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Changing the Clinical Paradigm of Hydroxyurea Treatment for Sickle Cell Anemia Through Precision Medicine

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Abstract

Sickle cell anemia (SCA) is a common and devastating inherited blood disorder, affecting millions of people across the world. Without treatment, SCA results in tremendous morbidity and early mortality. Hydroxyurea is the primary and most well-established pharmacologic therapy with proven benefits to ameliorate the clinical course of SCA, primarily due to its ability to increase the expression of fetal hemoglobin (HbF), which prevents sickling of red blood cells. The optimal induction of HbF depends upon selection and maintenance of the proper dose that maximizes benefits and minimizes toxicity. Due to the significant interpatient variability in hydroxyurea pharmacokinetics, pharmacodynamics, and dosing, most patients treated with hydroxyurea receive suboptimal doses and have only modest treatment responses. Recognizing this variability, using a precision medicine approach, we developed and prospectively evaluated an individualized dosing model for children with SCA, designed to optimize the hydroxyurea dose and clinical response. We utilize novel laboratory methods and a sparse sampling strategy requiring only 10 μL of blood collected 15 minutes, 60 minutes, and 180 minutes after a test dose. We use Bayesian adaptive control to estimate hydroxyurea exposure and to select an individual, optimal starting dose. This dosing model has resulted in HbF responses >30–40%, levels beyond what is achieved with traditional weight-based dosing and trial and error dose escalation. This hydroxyurea dosing strategy, if widely implemented, has the potential to change the treatment paradigm of hydroxyurea therapy and improve outcomes for the millions of patients with SCA across the world.

OVERVIEW OF SICKLE CELL DISEASE

Sickle cell disease (SCD) is a devastating and life-threatening inherited disorder of hemoglobin, affecting nearly 100,000 persons in the United States and millions worldwide.[1,2] SCD is an autosomal recessive condition and collectively refers to a closely related group of inherited anemias characterized by the predominance of sickle hemoglobin (HbS). The

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CONFLICT OF INTEREST

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most common and severe forms of SCD (homozygous HbSS disease and HbS/β^0-thalassemia) are referred to as sickle cell anemia (SCA) and will be the focus of this paper. The abnormal HbS is the result of a single point mutation in the *HBB* that results in an amino acid substitution (glutamic acid to valine) and, subsequently, the polymerization of HbS within red blood cells (RBCs) due to hydrophobic interactions between hemoglobin molecules. This polymerization results in elongated and stiffened RBCs that cause vaso-occlusion due to the decreased deformability and inability to easily travel through blood vessels. Painful vaso-occlusive crises are the hallmark of SCD, but without adequate treatment, sickled RBCs and the associated hemolytic anemia results in innumerable acute and chronic clinical complications, including increased susceptibility to invasive bacterial infection due to splenic autoinfarction, acute splenic sequestration crisis, acute chest syndrome, stroke, chronic organ damage, and shortened lifespan.[3] Without early diagnosis and appropriate disease-modifying treatment, SCA results in significant morbidity and early mortality.

HEMOGLOBIN SWITCHING AND THE IMPORTANCE OF FETAL HEMOGLOBIN

Humans express three distinct types of hemoglobin with unique physiologic characteristics at different stages of development: embryonic (α_2/ε_2), fetal (α_2/γ_2), and adult (α_2/β_2) hemoglobin (Figure 1). Each hemoglobin tetramer includes two α-like and two β-like globin chains, with expression determined by complex and tightly regulated genetic mechanisms of gene activation and silencing on chromosomes 11 (β-globin locus, including *HBB* and the γ-globin genes *HBG1* and *HBG2*) and 16 (α-globin locus).[4] Most hemoglobinopathies, including SCA, are the result of genetic mutations in the β-globin locus. Although the switch from the embryonic to the adult form of α-globin occurs within the first weeks of embryonic development, the hemoglobin switch within the β-globin locus, from fetal to adult hemoglobin, is much more complex and is associated with significant clinical implications for those with β-globinopathies, such as SCA. Fetal hemoglobin (HbF) is the predominant hemoglobin type during much of gestation due to its increased oxygen affinity. Following birth, this increased oxygen affinity is no longer necessary, and the hemoglobin switch occurs, from fetal to adult hemoglobin. For infants who express only normal adult hemoglobin, this hemoglobin switch occurs quickly with loss of HbF expression by 6 months of age to virtually no expression by 1 year of age (Figure 1).[5–7] Infants with SCA express only the abnormal HbS and have a more gradual reduction in HbF than normal infants (Figure 1).[8] Although this switch from fetal to adult hemoglobin occurs in all people, the switch is not total or reversible with significant interpatient variability in residual HbF expression. However, most children with SCA have levels of HbF lower than 20% by 2 years of age, which is insufficient to inhibit sickling.[8]

