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Research Article

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Sickle Cell Anemia: Therapeutic Advances, Disease-Modifying Therapies, and Future Prospects

Rosane Rezende de Souza Giuliani[1], Felipe Santos Teixeira Martiniano[3], Nicole Mioto Medeiros[4,5], Lorenzo Francesco Giuliani[6], Ana Laura Munerato Zoega Marotti[7,8], Milena Zanqui Calegari[9], Mateus Soares Santos Araújo[10], João Marcelo Vieira Morais[10], Rodrigo dos Santos Oliveira Alves[10], Maria Beatriz Mendonça Ventura[11], Filipe J. L. Garcia[12], Milena Gabriele Coelho Freitas[12], Carlos Henrique B. Figueiredo de Mendonça[11], Joel Eloi Belo Junior[13] and Thiago Augusto Rochetti Bezerra[2,12*]

[1]*Head of the Hematology Department, Portuguese Beneficent Society of Santos, Santos, São Paulo, Brazil*

[2]*School of Medicine, University of Ribeirão Preto (UNAERP), Ribeirão Preto, São Paulo, Brazil*

[3]*Internal Medicine Residency Program, Portuguese Beneficent Hospital of Santos, Santos, São Paulo, Brazil*

[4]*School of Medicine, University of Vale do Sapucaí (UNIVÁS), Pouso Alegre, Minas Gerais, Brazil*

[5]*Department of Hematology and Hemotherapy, Amaral Carvalho Hospital, Jaú, São Paulo, Brazil*

[6]*Department of Anesthesia, Resuscitation, Intensive Care and Pain Medicine, Sapienza University of Rome, Rome, Italy*

[7]*School of Medicine, University of Marília (UNIMAR), Marília, São Paulo, Brazil.*

[8]*Department of Hematology, Marília Medical School (FAMEMA), Marília, São Paulo, Brazil*

[9]*Humanitas Faculty of Medical Sciences of São José dos Campos, São José dos Campos, São Paulo, Brazil*

[10]*Euro-American University Center (UNIEURO), Brasília, Federal District, Brazil*

[11]*School of Medicine, Federal University of Roraima (UFRR), Boa Vista, Roraima, Brazil*

[12]*School of Medicine, University of Ribeirão Preto (UNAERP), Guarujá Campus, Guarujá, São Paulo, Brazil*

***Corresponding Author**

Thiago Augusto Rochetti Bezerra, School of Medicine, University of Ribeirão Preto (UNAERP), Brazil.

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[13]*PhD in Technological Innovation, Professional Graduate Program in Technological Innovation, Federal University of São Paulo (UNIFESP), São Paulo, Brazil*

[14]*Ribeirão Preto Medical School, University of São Paulo (FMRP-USP), Ribeirão Preto, São Paulo, Brazil*

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Abstract

Introduction: *Sickle cell disease is the most prevalent inherited hemoglobinopathy worldwide, characterized by chronic hemolysis, systemic inflammation, and recurrent episodes of vaso-occlusion, which are responsible for high morbidity and mortality. In recent decades, therapeutic advances have expanded treatment options, including disease-modifying therapies, hematopoietic stem cell transplantation, and gene therapy.*

Objective: *To analyze the scientific evidence regarding therapeutic advances, disease-modifying therapies, and future prospects for the treatment of sickle cell anemia.*

Methods: *A systematic review conducted in accordance with PRISMA guidelines, using the databases PubMed, Scopus, Web of Science, Embase, the Cochrane Library, and ScienceDirect. Studies published between 2016 and 2026 were included, covering pharmacological therapies, hematopoietic stem cell transplantation, gene therapy, and gene editing. After the selection process, 124 studies comprised the final sample.*

Results: *Hydroxyurea remained the primary disease-modifying drug, while crizanlizumab, voxelotor, and L-glutamine demonstrated additional benefits in reducing vaso-occlusive crises, hemolysis, and clinical complications. Hematopoietic stem cell transplantation showed the greatest curative potential, and gene therapies based on lentiviral vectors and CRISPR-Cas9 revealed promising results in terms of reducing clinical events and achieving transfusion independence. However, limitations related to cost, specialized infrastructure, access, and the lack of long-term follow-up still restrict their widespread implementation.*

Conclusion: *The evidence demonstrates that advances in disease-modifying therapies and potentially curative strategies are transforming the management of sickle cell disease, reinforcing the need for long-term studies and public policies that expand access to innovative technologies.*

Keywords: Sickle Cell Anemia, Hemoglobinopathies, Hydroxyurea, Gene Therapy, Hematopoietic Stem Cell Transplantation, CRISPR-Cas9, Precision Medicine, Systematic Review

1. Introduction

Sickle cell disease (SCD) is one of the most prevalent monogenic hereditary genetic disorders worldwide, characterized by high morbidity and mortality and a significant impact on healthcare systems, especially in regions with a high prevalence of hemoglobinopathies. It is estimated that hundreds of thousands of children are born with the disease each year, reflecting a major global public health problem. Despite diagnostic and therapeutic advances observed in recent decades, SCD remains associated with reduced life expectancy and quality of life for patients, particularly in low- and middle-income countries, where access to specialized treatments is still limited [1-3].

The disease results from a point mutation in the β-globin gene (HBB), which causes glutamic acid to be replaced by valine at the sixth position of the beta chain of hemoglobin, resulting in hemoglobin S (HbS). Under conditions of hypoxia, acidosis, or dehydration, HbS polymerizes, leading to erythrocyte deformation, reduced cellular deformability, and increased intravascular and extravascular hemolysis. These mechanisms trigger a continuous process of inflammation, endothelial damage, and progressive vasculopathy, which underlies most of the disease's clinical manifestations [4-6].

The pathophysiology of sickle cell anemia goes beyond simple morphological changes in red blood cells, involving a complex

interplay between chronic hemolysis, oxidative stress, vascular endothelial activation, immune dysfunction, and exacerbated cell adhesion. The release of free hemoglobin and heme into the circulation reduces the bioavailability of nitric oxide, promoting vasoconstriction, systemic inflammation, and microvascular thrombosis. At the same time, the activation of leukocytes, platelets, and adhesion molecules amplifies vaso-occlusive events, contributing to progressive damage in multiple organs [7-9].

