Advances and Challenges in the Treatment of Sickle Cell Disease Using Gene Therapy

Lillian Ren

ABSTRACT

Sickle cell disease (SCD) is a hereditary blood disorder that affects nearly 8 million people worldwide and causes abnormal hemoglobin production. Furthermore, SCD worsens quality of life through chronic anemia and vaso-occlusive events, reducing life expectancy. Non-curative treatments have been established to help manage the symptoms of SCD, while curative therapies such as allogeneic hematopoietic stem cell transplantation face limitations due to a lack of donor availability and complications from graft rejection. In recent years, early phase clinical trials have been conducted to analyze the efficacy and safety of using new gene editing based technologies, such as CRISPR, as alternative cures for SCD. This paper will assess these advances with a focus on autologous hematopoietic stem cell-based gene therapies including exagamglogene autotemcel and lovotibeglogene autotemcel. Clinical studies have found that these therapies are able to consistently stabilize patient's hemoglobin levels and effectively reduce vaso-occlusive events. Despite these successes, continued research is necessary to monitor the long-term safety of the different forms of gene therapy, address their high costs and limited accessibility, and further improve the safety of their pre-conditioning processes.

KEYWORDS

Sickle cell disease, gene editing, blood disorder, clinical trials, CRISPR, vaso-occlusive event, hematopoietic stem cells

INTRODUCTION

Sickle cell disease (SCD) is an inherited blood disorder characterized by an abnormal production of hemoglobin (1). This condition causes red blood cells to become sticky, rigid, and sickle shaped, causing clogs in blood vessels and a disruption to the flow of oxygen to the body. These sickle cells tend to die at a faster rate than normal blood cells, which can lead to shortages in blood cells. SCD was estimated to affect 7.74 million people worldwide as of 2021 (2), with there being around 100,000 cases present in the United States (1). Those with SCD in the U.S. experience an estimated life expectancy that is more than 20 years shorter than the life expectancy of a person without SCD. In 2021 alone, more than 375,000 people died from SCD worldwide, with over 80,000 of those deaths being in children under the age of 5 (2).

The disease is prevalent in people with ancestors from countries that are historically affected by malaria, since the red blood cell death characteristic of SCD makes people more resistant to developing that disease. Those who carry only one sickle cell causing allele have protection and advantages against the malaria-causing parasite, which allows the SCD to persist in regions where the infection is common, despite the costs that come with inheriting two alleles (3). In the U.S., 90% of SCD cases affect non-Hispanic Black or African American people, while about 3-9% affect Hispanic or Latino people (1).

SCD can cause a variety of serious health problems, such as anemia from the faster death rate of sickle cells, which contributes to fatigue through a lack of blood cells available for oxygen transportation (4). This could cause delayed growth and puberty in children, since red blood cells are also responsible for carrying nutrients necessary for growth around the body.

The sickle cells' tendency to block blood flow often leads to pain crises, alternatively called vaso-occlusive events (VOEs), which can vary in intensity and require possible hospitalization. The blocking of blood vessels can additionally trigger swelling in the hands and feet, as it reduces blood circulation in those areas. It is possible for blockages to affect vessels in the eyes as well, creating vision problems through damage to the retina. Moreover, those with SCD experience higher susceptibility to infections due to the presence of sickle cells damaging the spleen, which serves a central hub for the body's immune system.

In most cases, lifelong treatment is required to manage SCD, with the majority of treatment options addressing symptom relief and the prevention of complications. There are few therapies available to correct the disease's underlying cause. Pain crises are handled through trigger avoidance, while a patient's sensitivity towards infections is taken care of with daily administration of antibiotics, as well as routine and additional vaccinations (5). Medicines like hydroxyurea, L-glutamine oral powder, and narcotics are used to further treat pain, lower the chance of acute chest syndrome, and prevent stroke, but they are not effective in all patients due to differences in disease severity or treatment adherence (4). Blood transfusions are available for the management of SCD-related complications, as they substantiate normal red blood cell levels to improve oxygen carrying efficiency and to reduce the severity of VOEs (6). An established method for curing SCD is allogeneic hematopoietic stem cell (HSPC) transplantation, where stem cells from a healthy donor without SCD are given to a patient through an intravenous drip, which then travel to the bone marrow and begin to produce healthy red blood cells to replace the sickle cells (5). The use of this method is restricted by a difficulty in finding compatible donors and the high risk of the patient contracting graft-versus-host disease or other immunologic complications (7). As a result of the limitations of the treatment options for SCD, many patients experience lasting complications from the disease despite there being available curative measures.