The protective effects of HbF for children with SCA were first described in 1948 by Janet Watson as she observed that infants and young children had fewer sickled cells than older children and adults.[9] The subsequent discovery of hereditary persistence of fetal hemoglobin (HPFH) and the demonstration that those who co-inherit SCA and HPFH live a healthy life without any manifestations of SCA confirmed the protective effects of HbF.[10,11] High levels

of HbF inhibit HbS polymerization and subsequent sickling of RBCs. Importantly, the levels of HbF and its distribution among RBCs are critical determinants of its ability to prevent HbS polymerization. In mature adult RBCs, HbF is distributed unequally across RBCs and most mature RBCs have no detectable HbF. As an example, the co-inheritance of HbS with HPFH results in HbF levels of 30–40% with near-pancellular HbF distribution within RBCs (>80–90% F cells).[10] Published modeling studies have suggested that overall HbF levels of ≥30% with ≥70% F-cells or ≥10 pg HbF/F-cell is a curative target that should completely prevent RBC sickling.[12,13] This target is the ultimate pharmacological end point for any treatments designed to induce HbF expression in patients with SCA, including hydroxyurea. It has been commonly stated that hydroxyurea is incapable of producing such a robust HbF effect with pancellular distribution of HbF, which has contributed to decreased enthusiasm for universal hydroxyurea use and continued efforts to develop novel therapies capable of inducing HbF to levels sufficient to prevent RBC sickling. Our work using a precision medicine approach to hydroxyurea therapy challenges these skeptical views and suggests that hydroxyurea can indeed achieve these HbF targets capable of preventing HbS sickling and SCA complications, particularly when initiated early in life.

HYDROXYUREA THERAPY FOR SCA

Hydroxyurea is the primary disease-modifying therapy for SCA with decades of evidence demonstrating the salutary laboratory and clinical effects, including reduction in both morbidity and mortality.[14–18] Despite a recent surge in the development of new therapies,[19] hydroxyurea remains the only widely available and well-established disease modifying treatment for SCA. Hydroxyurea exerts its disease-modifying effects primarily through the induction of HbF, a potent inhibitor of the polymerization of HbS, as described above.

Mechanism of action

Hydroxyurea is a potent inhibitor of ribonucleotide reductase and is classified as an antimetabolite acting as an S-phase specific cytostatic agent.[20] The intermittent effect of hydroxyurea upon rapidly proliferating erythroid progenitors causing stress erythropoiesis has been postulated as the most likely mechanism of HbF induction, although exact mechanisms are likely to be multifaceted and not yet well understood.[21] In addition to the induction of HbF, hydroxyurea also provides additional hematologic benefits for patients unrelated to HbF expression, including improved rheology of RBCs and reduction in degree of hemolysis resulting in reduction in inflammation, as well as multiple nonhematologic effects, such as increased nitric oxide production and both cGMP and CAMP levels, and reduction in inflammation.[18,22–25] Hydroxyurea has been shown to have an effect upon known genetic modifiers of HbF expression, such as *BCL11A*, *KLF-1*, and MYB,[26,27] but despite many years of research, the exact cellular and molecular mechanisms by which hydroxyurea induces HbF remains incompletely understood.

Possible toxicities and notoriety of hydroxyurea

Due to its mechanism of action and historical use to treat cancer, hydroxyurea is often described as a chemotherapy drug, resulting in significant notoriety and concerns regarding short-term and long-term toxicities. Notably, many still have concerns that hydroxyurea may