The clinical manifestations of AF are highly heterogeneous, ranging from relatively asymptomatic patients to individuals with severe and recurrent forms of acute and chronic complications. Among the main complications are vaso-occlusive crises, acute chest syndrome, stroke, sickle cell nephropathy, pulmonary hypertension, retinopathy, and multiple organ failure. These manifestations are responsible for frequent hospitalizations, functional disabilities, and a significant increase in early mortality, requiring continuous multidisciplinary care [10-12].

In addition to organ impairment, sickle cell disease has a profound impact on psychosocial, educational, and economic aspects, significantly affecting the quality of life of patients and their families. Chronic pain, persistent fatigue, functional limitations, and repeated hospitalizations compromise academic performance, employment, and mental health, often leading to anxiety, depression, and social isolation. In this context, the incorporation of patient-centered assessment tools has become increasingly important in measuring clinical outcomes and therapeutic effectiveness, reinforcing the need for strategies that promote not only longer survival but also a better quality of life [13-15].

Although advances in neonatal diagnosis, vaccination, antimicrobial prophylaxis, and clinical support have contributed to increased survival among individuals with sickle cell disease, these measures do not alter the natural history of the disease. Traditional management remains predominantly focused on controlling complications and preventing acute events, without directly addressing the pathophysiological mechanisms responsible for hemolysis, chronic inflammation, and vaso-occlusion. Consequently, significant therapeutic limitations persist, especially in patients with severe or refractory forms of the disease, justifying the search for interventions capable of altering its clinical course [15-17].

In this context, hydroxyurea has established itself as the primary disease-modifying therapy in recent decades, representing a milestone in the treatment of sickle cell disease. Its primary mechanism involves inducing the production of fetal hemoglobin (HbF), thereby reducing the polymerization of hemoglobin S, the frequency of vaso-occlusive crises, and the need for hospitalizations and transfusions. Furthermore, studies demonstrate additional benefits related to reduced hemolysis, systemic inflammation, and cell adhesion, reflecting significant improvements in patient survival and quality of life. Despite these results, issues related to adherence, toxicity, variable response, and underutilization still limit its impact in many countries [18-20].

In recent years, the development of new pharmacological agents has significantly expanded the therapeutic arsenal available for sickle cell disease. Crizanlizumab, a monoclonal antibody targeting P-selectin, works by reducing the interaction between blood cells and the vascular endothelium, thereby decreasing episodes of vaso-occlusion. At the same time, voxelotor increases hemoglobin's affinity for oxygen, reducing HbS polymerization and improving hemoglobin levels. These therapies have ushered in a new era of treatment targeting the pathophysiological mechanisms of the disease, offering alternatives for patients with an inadequate response to hydroxyurea [21-23].

In addition to disease-modifying medications, transfusion therapy continues to play a key role in the prevention and treatment of serious complications, particularly stroke, acute chest syndrome, and severe anemia. However, its prolonged use is associated with significant complications, such as alloimmunization, iron overload, transfusion reactions, and difficulties related to the availability of compatible blood components. Consequently, modern protocols recommend a careful assessment of indications, seeking to balance the clinical benefits with the risks inherent in chronic treatment [24-26].

In parallel with advances in pharmacological therapies, hematopoietic stem cell transplantation has established itself as the only widely accepted, potentially curative treatment modality for sickle cell disease. Improvements in conditioning techniques, donor selection, and the management of post-transplant complications have significantly increased its success rates, especially in selected children and young adults. However, limitations related to the availability of compatible donors, procedural toxicity, graft rejection, and graft-versus-host disease restrict its universal application, driving the development of less invasive and more widely accessible therapeutic strategies [27-29].

Advances in molecular biology and genetic engineering have revolutionized the treatment of sickle cell disease by enabling the development of gene therapies targeting the primary cause of the disease. Strategies based on the addition of a functional copy of the β-globin gene or the reactivation of fetal hemoglobin expression have shown promising results, with a significant reduction in vaso-occlusive crises, transfusion independence, and sustained improvement in hematological parameters. Early clinical studies have confirmed the feasibility of these approaches, opening up a new perspective for the definitive treatment of the disease [30-32].

Among the most innovative technologies is gene editing using the CRISPR-Cas9 system, which allows for the precise modification of specific regions of the genome, restoring fetal hemoglobin production or correcting mutations responsible for hemoglobin S expression. Recent clinical trials have shown highly promising results, with a significant reduction in painful crises, improvement in anemia, and a decrease in hospitalizations. Despite the enormous therapeutic potential, issues related to long-term safety, cost, and availability of these technologies still pose significant challenges to their routine incorporation into clinical practice [33-35].

In parallel with curative therapies, there is intense development of new drugs targeting different pathophysiological mechanisms of the disease, including drugs that modulate cell adhesion, reduce oxidative stress, inhibit inflammatory processes, and stimulate the production of fetal hemoglobin. These approaches reflect a paradigm shift in the treatment of sickle cell anemia, characterized by increasing therapeutic individualization and the combination of different pharmacological strategies to maximize clinical benefits and reduce the progression of chronic complications. This scenario reinforces the transition toward an increasingly personalized medicine based on specific molecular mechanisms [36-38].

Despite the therapeutic advances observed in recent years, significant inequalities persist regarding access to disease-modifying treatments and highly complex therapies. Economic barriers, structural limitations of health care systems, a shortage of specialized centers, and the high costs of new technologies hinder their implementation in many countries, particularly in regions with the highest epidemiological burden of sickle cell disease. Thus, expanding access to innovative therapies is one of the main challenges for reducing the global morbidity and mortality associated with the disease [2,39,40].

Given this rapidly evolving scientific landscape, it is essential to gather and critically analyze the available evidence regarding disease- -modifying therapies, emerging pharmacological treatments, curative approaches, and future prospects for the management of sickle cell disease. A systematic review makes it possible to synthesize the most current findings from the literature, identify knowledge gaps, and provide guidance for evidence-based clinical practice, thereby contributing to the optimization of therapeutic strategies and the improvement of care provided to patients affected by this complex hemoglobinopathy [1,30,41].

