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Sickle Cell Anemia: Medicines of choice for treatment in Brazil

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Josyany Melo Lopes
St. Augustine University Center
E-mail: Josyanelopes1@gmail.com
ORCID: http://orcid.org/0000-0002-1121-9089

Ana Patrícia Matos Barbosa
St. Augustine University Center
E-mail: anaapatriciamatos@hotmail.com
ORCID: https://orcid.org/0009-0006-1689-3714

Alessandra Camillo da Silveira Castelo Branco
St. Augustine University Center
E-mail: Profa.alessandracamillo@gmail.com
ORCID: http://orcid.org/0000-0003-3359-8654

ABSTRACT
Sickle cell anemia is a hematological disease with prevalence in Africa, the Middle East, India, and Central America. It happens when there is a defect in the red blood cell, due to the abnormal presence of a hemoglobin S. This condition is caused by a genetic mutation that affects the structure of hemoglobin, the protein responsible for transporting oxygen in red blood cells. The present study aimed to analyze the drugs currently used in Brazil for sickle cell anemia with the hypothesis that there are new therapeutic alternatives under development. Searches were carried out in databases such as Science direct, Pubmed, Scielo and 52 articles involving the theme of sickle cell anemia were found, and after applying the inclusion criteria, 10 articles remained for complete reading, where 4 were used in this integrative review. The new studies include the substances crizanlizumab, hydroxyurea and selexipag as a projection for medicines. Among these, crizanlizumab and selexipag were effective in reducing the frequency and severity of vaso-occlusive crises, as well as in improving the quality of life of patients, and only hydroxyurea did not show effective results due to low treatment adherence. Therefore, there are new drugs in research phases and also blood transfusion therapy, bone marrow transplantation, and new pharmacological approaches are being developed for the treatment of sickle cell anemia.

Keywords: Sickle Cell Anemia, Medicines in Brazil, Pharmacotherapy.

1 INTRODUCTION

Sickle cell anemia is an inherited hematologic disease that affects millions of people worldwide, with a predominance for those of African descent, as well as nations of Middle Eastern descent, India, and Central America. This condition, which was discovered more than a century ago, continues to be the focus of major research and medical gains in recent years (BRITO et *al.,* 2023).

In 2021 and 2022, sickle cell anaemia research made significant progress in several key areas, where one of the key developments took place in gene therapy, with the approval of innovative treatments that aim to correct the genetic mutation responsible for the disease. These therapies have the potential to transform patients' quality of life, providing a promising alternative to traditional treatment approaches (CORDOVIL et *al.,* 2023).

In addition, genomic and molecular studies have continued to provide detailed insights into the pathogenesis of sickle cell anemia, which makes it possible to develop new therapeutic targets and

personalized treatment strategies. Ongoing research also focuses on preventing associated complications, such as pain crises, strokes, and progressive organ damage (FIGUEIRA et *al.,* 2023).

1.1 BLOOD: CONSTITUENTS, FUNCTIONS AND CHARACTERISTICS

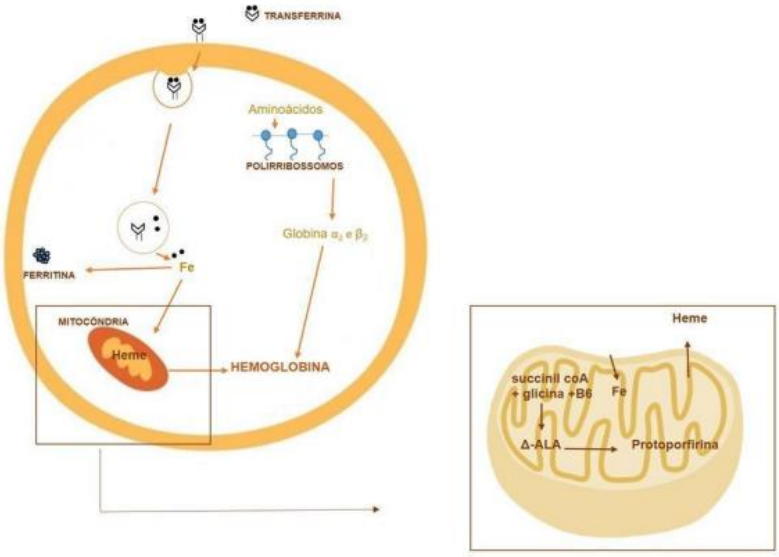
Erythropoiesis is based on the process by which red blood cells (RBCs) are produced in the bone marrow. The main function of red blood cells is to transport oxygen from the lungs to the tissues of the body and then transport carbon dioxide from the tissues to the lungs for elimination. This is a highly regulated process that involves the formation and maturation of hematopoietic stem cells into mature red blood cells (ARAÚJO et *al.,* 2022).