Recent advances in gene therapy have provided new methods of curing SCD that do not rely on the accessibility of matching donors. In stem cell addition therapy, a patient's own stem cells are extracted and sent to undergo genetic modification in a laboratory to replace the mutated gene with a normal hemoglobin producing gene. The stem cells are given back through autologous transplant, infusing the cells back into the patient's body, resulting in a permanent increase in healthy hemoglobin production and reduced sickling (4). A variation of this treatment is gene editing therapy, where no gene addition is present, and instead, the sickling gene in the patient's stem cells is directly modified before the cells are returned to the patient (4). Gene therapy's ability to address earlier limitations relating to donor necessity make it a potential option to more effectively treat SCD. In this review, I will discuss the advantages and challenges of using gene therapy as a treatment option for SCD.

CRISPR BASED GENE EDITING THERAPY TARGETING A BCL11A GENE ENHANCER

In recent years, several forms of gene therapy have been approved by the U.S. Food and Drug Administration (FDA), with the first being Casgevy (exagamglogene autotemcel; exa-cel), a CRISPR-based therapy approved for patients above 12 years with recurring VOEs (8, 9) (Figure 1A). This treatment is a form of gene editing therapy. Unlike previous treatment options, it does not require a compatible donor to function, as it uses the patient's own HSPCs. Exa-cel utilizes the CRISPR/Cas9 system to manipulate stem cells, editing an enhancer on the BCL11A gene to reduce its expression (9). BCL11A typically suppresses the production of fetal hemoglobin after birth, while encouraging the production of adult hemoglobin, so its inhibition

leads to an increase in fetal hemoglobin and a depletion of adult hemoglobin in the body. The mutated hemoglobin in adult hemoglobin is responsible for the characteristic sickle cells present in SCD, meaning that its reduction effectively prevents red blood cell sickling and allows for relief from VOEs. Fetal hemoglobin is a solution because it does not contain the mutated sickle hemoglobin, and so will not present the same sickling effects on blood cells. Patients undergo myeloablative conditioning to obliterate the body's original stem cells with an unchanged BCL11A gene before being infused with the modified stem cells (7).