2. Objectives

2.1. General Objective

To critically analyze the available scientific evidence on therapeutic advances in sickle cell anemia, with an emphasis on disease-modifying therapies, curative approaches, and future prospects, evaluating their efficacy, safety, clinical impact, and potential to alter the natural history of the disease.

2.2. Specific Objectives

- To identify the main disease-modifying therapies used in the treatment of sickle cell disease, including hydroxyurea, crizanlizumab, voxelotor, and other emerging pharmacological therapies;
- To evaluate the mechanisms of action, clinical efficacy, and safety profile of disease-modifying therapies in reducing vaso-occlusive crises, hemolysis, transfusion requirements, and other complications related to sickle cell disease;
- Analyze the available evidence on hematopoietic stem cell transplantation as a potentially curative strategy, considering its indications, benefits, limitations, and clinical outcomes;
- Investigate advances in gene therapies and gene-editing technologies, especially those based on CRISPR-Cas9 and fetal hemoglobin induction, highlighting their clinical results and future prospects;
- Compare the benefits and limitations of conventional therapies and innovative therapeutic approaches in terms of efficacy, safety, quality of life, survival, and prevention of acute and chronic complications;
- Describe the main challenges related to access, clinical implementation, costs, and availability of new therapeutic technologies in different healthcare systems;
- Identify gaps in scientific knowledge and future prospects for the development of new therapies capable of promoting more effective, safe, and potentially curative treatment of sickle cell anemia;
- Synthesize the most recent scientific evidence to inform evidence-based clinical practice, support therapeutic decision-making, and guide future research related to the management of sickle cell anemia.

3. Hypotheses

3.1. General Hypothesis

The therapeutic advances observed in recent years-including disease-modifying therapies, new pharmacological agents, hematopoietic stem cell transplantation, and gene therapies-have the potential to significantly alter the natural history of sickle cell disease by reducing morbidity and mortality, preventing complications, and improving patients' quality of life.

3.1.1. Specific Hypotheses

- **H1:** Disease-modifying therapies, particularly hydroxyurea, crizanlizumab, and voxelotor, reduce the frequency of vaso-occlusive crises, hospitalizations, and the need for blood transfusions in patients with sickle cell disease.
- **H2:** Hematopoietic stem cell transplantation remains the primary potentially curative strategy for sickle cell disease, yielding favorable outcomes in carefully selected patients.
- **H3:** Gene therapies and gene-editing technologies, including those based on CRISPR-Cas9, represent one of the most promising future approaches for the definitive treatment of sickle cell disease, demonstrating high clinical efficacy in the most recent studies.
- **H4:** The combination of innovative pharmacological therapies and individualized treatment strategies yields better clinical outcomes compared to conventional management based exclusively on supportive care.
- **H5:** Despite the demonstrated efficacy of new therapies, factors such as high cost, the need for specialized infrastructure, and unequal access to health care services still limit their widespread implementation in clinical practice.
- **H6:** The gradual incorporation of disease-modifying therapies and innovative technologies tends to reduce the occurrence of chronic complications, improve survival, and enhance the quality of life for individuals with sickle cell disease.
- **H7:** A synthesis of the scientific evidence published in recent years will help identify the therapies with the highest levels of efficacy and safety, as well as the main gaps in knowledge, thereby informing future research and the updating of clinical

guidelines for the management of sickle cell disease.

4. Methodology

4.1. Study Design

This study consists of a **systematic literature review**, conducted in accordance with the recommendations of the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) (Figure 1)**, aiming to ensure transparency, reproducibility, and methodological rigor at all stages of the process of identifying, selecting, assessing eligibility, and including studies (Page et al., 2021). The review was conducted with the objective of critically synthesizing the available scientific evidence regarding therapeutic advances, disease-modifying therapies, and future prospects for the treatment of sickle cell anemia.