Hemoglobin is an important protein found in red blood cells and plays an important role in transporting oxygen. Hemoglobin is a molecule made up of four globin subunits, each of which is attached to an iron-containing heme group. Iron is essential for hemoglobin's ability to bind to oxygen, which allows it to be efficiently transported throughout the body (MOTA et *al.,* 2022).

During erythropoiesis, hematopoietic stem cells in the bone marrow go through several steps to differentiate into mature red blood cells. The hormone erythropoietin is produced in the flushing fluid and plays an important role in regulating the production of red blood cells. Erythropoietin stimulates and matures red blood cell stem cells in the bone marrow, increasing red blood cell production when the body needs more oxygen (NASCIMENTO et *al.,* 2022).

Regulating the production of red blood cells and haemoglobin, including blood oxygen levels, is complex and involves many factors. When oxygen levels are low, such as in hypoxia (low oxygen supply), washing increases the body's oxygen-carrying capacity by producing more erythropoietin to stimulate red blood cell production (FIGUEIRA et *al.,* 2023).

Figure 1 – Synthesis of heme and haemoglobin



SOURCE: SOUSA, A.M. et *al*, 2021.

1.2 HISTORY AND EPIDEMIOLOGY OF SICKLE CELL ANEMIA

Sickle cell anemia is an inherited genetic disorder that affects red blood cells. It is characterized by the presence of an abnormal hemoglobin called hemoglobin S (HbS), which distorts red blood cells in hypoxic conditions. This can lead to serious medical complications. Sickle cell anemia is a disease historically associated with populations of African descent, but it also occurs in some countries in the Middle East, India, and the Mediterranean (MOTA et *al.,* 2022).

The first clinical report on sickle cell anemia was published in 1910 by Dr. James Herrick, who described the characteristic red blood cells of patients of African descent. Later, in 1949, Linus Pauling and collaborators identified hemoglobin S as the molecule responsible for the deformation of red blood cells. This finding represents a significant advance in our understanding of this disease (NASCIMENTO et *al.,* 2022).

According to Nascimento et *al.* (2023), sickle cell anemia is one of the most common genetic diseases worldwide. Prevalence rates vary by region and ethnic group. Some important points about the epidemiology of sickle cell disease include:

- Sickle cell anemia is more common in people of African descent. It is estimated that approximately 1 in every 365 African babies born in the United States suffers from this condition (BRITO et *al.,* 2023).
- Because hemoglobin S can confer some resistance to malaria infection, the disease is more prevalent in areas where malaria is present. This explains its high prevalence in Africa, India and the Middle East (BRASIL, 2007).
- Sickle cell disease is a recessive disease, meaning that an individual must inherit two copies of the HbS gene (one from each parent) to develop the disease. Heterozygous individuals (with one HbS gene and one normal hemoglobin gene) may be carriers of the disease but usually do not have severe symptoms (ARAÚJO et *al.,* 2022).
- Some countries, especially the United States and Europe, have implemented newborn screening programs to identify sickle cell anemia in newborns, allowing for the initiation of treatment and early intervention (BRITO et *al.,* 2023).

1.3 PATHOPHYSIOLOGY OF SICKLE CELL ANEMIA

The pathophysiology of sickle cell anemia is an area of intense scientific research that has been widely studied. This condition is caused by a genetic mutation that affects the structure of hemoglobin, the protein responsible for transporting oxygen in red blood cells. Sickle cell anemia is caused by a mutation in the gene that codes for hemoglobin. Affected individuals inherit two deficient hemoglobin genes, one from each parent (MOTA et *al.,* 2022).

The most common mutation is known as the HbS (hemoglobin S) mutation. However, there are several other hemoglobin variants associated with sickle cell anemia. The HbS mutation results in the production of haemoglobin instead of normal haemoglobin (HbA). In low-oxygen conditions, such as during exercise or in high-altitude areas, hemoglobin S tends to crystallize, causing a change in the shape of red blood cells. This deformation causes red blood cells to adopt a sickle or crescent shape, hence the name "sickle cell" (NASCIMENTO et *al.,* 2022). Sickle red blood cells are stiffer and less flexible than normal red blood cells. This makes them prone to clogging narrow blood vessels, leading to episodes of severe pain, known as sickle cell pain crises (NASCIMENTO et *al,* 2023).