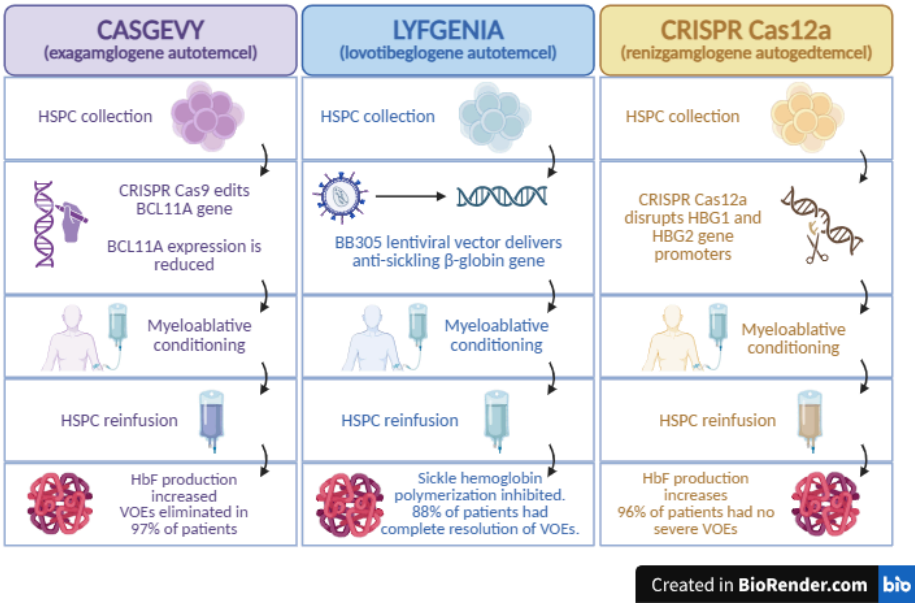

Figure 1. Types of autologous hematopoietic stem cell-based gene therapies (10)**. A.** CASGEVY relies on CRISPR Cas9 editing of the BCL11A gene to increase HbF production. **B.** LYFGENIA uses lentiviral gene addition therapy to inhibit sickle hemoglobin production. **C.** CRISPR Cas12a can be utilized to edit the HBG1 and HBG2 gene to increase HbF production. Abbreviations: HbF - fetal hemoglobin; HSPC - hematopoietic stem and progenitor cell; VOE - vaso-occlusive event

Clinical trials of exa-cel have demonstrated the consistency of the treatment's intended effects. In a Phase 3 single group clinical trial utilizing CRISPR/Cas9, 97% of patients with sufficient follow-up to be evaluated did not experience severe VOEs for at least 12 consecutive months following treatment, while all evaluable patients avoided hospitalizations related to VOEs during the same period (7). In another Phase 1/2 trial treating both adult and adolescent patients, the means of fetal hemoglobin and total hemoglobin were measured, with results showing that all patients achieved successful engraftment of the modified stem cells, and no graft rejection was reported during follow-up periods ranging from 4.9 to 22.4 months (8). By substantially increasing a patient's fetal hemoglobin levels, exa-cel was able to reduce or eliminate the need for chronic blood transfusions in many patients, improving quality of life through reduction of VOEs and further medical treatments (8).

LENTIVIRAL GENE ADDITION THERAPY

Another recently approved form of gene therapy targeting SCD is Lyfgenia (lovotibeglogene autotemcel; lovo-cel), which employs a different method than CRISPR/Cas9 genome editing in its treatment (Figure 1B). It utilizes the autologous BB305 lentiviral vector to introduce an altered beta-globin gene into a patient's stem cells ex vivo (8). After successful transduction of the stem cells into a patient's bone marrow, the beta-globin gene then codes for the production of HbAT87Q, a genetically modified form of hemoglobin A. HbAT87Q inhibits the polymerization of sickle hemoglobin, meaning that it can minimize the sickling of red blood cells (11).

Two clinical trials have been conducted in the U.S. to observe lovo-cel's efficacy, with a decreed outcome measure indicating success being that of resolved or decreased VOEs (12). An ongoing Phase 3 trial seeks to measure this factor, as well as the change in the annualized number of VOEs in a two year observational period after the infusion compared to the two years prior (13). A separate phase 1/2 study monitored lovo-cel's impact on SCD patients with severe conditions, and was able to demonstrate its effectiveness, as 88% of participants had completely resolved VOEs within a 6 to 18 month period after the treatment (8).

In addition, a Phase 1/2 clinical trial was conducted to analyze lovo-cel's safety and efficacy, while also creating proper dosage guidelines with the intent of stabilizing a patient's hemoglobin levels (14). The initial patients (Group A) were subjected to doses of lovo-cel, with the treatment method, specifically relating to cell collection and lovo-cel manufacturing, then being altered with the hopes of achieving greater effect in the later patients (Group B). Group B had higher peripheral blood vector copy numbers than Group A, implying a higher success rate of the integration of genetically modified vector genomes into the patients' stem cells. Group B also showed increased hemoglobin levels that were approaching stabilization, as well as decreased hemolysis, as key markers of this symptom were reduced after infusion. The trial concluded that modified stem cells could sustain erythropoietic hemoglobin A production, and that overall complications due to stem cell infusion were not present after treatment.

