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Review on Hydroxyurea Usage in Young Children with Sickle Cell Disease: Examining Hemoglobin Induction, Potential Benefits, Responses, Safety, and Effectiveness

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Abstract

Sickle cell disease (SCD) is a prevalent condition, particularly in the countries of sub-Saharan Africa, where the presence of specific genes associated with Malaria contributes to its high prevalence. Patients with sickle cell disease frequently experience painful episodes necessitating hospitalization, and their hemoglobin levels are typically lower than those of the general population. There are different treatment options available to manage complications, such as transfusing blood, hydroxyurea, and strong anti-pains. However, with all these treatments, patients still commonly experience pain crises and suffer from organ damage. Hydroxyurea, the sole approved medication for sickle cell anemia in developed and developing countries, is widely used in children despite being primarily indicated for adults. Multiple studies have demonstrated the efficacy of hydroxyurea in inducing HbF production in young children with SCD. Elevated HbF levels have been associated with improved clinical outcomes, including a reduction in vaso-occlusive crises, acute chest syndrome, and the need for blood transfusions. Furthermore, increased HbF levels have been shown to ameliorate disease-related organ damage, such as pulmonary hypertension and sickle cell retinopathy. The response to hydroxyurea treatment in young children with SCD is variable. Some patients achieve substantial increases in HbF levels and experience significant clinical benefits, while others may have a more modest response. Factors influencing the response include baseline HbF levels, genetic modifiers, treatment adherence, and dose optimization. Safety is a crucial consideration when using hydroxyurea in young children. Studies have shown that hydroxyurea is generally well-tolerated, with the most common adverse effects being myelosuppression, gastrointestinal symptoms, and dermatological manifestations. However,

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long-term effects and potential risks, such as renal dysfunction and reproductive impacts, require further investigation. The effectiveness of hydroxyurea in young children with SCD has been demonstrated in various clinical trials and observational studies. These studies have shown a significant reduction in disease-related complications and improved quality of life. However, optimal dosing, treatment duration, and long-term outcomes are still areas of ongoing research. This review focuses on recent studies investigating the benefits, effectiveness, responses, and safety of hydroxyurea in pediatric individuals diagnosed with sickle cell disease.

Keywords

Effectiveness, Hydroxyurea, Sickle Cell Disease, Sickle Cell Anemia, Minimally Effective Dose, Maximum Tolerated Dose

1. Introduction

A widespread and heritable disease, Sickle cell disease (SCD) affects millions of people in the world, with significant impact and healthcare costs in the world. Particularly in European countries, hundreds of thousands of people, primarily of African descent, have Sickle cell disease, and newborn screening identifies approximately 1:375 African-American infants with the disease every year. While the average lifespan of sicklers for publically insured individuals with SCD is 56 years, males' life expectancy at birth is 49.3 years, which is lower than that for females (at birth 55 years), but in well-resourced countries can live up to 70 years as adults. However, underdeveloped countries, particularly in sub-Saharan Africa, experience a high mortality rate of 50% - 80% within the first five years of life. Recognizing the severity of this issue, the WHO declared Sickle cell disease a world health problem in 2006, emphasizing the urgent need for accessible and effective treatment options worldwide [1] [2] [3].

According to the Centers for Disease Control and Prevention (CDC) in the United States, SCD affects approximately 100,000 Americans. The CDC estimates that about 1 in 365 African-American births and 1 in 16,300 Hispanic-American births are affected by SCD [4]. The UK Sickle Cell Society estimates that there are around 12,500 individuals living with SCD in the UK [5]. Nevertheless, SCD is prevalent among individuals of African and Afro-descendant populations in Brazil. Exact prevalence figures for SCD in Brazil may vary as estimates range from 25,000 to 30,000 individuals affected [6].

Sub-Saharan Africa is where the majority of these births take place, and it ranges from 50% to 90% of children having anemia-associated Sickle cell disease, will not survive beyond the age of 5, often without being diagnosed. The presence of the heterozygous mutated sickle gene provides a significant survival advantage against malaria, which is why the frequency of this allele is highest in regions of Africa where malaria is prevalent [7].

Despite the existence of effective treatments to improve clinical outcomes, mortality remains alarmingly high among African children aged 6 months to 5 years, often before a confirmed diagnosis is made in this setting. This is likely due to delayed detection and intervention, which hampers efforts to alleviate the burden of this disease in the pediatric population [8].

