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A CURRENT TREATMENT AND PROSPECTIVE GENE AND STEM CELL THERAPIES TO MANAGE SICKLE CELL DISEASE

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ABSTRACT

Sickle Cell Disease (SCD) management has significantly evolved, improving patient survival and quality of life. Traditional therapies focus on symptom management, such as blood transfusions to alleviate anemia and prevent complications like strokes. Hydroxyurea, a disease-modifying drug, increases fetal hemoglobin levels, reducing red blood cell sickling and vaso-occlusive crises (VOC). Similarly, L-glutamine decreases oxidative stress and hemolysis, minimizing pain episodes. Newer therapies like voxelotor, which stabilizes hemoglobin to prevent sickling, and crizanlizumab, a monoclonal antibody targeting P-selectin to reduce VOC, offer additional relief from severe complications. These advancements have substantially improved life expectancy and reduced the burden of SCD symptoms. For patients seeking a potential cure, hematopoietic stem cell transplantation (HSCT) from matched sibling donors remains the standard. Advances in cord blood and haploidentical donor transplantation with modified conditioning regimens have expanded the donor pool, making this option more accessible. Gene therapy is an emerging curative approach currently in clinical trials, offering promising results. It involves modifying the patient's stem cells to correct the underlying genetic mutation. This multidisciplinary approach to SCD treatment reflects significant progress in addressing both the symptoms and root cause of the disease.

INTRODUCTION

Sickle Cell Disease is caused by a single genetic mutation in the hemoglobin beta gene, where valine replaces the normal glutamic acid at the sixth position of the protein chain. This mutation leads to the production of abnormal hemoglobin known as hemoglobin S (HbS). Under low oxygen conditions, HbS molecules aggregate, causing red blood cells to adopt a rigid, crescent-shaped "sickle" form. These deformed cells are inefficient at transporting oxygen and tend to stick to blood vessel walls, leading to blockages, painful vaso-occlusive crises (VOC), and progressive damage to tissues and organs. First described by Herrick JB in 1910, SCD predominantly affects individuals in Sub-Saharan Africa, with smaller occurrences in the Middle East, Indian subcontinent, Mediterranean regions, and among those of African descent.[3]

Under normal conditions, hemoglobin binds with oxygen or carbon dioxide, maintaining the biconcave shape of red blood cells. In SCD, however, the removal of oxygen causes HbS to polymerize, leading to the sickling of erythrocytes. This rigid state results in acute and chronic complications, such as acute chest syndrome (ACS), hepatic and splenic sequestration, painful episodes, and strokes. Long-term consequences, including osteomyelitis and damage to the liver, lungs, kidneys, and heart, significantly reduce life expectancy—typically by about 20 years compared to the general population. Individuals with homozygous HbS or compound heterozygous conditions experience more severe complications, though modern interventions have improved pediatric survival rates.[3]

SCD is one of the most common inherited monogenic disorders globally, disproportionately affecting individuals of African descent. It's estimated that over 20 million people worldwide are affected, including approximately 80,000–100,000 Americans, with 3,000 new cases diagnosed annually in the U.S. While newborn screening and early medical interventions have significantly improved pediatric survival rates, the average life expectancy for individuals with SCD remains about 20 years shorter than the general population.

Current therapies for SCD primarily focus on symptom management. Pain relief and supportive care are the foundation of treatment, with blood transfusions often used to raise functional hemoglobin levels, prevent strokes, and alleviate anemia. These transfusions can be performed as simple transfusions, chronic transfusion

therapy, or red blood cell exchanges. However, transfusion-related risks, such as alloimmunization, iron overload, and adverse reactions, limit their long-term effectiveness.

Hematopoietic stem cell transplantation (HSCT) is currently the only curative option for SCD. This approach involves replacing the patient's defective stem cells with healthy donor cells capable of producing normal hemoglobin. While HSCT can restore normal blood cell production, complications such as graft-versus-host disease (GVHD), donor rejection, and difficulties in finding an ideal human leukocyte antigen (HLA)-matched donor present significant barriers. Advances in using cord blood and haploidentical donors have expanded access to this treatment, but these challenges remain.

