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Hydroxyurea for sickle cell anemia: What have we learned and what questions still remain?

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Abstract

Purpose of review—Sickle cell anemia (SCA) is a well-characterized severe hematological disorder with substantial morbidity and early mortality. Hydroxyurea is a potent inducer of fetal hemoglobin, and evidence over the past 25 years has documented its laboratory and clinical efficacy for both adults and children with SCA.

Recent findings—The Phase III study of hydroxyurea in infants (BABY HUG) has just been completed and preliminary results indicate equivocal benefits for organ protection during the two-year treatment period, but significant benefits for pain, acute chest syndrome, hospitalizations, and transfusions. Three new reports document the benefits of hydroxyurea on reducing mortality in SCA: two adult trials (LaSHS and MSH) and one pediatric study (Brazilian cohort). Recent results from the HUSTLE protocol suggest minimal genotoxicity or carcinogenicity with long-term hydroxyurea exposure.

Summary—The potential utility of hydroxyurea for all patients with SCA is clear and indisputable. With decades of accumulated evidence and documented efficacy with an acceptable long-term safety profile, it is time to consider hydroxyurea treatment the standard of care for all young patients with SCA. Exporting our knowledge and experience with hydroxyurea to developing nations with large medical burdens from SCA can help relieve global suffering from this condition.

Keywords

hydroxyurea; sickle cell anemia; mortality; global health

Introduction

Sickle cell disease refers to a group of closely related inherited anemias characterized by the predominance of sickle hemoglobin (HbS) within circulating erythrocytes, which causes erythrocyte shape changes with subsequent hemolytic anemia and vascular occlusion. In most cases, the patient inherits the abnormal HbS allele from both parents and has homozygous HbSS, a condition usually referred to as sickle cell anemia (SCA), but compound heterozygous conditions such as HbSC and HbS/β-thalassemia also contribute to the clinical spectrum of sickle cell disease. The molecular basis for erythrocyte sickling is clear: a single nucleotide substitution in codon 6 of the β-globin gene leads to an amino acid

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substitution (Glu→Val) that is responsible for the sickle mutation in beta globin (β^S), which forms the abnormal HbS tetramer. Upon deoxygenation, HbS undergoes rapid intracellular polymerization with subsequent cellular dehydration, altering the shape of the erythrocyte membrane into a sickled form, and adversely affecting the usual physiologic deformability of erythrocytes that allows them to traverse the circulation freely. These rigid and deformed sickle erythrocytes have a shortened lifespan and undergo both intravascular and extravascular hemolysis; vaso-occlusion and abnormal erythrocyte-endothelial interactions lead to acute tissue hypoxia and chronic organ damage. Clinical manifestations of SCA include acute vaso-occlusive events, chronic hemolytic anemia, and organ dysfunction due to repeated sickling episodes.

SCA is among the world's most common inherited hemolytic anemias, affecting an estimated 50,000–70,000 persons in the United States and likely millions more worldwide [1**, 2]. Despite the well-described genetics and pathophysiology of SCA, clinical care for affected individuals has been mostly supportive, typically including red blood cell transfusions, intravenous hydration, analgesics and antibiotics. Increased fetal hemoglobin has been associated with a less severe phenotype [3, 4], which has spurred interest in the identification of pharmacologic agents capable of inducing HbF expression. Hydroxyurea was identified as a potent HbF inducer and was subsequently found to be both a feasible and effective treatment option for SCA [5]. In this review, we describe recent advances in the utility of hydroxyurea for children and adults with SCA, highlighting new information about its expanding indications, providing additional safety data, and recommending its broader use in developing nations.