The primary approach to treating patients with Sickler patients is generally supportive, hydroxyurea (HU) being the main drug used thus far. HU can modify the progression of the disease and has shown positive effects on clinical outcomes. It achieves this through raising levels of alpha-2 gamma-2 hemoglobin, which in turn reduces the occurrence of sickling events. In adults, HU decreases incidences of hospitalizations, episodes of acute chest syndrome, strokes, as well as painful crises, ultimately leading to improved quality welfare of living [9].

In sickle cell anemia (SCA), fetal hemoglobin (HbF) levels play a protective role. However, it decreases significantly during the first year of life, but finally picks its lowest point at the age of 5. This particular value, commonly known as the "baseline" HbF level for each patient, is potentiated by genetic factors that are not well explained [10].

The primary mechanism by which fetal hemoglobin (HbF) provides protection against sickling is by downregulating the rate of hemoglobin S (HbS) combination inside the red blood cells. HbS concentration is diluted by HbF tetramers inside the cells and does not participate in the process of polymerization. Based on these discoveries, researchers aimed to find remedial substances that could stimulate HbF production. Among various effective compounds, hydroxyurea stood out. Although hydroxyurea is known for its potential toxicity, it has remained the primary focus of efforts to stimulate the production of alpha-2 gamma-2 hemoglobin due to its convenient oral administration and significant laboratory and clinical effects. In the early 1980s, straightforward yet impressive "proof-of-principle" research showcased the great advantages of hydroxyurea treatment for elderly patients having SCA [11].

Larger amounts of the drug in oral pulses of hydroxyurea have been shown to increase the presence of reticulocytes with elevated levels of alpha-2 gamma-2 hemoglobin in the systemic circulation. This leads to a whole rise in the amount of hemoglobin present in the bloodstream and the percentage of HbF, providing strong evidence of hydroxyurea's ability to stimulate HbF production. Extensive research and clinical experience spanning three decades have established hydroxyurea as a great therapeutic agent for inducing alpha-2 gamma-2 hemoglobin in individuals with sickle cell anemia (SCA). It has demonstrated efficacy across all age groups, from infants to adults, and offers additional benefits such as mild suppression of bone marrow function, increased red blood cell size, reduced cellular adhesion, improved blood flow, and the potential to enhance nitric oxide release in affected areas [12].

Hydroxyurea functions by increasing the activity of the γ-globin gene, leading to a redirection of gene expression away from the β-globin gene. This shift re-

sults in higher levels of fetal hemoglobin (HbF: $\alpha 2\gamma 2$) and a reduction in the production of adult hemoglobin (HbA: $\alpha 2\beta 2$). Although hydroxyurea may lead to gastrointestinal side effects such as nausea and loss of appetite, the most notable adverse effect is myelosuppression, which impairs the bone marrow's ability to generate blood cells [13].

2. Molecular Explanation for HbF Gene Expression

The human HBB locus comprises five globin genes that undergo regulation throughout their development of different stages. During utero development, these genes are organized in a sequential manner that corresponds to the order of their expression: HBE1, HBG1, HBG2, HBD, and HBB. These genes are located on chromosome 11. The locus control region (LCR), located upstream of HBE1, plays a pivotal role in gene regulation. It consists of five DNase I hypersensitive sites that are specifically active in erythroid cells. Each LCR element contains enhancer sequences that bind to transcription factors, ensuring proper hemoglobin switching. The LCR plays a vital role in regulating the expression of the HBB locus by directly interacting with the promoters of individual globin genes. Several factors, such as transcription factors, epigenetic remodeling proteins, and DNA looping, contribute to facilitating this interaction [14].

DNA-binding proteins, including GATA1, TAL1, E2A, LMO2, LRF/ZBTB7, and LDB1, work together to boost gene transcription. They help create loops between the locus control region (LCR) and individual globin promoters. This looping is crucial for regulating the transcription of globin genes and ensuring their proper expression [15].

Extensive researches have focused on understanding the molecular mechanisms behind hemoglobin transition from fetal to adult form. These researches have been crucial for developing innovative drugs to treat sickle cell disease (SCD). Tightly regulated interactions between a locus control region and repressive transcription factors play a crucial role in governing the transcription of globin genes. One such factor, BCL11A, binds to the HBG promoters or the HBD/HBB intergenic region. BCL11A has emerged as a promising target for drug interventions that aim to increase HbF production effectively [15].

In 1948, Dr. Janet Watson noted that infants showed a delay in the emergence of clinical symptoms, which was linked to higher levels of HbF during their initial life of living [16].