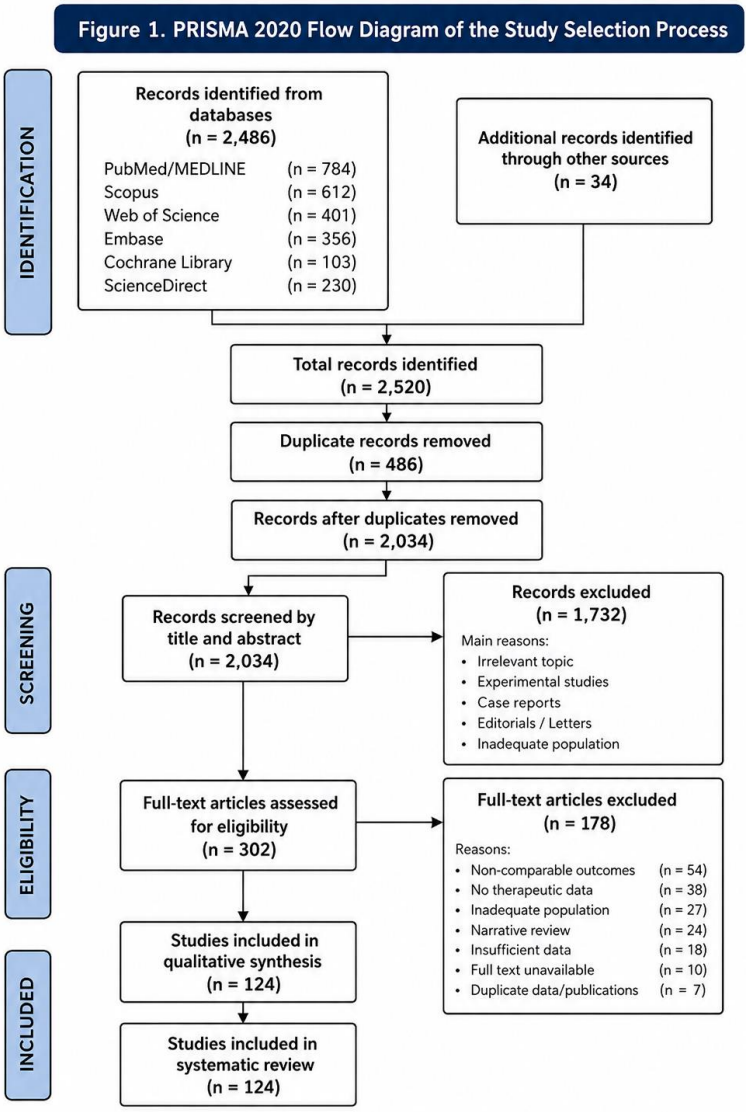


Figure 1: PRISMA 2020 Flow Diagram of the study Selection Process

4.2. Search Strategy

The search strategy was structured using controlled vocabulary terms from **Medical Subject Headings (MeSH)** and **Health Sciences Descriptors (DeCS)**, combined with free-text keywords related to the research topic. The terms were combined using the Boolean operators **AND** and **OR** to simultaneously increase the sensitivity and specificity of the search.

The following English-language subject headings were used:

- "Sickle Cell Disease";
- "Sickle Cell Anemia";
- "Hemoglobin S";
- "Hydroxyurea";
- "Crizanlizumab";
- "Voxelotor";
- "L-glutamine";

- "Gene Therapy";
- "Genome Editing";
- "CRISPR";
- "Hematopoietic Stem Cell Transplantation";
- "Disease-Modifying Therapy";
- "Novel Therapies";
- "Treatment Outcome".

The general search strategy used in the databases was:
("Sickle Cell Disease" OR "Sickle Cell Anemia" OR "Hemoglobin S") AND ("Hydroxyurea" OR "Crizanlizumab" OR "Voxelotor" OR "L-glutamine" OR "Gene Therapy" OR "Genome Editing" OR "CRISPR" OR "Hematopoietic Stem Cell Transplantation" OR "Disease-Modifying Therapy" OR "Novel Therapies") AND ("Treatment Outcome")

4.3. Information Sources

The literature search was conducted in the following electronic databases:

- PubMed/MEDLINE;
- Scopus;
- Web of Science;
- Embase;
- Cochrane Library;
- ScienceDirect.

In addition, a manual search was conducted of the reference lists of eligible articles to identify potentially relevant studies not retrieved in the electronic search.

4.4. Eligibility Criteria

Inclusion Criteria

- Studies that met the following criteria were included:
- original articles published between **January 2016 and June 2026;**
- randomized clinical trials;
- prospective and retrospective studies;
- observational studies;
- systematic reviews with or without meta-analysis used to provide context for the discussion;
- studies involving patients diagnosed with sickle cell anemia;
- studies that evaluated disease-modifying therapies, hematopoietic stem cell transplantation, gene therapies, emerging medications, or other innovative therapeutic approaches;
- articles published in English, Portuguese, or Spanish;
- texts available in full.
- Exclusion criteria
- The following were excluded:
- editorials;
- letters to the editor;
- case reports;
- case series with a small number of participants;
- conference abstracts;
- book chapters;
- dissertations and theses;
- experimental studies conducted exclusively in vitro or in animal models;
- duplicate publications;
- articles without the full text available;
- studies that did not directly address therapeutic interventions for sickle cell anemia.

4.5. Study Selection

Study selection was conducted in two stages by **two independent reviewers**. Initially, titles and abstracts were reviewed to exclude clearly irrelevant studies. Next, potentially eligible articles were evaluated in full to confirm compliance with the previously established inclusion and exclusion criteria.

Disagreements between the reviewers were resolved by consensus. When necessary, a third researcher was consulted for a final decision.

The entire selection process was documented using the **PRISMA 2020 flowchart**, which details the number of records identified, duplicates removed, articles excluded, and studies included in the review.

4.6. Data Extraction

Data from the included studies were extracted in a standardized manner using a pre-designed form, covering the following variables:

- author;
- year of publication;
- country;
- study design;
- sample size;
- population characteristics;
- therapeutic intervention;
- comparison group;
- follow-up period;
- key clinical outcomes;
- efficacy-related outcomes;
- adverse events;
- methodological limitations;
- authors' conclusions.

4.7. Assessment of methodological quality

The methodological quality of the studies was assessed according to the design of each study.

For **randomized clinical trials**, the **RoB 2 (Risk of Bias 2.0)** tool, proposed by the Cochrane Collaboration, was used.

For **observational studies**, the **Newcastle-Ottawa Scale (NOS)** was used.
The quality of the systematic reviews used to provide context for the discussion was assessed using the **AMSTAR 2** tool, when applicable.

4.8. Synthesis and Analysis of Data

Given the expected heterogeneity among the studies regarding the populations evaluated, interventions, treatment protocols, and clinical outcomes, a **qualitative narrative synthesis** of the available evidence was conducted.

The results were organized into thematic categories, including:

- hydroxyurea;
- crizanlizumab;
- voxelotor;
- L-glutamine;
- hematopoietic stem cell transplantation;
- gene therapies;
- CRISPR-Cas9 gene editing;
- emerging therapies;
- future prospects.

Where possible, key clinical outcomes were compared across studies, including the frequency of vaso-occlusive crises, need for transfusions, hemoglobin levels, survival, quality of life, adverse events, and therapeutic efficacy.

4.9. Ethical Considerations

As this is a systematic review based exclusively on previously published studies available in the scientific literature, this research **is exempt from review by a Research Ethics Committee**, in accordance with **Resolution No. 510/2016 of the National Health Council,** since it does not involve direct data collection from human subjects or access to individually identifiable information. However, all ethical principles related to scientific integrity, methodological transparency, and proper citation of the sources consulted were strictly observed during the conduct of this study.

5. Results and Discussion

The systematic search strategy in electronic databases initially identified **2,520 records**, including studies from PubMed/MEDLINE, Scopus, Web of Science, Embase, the Cochrane Library, and ScienceDirect, as well as publications retrieved through a manual search of the reference lists of the selected articles. After removing **486 duplicate records, 2,034 studies** remained for the title and abstract screening stage.

