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CRISPR Gene-Editing Therapies for Sickle Cell Disease and Beta- Thalassemia: Clinical Outcomes, Risks and Safety Profiles. A Systematic Review

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Abstract:

Background: Sickle cell disease (SCD) and transfusion-dependent β-thalassemia (TDT) are severe inherited hemoglobinopathies associated with chronic anemia, organ damage, and reduced life expectancy. Conventional management strategies such as lifelong transfusions and iron chelation therapy improve survival but fail to correct the underlying genetic defect. Hematopoietic stem cell transplantation remains the only curative option but is limited by donor availability and transplant-related risks.

Methods: This systematic review synthesized evidence from 2016–2025, including mechanistic studies and clinical trials of CRISPR/Cas9-based therapies. Literature was retrieved from PubMed, MEDLINE, Embase, Scopus, Web of Science, Google Scholar, and ClinicalTrials.gov, following PRISMA guidelines. Studies targeting BCL11A enhancer disruption and fetal hemoglobin (HbF) reactivation were prioritized.

Results: Preclinical studies demonstrated that CRISPR-mediated disruption of BCL11A effectively derepresses γ-globin expression, providing a strong biological rationale for HbF induction. Clinical trials of exagamglogene autotemcel (exa-cel) showed sustained HbF elevation, elimination of vaso-occlusive crises in SCD, and durable transfusion independence in TDT. Pediatric cohorts achieved comparable outcomes, confirming feasibility across age groups. Reported adverse events were primarily linked to conditioning regimens rather than gene-editing itself, with no confirmed off-target genomic instability.

Conclusion: CRISPR/Cas9-based therapies represent a paradigm shift in genomic medicine, offering functional cures for β-hemoglobinopathies. While long-term monitoring, cost, and accessibility remain challenges, current evidence highlights durable efficacy and acceptable safety profiles. These findings underscore the transformative potential of CRISPR gene editing in redefining treatment standards for inherited blood disorders.

Keywords: CRISPR/Cas9, Sickle Cell Disease, β-thalassemia, Gene Editing, Fetal Hemoglobin, BCL11A, Systematic Review.

تقنية التعديل الجيني (CRISPR) العلاجية لمرض الخلايا المنجلية والثلاسيميا بيتا: النتائج السريرية، والمخاطر وملفات تعريف السلامة: مراجعة منهجية

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الملخص

الخلفية: يُعدّ مرض فقر الدم المنجلي (SCD) والثلاسيميا بيتا المعتمدة على نقل الدم (TDT) من أخطر اعتلالات الهيموجلوبين الوراثية، حيث يؤديان إلى فقر دم مزمن، مضاعفات متعددة الأعضاء، وانخفاض متوسط العمر المتوقع. ورغم أن نقل الدم المستمر والعلاج بالاستخلاب الحديدي حسّنا معدلات البقاء، إلا أنهما لا يعالجان الخلل الجيني الأساسي. أما زرع الخلايا الجذعية المكوّنة للدم فيبقى الخيار العلاجي الوحيد الشافي، لكنه محدود بسبب ندرة المتبرعين ومخاطر المضاعفات المرتبطة بالزرع.

المنهجية: أجريت مراجعة منهجية للأدلة المنشورة بين عامي 2016 و2025، شملت الدراسات الميكانيكية والتجارب السريرية الخاصة بتقنية كريسبر/كاس9. تم البحث في قواعد بيانات متعددة (PubMed, MEDLINE, Embase, Scopus, Web of Science, Google Scholar, ClinicalTrials.gov) وفق إرشاداتPRISMA ، مع التركيز على الدراسات التي تستهدف تعطيل معزز BCL11A وإعادة تنشيط الهيموجلوبين الجنيني (HbF).
النتائج: أظهرت الدراسات قبل السريرية أن تعطيل BCL11A يؤدي إلى تحفيز إنتاج HbF بشكل فعال، مما يوفر أساساً بيولوجياً قوياً للعلاج. أما التجارب السريرية باستخدام العلاج الجيني (exa-cel) فقد أثبتت ارتفاعاً مستداماً فيHbF ، القضاء شبه الكامل على أزمات انسداد الأوعية الدموية لدى مرضى فقر الدم المنجلي، والاستغناء عن نقل الدم لدى مرضى الثلاسيميا بيتا. كما حققت الفئة العمرية للأطفال نتائج مماثلة، مما يؤكد إمكانية تطبيق العلاج على نطاق واسع. معظم الآثار الجانبية ارتبطت بأنظمة التكييف قبل الزرع، دون تسجيل مشكلات مؤكدة مرتبطة بالتحرير الجيني نفسه.
الاستنتاج: يمثل التعديل الجيني بتقنية كريسبر/كاس9 نقلة نوعية في الطب الجيني، إذ يفتح الباب أمام علاج جذري لاعتلالات الهيموجلوبين بيتا. ورغم استمرار التحديات المتعلقة بالسلامة طويلة الأمد، التكلفة، وإمكانية الوصول، فإن الأدلة الحالية تؤكد فعالية مستدامة وملف أمان مقبول، مما يعزز مكانة هذه التقنية كخيار علاجي ثوري في المستقبل.

