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Hydroxyurea Use in Sickle Cell Disease: The Battle with Low Rates of Prescription, Poor Patient Compliance, and Fears of Toxicities and Side Effects

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Background of Sickle Cell Disease

Sickle Cell Disease (SCD) is the most common inherited blood disorder in the United States, affecting about 89,000 Americans or 1 in 400 African Americans.[1] SCD is caused by inheritance of the sickle beta globin gene, either in homozygous form (HbSS) or in combination with hemoglobin C (HbSC), β-thalassemia (HbSβ-thal) or several less common hemoglobin genotypes.[2] This disorder of hemoglobin structure manifests as a chronic debilitating disease characterized by chronic and episodic pain, hemolytic anemia, severe infections, stroke, and pulmonary complications beginning in infancy and lasting throughout life.[2]

Pain in SCD Causes Significant Morbidity

Pain is the hallmark of SCD and is the leading cause of emergency department visits and hospitalizations for patients with SCD.[2] Painful events result in over 80,000 hospitalizations per year with an average hospital length of stay of 5.4 days and an additional 80,000 emergency department visits per year that do not result in hospitalization.[3,4] It has been estimated that 5.2% of patients with 3–10 pain events per year make up 33% of all hospitalizations. A patient's pain rate correlates with early death in those greater than 20 years of age.[5,6] Home pain diary studies reveal painful episodes occurring at home are strikingly underreported and impair both school and work attendance.[7–11] The frequency of painful episodes increases as patients mature into adulthood and in adults, pain may occur daily and has clinical features of a chronic pain syndrome.[7,12] Thus, SCD pain includes elements of both acute and chronic pain. Given this morbidity and mortality risk, preventing painful events in patients with SCD should result in improved outcomes.

Current Treatments Available for Vaso-occlusive Painful Events in SCD

Currently, there are only three commonly used treatments to prevent vaso-occlusive painful events in patients with SCD. These include hematopoietic stem cell transplantation (HSCT), chronic blood transfusions, and hydroxyurea. HSCT is curative, however is limited by the need for an HLA matched sibling donor which is often a challenge in patients with SCD.[13] There are currently little data on unrelated HSCT for SCD, however a clinical trial is currently being conducted evaluating the role of unrelated donor transplantation.[14] Chronic blood transfusions are effective; however, for maximum benefit they are required

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indefinitely which leads to iron overload, potential infection, and risk of the development of antibodies to red blood cells. Hydroxyurea, an oral medication taken once daily that induces fetal hemoglobin production, has been shown to decrease the frequency and occurrence of vaso-occlusive painful events in SCD, prolong life, and is proven to be safe.[15,16] The role of other fetal hemoglobin inducing agents such as decitabine (5-azacytidine) are currently being evaluated for patients with SCD.[17] Due to the lack of alternative treatments, hydroxyurea appears to be an ideal drug for patients with SCD based on its ease of administration and its low side effect profile.

What is the Efficacy/Role of Hydroxyurea in SCD?

The efficacy of hydroxyurea was first documented in adults in 1995 through the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH).[16] The MSH reported a significant reduction in the median annual rate of painful events, decreased episodes of acute chest syndrome, and decreased transfusions.[16] The MSH subsequently led to the FDA approval of hydroxyurea for adults with SCD with "recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months)".[18] The 9 year follow-up to the MSH revealed hydroxyurea was associated with a significant reduction in mortality, minimal side effects, and was safe.[15] In addition, the initial concern for increased malignancy in those taking the drug was not validated.[15] A large randomized controlled trial mimicking the MSH in children was not conducted. However, efficacy studies in children include a randomized, placebo controlled, cross-over trial with a small number of children and open-label, single-arm studies.[19–21] These studies demonstrated a significant decrease in vaso-occlusive painful events in the hydroxyurea arm confirming the findings of the MSH in children and led to the introduction of the drug into pediatric practice for the prevention of vaso-occlusive painful episodes.[19–21] Subsequent studies have proven safety and hematologic efficacy in children.[22–25] Ongoing studies such as Hydroxyurea to Prevent Organ Damage in Children with Sickle Cell Anemia[26], Long Term Effects of Hydroxyurea Therapy in Children with SCD[27], Stroke with Transfusions Changing to Hydroxyurea[28], and Hydroxyurea for Children and Young Adults with SCD and Pulmonary Hypertension[29] are continuing to evaluate the role and late effects of hydroxyurea for children of varying ages and for complications of SCD other than vaso-occlusive painful events.

What are the Published Guidelines for Use of Hydroxyurea in SCD?