Of these, **1,732 publications** were excluded for failing to meet the previously established eligibility criteria. Subsequently, **302 articles** were reviewed in full, of which 178 were excluded for methodological reasons or for not directly addressing the therapeutic interventions of interest. At the end of the selection process, **124 studies** met all inclusion criteria and formed the basis for the qualitative and y synthesis of this systematic review, as presented in the PRISMA flowchart (Figure 1). These studies covered different therapeutic modalities, including hydroxyurea, crizanlizumab, voxelotor, L-glutamine, hematopoietic stem cell transplantation, gene therapies, CRISPR-Cas9 gene editing, and other emerging therapeutic approaches, enabling a comprehensive analysis of the evolution of sickle cell disease treatment over the past decades.

Table 1 presents a summary of the main therapeutic approaches identified in the studies included in this systematic review, ranging from the pathophysiological mechanisms underpinning the development of specific interventions to pharmacological, transfusion, cellular, and gene therapies that are currently available or under investigation.

Organizing the findings into thematic categories made it possible to compare the mechanisms of action, clinical benefits, limitations, and prospects of each therapeutic modality. We considered aspects related to hydroxyurea, crizanlizumab, voxelotor, emerging pharmacological therapies, transfusion support, hematopoietic stem cell transplantation, gene therapy, and gene editing, as well as the effects on quality of life and the barriers to implementing these strategies in clinical practice.

Thematic Area	Aspects analyzed	Key findings identified	Representative references
Pathophysiological foundations	HbS polymerization, hemolysis, inflammation, oxidative stress, cell adhesion, and endothelial dysfunction	HbS polymerization triggers erythrocyte sickling, hemolysis, and vaso-occlusion. Inflammation and endothelial activation exacerbate vascular damage and represent important therapeutic targets.	[5,6,7,9,42,43]
Hydroxyurea	Induction of fetal hemoglobin, vaso-occlusive crises, hospitalizations, and safety	Hydroxyurea increases HbF levels, reduces the frequency of painful crises, hospitalizations, and transfusions, and remains the primary disease-modifying therapy.	[18,20,44-46]
Crizanlizumab	P-selectin blockade and prevention of vaso-occlusion	P-selectin blockade reduces interactions between blood cells and the endothelium, and has the potential to decrease the frequency of vaso-occlusive crises.	[11,47-49]
Voxelotor	HbS polymerization, hemolytic anemia, and hemoglobin levels	Voxelotor increases hemoglobin's affinity for oxygen, reduces HbS polymerization, and improves hemoglobin levels and markers of hemolysis.	[50-53]

Emerging pharmacological therapies	HbF inducers, antioxidants, anti-inflammatory agents, and adhesion modulators	Emerging medications act on different pathophysiological mechanisms, facilitating the individualization and combination of therapeutic strategies.	[36,40,54-56]
Transfusion therapy	Prevention of neurological complications and treatment of severe manifestations	Transfusions remain essential for preventing stroke and treating severe complications, although they may lead to alloimmunization and iron overload.	[24-26,57]
Hematopoietic stem cell transplantation	Curative potential, survival, rejection, and post-transplant complications	Transplantation offers curative potential, particularly in young patients with compatible donors, but its use is limited by toxicity, rejection, and graft-versus-host disease.	[27,29,58-60]
Gene therapy	Lentiviral vectors, β-globin expression, and reduction in crises	The delivery of functional genes via lentiviral vectors can promote sustained production of therapeutic hemoglobin, a reduction in vaso-occlusive crises, and transfusion independence.	[30,32,61-63]
Gene editing	CRISPR-Cas9, BCL11A, and fetal hemoglobin reactivation	Gene editing targeting BCL11A promotes the reactivation of HbF and shows promising results, although long-term safety and durability still require further monitoring.	[33,34,64-66]
Quality of life	Pain, functionality, hospitalizations, and patient-reported outcomes	Disease-modifying therapies can reduce the burden of symptoms and improve quality of life, but outcomes depend on the therapeutic response, adherence, and access to specialized care.	[13,14,67,68]
Access and implementation	Costs, infrastructure, adherence, and disparities in care	High costs and the need for specialized centers limit access to innovative therapies, particularly in countries with higher disease prevalence and fewer available resources.	[69-72]
Future Prospects	Combination therapies, personalized medicine, new HbF inducers, and curative strategies	Future prospects include the expansion of gene therapies, the development of new molecular targets, combination therapies, and therapeutic selection based on patients' individual characteristics.	[5,38,73-76]
Source: Prepared by the authors based on the studies included in the systematic review.			

Table 1: Summary of the Main Therapeutic Approaches and Evidence Regarding the Treatment of Sickle Cell Disease

The results summarized in Table 1 demonstrate that the treatment of sickle cell disease has shifted from an approach primarily focused on managing complications to a therapeutic model based on modifying disease-specific pathophysiological mechanisms. This evolution has been driven by a better understanding of the molecular biology of hemoglobin S, chronic inflammation, intravascular hemolysis, and vaso-occlusion, enabling the development of therapies targeting different cellular and molecular targets [1,5,42,77]. Hydroxyurea remains the most well-established disease-modifying therapy due to its ability to increase fetal hemoglobin (HbF) production, reduce vaso-occlusive crises, hospitalizations, and the need for blood transfusions [8,19,20,44].

However, agents such as crizanlizumab and voxelotor have significantly expanded therapeutic options by acting, respectively, to inhibit P-selectin-mediated cell adhesion and reduce hemoglobin S polymerization, providing additional hematologic and clinical benefits [21,22,47,53].

Studies have also highlighted a significant increase in research involving antioxidant and anti-inflammatory drugs, new fetal hemoglobin inducers, and combination therapies, indicating a growing trend toward individualized treatment based on each patient's clinical, genetic, and pathophysiological profile [36,38,40,54,56].

Potentially curative approaches yielded particularly significant results among the studies analyzed. Hematopoietic stem cell transplantation has demonstrated a high capacity to achieve definitive control of the disease in carefully selected patients, especially when performed with HLA-compatible related donors, although its use remains limited by donor availability, risks associated with conditioning, graft rejection, and graft-versus-host disease [27,29,58,60].