CRISPR CAS9/CAS12A EDITING OF THE HBG GENES

A third variation of SCD treatment features the use of CRISPR Cas9 or Cas12a in the modification of the HBG gene, which comes with the goal of disrupting globin genes and gene promoters to increase fetal hemoglobin production (15) (Figure 1C). Prior to the treatment, the patient's HBG1 and HBG2 genes are screened to select the guide RNA used in CRISPR, with the one producing the highest level of fetal hemoglobin-containing premature red blood cells being selected for use.

In a multicenter Phase 1-2 clinical study overlooking the safety and side effects of CRISPR based HSPC therapy, CRISPR Cas9 was used to edit HSPCs from SCD patients, with all patients having successful engraftment and secure production of fetal hemoglobin at the end of a 6 to 18 month follow up period (15). Following the stem cell editing and successful transfusion back into the body, all patients experienced reduced SCD symptoms and improved total red blood cell counts. The study observed no off-target effects from the gene therapy, and judged that disrupting the HBG1 and HBG2 gene promoters did indeed lead to increased fetal hemoglobin levels. Participants were noted to have side effects that resulted not from the gene therapy portion of the treatment, but rather from the busulfan myeloablative conditioning they went through during mobilization, as well as symptoms from SCD itself. The CRISPR Cas9 treatment was determined to be partially effective, as all participants had at least one SCD

related event after treatment, hemolysis, and fetal hemoglobin levels insufficient to completely stop sickling. It is concluded that alternative treatment options should be explored (15).

CRISPR Cas12a is functionally similar to CRISPR Cas9, but it is theorized to have higher specificity and effectiveness due to the production of staggered ends by cuts made in the CRISPR process that give it an advantage in editing efficiency over Cas9's blunt ends (16). Researchers are exploring the use of CRISPR Cas12a in hematopoietic stem cell therapy in a new treatment called reni-cel. A Phase 1/2 clinical trial was conducted on 28 participants with severe SCD symptoms to determine the safety, efficacy, and effects of reni-cel treatment (16). CRISPR Cas12a was used to disrupt the BCL11A binding sites in the HBG1 and HBG2 promoters with the goal of blocking the production of adult hemoglobin and therefore re-activating the production of fetal hemoglobin as a method to treat SCD. The study found that the mean total hemoglobin level of the patients increased, as the percentage of fetal hemoglobin in patients advanced to nearly 50% after reni-cel, and it remained above 40% in the months following. 96% of the patients had no severe VOEs after treatment, and 100% had no non-severe VOEs after treatment (16). Reni-cel could possibly provide patients with improved lifelong wellbeing from lessened experiences of severe symptoms of SCD.

LIMITATIONS AND CHALLENGES OF GENE THERAPY FOR SICKLE CELL DISEASE

Though exa-cel and lovo-cel have shown remarkable short-term efficacy, concerns regarding their safety and societal equity remain strong. This includes the possibility of off-target genome editing, where CRISPR modifies DNA at an unintended location, the effects of which are currently unknown (8). Even after their approval, both treatments are still undergoing monitoring to consider their long-term safety and effectiveness (7). Exa-cel and lovo-cel also require specialized facilities that suit the complexity of stem cell collection and ex vivo gene editing, which have the side effect of persistently high treatment costs and limited accessibility for patients without highly developed healthcare systems (8).

Overall, patients who underwent CRISPR Cas12a or Cas9 therapy showed decreased hemolysis and maintained that state over the course of a year (16). They also had no off-target effects from the genetic editing, the treatment was efficient and specific, and no major side effects were observed. Any adverse effects present during and after the administration of reni-cel were consistent with that of busulfan myeloablative conditioning and cell collection, not reni-cel itself.