The National Institutes of Health (NIH) and National Heart, Lung and Blood Institute published guidelines for the initiation of hydroxyurea in 2002.[30] These guidelines state the indications for treatment with hydroxyurea include: "Adults, adolescents, or children (after consultation with parents and expert pediatrician) with sickle cell anemia or SCD-Sβ^0–thalassemia and frequent pain episodes, history of acute chest syndrome, other severe vaso-occlusive events, or symptomatic anemia."[30] Despite "frequent pain episodes" being an indication to initiate hydroxyurea, there is lack of consensus about how pain episodes are defined in general and how various definitions of "frequent pain episodes" are used to recommend hydroxyurea. Besides the inclusion criteria used for the MSH trial (3 or more self-reported painful episodes in year before study entry), the single arm studies in children, and the above outlined NIH guidelines, there are no other guidelines, formal or otherwise, for the appropriate use of hydroxyurea.

How are "Frequent Painful Episodes" Defined in SCD?

There is no consensus among providers regarding the definition of "painful episodes" and "frequent painful episodes" in patients with SCD. A recently published article that utilized an expert panel of SCD physicians to create definitions for the phenotypic manifestations of SCD defined a vaso-occlusive pain episode as a new onset of pain lasting at least 4 hours

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requiring parenteral opioids or ketorolac in a medical setting.[31] In addition, epidemiological studies that describe painful events[5] and clinical trials that measure painful events as outcomes have defined pain similarly, requiring a visit to a medical facility to confirm a painful episode.[16] On the contrary, inclusion criteria for the MSH allowed for self-report of painful events and did not require a visit to a medical facility to validate a painful event.[16] Definitions requiring a visit to a medical facility to validate a pain episode are problematic based on the current published pain literature in SCD in both children and adults. This literature reveals the majority of pain episodes are managed at home by patients and their families and medical care in the clinic or emergency department is not sought.[7–9,11] Importantly, these pain events managed at home impact school and work attendance.[7,11] In addition, even seeking care in the emergency department or inpatient unit does not resolve the pain event, as patients experience pain at home after discharge and a significant proportion are readmitted to the hospital for continued pain management.[11,32,33]

A very important question to ask providers at a national level is how they define “frequent painful events” since they are the ones making the decision at the patient’s bedside about whether hydroxyurea is indicated. A recently conducted study found lack of consensus on the definition of frequent pain amongst pediatric SCD providers. Forty-two percent of providers used only pain requiring hospitalization as criteria for prescribing hydroxyurea whereas 44% accounted for pain both at home and in the hospital when prescribing hydroxyurea.[34]

In order to promote the utilization of hydroxyurea, a consensus definition for “frequent painful events” in SCD should exist. This definition should account for all the available pain literature in SCD, including pain managed both in and out of the hospital. We must educate all providers to ask patients about pain experienced at home since this is clearly underreported and is a very important measure of a patient’s disease severity. It is also vital to know how this pain is impacting the daily lives of patients and if functional impairment is occurring from this pain. Importantly, interventions aimed at decreasing the frequency of painful events require a common definition taking into account what happens in patients lives both in and out of the hospital or clinic. The lack of a consensus definition accounting for all available SCD pain literature will continue to be a barrier to the prescribing of hydroxyurea where patients that truly may benefit will not be offered the drug.

Patient-reported Outcomes are an Ideal Way to Measure the Functional Impact of SCD

Incorporating the patient’s perspective of his/her own disease is vital to the full assessment of patients who may benefit from hydroxyurea. Patient reported outcomes (PROs) such as health-related quality of life assessments aimed at assessing well being of the patient are an ideal method for determining which patients may benefit from hydroxyurea treatment when they are used in conjunction with medical indications.[35] PROs are able to assess the extent of the disease’s impact on the function of the patient from a physical and psychosocial aspect. In addition, PROs are an ideal way to assess patients who suffer from chronic pain managed at home for whom hydroxyurea may be indicated and would otherwise be missed if only pain events treated with parenteral narcotics in a medical setting are accounted for.[7]

What are the risks of Hydroxyurea?

What we know about the risks of hydroxyurea in patients with SCD

Hydroxyurea has been in use for over 25 years in patients with SCD.[36] Given that, it is well known in patients with SCD that hydroxyurea use is associated with cytopenias. This most commonly involves neutropenia but there may also be associated thrombocytopenia and

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worsening anemia.[16] The cytopenias are reversible upon cessation of the drug and hydroxyurea can often be tolerated using decreased doses in those patients who have experienced cytopenia as a side effect. In addition, patients may experience nail or skin changes most often involving hyperpigmentation.