Gene therapy represents a promising frontier for SCD treatment by addressing the underlying genetic defect. This approach involves either inserting a functional gene or correcting the mutation in a patient's stem cells. The process involves harvesting hematopoietic stem cells, performing ex vivo genetic modifications, and reinfusing the corrected cells after conditioning the patient's bone marrow. This innovative method holds significant potential for providing a long-term cure while minimizing the risks associated with allogeneic transplants.

Disease modifying drug therapies

Hydroxyurea

Hydroxyurea (HU) is a disease-modifying therapy that was approved by the U.S. FDA in 1998 for the treatment of adults (>18 years) with SCD who have experienced at least three painful crises in the past year. HU works by increasing the production of fetal hemoglobin (HbF), which reduces the tendency of hemoglobin S (HbS) to polymerize. This prevents red blood cells (RBCs) from sickling and reduces the occurrence of vaso-occlusive crises (VOC). Additionally, HU decreases the number of circulating leukocytes and inflammatory mediators.

A double-blind, randomized clinical trial enrolled 148 men and 151 women, all aged 18 or older, with sickle cell anemia at 21 clinics. Participants were required to have experienced at least three painful crises in the year prior to entering the study. The results showed that the 152 patients who received HU had a significantly lower annual rate of crises compared to the 147 patients who received a placebo (median of 2.5 vs. 4.5 crises per year, $P < 0.001$). The median time to the first crisis was longer in the HU group (3.0 vs. 1.5 months, $P = 0.01$), as was the time to the second crisis (8.8 vs. 4.6 months, $P < 0.001$).

Fewer patients in the HU treatment group developed acute chest syndrome (25 vs. 51, $P < 0.001$), and fewer required blood transfusions (48 vs. 73, $P = 0.001$). While no significant adverse effects were observed, HU treatment requires careful monitoring. The beneficial effects of HU may take several months to become apparent, and the maximum tolerated dose may not be necessary to achieve a therapeutic benefit.

In 2017, HU was also approved for pediatric use in children over 2 years of age with SCD who experience recurrent moderate to severe painful crises, to reduce the frequency of crises and the need for blood transfusions.

L-glutamine

In 2017, L-glutamine was approved by the FDA for the treatment of SCD. L-glutamine is an amino acid essential for the synthesis of nicotinamide adenine dinucleotide (NAD+) and its reduced form, NADH. NAD+ serves as an important antioxidant in red blood cells (RBCs). The rationale for using L-glutamine in SCD patients is to improve the redox balance, which helps reduce oxidative stress, RBC sickling and hemolysis, and decrease the frequency of vaso-occlusive crises (VOC).

A multicenter, randomized, placebo-controlled, double-blind Phase 3 trial enrolled patients with sickle cell anemia (including HbSS and HbS-thalassemia) aged 5 years and older at 31 sites across the United States. Eligible participants had a history of at least two painful crises in the previous year. The study investigated the efficacy of pharmaceutical-grade L-glutamine (0.3 g per kilogram of body weight per dose), administered twice daily, compared to placebo in reducing the incidence of pain crises. Patients who had been receiving hydroxyurea (HU) for at least 3 months prior to screening continued their treatment throughout the 48-week study period.

A total of 230 patients (age range: 5-58 years; 53.9% female) were randomly assigned in a 2:1 ratio to receive either L-glutamine ($n = 152$) or placebo ($n = 78$). The results showed that patients receiving L-glutamine had significantly fewer pain crises than those on placebo (median of 3 vs. 4, $P = 0.005$), as well as fewer hospitalizations (median of 2 vs. 3, $P = 0.005$).

Adverse effects reported more frequently in the L-glutamine group compared to placebo included low-grade nausea, non-cardiac chest pain, fatigue, and musculoskeletal pain.

Crizanlizumab

Crizanlizumab is an anti-P-selectin inhibitor that reduces the adhesion of white blood cells and red blood cells to the endothelium. It was approved by the FDA in 2019 based on the results of a Phase 2, randomized, double-blind, placebo-controlled trial. The trial included patients with SCD (including HbSS, HbSC, HbSß°-thalassemia, HbS*-thalassemia, and other genotypes), aged 16 to 65 years, who had experienced 2 to 10 sickle cell-related pain crises in the 12 months prior to enrollment. Participants were randomized to receive either low-dose crizanlizumab (2.5 mg/kg), high-dose crizanlizumab (5 mg/kg), or a placebo, administered intravenously 14

times over 52 weeks. A total of 198 patients were enrolled across 60 study sites.

