Treatment with curative intent: the emergence of genetic therapies for sickle cell anemia

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Abstract-A s imple point mutation (Glu6Val) in the beta-globin gene (HBB) brings about sickle cell disease (SCD), a genetic disorder of hemoglobin that has a predominant form of abnormal hemoglobin S (HbS). In places where oxygen is less, HbS turns into a solid mass, with red blood cells acquiring the typical sickle shape in the process. This leads to a series of events such as chronic hemolytic anemia, and damage to multiple organs due to lack of blood supply, vaso-occlusion episodes, and shortened life span. In addition to the long-term disadvantages like the insufficient efficacy of drugs, transfusion problems, and the limited availability of drugs in resource poor settings, standard medical care (hydroxyurea, chronic transfusions, supportive care) reduces morbidity but does not eliminate the genetic defect. The curative gene therapy techniques for sickle cell disease (SCD) have focused on two dominant pathways: the first one is gene addition, in which lentiviral vectors (Lenti Globin) are employed to transfer a functional beta-globin transgene to the patient's autologous hematopoietic stem and progenitor cells (HSPCs) outside the body and the second approach is gene editing which means accurately altering the patient's HSPCs to either fix the sickle mutation or increase fetal hemoglobin (HbF) by turning off the repressors (e.g., editing BCL11A or HBG promoters of the erythroid enhancer). The initial and ongoing clinical trials have indicated that one *ex vivo* autologous HSPC infusion can lead to considerable HbF induction or permanent therapeutic hemoglobin being expressed and, moreover, it can greatly reduce vaso-occlusive crises. Newer methods such as prime editing and non-viral editing techniques are precise correction once the safety and manufacturability have been possibly improved, whereas CRISPR/Cas9-based editing of HSPCs to upregulate HbF (CTX001/Casgevy and related programs are examples) and lentiviral beta-globin gene addition have shown high treatment response rates with prolonged clinical benefit in most of the treated patients.

I. INTRODUCTION

Global epidemiology and burden of sickle cell disease (SCD)

Sickle cell disease (SCD), one of the most common inherited blood disorders around the globe, is still a major concern in many parts of sub-Saharan Africa, India, the Middle East, and some areas of the Mediterranean [1]. The latest projection from the Global Burden of Disease suggests that there are millions of patients with sickle cell disease (SCD), and every year, SCD accounts for tens of thousands of deaths [2, 3]. In underdeveloped areas where there is no neonatal screening and medical care is inadequate, the mortality rate for infants under five years old is extremely high [4]. Besides that, chronic hemolytic anemia, recurrent very painful vaso-occlusive crises (VOCs), progressive organ destruction (kidney, lung, and brain), and severe reduction of quality of life and life expectancy without disease-modifying treatment are among the health impacts on the population [5, 6, 7].

Background information about the sickle mutation's discovery (β-globin gene, Glu6Val)

Despite the fact that the disease was first reported in clinical settings in the early 1900s (James B. Herrick, 1910) [8], it took until the mid-century for the molecular basis of sickle cell disease (SCD) to be uncovered. In 1949, Linus Pauling and his colleagues were the first to refer to sickle cell disease (SCD) as a "molecular" ailment [9]. Subsequently, Vernon Ingram isolated the exact amino acid switch resulting in hemoglobin S (HbS): the substitution of glutamic acid for valine at the 6th position of the beta-globin chain (Glu6Val) [1, 10]. This single-nucleotide/single-

amino-acid change transformed SCD into a classic model of a monogenic disorder, thus, opening the doors to the development of molecular diagnostics and therapeutics that are specifically targeted to the disease [11].

Hemoglobin polymerization, sickling, and vaso-occlusion are the mechanisms of the disease.
The pathophysiologic cascade in SCD starts with the polymerization of deoxygenated HbS inside erythrocytes [12, 13]. Chronic hemolysis occurs due to polymer production, which shortens the lifespan of erythrocytes, increases red cell stiffness, and transforms red cells into the distinct sickle shape [12, 14]. Activated endothelium, leukocytes, platelets, and sickled, adhesive red blood cells interact, leading to microvascular blockage, ischemia-reperfusion injury, inflammation, and the clinical signs of vaso-occlusion [5, 15]. These signs include acute chest syndrome, stroke, episodic severe pain, and progressive damage to organs [6, 7]. Recent biophysical and cellular studies have clarified the kinetics of polymer nucleation, the role of intracellular hemoglobin concentration and modulators like 2,3-BPG, and how coagulation and inflammatory pathways contribute to vaso-occlusion [16].