cause cancer, infertility, or birth defects. These concerns have been shown to have a significant impact upon hydroxyurea perception and utilization by both providers and patients.[28–30] The historical data leading to these concerns are mostly derived from *in vitro* experiments, animal studies, and studies including patients with premalignant conditions, such as myeloproliferative neoplasms.[28,31–34] There have been thousands of patients treated with hydroxyurea over the past several decades and there has yet to be a signal to suggest that the dosing strategies used for SCA carry any true carcinogenic risk. There remain many questions regarding the safety of hydroxyurea during pregnancy, primarily due to insufficient data, although there have been a number of healthy babies conceived by men and women while they were taking hydroxyurea.[35,36] At this time, the most common recommendation is to suspend hydroxyurea during pregnancy, but the safety of hydroxyurea during pregnancy should be carefully evaluated given the known risks of untreated SCA during pregnancy and the growing population of young women who will have been free of major SCA complications due to lifelong hydroxyurea therapy. Recent data suggests that the use of hydroxyurea is likely to be safe during lactation, with only small amounts of hydroxyurea transferred into breastmilk, which is important as young women consider how to manage their SCA both during and after pregnancy.[37] Finally, due to its direct effects upon the bone marrow as a myelosuppressive agent, there are concerns that long-term hydroxyurea use may result in marrow exhaustion, resulting in a waning effect over time. Although it is likely true that an exhausted bone marrow, as is common for adults with SCA who have not received treatment for most of their lives, limits the ability to tolerate as high of a dose, there is no evidence that the effects of hydroxyurea wear off with long-term use. There are a growing number of reports demonstrating the sustained benefits of hydroxyurea for both adults and children treated for over 15 years.[17,38,39] The safety concerns of hydroxyurea are becoming less of a concern with expanded use and longer follow-up times, but it is important to recognize and address these concerns with patients, as access to this information, whether truth or myth, is widely available through the internet and many patient networks.

HYDROXYUREA PHARMACOKINETICS AND PHARMACODYNAMICS

Hydroxyurea is a small molecule with high oral bioavailability and rapid clearance with a short half-life (~ 2–4 hours).[40–42] The primary pharmacodynamic (PD) effect of hydroxyurea is induction of HbF, although there are many additional hematological and nonhematological effects of hydroxyurea, discussed above. Multiple studies have demonstrated significant interpatient variability in hydroxyurea pharmacokinetic (PK) and PD parameters, both of which have an important implication on hydroxyurea dosing and suggest that a “one-size-fits-all” approach is not appropriate.[41–43] In the Hydroxyurea Study of Long-term Effects (HUSTLE; NCT00305175) trial, the hydroxyurea maximum tolerated dose (MTD) ranged from 14.2 to 35.5 mg/kg/day in children.[42] In adults, hydroxyurea exposure, as defined by the area under the concentration-time curve (AUC), following the same dose varied approximately fivefold in adults.[42,43] In addition to significant interpatient variability in hydroxyurea dosing and PK, there are similar differences in baseline HbF and treatment HbF. Data from the HUSTLE trial demonstrated baseline HbF levels of 0–30.6%

prior to starting hydroxyurea and HbF levels upon reaching MTD that ranged from 9.4% to 55.9%.[42]

INDICATIONS AND UTILIZATION

Over the past 35 years, multiple clinical trials and extensive clinical experience has consistently demonstrated the safety and clinical benefits of hydroxyurea as a disease-modifying therapy for SCA.[18,22,23] With this mounting body of evidence, hydroxyurea has been increasingly utilized to treat patients with SCA. Initially, hydroxyurea was reserved for patients with frequent or severe clinical complications and was rarely used in children. The 2014 guidelines from the National Heart, Lung, and Blood Institute included strong wording to stimulate expanded use of hydroxyurea, including a recommendation that hydroxyurea be offered to all infants with SCA starting at 9 months of age, regardless of clinical severity.[44] These guidelines have resulted in increased use of hydroxyurea, including early initiation of hydroxyurea for infants and young children, which has significant implications related to normal developmental physiology and the production of HbF, and specifically "hemoglobin switching" from HbF to HbS that occurs during the first months and years of life (Figure 1).[5,7]

TRADITIONAL HYDROXYUREA DOSING

Initially, due to its short half-life, early studies dosed hydroxyurea twice or three times daily,[45] but due to concerns regarding hematologic toxicity and in an attempt to optimize medication adherence, hydroxyurea has since become a once daily medication for patients with SCA. Initial dosing is typically weight-based and conservative, focused on avoidance of toxicity rather than optimizing clinical and laboratory benefits. The clinical benefits of hydroxyurea are maximized when the HbF production is greatest, usually accomplished through careful dose escalation to an optimal dose, commonly referred to as MTD.[46] Dose escalation is performed based on complete blood counts and target mild myelosuppression, usually determined by absolute neutrophil count. Over time, as evidence has demonstrated that severe neutropenia is rare, the absolute neutrophil count target has become less conservative (now ~ 1.0–3.0 × 10^9/L), resulting in higher HbF levels and improved clinical benefits. The dose escalation process, however, requires serial laboratory monitoring and expertise of the clinical provider and often takes at least 6–12 months to achieve the optimal dose. Due to the significant interpatient variability in drug PKs and PDs, there is a wide range in optimal dosing from to ~ 15 to 35 mg/kg/day.[42,43,47,48] A one-size-fits-all dosing approach results in many patients receiving less than 50% their ideal dose.