The results showed that the median rate of pain crises per year was significantly lower in the high-dose crizanlizumab group compared to the placebo group (1.63 vs. 2.98, P = 0.01). Additionally, the median time to the first and second crises was significantly longer with high-dose crizanlizumab than with placebo (first crisis: 4.07 vs. 1.38 months, P = 0.001; second crisis: 10.32 vs. 5.09 months, P = 0.02). The median rate of uncomplicated pain crises per year was also lower in the high-dose crizanlizumab group compared to placebo (1.08 vs. 2.91, P = 0.02).

Adverse events observed with crizanlizumab included arthralgia, diarrhea, pruritus, vomiting, and chest pain, which occurred more frequently than in the placebo group.

Voxelotor

Voxelotor is another disease-modifying drug (DMD) approved by the FDA in 2019 for the treatment of SCD. It works by inhibiting the polymerization of hemoglobin S (HbS) through covalent binding to the N-terminal valine of the β-globin chain, stabilizing the oxygenated form of HbS.

A Phase 3, multicenter, double-blind, randomized, placebo-controlled trial (HOPE trial) assessed the efficacy and safety of two doses of voxelotor (1500 mg and 900 mg) compared to a placebo in patients aged 12 to 65 years with various forms of SCD, including HbSS, HbSC, HbS-thalassemia, and other genotypes. A total of 274 participants were randomly assigned in a 1:1:1 ratio to receive a once-daily oral dose of either 1500 mg voxelotor, 900 mg voxelotor, or placebo.

Results showed a significantly higher percentage of patients achieving a hemoglobin (Hb) response in the 1500 mg voxelotor group (51%; 95% confidence interval [CI], 41-61) compared to the 900 mg voxelotor group (33%; 95% CI, 23-42) and the placebo group (7%; 95% CI, 1-12) at 24 weeks. The annualized adjusted incidence rate of vaso-occlusive crises (VOC) was 2.77 in the 1500 mg group, 2.76 in the 900 mg group, and 3.19 in the placebo group. Additionally, there was a trend indicating a reduced incidence of crises over time in the voxelotor groups compared to placebo.

Most adverse events were determined to be unrelated to voxelotor or placebo. There were no significant differences in the occurrence of SCD-related adverse events between the three groups, with 76% of patients in the 1500 mg voxelotor group, 73% in the 900 mg voxelotor group, and 73% in the placebo group reporting such events.

Complement inhibitors

One area of increasing interest in the pathogenesis of SCD is complement activation, which represents the protein-based arm of the innate immune system. The first report of complement activation in SCD was published in 1967 by Francis and Womack, who discovered elevated levels of serum complement markers in SCD patients. The alternative pathway (AP) of complement activation is believed to play a role in SCD, with increased levels of anaphylatoxins C3a and C5a identified during vaso-occlusive crises (VOC).

In adults with SCD, levels of sC5b-9, a marker of complete complement activation, were significantly higher compared to those without SCD. Notably, hydroxyurea has been shown to reduce complement activation: 61% of SCD patients not on hydroxyurea had elevated sC5b-9 levels, compared to a lower proportion of those receiving the treatment.

As of now, no complement inhibitors have been FDA-approved specifically for use in SCD, and large-scale clinical trials focusing on complement inhibition in SCD are yet to be conducted. However, case reports of small-scale use of complement inhibitors, such as eculizumab and ravulizumab, have been published, particularly in specific SCD scenarios like pregnancy, delayed hemolytic transfusion reactions, and VOC. Further research is needed to fully understand the relationship between complement activation and SCD.