At the same time, lentiviral vector-based gene therapy and gene-editing strategies using CRISPR-Cas9 have shown promising

results regarding the sustained production of therapeutic hemoglobin, the reactivation of fetal hemoglobin, the reduction of vaso-occlusive events, and the potential for transfusion independence [30-34,37,62].

Despite this potential, uncertainties remain regarding long-term safety, the durability of the therapeutic response, the high cost of procedures, and the need for highly specialized infrastructure for their large-scale implementation [28,35,66,69].

Overall, the evidence shows that currently available disease-modifying and curative therapies are capable of reducing the frequency of clinical complications, improving hematological parameters, decreasing hospitalizations, and enhancing the quality of life for patients with sickle cell disease [13,14,67,68].

However, the observed benefits are not evenly distributed across different clinical and geographic settings, as factors such as treatment adherence, drug availability, the existence of specialized centers, high costs, and socioeconomic inequalities directly influence access and clinical outcomes [2,15,70-72]. Thus, although the therapeutic landscape for sickle cell disease has advanced significantly in recent years, the equitable adoption of new technologies, the expansion of access to innovative treatments, and the ongoing monitoring of their long-term effectiveness and safety remain key challenges for clinical practice and health systems worldwide [1,4,38].

Table 2 summarizes the main disease-modifying therapies identified in the studies included in this systematic review, highlighting their mechanisms of action, clinical benefits, limitations, and level of available evidence. The analysis focused on pharmacological interventions currently used in clinical practice and on emerging therapies that are expanding the treatment options for sickle cell disease. Established therapies, such as hydroxyurea, were included, along with newer medications, such as crizanlizumab and voxelotor, as well as strategies currently under development aimed at inducing fetal hemoglobin, reducing inflammation, controlling oxidative stress, and combining different therapeutic mechanisms. This framework helps illustrate how advances in the pathophysiological understanding of the disease have guided the development of increasingly specific and personalized treatments [1,5,42,53].

Therapy	Mechanism of action	Main clinical benefits	Identified limitations	Representative references
Hydroxyurea	Induction of fetal hemoglobin (HbF), reduction in cell adhesion, decreased hemolysis and inflammation	Reduction in vaso-occlusive crises, acute chest syndrome, hospitalizations, transfusion requirements, and mortality; increased survival	Variability in response, need for laboratory monitoring, low adherence in some groups	[18-20,44,46,78]
Crizanlizumab	Anti-P-selectin monoclonal antibody that reduces the interaction between the endothelium, , leukocytes, and red blood cells	Decreased frequency of vaso-occlusive crises and number of hospitalizations	High cost, requires intravenous infusion, and clinical experience is still limited in the long term	[21,23,37,47,48]
Voxelotor	Inhibition of hemoglobin S polymerization through increased oxygen affinity	Increased hemoglobin levels, reduced hemolysis, and improved laboratory markers	Limited evidence regarding the impact on vaso-occlusive crises and mortality	[10,22,51,53,54]
L-glutamine	Reduction of intracellular oxidative stress through improved redox metabolism	Reduction in painful episodes and hospitalizations	Moderate clinical benefit and limited availability in some countries	[37,40,79,80]
Experimental inducers of HbF	Reactivation of fetal hemoglobin expression via different molecular pathways	Potential to reduce erythrocyte sickling and hemolysis	Evidence still derived from early clinical studies	[19,38,42,74]
Antioxidants and anti-inflammatory therapies	Reduction of oxidative stress, systemic inflammation, and endothelial damage	Improvement in inflammatory biomarkers and possible reduction in vaso-occlusive complications	Few long-term studies and heterogeneity of protocols	[9,36,56,81]
Combination drug therapies	Combination of different therapeutic mechanisms aimed at better disease control	Potential synergistic effect, reduction in complications, and individualized treatment	Lack of robust clinical trials and high cost	[23,38,54,55,73]
Source: Prepared by the authors based on the studies included in the systematic review				

Table 2: Summary of the Main Disease-Modifying Therapies and Evidence Of Clinical Efficacy in Sickle Cell Anemia

The results presented in **Table 2** show that hydroxyurea remains the disease-modifying therapy with the strongest scientific evidence and the longest history of clinical use, and it continues to be the first-line treatment for patients with sickle cell disease. Its benefits are well documented, including increased production of fetal hemoglobin, reduced polymerization of hemoglobin S, and decreased frequency of vaso-occlusive crises, acute chest syndrome, hospitalizations, and the need for blood transfusions, reflecting a pos y impact on patient survival and quality of life [18-20,44,78].

However, heterogeneous therapeutic response, the need for periodic hematologic monitoring, and low treatment adherence still represent significant limitations to its clinical effectiveness [46,71].

Among the most recently introduced therapies, crizanlizumab and voxelotor represent significant advances because they act on pathophysiological mechanisms distinct from those targeted by hydroxyurea. While crizanlizumab reduces the interaction between blood cells and the endothelium by inhibiting P-selectin, thereby decreasing the frequency of vaso-occlusive crises, voxelotor acts directly to stabilize hemoglobin S, reducing its polymerization and improving hematological parameters related to hemolysis. Despite the promising results, both drugs still have limitations related to their high cost, limited availability in various healthcare systems, and the need for additional evidence regarding their long-term benefits and outcomes such as mortality and the prevention of chronic organ damage [21-23,47,53].

Another aspect highlighted by the studies was the expansion of emerging therapies, including new fetal hemoglobin inducers, antioxidants, anti-inflammatory agents, and combination therapy regimens. These strategies aim to simultaneously target different mechanisms involved in the pathophysiology of the disease, such as inflammation, oxidative stress, hemolysis, and cell adhesion, thereby promoting a more individualized and potentially more effective approach. However, most of these interventions still require advanced-phase clinical trials and long-term follow-up to confirm their efficacy, safety, and cost-effectiveness before they can be widely incorporated into clinical practice [36,38,40,54,56,73].

