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REVIEW

Emerging Gene Therapies in Sickle Cell Disease: A Comparative Review of Efficacy and Safety Against Standard Treatments

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Abstract: Sickle cell disease (SCD) is an inherited haemoglobinopathy caused by a point mutation in the β-globin gene, resulting in abnormal sickle haemoglobin (HbS) and variable clinical expression ranging from mild to severe. While individuals with sickle cell trait are usually asymptomatic, those with homozygous disease may experience chronic haemolytic anaemia, recurrent vaso-occlusive crises, and progressive organ injury. Current standards of care, including hydroxyurea therapy, chronic blood transfusions, and allogeneic haematopoietic stem cell transplantation (HSCT), have substantially improved survival and reduced complications. However, each approach has limitations, such as incomplete disease control, toxicity, and limited donor availability. Recent advances in non-myeloablative and haploidentical HSCT have expanded curative options, achieving high survival with minimal graft-versus-host disease, though accessibility and cost remain challenges. Emerging gene therapies, particularly lentiviral vector-mediated gene addition and CRISPR-Cas9 genome editing, represent major progress by directly targeting the underlying genetic defect. These autologous approaches eliminate donor-related immune risks and have demonstrated durable haemoglobin correction, near-complete resolution of vaso-occlusive events, and encouraging outcomes in stroke prevention. This review synthesises evidence comparing gene therapies with standard treatments, outlining molecular mechanisms, efficacy, safety, and long-term considerations. Key challenges include stem-cell mobilisation, fertility preservation, conditioning toxicity, and equitable access. Early trials show substantial clinical benefit, improved quality of life, and favourable safety profiles. Emerging in vivo editing technologies may further simplify delivery and enhance global accessibility. Integrating gene therapy into evolving standards of care could transform SCD management, offering realistic prospects for durable remission or cure.

Keywords: sickle cell disease, gene therapy, CRISPR-Cas9, lentiviral vector, hydroxyurea

An Overview of Sickle Cell Disease and Its Treatments

Sickle cell disease (SCD) is a hereditary haemoglobinopathy resulting from a single point mutation in the β-globin gene (*HBB*) on chromosome 11, in which adenine is replaced by thymine at codon 6, substituting valine for glutamic acid (Glu6Val) in the β-globin chain. This mutation leads to the production of abnormal sickle haemoglobin (HbS). Under hypoxic or acidic conditions, HbS polymerises within red blood cells (RBCs), causing them to adopt a rigid, sickle-shaped morphology that promotes vaso-occlusion, chronic haemolysis, and progressive multiorgan damage. Clinically, SCD manifests with recurrent painful vaso-occlusive crises (VOCs), acute chest syndrome (ACS), stroke, and other severe complications that contribute to markedly reduced life expectancy and substantial morbidity worldwide (Figure 1 illustrates the molecular basis and pathophysiological cascade of SCD, not therapeutic targets).[1,2] Despite extensive research and therapeutic advances, SCD remains a formidable clinical challenge with significant unmet needs.

Current standards of care for SCD aim to ameliorate disease severity and reduce complications, but do not address the fundamental genetic defect (Figure 1 presents therapeutic targets). Hydroxyurea (HU), the cornerstone pharmacologic therapy, induces fetal haemoglobin (HbF) synthesis and has demonstrated efficacy in decreasing vaso-occlusive events

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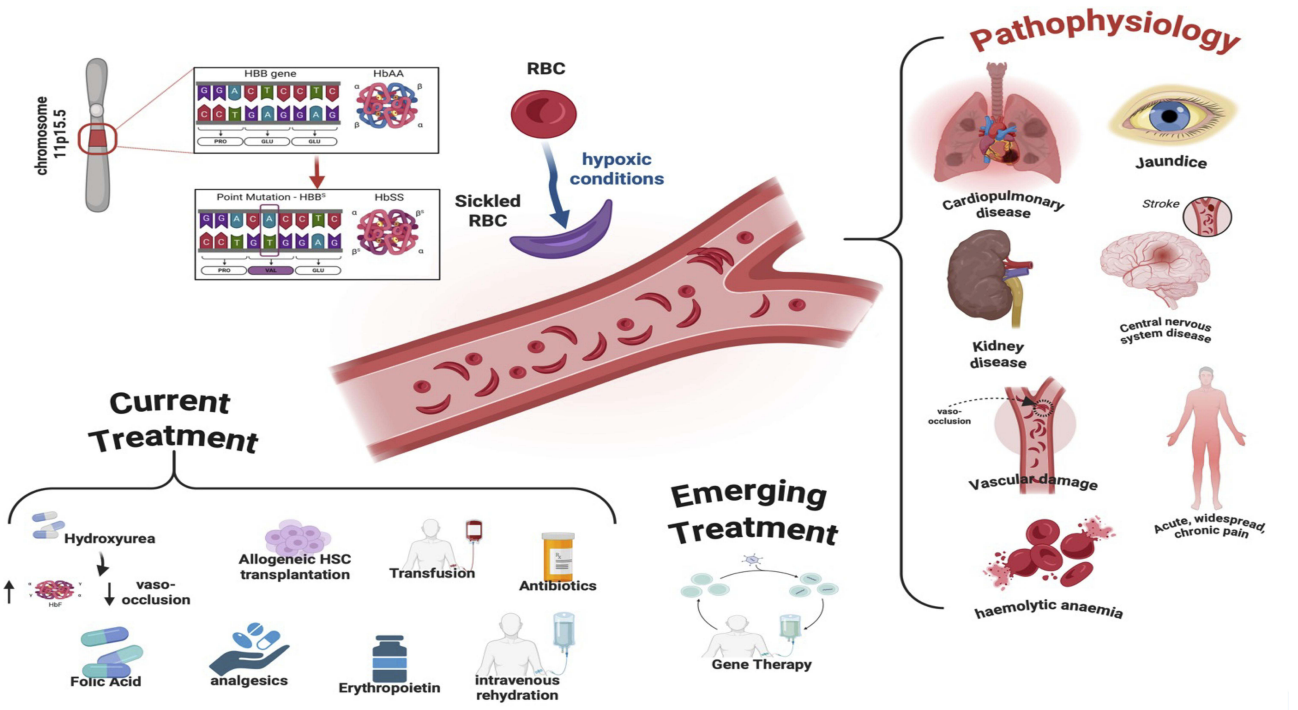

Figure 1 Molecular Basis, Pathophysiology, and Treatment Landscape of Sickle Cell Disease (SCD). Sickle cell disease (SCD) arises from a single point mutation in the β-globin gene (HBB) on chromosome 11, where adenine (A) is replaced by thymine (T) at codon 6, resulting in the amino acid substitution of valine for glutamic acid (Glu6Val). This mutation produces abnormal sickle haemoglobin (HbS), which polymerises under hypoxic conditions, causing red blood cells (RBCs) to assume a rigid, sickle shape. The deformed cells lead to vaso-occlusion, chronic haemolysis, and progressive multiorgan injury, including cardiopulmonary disease, stroke, kidney dysfunction, and widespread pain crises. Current treatments aim to alleviate symptoms and prevent complications, including hydroxyurea, chronic transfusions, allogeneic haematopoietic stem cell transplantation (HSCT), and supportive care with folic acid, analgesics, erythropoietin, antibiotics, and intravenous rehydration. However, these approaches do not correct the underlying genetic defect. Emerging gene therapies—including lentiviral vector-mediated gene addition and CRISPR-Cas9 genome editing—target the molecular cause of SCD by introducing functional β-globin genes or reactivating fetal haemoglobin (HbF), offering the potential for a durable and curative intervention.