Gene therapy: A Promising Alternative to HSCT

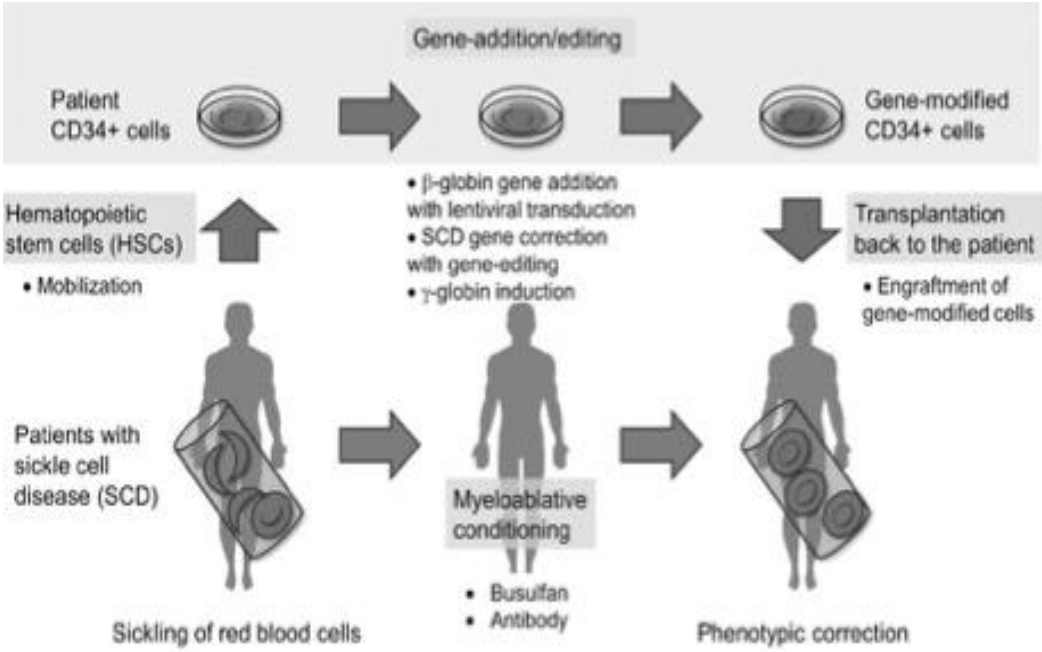
Recently, HSC gene therapy has emerged as a promising treatment for various hereditary genetic diseases, including primary immunodeficiencies, hemoglobinopathies, inherited bone marrow failure, and metabolic disorders. While it is being explored in the context of SCD, achieving efficient gene modification at the HSC level and ensuring robust globin expression in erythroid cells remains a significant challenge. Despite these hurdles, substantial progress in HSC gene therapy has been made over the past decade, paving the way for the clinical application of ex vivo gene therapy.

In recent years, gene therapy has emerged as a promising alternative to HSCT, potentially offering a curative option without the need for a donor. Gene therapy involves editing or replacing the sickle cell mutation in the patient's own hematopoietic stem cells, offering a personalized and less invasive approach to treatment. Preliminary results from gene therapy trials have been promising, with some patients achieving normal hemoglobin production and experiencing a reduction in disease-related symptoms.

However, gene therapy is still in the experimental phase, and significant challenges remain in terms of cost, scalability, and long-term safety. While gene therapy avoids the risks of GVHD and donor mismatch, the need for highly specialized medical infrastructure and the high

costs of these therapies presents barriers to widespread implementation, particularly in resource-limited settings. Nonetheless, as research progresses and these therapies become more refined, gene therapy may complement or even rival HSCT as a first-line curative treatment for SCD.[2]

In brief, the HSC gene therapy process for SCD involves harvesting bone marrow HSCs, selecting and genetically modifying the CD34+ cells, and reinfusing the engineered cells into the patient, as shown in Figure 1.



Cell-based gene therapy

Casgevy™, a cell-based gene therapy, has been approved to treat SCD in patients aged 12 and older who experience recurrent vaso-occlusive crises. This therapy is the first FDA-approved treatment to utilize CRISPR/Cas9 genome-editing technology. CRISPR/Cas9 enables precise modifications of hematopoietic (blood) stem cells by cutting DNA at specific locations, allowing for accurate editing to remove, add, or replace DNA segments. The modified stem cells are transplanted back into the patient, where they engraft (attach and multiply) in the bone marrow and increase the production of fetal hemoglobin (HbF), a type of hemoglobin that enhances oxygen delivery. Elevated HbF levels prevent red blood cell sickling, reducing disease complications and improving patient outcomes. The FDA has granted approval of Casgevy to Vertex Pharmaceuticals Inc.

