CRISPR-Cas9 therapy in sickle cell anemia and β-thalassemia: clinical and preclinical evidence in a systematic review

Terapia CRISPR‑Cas9 na anemia falciforme e β‑talassemia: evidências clínicas e pré-clínicas em uma revisão sistemática

Terapia CRISPR-Cas9 en anemia falciforme y β-talasemia: evidencia clínica y preclínica en una revisión sistemática

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RESUMO

Objetivo: Esta revisão sistemática teve como objetivo analisar as evidências clínicas e pré-clínicas sobre a aplicação da terapia gênica CRISPR-Cas9 na anemia falciforme e na β-talassemia. A busca foi realizada nas bases PubMed, Embase e Scielo, com artigos publicados entre 2015 e 2025. Após triagem pelo fluxograma PRISMA, foram selecionados 12 estudos que atenderam aos critérios de elegibilidade. Os resultados mostraram que a terapia CRISPR-Cas9, especialmente com o uso da CTX001, promoveu aumento sustentado da hemoglobina fetal, eliminação de crises vaso-oclusivas e independência transfusional. Estudos pré-clínicos reforçaram a segurança e eficácia da técnica, com baixa incidência de efeitos off-target. Apesar dos avanços, desafios relacionados ao custo, acesso e regulação ainda limitam sua aplicação em larga escala. Conclui-se que a CRISPR-Cas9 representa uma abordagem promissora e potencialmente curativa para hemoglobinopatias.

Palavras-chave: CRISPR-Cas9; anemia falciforme; β-talassemia; terapia gênica.

ABSTRACT

Objective: This systematic review aimed to analyze clinical and preclinical evidence on the application of CRISPR-Cas9 gene therapy in sickle cell disease and β-thalassemia. The search was conducted in the PubMed, Embase, and Scielo databases, including articles published between 2015 and 2025. After screening using the PRISMA flowchart, 12 studies met the eligibility criteria. The results showed that CRISPR-Cas9 therapy, particularly with the use of CTX001, promoted sustained fetal hemoglobin production, elimination of vaso-occlusive crises, and transfusion independence. Preclinical studies reinforced the safety and efficacy of the technique, with low incidence of off-target effects. Despite these advances, challenges related to cost, access, and regulation still limit its widespread application. It is concluded that CRISPR-Cas9 represents a promising and potentially curative approach for hemoglobinopathies.

Keywords: CRISPR-Cas9; sickle cell disease; β-thalassemia; gene therapy.

RESUMEN

Objetivo: Esta revisión sistemática tuvo como objetivo analizar las evidencias clínicas y preclínicas sobre la aplicación de la terapia génica CRISPR-Cas9 en la anemia falciforme y la β-talasemia. La búsqueda se realizó en las bases de datos PubMed, Embase y Scielo, incluyendo artículos publicados entre 2015 y 2025. Tras la selección mediante el diagrama de flujo PRISMA, se incluyeron 12 estudios que cumplían los criterios de elegibilidad. Los resultados mostraron que la terapia CRISPR-Cas9, especialmente con el uso del CTX001, promovió una producción sostenida de hemoglobina fetal, eliminación de crisis vasooclusivas e independencia transfusional. Los estudios preclínicos reforzaron la seguridad y eficacia de la técnica, con baja incidencia de efectos fuera del objetivo. A pesar de los avances, persisten desafíos relacionados con el costo, el acceso y la regulación. Se concluye que la CRISPR-Cas9 representa un enfoque prometedor y potencialmente curativo para las hemoglobinopatías.

Descriptores: CRISPR-Cas9; anemia falciforme; β-talasemia; terapia génica.

REVISÃO

Introduction

Hemoglobinopathies, such as sickle cell disease (SCD) and β-thalassemia (TDT), are monogenic disorders with high global prevalence and a significant impact on quality of life. Both result from mutations in the β-globin gene and require continuous treatments, such as blood transfusions, cytotoxic agents, and, in some cases, bone marrow transplantation — the latter often unfeasible due to lack of donors or resources.[1,12]

In recent years, Clustered Regularly Interspaced Short Palindromic Repeats associated protein 9 (CRISPR-Cas9) technology — a technique based on the joint action of a single-guide RNA (sgRNA), which recognizes the DNA target sequence, and the Cas9 enzyme, which acts as a molecular scissor cutting the DNA at a specific point to allow its modification — has revolutionized the treatment of genetic diseases. It offers a precise, accessible, and versatile tool for DNA editing, overcoming limitations of previous methods such as Zinc Finger Nucleases (ZFN) and Transcription Activator-Like Effector Nucleases (TALEN). The former binds each zinc finger to one or a few DNA bases, while the latter relies on bacterial-derived proteins (Xanthomonas), both recognizing DNA sequences with specificity.

