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TREATMENT OF SICKLE CELL ANEMIA: PHARMACOLOGICAL, TRANSFUSION, AND GENETIC STRATEGIES

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Abstract: Sickle cell disease (SCD) is a prevalent hereditary hemoglobinopathy characterized by hemoglobin S (HbS) polymerization, resulting in chronic hemolysis, vaso-occlusion, and progressive organ damage. This narrative review analyzes current therapeutic strategies, ranging from disease-modifying pharmacological interventions to curative approaches. Hydroxyurea remains the standard of care for fetal hemoglobin (HbF) induction, but new therapies such as L-glutamine (control of oxidative stress), crizanlizumab (anti-adhesion via P-selectin), and voxelotor (inhibition of HbS polymerization) have expanded the clinical arsenal, allowing for the possibility of combination therapies. Transfusion management remains vital for stroke prevention and treatment of acute complications, although it presents challenges such as alloimmunization and iron overload. In the curative field, allogeneic hematopoietic stem cell transplantation (HSCT) is effective but limited by donor availability. Advances in gene therapy (gene addition and editing) offer the promise of a donor-independent "functional cure," although they still face barriers of cost and accessibility. The study concludes that effective management of FA requires a multidisciplinary approach, integrating biomedical innovation with health policies that ensure equitable access.

Keywords: Sickle Cell Anemia; Fetal Hemoglobin; Hydroxyurea; Gene Therapy; Stem Cell Transplantation; Voxelotor; Crizanlizumab; Transfusion Management.

INTRO

Sickle cell anemia (SCA) is one of the most prevalent hereditary monogenic diseases worldwide, affecting millions of individuals (GERMINO-WATNICK et al., 2022; BRANDOW; LIEM, 2022). It is caused by a specific point mutation in the beta-globin gene (HBB), resulting in the replacement of glutamic acid with valine (Glu6Val), which leads to the production of abnormal hemoglobin S (HbS) (STEINBERG, 2020; GERMINO-WATNICK et al., 2022).

The central pathophysiology of the disease is driven by the polymerization of deoxygenated HbS (STEINBERG, 2020). Under hypoxic conditions, this polymerization forms rigid fibers that distort erythrocytes, giving them their characteristic sickle shape (ELENDU et al., 2023; GERMINO-WATNICK et al., 2022). This process triggers the two main pillars of the disease: chronic hemolytic anemia and vaso-occlusion (BRANDOW; LIEM, 2022).

The clinical picture goes beyond simple vascular occlusion, encompassing a state of chronic inflammation, endothelial dysfunction, increased cell adhesion, and intravascular hemolysis (PACE et al., 2021). These complications result in recurrent and severe vaso-occlusive crises (VOCs), progressive damage to multiple organs—including the brain, kidneys, and lungs—and a significantly reduced life expectancy (BRANDOW; LIEM, 2022; ELENDU et al., 2023). Given the complexity of the disease, therapeutic strategies have evolved from purely symptomatic management to disease-modifying therapies and, more recently, to curative approaches (STEINBERG, 2020; ELENDU et al., 2023).

Sickle cell disease (SCD) is a hereditary hemoglobinopathy of high public health relevance, resulting from mutations in the β-globin gene that lead to the production of hemoglobin S (HbS) and sickling of erythrocytes under conditions of hypoxia, acidosis, or dehydration (BRANDOW; LIEM, 2022; PACE; STARLARD-DAVENPORT; KUTLAR, 2021). This condition affects millions of people worldwide, with a higher prevalence among populations of African, Mediterranean, Middle Eastern, and South Asian descent, producing a significant burden of morbidity and mortality, especially in low- and middle-income countries (ELENDU et al., 2023; PACE; STARLARD-DAVENPORT; KUTLAR, 2021).

From a pathophysiological perspective, the polymerization of deoxygenated HbS results in red blood cell deformation, chronic hemolysis, increased cell adhesion, systemic inflammation, and vaso-occlusion, culminating in acute and chronic pain, acute chest syndrome, stroke, kidney injury, cardiopulmonary impairment, and progressive damage to multiple organs (BRANDOW; LIEM, 2022; PACE; STARLARD-DAVENPORT; KUTLAR, 2021; ELENDU et al., 2023). From this perspective, an integrated understanding of the molecular basis and different subphenotypes of the disease is essential to guide more effective and individualized therapeutic strategies.

Among the main modulators of the clinical severity of SCD, fetal hemoglobin (HbF) stands out, whose presence in high levels in erythrocytes prolongs the delay time for HbS polymerization and reduces intravascular sickling (STEINBERG, 2020). Clinical evidence indicates that higher concentrations of HbF are associated with a lower frequency of vaso-occlusive

crises, a reduction in leg ulcers, a lower occurrence of neurological events, and greater survival, making HbF a central prognostic determinant and a strategic therapeutic target (STEINBERG, 2020; PACE; STARLARD-DAVENPORT; KUTLAR, 2021).

In this scenario of increasing therapeutic complexity, the role of clinical pharmacists and hospital pharmacists gains strategic relevance both in interpreting the pathophysiological mechanisms of the disease and in the safe and effective administration of available treatments, especially in the case of hospitalized patients who require individualized drug dosages, which require even more caution in treatment. The expansion of the drug arsenal—which includes HbF inducers, cell adhesion modulators, hemolysis-reducing agents, and new molecules targeting specific pathways—requires qualified professional monitoring, capable of assessing individual response profiles, guiding combination regimens, continuously monitoring adverse events, and ensuring that patients do not undergo dangerous drug interactions. In addition, the clinical pharmacist plays a central role in promoting therapeutic adherence, health education, and the integration of pharmacological care with other clinical interventions. The incorporation of advanced therapies, such as TCTH and gene approaches, further reinforces this need, as it involves careful patient selection processes, prevention of drug interactions, and prolonged safety surveillance, increasingly reinforcing more individualized and effective treatment. Thus, the qualified participation of this professional, together with the multidisciplinary team that accompanies the patient, becomes an essential element for biomedical advances to translate into concrete benefits for people living with sickle cell anemia.