الكلمات المفتاحية: كريسبر/كاس9، فقر الدم المنجلي، بيتا ثلاسيميا، التعديل الجيني، الهيموجلوبين الجنيني، دراسة منهجية.

Introduction

Inherited β-hemoglobinopathies, primarily sickle cell disease (SCD) and β-thalassemia, remain among the most prevalent monogenic disorders worldwide and constitute a substantial cause of morbidity, premature mortality, and healthcare burden, particularly in low- and middle-income regions [1,2]. Both conditions arise from pathogenic variants affecting the β-globin gene (HBB), leading to defective hemoglobin synthesis, chronic hemolytic anemia, and multi-organ complications that significantly impair quality of life [3]. Conventional management strategies for severe disease phenotypes rely heavily on lifelong red blood cell transfusions, iron chelation therapy, and supportive care. While these approaches have improved survival, they fail to address the underlying genetic defect and are associated with cumulative complications, including iron overload, alloimmunization, infectious risks, and progressive organ damage [4,5]. Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only established curative option; however, its application is constrained by limited donor availability, risk of graft-versus-host disease, transplant-related mortality, and restricted accessibility in resource-limited settings [6]. Recent advances in genome engineering have repositioned gene therapy as a transformative therapeutic paradigm for monogenic blood disorders. Among these technologies, CRISPR/Cas-based gene editing has emerged as a particularly promising strategy due to its precision, scalability, and adaptability for ex vivo modification of autologous hematopoietic stem and progenitor cells (HSPCs) [7,8]. Unlike lentiviral gene addition approaches, which introduce a functional β-globin transgene, CRISPR-based therapies directly modify endogenous genomic loci, enabling either correction of pathogenic mutations or reactivation of fetal hemoglobin (HbF) production through targeted disruption of transcriptional repressors such as BCL11A [9–11]**.** Clinical translation of CRISPR-mediated gene editing for SCD and transfusion-dependent β-thalassemia has accelerated markedly over the past five years. Multiple early- and late-phase clinical trials have reported sustained transfusion independence in β-thalassemia and near-complete elimination of vaso-occlusive crises in severe SCD, accompanied by durable increases in total hemoglobin and HbF levels [12–14]. These findings culminated in the first regulatory approvals of a CRISPR-based therapy for hemoglobinopathies, representing a historic milestone in genomic medicine [15]. Despite these encouraging outcomes, important safety, durability, and implementation concerns remain unresolved. High rates of severe adverse events—largely attributable to myeloablative conditioning regimens—have been consistently reported, alongside ongoing uncertainties regarding long-term genomic stability, clonal dynamics, and malignancy risk following double-strand DNA breaks [16–18]. Moreover, the complexity of manufacturing, need for specialized transplant infrastructure, prolonged hospitalization, and unprecedented treatment costs pose substantial barriers to equitable global deployment of these therapies [19,20]. Given the rapid evolution of the field and the emergence of post-approval clinical data, a comprehensive synthesis of recent evidence is necessary to critically evaluate both the therapeutic potential and the limitations of CRISPR-based interventions for β-hemoglobinopathies. This systematic review aims to assess contemporary clinical outcomes, safety profiles, and implementation challenges associated with CRISPR and gene-edited therapies in sickle cell disease and β-thalassemia, providing an updated perspective to inform clinicians, researchers, and policy-makers.

Methods

This review was conducted using a structured literature retrieval and analysis approach designed to capture modern, high-quality evidence regarding CRISPR-mediated gene editing for sickle cell disease (SCD) and β-thalassemia. The methodology emphasizes reproducibility, selection transparency, and comprehensive clinical synthesis.