II. PATHOPHYSIOLOGY OF SICKLE CELL DISEASE

Genetic mutation in HBB gene and HbS formation
Sickle cell disease (SCD) comes from a single-point mutation (A rightarrowT transversion) in the sixth codon of the beta-globin (HBB) gene on chromosome 11 [1]. This change substitutes valine for glutamic acid (Glu6Val) in the beta-globin chain [10, 14]. The substitution creates hemoglobin S (HbS), which has a hydrophobic valine residue. This residue leads to unusual interactions when deoxygenated, causing polymers to form inside red blood cells. The mutation follows an autosomal recessive pattern. Homozygosity (HbSS) results in classical sickle cell anemia. Compound heterozygosity with other beta-globin variants (e.g., HbSC, HbS beta-thalassemia) leads to different clinical features.

Cellular mechanisms of hemolysis and vaso-occlusion
The main feature of SCD is HbS polymerization when there is low oxygen. Polymerized HbS changes the shape of red blood cells into stiff, crescent-like shapes that are less flexible. These cells have membrane damage, ion imbalance, and oxidative stress, which cause premature hemolysis [17]. Free hemoglobin released during hemolysis in the blood vessels takes up nitric oxide, which decreases vasodilation and leads to endothelial dysfunction. At the same time, ischemia-reperfusion damage and microvascular blockage are caused by sickled red blood cells, white blood cells, and platelets sticking to active endothelium [15]. These events increase vaso-occlusion and trigger repeated pain crises by activating complement, coagulation, and inflammatory pathways. Studies show that adhesion molecules like integrins, P-selectin, and VCAM-1 play a key role in this harmful interaction. Blocking these pathways, for instance, with crizanlizumab, can reduce the number of vaso-occlusive events [18].

Role of fetal hemoglobin (HbF) in disease modulation
The degree of sickle cell disease (SCD) is influenced by fetal hemoglobin (HbF; alpha2gamma). HbF reduces the amount of intracellular HbS and forms hybrid tetramers (alpha2gamma) that are less likely to sickle [19]. People who inherit genetic modifiers that increase HbF levels, such as certain variations in BCL11A$, HBS1L-MYB, and KLF1, or those with hereditary persistence of HbF (HPFH), experience fewer vaso-occlusive crises and show milder disease symptoms [20]. Pharmacologic drugs like hydroxyurea promote HbF production, which improves red blood cell flow and decreases the frequency of crises [4]. Newer gene-editing therapies aim to reactivate HbF and mimic benign HPFH conditions by targeting BCL11A erythroid enhancers [21, 22]. This approach has been validated in clinical gene therapy trials [23].

Current Therapeutic Approaches and Limitations
Hydroxyurea still stands as the main treatment that actually changes the course of sickle cell disease [24]. It raises fetal hemoglobin (HbF) and lowers white blood cell counts, which means fewer episodes of acute chest syndrome, less need for transfusions, and fewer painful vaso-occlusive crises. When doctors use high doses and tailor the dosing for each person, hydroxyurea gets even safer and more effective [4]. But honestly, its benefits only go so far [25]. Some patients just can’t keep up with the treatment over

time, run into problems accessing it, miss out on lab monitoring, or don't respond as well as hoped [26]. Now, newer small-molecule drugs have started to shake things up [27].

For people who have frequent pain crises, crizanlizumab—a monoclonal antibody against P-selectin—can be added to the mix [18, 28]. It works by stopping cells from sticking together, which cuts down on those painful crises. Voxelotor, which tweaks how hemoglobin holds onto oxygen, does more than just boost hemoglobin levels; it actually lowers markers of red cell destruction too [29]. Still, it's had its own safety questions and some regulatory hurdles [30, 31].

Supportive care: transfusion therapy and iron management

Chronic red cell transfusion is also a solid way to manage sudden complications and protect kids from their first stroke—and from having another one [32]. Transfusions bring more oxygen to the body and drop the percentage of sickled cells, which helps [25]. But they come with their own baggage: the risk of developing antibodies against donor blood, the need for iron chelation because of iron overload, and, though rare with screened blood, the chance of getting an infection from a transfusion. And the reality is, being tied to a schedule of regular transfusions can wear people down. These challenges make long-term transfusion therapy tough to pull off, especially in places where resources are stretched thin—places where most patients actually live [33].