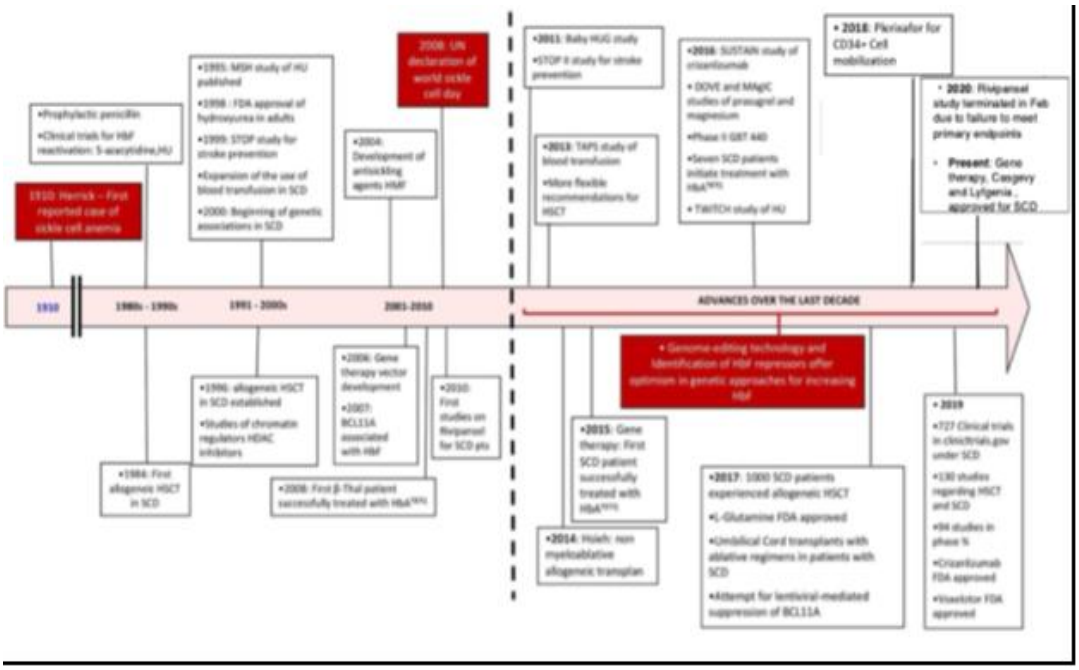
Lyfgenia™, another cell-based gene therapy, is also approved for treating SCD in patients aged 12 and older with a history of vaso-occlusive events. This therapy employs a lentiviral vector to genetically modify the patient's blood stem cells, enabling the production of HbAT87Q, a gene-therapy-derived hemoglobin that mimics hemoglobin A, the standard adult hemoglobin found in individuals without SCD. Red blood cells containing HbAT87Q have a significantly lower risk of sickling and blood flow blockage. The modified stem cells are transplanted back into the patient to achieve therapeutic effects. The FDA granted approval of Lyfgenia to Bluebird Bio Inc.

Both Casgevy and Lyfgenia are personalized treatments, using the patient's own blood stem cells. These cells are genetically modified and administered as a one-time, single-dose infusion during a hematopoietic stem cell transplant. Before treatment, patients undergo myeloablative conditioning (high-dose chemotherapy) to clear the bone marrow of existing cells, allowing the modified cells to engraft and function effectively. Patients treated with either therapy will be monitored through long-term studies to assess their safety and effectiveness.

While stem cell transplantation offers a potentially curative option for SCD, it is not accessible for most patients due to the lack of suitable donors and the toxicity of intensive chemotherapy. However, a recent study presented at the 65th American Society of Hematology (ASH) Annual Meeting demonstrated promising outcomes with a modified transplantation procedure. This approach broadens the donor pool and uses a gentler conditioning regimen, making treatment safer and more feasible for a wider range of patients.