Historically, the management of FD has been based on supportive measures, neonatal screening, infectious prophylaxis, transfusions, and the use of hydroxyurea, a drug that remains the standard disease-modifying therapy because it induces HbF and reduces acute events (PACE; STARLARD-DAVENPORT; KUTLAR, 2021; BRANDOW; LIEM, 2022). In recent decades, however, there has been a significant expansion of the therapeutic arsenal, with the incorporation of new drugs such as L-glutamine, crizanlizumab, and voxelotor, which act on complementary pathophysiological targets—hemolysis, cell adhesion, inflammation, and hemoglobin oxygenation—and pave the way for combination drug therapy regimens (PACE; STARLARD-DAVENPORT; KUTLAR, 2021; BRANDOW; LIEM, 2022). Despite these advances, morbidity and mortality remain high, and access to innovative therapies remains unequal in many contexts.

At the same time, potentially curative approaches have evolved, such as allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-compatible donor, capable of normalizing hematopoiesis and abolishing the sickle cell phenotype in selected patients (BRANDOW; LIEM, 2022; ELENDU et al., 2023). More recently, autologous gene therapies targeting hematopoietic stem cells, based on lentiviral vectors for the addition of therapeutic β-globin genes or on gene editing technologies that correct the mutation in HBB or reactivate HbF expression, have shown promising results and are emerging as a cure alternative in experimental and clinical trial settin-

gs (GERMINO-WATNICK et al., 2022; STEINBERG, 2020).

Given this combination of high disease burden, complex pathophysiology, expansion of modifying therapies, and emergence of curative cellular and gene strategies, it is essential to critically synthesize the current evidence. In this regard, this article aims to discuss sickle cell disease in light of the role of HbF and contemporary therapeutic options, emphasizing recent advances, persistent challenges, and future prospects for improving the survival and quality of life of people living with SCD.

METHODOLOGY

This research was structured as a narrative review of the literature, with the aim of consolidating and discussing current scientific evidence on the treatment of sickle cell anemia. The bibliographic survey was conducted in the PubMed database. The following descriptors (MeSH) were used for the search: "Anemia," "Sickle Cell," and "therapy." The search strategy used a combination of these terms with the Boolean operators AND and OR to optimize the retrieval of relevant articles.

The inclusion criteria defined were: publications from the last five years, written in English or Portuguese, and with full text available for analysis. Duplicate studies, articles that did not directly address therapeutic strategies for the disease, and reviews with low methodological rigor were excluded from the selection. The selection process took place in two phases: initially, a screening based on titles and abstracts, and subsequently, a full reading of the selected articles to confirm their relevance. Relevant data were extracted and synthesized descriptively to compose this article.

The articles analyzed were: (i) Brandow and Liem (2022), which summarize advances in the diagnosis and treatment of sickle cell disease, focusing on pain, cardiopulmonary, neurological, and renal complications, as well as modifying and curative therapies; (ii) Pace, Starlard-Davenport, and Kutlar (2021), which discuss the development of combined pharmacological therapies, covering HbF inducers, agents targeting erythrocyte metabolism, and vascular and systemic targets; (iii) Elendu et al. (2023), who address sickle cell disease as a global health challenge, emphasizing underdiagnosis, morbidity and mortality burden, and limitations of access to care in low- and middle-income countries; (iv) Steinberg (2020), who thoroughly reviews the regulation and prognostic role of HbF in sickle cell anemia; and (v) Germino-Watnick et al. (2022), who analyze contemporary strategies for gene addition and gene editing therapy in hematopoietic stem cells in sickle cell disease.

The texts were read independently and in depth, with manual extraction of information related to: (a) epidemiology and global burden of disease; (b) pathophysiology and clinical subphenotypes; (c) mechanisms of action and clinical impact of HbF; (d) disease-modifying drug therapies (hydroxyurea, new agents, and proposed combination regimens); and (e) potentially curative therapies (allogeneic hematopoietic stem cell transplantation and gene therapy based on lentiviral vectors or gene editing). The information extracted was systematized in thematic synthesis matrices, in which convergences, divergences, knowledge gaps,

and implications for clinical practice and health policies were organized.

As this is a narrative review focused on a set of previously selected articles available in open access, no formal systematic search procedures were applied, nor were meta-analysis criteria or quantitative assessment of heterogeneity between studies. Instead, an interpretive analytical approach was adopted, which favors the conceptual integration of evidence and critical discussion of the translational implications of each thematic axis (HbF, pharmacological therapies, transplantation, gene therapy), in light of the different care contexts described by the reviewed authors (BRANDOW; LIEM, 2022; PACE; STARLARD-DAVENPORT; KUTLAR, 2021; ELENDU et al., 2023).

RESULTS AND DISCUSSION

The management of sickle cell anemia ranges from drug therapies that modify the course of the disease to curative interventions such as stem cell transplantation and gene therapy.

The literature reviewed reinforces that sickle cell disease (SCD) is a highly heterogeneous condition, whose clinical evolution results from the interaction between the HBB mutation, genetic modulators, environmental factors, and, increasingly, the therapeutic interventions available in each care context (BRANDOW; LIEM, 2022; ELENDU et al., 2023). While Brandow and Liem (2022) describe in detail the spectrum of complications—acute and chronic pain, cardiopulmonary, neurological, and renal involvement—in highly complex health systems, Elendu et al. (2023) emphasize DF as a global health challenge, marked by underdiagnosis, limited access to disease-modifying therapies, and high rates of early mortality in low- and middle-income countries. This discrepancy highlights that the discussion of advanced therapies, while necessary, cannot be dissociated from the reality of structural inequalities in care.