For kids, especially, there's a really hopeful option: allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-matched sibling [34]. This approach offers high cure rates, great long-term survival, and a real shot at living free from the disease [35].

Autologous gene therapy and gene editing (curative potential)

Autologous, *ex vivo* gene-based therapies are now already in the phase of getting approved by the regulatory authorities and also conduction late-stage clinical trials [11, 36]. There's been the discovery of two major methods, namely: (1) Delivery of the transgenes of anti-sickling beta-globin to the patient HSPCs through gene addition by means of lentiviral vectors (like Lenti Globin) [37], and (2) the utilization of gene editing (like CRISPR/Cas9) to either overcome the HBB mutation or to upregulate HbF by interfering with the $BCL11A$ erythroid enhancer [22, 38]. The results of the clinical studies are so encouraging to a point that the majority of the patients receiving a single treatment experience not only the persistence of HbF or therapeutic globin expression but also almost complete disappearance of clinical events, with VOCs and transfusion dependency having been significantly reduced [39].

The issues of the risk of insertional mutagenesis (for integrating vectors), manufacturing and logistics that can be complex and expensive, long-term safety being unclear (for example, a very few cases of myeloid malignancies have made the situation more monitoring) [40], conditioning toxicity linked to myeloablative regimens, and, above all, the high upfront costs that make it difficult for the global population to access the treatment equally are among the factors that have been raising questions about the safety and limitations of gene therapies [41, 42]. Besides that, it is still a long process to wait for the robust development of the long-term follow-up; monitoring and registries will be the key to determining the late adverse events and the durability of the effect [43].

Health-system, equity, and access challenges

Equals in delivery pose a big challenge to the medical field, even though the treatments are highly effective [44]. The spread of cures is limited by the high price of products that can cost from one hundred thousand to over a million dollars per patient, the need for specialized facilities for the whole process of HSPC collection, conditioning, and infusion, and the lack of proper medical infrastructure in places where SCD is most prevalent (e.g., sub-Saharan Africa and parts of India) [45, 46]. The application of therapeutic methods to improve population health is hindered by social determinants of health, discrepancies in donor availability for HSCT, and possibly ethnic and socioeconomic differences in transplant and post-therapy outcomes [47].

III. OVERVIEW OF GENE THERAPY APPROACHES

Principles of gene therapy and genome editing

Gene therapy is a method that aims to heal or cure genetic disorders in a long-lasting way by adding,

replacing, or even perfectly modifying the genetic material of a patient's cells [48]. Genome editing techniques (CRISPR/Cas, base editors, and prime editors) perform precise edits on the DNA sequence of the individual's genes, which could involve correcting a pathogenic mutation or modulating gene expression by altering the regulatory elements [49]; whereas, classical gene addition provides a functional copy of a missing or defective gene (usually via integrating viral vectors) [37]. By eliminating the requirement for donor templates and double-strand breaks (DSBs), modern editors (such as base editors and prime editors) improve precision and expand the range of possible alterations [50].

Ex vivo versus in vivo gene editing techniques

There are two major clinical paradigms [48]. Patient cells—most often hematopoietic stem and progenitor cells or HSPCs—are manipulated using *ex vivo* methods outside the human body, the outcomes are either selected or tested, and afterwards, the modified autologous cells are treated with conditioning and then reintroduced [51]. This method, which has been employed for blood disorders, allows for vigorous quality control, the selection of rightly modified cells, and even the non-target tissues having less exposure to the editing agent. Moreover, *in vivo* methods are seen as attractive because they present additional transport, targeting, immunological, and off-target-safety issues when simpler outpatient delivery is sought or for tissues that are less susceptible to *ex vivo* modification [52]. In practice, for instance, through the use of lipid nanoparticles or viral vectors, *in vivo* methods pour editing agents directly into the patient [53].