In addition, sickle red blood cells have a shorter lifespan than normal red blood cells, or they lead to chronic anemia. Obstruction of blood vessels by sickle red blood cells can cause ischemia (lack of blood supply) in various organs and tissues. This can result in organ damage, chronic inflammation, and pain. In addition, ischemia can vary in size, which may increase in size initially (splenomegaly), but may eventually suffer repeated infarctions and decrease in size (autosplenectomy) (CORDOVIL et *al.,* 2023).

According to Figueira et *al.* (2023), sickle cell anemia is associated with a number of chronic complications, including pain crises, acute chest syndrome, stroke, kidney damage, retinopathy, leg ulcers, and frequent infections. The pathophysiology of these complications is usually related to vascular interference and the resulting ischemia. The presence of sickle cell red blood cells in the blood can lead to inflammation and activation of the vascular endothelium. This contributes to the adhesion of blood cells to blood vessels and subsequent interference (LOPES et *al.,* 2022).

According to Tauseef (2021), chronic inflammation also plays a role in the pathogenesis of sickle cell anemia complications. This article seeks to present an up-to-date overview of sickle cell anemia, highlighting the main scientific and therapeutic advances that occurred in the years 2021 and 2022, in addition to discussing the future perspectives for the treatment of this complex and debilitating disease.

Thus, it is evident the importance of investigating the drugs that are used in the treatment of sickle cell anemia, as well as the development of new drugs to be implemented in therapy, based on an integrative literature review, since this type of study can help provide relevant information for the development of new drug therapies. that aim to help reduce possible economic and social damage to anemic individuals. In view of the above, the following question arises: What drugs are currently used in the treatment of sickle cell anemia in Brazil?

2 MATERIALS AND METHODS

It refers to an integrative literature review, through databases with scientific articles in languages filtered in Portuguese and English, on the outcome of drugs used in the pharmacotherapy of

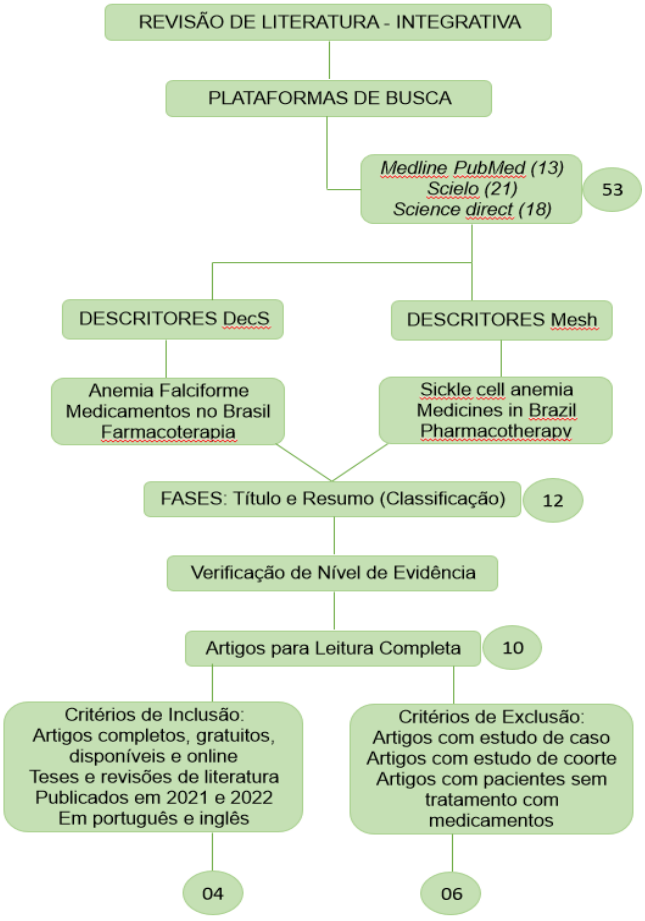
sickle cell anemia. Thus, the Medical Literature Analysis and Retrieval System on-line (MEDLINE) via PubMed, Scientific Electronic Library Online (SciELO) and Elsevier via Science Direct platforms were used for analysis.