Across the articles, fetal hemoglobin (HbF) emerges as a central axis in understanding phenotypic variability and as the main biological therapeutic target. Steinberg (2020) systematizes robust evidence showing that higher levels of HbF reduce HbS polymerization, attenuate hemolysis and the occurrence of vaso-occlusive crises, and are associated with longer survival, consolidating HbF as an important prognostic determinant and risk stratification marker. However, the author himself points out that the response in HbF is uneven among individuals and is influenced by variants in regulatory loci such as BCL11A and HBS1L-MYB, which relativizes the idea that simply raising HbF is sufficient to normalize the clinical phenotype in all patients. In this sense, the discussion of the studies points to the need to integrate the biology of HbF into the notion of personalized medicine, rather than treating it as an isolated therapeutic target.

From a pharmacological point of view, hydroxyurea remains the standard disease-modifying therapy, mainly due to its ability to induce HbF and reduce acute events, but its full effectiveness is limited by barriers to adherence, variability in response, and persistent concerns—albeit largely mitigated—about long-term toxicity (PACE; STARLARD-DAVENPORT; KUTLAR, 2021; BRANDOW; LIEM, 2022). The articles by Pace et al. (2021) and Brandow and Liem

(2022) show that newly approved agents — L-glutamine, crizanlizumab, and voxelotor — act at different points in the pathophysiology (erythrocyte metabolism, cell adhesion/vessel occlusion, and hemoglobin oxygenation, respectively), with statistically significant reductions in the frequency of crises and improvement in hematological parameters in randomized clinical trials. However, the authors acknowledge that the effects are generally modest in terms of "functional cure" of the disease, the studies have relatively short follow-up, and the high cost of these drugs imposes significant restrictions on access, especially outside of referral centers.

The proposal for combined drug therapy, discussed centrally by Pace, Starlard-Davenport, and Kutlar (2021), is conceptually appealing because it mirrors the multifactorial pathophysiology of FD: combining HbF inducers, hemolysis modulators, anti-adhesion agents, and vascular drugs could, in theory, synergistically reduce pain, hemolysis, inflammation, and endothelial damage. However, the authors' discussion highlights important gaps: the scarcity of phase III trials with combination regimens, the absence of validated biomarkers to guide the rational choice of combinations, and the need to evaluate pharmacokinetic interactions, impact on therapeutic adherence, and cost-effectiveness of these regimens in real-world settings. Thus, although the horizon for combination therapy is promising, the body of evidence does not yet warrant its widespread adoption without well-defined protocols and without considering the capacity of health systems to absorb the additional complexity that these combinations bring.

In the field of potentially curative therapies, articles converge in recognizing allogeneic hematopoietic stem cell transplantation (HSCT) as an established modality for a subset of patients, especially when there is an HLA-identical related donor. Brandow and Liem (2022) report high overall and event-free survival rates at five years in recent series, while pointing out that advances in the prophylaxis of graft-versus-host disease and the use of post-transplant cyclophosphamide have allowed for the expanded use of alternative donors, including haploidentical donors. However, HSCT remains limited by conditioning toxicity, risk of GvHD, and the restricted availability of specialized centers, making it a distant option for most patients in countries with incipient hematological infrastructure (ELENDU et al., 2023).

Autologous gene therapies targeting hematopoietic stem cells, detailed by Germino-Watnick et al. (2022), represent a conceptual leap forward by combining molecular correction of the disease with elimination of the need for an allogeneic donor. The article describes three main strategies: (i) gene addition by lentiviral vectors containing β- or β-globin variants; (ii) gene editing for direct correction of the mutation in HBB; and (iii) editing/addition aimed at inducing HbF by modulating regulatory elements such as BCL11A or the β-globin locus. Preliminary results from clinical trials indicate normalization or substantial improvement in hematopoiesis, with a marked reduction in painful crises and transfusions, reinforcing the potential for a "functional cure" for FD (GERMINO-WATNICK et al., 2022; STEINBERG, 2020). However, Steinberg (2020) and Germino-Watnick et al. (2022) emphasize that significant uncer-

tainties remain regarding long-term safety—including the risk of myelodysplastic events, consequences of CRISPR-Cas9-induced double-strand breaks, and conditioning toxicity—as well as logistical, regulatory, and economic challenges that restrict these interventions to a few centers in high-income countries.

A critical point that runs through the articles, although not always explicitly, is the risk of deepening health inequalities. While Pace et al. (2021) and Brandow and Liem (2022) discuss new drugs, therapeutic combinations, and gene therapies in detail, Elendu et al. (2023) point out that in many African, Caribbean, and other high-prevalence countries, there are still obstacles to the full implementation of basic measures such as neonatal screening, infectious disease prophylaxis, and structured follow-up in specialized outpatient clinics. In this context, sophisticated therapies that require advanced technology and extremely high costs risk benefiting only a global minority, leaving the majority of patients exposed to an ever-widening "therapeutic gap." The authors' discussion, therefore, reinforces the need to link cutting-edge translational research to agendas of distributive justice and health system strengthening.

Considering the evidence analyzed as a whole, it is clear that scientific progress in FD coexists with substantial practical challenges. On the one hand, a deeper understanding of HbF regulation, the expansion of disease-modifying therapies, and advances in cellular and gene approaches present unprecedented opportunities to alter the natural course of the disease (STEINBERG, 2020; PACE; STARLARD-DAVENPORT; KUTLAR, 2021; GERMINO-WATNICK et al., 2022). On the other hand, important gaps remain: the need for long-term real-world studies, systematic evaluation of therapeutic combinations, incorporation of biological markers—such as HbF and other genetic modifiers—into clinical decision models, and, above all, the development of implementation strategies that are feasible, sustainable, and equitable in different socioeconomic contexts (BRANDOW; LIEM, 2022; ELENDU et al., 2023).