Recognizing the interpatient differences in PK, PD, and dose, using a precision medicine approach, we developed a model to individualize hydroxyurea dosing to optimize clinical benefit without increased toxicity to prevent, instead of ameliorate, the clinical manifestations of SCA. Through our experiences over the past 5 years using a precision medicine approach, we challenge these beliefs and describe the development and implementation of an individualized treatment strategy of hydroxyurea for children with SCA that is safe and able to induce HbF to levels in the described "curative" range.

DEVELOPMENT OF A PK-GUIDED DOSE INDIVIDUALIZATION MODEL FOR CHILDREN WITH SCA

We developed a PK-guided precision dosing method using Bayesian adaptive control to individualize the hydroxyurea dose for children with SCA.[49] A total of 712 hydroxyurea plasma concentrations from 96 pediatric patients with SCA from the HUSTLE trial who had achieved clinically defined MTD were included in the analysis.[42,49] A population PK model of hydroxyurea was developed using Nonlinear Mixed Effects Modeling (NONMEM).[50,51] Based on this model, a D-optimal design was conducted under the consideration of clinical constrains for optimal sampling times. This sampling strategy includes three informative and clinically feasible time points (15–20 minutes, 50–60 minutes, and ~ 3 hours) after a test dose of 20 mg/kg (the typical starting dose). With a validated concentration measurement approach, microsampling using plasma volumes as low as 10 μL would be enough for determination of hydroxyurea concentration.[52] One of the challenges we were facing in the development of this Bayesian dosing strategy was the lack of a clear exposure target of hydroxyurea associated with the likelihood of achieving desired clinical and laboratory outcomes. As the HUSTLE study participants had achieved a clinically defined MTD, we utilized these data to define a target hydroxyurea exposure. Among HUSTLE participants, the average total hydroxyurea exposure, as defined by the AUC, was 115 mg*hour/L, which was adopted as the initial exposure target. With the population PK model as a prior, a patient's own PK profile could be reconstructed from three concentrations using Bayesian estimation software platform, such as MW/Pharm,[53] and an individualized dose would be recommended to achieve an AUC of 115 mg*hour/L. Figure 2 illustrates how individual PK timepoints are used to choose an optimal starting dose to target this AUC. This dosing model was prospectively evaluated in the Therapeutic Response Evaluation and Adherence Trial (TREAT; NCT02286154).

PROSPECTIVE EVALUATION OF PK-GUIDED INDIVIDUALIZED DOSING: RESULTS FROM THE TREAT COHORT

TREAT was a single-center study designed to prospectively validate a novel personalized PK-guided hydroxyurea dosing strategy with the primary end points of optimizing dose and reducing time to achieving MTD.[54] Enrolled participants received a single 20 mg/kg oral dose of liquid hydroxyurea, followed by sparse PK sampling with three samples collected at three timepoints over 3 hours (15 minutes, 60 minutes, and 180 minutes); hydroxyurea concentrations were incorporated into a population PK model in order to generate a starting dose that targets MTD. The TREAT cohort ($n = 50$) was young (median age at hydroxyurea initiation, 11 months), and PK-guided starting doses were high (27.7 ± 4.9 mg/kg/day). Time to MTD was 4.8 months (interquartile range 3.3–9.3), which is significantly shorter than comparison studies, meeting the primary end point. Despite relatively high baseline Hb (9.1 ± 1.3 g/dL) and HbF (25.1 ± 11.6%) due to the early starting age, further significant improvements in all hematological parameters were noted within 6 months of treatment initiation. The average Hb concentration increased by 1.0 g/dL with 58% of participants achieving Hb ≥ 10.0 g/dL and 29% reaching Hb ≥ 11.0 g/dL after 12 months of therapy. Despite high initial HbF levels, 87% of the children had further increases, with an average

