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Shared Decision Making for Hydroxyurea Treatment Initiation in Children with Sickle Cell Anemia

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Abstract

Clinical trials have demonstrated hydroxyurea's efficacy in improving health outcomes for children with sickle cell anemia (SCA) who have medical complications. New NHLBI clinical guidelines will recommend offering hydroxyurea to young patients regardless of clinical severity. Shared decision making may be an effective approach for implementing this practice change. Decision aids that help patients/parents feel empowered to make this decision and help providers feel comfortable discussing hydroxyurea as a preventive treatment may facilitate shared discussions between families and providers. We recommend six strategies providers can use to facilitate these discussions while decision aids and tools are being developed.

Keywords

decision making; pediatrics; sickle cell anemia; guidelines; therapeutics

The first report of hydroxyurea for fetal hemoglobin (HbF) induction in sickle cell anemia (SCA) was published 30 years ago, which was followed sequentially by Phase I/II and Phase III studies that have consistently documented both laboratory benefits (increased hemoglobin and HbF) and clinical efficacy (fewer episodes of pain and acute chest

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syndrome, fewer hospitalizations and transfusions) of hydroxyurea for both adults and children with SCA.[1] For most pediatric hematologists, the Phase I/II trial (HUG-KIDS),[2] numerous single-institution experiences, and the recent multicenter Phase III trial (BABY HUG)[3] have together provided sufficient evidence for the safety and efficacy of hydroxyurea for prevention of acute vaso-occlusive events, even in young patients with SCA. Many children with sickle-related complications are now prescribed hydroxyurea therapy, but there is still no clear consensus regarding the proper age, dose, or severity threshold for treatment initiation. Importantly, the BABY HUG study allowed the enrollment of clinically asymptomatic infants, and the benefits of hydroxyurea treatment were documented in both children with or without prior clinical severity.[4]

The National Heart, Lung, and Blood Institute (NHLBI) has now published guidelines that provide strong recommendations for the use of hydroxyurea in children with SCA.[5] Using an evidence-based approach, a selected expert panel wrote 11 specific hydroxyurea treatment recommendations including one for children: In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD [sickle cell disease]- -related complications (e.g., pain, dactylitis, ACS [acute chest syndrome], anemia). (Strong Recommendation, High-Quality Evidence for ages 9–42 months; Moderate Recommendation, Moderate Quality Evidence for children >42 months and adolescents). The panel then adds that the term “offer” was intentional, realizing that the patients’ values and preferences may differ particularly considering treatment burden, cost, and other issues. Finally, the panel strongly encourages shared decision making and discussion of hydroxyurea therapy with all patients.

Pediatric hematologists and other healthcare providers including some primary care providers now find themselves in a new position, challenged to offer hydroxyurea therapy to all infants 9 months of age or older, regardless of clinical severity to prevent or reduce complications. For many providers, such a stance will be welcomed since the clinical severity of SCA is unpredictable, and they are familiar with hydroxyurea treatment and its risks and benefits. For others, however, this recommendation represents uncharted territory and requires a new skill-set to navigate the discussion of preventive disease-modifying treatment for asymptomatic children with SCA.

Shared decision making is a process to ensure that clinical decisions are consistent with the best research evidence as well as the values and preferences of informed patients/parents.[6] Clinicians share information about treatment options, and patients/parents share their preferences and concerns. Together, a treatment plan is developed that is the best fit for individual patients and their families. Utilizing a shared decision-making approach with parents regarding hydroxyurea treatment initiation will require an in-depth understanding of parents’ decisional needs. For example, what will make parents feel empowered in the decision-making process? How do parents typically make the decision to initiate hydroxyurea? Do they scour the internet for information? Do they reach out to family members/friends for help in making the decision? What questions do parents need answered about hydroxyurea’s risks and benefits to feel they have made an informed decision? What supports do parents need to avoid delaying the decision? Of course, parents’ needs may vary. Some parents may choose to initiate hydroxyurea because they trust their provider’s

recommendation while others may make the decision only after consulting with the family of another child taking the medication. Still others may make the decision after evaluating the benefits and risks with respect to their personal values (e.g., taking daily medications, child participation in age-appropriate activities). Recent research has brought to light some parental concerns about hydroxyurea such as feelings of uncertainty and concerns about efficacy, safety, and side-effects,[7] but additional research is needed to better delineate parents' needs when making the decision to initiate hydroxyurea.