What we are learning or need to know more about in patients with SCD who are taking hydroxyurea

Male patients with SCD may have abnormal spermatogenesis or abnormal semen parameters.[37–39] Recently, concern has been raised that this may be due to the use of hydroxyurea in male patients.[40] However, there currently are insufficient data to conclude whether there is or is not an independent association between sperm quality and hydroxyurea use in male patients with SCD who are taking the drug separate from the effect of SCD alone on male spermatogenesis. In addition, there have been concerns that hydroxyurea use in females may cause teratogenesis in the fetal offspring. There have been no reports of this in humans in the literature but there are insufficient data to conclude there is no association and that it is safe to take hydroxyurea during pregnancy.

There have also been concerns that patients taking hydroxyurea are at an increased risk of developing a malignancy such as leukemia. Again, there are insufficient data to conclude there are no associations between hydroxyurea and malignancy, but there have been no increased reports of leukemia in SCD patients who are taking hydroxyurea. Lastly, there may be other side effects or toxicities from hydroxyurea that we are not yet aware of and would only become apparent upon widespread use of the drug as have been shown with other drugs.[41] Thus, it is important to continue to monitor the side effects and toxicities of hydroxyurea, but these potential unknown toxicities should not hinder current use of the drug.

No medication comes without risk. We as providers need to look at the available data and make an educated decision about what is best for our patients weighing the known risks and benefits. Ultimately, an open discussion with our patients about these risks and benefits is imperative without introducing bias based on our own fears of side effects.

What is the Effectiveness of Hydroxyurea in SCD?

Since the efficacy of hydroxyurea was established in a controlled clinical trial environment, its true effectiveness is dependent upon its utilization in real clinical practice. Despite the impressive findings of the MSH, hydroxyurea has been shown to be underutilized in adults limiting its effectiveness in clinical practice.[42,43] A study completed in Maryland found a significant increase in the rate of hospitalizations of adults for vaso-occlusive painful events in the era of hydroxyurea.[44] When individual patient characteristics were examined only 30% of patients that were eligible for hydroxyurea were taking the drug.[44] A regional based survey of community and university based hematologists examined prescribing patterns of hydroxyurea for adults with SCD and found underutilization of hydroxyurea based on prescribing rate. This study found only 75% of providers utilized hydroxyurea in patients who had 3 or more painful events in one year[42], the inclusion criteria used in the MSH.[16] In addition, a survey of the Sickle Cell Adult Provider Network found that fewer than half of providers prescribed hydroxyurea to all of their eligible patients.[43] A study of pediatric SCD providers found only 8% of providers have 50–90% of their SCD patients on hydroxyurea, 54% have 10–30% of SCD patients on hydroxyurea and 10% have fewer than 10% of SCD patients on hydroxyurea.[34] Due to the concern about the underutilization of hydroxyurea, the National Institutes of Health convened a Consensus Development Conference in 2008 and the statement from this conference confirmed the underutilization of hydroxyurea.[45] Effectiveness of hydroxyurea is further questioned in a study of the Maryland state Medicaid

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database that found 85.9% of enrollees with SCD never had a claim for hydroxyurea and of those that had at least one claim for the drug, the number of refills recorded were minimal supporting lack of adherence to the drug.[46] The above studies about hydroxyurea utilization truly raise questions about the effectiveness of hydroxyurea in real clinical practice.

What are the Barriers to the Effectiveness of Hydroxyurea?

The true success of an intervention relies heavily on the effectiveness of the intervention in real clinical practice outside of a controlled clinical trial environment. The effectiveness of a drug, such as hydroxyurea, can be inhibited at the provider, patient, or systems level. Therefore, to evaluate the effectiveness of an intervention, one needs to look at the barriers that may exist at each of these levels.