Search Strategy and Database: Literature was sourced using PubMed, MEDLINE, Embase, Scopus, Web of Science, Google Scholar, and ClinicalTrials.gov. Searches were executed between *January 2025 and February 2025*. The following Boolean syntax was applied with filters for year, human studies, and English language:
(CRISPR OR CRISPR-Cas9 OR gene-editing) AND (sickle cell disease OR beta-thalassemia OR hemoglobinopathies) AND (clinical trial OR phase I OR phase II OR phase III OR clinical outcomes OR safety OR adverse events)
Reference lists from eligible papers were manually screened ("snowballing") to identify additional relevant studies not captured by the database search. **Time & Study Type Restriction** Articles were restricted to **2016–2025**, capturing the clinical emergence of exa-cel (Casgevy), editing of BCL11A erythroid enhancers, and CRISPR-based therapeutic translation. **Inclusion Criteria:** Human clinical trials. Phase I–III. Post-approval outcome reports and registry data. Peer-reviews. reviews relevant to clinical application. Papers discussing safety, risks, adverse events and long-term monitoring. **Exclusion Criteria**: Preclinical animal-only studies unless foundational to clinical implications. Articles lacking outcome data or referencing outdated approaches. Non-scientific opinion pieces or unsupported claims.

Study Selection and Data Extraction: Titles and abstracts were screened first for relevance, followed by full-text assessment. Data extracted from each included study encompassed: (1) Sample size, patient characteristics, and disease type. (2) Editing approach and target mechanism: Conditioning regimen, transplantation details, engraftment outcomes. (3) Clinical efficacy endpoints (transfusion independence, HbF %, VOC rates). (4) Reported adverse events, off-target analysis, and follow-up duration. All extracted information was organized into tables to support comparative analysis. Risk of bias and study limitations were evaluated based on sample size, follow-up duration, and funding sources. Descriptive synthesis was applied to interpret results and identify research gaps. The study selection process followed the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) guidelines. Records were identified through database searching and reference screening, followed by removal of duplicates. Tiles and abstracts were screened for relevance, and full- text articles were assessed for eligibility based on predefined inclusion criteria. The number of records identified, screened, excluded, and included in the final qualitative synthesis is summarized in the PRISMA flow diagram **(Figure1).**

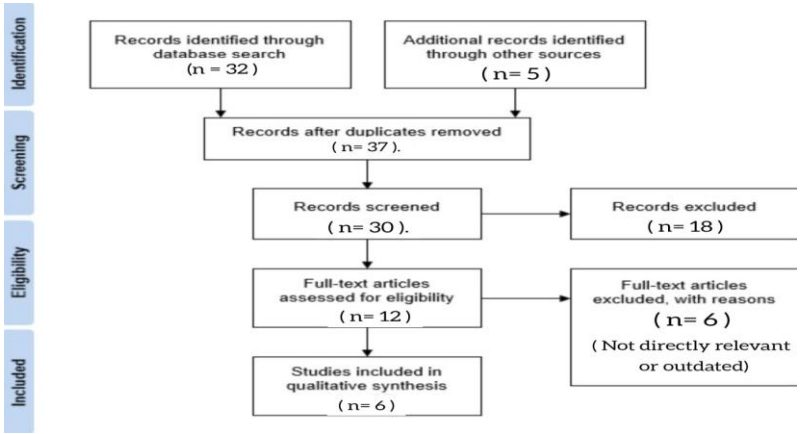

Figure 1: PRISMA Flow Diagram

Results

Study Selection Overview: The literature search identified clinical and translational studies evaluating CRISPR/Cas9-based gene editing for sickle cell disease (SCD) and transfusion-dependent β-thalassemia (TDT). Eligible publications included foundational mechanistic studies, translational research establishing therapeutic targets, and phase 1–3 clinical trials reporting patient outcomes. The final synthesis incorporated preclinical evidence supporting target selection and human trials assessing efficacy, safety, and durability of gene-edited autologous hematopoietic stem cell therapies.