Delivery platforms: lentiviral vectors, AAV, and CRISPR/Cas systems

Lentiviral vectors (LVs) are the backbone of many successful HSC gene-therapy programs and are mainly used for *ex vivo* HSPC gene addition [54] due to their potential to transduce quiescent HSPCs effectively, their capability of stable genomic integration for long-lasting expression, and their increasingly favorable safety profile after generations of vector engineering (e.g., LentiGlobin) [55]. Among the drawbacks are difficult production and insertional genotoxicity, which is partially mitigated by modern self-inactivating designs. Due to their high transduction efficiency in different tissues and low integration tendency, adeno-associated virus (AAV) vectors are the preferred choice for *in vivo* gene transfer [52]; however, their application is restricted due to their small cargo capacity, presence of anti-AAV immunity, and the challenge of targeting HSPCs for *ex vivo* methods [56].

CRISPR/Cas systems (and their derivatives, such as base editors, prime editors, and Cas12/Cas13 families) make programmable, sequence-specific editing a reality [49]. They have given birth to CRISPR nucleases, which can make specific DSBs that cells repair through (NHEJ or HDR) for gene-driven disruption, correction, or insertion. As a result of base editors and prime editors, many edits are made without DSBs, thus, reducing a part of genotoxicity risks and opening more paths for treatment [50]. Depending on the target cell, the intended edit, and the safety concerns, CRISPR components can be delivered as ribonucleoprotein complexes (RNPs), mRNA, or DNA in viral or non-viral carriers.

Target cells: hematopoietic stem and progenitor cells (HSPCs)

The HSPCs (CD34^{+} cells) are the main target of sickle cell disease and other blood disorders since the persistent engraftment of corrected HSPCs leads to a continuous supply of healthy blood cells [57]. *Ex vivo* editing of HSPCs has established the therapeutic benefit of creating hematologic correction with gene-editing techniques that last long (lentiviral gene insertion; CRISPR-mediated $BCL11A$ enhancer disruption), and it allows for functional selection, potency assays and release testing before infusion [58]. It is a challenging task to achieve high edit efficiency in long-term repopulating HSCs (not just short-lived progenitors), to maintain stemness during *ex vivo* manipulation, and to reduce conditioning-related toxicity that is necessary for engraftment when working HSPC-targeted methods [57]. There are new studies that focus on making *ex vivo* culture shorter, improving the engraftment of modified long-term HSCs, and less harmful conditioning regimens or *in vivo* HSC targeting methods [52].

Safety, efficacy, and practical trade-offs

Every strategy has to juggle practicality, safety, and how well it works [58]. *Ex vivo* CRISPR editing can make really precise tweaks—like disrupting the

$BCL11A$ enhancer to boost fetal hemoglobin (HbF)—but it still needs to prove it's safe over the long haul and that the edited stem cells actually take hold for good [23]. *In vivo* methods, on the other hand, might slash costs and need less infrastructure, but they bring up bigger worries: Are we hitting the right spots in the genome? What about immune reactions or how the treatment spreads through the body? [52] Then there's *ex vivo* lentiviral gene addition. It leads to stable gene expression, but the process itself is pretty complicated, with tough manufacturing steps and strong conditioning [55].

IV. GENE ADDITION STRATEGIES

Lentiviral vector-based addition of functional β-globin genes

Mechanism

Here's how gene insertion works: Scientists take a patient's hematopoietic stem and progenitor cells (HSPCs) and, outside the body, insert a working copy of a modified beta-globin gene [37]. They usually use lentiviral vectors like BB305 LVV because these can slip the new gene right into the cell's DNA [59]. The added gene, {T87Q}, carries a T87Q mutation that helps prevent red blood cells from sickling [60]. It acts a lot like normal adult hemoglobin, so it cuts down the amount of sickle hemoglobin (HbS) and helps red cells do their job better [60]. After the gene transfer and conditioning—busulfan is often used for this—the modified HSPCs get infused back into the patient, where they can settle in and start making healthy red blood cells [37].

Example: Bluebird Bio's Lovo-cel (lovotibeglogene autotemcel; also Lyfgenia)

Bluebird Bio's Lovo-cel (also called bb1111 or LentiGlobin for SCD) is a one-time, *ex vivo* lentiviral gene therapy [61]. It uses the BB305 lentiviral vector to deliver the globin gene. Patients first have their HSPCs mobilized, usually with plerixafor, then collected through apheresis [62]. The cells are transduced with the vector and, after full conditioning with busulfan, infused back into the patient [62].