Thus, the discussion points to a dual imperative: to continue investing in innovative therapies based on well-defined molecular targets and, at the same time, to ensure that such advances are integrated into health policies that expand access to proven interventions and reduce inequalities in care. By emphasizing the modulatory role of HbF and critically reviewing the main contemporary therapeutic options, this article reinforces the importance of multidisciplinary approaches centered on people with FD as an indispensable condition for translating scientific knowledge into real gains in survival and quality of life for this population.

Disease-Modifying Drug Therapies

Historically, hydroxyurea (HU) has been the mainstay of pharmacological treatment (BRANDOW; LIEM, 2022). Approved for adults in 1998 and later for children, HU acts primarily by inducing the production of fetal hemoglobin (HbF), a hemoglobin that inhibits the polymerization of HbS (ELENDU et al., 2023; PACE et al., 2021). Studies show that HU reduces the frequency and severity of pain crises and the need for transfusions (ELENDU et al., 2023; BRANDOW; LIEM, 2022). Its benefits also include reduced cell adhesion and decreased white blood cell count (PACE et al., 2021).

Recently, the therapeutic arsenal has been expanded with the approval of three new drugs that offer alternatives or complements to HU (BRANDOW; LIEM, 2022; PACE et al., 2021).

1. **L-glutamine (Endari):** Approved in 2017, it acts by reducing oxidative stress in sickle cell erythrocytes (PACE et al., 2021). Phase 3 clinical trials have shown that L-glutamine reduced the median number of pain crises and hospitalizations, as well as the incidence of acute chest syndrome (BRANDOW; LIEM, 2022; PACE et al., 2021).
2. **Crizanlizumab (Adakveo):** This is a humanized monoclonal antibody approved in 2019 that targets P-selectin (BRANDOW; LIEM, 2022). P-selectin is an adhesion molecule that promotes interaction between sickle cell erythrocytes, neutrophils, platelets, and the vascular endothelium, a key step in vaso-occlusion (BRANDOW; LIEM, 2022). The phase 2 study that led to its approval showed a significant reduction in the median frequency of CVO compared to placebo (BRANDOW; LIEM, 2022).
3. **Voxelotor (Oxbryta):** Also approved in 2019, it is the first in its class to act as an allosteric modifier of HbS (BRANDOW; LIEM, 2022). It increases hemoglobin's affinity for oxygen, stabilizing HbS in its oxygenated state and directly inhibiting polymerization (BRANDOW; LIEM, 2022; PACE et al., 2021). Phase 3 trials have shown that voxelotor significantly increased total hemoglobin levels and reduced markers of hemolysis, although it did not demonstrate a statistically significant reduction in CVO rates (BRANDOW; LIEM, 2022).

Disease-modifying drug therapy

Pharmacological therapy for sickle cell disease is based primarily on intervention in the main pathophysiological mechanisms of the disease—especially HbS polymerization, chronic hemolysis, vaso-occlusion, and systemic inflammation—with the aim of reducing acute events, delaying organ damage, and prolonging survival (BRANDOW; LIEM, 2022; PACE; STARLARD-DAVENPORT; KUTLAR, 2021). In this context, hydroxyurea remains the drug of choice, as it induces the production of fetal hemoglobin (HbF), reduces white blood cell and reticulocyte counts, decreases cell adhesion, and improves hematological parameters, with a proven impact on reducing vaso-occlusive crises, acute chest syndrome, transfusion requirements, and mortality (BRANDOW; LIEM, 2022; STEINBERG, 2020). Although widely recommended in international guidelines, its full effectiveness is limited by interindividual variability in response, barriers to adherence, and inequities in access in low- and middle-income countries (ELENDU et al., 2023).

In recent decades, new agents have been incorporated into the therapeutic arsenal, targeting specific pathophysiological targets. L-glutamine acts by reducing erythrocyte oxidative stress, improving redox balance and thereby decreasing the frequency of painful crises in patients with sickle cell disease, although it has no direct effect on HbF (PACE; STARLARD-DAVENPORT; KUTLAR, 2021). Crizanlizumab, an anti-P-selectin monoclonal antibody, interferes with the adhesion of erythrocytes, leukocytes, and platelets to the endothelium, redu-

cing vaso-occlusive events in clinical trials, especially in patients with a history of recurrent crises (BRANDOW; LIEM, 2022; PACE; STARLARD-DAVENPORT; KUTLAR, 2021). Voxelotor increases the affinity of HbS for oxygen and thus inhibits the polymerization of deoxygenated hemoglobin, promoting elevated hemoglobin levels and reduced hemolysis markers, with potential benefits in chronic anemia and associated complications (PACE; STARLARD-DAVENPORT; KUTLAR, 2021).

Based on these developments, the concept of combination therapy, discussed centrally by Pace, Starlard-Davenport, and Kutlar (2021), is gaining momentum. They propose the rational combination of drugs with complementary mechanisms – for example, hydroxyurea as an HbF inducer associated with L-glutamine, crizanlizumab, or voxelotor – with the aim of simultaneously attacking different pathogenic axes (HbS polymerization, oxidative stress, cell adhesion, and inflammation). Initial studies suggest that combination regimens may provide additional reductions in crisis frequency, transfusion requirements, and hospitalizations compared to the use of each agent alone (PACE; STARLARD-DAVENPORT; KUTLAR, 2021; BRANDOW; LIEM, 2022). However, the evidence is still incipient, with short-term follow-up, a limited number of participants, and a lack of robust phase III trials designed specifically to test drug combinations.