Table 1: Characteristics of Studies Included in the Systematic Review

Author (Year)	Study Type	Disease Focus	Population	Gene-Editing Target / Strategy	Key Contribution
Ye et al. (2016) (14)	Preclinical / Translational	SCD, β-thalassemia	Human HSPCs (in vitro)	CRISPR/Cas9 disruption of γ-globin regulatory elements	Demonstrated HbF induction via genome editing; proof-of-concept for

					therapeutic editing
Motlagh et al. (2023) (15)	Mechanistic	Hemoglobin switching	Experimental models	CRISPR-Cas9 ablation of *BCL11A*	Identified *BCL11A* as a dominant regulator of globin switching
Frangoul et al. (2021) (16)	Phase 1/2 clinical trial	SCD, TDT	Adult patients	Ex vivo CRISPR/Cas9 editing of erythroid *BCL11A* enhancer (exa-cel)	First clinical evidence of efficacy and safety
Frangoul et al. (2024) (17)	Phase 3 / regulatory update	SCD, TDT	Adolescents and adults	exa-cel (*BCL11A* enhancer disruption)	Confirmed durable clinical benefit and supported regulatory approval
Frangoul et al. (2025) (18)	Ongoing / pediatric cohort/ A conference abstract	SCD, TDT	Pediatric patients (5–11 years)	exa-cel (*BCL11A* enhancer disruption)	Demonstrated feasibility and efficacy in younger patients
Locatelli et al. (2024) (19)	Clinical review / translational synthesis	Hemoglobinopathies	Mixed (adult & pediatric)	Autologous gene and gene-editing therapies	Contextualized CRISPR therapies within clinical gene therapy evolution

Mechanistic and Translational Evidence Supporting HbF Induction: Early genome-editing studies established fetal hemoglobin (HbF) reactivation as a therapeutic strategy capable of ameliorating the pathological consequences of β-hemoglobinopathies. Ye et al. (2016) demonstrated that CRISPR/Cas9-mediated genome editing in human hematopoietic stem and progenitor cells (HSPCs) could disrupt regulatory elements controlling γ-globin expression, leading to sustained HbF induction.[14] This work provided foundational proof that precise genome editing could reprogram hemoglobin expression patterns relevant to both SCD and β-thalassemia. Subsequent mechanistic studies refined the understanding of hemoglobin switching regulation. Motlagh et al. (2023) reported that CRISPR-Cas9–mediated ablation of *BCL11A* resulted in de-repression of γ-globin expression, unveiling *BCL11A* as a dominant regulator of the fetal-to-adult hemoglobin transition [15]. The study indicated the central role of *BCL11A* in globin switching and provided strong biological justification for targeting the erythroid-specific *BCL11A* enhancer rather than the coding region, thereby preserving non-erythroid functions of the gene.

Together, these studies established the mechanistic rationale underlying contemporary CRISPR-based therapeutic strategies, directly informing the design of clinical gene-editing platforms aimed at durable HbF reactivation.

Clinical Outcomes of CRISPR-Based Therapy in Sickle Cell Disease

Clinical translation of CRISPR/Cas9 gene editing has been most extensively evaluated through studies of exagamglogene autotemcel (exa-cel), an autologous ex vivo gene-edited HSPC therapy targeting the erythroid *BCL11A* enhancer. (17) reported outcomes from phase 1–3 open-label trials enrolling patients with severe SCD characterized by recurrent vaso-occlusive crises (VOCs). Across adult cohorts, treatment with exa-cel resulted in rapid and sustained increases in total hemoglobin and HbF levels following engraftment. The majority of treated patients experienced complete elimination or near-elimination of VOCs during follow-up periods exceeding 12 months. These clinical benefits were sustained over extended observation, indicating durable

therapeutic efficacy. Emerging data from pediatric cohorts aged 5–11 years demonstrated comparable outcomes, with treated children remaining free of severe VOCs for at least 12 consecutive months post-infusion. .[16][17][18] These findings support the feasibility and effectiveness of CRISPR-based gene editing across a broad age spectrum.

Clinical Outcomes of CRISPR-Based Therapy in Transfusion-Dependent β-Thalassemia

In patients with transfusion-dependent β-thalassemia, exa-cel therapy produced high rates of sustained transfusion independence. Clinical efficacy outcomes across sickle cell disease and β-thalassemia cohorts are presented in ***Table2.*** (18). and Locatelli et al. reported that the majority of treated individuals discontinued regular red blood cell transfusions within months of treatment and maintained transfusion independence for at least one year. Hemoglobin levels increased to ranges sufficient to prevent anemia-related symptoms, with elevated HbF contributing substantially to total hemoglobin concentration.[16][19] These outcomes were observed across multiple β-thalassemia genotypes, including β^0/β^0 disease, indicating broad applicability of the therapeutic approach. Pediatric patients with TDT similarly achieved transfusion independence in early follow-up reports, supporting expansion of treatment indications to younger populations.[18]