Further support for the disease-modifying effects of alpha-2 gamma-2 comes from the occurrence of HbS in particular individuals, who also inherited a genetic variant causing the continuous presence of fetal hemoglobin (HbS-HPFH), generally exhibiting minimal symptoms associated with the condition [16]. The occurrence of alpha-2 gamma-2 in sickle red blood cells inhibits the development of deoxy-HbS polymers. Various hereditary persistence of fetal hemoglobin variants results from deletions in binding sites for factors within the HBB locus, reducing HbA production. In the process of globin gene switching, the

HBG promoter undergoes binding by negative transcription factors when mutations are present. However, across diverse populations, an increase in HBG expression in adults is observed due to a particular point mutation occurring in the Xmn1 site. The intergenic region of HBS1L-MYB and BCL11A has been identified through genetic mapping and studies as having quantitative trait loci that have a substantial impact on the regulation of HbF levels [17].

The ideal level of HbF to reduce the severity of clinical disease is a commonly asked question. Historical evidence suggests that HbF levels above 8.6% lead to fewer microvascular crises, episodes of pulmonary crisis with respiratory distress, and improved survival rates. HbF levels exceeding 20% also offer protection against strokes. Recent studies recommend using hydroxyurea in children to achieve an HbF level above 20%. Considering the allocation of HbF within erythrocytes is important for clinical effectiveness. Laboratory studies have shown that HbF can form hybrid hemoglobin molecules that inhibit the polymerization of HbS [17].

3. The Way by Which Hydroxyurea Induces the Production of Fetal Hemoglobin

Hydroxyurea is a potent compound that has anti-cancer and anti-metabolic properties. While the exact mechanism for its stimulation of fetal hemoglobin (HbF) production is not fully understood, however, it's believed that hydroxyurea induces a response known as "stress erythropoiesis," altering the timing of red blood cell differentiation and leads to the release of reticulocytes and erythrocytes having high levels of HbF. Hydroxyurea also interacts with heme-containing proteins, releasing nitric oxide (NO) that activates soluble guanosine monophosphate (sGC) and promotes HbF synthesis. In animal studies, it has been demonstrated that hydroxyurea activates the NO-sGC-cGMP and protein kinase cascades, leading to HBG activation. Hydroxyurea also affects the phosphorylation of specific proteins that participate in the maturation of erythrocytes and the expression of HBG (hemoglobin gamma). Ongoing research suggests that microRNAs, like miR-494, miR-26b, and miR-151-3p, may contribute to the variations in HbF levels observed in SCD patients treated with hydroxyurea. Hydroxyurea can downregulate genes such as BCL11A, KLF1, and MYB while upregulating miR-15a, miR-16-1, and TAL1. Methylation of CpG islands in the HBG2 promoter has also been correlated with HbF levels in individuals with sickle cell disease (SCD). To evaluate hydroxyurea's effectiveness, a hydroxyurea responsiveness index has been proposed, which considers changes in GATA-1, GATA-2, and BCL11A protein levels in cultured sickle cell precursors [18] (**Figure 1**).

Hydroxycarbamide induces fetal hemoglobin (HbF) through multiple mechanisms, impacting the symptoms of Sickle Cell Disease (SCD). Hydroxyurea triggers the generation of nitric oxide (NO), which activates soluble guanylyl cyclase (sGC). This activation sets off a signaling pathway known as cyclic guanosine monophosphate-protein kinase G (cGMP-PKG). As a result, p38 mitogen-activated