Hydroxyurea Overview

Hydroxyurea is a cytotoxic, antimetabolic, and antineoplastic agent used for several decades to treat a variety of medical disorders, most notably myeloproliferative neoplasms [6, 7], chronic myelogenous leukemia [8], and HIV [9]. The efficacy of hydroxyurea for these varied medical conditions is due to its mechanism of action as a potent inhibitor of ribonucleotide reductase, a ubiquitous intracellular enzyme that converts ribonucleotides to deoxyribonucleotides, which are required for DNA synthesis and repair [10]. The first clinical application of hydroxyurea for patients with SCA was reported in 1984, when Platt and colleagues demonstrated a rapid and dramatic increase in HbF-containing reticulocytes without significant bone marrow toxicity [5]. These and other 'proof of principle' experiments led to a critical phase I/II study of adults with SCA treated with hydroxyurea at maximum tolerated dose (MTD), which demonstrated significant dose-dependent increases in Hb and HbF along with concurrent reduction in total WBC, neutrophils, and reticulocytes [11]. Similar results were observed in Phase I/II studies involving school-age children [12], toddlers [13, 14], and infants [15**], all documenting the safety, laboratory benefits, and clinical efficacy of hydroxyurea for young patients with SCA.

Although these salutary laboratory effects have been demonstrated repeatedly over the past 25 years, the mechanisms by which hydroxyurea induces HbF production have not been fully elucidated. Several mechanisms have been proposed, most notably the cytotoxic effects of hydroxyurea resulting in 'stress erythropoiesis' with increased HbF levels [16]. More complex effects involving the production of nitric oxide and the soluble guanylyl cyclase and cGMP-dependent protein kinase pathway, are also thought to play a role in induced expression of the γ -globin gene [17–19]. The benefits of hydroxyurea do not appear to be limited solely to the increase in HbF levels, however, since improved erythrocyte morphology and deformability, lowering of circulating leukocyte and reticulocyte counts, reduction in hemolysis, and potentially local release of nitric oxide also appear to contribute

to improved clinical outcomes. Figure 1 illustrates some of the multiple mechanisms by which hydroxyurea may provide therapeutic benefits for individuals with SCA [20**].

Clinical Efficacy

Since the initial pilot and Phase I/II studies, the clinical and laboratory benefits of hydroxyurea for patients with SCA have been repeatedly and consistently demonstrated. The hematological effects of hydroxyurea therapy are important for obtaining clinical benefits, but also are the parameters used for dose escalation to MTD. Laboratory effects include a predictable rise in the hemoglobin concentration, %HbF, and mean corpuscular volume along with a concurrent decrease in absolute reticulocyte count, total leukocyte count, and absolute neutrophil count. These laboratory values, in addition to examination of the peripheral blood smear for erythrocyte morphology, are used to escalate patients to MTD, and also can be used to monitor medication adherence [21*]. These laboratory effects have been demonstrated to be consistent and sustainable in both adults and children with SCA [22, 23] with similar effects regardless of age (Table I) [11–13, 23–25].

The clinical efficacy of hydroxyurea therapy for patients with SCA was most notably demonstrated in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), an NHLBI-funded phase III double-blinded, placebo-controlled randomized trial of 299 adults with severe SCA, which was halted early due to highly significant reductions in the time to first painful vaso-occlusive event. Subjects randomized to the hydroxyurea treatment arm also showed a significant reduction in incidence of painful events, acute chest syndrome, hospitalizations, and number of blood transfusions [26]. The Food and Drug Administration (FDA) approved the use of hydroxyurea in severely affected adults with SCA in 1998, and the NHLBI formally recommended the use of hydroxyurea in select patients with SCA in 2002. More recently the National Institutes of Health Office of Medical Applications of Research (OMAR) and the Agency for Healthcare Research and Quality (AHRQ), after a comprehensive review of the evidence, concluded that hydroxyurea is efficacious in both children and adults with SCA due to its predictable induction of HbF production and subsequent reduction in pain crises and hospitalizations [27–29].