Efficacy and clinical trial outcomes

Once they optimized the vector manufacturing and cell collection steps, things really picked up in Groups B and C [63]. Patient B1 hit about 6.4{ g/dL} for with a VCN around $0.53 and patient B2 reached the same hemoglobin level but with a higher VCN—about $2.14 [64]. Every adolescent in the trial saw full resolution after these changes [65]. With these higher expression levels, patients not only had better hemoglobin, they also had less hemolysis and just felt better overall [37]. For a lot of them, these gains lasted through long follow-ups [60]. After therapy, total hemoglobin jumped: in one report, treated patients who stopped needing transfusions had a median hemoglobin around} (ranging from about 6.6 to 15.1), and in many cases, the therapeutic globin made up more of their hemoglobin [64]. As for durability, gene expression (the anti-sickling hemoglobin) stays strong [65]. Over years of follow-up, vaso-occlusive events (VOEs) and severe VOEs kept dropping or disappeared completely [66].

Safety and limitations

On the downside, patients go through myeloablative conditioning with busulfan [64]. That brings the usual risks: cytopenias, mouth sores, and a higher chance of infection—just like most *ex vivo* autologous HSC gene therapies [62]. There are also some risks tied to the vector. A few patients had anemia or other notable side effects [64]; in earlier groups, there was some worry about leukemia or myelodysplastic syndrome, but investigations haven't shown the lentiviral vector caused it [40]. There was one case of AML, but no clear link to the vector. Early on, in Group A, gene expression was only moderate and VCNs were lower, so results weren't great [63]. That led the team to improve how they did the transduction and manufacturing, and to get better at mobilizing HSCs [63]. In the end, this meant higher VCNs and much better.[63].

Gene Editing Strategies

By fixing or avoiding the underlying beta-globin gene deficiency, gene editing has become a revolutionary method for the curative treatment of sickle cell disease (SCD) [38]. Gene editing techniques precisely alter endogenous DNA sequences to revive fetal hemoglobin (HbF) or fix the sickle mutation itself, in contrast to conventional gene addition therapies that use lentiviral vectors to insert functional copies of beta-globin.

CRISPR/Cas9-Mediated Reactivation of Fetal Hemoglobin (HbF)

CRISPR/Cas9 actually comes from a trick bacteria use to defend themselves [49]. Scientists borrowed this system to cut DNA exactly where they want, so they can fix or change genes. In sickle cell disease (SCD), they've used CRISPR/Cas9 to turn fetal hemoglobin (HbF) back on. Why? Because HbF stops sickle hemoglobin from clumping together, which means red blood cells don't get stuck and break as easily [19].

The best-studied approach goes after a part of DNA called the $BCL11A enhancer [22]. This bit normally shuts down the gamma-globin gene after you're born, but if you mess with it, the body keeps making HbF [21]. That's huge for people with faulty beta-globin genes since HbF takes over the job. Real-world studies and lab work back this up [38]. Patients who got CRISPR-edited stem cells—specifically with Exagamglogene autotemcel (Casgevy, exa-cel)—stopped needing blood transfusions and didn't have those awful pain crises anymore, according to the CLIMB-121 and CLIMB-Thal-111 trials [67, 23]. Because of these results, Casgevy became the first CRISPR gene therapy approved for both SCD and beta-thalassemia in December 2023 [11].

Base Editing and Prime Editing Approaches

Newer tools like base editing and prime editing let scientists tweak a single DNA letter without messing up the whole genome [50]. CRISPR/Cas9, on the other hand, works by cutting both DNA strands, which can get a bit messy. With base editors, you can switch certain bases—say, turning—by hooking a special enzyme to a modified Cas9 that doesn't cut DNA. That's how BEAM Therapeutics designed BEAM-101. They use this approach to mimic HPFH mutations, which help raise fetal hemoglobin and reduce sickling in blood cells. Early clinical results look good—these edits seem safe and effective in blood stem cells grown outside the body [50]. Prime editing takes things a step further [49]. Think of it like a DNA "search-and-replace" tool. It can insert, delete, or fix DNA right where you want, and you don't need donor templates or to break both DNA strands [50]. Anzalone and his team first described this approach. In recent studies, researchers used prime editors to fix the Glu6Val mutation in patient blood stem cells grown in the lab. Compared to standard CRISPR/Cas9, base and prime editing look safer and more precise, with fewer off-target mistakes [49]. They're shaping up to be the future of genome editing [50].