To facilitate shared decision making, pediatric hematologists and other health care providers, including some primary care providers, need to feel comfortable discussing hydroxyurea as a preventive therapy. A recent study by Brandow and colleagues identified a number of barriers to engaging in this conversation, including healthcare provider concerns about hydroxyurea toxicities, monitoring and adherence.[8] Research is needed to better understand what providers need to know with respect to hydroxyurea's mechanisms of action, efficacy and safety, titration and monitoring to feel comfortable prescribing and managing hydroxyurea in SCA patients.

Decision aids are one strategy to help clinicians share the evidence about potential benefits and downsides of treatment in ways that can be understood by patients/parents and create a two-way conversation about what matters most to patients/parents when choosing treatments.[6] A systematic review with 115 randomized controlled trials demonstrates that, compared to usual care, decision aids consistently increase patient knowledge of treatment options, the accuracy of their risk perceptions, and their involvement in the decision-making process while decreasing decisional conflict (i.e., uncertainty in choosing options from feeling uninformed, unclear about personal values, or unsupported in decision making).[9] These findings are comparable within the 25% (29/115) of studies involving adult patients facing a medical treatment decision related to their chronic condition. While evidence from pediatrics settings is just starting to accrue, our initial research suggests that similar benefits are likely.[10] As such, shared decision making, facilitated with a decision aid, holds tremendous potential as a strategy to address the decision support needs of parents and clinicians facing a decision about preventive treatment with hydroxyurea for asymptomatic children with SCA. Ultimately, we expect that parents who are better informed about hydroxyurea and better supported through a shared decision-making process will have fewer unaddressed concerns and less uncertainty about initiating hydroxyurea.

Clinicians will likely be faced with discussing hydroxyurea as a preventive treatment for children with SCA before shared decision-making tools can be developed and evaluated. Therefore, we recommend the following: 1) Ask the family to invite all persons involved in the decision to initiate hydroxyurea (i.e., family members, trusted advisors) to attend a clinic appointment, or talk with the medical team via Skype or phone. In this way, all stakeholders will have the opportunity to obtain reliable medical information and voice their concerns. Any conflicts between stakeholders (e.g., between parents or between parent and patient) can be identified and discussed. For some families, an open discussion of values, preferences, and concerns can help identify a mutually agreeable path forward. For others, a time-limited, structured trial of HU can help resolve conflicts; 2) Provide the family education about hydroxyurea use in SCA, and/or refer parents to trustworthy internet

resources (e.g., NLHBI, Centers for Disease Control). It is important that parents make a decision based on SCA-specific hydroxyurea information, not general information about hydroxyurea or its former role as an anti-neoplastic agent. Also, parents may be unaware that some websites are not monitored for accuracy and may contain outdated information (e.g., hydroxyurea will result in hair loss); 3) Address safety concerns (e.g., parents wearing gloves when dispensing hydroxyurea) during your discussion. Explain hydroxyurea package inserts may contain these warnings specific to use for cancer chemotherapy not for SCA; 4) Mention hydroxyurea as a possible preventive treatment during the child's initial visits with the goal of offering it as a treatment option once the child is 9 months of age or older. The BABY HUG data [4] suggest that hydroxyurea is safe and efficacious for use in children age 9 months and older; 5) Plan multiple follow-up conversations about hydroxyurea with parents. Remember this is a process; most families will not make a decision during the first discussion of hydroxyurea but will feel more prepared and supported over time; and 6) Develop a hydroxyurea treatment protocol that includes your management strategy in regards to lab draw intervals, labs to monitor toxicity and adherence (e.g., mean corpuscular volume, absolute neutrophil count, absolute reticulocyte count, and fetal hemoglobin), and methods for promoting hydroxyurea adherence (e.g., home reminder systems, frequent visits, review of the peripheral blood smear) among those families that choose to initiate treatment. These strategies will serve to decrease barriers to hydroxyurea initiation and improve the quality of care provided to children with SCA taking hydroxyurea.

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