ), an error-prone process that introduces insertions or deletions at the cleavage site, and homology-directed repair (HDR), which requires a donor template for precise correction. While HDR offers the possibility of repairing specific *HBB* mutations, its efficiency in hematopoietic stem and progenitor cells (HSPCs) is low. For this reason, therapies for blood disorders such as beta thalassemia utilize NHEJ to inactivate disease-causing switches rather than directly repairing the *HBB* mutation (4).

In the case of beta thalassemia, researchers target a gene called BCL11A, which normally represses fetal hemoglobin (HbF) production (5). Unlike adult hemoglobin, HbF, which is naturally produced before birth and during infancy, is not affected by mutations in the HBB gene. Disabling BCL11A in adults can reactivate HbF production, allowing red blood cells to carry oxygen even without functional β-globin chains (6).

Foundational studies established the rationale for targeting BCL11A in beta thalassemia. Xu *et al*. [2011] demonstrated that BCL11A knockout restores HbF in murine and humanized models (7), while Bauer and Orkin (2015) identified BCL11A as a "master repressor" of HbF (8). Building on this, Canver *et al*. [2015] used CRISPR to disrupt BCL11A enhancers and successfully restored HbF expression in human hematopoietic cells (9). Wu *et al*. [2019] further reported successful HbF reactivation through CRISPR-Cas9 in preclinical exa-cel studies (10).

This growing body of evidence led to the development of Casgevy (exa-cel), a therapy by CRISPR Therapeutics and Vertex Pharmaceuticals. The treatment begins by collecting hematopoietic stem cells from the patient, which are then edited ex vivo with CRISPR-Cas9 to target the erythroid-specific enhancer of *BCL11A*. The edited cells are introduced using electroporation, a non-viral delivery method that temporarily opens cell membranes with a mild electric pulse, allowing Cas9 protein and sgRNA to enter. This strategy avoids the risks of viral vectors, such as insertional mutagenesis. The patient undergoes conditioning chemotherapy to clear space in the bone marrow, and the edited cells are reinfused, where they proliferate and produce red blood cells rich in fetal hemoglobin (11).

Casgevy was accepted into the EMA PRIME scheme in 2020 and 2021 (12) and received FDA approval in 2023 (11). It is currently under long-term review for commercialization in Europe.

A critical aspect of Cas9's safety lies in minimizing off-target effects, where Cas9 may cut unintended sites in the genome. To reduce this risk, scientists design highly specific sgRNAs with computational tools, use engineered "high-fidelity" Cas9 variants with improved accuracy, and test edited cells extensively with whole-genome sequencing and assays such as GUIDE-seq before reinfusion. These strategies ensure that edited hematopoietic stem cells are both effective and safe for clinical use.

In clinical trials, 42 patients with transfusion-dependent beta thalassemia (including 13 adolescents) received Casgevy, with 39 achieving transfusion independence for at least 12 months. A separate study

of 29 severe sickle cell disease patients (including 6 adolescents) showed that 28 experienced no vaso-occlusive crises (VOCs) for a year (13, 14). While results demonstrate durability and over 80% gene correction in some patients, reported side effects include cytopenias, nausea, vomiting, and headaches. Patients will be monitored for 15 years to assess long-term safety and efficacy (15).

ETHICAL CONCERNS

While CRISPR-Cas9 therapies like Casgevy represent a major breakthrough in the treatment of genetic blood disorders such as beta thalassemia and sickle cell disease, they also raise significant ethical questions. One of the primary concerns is the equity of access. Currently, gene editing treatments are expensive and available only in specialized clinics in high-income countries, which excludes most patients in low- and middle-income regions where beta thalassemia is most prevalent, such as sub-Saharan Africa, South Asia, and the Mediterranean, creating a risk of deepening global health inequalities (16). WHO (2021) emphasizes that unless international funding mechanisms and technology transfer initiatives are established, the majority of patients in low- and middle-income countries will continue to be excluded from access (17).

Another concern involves the long-term safety and unintended consequences of genome editing. Even though Casgevy is ex vivo, meaning the edits are made outside the body, there is still the possibility of off-target effects or unforeseen complications in the future. The fact that patients must be monitored for 15 years highlights this uncertainty. Moreover, the required conditioning chemotherapy before reinfusion of edited cells can be toxic and carries its own risks (15).

There are also broader societal concerns about how gene editing technologies may eventually be used beyond therapeutic purposes. As the line between curing disease and enhancing traits becomes blurred, debates arise about the ethical limits of modifying the human genome. For instance, Baylis [2019] warns of the normalization of genome editing without robust public deliberation, raising issues of consent, intergenerational impact, and the possibility of creating social pressure to edit (18).