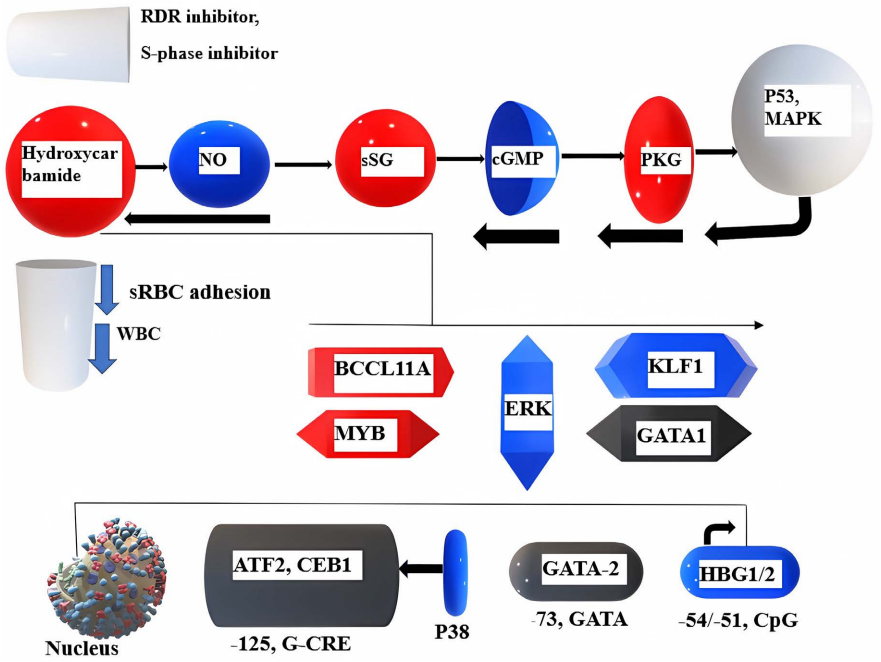

Figure 1. Fetal hemoglobin induction by Hydroxyurea.

protein kinase (MAPK) is phosphorylated, while extracellular signal-regulated kinase (ERK) MAPK is inhibited. The phosphorylated p38 MAPK then enters the nucleus and stimulates ATF2 and CREB1 transcription factors that are involved in the regulation of gene expression. Ultimately, this results in a rise in the expression of HBG2, the gene responsible for fetal hemoglobin production. Additionally, hydroxyurea targets ribonucleoside diphosphate reductase (RDR), affecting both red and white blood cells. Together, these mechanisms contribute to the therapeutic effects of hydroxyurea in sickle cell anemia.

3.1. Increased HbF Production by Hydroxyurea

Hydroxyurea increases HbF production by promoting the transcription of gamma-globin genes. The drug activates the enzyme ribonucleotide reductase, leading to an increase in intracellular levels of deoxyribonucleotide triphosphates (dNTPs). The elevated dNTP levels favor the incorporation of fetal hemoglobin subunits into newly synthesized hemoglobin molecules [19].

3.2. Impact of Hydroxyurea on SCD Pathophysiology

Hydroxyurea reduces the frequency of vaso-occlusive crises, acute chest syndrome, and the need for blood transfusions in SCD. It improves red blood cell hydration, therefore, reducing endothelial activation and adhesion molecule expression, and decreasing the release of pro-inflammatory cytokines. Hydroxyurea also decreases the expression of adhesion molecules on red blood cells, reducing their adherence to the endothelium and preventing vaso-occlusion [20] [21].

3.3. The FDA Has Given Its Approval for the Use of Hydroxyurea as a Treatment for Individuals with Sickle Cell Anemia

Hydroxyurea has been extensively used in clinical practice for over twenty years and has demonstrated its safety and efficacy. Although regular peripheral blood counts and chemistries monitoring are necessary, the side effects of hydroxyurea, such as bone marrow suppression, are mostly reversible. The standard of care for infants between the ages of 6 to 9 months diagnosed with sickle cell anemia (SCA) and adults experiencing severe clinical symptoms of sickle cell disease is highly recommended [22].

3.4. The Treatment Indications for Hydroxyurea

The clinical recommendations regarding the initiation of hydroxyurea therapy are continuously evolving, and there is currently no established consensus guideline. Hydroxyurea has undergone extensive experimental tests including infants, children, and adults, with sickle cell anemia (SCA). These trials consistently show that hydroxyurea is effective in reducing pain, episodes of pulmonary crisis, the requirement for blood infusions, and hospitalizations in individuals with SCA [23].

Clinical trials have confirmed the effectiveness of hydroxyurea therapy, which is considered based on various factors including the intensity and incidences of painful events and episodes of pulmonary crisis. Hydroxyurea is also prescribed for other conditions such as hand-foot syndrome, hemolytic anemia, increased cerebral blood flow velocities, failure to thrive or stunted growth, and repeated hospital stays. Additionally, hydroxyurea may help preserve or reverse organ insufficiency in patients with oxygen deficiency, albuminuria, or stroke. Disease severity markers, such as leukocytosis and reduced percentage of alpha-2 gamma-2, are taken into account. Ongoing researches will provide further insights into the effectiveness of hydroxyurea for different indications. Increasingly, families are requesting hydroxyurea treatment, particularly when one sibling is already receiving it. In these cases, practitioners are required to carefully assess potential advantages for patients who have not yet shown signs of severe symptoms [23].