Last year witnessed the culmination of a decade-long Phase III clinical trial involving infants with SCA randomized either to hydroxyurea (fixed dose 20 mg/kg/day) or placebo. Sponsored by NHLBI and NICHD, BABY HUG (ClinicalTrials.gov NCT00006400) was a phase III double blinded, placebo-controlled randomized clinical trial that tested the hypothesis that hydroxyurea therapy in very young children (age 9–17 months at study entry) with SCA could delay or prevent chronic organ damage. The primary endpoints included splenic function (qualitative liver-spleen scan) and renal function (glomerular filtration rate), along with a variety of secondary endpoints related to acute vaso-occlusive events and additional functional measures of the kidneys, spleen, lungs, and brain [30*]. BABY HUG demonstrated that hydroxyurea has equivocal benefits for prevention of organ damage in a two-year treatment timeframe, but clear clinical efficacy for vaso-occlusive events similar to its effects in older patients. Specifically, hydroxyurea treatment was associated with a significant decrease in pain, acute chest syndrome, hospitalizations, and transfusions compared to placebo treatment [15**]. With these findings of laboratory and clinical efficacy, it is likely that hydroxyurea use will increase broadly since prior clinical severity was not an eligibility criterion in BABY HUG. Indeed, with an ongoing safety profile that indicates no apparent increased risk of genotoxicity (see below), hydroxyurea treatment may soon become standard of care for young patients with SCA.

Prevention of organ damage

The efficacy of hydroxyurea for the alleviation, prevention, or even reversal of chronic organ damage and effects on long-term mortality in individuals with SCA, particularly children initiating therapy at a very young age, has yet to be proven. However, several non-randomized cohorts of children have recently reported benefits of hydroxyurea treatment on chronic organ damage, which remains the most common cause of death among adults with SCD [31, 32]. Documentation of preserved splenic filtrative function [33], prevention of new silent cerebral infarction [33], lowering of TCD velocities [34], and prevention of glomerular hyperfiltration [13] in children receiving hydroxyurea provides evidence that hydroxyurea may help prevent organ dysfunction and subsequent morbidity and mortality.

BABY HUG focused on prevention of organ damage in very young patients with SCA; loss of splenic function in SCA has been identified as early as 4–6 months of age and by 5 years of age, 94% of children with SCA are functionally asplenic [35, 36]. Similarly, hyposthenuria and elevated glomerular filtration rate begins at a young age in SCA [37, 38] and have been identified as early indicators of renal dysfunction [39, 40]. Initial results from BABY HUG indicate that hydroxyurea treatment failed to achieve the primary objectives but did demonstrate laboratory and clinical efficacy, along with evidence of organ protection using secondary objectives [15^{**}]. The lack of clear demonstration of the protective effects of hydroxyurea on chronic organ damage could be the result of study design (e.g., low-dose treatment without escalation to MTD, 24-month treatment period) or events that occurred during the study such as a 3-month FDA-mandated clinical hold. The associated difficulties in effectively quantifying organ dysfunction in very young children with SCA by routine laboratory or imaging modalities are also relevant [30^{*}]. It will be critical to continue to follow these children carefully in planned prospective follow-up trials, particularly as they reach adolescence when more significant organ damage becomes clinically manifest, in order to more accurately evaluate the effects of hydroxyurea on preservation of organ function.

Reduction in mortality

Long-term results up to 17.5 years from the aforementioned MSH study have recently been reported, demonstrating sustained clinical and laboratory efficacy of hydroxyurea for adults with SCA [41^{**}]. After early study closure due to the profound clinical efficacy of hydroxyurea, MSH patients have been followed to evaluate the long-term risks and benefits of hydroxyurea therapy. During this follow-up period, hydroxyurea use was based upon patient and clinician discretion; many patients initially randomized to placebo were started on hydroxyurea therapy and a few initially randomized to the treatment arm discontinued hydroxyurea. Overall, 43.1% of the original MSH cohort had died as of this 17.5-year follow-up report, but mortality was significantly reduced in individuals with long-term hydroxyurea exposure.

The Laikon Study of Hydroxyurea in Sickle Cell Syndromes (LaSHS) in Greece also recently reported the long-term results of a 17-year open-label trial evaluating the safety and efficacy of hydroxyurea in sickle cell disease [25^{**}]. A large cohort of 330 adult patients (34 Hb SS, 131 HbS/ β^0 thalassemia, 165 HbS/ β^+ thalassemia) was followed, including 131 identified as hydroxyurea candidates based on clinical severity. Hydroxyurea-treated patients had consistent and significant laboratory effects including increase in HbF levels (median 5-fold increase), and significant reductions in leukocyte, platelet and neutrophil counts and serum LDH and bilirubin levels. Clinically, patients taking hydroxyurea had a dramatic and significant reduction in the frequency of pain crises, transfusion requirements, hospital admissions and the incidence of acute chest syndrome. Most importantly, the