Another relevant aspect concerns patient selection and therapeutic monitoring. The literature highlights that the response to different agents is heterogeneous, influenced by baseline HbF levels, genetic profile, clinical severity, and the presence of comorbidities, which points to the need to incorporate biomarkers (such as HbF, markers of hemolysis, and inflammation) and standardized clinical criteria in deciding which drug to start, at what dose, and in what combination (STEINBERG, 2020; BRANDOW; LIEM, 2022). In addition, factors such as cost, availability in public health systems, the need for intravenous infusion (in the case of crizanlizumab), and the impact of the "therapeutic burden" on medication adherence should be considered in clinical practice, especially in settings with limited resources (ELENDU et al., 2023).

In summary, disease-modifying drug therapy for sickle cell anemia has evolved from a model focused almost exclusively on hydroxyurea to a more complex scenario in which multiple agents with different targets can be used sequentially or in combination. Despite these advances, the literature highlights the need for "real-world" studies, clinical trials testing combination regimens, cost-effectiveness assessments, and the development of protocols adapted to different care contexts, in order to ensure that these advances translate into concrete and equitable benefits for the sickle cell disease population (PACE; STARLARD-DAVENPORT; KUTLAR, 2021; BRANDOW; LIEM, 2022; ELENDU et al., 2023).

Current Pharmacological Expectations in the Treatment of Sickle Cell Anemia

The pharmacological approach to sickle cell anemia (SCA) has advanced significantly, enabling not only clinical improvement but also more direct intervention on cellular mechanisms that influence disease progression. Among the available drugs, hydroxyurea (HU) remains one of the therapeutic pillars. In addition to stimula-

ting fetal hemoglobin production through the pathway involving nitric oxide, soluble guanylate cyclase, and cGMP, HU also exerts a selective effect on erythroid precursors, favoring lines with higher HbF expression (PACE et al., 2021). Another relevant aspect is its ability to modulate adhesion molecules—such as L-selectin and certain integrins—reducing the interaction between neutrophils and erythrocytes, a central process in the genesis of vaso-occlusive episodes.

L-glutamine emerges as an alternative that acts mainly on the redox balance of sickle cells. By participating in the synthesis of NAD+, it contributes to increasing the availability of this essential molecule and antioxidant enzymes, reducing oxidative stress on the erythrocyte membrane (PACE et al., 2021). This results in less structural damage, reduced hemolysis, and longer erythrocyte survival—something particularly relevant considering the typical fragility of sickle cell red blood cells.

Among the most recent therapies, crizanlizumab represents a milestone because it acts on a specific target: P-selectin. By blocking this receptor, the drug prevents the formation of aggregates involving endothelial cells, platelets, leukocytes, and rigid erythrocytes. Translational studies show that this inhibition reduces endothelial activation and the release of inflammatory mediators, such as IL-1β and TNF-β, which are often elevated during vaso-occlusive crises.

Voxelotor, on the other hand, offers a different strategy by stabilizing hemoglobin in its oxygenated conformation (R-state), which prevents HbS polymerization—a critical step that gives rise to the sickle shape of the cell. With good oral bioavailability and metabolized mainly via CYP3A4, the drug requires special attention from the pharmacist during the dispensing phase in relation to possible drug interactions such as enzyme inducers and inhibitors, if the patient is a user. Although it does not directly reduce the frequency of crises, voxelotor has an important impact on hemolysis, reflected in consistent reductions in LDH, indirect bilirubin, and reticulocyte count (PACE et al., 2021).

Another growing topic in the literature is the use of therapeutic combinations. Combinations such as HU + crizanlizumab or HU + L-glutamine show potential to act simultaneously on inflammatory, oxidative, and vascular mechanisms, suggesting an additive or even synergistic effect on different aspects of pathophysiology (PACE et al., 2021). This trend reinforces the need for increasingly individualized management, in line with modern principles of personalized pharmacotherapy. In special cases, such as hospitalized pediatric patients and/or patients with special needs who require HU to be administered in oral suspension at individualized doses, the role of the hospital pharmacist is indispensable. For the manipulation and/or fractionation (if necessary) of drugs in the appropriate dose, as in the case of HU in oral suspension, which requires manipulation because it is cytotoxic, manipulation must be restricted to appropriate environments requiring laminar flow, PPE, and a clean area.

Finally, I would like to add that clinical pharmacists play an indispensable role in monitoring these patients, ensuring that they receive drug therapy and pharmacological guidance in an effective manner that is appropriate to their needs. HU requires frequent hematological monitoring due to the risk of myelosuppression, while voxelotor

demands continuous attention to possible interactions. Thus, integrating knowledge of pharmacology, genetics, clinical practice, and multidisciplinary teamwork is essential to optimize care and ensure greater therapeutic safety in the management of sickle cell anemia.

Transfusion Management

Red blood cell transfusions are crucial in the management of FA, both in acute and chronic scenarios (ELENDU et al., 2023). The goal is to increase oxygen-carrying capacity and dilute HbS concentration (ELENDU et al., 2023). In addition, regular transfusions may be indicated for individuals with severe complications of the disease, such as stroke or recurrent episodes of cerebral ischemia, contributing to reducing the percentage of circulating sickle cells and preventing clinical events associated with sickling (ELENDU et al., 2023).

In children with abnormal transcranial Doppler (TCD) velocities, chronic monthly transfusions are the gold standard for **primary prevention** of stroke, with the goal of maintaining HbS below 30% (BRANDOW; LIEM, 2022). This regimen is also the treatment of choice for **secondary prevention** in patients who have already suffered a stroke (BRANDOW; LIEM, 2022). In the management of **acute stroke,** exchange transfusion (red blood cell exchange) is recommended to rapidly reduce the percentage of HbS (BRANDOW; LIEM, 2022).