HbF value of 33.3 ± 9.1% after 12 months of therapy and nearly one-third of participants achieving HbF values >40%. The HbF responses were robust across all ages, but were greatest for those who started ≤ 1 year of age, with 48% of these infants achieving HbF > 40% after 12 months of therapy.[54] As anticipated with these hematologic responses, acute sickle cell complications were infrequent, particularly among children initiating hydroxyurea within the first 2 years of life.[54] Importantly, these results have been sustained with the earliest enrolled participants now 5–6 years of age. With the early successes of TREAT, we began enrolling patients at an earlier age, aiming to initiate hydroxyurea therapy by 6 months of age, with even more robust induction of HbF. Figure 3 illustrates several examples of HbF induction using our approach, for children of varying ages, demonstrating the ability of individualized hydroxyurea dosing to achieve and sustain HbF levels beyond the expected 30% target to prevent HbS polymerization and associated SCA complications. The primary limitation of hydroxyurea and the only reason for TREAT patients to have a decrease in HbF levels is medication nonadherence, as illustrated in Figure 3d. These unprecedented results have allowed a key paradigm shift for hydroxyurea therapy; specifically, we can now aim to prevent rather than ameliorate most short-term and long-term clinical complications, with the ultimate goal of improving quality of life, reducing excessive morbidity, and avoiding premature mortality. Previously, HbF levels ≥15–20% were considered a therapeutic success because they were associated with a reduction in (but not elimination of) many clinical complications of SCA. However, because this degree of HbF production decreases HbS polymerization, but does not fully prevent the sickling of most erythrocytes, traditional hydroxyurea therapy has been largely considered an ameliorative and not curative therapy. Our data from the TREAT study strongly indicate that >30% HbF levels are readily achievable and sustainable using early treatment initiation with PK-guided dosing for optimal laboratory and clinical effects. We now believe that early initiation of hydroxyurea (within the first 1–2 years of life) using robust, personalized dosing strategy, has the potential to reverse the sickle phenotype by increasing HbF levels to 30–40%, mimicking the benign HbS/HPFH phenotype.[54] We are currently prospectively evaluating this hypothesis in the Hydroxyurea Optimization through Precision Study (HOPS; NCT03789591), a prospective, randomized trial of children (age 6 months to 21 years of age) comparing the benefits of the PK-guided hydroxyurea dosing strategy used in the TREAT study vs. standard weight-based dosing with subsequent dose escalation. The study will help to clarify whether the results found in TREAT (very high HbF levels) are the result of early initiation before 1–2 years of age, robust, individualized starting doses, or a combination of both.

ANALYSIS OF PK DATA FROM TREAT AND THE IMPORTANCE OF BAYESIAN ESTIMATION

As described, for participants enrolled in TREAT, we used hydroxyurea concentrations measured at three time points to constructed individual PK profiles using Bayesian estimation with a previously developed population PK model of pediatric patients with SCA.[49] PK studies were performed at baseline, prior to hydroxyurea therapy, and repeated when a patient had achieved clinically determined MTD. Although the population PK model was developed using data from an older patient cohort (median age 8.8 years), TREAT data

demonstrate that the model is also accurate for Bayesian estimation for the young TREAT cohort (median age 0.9 years), as shown in Figure 4. Analysis of the TREAT PK data also confirm the significant interpatient variability in hydroxyurea PK following individual AUC ranges from 40 to 140 mg*hour/L following a single 20 mg/kg dose. Importantly, the Bayesian estimated AUCs are significantly different from those predicted by the population model ($P = 0.01$; Figure 5), confirming the need of using Bayesian adaptive control for dose recommendations.

EXTENSION OF PRECISION DOSING TO ADULTS WITH SCA: ADULTS ARE NOT LARGE CHILDREN

The earliest studies of hydroxyurea for SCA were performed in adults with the definitive benefits of hydroxyurea most clearly demonstrated in the randomized, placebo-controlled Multicenter Study of Hydroxyurea (MSH).[55] These early trials included dose-finding studies with an emphasis on minimizing toxicity and clearly demonstrated significant interpatient variability in hydroxyurea dosing, response, and toxicity.[55,56] Early investigators noted the narrow therapeutic window of hydroxyurea for adults with SCA with a purported optimal dose (a “sweet spot”) where the HbF response is maximized without excess bone marrow toxicity.[56] Dosing for adults enrolled in MSH was highly variable with doses ranging from 0 (persistent marrow toxicity with any hydroxyurea dose) to 35 mg/kg/day (21% of patients).[16] Although clinical benefits were evident, the HbF response was modest with mean HbF levels of only 8.6%,[57] well below the historical target of 20% of the new target of 30% necessary to be truly protective against HbS polymerization and RBC sickling.[13]