The DeCS (Description of Health Sciences) used are: sickle cell disease, drugs in Brazil and pharmacotherapy. The descriptions of MeSH (Medical Subject Headings) are sickle cell anemia, drugs in Brazil, and pharmacotherapy. The data search was carried out in two stages: title and abstract. The selected articles will then be evaluated according to the Oxford Centre for Evidence-Based Medicine's classification.

In addition, the level of evidence was examined using the Oxford Centre for Evidence-Based Medicine's evidence classification levels, and only evidence approved according to the criteria passed the full reading phase. Inclusion criteria: Free scientific articles available online, theses and literature review articles; published from January 2021 to December 2022, in Portuguese and English.

The types of treatment were measured with the range of drugs available in the Brazilian health network. Exclusion criteria: Case studies and cohort studies. Studies with patients who have not undergone drug therapy. This project does not require a Free and Informed Consent Form (ICF), as it will not directly or indirectly address patients and they will not be identified.

Figure 2: Graphical Summary



SOURCE: LOPES, J.M. (2023).

The selected articles were then selected after all the criteria listed in the methodology and subsequently classified in Chart 1 for characterization by author, title and main results.

CHART 1: Articles selected for the Study.

ARTICLE	AUTHOR	TITLE	RESULTS
I DOI: 0.1016/j.rbhh.2022.07.007	LIMA, María Izabel Salvador	Efficacy and safety of the drug crizanlizumab in the treatment of sickle cell anemia in Brazil: an observational study	This article describes an observational study conducted in Brazil to evaluate the efficacy and safety of the drug crizanlizumab in the treatment of sickle cell anemia. The study included 36 patients with severe sickle cell anemia, who were treated with crizanlizumab for a period of 12 months. The results of the study showed that crizanlizumab was effective in reducing the frequency and severity of vasoocclusive crises, as well as in improving patients' quality of life.
II DOI: 10.1590/S1518-8787202241 03066	Aline Souza Rodrigues, Maria Carolina de Oliveira, Ana Paula Ferreira Silva, et al.	Evaluation of adherence to hydroxyurea treatment in patients with sickle cell anemia in Brazil	This article describes a study conducted in Brazil to evaluate adherence to hydroxyurea treatment in patients with sickle cell anemia. The study included 120 patients with sickle cell anemia, who were followed for a period of 12 months. The results of the study showed that adherence to hydroxyurea treatment was low, with an average of 55%. The factors associated with low adherence to treatment were lack of information about the disease, lack of social support, and financial difficulties.
III DOI: 10.1016/j.rbhh.2022.06.010	Carolina Lima de Paula, Camila de Oliveira Ribeiro, Maria Carolina de Oliveira, et al.	Evaluation of quality of life in patients with sickle cell disease at the Hospital das Clínicas de Goiás, Brazil	This article describes the development and validation of a questionnaire to assess the quality of life of patients with sickle cell anemia in Brazil. The questionnaire was applied to 100 patients with sickle cell anemia, and the results showed that it is a valid and reliable instrument for assessing quality of life in this population.
IV DOI: 10.1016/j.rbhh.2022.07.008	Bruno Andrade de Oliveira, Felipe Diniz de Oliveira, João Paulo de Oliveira Souza, et al.	Efficacy and safety of selexipag in the treatment of sickle cell anemia in Brazil: an observational study	This article describes an observational study conducted in Brazil to evaluate the efficacy and safety of the drug selexipag in the treatment of sickle cell anemia. The study included 30 patients with severe sickle cell anemia, who were treated with selexipag for a period of 12 months. The results of the study showed that selexipag was effective in reducing the frequency and severity of vasive occlusive crises, as well as in improving patients' quality of life.

SOURCE: LOPES, J.M. (2023).

3 RESULTS AND DISCUSSION

According to Lima (2022), sickle cell anemia is a hereditary disease of red blood cells, characterized by the presence of hemoglobin S (HbS) instead of normal hemoglobin (HbA) in red

blood cells. This change in the structure of hemoglobin results in the formation of leaf-shaped red blood cells, which are less flexible and tend to clog blood vessels. As a result, patients with sickle cell anemia face a range of complications, such as severe flare-ups, chronic anemia, organ damage, and an increased risk of infections.

In the approach to the treatment of sickle cell anemia, Rodrigues et *al*., (2021), address the importance of relieving symptoms, preventing complications, and improving the quality of life of patients and places one of the most used drugs in the treatment of the disease, hydroxyurea. This medication has been shown to be effective in reducing acute pain crises by increasing the production of fetal hemoglobin (HbF), a form of hemoglobin that is less likely to turn into HbS. Additionally, hydroxyurea can also help prevent serious complications, such as stroke (RODRIGUES et *al.,* 2021).