CONCLUSION

Sickle cell disease is a destructive lifelong condition that affects millions of people worldwide, and it drastically decreases the life expectancy of those suffering from it (2). Current treatment options for SCD are not sufficient due to donor shortages and other underlying difficulties, so improved methods are needed. Recent advancements in gene editing technologies have the potential to greatly improve treatment options for patients. There are numerous ongoing and completed clinical trials assessing the safety and efficacy of gene editing therapy using CRISPR. Various Phase 1/2 studies have shown that using CRISPR in combination with autologous homopoietic stem cell therapy offers patients an effective curative treatment option that is demonstrated to be both safe and effective in the short-term. More monitoring, as well as Phase 3 and 4 clinical trials, with larger control and variable groups, should be conducted to certify the efficacy of this form of treatment.

At present, several difficulties exist in the pretransplant conditioning and preparation process of the different variations of gene therapy. Notably, the optimal gene-modified cell dose a patient should receive is still under consideration; however, it is known that high numbers of hematopoietic stem cells must be collected from a patient in order to go through with a selected treatment (17). This creates challenges if a patient does not have sufficient access to medical care, as numerous collection days are needed to secure the required amount.

The process of gene therapy involves weeks of patients undergoing procedures including cell collections, blood transfusions, and reinfusions of stem cells into the body (18). Unsurprisingly, concerns have been raised over patient comfort and the painfulness of the treatment, as well as the combined cost from the treatment itself and the patient's extended hospitalization at a transplant center. In the United States, gene therapy products like lovo-cel and exa-cel are priced upwards of $2.2 million dollars for a one-time treatment, excluding any additional expenses from hospital care (18). This creates ethical and practical challenges in treating those with SCD, as the vast majority of the affected population worldwide is located in sub-Saharan Africa, with highly limited access to treatment.

Furthermore, long-term toxicities related to pretransplant myeloablative conditioning and issues with engraftment of the edited cells following infusion into the body may negatively impact a patient's health (18, 19). In the case of myeloablative conditioning, the effects may arise in the form of transplant-related infertility or death, while engraftment rejection could lead to fever, pulmonary infiltration, and pulmonary edema in patients (19). The effects of this part of the procedure remain unclear, as most SCD gene therapy studies have short follow-up periods, so the long-term endurance of transplanted stem cells and any other potential drawbacks have yet to be established.

Future directions for the development of gene therapy for SCD must include a focus on lowering treatment costs and maintaining its effectiveness while avoiding or removing the toxic pre-conditioning required at the beginning of the procedure. Though gene editing has been shown to have significant potential as a curative treatment for SCD, advancements in its safety and accessibility should be made to reduce its risk and cement it as a reliable treatment for patients.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