Hydroxyurea therapy is safe to start at any age, including infants as young as 6 - 9 months old. Younger patients tend to respond better to treatment and are more likely to stick to their medication regimen. It is recommended to consider beginning hydroxyurea therapy early in life, ideally before the age of 5 - 10 years. However, clinical effectiveness has been observed at all ages, as demonstrated by significant reductions in pain, episodes of pulmonary crisis with respiratory distress, blood infusions, and repeated admission stay days even in elderly patients with severe symptoms who started hydroxyurea therapy [24].

3.5. Hydroxyurea Dosage

Hydroxyurea can be taken orally either in the form of capsules or through a liq-

uid formulation that is prepared as needed. The medication is typically administered once a day [25].

In developed countries, the typical starting dose of administration of hydroxyurea in the treatment of sickle cell anemia (SCA) patients is at initial of 20 mg/kg/day in children above 2 years, and it is generally well endured. The dose is gradually increased every two months until reaching the maximum tolerated dose (MTD), which is determined by a mild decrease in bone marrow function that is safe and does not cause severe infections. About 25% of patients may experience lower reticulocyte levels. Most young patients reach their MTD at a dose of 30 mg/kg/day, allowing them to achieve important laboratory thresholds without excessive bone marrow suppression. Most medical practitioners have a preference for a lower dose called the minimally effective dose (MED), which is determined by clinical improvement and overall well-being. However, patients receiving the MED may have lower treatment responses compared to those receiving the MTD [26].

3.6. The Treatment Responses Observed with Hydroxyurea

It is crucial for patients and their families to comprehend that hydroxyurea does not provide immediate results. Usually, it takes approximately 6 months to observe changes in laboratory measurements, including an increase in average red blood cell size and a reduction in absolute neutrophil count (ANC) and reticulocyte index. When the hydroxyurea dosage is increased towards the maximum tolerated dose (MTD), changes can be noticed in the examination of the peripheral blood film. These changes include an occurrence of macrocytosis without the presence of polychromasia, a decrease in half-mooned cells red blood cells, an increase in target cells, and a reduction in residing neutrophils and erythroid cells. It is worth noting that the positive effects on fetal hemoglobin (%HbF) may not be immediately noticeable during early treatment, and the maximum effects are typically observed after 6-12 months of therapy [27].

4. The Previous Researches

Research on hydroxyurea in sickle cell anemia (SCA) has accumulated almost three decades of experience. The initial study in 1984 provided the first evidence of its effectiveness, leading to subsequent infants, children, and adults phase one/two. A major breakthrough came in 1995 with the publication of the third-phase multicenter trial study of hydroxyurea (HU). The results of this trial, which employed an experiment utilizing a double-blind methodology and a placebo group for comparison, definitively validated the effectiveness of hydroxyurea in preventing pain, episodes of pulmonary crisis, blood infusions, and frequent admissions in elderly people diagnosed with SCA.

The National Institutes for Health (NIH) sponsored two clinical research investigating the effectiveness of hydroxyurea, one of which focused on babies diagnosed with sickle cell anemia, called the BABY HUG trial. Participants were

arbitrarily put to receive either hydroxyurea or a dummy treatment for a duration of 24 months. While the main goal of preventing organ dysfunction was not achieved, the secondary outcomes demonstrated encouraging findings. The group receiving hydroxyurea treatment experienced significantly reduced occurrences of agony, dactylitis, instances of pulmonary crisis, blood infusions, and repeated hospital stays in contrast to the placebo group [28].

As part of a research investigation comparing treatment options for young patients with sickle cell anemia, hydroxyurea has emerged as a viable option. The study, known as the Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) study, divided the patients having a history of stroke and hemochromatosis into two groups. One group received standard treatment with transfusions and chelation, while the other group received complementary therapy with hydroxyurea and bloodletting. The objective was to avoid subsequent strokes and improve the management of excessive iron levels. However, the alternative treatment arm was stopped early due to its inability to improve iron overload management compared to the standard treatment. Significantly, there was a notable disparity in the incidence of strokes, with 10% of patients on hydroxyurea experiencing strokes compared to 0% of patients on transfusions at the end of the study [29].

The findings from the SWiTCH trial provided valuable insights into pediatric patients with sickle cell anemia (SCA) who previously experienced stroke. The study revealed that many of these children had severe vasculopathy and clinical fragility. Additionally, the trial highlighted the challenges associated with using the combined primary outcome in a randomized clinical trial conducted across multiple centers.