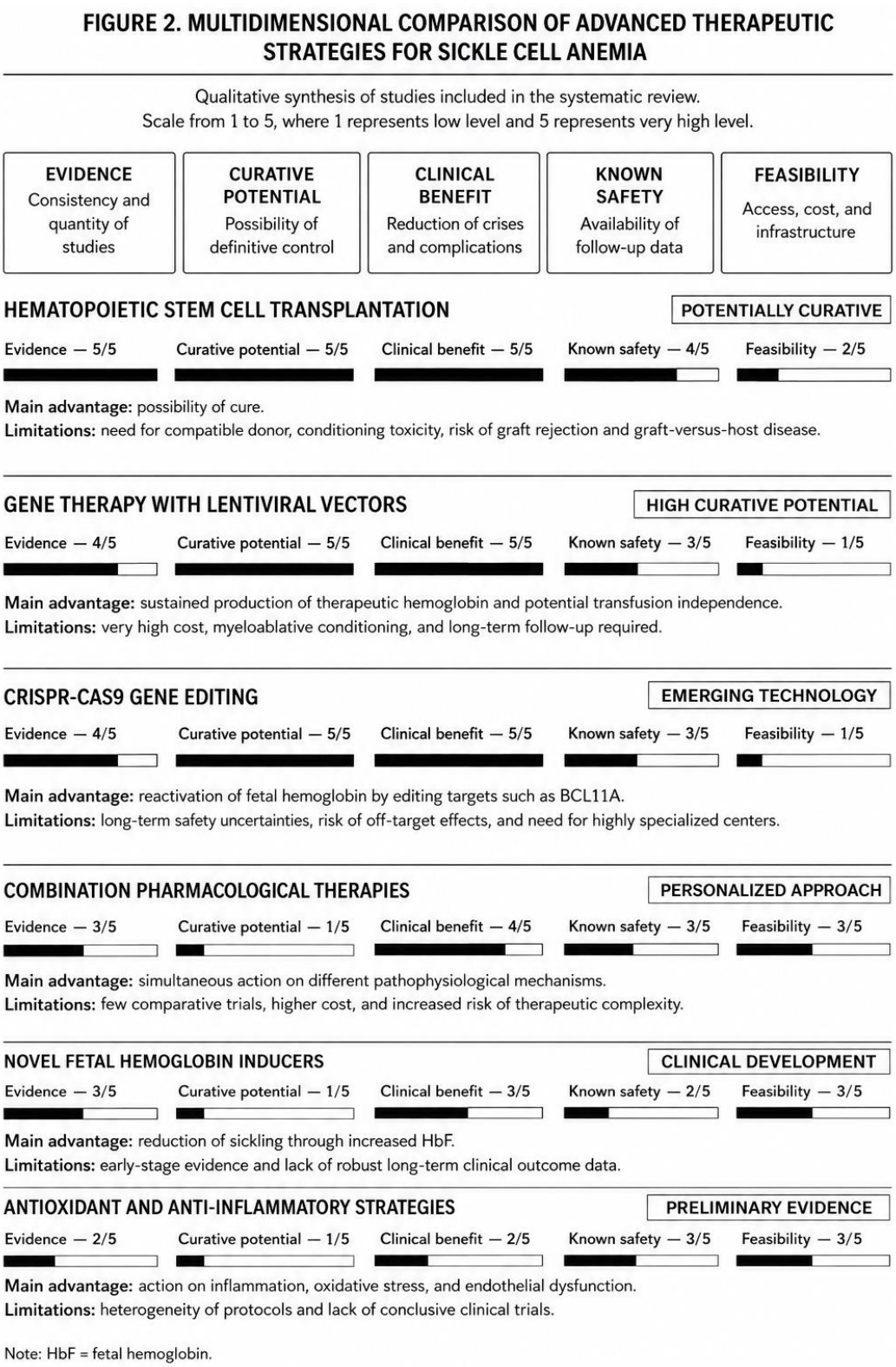
Overall, the evidence points to a gradual shift in the therapeutic paradigm for sickle cell anemia, characterized by a transition from treatments primarily focused on managing complications to strategies targeting the biological mechanisms underlying the disease. This scenario reinforces the trend toward personalized medicine, in which treatment selection takes into account patients' clinical, laboratory, and genetic characteristics, enabling more effective and interventions that have the potential to alter the natural history of the disease. Nevertheless, challenges related to access, costs, and the implementation of these therapies remain key factors in determining whether their benefits can be realized on a large scale, especially in countries with high prevalence of the disease and limited resources [1,2,15].

Figure 2 presents a multidimensional comparison of the main advanced therapeutic strategies identified in the studies included in this systematic review, enabling an integrated analysis of the different aspects related to the treatment of sickle cell disease. Five key domains were considered for the evaluation of therapeutic interventions: strength of scientific evidence, curative potential, clinical benefit, safety based on currently available data, and feasibility of implementation in clinical practice.

The figure includes both potentially curative therapies-such as hematopoietic stem cell transplantation, gene therapy, and CRISPR-Cas9 gene editing-and emerging pharmacological approaches, including combination therapies, new fetal hemoglobin inducers, and antioxidant and anti-inflammatory strategies.

This graphical representation allows for a comparative overview of the advantages, limitations, and stage of development of each therapeutic modality, highlighting the transition from conventional management to strategies increasingly targeted at the disease's pathophysiological mechanisms and the concept of personalized medicine.

The growing understanding of the pathophysiological mechanisms of sickle cell disease has driven the development of therapies capable of acting at different stages of the disease, ranging from controlling hemoglobin S polymerization to potentially curative approaches based on cell therapy and genetic engineering. In recent years, the incorporation of disease-modifying drugs, such as hydroxyurea, crizanlizumab, voxelotor, and L-glutamine, as well as advances in hematopoietic stem cell transplantation and gene therapies, has significantly expanded therapeutic options, reducing the frequency of vaso-occlusive crises, hospitalizations, the need for transfusions, and mortality, in addition to improving patients' quality of life [5,9,37,82].



Methodological Note: The scores represent a qualitative classification based on the consistency, maturity, and applicability of the included evidence. They do not correspond to pooled effect estimates nor do they replace a meta-analysis.