(VOEs) and improving quality of life. Nevertheless, HU's effectiveness is variable, and many patients continue to experience recurrent crises despite optimal therapy. Chronic red cell transfusions provide effective stroke prophylaxis and symptomatic relief but are burdened by alloimmunisation and iron overload risks. Allogeneic haematopoietic stem cell transplantation (HSCT) remains the only established curative treatment; however, its application is severely limited by donor availability, risk of graft-versus-host disease (GvHD), and significant treatment-related toxicity. In addition, the high financial cost of HSCT, including donor matching, conditioning, hospitalisation, and post-transplant care, renders it inaccessible to many patients, particularly in low- and middle-income countries where SCD prevalence is greatest.

Recently, emerging gene therapies have offered transformative potential by directly targeting the genetic basis of SCD. Lentiviral vector-mediated gene addition introduces a functional β-globin gene into autologous haematopoietic stem cells, enabling production of anti-sickling haemoglobin variants. Concurrently, CRISPR-Cas9-based genome editing permits the precise disruption of genetic elements that repress HbF expression or the direct correction of the sickle mutation, thereby restoring normal haemoglobin production. These novel approaches circumvent immunologic complications inherent to allogeneic transplantation and offer the promise of durable clinical benefit. These autologous approaches circumvent donor dependency and immunological complications inherent to allogeneic transplantation, offering the promise of durable clinical benefit and potential cure.

Given the rapid evolution and clinical introduction of these gene-based therapies, systematic evaluation of their comparative effectiveness and safety relative to existing treatments is essential. A comprehensive assessment will inform clinical decision-making, optimise therapeutic strategies, and identify outstanding challenges to broad implementation.[1–3]

Accordingly, the present review aims to synthesise current evidence on the efficacy and safety of emerging gene therapies versus traditional treatments in SCD. Particular emphasis will be placed on underlying mechanisms of action,

clinical outcomes including morbidity and mortality reduction, safety profiles, and the hurdles facing future development and integration into standard care.

Pathophysiological and Molecular Basis for Therapy

Sickle Cell Disease (SCD) Molecular Pathology

SCD is a result of an autosomal recessive mutation in the gene *HBB* that codes for the 2-globin subunits of intellectual haemoglobin (HbA, α2 β2). A single nucleotide change, resulting in a missense mutation, is the most frequent type, introducing the amino acid change p.Glu6Val, thereby causing the aberrant HbS.[1,4] When such environments are hypoxic, the HbS polymerises and RBCs acquire a typical sickle form; the longer and firmer cells are fragile and liable to haemolysis as well.[1] This haemolysis causes microvascular occlusions, which trigger conditions such as tissue ischaemia, stroke, and systemic inflammatory responses. At the clinical level, the main characteristics of SCD are chronic haemolytic anaemia and frequent painful VOCs that give rise to repeated VOEs involving multiple organs, as they develop over time.[5] This gradual destruction has led to high morbidity of the disorder, and premature death is more likely. Such difficulties are the most frequent in infancy, when there is a physiological switch between the production of protective fetal haemoglobin (HbF, α 2 γ 2) and adult haemoglobin production.[4]

Therapeutic Targets

The innovative therapies for SCD aim to address the defective protein at the molecular and cellular levels, which is achieved by either directly correcting the mutated HBB gene or reactivating the protective haemoglobin isoforms. Direct editing of the HBB mutation is one method that could address the latter priority.[6] It is a homology-directed repair gene-editing system approach, exemplified by the investigational product nulabeglogene autotemcel, which is used to edit autologous CD34+ haematopoietic stem and progenitor cells (HSPCs).[6,7] This type of gene editing reconstitutes normal β-globin expression in vitro, resulting in decreased pathological HbS levels and their negative influences on red-cell physiology.[7] Preclinical trials revealed an extremely efficient corrective effect at the site of the HBB mutation and a considerable replacement of adult HbA.[7] Another treatment option is restoring HbF, which blocks HbS polymerisation, alleviating the clinical sequelae of SCD. An example of this strategy is the variant condition, called hereditary persistence of fetal haemoglobin, which bears a protective association with co-inherited SCD and is a model. Transcriptional regulators of the switch from γ-globin (HbF) to β-globin (HbA) comprise transcriptional repressors, primarily BCL11A and LRF/ZBTB7A, which occupy the regulatory elements of the HBG1 and HBG2 genes in the genome.[1] The therapeutic goal, therefore, is to decoy or destabilise these complexes of repressors as a means of restoring HbF production by adult erythropoietic cells.

The mechanisms involved in the production of elevated levels of HbF in human RBCs have led to a formulation of a variety of gene-therapy modalities that exploit these processes. CRISPR-Cas9 gene editing has been proven to target the HBG1 and HBG2 promoters directly, similar to OTQ923, and induce high production of HbF.[1] The other approach targets the erythroid-specific enhancer of BCL11A, a central regulatory element of the receptor expression.[3] Targeting this enhancer with CRISPR-Cas9, as was done in ex vivo gene editing (exa-cel), restores the production of HbF without deleting BCL11A, thereby restoring erythropoiesis and reducing sickling. Complementary strategies utilise lentiviral vectors to express short hairpin RNA (shRNA) against BCL11A mRNA, allowing silencing to be explicitly made post-transcriptionally within the erythroid line only, as seen with BCH-BB694.[3,8] The BCL11A enhancer region is also targeted by zinc finger nucleases (ZFNs), as seen in gene therapeutics such as BIVV003, where HbF is induced by precisely disrupting the gene.[9]

Advantages and Risks of Targeting Each Mechanism

Each of these therapeutic strategies presents distinct benefits and challenges. Direct correction of the sickle mutation offers the theoretical advantage of restoring normal adult haemoglobin synthesis while eliminating the deleterious HbS protein.[6] However, its long-term clinical durability remains under evaluation, and efforts continue to optimise manufacturing and engraftment to enhance therapeutic efficacy and reduce transfusion requirements.[7]

Induction of HbF, by contrast, capitalises on a well-validated protective mechanism.[1] Increasing HbF levels diminishes HbS polymerisation and improves red cell resilience.[1,10] Nonetheless, some patients may not achieve sufficiently high HbF concentrations to completely suppress sickling, allowing residual haemolysis and symptoms to persist.