4.1. Ongoing Researches on Clinical Trials

There are several clinical trials funded by the NIH that are currently underway to explore the effectiveness of hydroxyurea in treating patients with SCA. One of these trials, known as TWiTCH (NCT01425307), is specifically focused on children who currently receive chronic transfusions and have abnormal Transcranial Doppler velocities. These children will be randomly assigned to either continue with transfusions or switch to hydroxyurea treatment. The primary goal of this trial is to assess the alteration in TCD velocity.

Another trial, called SCATE (NCT01531387), is targeting children with conditional TCD velocities. Similar to the TWiTCH trial, these children will also be randomly assigned to either continue with observation or switch to hydroxyurea treatment in order to prevent their TCD velocities from reaching abnormal levels. The SCATE trial is being conducted in the US, Jamaica, and Brazil.

The HUSTLE trial (NCT00305175) seeks to collect data on the pharmacokinetics, pharmacogenetics, as well as lasting impacts of hydroxyurea treatment on organ functionality in children with SCA. Additionally, the ongoing study (NCT00890396) is closely monitoring the BABY HUG cohort to evaluate

the potential benefits and drawbacks of initiating hydroxyurea treatment at an early age, specifically before the age of six months.

4.2. The Follow-Up over an Extended Period of Time

It is crucial to regularly monitor SCA patients who are receiving hydroxyurea therapy for possible long-term toxicities. Fortunately, studies involving extended treatment periods ranging from 15 to 20 years in adults and 10 to 15 years in children have not indicated an elevated risk of stroke, myelodysplasia, or carcinogenicity. When evaluating rare instances of malignancy in hydroxyurea-treated patients, it is of paramount important to take into account the background cancer rate in SCA. This approach helps prevent unnecessary concerns or inaccurate connections [30].

Although concerns have been raised about hydroxyurea's potential negative effects on fertility, particularly in terms of sperm production, there is currently no conclusive evidence to support these claims. Clinical experience suggests that hydroxyurea does not affect fertility in both men and women with SCA. Additionally, while there is a theoretical risk of teratogenicity, no clinical observations have confirmed this concern. Recent findings from an adult cohort study offer reassurance regarding the outcomes of pregnancies in individuals receiving hydroxyurea treatment [31].

While it is crucial to exercise prudence regarding pregnancy or conception during hydroxyurea therapy, the existing data suggest negligible adverse consequences. When it comes to pregnant women with SCA who are undergoing hydroxyurea treatment, it is of utmost importance to thoroughly consider the potential hazards of continuing the therapy versus the risks associated with ceasing an efficacious treatment in a pregnancy that carries a high degree of risk.

Regarding long-term benefits, hydroxyurea therapy has shown promising outcomes. Numerous studies have provided evidence of consistent enhancements for indicators in the laboratory and clinical settings for patients adhering to the treatment, including enhanced growth and development in young individuals. Notably, newly conducted studies over an extended period, conducted in the USA and Greece have shown even better endurance rates among individuals afflicted with sickle cell anemia (SCA) who are administered hydroxyurea as treatment. A positive impact on mortality further reinforces the importance of considering hydroxyurea treatment for all affected patients [32] [33].

4.3. Comparable Therapies for SCD with Hydroxyurea in Children and Adults

Gene therapy and hydroxyurea: Gene therapy aims to correct the genetic mutation responsible for SCD by introducing a functional copy of the gene into the patient's cells. Recent advances in gene therapy, such as lentiviral vectors, have shown promising results in early clinical trials in both children and adults. Gene therapy has the potential to provide a long-term cure for SCD by enabling

the production of healthy red blood cells with normal hemoglobin. However, gene therapy approaches are still in the experimental stage and require further research and refinement. On the other, hydroxyurea has been extensively studied in both children and adults and has been shown to increase fetal hemoglobin (HbF) production, reducing the proportion of sickle hemoglobin (HbS) and improving symptoms in SCD. Hydroxyurea has been shown to reduce vaso-occlusive crises, acute chest syndrome, and the need for blood transfusions [34] [35]. It's important to note that while gene therapy holds promise, it is still in the early stages of development and has not yet been approved as a standard treatment for SCD. Hydroxyurea remains the established and widely used treatment for both children and adults with SCD. Further research and clinical trials are ongoing to evaluate the long-term safety and efficacy of gene therapy in SCD.