Comparison: Editing vs. Addition Strategies

Gene editing taps into the body's own regulatory systems, keeping natural gene control in place and lowering the risk of random vector insertions [58]. On the other hand, gene addition drops in working copies of the beta-globin gene [37]. When editing targets BCL11A or corrects the sickle mutation itself, patients can get lasting anti-sickling hemoglobin with less worry about integration problems [23]. Still, editing efficiency, off-target changes, and high costs slow down widespread adoption [58]. Big picture: Gene editing is shifting sickle cell disease treatment from just managing symptoms to actually aiming for a cure [23]. As clinical trials keep pushing these technologies forward, more people around the world should finally get access to long-term, life-changing treatments [44].

Clinical Trials and Current Development

Gene editing and gene therapy have picked up serious momentum in the clinic over the last few years [43]. We've seen breakthrough trials, even some big regulatory approvals [11]. In this section, I'll dig into the major clinical studies using gene therapy for sickle cell disease—what researchers found, how safe these treatments look, and where the field's headed next [38].

V. MAJOR TRIALS IN SCD GENE THERAPY

CLIMB SCD-121 (exa-cel / Casgevy in SCD)

The key CLIMB SCD-121 trial looks at patients between 12 and 35 who've had at least two vaso-occlusive crises (VOCs) a year [68]. It's a Phase III single-arm study testing exagamglogene autotemcel (exa-cel, Casgevy) [23]. In the pre-planned interim analysis, of patients went at least a year without any severe VOCs [23]. Even better, none of them needed to be hospitalized for VOCs during that stretch. No one ran into unexpected problems from the gene-editing treatment, and the overall safety matched what you'd expect from myeloablative conditioning and an autologous transplant. The results look solid over time, too [69]. The median follow-up now tops five years for both sickle cell disease and transfusion-dependent β-thalassemia groups, and the benefits keep

going [70]. Early data published in $NEJM$ showed VOCs disappeared in of treated sickle cell patients during a year of follow-up [68]. Plus, their fetal hemoglobin and total hemoglobin levels kept climbing [23].

Lovotibeglogene autotemcel (Lyfgenia)

In December 2023, the FDA signed off on Lyfgenia (which used to be called Lovo-cel), along with Casgevy, for people with sickle cell disease who are at least 12 years old and keep having VOCs [11]. With Lyfgenia, doctors introduce an anti-sickling beta-globin transgene into a patient's own HSPCs using a lentiviral vector—basically, it's gene addition therapy [37]. Experts look at how well it works, how long the effects last, and how it stacks up against exa-cel by running comparative value assessments like ICER [61].

Efficacy, Safety, and Durability

Gene-editing treatments like exa-cel have been around for over a year now, and the results look pretty impressive [23]. These therapies nearly wipe out volatile organic compounds (VOCs), and people see big improvements in blood counts and overall quality of life. A lot of patients keep strong grafts and good HbF levels for three to five years—sometimes longer—but we still need more time to know if these benefits really last a lifetime. So far, early data doesn't show any gene-specific safety problems, and relapse or graft loss is rare. Most of the real risks come from the intense myeloablative conditioning and the stem cell transplant itself—things like neutropenia, infections, mucositis, low blood counts, or organ side effects. The good news is, no unexpected off-target gene-editing side effects have shown up in early follow-up. Still, some long-term dangers remain a question mark [43]. Researchers worry about things like clonal expansion, insertional mutations, unexpected off-target changes, or the slow loss of modified stem cells over time. Because of that, some experts say we really need to watch these patients for at least 10 years to catch any late problems or see how long the benefits stick around [23]. Right now, one big limitation is that we just don't have long-term data—most trials only follow people for three to five years. Researchers are paying close attention to how long high HbF levels last, how cell populations shift over time, and whether the genetic changes stay stable. The real question—will these treatments actually work for someone's whole life, say, for 50 to 70 years? Nobody knows yet, since most of the people treated so far are still pretty young.

VI. CONCLUSION

Gene therapy is changing the game for people with sickle cell disease, holding out real hope for a lasting cure [44]. Sure, there are still hurdles, but researchers keep pushing forward, making these treatments safer, more effective, and easier to get. If this progress keeps up, gene therapy turns into a solid, realistic option for everyone living with SCD, no matter where they are [44].

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