Lentiviral gene addition therapies, such as LentiGlobin (lovotibeglogene autotemcel), introduce a modified β-globin gene encoding an anti-sickling haemoglobin variant (HbAT87Q).[11] Clinical trials have demonstrated sustained expression of HbAT87Q, leading to reduced haemolysis and resolution of severe VOEs in many patients.[11] This approach offers the advantage of autologous transplantation, eliminating the risks of GvHD associated with allogeneic HSCT.[12] However, it introduces the risk of globin chain imbalance since HbS production is not suppressed, which may contribute to ineffective erythropoiesis and erythroid dysplasia.[1] Additionally, the random integration of the lentiviral vector carries a theoretical risk of insertional mutagenesis.[13] While some cases of myeloid malignancies have occurred in clinical trials, current evidence often attributes these to conditioning regimen toxicity or pre-existing clonal haematopoiesis rather than vector integration.[14]

CRISPR-Cas9-based gene editing therapies offer highly targeted modifications, generally avoiding the risks associated with viral vector insertion.[14] Clinical studies report robust and stable HbF induction with broad distribution in RBCs, and a profound reduction or elimination of disease manifestations, such as VOCs.[14] This precision enables the preservation of α- to β-globin chain balance and the maintenance of normal erythropoiesis. Nonetheless, concerns remain regarding potential off-target effects, long-term toxicity to haematopoietic stem cells, and challenges in stem cell collection, given the contraindications for standard mobilisation agents such as granulocyte colony-stimulating factor (G-CSF) in SCD patients.[15,16] Furthermore, myeloablative conditioning, typically with busulfan, remains necessary prior to infusion of gene-modified cells, and adverse events are primarily attributable to this preparative regimen.[16]

Overall, while both lentiviral gene addition and CRISPR-Cas9 gene editing therapies show significant promise in transforming the treatment landscape of SCD, definitive determination of the optimal genetic modification strategy requires ongoing comparative studies and extended follow-up. Standardised outcome measures and long-term safety surveillance are essential to establish these novel therapies as standard care options.

Standard Treatments in SCD

SCD is a chronic and debilitating haematological disorder characterised by persistent anaemia and recurrent VOCs, which contribute to progressive multiorgan damage and substantially increase the risk of premature mortality. Contemporary management strategies primarily focus on alleviating symptoms and preventing complications rather than addressing the underlying genetic cause of the disease.

HU remains the most effective medical regimen for patients with SCD. Its effectiveness is usually ascribed to the upregulation of HbF, a consequence that inhibits the polymerisation of HbS, hence hindering red cell sickling.[10] Although scientists are still exploring the exact molecular mechanisms, it is believed that HU differentially upregulates or downregulates erythroid progenitor cells, thereby increasing the production of HbF.[17] HU has been proven effective in reducing the occurrence and intensity of pain crises in clinical practice.[10] Thus, doctors recommend it as part of the standard care, particularly to those with severe genotypes. However, inter-patient variability still exists, and several patients are still exhibiting severe VOCs even with optimised dosing, with myelosuppressive effects and consequences.[5,10,17] There are myelosuppressive effects manifested by decreased counts of neutrophils and platelets that can complicate follow-up stem-cell mobilisation.[17] There are also concerns about the potential long-term risks, particularly the possibility of a high rate of malignancies. Epidemiological statistics, however, fail to support an enhanced risk of leukaemia from the HU therapy in the SCD population.[13] Despite these merits, morbidity and mortality of SCD are still high, a situation that implies the need to develop more efficient treatment options. Comparative studies on the quality and performance of RBCs reveal that optimal responders for HU exhibit a form of correction that aligns with the parameters of newer gene therapies, particularly in terms of haemoglobin composition and functional oxygen delivery.[18]

Chronic blood transfusion has continued to be essential to the treatment of SCD, particularly in primary and secondary prophylaxis of strokes.[3] Repeated transfusion reduces levels of circulating HbS, thus reducing VOEs. The most common procedure involving exchange transfusions includes those involving the replacement of affected RBCs

with normal donor erythrocytes before procedures such as HSC mobilisation to transfer a gene or to increase perioperative safety.[1] Despite being effective, chronic transfusions are subject to significant morbidities. There may be the formation of alloimmunisation following repeated transfusions,[3] which makes future compatibility difficult. Iron loading requires chelation treatment, which should be lifelong to prevent damage to organs.[2] The frequent need for durative hospital accessions and consequent complications restrain the viability of such a modality in the long-term perspective as well.

Allogeneic HSCT currently represents the only established curative intervention for SCD. Successful transplantation replaces the patient's defective haematopoietic system with donor healthy stem cells, producing normal adult haemoglobin (HbA), effectively curing the disease.[19] Matched sibling donor HSCT achieves cure rates exceeding 90%, particularly in paediatric populations where disease-free survival beyond six years surpasses 90%.[2] Despite these promising outcomes, the applicability of HSCT is severely constrained by donor availability, as fewer than 20% of patients have an HLA-matched sibling donor.[20] Recent advances have, however, expanded the transplant landscape through the introduction of both haploidentical and non-myeloablative conditioning approaches, aiming to make curative transplantation accessible to a wider patient population.

Non-myeloablative conditioning regimens, often using lower-dose busulfan or fludarabine-based protocols combined with immunosuppressive agents such as alemtuzumab, have demonstrated remarkable safety improvements, with transplant-related mortality (TRM) approaching 0% and minimal rates of acute and chronic GVHD. In particular, the NIH non-myeloablative protocol,[21,22] which involves 300 cGy total body irradiation, alemtuzumab, and sirolimus, has achieved durable mixed chimerism and stable donor engraftment in over 85% of adult SCD patients, without graft rejection or severe GVHD.[3] These findings underscore that reduced-intensity or non-myeloablative HSCT can offer curative potential with significantly improved safety profiles compared with traditional myeloablative approaches, particularly in adults or patients with comorbidities.