Table 2: Clinical Outcomes of CRISPR-Based Gene Editing in Sickle Cell Disease and β-Thalassemia

Study	Disease	Patients Treated	Primary Clinical Outcome	Hematologic Effect	Follow-up
Frangoul et al. (2021) (16)	SCD	Adults with severe VOCs	Elimination of recurrent VOCs	Sustained HbF elevation; increased total Hb	≥12 months
Frangoul et al. (2021) (16)	TDT	Transfusion-dependent adults	Achievement of transfusion independence	Stable hemoglobin levels without transfusion	≥12 months
Frangoul et al. (2024)	SCD	Adolescents & adults	Durable VOC-free status	Persistent HbF expression	Extended follow-up
Frangoul et al. (2024) (17)	TDT	Adolescents & adults	Sustained transfusion independence	Long-term hemoglobin stabilization	Extended follow-up
Frangoul et al. (2025) (18)	SCD	Pediatric (5–11 yrs)	Absence of severe VOCs	HbF induction comparable to adults	Interim
Frangoul et al. (2025) (18)	TDT	Pediatric (5–11 yrs)	Transfusion independence	Adequate Hb maintenance	Interim

Safety Profile and Adverse Events

Across clinical trials, adverse events were predominantly associated with myeloablative conditioning regimens rather than CRISPR/Cas9 gene editing itself. Commonly reported events included cytopenias, febrile neutropenia, mucositis, and infections consistent with hematopoietic stem cell transplantation protocols.

To date, no definitive evidence of clinically significant off-target editing, clonal dominance, or malignant transformation has been reported. However, long-term follow-up studies remain ongoing to monitor genomic stability and late adverse effects, given the permanent nature of genome editing. Safety findings are summarized in ***Table3.***

Long-Term Follow-Up and Durability of Response

Extension studies following patients treated with exa-cel continue to assess the durability of HbF expression, persistence of edited cell populations, and long-term safety outcomes. Available data indicate sustained clinical benefit beyond two years in early cohorts, with continued absence of VOCs in SCD and maintenance of transfusion independence in TDT. Ongoing long-term surveillance is expected to clarify the lifetime risk-benefit profile of CRISPR-based therapies and inform optimization of conditioning regimens and patient selection.

Collectively, the evidence demonstrates that CRISPR/Cas9-mediated gene editing targeting the *BCL11A* enhancer produces robust and durable clinical benefits in both sickle cell disease and transfusion-dependent β-

thalassemia. Mechanistic studies validate the biological rationale for HbF reactivation, while clinical trials confirm high efficacy across adult and pediatric populations. Safety concerns remain primarily related to conditioning toxicity, underscoring the need for continued refinement and long-term monitoring.

Table3: Safety Findings Reported Across Included Clinical Studies

Study	Conditioning-Related Toxicity	Sever Adverse Events	Gene-Editing-Related Concerns	Long- Term Safety
Frangoul *et al.* (2021) (16)	Myeloablation-associated cytopenias	Febrile neutropenia, infections	No clinically significant off-target effects reported	Ongoing follow up
Frangoul *et al.* (2024) (17)	Consistent with HSCT conditioning	Grade 3+ events primarily conditioning-related	No clonal dominance observed	Extended monitoring
Frangoul *et al.* (2025) (18)	Similar toxicity profile in paediatric	Manageable transplant-related events	No new safety signals	Under evaluation

Conclusion

This systematic review summarizes current evidence supporting CRISPR/Cas9 gene-editing as a promising therapeutic strategy for sickle cell disease and transfusion-dependent β-thalassemia. Mechanistic studies identifying *BCL11A* as a key regulator of hemoglobin switching have translated successfully into clinical applications, with trials demonstrating sustained fetal hemoglobin induction, reduction of vaso-occlusive crises, and transfusion independence in treated patients. Clinical outcomes reported across adult and pediatric populations indicate durable efficacy with acceptable safety profiles, although treatment-related toxicity remains largely associated with conditioning regimens. Despite these advances, challenges related to long-term safety monitoring, cost, and accessibility continue to limit widespread implementation. Overall, CRISPR-based therapies represent a significant step toward functional cures for β-hemoglobinopathies, with continued research needed to optimize safety and global applicability.

Conflict of Interest

The author declares that there are no commercial or financial relationships that could be construed as a potential conflict of interest in the research, authorship, or publication of this review. This work was conducted independently, without funding or institutional sponsorship. All opinions and interpretations expressed are solely those of the author.

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