"Sickle cell disease is a rare, debilitating, and life-threatening blood disorder with significant unmet need. We are thrilled to advance the field, particularly for individuals whose lives have been severely impacted by the disease, by approving two cell-based gene therapies

today," said Nicole Verdun, M.D., director of the Office of Therapeutic Products within the FDA's Center for Biologics Evaluation and Research. "Gene therapy holds the promise of delivering more targeted and effective treatments, especially for individuals with rare diseases where current options are limited."



Hematopoietic stem cell transplantation

Although significant progress has been made in managing SCD, the safety and accessibility of treatments remain global challenges. Hematopoietic stem cell transplantation (HSCT) is the only known cure, with gene therapy emerging as a promising alternative. However, HSCT faces limitations, including patient selection (end-organ damage, disease severity, and age), risks of toxicity, long-term complications like graft-versus-host disease (GVHD), and the availability of compatible donors. This article explores recent advancements in HSCT, current challenges, and future directions.

Patient selection for HSCT depends on a personalized analysis of benefits versus risks. The procedure is recommended only for those with a compatible donor, where recovery advantages outweigh transplant risks. Age and suitable donors significantly impact HSCT outcomes. Research shows that pediatric patients with HLA-matched sibling donors and a myeloablative conditioning regimen have the highest success rates. A global study found 5-year overall survival (OS) rates of 95% for those under 16, and 81% for those over 16. Event-free survival (EFS) rates were 93% and 81%, respectively. The hazard ratio for treatment failure increases by 9% with each additional year of age, while GVHD risk rises by 4% **(1)**.

Previous studies

Fifty patients with sickle cell anemia underwent transplantation using HLA-identical hematopoietic stem cells (bone marrow, 48; cord blood, 2). These patients were divided into two groups for transplantation[5]:

- **Group 1:** Included 36 patients who were permanent residents of a European country and retrospectively met the inclusion criteria established at the 1990 Seattle consensus conference. In this group, children were selected due to evidence of a severe disease course.
- **Group 2:** Consisted of 14 patients who were transplanted earlier, had received no more than three blood transfusions, and chose to return to their country of origin for treatment.

Kaplan-Meier estimates for overall survival, event-free survival (EFS), and disease-free survival (DFS) at 11 years for the entire grafted population were 93%, 82%, and 85%, respectively. In **Group 1**, these rates were 88%, 76%, and 80%, while in **Group 2**, they reached 100%, 93%, and 93%, respectively. These outcomes demonstrate the potential for long-term success in managing SCD through stem cell transplantation.

In successfully treated patients, clinical manifestations of SCD and associated hemolytic anemia resolved completely. Spleen function also recovered in seven out of 10 patients evaluated, highlighting significant improvements in overall health.

While adverse events such as death, graft failure, mixed chimerism, and relapse did occur, they were less frequent in **Group 2** compared to **Group 1** (7% vs 25%, **P < 0.001**). Acute graft-versus-host disease (GVHD) was managed in 20 patients (grade I or II in 19, grade III in 1), and chronic GVHD was present in 10 patients (limited in 7, extensive in 3). Importantly, one patient

developed acute myeloid leukemia, but these events are relatively rare.

Gonadal dysfunction was observed in all patients (six boys and eight girls) who underwent transplantation during or after puberty, though it was transient in one adolescent girl. These outcomes underscore the potential for significant positive health improvements with careful management and follow-up.[7]

This study has been supported by other research, including: Hematopoietic stem-cell transplantation has primarily been used as a treatment option for severe SCD through myeloablative matched sibling donor transplants over the past two decades, demonstrating the potential benefits of this approach. While it served as proof of concept, the challenges and limitations of transplantation have become increasingly clear. It has since been recognized that transplantation for SCD doesn't need to follow the same strict principles as those used for malignant disorders, such as achieving full donor cell chimerism. In recent years, the transplant community has focused on expanding access to stem-cell transplantation for patients with the disease, refining indications and timing, and reducing toxicities through novel conditioning techniques and improved supportive care.[5]

Adults matched unrelated donors

Allogeneic hematopoietic stem cell transplantation (HSCT) is rarely performed in adult patients with SCD. In this study, 13 high-risk SCD adults received a chemotherapy-free regimen using alemtuzumab, total body irradiation (300 cGy), and sirolimus as post-transplant immunosuppression between November 2011 and June 2014. Patients received matched related donor (MRD) granulocyte colony-stimulating factor-mobilized peripheral blood stem cells, including two ABO-incompatible cases.