Haploidentical transplantation has also emerged as a major recent advance, particularly in the last five years, with several landmark publications demonstrating that post-transplant cyclophosphamide-based haploidentical HSCT can achieve event-free survival rates exceeding 85% and overall survival above 90%, with manageable rates of GVHD.[20,22,23] These studies highlight the feasibility of using partially matched family donors, greatly expanding donor availability to nearly all patients with SCD. Furthermore, the use of T-cell replete grafts and modern immunomodulatory strategies has reduced graft rejection rates to under 10% while preserving long-term immune reconstitution. Such advances position haploidentical HSCT as a realistic curative option for patients lacking matched siblings, narrowing the accessibility gap that has long limited transplantation as a treatment modality for SCD.

Conditioning regimens, when busulfan-based, continue to contribute to both acute and chronic toxicities, and traditional myeloablative transplant-related mortality rates range between 5 and 7%.[24,25] However, contemporary haploidentical and non-myeloablative strategies have markedly reduced this risk, with most studies now reporting TRM below 2%. The risk of therapy-related myeloid malignancies such as AML and myelodysplastic syndrome (MDS) remains recognised,[26] albeit rare, and is primarily associated with historical high-dose conditioning or pre-existing clonal haematopoiesis.

From an economic perspective, emerging cost-effectiveness analyses suggest that haploidentical HSCT may represent a more economically viable curative option compared with ex vivo gene therapies such as lovotibeglogene or exa-cel, particularly in resource-limited settings. While upfront costs for haplo-HSCT (estimated at US$250,000–400,000) are significantly lower than those for gene therapy (US$2–3 million per treatment),[27,28] the long-term cost-benefit balance remains dependent on post-transplant morbidity, quality of life, and healthcare infrastructure to manage potential complications.[27] Nevertheless, haploidentical HSCT offers a scalable curative approach that may bridge the accessibility divide until gene therapy becomes more affordable and widely deployable.[29]

Furthermore, despite successful engraftment, some patients experience persistent haemolysis even with suboptimal donor chimerism. HSCT continues to be recommended primarily for younger patients, given the increased toxicity and poorer outcomes associated with older age groups, though non-myeloablative and haploidentical strategies now offer safer avenues for extending curative therapy to adult populations.[24]

Contemporary standardised treatments, such as HU, chronic transfusions, and allogeneic hematopoietic stem cell transplantation, have simultaneously contributed to the improvement of clinical outcomes for many patients affected by SCD. However, the modalities in use are ineffective in correcting the root genetic defect, are homogeneous in various therapeutic activities, and are associated with significant side effects and limitations on operative placement. This combination of restrictions has driven the development of gene-based therapeutics that would provide more secure, long-lasting and even curative solutions.

Emerging Gene Therapies

The proposed solutions to addressing gene-based interventions for SCD currently revolve around two major branches: lentiviral vector-based gene addition and gene-editing modalities, which incorporate the use of inactivated nucleases, eg, CRISPR-Cas9. Both of these strategies aim to either modify the pathologic β-globin abnormality or induce the expression of new *de-novo* HbF to mitigate the clinical manifestations of SCD.

Lentiviral Vector-Mediated Gene Addition

Ex-vivo lentiviral vector-mediated addition of genes consists of the autologous HSPCs being transduced using a lentiviral vector that transduces a modified version of the β-globin gene in-vitro, such as βA-T87Q with an amino acid substitution.[20] The new gene synthesises an anti-sickling haemoglobin, HbAT87Q, which aims to correct a deficient endogenous β-globin.[19] Through the grafting of the same genetically modified cells to the same individual (after undergoing myeloablative conditioning), the therapy aims to restore functional haemoglobin production, and the pathology resulting in sickling is likely to be significantly diminished. One significant benefit of this autologous transplantation technique is that it prevents GvHD, which is a crucial complication brought about by allogeneic transplantation.

Succinct outcomes have been obtained using lentiviral gene therapy in clinical studies. Patients usually maintain a therapeutic range of haemoglobin (10–12 g/dL),[30,31] which is associated with a stable expression of transgenes. In the HGB-206 Group C study, for example, patients showed a median total haemoglobin value of 11.5 g/dL six months following infusion, and some of them exhibited significant increases compared to their baseline measurements.[32] At the same time, the rates of VOCs and ACS were significantly reduced; a single study reported a 99.5% decline in the combined rate of VOCs and ACS.[33] The number of patients who have achieved transfusion independence is substantial today, which is a testament to the profound effect of the therapy on the disease burden. The biochemical measurement of the transduced RBCs reveals that the cells have a longer life span and are less prone to sickling,[34] thus demonstrating the clinical efficacy of this method.

The safety profile of lentiviral gene transfer is generally favourable, with predominantly reactions which can be related to the conditioning regimen.[35] Myeloablative conditioning regimens are most often associated with adverse events, most commonly busulfan-based. Febrile neutropenia and mucositis are universally experienced to some degree but are generally manageable within the terms of existing protocols.[30] The focus on insertional mutagenesis, which was raised after the initial experiments with oncoretroviral vectors, has not been verified in modern lentiviral vector clinical trials.[3] Although rare cases of AML and MDS have been described after allogeneic stem cell transplantation, there is no evidence to suggest that these malignancies are vector-related.[13] Instead, they may represent conditioning toxicity or pre-existing clonal haematopoiesis. Long-term follow-up (up to 5 years) demonstrates the durable expression of the gene and lasting clinical benefit, with zero mortality that can be attributed to treatment.[13,20] Moreover, the overall survival and event-free survival of lentiviral gene therapy demonstrate favourable results in comparison with a similar allogeneic HSCT with a sibling donor.[13]

CRISPR-Cas9 and Other Gene Editing Technologies

Gene editing strategies, predominantly using CRISPR-Cas9, have revolutionised the therapeutic landscape by enabling precise genomic alterations to reactivate HbF or correct the sickle mutation. CRISPR-Cas9 utilises a guide RNA to direct the Cas9 nuclease to specific DNA sequences, inducing double-strand breaks which are subsequently repaired by endogenous cellular mechanisms, leading to targeted gene disruption or correction.[36,37] The principal therapeutic target

is the erythroid-specific enhancer of BCL11A, a transcriptional repressor of γ-globin genes (HBG1 and HBG2).[37] Disruption of BCL11A enhancer activity reactivates HbF expression, which inhibits HbS polymerisation and ameliorates disease symptoms.[7] Alternatively, some approaches directly target the γ-globin gene promoters or aim to correct the pathogenic HBB mutation.[1]

Clinical trials of CRISPR-Cas9 therapies, such as exagamglogene autotemcel (exa-cel), have reported remarkable efficacy. Patients treated with exa-cel exhibited sustained HbF levels exceeding 20% of total haemoglobin, with broad distribution of HbF across erythrocytes.[1] This biochemical effect translated into clinical benefits, with nearly all treated patients remaining free of VOC during extended follow-up periods of up to 32 months.[35] Similarly, investigational agents like OTQ923 have demonstrated significant reductions in sickle cell manifestations alongside durable HbF induction.[1]

The therapeutics that rely on CRISPR-Cas9 gene editing are safe. Both preclinical and clinical evidence suggest that there are low levels of off-target gene edits, and no insertional mutagenesis is seen, a problem that is highly problematic with viral vector-based gene therapies. However, in doing so, the system induces double-strand DNA breaks, which impart genotoxicity to the system that may potentially impair long-term stem cell functionality. Conditioning regimens are therefore still necessary, and adverse effects so far have been similar to those of myeloablative chemotherapy, with no treatment-related deaths or malignancies.