Blood transfusion and hydroxyurea: Regular blood transfusions involve the administration of healthy red blood cells with normal hemoglobin to replace the sickled red blood cells in patients with SCD. Transfusions can alleviate symptoms, reduce the risk of stroke, and improve overall well-being in both children and adults with SCD. However, long-term transfusion therapy may lead to complications such as iron overload and alloimmunization [36]. In general, both blood transfusion and hydroxyurea have shown benefits in the treatment of SCD in children and adults. However, blood transfusions provide immediate relief by replacing sickled cells with healthy ones, while hydroxyurea offers a long-term approach by increasing HbF production. The choice of treatment depends on various factors, including the severity of the disease, the patient's age, and individual patient needs.

Bone Marrow Transplant (BMT) and hydroxyurea: BMT, also known as hematopoietic stem cell transplantation, involves replacing a patient's diseased bone marrow with healthy donor cells. BMT provides a potential cure for SCD by restoring the production of healthy red blood cells. It is most effective when performed in younger patients with a matched sibling donor. However, BMT is associated with significant risks, including graft-versus-host disease and transplant-related complications. In a study by Lena *et al.*, found that the overall survival (OS) and disease-free survival (DFS) in the Roma cohort were 84% and 69%, respectively, while OS and DFS were 100% in the Berlin cohort. Immune reconstitution was satisfactory. Although asymptomatic viral reactivation was common, no severe viral infection occurred. These data confirm that TCR-α/β^{+}/CD19^{+} depletion is a well-suited haplo-HSCT (HLA-haploidentical hematopoietic stem cell transplantation)strategy for children with hemoglobinopathies [37]. While BMT offers the potential for a cure, it is associated with significant risks and challenges, including the need for a suitable donor. Hydroxyurea, on the other hand, provides symptom relief and has a well-established safety profile. The choice between BMT and hydroxyurea depends on factors such as the severity of the disease, availability of a suitable donor, and patient-specific considerations.

Erythropoietin (EPO) and hydroxyurea: Erythropoietin is a hormone that stimulates the production of red blood cells in the bone marrow. In SCD, EPO has been used to increase red blood cell production and improve anemia. However, the use of EPO in SCD is limited and controversial, as it may increase the risk of vaso-occlusive events and thrombosis [38]. In a study by John N *et al.*, it was found that α-thalassemia not only increases hemoglobin in patients with HbSS but also reduces erythropoietin values, demonstrating a measurable response to improved tissue oxygenation. Furthermore, α-thalassemia had a reduced annualized transfusion burden in both HbSS and HbSC, but α-thalassemia had no impact on annualized admission rates in either group [39]. In a nutshell, hydroxyurea is the preferred treatment for SCD due to its well-established efficacy and safety profile. Although Erythropoietin, on the other hand, has limited evidence and potential risks, however, in certain cases where anemia is severe and hydroxyurea is contraindicated or ineffective, erythropoietin may be considered under close medical supervision.

4.4. Other Emerging Strategies for SCD

CRISPR/Cas9 Genome Editing: CRISPR/Cas9 is a gene-editing technology that allows precise modification of the DNA sequence. Researchers are exploring the potential of CRISPR/Cas9 to correct the genetic mutation responsible for SCD. Preclinical studies have demonstrated successful correction of the sickle cell mutation in stem cells [40].

Small Molecules and Targeted Therapies: Various small molecules and targeted therapies are being investigated to interfere with specific pathways involved in SCD pathophysiology. These therapies aim to reduce inflammation, oxidative stress, and adhesion of sickle red blood cells. Some examples include Nrf2 activators, anti-inflammatory agents, and adhesion molecule inhibitors [41].

These emerging therapies hold promise for the future treatment of SCD. However, it's important to note that further research and clinical trials are needed to establish their safety, efficacy, and long-term effects.

4.5. Potential Long-Term Side Effects of Hydroxyurea Use in Children with Sickle Cell Disease (SCD)

Hematologic Effects: Hydroxyurea can cause bone marrow suppression, leading to decreased production of red blood cells, white blood cells, and platelets. Prolonged use of hydroxyurea may increase the risk of developing myelosuppression and hematologic malignancies [42].

Reproductive Effects: Hydroxyurea may have reproductive effects in both males and females. In males, it can cause reduced sperm count and motility, leading to infertility. In females, it may disrupt the menstrual cycle and affect fertility [43].

Renal Effects: Some studies have suggested a potential association between long-term hydroxyurea use and renal dysfunction. Hydroxyurea may cause kid-

ney damage and impaired renal function, although the exact mechanism is not fully understood [44].

It is important to note that while these potential long-term side effects have been reported in some studies, the overall benefits of hydroxyurea in reducing SCD-related complications often outweigh the risks. Regular monitoring and close follow-up with healthcare providers are essential to manage and mitigate any potential side effects.