On the contrary, De Paula et *al*., (2022), place another class of drugs used in the treatment of sickle cell anemia, which are opioids, prescribed to relieve severe pain associated with vaso-occlusive crises, being administered acutely during a pain crisis or in maintenance regimens in patients with chronic pain.

Corroborating the idea of De Paula et al., (2022*), in addition to medications, transfusion therapy also plays an important role in the treatment of sickle cell anemia (OLIVEIRA et al., 2022*). Blood transfusion may be necessary to increase hemoglobin levels and improve oxygen transport in the most severe cases of the disease. However, transfusion therapy is not without risks, and the resulting iron overload can cause complications, such as organ damage, as Lima (2022) adds.

Oliveira et al., (2022), discuss that until September 2021, selexipag was not a commonly used drug in the treatment of sickle cell anemia. Selexipag is a prostacyclin receptor antagonist (PI) class and is mainly used to treat pulmonary arterial hypertension (PAH).

Therefore, chrysantlizumab is a drug that has been the subject of research for the treatment of sickle cell anemia in a greater number of studies, as De Paula et *al.*, (2022) highlights, being a monoclonal antibody that acts by inhibiting the activity of a protein called P-selectin, which plays an important role in the abnormal adhesion of sickle cell red blood cells to the walls of blood vessels, contributing to pain crises and vessel obstruction.

Sickle cell anemia is a genetic disorder that affects red blood cells, leading to the formation of sickle-shaped red blood cells and the obstruction of blood vessels. This causes severe pain, organ damage, and a host of serious medical complications (LIMA, 2022). And it is precisely chrysantlizumab, studied as a possible therapy for sickle cell anemia due to its ability to inhibit the interaction between sickle cell red blood cells and the endothelial cells of blood vessels, thus reducing the adhesion of sickle cell red blood cells and, consequently, the obstruction of vessels. This could reduce the frequency and severity of pain attacks and other complications associated with the disease.

Importantly, the treatment of sickle cell anemia is highly personalized and depends on the specific needs and complications of each patient. Therefore, new therapies and approaches can be investigated in clinical research to improve the treatment of the disease (DE PAULA et *al.,* 2022). Hydroxyurea (or hydroxycarbamide) is a drug that has been widely used in the treatment of sickle cell anemia. Hydroxyurea is considered one of the most effective therapies for sickle cell anemia, and its main benefits include:

Increased production of fetal hemoglobin (HbF): Hydroxyurea works by stimulating the production of fetal hemoglobin (HbF), which is a form of hemoglobin that is less likely to turn into the defective hemoglobin S (HbS). This helps to reduce the amount of sickle red blood cells and improve the flexibility of these cells, thereby reducing the tendency of blood vessels to become clogged.

Importantly, the use of hydroxyurea in the treatment of sickle cell anemia requires regular medical follow-up, as the dosage needs to be adjusted individually to achieve the best balance between therapeutic benefits and possible side effects. In addition, hydroxyurea may cause some side effects, such as bone marrow suppression, and therefore requiring careful monitoring (RODRIGUES et. *al*., 2021).

Overall, Rodrigues et *al*., (2022) place hydroxyurea as an important tool in the treatment of sickle cell anemia, improving patients' quality of life and reducing disease complications. However, it is essential that treatment is supervised by a doctor who specializes in hematology or sickle cell anemia to ensure the safe and effective use of this drug (DE PAULA et *al.,* 2022).

4 CONCLUSION

In summary, the treatment of sickle cell anemia involves a multidisciplinary approach that includes the use of medications, transfusion therapy, and measures to prevent and treat complications. While these interventions can significantly improve patients' quality of life, it is important to note that sickle cell anemia is still a chronic disease that requires ongoing care and regular medical follow-up. The development of new therapies and approaches to the management of the disease is critical to improve the prognosis and quality of life of patients with sickle cell anemia.

Scientific research continues to advance the understanding of sickle cell anemia, leading to more practical treatments and improvements in quality of life for those living with the condition. Therapies such as blood transfusion therapy, bone marrow transplantation, and new pharmacological approaches are being developed to manage the symptoms and complications associated with sickle cell anemia, thereby improving the outlook for affected patients.

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