Other Gene Editing Approaches

Besides CRISPR-Cas9, other gene-editing platforms are actively being researched. Specifically, ZFNs have been used to target the BCL11A erythroid enhancer, causing the creation of double-strand breaks in the regulatory motifs to promote the expression of HbF.[9] Initial early-stage clinical trials with ZFNs-derived therapy, eg, BIVV003, have shown promising preliminary outcomes, including increases in haemoglobin levels, strong induction of HbF, and a marked reduction in vaso-occlusive attacks.[9] Additionally, these strategies offer the advantage of utilising a non-viral delivery route and demonstrate sustained multilineage engraftment in animal models.[9]

Transcription activator-like effector nucleases can be seen as similar in terms of their ability to perform precise genome editing, with preclinical results showing that HBSCs are corrected efficaciously and safely when targeting the sickle cell mutation.[9] Simultaneously, new base and prime editing platforms, designed to modify single nucleotides without creating double-strand breaks, are being tested in preclinical models of SCD. In combination, these are strategies which will create a new era of gene-therapy paradigms featuring increased specificity and reduced off-target effects.[38]

Comparative Effectiveness of Emerging Gene Therapies Versus Standard Treatments

Reduction in Disease Morbidity

A critical measure of therapeutic efficacy in SCD is the reduction of VOCs and ACS, two of the disease's most debilitating and life-threatening complications. CRISPR-Cas9-based therapies have shown remarkable success in this regard. For instance, the CLIMB SCD-121 trial of exa-cel reported that 97% of patients with adequate follow-up remained free from severe VOCs for at least 12 consecutive months, with all participants avoiding inpatient hospitalisation for such events during this period.[37] Before treatment, these patients experienced an average of nearly four severe VOCs per year. Similarly, therapies such as OTQ923 have demonstrated a notable reduction in VOC frequency, albeit with some breakthrough events in a limited number of participants.[1] In contrast, nula-cel has reported complete VOC elimination at one year in the first treated patient.[7] Furthermore, AsCas12a-based EDIT-301 therapy reduced VOEs from an average of 4.2 per year to zero, illustrating profound clinical benefit.[39]

Lentiviral gene therapies have similarly produced compelling results. The LentiGlobin product (lovotibeglogene autotemcel) markedly decreased the median annualised VOC and ACS rate from over five episodes pre-treatment to zero post-treatment in pivotal studies.[30] Importantly, patients in the HGB-206 study achieved near-complete resolution of severe VOEs, accompanied by improvements in pain control and quality of life.[32] Other lentiviral constructs targeting BCL11A, such as BCH-BB694, have been shown to result in the absence of VOCs, ACS, or stroke over extended follow-

up.[3] Modified γ-globin lentiviral vectors administered with reduced-intensity conditioning (RIC) have similarly yielded substantial reductions in annualised VOCs, including cases with complete cessation of crises.[15]

Comparative studies indicate that gene therapy approaches targeting BCL11A yield RBCs with greater resistance to sickling under physiologic oxygen tensions compared to patients treated with HU who achieve similar levels of HbF.[10] This suggests that gene therapies confer a more robust anti-sickling effect beyond what is achievable with conventional pharmacotherapy.

Hospitalisation rates reflect the burden of disease and treatment efficacy. Exa-cel recipients demonstrated complete freedom from hospital admissions for severe VOCs over 12 months, a striking improvement compared to pre-treatment baselines where patients spent an average of nearly 20 days per year hospitalised.[36] Although not always explicitly reported, the significant reductions in VOC and ACS rates observed in gene therapy trials imply commensurate decreases in hospitalisations.[37] Comparative analyses of hospitalisation rates between gene therapy recipients and matched sibling donor HSCT recipients reveal broadly similar outcomes,[40] despite gene therapy patients often presenting with older age and greater comorbidities.

Transfusion dependence, a key contributor to morbidity in SCD, is significantly reduced or eliminated following gene therapy. CRISPR-Cas9 therapies such as EDIT-301 have enabled transfusion independence in patients with transfusion-dependent thalassaemia, highlighting the broader applicability of genome editing.[39] Lentiviral gene therapy trials similarly report sustained erythropoiesis without the need for ongoing transfusions in most patients, with documented cases of patients remaining transfusion-free for extended durations. Nevertheless, challenges remain in collecting sufficient autologous haematopoietic stem cells for gene therapy manufacturing.[11] Traditional bone marrow harvests pose procedural risks and often require multiple attempts. Plerixafor mobilisation, preferred over granulocyte G-CSF due to safety concerns in SCD, has emerged as a safer alternative, albeit requiring more frequent cycles to achieve adequate cell yields.[17]

Mortality and Survival Outcomes

Treatment-related mortality (TRM) is a key variable in determining the efficacy of treatment in SCD. Very early-phase and preclinical studies of modern gene therapies have already demonstrated very low TRM,[37] with most trials reporting rates of near zero. Although infrequent death cases have been reported, such as a case of acute respiratory failure, without relation to treatment recorded concerning an ex-vivo recipient, such events are not linked to the gene therapy itself.[37] Also, a small proportion of patients in the initial trials of lentiviral vectors have acquired AML.[20] Although the analysis suggests that such events cannot be explained by the integration of vectors or oncogenic insertion sequences, they may be related to the toxicity of the conditioning regimens or clonal haematopoiesis that occurred before implementation. In turn, close monitoring and long-term monitoring are necessary.