All 13 patients initially engrafted. A stable mixed donor/recipient chimerism was maintained in 12 patients (92%), while one patient experienced secondary graft failure due to non-compliance with sirolimus. With a median follow-up of 22 months (range, 12 to 44 months), there was no mortality, no acute or chronic graft-versus-host disease (GVHD), and no severe side effects. One year after transplantation, patients with stable donor chimerism had normalized hemoglobin levels and improvements in cardiopulmonary function and quality of life, including reduced pain and better overall health.

In four patients, sirolimus was stopped without any rejection or complications from SCD. These results underscore the successful use of a chemotherapy-free regimen in MRD HSCT for high-risk adult SCD patients and demonstrates a high cure rate, absence of GVHD or mortality, and improvement in QoL including the applicability of this regimen in ABO mismatched cases.[4]

DISCUSSION

Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for SCD. Over the past few decades, this procedure has demonstrated remarkable success, particularly in pediatric patients with a matched sibling donor. By replacing defective hematopoietic stem cells with those capable of producing normal hemoglobin (HbA), HSCT offers the potential to resolve the underlying genetic mutation in SCD and eliminate the life-threatening complications associated with the disease. Clinical outcomes, particularly in younger patients and those with fewer disease-related complications, have shown that HSCT can dramatically improve survival, quality of life, and long-term health outcomes. However, despite its curative potential, the widespread application of HSCT for SCD faces several challenges, including donor availability, patient eligibility, treatment-related complications, and accessibility, all of which need to be carefully considered in clinical decision-making.

Advancements in HSCT: Expanding access to a cure

The landscape of HSCT for SCD has evolved significantly over the years, primarily through advancements in donor selection and conditioning regimens. Traditionally, matched sibling donors were considered the ideal source of hematopoietic stem cells, as these transplants have the highest success rates. However, recent advances in the use of alternative donor sources, such as umbilical cord blood and haploidentical (partially matched) donors, have expanded the pool of eligible patients. These alternative donor strategies have increased the number of patients who can access curative HSCT, particularly those who lack a fully matched sibling donor.

Furthermore, the refinement of conditioning regimens, particularly those that reduce chemotherapy-related toxicity, has made HSCT a viable option for older patients and those with significant comorbidities, expanding the eligibility for transplant.

One promising development is the use of chemotherapy-free or reduced-intensity regimens. These less toxic approaches have demonstrated promising results in reducing the risk of graft-versus-host disease (GVHD) and other complications, particularly in adults and high-risk patients. Additionally, improvements in post-transplant care, such as more effective immunosuppressive protocols, have further enhanced the safety profile of HSCT.

However, despite these innovations, challenges remain. The requirement for a suitable donor—whether a fully matched sibling, haploidentical relative, or umbilical cord blood—still represents a significant barrier to accessing HSCT. For patients in regions where bone marrow registries are underdeveloped or those without family members who are compatible donors, the options for curative HSCT are limited. These limitations are

compounded by logistical challenges, such as the availability of transplant centers with the requisite infrastructure and expertise.

Challenges and Limitations of HSCT for SCD

While HSCT offers a curative solution, it is not without its risks and challenges. One of the most significant barriers is patient eligibility. HSCT is typically recommended for patients with severe forms of SCD who experience frequent pain crises, organ damage, or other life-threatening complications. However, determining the appropriate timing for transplant is complex. For patients with less severe disease, the risks associated with HSCT—such as infection, GVHD, graft failure, and relapse—may outweigh the benefits. Moreover, transplant outcomes tend to be better in younger patients, particularly those under the age of 16, which raises questions about the optimal age for transplant. Some studies have suggested that delaying HSCT until later in life could increase the risk of complications, especially in patients with advanced organ damage.

GVHD, a major complication of allogeneic stem cell transplants, remains a significant concern. Even with improved immunosuppressive strategies, GVHD continues to pose risks to both patient survival and quality of life. The incidence of GVHD can be reduced by using reduced-intensity conditioning regimens or by employing alternative donor sources, but these strategies are not without their own set of challenges. The long-term effects of GVHD, including chronic GVHD, can have a profound impact on patients' physical and psychological well-being, underscoring the need for careful post-transplant monitoring and management.