incidence of stroke, death from liver dysfunction, and overall mortality were also significantly decreased in the hydroxyurea group. Overall survival was 86% for the hydroxyurea-treated group, despite their increased clinical severity, compared to 65% for the conventionally treated group. This reduction in mortality was most notable among patients with HbS/ β^0 thalassemia or HbSS (Figure 2). The study reconfirmed that HbF is an independent predictor of survival for patients with sickle cell disease, regardless of hydroxyurea exposure.

A recent abstract reported a retrospective comparison of clinical and survival outcomes among Brazilian children (age 3–18 years) with sickle cell disease, with and without hydroxyurea exposure over a 10-year period. A total of 224 children (205 HbSS or HbS/ β^0 thalassemia, 7 HbSC, 3 HbSD, and 9 HbS/ β^+ thalassemia) met local consensus clinical criteria to initiate hydroxyurea therapy based on clinical severity and were escalated to MTD. The comparison group included the remaining 1419 children who did not meet criteria to initiate hydroxyurea therapy. Children receiving hydroxyurea therapy demonstrated a significant reduction in the number of hospitalizations, emergency room visits and transfusions compared to untreated children. The most notable finding in this report, however, was the dramatic and statistically significant reduction in mortality of hydroxyurea-treated children compared to untreated patients. There were 46 total deaths in the Brazilian cohort, but only 2 among those treated with hydroxyurea. Despite pre-selection of the more severely affected children for hydroxyurea treatment, untreated children had a 4.6-fold increased risk of mortality than did hydroxyurea-treated children [42*].

Safety

In addition to its proven laboratory and clinical efficacy, hydroxyurea is a well-tolerated medication with few significant short-term toxicities [21*]. Occasional gastrointestinal discomfort can be overcome by modifying daily dosing to evening administration, while nail and skin hyperpigmentation does not cause more than cosmetic concerns. Specifically, skin ulceration that has occurred rarely in persons with myeloproliferative neoplasms taking hydroxyurea [43] has never been reported in SCA. Other expected short-term toxicities, which also contribute to its clinical benefits, include transient and reversible myelosuppression, particularly mild neutropenia and reticulocytopenia. Thus, complete blood counts should be monitored closely, ideally at monthly intervals, particularly when initiating hydroxyurea therapy and escalating to MTD [12, 23]. Investigations of the potential long-term toxicities of hydroxyurea are still ongoing, but with clinical experience approaching thirty years, there have yet to be any significant long-term toxicities associated with hydroxyurea therapy for SCA. However, given its primary mechanism of action as a potent inhibitor of ribonucleotide reductase and in vitro reports of hydroxyurea as a clastogen [44], mutagen [45], teratogen [46] and carcinogen [47], the long-term safety profile of hydroxyurea treatment in SCA remains an ongoing concern.

Long-term Safety in Adults

The recent reports of long-term hydroxyurea exposure in adults with SCA provide further clinical evidence in support of its safety profile. The LaSHS study with 17-year follow-up demonstrated that hydroxyurea was well tolerated with mild, transient and reversible cytopenias as the only reported toxicities. Importantly, there were no reported cases of myelodysplasia or leukemia in the hydroxyurea-treated patients [25**]. Long-term results from the MSH study with similar long-term follow-up also did not identify any long-term toxicities of hydroxyurea for adults with severe SCA, specifically no increase in cancer or stroke [41**].

Long-term Safety in Children

The long-term safety profile of hydroxyurea for children with SCA is less well-characterized, but results to date are similar to that for adults [26, 48]. With expanding use of hydroxyurea in very young children with SCA, it will be important to monitor the long-term safety profile of hydroxyurea in the pediatric population, where hydroxyurea could potentially be started at a very young age and continued indefinitely. A large open-label study demonstrated a modest toxicity profile and overall short-term safety of hydroxyurea at MTD in 122 children with SCA. Mild, transient and reversible cytopenias were the only consistently observed toxicities and there were no adverse effects on growth, development, or number of acquired DNA mutations [23].