The risk of TRM associated with allogeneic HSCT is elevated at 5–7%, with a significant proportion of TRM due to graft failure, GvHD, and conditioning-related toxicity.[24] Long-term overall survival is greater than 90% at both two and five years. The same scenario applies to event-free survival, which is also high, even in children.[14] Encouraging data are available on gene-therapy survival, which will meet or exceed these comparisons; but since the procedure is relatively new, long-term follow-up should be considered. The direct head-to-head clinical comparison is scarce, but early evidence shows similarity in the short-term safety record and healthcare resource use between gene therapy and matched sibling donor HSCT regarding their dissimilarity in patient demographics.[40]

Beyond general survival benefits, a critical emerging area is the role of gene therapy in secondary stroke prevention in SCD. Stroke remains one of the most severe complications of the disease, affecting up to 10% of children and contributing significantly to long-term disability and mortality. Evidence from recent trials indicates that gene therapies, by normalising or increasing haemoglobin levels and substantially reducing haemolysis, have the potential to eliminate recurrent cerebrovascular events. In the CLIMB SCD-121 trial of exa-cel, no cases of new or recurrent ischaemic or haemorrhagic stroke were reported during a median follow-up of over 24 months, despite many participants having prior cerebrovascular events.[37] Similarly, lentiviral gene addition trials (HGB-206 Group C and HGB-210) have documented the absence of new strokes after treatment, alongside cessation of chronic transfusion programmes instituted for stroke prophylaxis.[27]

By contrast, allogeneic HSCT, while historically effective in stroke prevention, particularly in paediatric matched sibling donor transplants, carries a residual risk of stroke recurrence if donor chimerism declines or haemolytic anaemia persists. Studies from the European Group for Blood and Marrow Transplantation and the NIH indicate that approximately 3–5% of transplanted children may still experience cerebrovascular events post-transplant, primarily in cases of incomplete engraftment.[41]

Overall, gene therapy appears to achieve comparable or superior stroke prevention outcomes relative to HSCT, with the added advantage of avoiding GvHD and the risks associated with partial donor chimerism. Ongoing long-term follow-up will clarify whether these benefits are sustained and whether gene therapy can fully supplant chronic transfusion and HSCT as standard approaches for stroke prophylaxis in SCD.

Quality of Life and Patient-Reported Outcomes

Beyond clinical endpoints, emerging gene therapies have demonstrated substantial improvements in quality of life (QoL) for individuals with SCD. Patients treated with lentiviral gene therapies, such as LentiGlobin, report significant improvements across multiple patient-reported outcome domains, including reductions in pain intensity and interference, alleviation of anxiety and depression, and enhanced physical functioning.[42] These benefits appear sustained up to one year post-treatment, with particularly pronounced improvements among those with greater baseline symptom burdens.

Similarly, recipients of CRISPR-Cas9 therapies, including exa-cel, have exhibited marked QoL enhancements at 24 months, as measured by validated instruments such as the SCD QoL Measurement Information System and the EuroQol Visual Analogue Scale.[37] Improvements in pain frequency and severity, overall health perception, and transplant-related QoL subscales have been documented, with changes exceeding minimal clinically significant differences.[20,43] Reductions in fatigue and psychosocial burden further corroborate the transformative impact of gene therapies on patient well-being.

However, interpretation of these data requires caution due to limitations including small sample sizes, heterogeneity of assessment tools, and variability in follow-up duration. Discrepancies between patient and caregiver reports, especially in paediatric populations, highlight the need for tailored and longitudinal QoL assessments to fully elucidate the sustained benefits and potential challenges associated with these novel therapies.

Safety Profiles of Emerging Gene Therapies Compared to Standard Treatments

New genomic interventions in SCD exhibit significantly different safety parameters compared to those of traditional interventions. Despite clinical evidence of a favourable safety profile for gene-based treatment, several pitfalls remain, the main ones being the conditioning regimens that facilitate long-term engraftment and the complexity of genetic manipulation itself.

Adverse Events Related to Conditioning

Both gene therapy and allogeneic HSCT make use of myeloablative conditioning regimes where busulfan is often used to make the bone marrow niche welcoming to the introduction of modified or donor stem cells post-therapy.[1] This preparative program presents an exciting source of side effects that are largely consistent across the two treatment modes. It is essential to note that typical adverse events include stomatitis, febrile neutropenia, thrombocytopenia, nausea, vomiting, and decreased appetite. Stomatitis occurred in over 70% of patients participating in lentiviral gene therapy trials, whose treatment relied on the use of LentiGlobin.[37] In contrast, febrile neutropenia and thrombocytopenia were observed in approximately 60% of the experimental participants.[37] Similar trends were noted in patients who received exa-cel. Although such events may reach high levels (Grade 3 or 4), they are generally short-term and are typically managed by clinical guidelines.[19] Besides, even adverse events directly related to the gene therapy products themselves are not very common; the primary cause of toxicity is conditioning regimens.

A promising approach is the application of Melphalan-based RIC regimens combined with *ARU-1801* gene therapy in treating the disease,[15,44] which is becoming the preferred choice due to the reduction in conditioning-

related toxicity and the widening of eligible patient populations. The initial results suggest that RIC is associated with shorter periods of neutropenia and thrombocytopenia, as well as fewer incidences of only severe adverse events.[15] However, the most relevant concerns pertain to the potential impact of RIC on the durability of engraftment and the long-term efficacy of gene-modified hematopoietic stem cell transplants. Initial sequelae in post-conditioning primarily result from increased susceptibility to infection due to prolonged neutropenia and damage to the mucosal barrier.[14] Most of the adverse events are reported before the neutrophil is restored, and it has been reported that clinical trial data show that they are generally related to either central venous access-related complications or chemotherapy-induced toxicity, such as the case of BCH-BB694.[3] Some side effects include rare complications that will arise later in the form of autoimmune diseases like type 1 diabetes mellitus.[3] However, these may be triggered by underlying risk factors that develop during treatment. Although long-term safety among the gene-edited recipient human population is uncertain, current evidence is mostly encouraging: most animals have stable or improving organ function (cardiac, lung, and kidney) up to 12 months after infusion.[1] However, there is persistent or aggravating osteonecrosis reported, and this could also be aggravated by the factors related to the treatments.

Gene Therapy–Specific Safety Concerns

The precision of genome editing is paramount to its safety profile. In CRISPR-Cas9-based therapies, off-target gene editing, where unintended genomic sites are altered, constitutes a principal concern.[45] However, extensive preclinical and clinical assessments have demonstrated minimal off-target activity. For example, OTQ923 and exa-cel have exhibited sustained on-target editing without detectable off-target mutations in CD34+.[1] Similarly, EDIT-301, utilising an AsCas12a nuclease, has not reported serious adverse events beyond those expected from conditioning.[35] ZFNs-mediated editing, such as with BIVV003, has also demonstrated high specificity, generating predominantly small indels confined to non-coding intronic regions of BCL11A; however, comprehensive long-range genomic analyses remain pending.[9]

In contrast to viral vector-based gene therapies, CRISPR-Cas9 utilises non-viral delivery methods that avoid random insertion of genetic material, thereby theoretically eliminating the risk of insertional mutagenesis. Lentiviral vectors, however, integrate semi-randomly into the host genome, raising concerns about potential activation of proto-oncogenes and subsequent leukemogenesis.[13] Although cases of AML and MDS have been reported in lentiviral gene therapy trials for SCD, detailed investigations frequently attribute these malignancies to conditioning regimens, underlying clonal haematopoiesis, or unrelated cytogenetic abnormalities rather than vector integration.[13] These events have prompted cautious regulatory oversight, with black box warnings and recommendations for long-term surveillance extending at least 15 years post-treatment.