REFERENCES

1. Centers for Disease Control and Prevention. About Sickle Cell Disease [Internet]. Sickle Cell Disease (SCD). 2025 Feb [cited 2026 Jul 16]. Available from: https://www.cdc.gov/sickle-cell/about/index.html
2. World Health Organisation. Sickle-cell disease [Internet]. Who.int. World Health Organization: WHO; 2025 Aug [cited 2026 Jul 16]. Available from: https://www.who.int/news-room/fact-sheets/detail/sickle-cell-disease
3. Luzzatto L. Sickle Cell Anemia and Malaria. Mediterranean Journal of Hematology and Infectious Diseases [Internet]. 2012 Oct 3 [cited 2026 Aug 9];4(1):e2012065. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3499995/
4. Mayo Clinic. Sickle Cell Anemia [Internet]. Mayo Clinic. 2025 May [cited 2026 Jul 16]. Available from: https://www.mayoclinic.org/diseases-conditions/sickle-cell-anemia/symptoms-causes/syc-20355876
5. NHS. Sickle Cell Disease [Internet]. NHS. NHS; 2022 [cited 2026 Jul 20]. Available from: https://www.nhs.uk/conditions/sickle-cell-disease/
6. Howard J. Sickle Cell disease: When and How to Transfuse. Hematology [Internet]. 2016 Dec 2 [cited 2026 Jul 20];2016(1):625–31. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6142434/
7. Frangoul H, Locatelli F, Sharma A, Bhatia M, Mapara M, Molinari L, et al. Exagamglogene Autotemcel for Severe Sickle Cell Disease. New England Journal of medicine/˜The New England Journal of Medicine [Internet]. 2024 Apr 24 [cited 2026 Jul 20];390(18). Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2309676
8. Zainab Syyeda Rahmat, Ali MH, Muhammad Talha, Md. Al Hasibuzzaman. FDA approval of casgevy and lyfgenia: A dual breakthrough in gene therapies for sickle cell disease. Annals of Medicine and Surgery [Internet]. 2024 July 24 [cited 2026 Jul 20];86(9):4966–8. Available from: https://doi.org/10.1097/MS9.0000000000002409
9. CASGEVY. How CASGEVYTM works | CASGEVYTM (exagamglogene autotemcel) [Internet]. www.casgevy.com. 2024 [cited 2026 Jul 24]. Available from: https://www.casgevy.com/sickle-cell-disease/how-casgevy-works
10. Created in BioRender. Ren, L. (2026) https://BioRender.com/z2zgh2z
11. LYFGENIA (lovotibeglogene autotemcel) Mechanism of Action | Lentiviral Vector (LVV) [Internet]. www.lyfgeniahcp.com. [cited 2026 Jul 24]. Available from: https://www.lyfgeniahcp.com/mechanism-of-action
12. A Study Evaluating the Safety and Efficacy of Lovo-cel in Severe Sickle Cell Disease. Clinicaltrials.gov. 2026 [cited 2026 Jul 26]. Available from: https://clinicaltrials.gov/study/NCT02140554?viewType=Card&intr=lovo-cel&rank=1
13. A Study Evaluating Gene Therapy With BB305 Lentiviral Vector in Sickle Cell Disease. Clinicaltrials.gov. 2026 [cited 2026 Jul 26]. Available from: https://clinicaltrials.gov/study/NCT04293185
14. Kanter J, Thompson AA, Pierciey FJ, Hsieh M, Uchida N, Leboulch P, et al. Lovo-cel gene therapy for sickle cell disease: Treatment process evolution and outcomes in the initial groups of the HGB-206 study. American Journal of Hematology [Internet]. 2023 Jan 1 [cited 2026 Jul 30];98(1):11–22. Available from: https://pubmed.ncbi.nlm.nih.gov/36161320/

15. Sharma A, Jaap Jan Boelens, Cancio M, Hankins JS, Bhad PA, Marjohn Azizy, et al. CRISPR-Cas9 Editing of the HBG1 and HBG2 Promoters to Treat Sickle Cell Disease. The New England Journal of Medicine [Internet]. 2023 Aug 31 [cited 2026 Jul 30];389(9):820–32. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2215643
16. Hanna R, Frangoul H, Pineiro L, McKinney C, Mapara M, Dalal J, et al. CRISPR-Cas12a Gene Editing of HBG1 and HBG2 Promoters to Treat Sickle Cell Disease. New England Journal of Medicine. 2026 Apr 2 [cited 2026 Jul 30];394(13):1281–91. Available from: https://doi.org/10.1056/NEJMoa2415550
17. Tanhehco YC, Thibodeaux S, Shi PA, Chou ST, Kelly SA, Monis GF, et al. Challenges and limitations of mobilization and stem cell collection for gene therapy of sickle cell disease. Blood Advances. 2025 Dec 15;9(24):6524–33.
18. Ballantine J, Tisdale JF. Gene Therapy for Sickle Cell Disease: Recent Advances, Clinical Trials, and Future directions. Cytotherapy. 2024 Nov [cited 2026 Jul 30];27(7). Available from: https://doi.org/10.1016/j.jcyt.2024.11.006
19. Curtis SA, Shah NC. Gene therapy in sickle cell disease: Possible utility and impact. Cleveland Clinic Journal of Medicine. 2020 Jan [cited 2026 Jul 30];87(1):28–9. Available from: https://doi.org/10.3949/ccjm.87a.19124