In urgent situations, a simple transfusion can be used as an initial measure while preparing for exchange transfusion, which is more effective in reducing HbS and preventing stroke recurrence (Brandow; Liem, 2022). The use of tissue plasminogen activator (tPA) is not recommended in children with sickle cell disease who have acute stroke, due to the non-thromboembolic nature of the event and the potential risk of complications (Brandow; Liem, 2022).

In some cases, after a year of chronic transfusions, children with abnormal DTC but no changes in angioresonance can be safely transferred to hydroxyurea as maintenance therapy (Brandow; Liem, 2022). Regular red blood cell transfusions contribute to reducing the proportion of sickle cells in circulation, improving tissue oxygenation and reducing the risk of serious complications such as stroke (Elendu et al., 2023).

Transfusion management

Transfusion management plays a central role in supportive care and in modifying the clinical course of sickle cell disease, being used both in acute situations and as a chronic strategy for preventing serious complications. In general terms, red blood cell transfusions have two main objectives: to rapidly increase oxygen-carrying capacity and to reduce the proportion of red blood cells containing HbS in circulation, thereby attenuating hemolysis, vaso-occlusion, and tissue hypoxia (ELENDU et al., 2023; BRANDOW; LIEM, 2022). In more serious scenarios—such as severe acute anemia, acute chest syndrome (ACS), or stroke—this intervention can be decisive in preventing irreversible organ damage (ELENDU et al., 2023).

In acute settings, transfusions are particularly important in the management of stroke and STA. Brandow and Liem (2022) highlight that, in children with acute ischemic stroke, the recommended treatment is red blood cell concentrate transfusion with

the aim of reducing the HbS fraction to less than 30%, preferably through exchange transfusion. Simple transfusion alone has been shown to be associated with a relative risk of subsequent stroke that is approximately five times higher than exchange transfusion, which justifies the preference for the latter whenever available (BRANDOW; LIEM, 2022). In practice, however, a simple transfusion is usually performed initially, on an urgent basis, while the exchange transfusion is being prepared, so as not to delay the correction of anemia and hypoxia (BRANDOW; LIEM, 2022). Regarding the use of thrombolysis, the authors emphasize that tissue plasminogen activator (tPA) is not recommended in children with FD and acute stroke, and in adults, its use should be carefully considered, without ever replacing or delaying immediate transfusion therapy.

In individuals with moderate or severe AHS, transfusions also play an important role by reducing viscosity, improving oxygenation, and decreasing the proportion of sickled red blood cells in the pulmonary beds. Elendu et al. (2023) point out that in situations of significant hypoxemia, severe chest pain, and clinical deterioration, red blood cell transfusion is indicated as part of a multimodal approach that includes ventilatory support, antibiotics, and strict pain control. Similarly, episodes of severe acute anemia—due to transient aplasia, marked hemolysis, or splenic/hepatic sequestration—require emergency transfusion to rapidly restore blood volume and prevent shock and organ failure (ELENDU et al., 2023).

In addition to these acute situations, transfusion can be used chronically, especially in the primary and secondary prevention of stroke in children with FD. Based on studies that used transcranial Doppler to identify high-risk children, the practice of regular transfusion schedules, usually every 3–4 weeks, has been established, with the goal of maintaining HbS < 30% and total hemoglobin around 10 g/dL, significantly reducing the incidence of first events and recurrence of stroke (BRANDOW; LIEM, 2022). Steinberg (2020) reinforces that the combination of high HbF levels and strict control of the HbS fraction through chronic transfusions is associated with less silent brain damage and a better long-term neurological prognosis.

Despite its effectiveness, chronic transfusion management poses significant challenges. Repeated use of red blood cells exposes patients to the risk of erythrocyte alloimmunization, hemolytic reactions, and iron overload, often requiring chelation and more complex follow-up (BRANDOW; LIEM, 2022; ELENDU et al., 2023). In many low- and middle-income settings, Elendu et al. (2023) emphasize that the availability of safe and properly typed blood is limited, making it difficult to implement large-scale chronic transfusion programs. In addition, the economic and organizational impact of these schemes is significant, requiring structured blood therapy services and frequent laboratory monitoring.

The relationship between transfusion management and other disease-modifying therapies has also been the subject of discussion. Brandow and Liem (2022) report that, in certain situations, hydroxyurea has been evaluated as a partial alternative to chronic transfusion, especially in primary stroke prevention in selected children, provided that clinical and imaging parameters are closely monitored. On the other hand, in the field of gene therapies, "transfusion independence" is one of the most valued ou-

tcomes: Germino-Watnick et al. (2022) describe that many patients undergoing gene addition or editing strategies become free from the need for regular transfusions or even any transfusion support after corrected hematopoiesis stabilization. This data reinforces how transfusion, although it remains an indispensable pillar of care, tends to be reconceptualized in a scenario in which potentially curative therapies become a reality for a portion of patients.

In summary, transfusion management in sickle cell disease should be understood as a high-impact but complex intervention that requires careful indication, clear goal setting (such as reducing HbS to <30% in certain situations), and continuous attention to associated complications. The coordination between transfusions, disease-modifying drug therapies, and, in the future, gene therapies points to increasingly individualized models of care, in which the rational and safe use of blood remains essential to reduce morbidity and mortality and preserve organ function in people with SCD (BRANDOW; LIEM, 2022; ELENDU et al., 2023; GERMINO-WATNICK et al., 2022).

Curative Therapies: HSCT and Gene Therapy

The only established curative treatment for FA is allogeneic hematopoietic stem cell transplantation (HSCT) (ELENDU et al., 2023). When performed with an HLA-matched sibling donor (MSD), the five-year overall and event-free survival rates are greater than 90% (BRANDOW; LIEM, 2022). The biggest challenge with this approach is donor availability, as less than 20%, and perhaps only 10%, of patients have an MSD (GERMINO-WATNICK et al., 2022; BRANDOW; LIEM, 2022). Recent advances, such as the use of haploidentical (semi-compatible) donors with post-transplant cyclophosphamide, are expanding donor options (BRANDOW; LIEM, 2022).