Immunologically, autologous gene therapies provide a significant advantage over allogeneic transplantation by obviating GvHD,[3] a major cause of morbidity and mortality in HSCT. Gene therapy recipients typically experience timely engraftment without graft failure, with neutrophil recovery occurring within the expected 18- to 26-day post-infusion period.[20] Studies consistently report the absence of replication-competent lentivirus and no evidence of clonal dominance or vector-induced malignancies in treated populations to date.[30] Immune reconstitution profiles are generally favourable, with stable lymphocyte recovery and no requirement for additional immunomodulation.[46]

Comparison to Standard Treatment Risks

HU, the current pharmacological standard, has a well-established safety profile; however, it is not without risks. Its myelosuppressive effects, including neutropenia and thrombocytopenia, can complicate stem cell mobilisation for gene therapy.[17] Although concerns about a theoretically increased risk of malignancy have been raised, epidemiological data do not support a causal relationship between HU and leukaemia in patients with SCD.[13] Despite optimal dosing, many patients on HU continue to experience vaso-occlusive complications.[10] In contrast, gene therapies targeting BCL11A appear to confer a more potent anti-sickling effect, as evidenced by a reduction in the proportion of high HbS-expressing RBCs.

Chronic transfusion therapy effectively mitigates certain SCD complications but carries significant risks of alloimmunisation and iron overload, necessitating ongoing chelation and posing substantial management challenges.[1,33] By reducing or eliminating transfusion dependence, gene therapies implicitly decrease the risks associated with transfusions.

Allogeneic HSCT remains the only established curative intervention but is constrained by donor availability and substantial toxicity.[19] GvHD remains a formidable complication, with acute and chronic forms reported in approximately 20% and 14% of recipients, respectively, and carries significant morbidity.[19] TRM in HSCT ranges between 5% and 7%, substantially higher than observed in gene therapy trials, which report near-zero mortality rates. Secondary malignancies, including therapy-related AML, MDS, and post-transplant lymphoproliferative disorders, have been documented following HSCT, emphasising the need for long-term surveillance in all curative treatment modalities.

Overall survival and event-free survival rates following HSCT and lentiviral gene therapy are broadly comparable in paediatric populations; however, gene therapy cohorts often include older patients with more comorbidities, highlighting its potential applicability to a broader patient demographic. While direct comparative trials remain limited, early data suggest that gene therapy may offer similar efficacy with reduced toxicity and improved safety.

Challenges and Future Directions

The field of gene therapy for SCD has witnessed remarkable progress, with gene addition and gene editing strategies offering unprecedented potential for curative intervention. However, the translation of these advances into widespread clinical practice faces substantial challenges related to safety optimisation, equitable access, and ongoing technological innovation.

A primary obstacle to improving patient outcomes lies in optimising conditioning regimens. Both gene therapy and allogeneic HSCT rely heavily on myeloablative conditioning, most commonly busulfan-based, to facilitate engraftment of gene-modified cells. While effective, these regimens contribute significantly to treatment-associated morbidity, manifesting as stomatitis, febrile neutropenia, thrombocytopenia, and other adverse events that often reach severe grades. Such toxicities can limit patient eligibility and negatively impact quality of life. Busulfan dosing requires careful pharmacokinetic (PK) monitoring and adjustment to maintain therapeutic levels while minimising toxicity, as interpatient variability in metabolism can significantly affect exposure and increase the risk of hepatic veno-occlusive disease, infertility, and long-term organ damage. Consequently, reducing the intensity and toxicity of conditioning protocols is a critical priority. RIC regimens, such as melphalan-based protocols investigated in conjunction with *ARU-1801* gene therapy, show promise by decreasing hematologic toxicity and resource demands. However, the impact of these milder regimens on durable engraftment remains to be fully elucidated. Novel agents, including treosulfan and non-genotoxic antibody-drug conjugates, are being evaluated as potential alternatives that may further enhance safety profiles.

An additional and often underappreciated challenge lies in the mechanical and procedural aspects of autologous stem cell collection. Patients undergoing gene therapy must undergo meticulous preparation, including exchange transfusions for at least 60 days before collection, to lower HbS levels and improve red cell rheology. Hydroxyurea treatment is discontinued approximately three months before mobilisation to enhance stem cell yield and reduce interference with progenitor proliferation. Mobilisation typically involves the administration of plerixafor for up to three consecutive days, followed by one or more apheresis sessions, depending on the efficiency of CD34+ cell collection. Many SCD patients require two to three apheresis cycles to achieve the target yield of 4–10 $\times$ 10^6 CD34+ cells/kg, compared to one cycle in β-thalassaemia cohorts, due to the absence of granulocyte colony-stimulating factor (G-CSF), which is contraindicated in SCD because of the risk of vaso-occlusive crises.

During collection, patients are often admitted or monitored as inpatients to manage potential complications such as hypovolaemia, pain crises, or access-related thrombosis. Technical challenges, including the fragility of red blood cells and the interface instability in the apheresis machine, require specialised expertise and real-time monitoring to avoid excessive haemolysis or circuit obstruction. Following collection, the harvested CD34+ cells are cryopreserved, allowing time for product testing and scheduling of conditioning.

Fertility preservation represents another major consideration in this patient population, particularly given the gonadotoxicity associated with busulfan-based conditioning. Both male and female patients should be counselled on reproductive risks before therapy. Sperm banking for men and oocyte or embryo cryopreservation for women are strongly

recommended where feasible. However, these options are often limited by age, disease severity, and access to fertility preservation services, highlighting an ethical and logistical challenge in current clinical practice. Future efforts should explore conditioning regimens that minimise gonadotoxicity or incorporate fertility-protective strategies, such as gonadal shielding or pharmacologic ovarian suppression.