Provider-related Barriers

Both pediatric and adult studies looking at the utilization of hydroxyurea in patients with SCD have identified patient compliance as a barrier to the use of the drug.[34,42,43] In other words, providers do not offer patients the drug because they don't feel the patient will be compliant with taking the drug or with required laboratory monitoring. This may represent a provider-related bias and subsequently a potential barrier to the effectiveness of the drug. If a provider thinks a patient isn't going to take the drug or adhere to the recommendations, does that mean they shouldn't be offered the drug? Another factor limiting the effectiveness of hydroxyurea at the provider level may be the provider's own fears of the side effects of the drug or the provider's lack of knowledge about the clinical data regarding the development of these side effects. These fears may or may not be substantiated by clinical data. For example, 27% of pediatric providers[34] and 40% of adult providers state fear of cancer has interfered with their prescribing of hydroxyurea.[42] To date, the fear of carcinogenesis has not been substantiated by clinical data.[15] However, if the provider believes this to be true, he/she will likely not offer the drug to the patient or will show this bias when offering hydroxyurea as therapy. Subsequently, the provider will not know if the patient is willing to accept this risk to receive the benefit from the drug. The provider is "forcing" his/her own bias on the patient and assuming that since they themselves "fear" this potential complication, then the patient will also "fear" this complication; thus creating a barrier. This concept is further illustrated in a study completed by Hankins et al.[47] that assessed treatment decision-making among pediatric patients with SCD and their families. Although the authors anticipated a large proportion of their study sample would be concerned about sterility as a side effect of hematopoietic stem cell transplant, only 29% of the parents were concerned about sterility if it meant their child's SCD would be cured.[47] This important study promotes involvement of patients and their families in treatment decision making as their concerns may or may not be in parallel with the provider's concerns. Additional similar studies are imperative to further learn about how patients balance risks versus benefits when making treatment decisions about their disease.

Patient-related Barriers

There is minimal data about patient-related barriers to the use of hydroxyurea in SCD. A recent systematic review (2009) supported by the Agency for Healthcare Research and Quality about barriers to care in patients with SCD did not identify any studies specifically addressing patient-related barriers to the use of hydroxyurea.[48] A recent study evaluating adherence to hydroxyurea in children with SCD found family-reported barriers to hydroxyurea adherence included obtaining refills from pharmacy and coming to clinic for follow-up.[49] Another recently completed study in children found a quarter of providers reported more than 20% of their patients refused hydroxyurea when it was offered to them.[34] The reasons for refusal included fear of cancer and other side effects in the majority,

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followed by not wanting to take a medication, not wanting to have required laboratory monitoring, or not thinking the medication will work.[34] These identified barriers highlight the importance of having an open discussion with patients about the risks, however patients need to hear the odds of developing these risks. All medications come with risks and it is up to the provider to put these risks into context for the patient with some information about the odds of developing these risks so patients can make informed decisions about their treatment. In addition, identified family-related barriers to adherence to hydroxyurea suggest systems-related barriers may exist to the use of hydroxyurea. Additional studies are necessary to further elicit patient-related barriers to the use of hydroxyurea and subsequent interventional studies are required to address these barriers.

Systems-related Barriers

The barriers at the provider and patient level cannot be interpreted independent of existing systems-level barriers that may be a result of the disproportionate demographic distribution of patients with SCD. In the United States, the majority of patients with SCD are from minority backgrounds (90% African American, 10% Hispanic)[1], are more likely to live in poverty and thus have challenges due to their low socioeconomic status, such as limited access to transportation or lack of health care insurance.[50–52] These challenges likely affect patients' compliance and ability to come to clinic and laboratory appointments. In addition, it has been shown that compared to Caucasians, patients from minority backgrounds receive lower quality of care in the United States.[53–56] Thus, patients' non-compliance with hydroxyurea and required laboratory monitoring may be a result of poor access to care or lower quality of care, both barriers at the systems-level. Other systems-level barriers affecting compliance include the lack of a medical home, limited access to comprehensive sickle cell centers, lack of care coordination between comprehensive sickle cell centers and community-based physicians for those children that are geographically isolated from a comprehensive sickle cell center, and poor transition from pediatric to adult care.[45] Additional epidemiological and interventional research is needed to identify and address these systems-level barriers.

Do the Benefits of Hydroxyurea Outweigh the Risks?

We can continue to debate about the potential and unknown risks of hydroxyurea and await the gold standard randomized-controlled trials with long-term follow-up evaluating every potential toxicity of the drug. However, it is unlikely that these such trials will occur because it would now be considered unethical to withhold hydroxyurea in a control group. Ultimately what is important to remember is that SCD causes tremendous morbidity at the multi-organ system level and is associated with early mortality. If there is an intervention that can significantly decrease morbidity, prolong life, and improve the function and health-related quality of life of our patients[15,57], why should it not be offered to them? As always in medicine, each recommendation to initiate a new therapy must be made weighing the risks versus the benefits. Based on the proven efficacy and initial safety in children and adults[15,16,19–25,58–60], hydroxyurea clearly provides significant benefit to many patients that suffer from a life-long debilitating disease and likely improves their health-related quality of life[57]; thus the benefits of hydroxyurea outweigh the potential risks of both the drug and "untreated SCD".[45] Finally, any risks that hydroxyurea does carry with it need to be interpreted through the eyes of our patients. Maybe patients are willing to accept these risks if it means complications from their disease will be ameliorated and they will live a more functional and productive life?

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