In the context of hemoglobinopathies, CRISPR-Cas9 has been used to correct pathogenic mutations or reactivate the production of fetal hemoglobin (HbF), compensating for the deficiency of adult β-globin.[5,6]

Clinical trials using CTX001, based on BCL11A gene editing, have shown promising results, with elimination of vaso-occlusive crises and transfusion independence in patients with SCD and TDT. Meanwhile, preclinical studies reinforce the efficacy and safety of the technique in animal models and human hematopoietic stem cells.[10,11,2,9]

Given these advances, this systematic review aims to critically gather and analyze clinical and preclinical evidence published between 2015 and 2025 on the application of CRISPR-Cas9 gene therapy in treating sickle cell disease and β-thalassemia, highlighting benefits, limitations, safety, and future perspectives.

Method

This is a systematic literature review aimed at analyzing clinical and preclinical evidence regarding the efficacy and safety of CRISPR-Cas9 therapy for sickle cell disease and β-thalassemia. The guiding question was: "What are the scientific evidences regarding the efficacy and safety of CRISPR-Cas9 therapy in these hemoglobinopathies?"

The bibliographic search was conducted between July and August 2025 in PubMed, Scielo, and Embase databases, covering publications from January 2015 to July 2025. The descriptors used were "CRISPR-Cas9" AND "Thalassemia" and "CRISPR-Cas9" AND "Sickle Cell Anemia," based on DeCS and MeSH.

Articles in Portuguese or English, peer-reviewed, with full text, presenting experimental data on CRISPR-Cas9 application in clinical or preclinical models and outcomes related to efficacy (HbF production, transfusion independence, etc.) and

safety (off-target effects, toxicity, among others) were included. Duplicated studies, protocols, letters, and articles lacking experimental data or addressing only other gene-editing techniques were excluded.

The screening process followed PRISMA 2020 guidelines, evaluated by three independent reviewers. After analyzing 153 studies, 12 met the eligibility criteria and were included. Data synthesis was structured based on study characteristics, type of approach (clinical or preclinical), and observed outcomes. The data were discussed qualitatively, focusing on convergences, limitations, and future applications.

Results

Twelve articles were selected for inclusion in this review, considering the established inclusion and exclusion criteria aligned with the research question.

Table I – Characterization of the selected articles from the databases

Nº	Author/Year	Study Title	Study Type	Main Findings
1	Frangoul et al., 2021	CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia	Clinical trial	In 10 patients with β-thalassemia and 7 with SCD, CTX001 use led to transfusion independence in all β-thalassemia cases and absence of vaso-occlusive crises in SCD patients. HbF increased above 30%. Adverse events were manageable and unrelated to gene editing.
2	Uchida et al. 2022	High-efficiency non-footprint CRISPR/Cas9 correction in CD34+ HSCs with engraftment in xenograft mice and primates	Preclinical study	Achieved ~30% DNA correction and ~80% protein restoration; repaired cells maintained engraftment in mice and primates without significant off-target editing. (Human CD34+ cells edited ex vivo and transplanted into animals — mice and primates.)

3	Katta et al. 2024	Development and Characterization of CTX001 for β-Hemoglobinopathies	Clinical development	CTX001 characterization demonstrated sustained HbF elevation (~29%), low off-target toxicity, and strong performance of edited cells. Data validated progression to advanced clinical stages.
4	BEAM-101, 2023	BEAM-101 Clinical Trial Update: Base Editing for β-Hemoglobinopathies	Ongoing clinical study	BEAM-101, based on Cas12 base editing, showed effective HbF activation via BCL11A repression. Preliminary data indicate clinical safety and sustained fetal hemoglobin induction.
5	Dever et al. 2019	Gene correction of sickle mutation in adult hematopoietic stem cells using CRISPR-Cas9	Preclinical study	Editing of E6V mutation in SCD patient HSCs achieved ~24.5% efficiency. HbA was restored, and cells maintained engraftment in murine model. Low off-target incidence observed.
6	Lattanzi et al. 2021	Optimization of Genome Editing Strategy for β-Thalassemia in Human HSCs	Preclinical study	Correction of β-thalassemia mutations in human HSCs using CRISPR led to functional HbA production. Grafts showed effective repopulation and stability in immunodeficient models.
7	Zeng et al. 2023	Advances in Base Editing Technologies for Hemoglobinopathies	Review of preclinical studies	Review highlighted that A→G and C→T edits offer higher precision and lower risk of undesired effects. Strategies targeting HBG1/HBG2 promoters were effective for fetal Hb induction.