Stem cell mobilisation represents another challenge integral to conditioning optimisation. The standard practice of plerixafor mobilisation followed by apheresis, while safer than G-CSF administration in SCD patients, frequently necessitates multiple collection cycles to obtain sufficient CD34+ cells.[2] The diminished mobilisation efficiency in SCD relative to other hematologic disorders, such as beta-thalassemia, may be influenced by prior HU exposure and bone marrow toxicity. Ongoing research aims to refine mobilisation timing, potentially synchronising plerixafor administration with peaks in hematopoietic progenitor cell availability, to improve collection efficiency and reduce patient burden.[2]

Long-term safety monitoring remains paramount given the potentially curative intent of gene therapies. Regulatory agencies mandate extended follow-up, often spanning 15 years, to surveil for delayed adverse effects, including secondary malignancies, insertional mutagenesis, and off-target gene editing consequences. Current registries and follow-up studies, such as the ongoing CLIMB-131 trial for exa-cel and extended monitoring of BCH-BB694 recipients, exemplify these efforts. The rare occurrence of myeloid neoplasms in lentiviral gene therapy trials underscores the need for careful evaluation of baseline clonal haematopoiesis and conditioning-related genotoxicity. Similarly, while CRISPR-Cas9-based therapies demonstrate high specificity with no currently detected off-target edits, the inflammatory milieu intrinsic to SCD may modulate genomic stability, necessitating vigilance. Furthermore, durability of engraftment and sustained gene expression, especially under RIC, constitute ongoing research foci critical to long-term efficacy.

Despite the remarkable clinical advances, the high cost of gene therapies presents a formidable barrier to broad implementation, particularly in low- and middle-income countries where SCD prevalence is most significant. Individual treatment costs for products such as ExaCel can exceed $2 million, imposing a substantial economic strain on healthcare systems and limiting accessibility. Additionally, the intricate manufacturing and delivery infrastructure required for ex vivo cell manipulation restricts availability predominantly to specialised centres in high-resource settings. Addressing these inequities necessitates innovative solutions, including negotiated pricing agreements, the establishment of regional manufacturing hubs in high-incidence areas, and the development of automated, good manufacturing practice-compliant closed systems for gene editing. Economic analyses suggest that despite substantial upfront investments, gene therapies may prove cost-effective over a patient's lifetime by reducing morbidity, hospitalisations, and caregiver burden; however, these projections are sensitive to long-term durability and equitable patient selection.

Technological innovation offers potential pathways to circumvent many current limitations. The emergence of in vivo gene editing and delivery platforms, currently in preclinical development, holds promise for significantly simplifying treatment by obviating the need for ex vivo cell collection and manipulation. Early successes with in vivo prime editing in murine models of SCD herald a future in which gene therapy could become less resource-intensive, more accessible, and safer. Continued research is focused on developing efficient and safe viral and non-viral delivery systems that ensure targeted, durable gene modification with minimal off-target effects, thereby expanding the therapeutic reach globally.

Ethical and regulatory considerations form an essential framework underpinning the responsible development and clinical integration of gene therapies. Given the profound capacity to permanently alter the human genome, stringent regulatory oversight ensures patient safety through rigorous trial monitoring and mandates long-term follow-up for delayed adverse outcomes. Ethical challenges related to cost, access, and equitable treatment allocation demand ongoing dialogue among clinicians, researchers, policymakers, and patient communities. Harmonisation of clinical trial designs and outcome reporting is imperative to enable robust comparative analyses and to inform evidence-based clinical decision-making. Importantly, multi-stakeholder engagement will be crucial in addressing these scientific, societal, and practical challenges to ensure that the promise of gene therapy is realised in a manner that is both effective and equitable.

Conclusion

The emerging potential of gene-based therapies, most notably CRISPR-Cas9 genome editing and lentivirus-based gene addition, has brought a revolutionary change in the management of SCD. Available evidence suggests that both

modalities offer higher efficacy, particularly in mitigating VOCs, ACS, and transfusion dependency. In addition, they have better safety profiles compared to standard treatments, such as HU, chronic transfusions, and HSCT.

Importantly, early clinical data also suggest a promising role for gene therapy in stroke prevention, a key area of morbidity in SCD. Patients treated with exa-cel or LentiGlobin have remained stroke-free during follow-up, with many able to discontinue chronic transfusion regimens previously required for cerebrovascular protection. This implies that gene therapy may offer durable cerebral vasculature protection comparable to, or potentially exceeding, that achieved through HSCT, but without the immunologic risks associated with donor transplantation.

These interventions have a reduced risk of immunological complications, including GvHD, due to their autologous nature. The targeted effects of genome editing also decrease such problems, which benefits the risk-benefit ratio. The reasonably long-term clinical benefits following early and continued use in studies suggest that the natural history of SCD could be radically altered by the use of gene therapies, which could correct haemoglobin over the long term and reduce life-threatening complications. Such stability, combined with the enhancement in patient quality of life, considers gene therapy a valuable future curative method that, over time, might replace the current standard medication.

Of particular emerging interest is the development of in vivo gene therapy, which aims to deliver gene-editing tools directly into the patient's body without the need for ex vivo stem cell manipulation or myeloablative conditioning. Although still in the preclinical and early translational stages, in vivo approaches, employing viral vectors (such as adeno-associated virus or lipid nanoparticles) to target haematopoietic stem cells in situ, could dramatically simplify treatment, reduce toxicity, and expand accessibility to low-resource settings. Early murine studies using in vivo prime editing and base editing platforms have successfully corrected the sickle mutation in haematopoietic stem cells, leading to stable expression of normal haemoglobin and reversal of disease phenotypes. If translated safely into human applications, in vivo strategies could represent a paradigm shift, enabling minimally invasive, one-time curative interventions for SCD.

The following steps, however, involve conducting full-scale validation of such therapies through long-term follow-up and the accumulation of real-world evidence to introduce them into routine clinical practice. It will be necessary to conduct longitudinal safety, durability of response, and severe adverse events that are infrequent but serious. The implementation in the real world will also require consideration of access, treatment costs, and fair access to treatments in various healthcare settings.

In summary, although new gene therapies mark a new dawn in the treatment of SCD, further research in this direction, including the maturation of in vivo editing technologies and comparative cost-effectiveness studies, is needed, and intensive follow-up of the results in patients on a post-marketing basis is necessary. This will enable the determination of the complete long-term efficacy and safety profiles of this promising gene therapy tool. These initiatives will be crucial to the widespread clinical adoption of these transformative treatments, enabling the delivery of results with clinical significance to patients worldwide.

Data Sharing Statement

The datasets used and/or analysed during this review are available from the author upon reasonable request.

Ethical Approval

Not applicable. This article is a review of previously published studies and did not involve human participants or animal research.

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Author Contributions

The author confirms that he made a significant contribution to the work reported, including the conception, study design, data analysis and interpretation, drafting, revising, and critically reviewing the article. The author gave final approval of

the version to be published, has agreed on the journal to which the article has been submitted, and agrees to be accountable for all aspects of the work.

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