The Hydroxyurea Study of Long Term Effects (HUSTLE, ClinicalTrials.gov NCT00305175) is a prospective observational study of children with SCA treated with hydroxyurea based on clinical severity, which attempts to evaluate the long-term cellular and molecular effects of hydroxyurea. The study consists of two patient groups. The first group (Old Cohort) includes patients previously receiving hydroxyurea therapy prior to enrollment on study; studies are completed at three-year treatment anniversaries. The second group (New Cohort) includes patients not on hydroxyurea prior to study entry, therefore allowing studies at baseline and at treatment anniversaries. Initial results on genotoxicity for both patient cohorts within the HUSTLE study have recently been analyzed. First, Flanagan *et al.* reported that children with SCA have a significantly higher number of circulating micronuclei-containing erythrocytes after hydroxyurea exposure; however, this change was observed within the first 3 months of therapy and did not accumulate over time with up to 12 years of exposure [49*]. A second report investigated the potential genotoxicity of in vivo hydroxyurea exposure by examining chromosomes directly for breakage abnormalities, including in vitro experiments designed to measure DNA repair capacity by directly examining chromosomes for abnormalities after damage induced by ionizing radiation. This report did not identify evidence of cumulative chromosomal damage in the hydroxyurea-exposed group with up to 12 years of treatment exposure [50*]. Finally, extended follow-up from a small teenage cohort from HUSOFT (with 14-years of treatment since infancy) indicated good health, normal growth and development, and no evidence of myelodysplasia or malignancy [51*]. Extended follow-up of the HUSTLE patient cohorts will provide additional critical data regarding the long-term safety profile of hydroxyurea treatment for young patients with SCA.

Global Opportunities

Although the clinical experience documenting the consistent efficacy and safety of hydroxyurea for SCA is approaching 30 years, the use of hydroxyurea has yet to extend into countries that are not medically or economically advanced, where the need is undoubtedly the greatest. In the United States and Europe, both of which include only about 1% of the global burden [52*], SCA is a medical condition with a tremendous impact upon both the quality and length of affected lives. Due to early identification with newborn screening, aggressive early intervention with pneumococcal immunizations and prophylactic penicillin, and now with availability of hydroxyurea therapy, the morbidity and mortality associated with SCA have dramatically improved with survival from childhood currently exceeding 95% [53]. This is not the case in the global setting, where the demand for impactful intervention for individuals with SCA is long overdue [1**].

The World Health Organization (WHO) has estimated that 220,000 babies are born each year with sickle cell disease in Africa, most of whom die before the age of 5 years of age, representing as much as 16% of under-five mortality [1**]. This global disparity in outcomes

for individuals with SCA is unacceptable and demands a partnership between the medically and economically equipped countries and the developing countries in need as discussed by Weatherall [54]. Research partnerships between economically rich and poor countries, particularly for a disease so clinically diverse as sickle cell, could serve to advance scientific understanding as well as advance clinical care and outcomes in countries where the burden is so high. These partnerships should include a wide array of interventions, starting with newborn screening programs, as currently the true impact of SCA in Africa is unknown. After identification of affected infants and means for follow-up care are established, further interventions could be initiated, including pneumococcal immunizations and prophylactic penicillin.

Hydroxyurea, as a once daily oral medication with a well-established short-term safety profile, is an intriguing and potentially ideal option for affected patients in the developing world, since both access and safety of other potential therapeutic options such as blood transfusions or hematopoietic stem cell transplantation, are not a realistic option. The potential impact of hydroxyurea therapy on health outcomes for children with SCA in developing countries, where virtually all children with SCA die before the age of 5 years, is tremendous. The limited medical capacities of these countries, coupled with the significant infectious and nutritional comorbidities of these populations, will undoubtedly present substantial challenges for initiation and maintenance of hydroxyurea therapy, but with a carefully planned approach and local medical personnel willing to be trained and involved in the care of these children, the time for these North-South partnerships has to be now.