Additionally, Greely HT highlights concerns about "slippery slopes" toward germline modifications, unequal access reinforcing social inequality, and misuse of CRISPR for non-therapeutic traits such as intelligence or physical appearance (19).

As shown in Table 1, while blood transfusions and chelation remain the most common approaches, Casgevy represents a potentially curative intervention. (5, 10, 12)

As shown in Figure 1, 93% of beta thalassemia patients (39 out of 42) and 97% of sickle cell disease patients (28 out of 29) experienced these positive outcomes in a clinical trial (12-14).

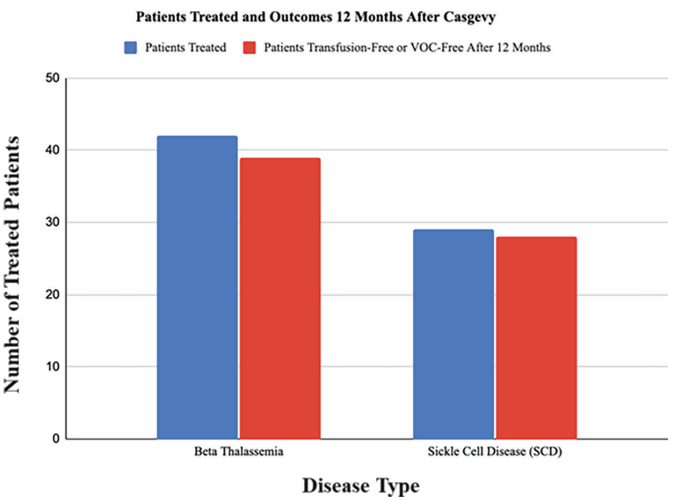

Figure 1. Bar graph showing the number of patients achieving transfusion- or VOC-free status after Casgevy.

Table 1. Comparison of standard therapies for beta thalassemia with the gene-editing Casgevy

Treatment	Mechanism	Pros	Limitations
Blood Transfusions	Supply functional RBCs	Widely available	Iron overload; lifelong need
Iron Chelation Therapy	Removes excess iron from transfusions	Prevents organ damage	Requires strict adherence; side effects
Stem Cell Transplant	Replaces faulty cells	Can be curative	Requires donor match; graft-versus-host risk
Casgevy (CRISPR-based)	Gene editing to boost fetal hemoglobin	Potentially curative with one procedure	Expensive; long-term effects still under study

CONCLUSION

Casgevy represents a groundbreaking step in genetic medicine, directly targeting the root cause of transfusion-dependent beta thalassemia through CRISPR-Cas9–mediated reactivation of fetal hemoglobin. Early clinical trials are highly promising: most patients achieved transfusion independence with sustained HbF production, and only limited serious side effects were reported (14, 15). These results mark the first time a CRISPR-based therapy has demonstrated durable benefits in a human population.

Despite this progress, significant challenges remain. Trial cohorts are still relatively small, and long-term outcomes will only become clear through extended monitoring over the planned 15-year follow-up. Conditioning chemotherapy poses major risks, including cytopenias, infertility, and infection, which restrict who can safely receive treatment. The procedure is technically complex and requires advanced medical infrastructure, making it inaccessible to most of the regions where beta thalassemia is most prevalent. Finally, Casgevy's high cost renders it unaffordable for the majority of patients worldwide (16, 17).

At the same time, Casgevy symbolizes the extraordinary progress of modern science. It demonstrates that genome editing can move from experimental research to clinical application, setting the stage for therapies that could address a wide range of genetic and acquired diseases. Beyond beta thalassemia, CRISPR-based treatments point toward a future of personalized medicine, where interventions are designed to correct the underlying genetic causes of illness rather than manage symptoms.

The promise of Casgevy must therefore be matched with ethical responsibility. Ensuring equitable access will require global collaboration among scientists, ethicists, policymakers, and healthcare systems. Without systemic changes, such breakthroughs risk deepening inequality rather than reducing it. Casgevy's legacy will ultimately depend not only on its scientific success but also on whether its benefits can be shared fairly across the populations that need it most.

While these findings highlight Casgevy's potential, it's important to note the limitations of this review. It relies solely on publicly available sources, including published articles and official reports, lacking original clinical data or firsthand interviews that could reveal patient experiences and challenges. The fast-paced nature of biotechnology means new studies and regulatory changes could impact the accuracy of the information. Additionally, most clinical outcomes cited are from company-sponsored trials, which may underreport risks, and limited access to laboratories restricted deeper exploration of technical details. The author declares no conflicts of interest regarding the publication of this article.

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