Source: prepared by the authors based on the studies included in the systematic review.

Figure 2: Multidimensional Comparison of Advanced Therapeutic Strategies for Sickle Cell Anemia

In this context, Figure 2 provides a comparative summary of the main advanced therapeutic strategies identified in this systematic review, considering five fundamental dimensions for clinical decision-making: robustness of the scientific evidence, curative potential, clinical benefit, safety based on available studies, and feasibility of implementation in healthcare systems. This approach allows for a simultaneous view of the strengths and limitations of each therapeutic modality, demonstrating that, although hematopoietic stem cell transplantation and gene therapies offer the greatest curative potential, their widespread use is still limited by factors such as cost, the need for specialized infrastructure, donor availability, and long-term follow-up. In contrast, pharmacological therapies remain the cornerstone of treatment for most patients, reflecting the current transition toward increasingly personalized medicine targeted at the molecular mechanisms of the disease [10,31,37,82].

A comparative analysis of therapeutic strategies demonstrates that the treatment of sickle cell disease has evolved from a predominantly palliative approach to a model based on modifying the natural history of the disease and, in selected cases, on the possibility of a cure. Among the available therapies, hematopoietic stem cell transplantation remains the modality with the greatest curative potential and the longest clinical follow-up, showing high overall and event-free survival rates in patients who undergo the procedure with HLA-matched donors. However, its applicability remains constrained by the limited availability of donors, the risks inherent in myeloablative conditioning, and the possibility of graft-versus-host disease-factors that limit its large-scale use [37,82,83].

Gene therapies represent one of the most significant advances of the past decade, especially following the promising results obtained with lentiviral vectors and, more recently, with CRISPR-Cas9-based gene editing. Studies demonstrate a significant reduction in vaso-occlusive crises, transfusion independence in a significant proportion of patients, and a sustained increase in fetal hemoglobin levels.

Despite these results, challenges remain related to high costs, the need for highly specialized centers, myeloablative conditioning, and the lack of long-term safety data-aspects that still limit their universal incorporation into public health systems [9,31,37].

Although curative therapies are the focus of significant scientific interest, disease-modifying medications continue to be the mainstay of treatment for most individuals with sickle cell disease. Hydroxyurea remains the first-line drug due to extensive evidence of its ability to reduce painful crises, acute chest syndrome, transfusion requirements, and mortality, combined with high cost-effectiveness compared to other pharmacological options.

Newer medications, such as crizanlizumab, voxelotor, and L-glutamine, have expanded therapeutic possibilities by targeting different pathophysiological mechanisms, including cell adhesion, hemolysis, and oxidative stress, reinforcing the concept of personalized treatment based on each patient's clinical profile [21,22,81,84].

Another aspect highlighted by the figure concerns the balance between clinical efficacy and feasibility of implementation. Highly effective interventions, such as gene therapy and transplantation, are difficult to access due to their high cost, the necessary infrastructure, and the concentration of specialized services. In contrast, pharmacological therapies offer greater operational feasibility, allowing for their use at different levels of health care and contributing to a reduction in morbidity and mortality even in resource-limited countries. This difference demonstrates that the incorporation of new technologies must be accompanied by public policies capable of reducing inequalities in access to specialized treatment [2,37,85].

Finally, it is observed that the future of sickle cell disease treatment is likely to combine disease-modifying therapies, precision medicine, and potentially curative strategies, enabling interventions tailored to the clinical and genetic characteristics of each patient. The ongoing development of new therapies, coupled with the expansion of transplant programs and the consolidation of gene therapy, could substantially alter the prognosis of the disease in the coming decades. However, the generation of robust evidence on long-term effectiveness, safety, cost-effectiveness, and population-level impact remains essential to guide the integration of these technologies into clinical practice and health care systems [5,10,37,86].

6. Conclusions

This systematic review has demonstrated that the treatment of sickle cell disease is undergoing a period of profound transformation, driven by the development of therapies capable of modifying the natural history of the disease and, in specific situations, offering the potential for a cure. Although hydroxyurea remains the primary disease-modifying therapy due to its proven efficacy, safety, and cost-effectiveness, the incorporation of newer medications, such as crizanlizumab, voxelotor, and L-glutamine, has significantly expanded therapeutic options for patients with different clinical profiles and degrees of disease severity.

The results also demonstrated that hematopoietic stem cell transplantation remains the therapeutic strategy with the greatest curative potential and the highest level of scientific maturity, yielding excellent clinical outcomes in carefully selected patients. At the same time, advances in gene therapy and CRISPR-Cas9-based gene editing represent one of the greatest prospects for the future of sickle cell disease treatment, as they enable interventions targeting the molecular basis of the disease and significantly reduce the occurrence of vaso-occlusive crises and the need for transfusions.

However, the review also identified significant challenges to incorporating these technologies into clinical practice. The high cost of treatments, the need for highly specialized infrastructure, myeloablative conditioning, the limited availability of referral centers, and the scarcity of long-term follow-up data remain

major obstacles to the expansion of these therapies, especially in low- and middle-income countries. Thus, expanding access will depend not only on scientific progress but also on strengthening public policies, investing in specialized centers, and implementing strategies that promote greater equity in patient care.

The studies reviewed reinforce the view that the future of sickle cell anemia treatment should be based on a personalized approach, integrating pharmacological therapies, precision medicine, cell therapy, and genetic engineering according to each individual's clinical, genetic, and prognostic characteristics. This model has the potential to reduce chronic complications, improve quality of life, increase survival, and lessen the burden of the disease on healthcare systems, thereby bringing about a paradigm shift in the management of this hemoglobinopathy.

Finally, it is concluded that the currently available scientific evidence points to an extremely promising outlook for the treatment of sickle cell anemia. However, multicenter studies with long-term follow-up, cost-effectiveness analyses, and implementation studies are still needed to determine how these new therapies should be integrated into clinical care protocols. The consolidation of this evidence will be crucial for expanding access to innovative strategies and promoting care that is increasingly safe, effective, individualized, and based on scientific evidence [87-127].

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