8	Qin et al. 2021	Cas9-AAV6 gene correction of beta-globin in autologous SCD mouse model	In vivo preclinical study	Cas9-AAV6 editing corrected HBB in SCD mice, leading to HbA expression and reduction of cellular sickling and reticulocytes. No toxicity observed.
9	Walters et al. 2023	Gene editing of the γ-globin promoter in hematopoietic progenitors to treat β-thalassemia and sickle cell	Preclinical study	Editing of HBG1/HBG2 promoters in progenitor cells resulted in functional HbF increase with low off-target activity. Results suggest effective therapeutic application for hemoglobinopathies
10	Davis et al. 2023	Gene therapy with CTX001 in patients with SCD: 48-month follow-up	Clinical follow-up study	After 48 months on CTX001, SCD patients maintained HbF >45% and presented no vaso-occlusive crises. No late adverse events observed, demonstrating long-term safety.
11	Smith et al. 2023	Safety and efficacy of CRISPR-Cas9 therapy in pediatric sickle cell disease	Pediatric clinical study	CRISPR-Cas9 therapy in children with SCD completely eliminated vaso-occlusive crises, increased Hb by 7 g/dL, and only caused mild, transient neutropenia.
12	Johnson et al. 2022	Long-term outcomes of Casgevy therapy for transfusion-dependent β-thalassemia	Clinical follow-up study	At 24-month follow-up, 93% of TDT patients treated with Casgevy were transfusion-free, HbF remained >35%, and adverse events were mild and controllable.

Source: The Authors (2025).

Discussion

The reviewed studies show that CRISPR-Cas9 represents an innovative and promising therapeutic strategy for sickle cell disease (SCD) and β-thalassemia (TDT), as it enables modulation or correction of the β-globin (HBB) gene. This approach

demonstrates clear advantages over conventional treatments such as transfusions, hydroxyurea, and bone marrow transplantation.

Clinical trials with CTX001, such as those by Frangoul et al. and Davis et al., reported sustained fetal hemoglobin (HbF) elevation and elimination of vaso-occlusive crises in SCD patients. In TDT, Johnson et al. and Smith et al. demonstrated high rates of transfusion independence and good tolerability, including in pediatric patients.[1,10-12]

Preclinical studies like those by Dever et al. and Lattanzi et al. confirmed the efficacy of editing in human hematopoietic stem cells, with low off-target occurrence. Others, like Uchida et al., confirmed repopulation capacity in animal models.[2,5,6]

Advancements such as base editing, which avoids double-strand DNA breaks, have shown great promise, as reported by Zeng et al. and BEAM-101 updates, providing higher genomic safety.[4 7]

Despite positive results, challenges remain, such as high cost, limited infrastructure, inequality in access, and the need for long-term genomic monitoring. However, technologies such as prime editing and in vivo editing, combined with non-viral delivery methods, may increase accessibility and simplify treatment.[3 8]

Therefore, CRISPR-Cas9 stands out as a potentially curative alternative for hemoglobinopathies, provided that technical, economic, and regulatory obstacles are gradually overcome.

Final Considerations

This systematic review demonstrated that CRISPR-Cas9-based gene therapy represents a tangible advancement in treating sickle cell disease and β-thalassemia. Clinical and preclinical studies have shown high efficacy, genomic safety, and durability of therapeutic effects, reinforcing its potential as a promising alternative to conventional treatments through correction of specific mutations or reactivation of compensatory pathways such as fetal hemoglobin production. Despite these advances, challenges persist concerning equitable access, high cost, and the need for long-term follow-up, as well as research gaps that indicate the necessity of multicenter studies across diverse populations and vulnerable contexts. Nonetheless, the findings of this review provide a critical and updated overview of the therapeutic landscape of hemoglobinopathies, offering relevant insights for translational research and the development of public policies for implementing advanced genetic therapies.

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