Conclusions

Hydroxyurea has proven laboratory and clinical efficacy for both adults and children, and even toddlers and infants, with SCA. Preliminary results are promising that in addition to the well-documented clinical effects of hydroxyurea on reducing painful events and hospitalizations, hydroxyurea also reduces mortality and may have benefits for preventing chronic organ damage associated with SCA. We have a tremendous amount of experience with the pharmacodynamics, pharmacokinetics and are beginning to understand the pharmacogenetics of hydroxyurea therapy. Despite this wealth of experience and success with hydroxyurea as a disease-modifying agent, only a small fraction of individuals with SCA in developed countries and virtually no patients in developing countries, currently receive hydroxyurea therapy.

In our opinion, hydroxyurea should now be considered for every patient with SCA, regardless of symptoms, since we know that all patients with SCA experience sickle-related vaso-occlusion and subsequent organ damage starting at a very early age. Ideally the time to intervene is early in life, just as fetal hemoglobin production declines in the first year. We also believe that the opportunities to offer hydroxyurea therapy as an affordable and effective agent for SCA in developing countries must be explored at this time. The extension of hydroxyurea to a broader population, particularly if offered in a setting with some research capabilities, will provide us with a better understanding of the effectiveness of this treatment for a disease with immense global burden.

Key points

- Hydroxyurea reduces the morbidity and mortality of both adults and children with sickle cell anemia
- Hydroxyurea is well tolerated in adults and children with SCA without significant short-term toxicities or long-term safety concerns

- With a large body of evidence demonstrating its safety and marked efficacy for SCA, hydroxyurea should now be considered as a disease-modifying therapy for all patients with SCA, regardless of age or clinical severity
- The extension of hydroxyurea treatment into economically and resource-poor countries could provide substantial benefits to the global sickle cell population

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Fig 1. Mechanisms of action involved in the beneficial effects of hydroxyurea for sickle cell anemia (20)

Legend: (1) Induction of fetal hemoglobin in erythroid compartment; (2) Marrow cytotoxicity and decreased neutrophil and reticulocyte counts; (3) Altered expression of adhesion molecules on circulating neutrophils and reticulocytes decreases adhesiveness and subsequent endothelial damage; (4) Macrocytosis and increased hydration reduces hemolysis and intracellular sickling; (5) Local release of nitric oxide (NO) results in vasodilation.

Source: Reference 20

Fig 2. Hydroxyurea improves survival across SCD phenotypes (40)

Legend: (A) Patients with HbS/ β^0 thalassemia and hydroxyurea exposure had improved 10-year overall survival (OS) compared to patients without hydroxyurea exposure (87% vs. 54%, $p=0.001$); (B) HbSS patients receiving hydroxyurea had a 10-year OS of 100% compared to 10% in those without hydroxyurea exposure ($p<0.01$).

Source: Reference 25

Table 1

Laboratory effects of hydroxyurea in adults and children with SCA

Reference	Thornburg <i>et al.13</i>	Ferster <i>et al.24</i>	Kinney <i>et al.12</i>	Zimmerman <i>et al.23</i>	Charache <i>et al.11</i>	Voskaridou <i>et al.25</i>
Age, years	3.9	8.0	9.8	10.3	27.6	33.0
Dose, mg/kg/day	28.0	~20	25.6	25.9	21.3	~20
Hemoglobin, g/dL	9.5	8.5	9.0	9.5	9.7	9.5
MCV, fL	99	96	99	107	117	97
HbF, %	25.9	15.3	15.5	19.7	15.0	17.4
WBC, x10 ⁹ /L	NA	8.9	9.2	7.2	8.4	8.0
ANC, x10 ⁹ /L	3.0	NA	4.6	3.6	4.6	4.0
ARC, x10 ⁶ /L	166	NA	215	193	243	NA
Bilirubin, mg/dL	1.3	NA	2.8	2.1	1.9	1.4

Legend: A number of studies have demonstrated similar laboratory effects of hydroxyurea for patients with SCA of all ages. These effects are greatest when hydroxyurea is escalated to maximum tolerated dose (MTD). NA = not available.

Source: Original table. See embedded references.