A call to start hydroxyurea by 6 months of age and before the advent of sickle cell disease complications

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Sickle cell disease (SCD), a group of inherited hemoglobin disorders characterized by the presence of sickle hemoglobin (HbS), can cause significant organ damage and death in both children and adults.1 Where it is available, universal newborn screening allows for early diagnosis and management shortly after birth, thereby reducing the incidence of serious complications.2 While three disease-modifying therapies, crizanlizumab, voxelotor, and L-glutamine, have recently been approved for the treatment of SCD, the most accessible and effective treatment is still hydroxyurea (HU). In children with severe sickle cell anemia (SCA), HU has been shown to increase fetal hemoglobin (HbF) levels and reduce pain and hospitalizations.3,4 Here, we discuss the rationale of starting HU treatment at 6 months of age and before the occurrence of any disease-specific complications such as severe anemia, dactylitis, and/or splenic sequestration.

HU, a direct but reversible ribonucleotide reductase inhibitor, interferes with the synthesis of deoxyribonucleic acid (DNA) by the reduction of deoxyribonucleotide triphosphate pools. While HU’s mechanisms of action remain poorly understood, the cytotoxic effects of HU cause an increase in the recruitment of HbF-rich erythroid progenitors, reduction in reticulocytes, white blood cells, and platelets, and increase in the bioavailability of nitric oxide all of which contribute to the many clinical benefits observed with its use.5 Benefits range from decreased emergency department visits, hospital admission rates, blood transfusion requirements, organ dysfunction, and death.

Newborns with SCD are asymptomatic because of the high value of HbF present at birth. The hemoglobin switch, largely orchestrated by the BCL11A gene, leads to a decrease in gamma globin production and increase in beta-like globin production. HbF falls rapidly during the first 24 months of life, but this fall is greatest during the first 6 months of life.6,7 By 6 months of age, most infants with SCA have between 30% and 40% HbF and those values will only drop further without treatment. In the absence of HU, the onset of symptoms can and is likely to occur once HbF levels fall below 30%, given uncontrolled sickle hemoglobin polymerization, further justifying the start of HU by 6 months of age.

National guidelines recommend starting HU anywhere from 9 months to 2 years of age. In the United States, the American Society of Hematology recommends starting those with SCA on HU at 9 months of age, while the United Kingdom’s national guidelines recommend the use of HU in children with SCA younger than 12 months.8 In France and Italy, HU is indicated for patients with SCA from the age of 2 years onward.9,10 However, the optimal age of HU initiation has not yet been established.

The idea of starting HU early in infants is not novel. Initially, the HUSOFT study11,12 involved infants aged 6–24 months and reported no major safety issues. Approximately 2 years ago, a retrospective study by Schuchard et al. demonstrated improved HbF induction and decreased hospitalizations, pain, and transfusions in children started on HU between 0 and 1 year of age compared to children started from 1–2 and 2–5 years of age.13 This study and the accompanying editorial by Ware et al. reinforced this concept.14 In addition, data from the Therapeutic Response Evaluation and Adherence Trial (TREAT) study and recent data on pharmacokinetic (PK)-guided HU dosing in children...
at 6 months of age show that infants started earlier on HU have higher, sustained values of HbF.15

The design of the BABY HUG trial6 called for recruitment between 9 and 18 months of age, which is the rationale for the recommended starting age of 9 months in the United States. However, complications of SCD can develop much earlier. If we want to achieve the goal of treating our patients before they develop chronic, inexorable, and ultimately fatal organ damage, the ideal age to start HU is before the advent of symptoms. As many children have laboratory and clinical manifestations of SCA by 6 months of age, early initiation of therapy at that age will be beneficial.