To overcome the limitations of allogeneic HSCT, autologous gene therapy has emerged as a promising cure (GERMINO-WATNICK et al., 2022). In this scenario, autologous hematopoietic stem cell transplantation stands out for eliminating the restriction of compatible donors, in addition to reducing the need for immunosuppressive drugs and the chance of graft failure or graft-versus-host disease and infection (PACE et al., 2021). “Khadija Hayek.” The procedure consists of collecting CD34+ hematopoietic stem cells (HSCs) from the patient, genetically modifying them in vivo, and subsequently reinfusing them after myeloablative conditioning (GERMINO-WATNICK et al., 2022). Current gene therapy strategies follow two main approaches:

1. **Gene Addition:** Uses lentiviral vectors (LV) to insert a functional copy of a therapeutic globin gene into the patient’s HSCs. This can be a modified β-globin gene with anti-sickling properties (such as βT87Q-globin, used in LentiGlobin BB305) or a β-globin gene (to induce HbF) (GERMINO-WATNICK et al., 2022).
2. **Gene Editing:** Uses tools such as CRISPR/Cas9 or zinc finger nucleases (ZFNs) to permanently modify the genome of HSCs (BRANDOW; LIEM, 2022). This approach may aim to directly correct the HbS mutation in the HBB gene (GERMINO-WATNICK et al., 2022) or, more commonly, to

induce HbF by disrupting β-globin repressors (GERMINO-WATNICK et al., 2022; STEINBERG, 2020). The main target for HbF induction is the **BCL11A** gene**,** a master repressor of HbF (STEINBERG, 2020). Editing the BCL11A-specific erythroid enhancer (as in CTX001) prevents its expression, reactivating HbF production (GERMINO-WATNICK et al., 2022). Early clinical studies with this approach have shown robust results, with patients achieving HbF levels of 40% to 50% and HbF expression in nearly 100% of erythrocytes (F-cells), effectively eliminating vaso-occlusive events (STEINBERG, 2020).

Curative therapies for sickle cell disease currently focus on two main strategies: allogeneic hematopoietic stem cell transplant (HSCT) and gene therapy targeting hematopoietic stem cells. Allogeneic HSCT, especially from an HLA-identical sibling, is the most established curative modality, with five-year overall survival and event-free survival rates exceeding 90% in large pediatric cohorts after myeloablative conditioning and an optimized graft-versus-host disease prophylaxis regimen (G-VHD) (BRANDOW; LIEM, 2022; GERMINO-WATNICK et al., 2022). Classic indications include a history of stroke, high risk of stroke by transcranial Doppler, recurrent acute chest syndrome, severe pain that is difficult to control, and progressive organ damage in patients with a compatible donor and clinical conditions to support transplantation (ELENDU et al., 2023; BRANDOW; LIEM, 2022).

In recent decades, less intense conditioning regimens and modern immunosuppression strategies, such as the use of post-transplant cyclophosphamide, have broadened eligibility for adults with severe phenotypes and enabled the use of alternative donors (haploidentical, unrelated cord blood), reducing graft failure and severe GED (BRANDOW; LIEM, 2022; GERMINO-WATNICK et al., 2022). Nevertheless, HSCT remains associated with significant short- and long-term risks, such as conditioning toxicity (infertility, organ damage), chronic GVHD, and opportunistic infections, in addition to requiring highly specialized infrastructure, which limits its availability in many low- and middle-income countries (ELENDU et al., 2023).

Autologous gene therapy seeks to circumvent some of these limitations by using the patient's own hematopoietic stem cells (HSCs), which are genetically modified ex vivo and reinfused after myeloablative conditioning. In the gene addition approach, autologous $CD34^+$ cells are collected, transduced with lentiviral vectors expressing a therapeutic β-globin (e.g., anti-sickling variants) or HbF-inducing γ-globin, and subsequently reinfused to reconstitute "corrected" hematopoiesis (GERMINO-WATNICK et al., 2022). Phase I/II clinical trials with vectors such as LentiGlobin have demonstrated a sustained increase in total hemoglobin, an elevation in the therapeutic hemoglobin fraction, and a marked reduction or even disappearance of vaso-occlusive crises and transfusion requirements in many participants (GERMINO-WATNICK et al., 2022).

At the same time, gene editing strategies use tools such as CRISPR/Cas9 or zinc finger nucleases to directly correct the mutation in the HBB gene or modulate regulatory elements, such as the erythroid enhancer region of BCL11A, reactivating fetal

hemoglobin production (STEINBERG, 2020; GERMINO-WATNICK et al., 2022). Initial reports indicate a significant increase in HbF (above 40–50%), almost universal F cells, and the abolition of severe crises in the short to medium term, which constitutes a "functional cure" in some of the patients treated (STEINBERG, 2020).

Despite the enthusiasm, both gene addition and gene editing are still considered approaches in consolidation, with significant challenges. Concerns remain about long-term safety (risk of myelodysplasia, events related to viral integration or DNA breaks), the need for myeloablative conditioning with toxicity similar to that of conventional HSCT, and logistical, regulatory, and economic barriers that restrict these therapies to a few centers in high-income countries (GERMINO-WATNICK et al., 2022). Furthermore, as Pace, Starlard-Davenport, and Kutlar (2021) point out, the development of curative therapies does not eliminate the importance of disease- -modifying interventions and transfusion support, which remain the basis of care for the vast majority of patients in the current setting.