5. Situation in the Developing Countries

Although there is substantial evidence that supports the advantages of the administration of hydroxyurea to pediatric patients suffering from sickle cell anemia (SCA), there is insufficient information pertaining to its utilization in underdeveloped nations where SCD is a significant issue. Considering that there are over 300,000 annual cases of sickle cell disease worldwide, it is crucial to prioritize the provision of the only treatment that can modify the disease. Nonetheless, the safety and practicability of employing hydroxyurea as a form of treatment alongside co-existing conditions like malnutrition, vitamin deficiencies, and infections such as malaria and helminthiasis have not been thoroughly evaluated. While the idea of utilizing hydroxyurea, especially in Africa, may seem appealing, it is necessary to conduct a comprehensive evaluation of the potential risks and benefits, preferably through prospective studies like the proposed pilot trial known as Unleashing Cross-Continental Effectiveness through Hydroxyurea (UCCEH), to obtain a comprehensive understanding. As African nations implement programs that screen newborns for SCA, the wide-ranging implementation of hydroxyurea has the potential to serve as an effective therapeutic option in resource-limited settings, helping to alleviate the impact of the disease [45].

6. Knowledge Gaps That Still Exist

Further investigation is needed to fill important knowledge gaps in several areas. One area of interest is the variation in how individuals respond to hydroxyurea treatment, which is influenced by differences in their phenotypes. Moreover, patients' tolerance to different doses of hydroxyurea varies as much as their response in terms of HbF levels. Recent research indicates that this variability may be attributed to differences in pharmacokinetics and pharmacogenetics [46].

Compared to our knowledge of hydroxyurea's effectiveness in individuals suffering from sickle cell anemia (SCA), our understanding of its use in individuals with HbSC and HbS/β^{+}-thalassemia is insufficient. Existing data for these patient populations is mostly anecdotal or based on small series, and it is not appropriate to extrapolate findings from SCA patients. To address this gap, there is an urgent need for prospective studies specifically focused on HbSC patients, as hydroxyurea is increasingly being prescribed to them. While the benefits of HbF for HbSC patients are not well-established, there are potential therapeutic ad-

vantages such as reduced white blood cell count and decreased cellular adhesion. In clinical trials involving HbSC patients, measuring blood viscosity may be valuable due to the common increase in hemoglobin concentration caused by hydroxyurea, which could have potentially negative effects [46]. Another critical knowledge gap is understanding the factors that contribute to the decline of HbF with age, as this area of research holds promise for identifying preventive agents.

7. Conclusion

At present, hydroxyurea stands as the sole approved treatment for altering the progression of SCD. Its safety and effectiveness have been demonstrated in children with SCA, irrespective of whether they reside in developed or developing nations. Hydroxyurea use has resulted in significant improvements in outcomes and safety for both adults and children, offering hope for enhancing the survival of SCD patients. However, it is important to recognize the global impact of this condition and the inadequate management often seen in countries with a high prevalence of SCD. Therefore, fostering scientific collaboration and research efforts between countries is crucial for future advancements in this field. The safety and effectiveness of hydroxyurea are consistently supported by reliable long-term data, establishing it as a cost-effective treatment option that should be taken into consideration for the majority of SCA patients. Ongoing and upcoming research will further contribute to understanding its role in preserving organ function and comprehending the variability in how SCD patients respond to hydroxyurea.

Author Contributions

Concept or design: Mkwambe Maiko Charles; Drafting of the article: Mkwambe Maiko Charles and Youping Deng; Critical revision with cornerstone intellectual content: Youping Deng and Zhao Dongchi.

Conflicts of Interest

The authors declare no conflict of interest.

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Abbreviations

SCD—Sickle Cell Disease
SCA—Sickle Cell Anemia
MED—Minimally Effective Dose
MTD—Maximally Tolerated Dose
HbF—Fetal Hemoglobin
WHO—World Health Organization
sGC—Soluble Guanosine Monophosphate
HBG—Hemoglobin Gamma
TCD—Transcranial Doppler
LDH—Lactate Dehydrogenase
ANC—Absolute Neutrophil Count
LCR—Locus Control Region
HU—Hydroxyurea
HbS—Hemoglobin S
NO—Nitric Oxide
HBB—Hemoglobin Subunit beta
CDC—Centers for Disease Control and Prevention
dNTPs—Deoxyribonucleotide Triphosphates
Nrf2—Nuclear Factor Erythroid 2-Related Factor 2