The fear of mutagenesis and infertility has largely contributed to a reluctance on the part of providers and families to start HU,16,17 despite preclinical and clinical studies that demonstrate HU as neither mutagenic nor carcinogenic to people with SCD.18,19 A fear that HU may cause cancer is still cited as a concern. Unfortunately, most of the information available regarding infertility is from small cohort studies. Studies in women have demonstrated no statistically significant difference in mean anti-Mullerian hormone (AMH) in women with SCA treated with HU compared to those not treated with HU, although a larger number of patients treated with HU were in the less than fifth percentile.20 In men with SCA, while HU has been shown to worsen already existing testicular dysfunction,21 other studies have shown no difference in sperm parameters in HU-exposed versus HU nonexposed patients.22 Given the lack of definitive data on infertility and real-life reports of pregnancy in women on HU and in partners of men on HU,19 HU remains the drug for SCA with the best risk/benefit profile.18

In practice, it may be simpler to start this treatment at the same time as penicillin, that is when the diagnosis is made. However, this may not allow for sufficient time for comprehensive counseling and, while rare, the potential for an allergic reaction secondary to one of the medications may result in the discontinuation of two life-saving medications and feelings of mistrust between families and their medical team. In addition, baseline white blood cell count values are generally lower in the young infants because the chronic inflammatory state of SCA is not yet established, which may result in lower than desired absolute neutrophil counts (ANCs) in early life. Lastly, a higher glomerular filtration rate means a faster clearance of the drug, so higher doses may be required than in older children. If treatment should be started due to symptoms, as early as 2 months of age, having some time between penicillin initiation is ideal and PK-guided dosing, as suggested by Dong et al.,23 may be useful.

With PK-guided dosing, children have fewer toxicities and blood draws,8,24,25 making the drug more appealing for even young infants. Previously, HU dosing was based solely on weight, with a gradual increase to the maximum tolerated dose (MTD). This strategy achieves predictable clinical and laboratory benefits, but often takes longer than 6 months to achieve. To achieve this more quickly, trials have been conducted to enable personalized, PK-guided HU dosing strategy.24–26 PK-guided dosing makes dosing easier and also more effective.

The clinical manifestations of SCD can appear as early as 3 months of age and can be potentially severe. Hand-foot syndrome or dactylitis, characterized by painful swelling of the feet and/or hands, is one of the first manifestations of the disease. It may be more common and severe in early childhood.27,28 Early use of HU has been shown to decrease pain and dactylitis, with minimal toxicity.29,30

HU, in addition to reducing the frequency of acute complications, may also prevent the development of chronic end-organ damage. One study has shown that hyperfiltration of the kidney was present in children 9 months to 1 year of age prior to any treatment.31 HU is associated with a decrease in hyperfiltration in young children with SCA32 and is also associated with better urine concentrating ability and less renal enlargement.33 HU also reduces the severity of anemia, and anemia in childhood is associated with poor brain development. Beyond reducing transcranial Doppler (TCD) velocities in children with SCA and primary stroke,34 HU may also prevent irreversible changes that impact cognitive function.35,36 While most studies have not been performed in very young children, the effects of HU on the brains of school-age children is evident.

In resource-limited countries, HU has been shown to reduce the incidence of vaso-occlusive events, infections, malaria, transfusions, and deaths, which argues for wider access to this treatment. This recommendation to start HU as early as 6 months of age may be even more powerful in these low-resource settings, where the mortality rate due to SCA is very high, especially in the first years of life.30 The insufficient blood supply37 as well as the lack of rapid access to care for many individuals with SCA in resource-limited countries may be directly compared to the less likely risk of acute anemia and increased splenic function with the use of HU.38

More than 25 years after its introduction in the management of SCA, HU is recognized as an effective drug without serious acute toxicity, especially when the benefit/risk ratio is considered. Determining the appropriate age to initiate HU is critical, as it could result in a new generation of children with significantly less acute and chronic complications. Based on the data available in the literature, we suggest the prescription of HU as early as 6 months of age and before the onset of SCD complications.

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AUTHOR CONTRIBUTIONS
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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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