Additionally, HSCT is an expensive procedure, with costs that include pre-transplant assessments, the transplant itself, and extended hospitalization periods for post-transplant care. In many low- and middle-income countries where SCD is most prevalent, the cost and resource-intensive nature of HSCT limits its availability, further exacerbating the disparities in SCD care. Despite the clear benefits of HSCT, it remains largely inaccessible to a significant portion of the global SCD population.

The Role of HSCT in the Context of Disease-Modifying Therapies

While HSCT represents a curative option, many patients may not be candidates for the procedure. For these individuals, disease-modifying drugs (DMDs) such as hydroxyurea, L-glutamine, voxelotor, and crizanlizumab offer substantial improvements in managing symptoms and preventing complications. These therapies have demonstrated significant efficacy in reducing the frequency of pain crises, preventing stroke, and improving overall survival. However, none of these treatments can cure the disease, and they often require lifelong administration.

The decision to proceed with HSCT is complex and requires a careful assessment of the patient's disease severity, response to DMDs, and the potential risks and benefits of transplant. For patients with severe disease and frequent complications, HSCT remains the preferred option, as it offers the possibility of a cure and the elimination of the long-term complications of SCD. For patients with milder forms of the disease, DMDs may provide sufficient symptom management, making the risks of HSCT less appealing.

An integrated approach that combines HSCT, DMDs, and gene therapy is a promising future direction in SCD management. For example, HSCT may be considered the gold standard curative approach for patients with severe SCD, while DMDs may serve as adjuncts to support patients in the peri-transplant period or to manage milder disease.

Future Directions and Areas for research

Looking ahead, several areas of research are critical to improving the outcomes of HSCT for SCD. Firstly, improving patient selection criteria will be vital to ensuring that HSCT is offered to those who will benefit most, while minimizing the risks to patients who may not be ideal candidates. Research into biomarkers that predict HSCT success could help identify the most suitable patients for the procedure.

Additionally, further research into optimizing donor matching and reducing complications such as GVHD will be essential for expanding the availability of HSCT to a broader range of patients. The development of novel gene-editing techniques, such as CRISPR-Cas9, and advances in gene therapy hold promise for reducing the need for allogeneic donors and providing a more accessible, personalized treatment option.

Finally, addressing the global disparities in access to HSCT remains a critical priority. Efforts to reduce the cost of the procedure, improve healthcare infrastructure, and expand donor registries in underserved regions will be essential to ensuring that the benefits of HSCT reach all patients who need it.

Gene-editing trials have recently gained momentum. These techniques use the body's natural repair mechanisms, endonucleases, bacterial defense systems, and advanced delivery systems. While progress has been made, further optimization is needed, as efficient gene editing and long-term cell engraftment remain challenging(2).

CONCLUSION

Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for SCD. Over the past few decades, HSCT has shown remarkable success, particularly in pediatric patients with a matched sibling donor. By replacing defective hematopoietic stem cells with those capable of producing normal hemoglobin

(HbA), HSCT offers the potential to eliminate the underlying genetic mutation responsible for SCD and resolve the life-threatening complications associated with the disease.

Clinical outcomes, especially in younger patients and those with fewer disease-related complications, demonstrate that HSCT can dramatically improve survival, quality of life, and long-term health. Studies have shown 5-year overall survival (OS) rates of 95% in pediatric patients with HLA-matched donors. However, challenges remain, including the availability of suitable donors, patient eligibility, treatment-related complications, and access to care.

In adult patients, chemotherapy-free regimens using matched related donors have yielded promising results, with stable donor chimerism and improvements in quality of life, including reduced pain and better overall health. Despite these advancements, HSCT remains limited by factors such as donor compatibility, age considerations, and the risks of graft-versus-host disease (GVHD).

Ongoing research continues to refine the procedure, expand access through alternative donor sources like haploidentical donors and cord blood, and develop innovative conditioning techniques to minimize risks. HSCT remains the gold standard for curing SCD, offering hope to many patients, but its success depends on careful patient selection and overcoming the barriers to wider application.

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