In summary, HSCT and gene therapy represent a continuum of curative strategies ranging from a donor-dependent allogeneic model to autologous approaches to molecular correction. While HSCT from an HLA-identical sibling offers a proven cure for a subset of patients, gene therapy theoretically expands the pool of candidates by eliminating the need for compatible donors. However, the potential benefits of these technologies will only be fully realized if accompanied by policies that address inequalities in access, integrate these therapies into comprehensive care programs, and ensure their ethical, safe, and sustainable provision in different health system contexts (BRANDOW; LIEM, 2022; ELENDU et al., 2023; GERMINO-WATNICK et al., 2022).

CONCLUSION

The narrative analysis of the selected studies shows that sickle cell disease remains one of the most important challenges in contemporary hematology, combining a high burden of morbidity and mortality, great clinical heterogeneity, and a profound influence of social and structural determinants of health (ELENDU et al., 2023; BRANDOW; LIEM, 2022). In this scenario, fetal hemoglobin (HbF) stands out as a central conceptual axis. In addition to explaining a relevant part of phenotypic variability, it constitutes a robust prognostic marker and a privileged therapeutic target, integrating the pathophysiology of the disease into the personalized medicine agenda (STEINBERG, 2020; PACE; STARLARD-DAVENPORT; KUTLAR, 2021).

From a therapeutic standpoint, there has been a transition from a model based almost exclusively on clinical support and hydroxyurea to a more complex scenario that includes new drugs with specific targets, structured transfusion management, allogeneic hematopoietic stem cell transplantation (HSCT), and rapidly evolving gene therapies (BRANDOW; LIEM, 2022; PACE; STARLARD-DAVENPORT; KUTLAR, 2021; GERMINO-WATNICK et al., 2022). Disease-modifying drug therapy is advancing from a "single-agent" paradigm to the prospect of rational combinations that simultaneously address HbS polymerization, hemolysis, cell adhesion, inflamma-

tion, and oxidative stress, although robust long-term trials are still lacking to define optimal regimens, with patient profiles and cost-effectiveness in different settings.

Transfusion management continues to play a fundamental role in care, especially in acute situations such as stroke and acute chest syndrome, as well as in chronic transfusion programs to prevent neurological events , but still at the cost of increased risk of alloimmunization, iron overload, and the need for highly organized blood transfusion services (BRANDOW; LIEM, 2022; ELENDU et al., 2023). In this context, HSCT with an HLA-identical donor remains a consolidated curative option for a subset of patients with a severe phenotype, while autologous gene therapies—both gene addition and gene editing—are emerging as a promising frontier for "functional cure," theoretically expanding the universe of candidates for definitive intervention (GERMINO-WATNICK et al., 2022; STEINBERG, 2020).

Despite these advances, the reviewed articles converge in emphasizing that most people with sickle cell disease live in low- and middle-income contexts, where there are still difficulties in ensuring neonatal screening, infectious prophylaxis, regular access to hydroxyurea treatment, safe transfusions, and specialized follow-up (ELENDU et al., 2023). In this sense, HSCT and gene therapy run the risk of becoming extremely high-cost technologies, reaching only a minority, if they are not accompanied by explicit policies of equity, sustainable financing, and strengthening of health systems. This implies articulating the biomedical innovation agenda with public health, regulation, and distributive justice strategies, under penalty of deepening already striking inequalities.

Due to its narrative nature and analysis of an intentionally selected set of recent reviews, this review does not claim to exhaust the available literature or produce quantitative syntheses of effectiveness. Among its limitations are the risk of study selection bias, the absence of meta-analysis, and the focus on English-language publications, which may underrepresent local experiences in countries with high prevalence. Nevertheless, by integrating findings on HbF, pharmacological therapies, transfusion management, HSCT, and gene therapy, this work contributes to critically organizing some of the main conceptual and practical axes that currently guide sickle cell disease care (BRANDOW; LIEM, 2022; PACE; STARLARD-DAVENPORT; KUTLAR, 2021; STEINBERG, 2020; GERMINO--WATNICK et al., 2022).

As a future agenda, the reviewed authors point to the need for: (i) long-term "real-world" studies evaluating drug combinations, clinical outcomes, quality of life, and cost-effectiveness; (ii) systematic incorporation of biomarkers—especially HbF and genetic modifiers—into clinical decision protocols; (iii) prolonged monitoring of the safety of gene therapies, including the risk of late hematological events; and (iv) development of implementation models that make these innovations accessible in resource-limited settings (PACE; STARLARD-DAVENPORT; KUTLAR, 2021; GERMINO-WATNICK et al., 2022; ELENDU et al., 2023).

It can therefore be concluded that tackling sickle cell disease requires integrated approaches, ranging from the optimization of modifying therapies and transfusion management to the careful incorporation of HSCT and gene therapies, necessarily

anchored in health policies that promote broad access, multidisciplinary care, and a focus on the person living with sickle cell disease. Only the combination of biomedical innovation and a commitment to equity will enable the significant recent scientific advances to be converted into concrete and sustainable gains in survival and quality of life for this population. (Daniele Diniz Neves).

In the field of current pharmacological expectations, there is a consistent movement toward therapies that act in an integrated manner on different pathophysiological axes of the disease. The combination of fetal hemoglobin inducers, NO–sGC–cGMP pathway modulators, agents that reduce cell adhesion, and strategies aimed at controlling oxidative stress represents a trend that seeks to extend the clinical benefit beyond what each drug has been able to offer individually. The diversification of this therapeutic arsenal, however, imposes new challenges in terms of monitoring, safety, and rational use. This is where the participation of clinical and hospital pharmacists becomes essential: by dispensing medications safely, evaluating response profiles, guiding complex regimens, monitoring specific risks, such as possible drug interactions that could harm the patient, and supporting treatment adherence, professionals contribute decisively to turning these innovations into effective gains in care, offering increasingly individualized and effective treatment in promoting patient health. As new molecules advance into clinical practice, the qualified work of pharmacists is no longer merely complementary but becomes part of the core of the therapeutic process, leading to more efficient results.

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