Despite the well-established benefits and guidelines from the National Institutes of Health (NIH)[44] and American Society of Hematology (ASH)[58] recommending widespread use of hydroxyurea therapy in both adults and children with SCA, hydroxyurea remains underutilized, particularly in adults. Although the use of hydroxyurea in children is growing rapidly (from 2.5% in 1997–1999 to 47% in 2015–2017), the increase in the rate of hydroxyurea use is much lower in adults (6.9 to 11% in same time frame).[31] The underutilization in adults with SCA is likely due to the perceived lack of clinical benefits by both providers and patients. Furthermore, an inadequate dose of hydroxyurea may lead to medication noncompliance or perceived poor adherence by the provider and subsequently cause provider-patient mistrust. Despite the claims of subpopulations of patients with SCA who do not respond to hydroxyurea therapy, we feel strongly that the primary reason for suboptimal response is inadequate hydroxyurea exposure (dose).

To date, our PK-guided dosing model has focused on treating young children with SCA, most who are in relatively good health and have not yet developed the chronic organ damage of untreated SCA. In contrast, most adolescents and adults have had decades of untreated SCA that has led to significant chronic organ damage, most notably to the kidneys and bone marrow, which both have important implications on hydroxyurea dosing. Chronic kidney disease alters hydroxyurea PK and AUC such that lower doses are tolerated. Decreased bone marrow reserve results in lower baseline neutrophil and reticulocyte counts, which increases the risk of hematologic toxicity from hydroxyurea therapy. In addition, children are treated

with liquid hydroxyurea (100 mg/mL) that allows for incremental doses as precise as 10 mg, whereas adults are treated with formulations (500 mg capsules or scoreable 1,000 mg tablets) that make exact dosing more difficult. These factors have resulted in an even more conservative dosing approach for adults with SCA with doses as low as 5–10 mg/kg, which certainly is insufficient to completely prevent HbS polymerization and RBC sickling. We hope to build upon our experiences in children to develop an individualized dosing strategy for adults with SCA that will certainly include factors such as renal function and bone marrow reserve.

PRECISION DOSING IN AFRICA

SCA is among the world's most common and devastating blood disorders, affecting >300,000 newborns per year.[1] The majority of infants with SCA are born in low-resource settings of sub-Saharan Africa, where an estimated 50–90% will die before 5 years of age due to lack of early diagnosis and appropriate care.[59] Despite a recent surge in the development of new therapies, hydroxyurea remains the primary treatment for SCA with the most well-established body of evidence demonstrating its ability to reduce morbidity and mortality. Until recently, hydroxyurea was rarely used in sub-Saharan Africa due to concerns regarding feasibility and safety in these low-resource settings. The NOHARM trial (NCT01976416) first established the safety and benefits of moderate, fixed-dose hydroxyurea in comparison to placebo.[60] The REACH trial (NCT01966731) then demonstrated, in four African countries, that open-label hydroxyurea with dose escalation is not only feasible and safe, but also results in substantial clinical benefits, including improved mortality.[61] Most recently, the NOHARM MTD trial (NCT03128515) showed that hydroxyurea dose escalation was safe and provided superior clinical and laboratory benefits compared to a fixed, moderate dose.[62] Although feasibility, safety, and efficacy of hydroxyurea for the treatment of SCA in sub-Saharan Africa is now well-established, the most significant remaining knowledge gap is the appropriate dosing and monitoring strategy to optimize benefits while avoiding toxicity. Importantly, in these limited-resource settings, laboratory monitoring is not available to many patients and there is limited provider expertise in the appropriate dosing and monitoring of hydroxyurea. An individualized, PK-guided approach to establish the optimal starting dose without the need for frequent laboratory monitoring or dose adjustment would be especially appealing in low-resource settings. We are working to develop and implement strategies to allow for PK-guided dosing even in the low-resource settings of sub-Saharan Africa.

EXTENSION OF INDIVIDUALIZED HYDROXYUREA DOSING BEYOND RESEARCH TRIALS

Through our work over the past 5 years, we have demonstrated the feasibility and clinical benefits of individualized hydroxyurea dosing for children with SCA. We have miniaturized the laboratory assay to allow for microsampling requiring only a drop of blood to measure hydroxyurea concentrations using liquid-chromatography tandem mass spectrometry and utilize a sparse sampling strategy requiring the collection of blood at three clinically practical timepoints over 3 hours. The model is being validated further in the HOPS trial to

further confirm the superiority of this dosing strategy compared with weight-based dosing with subsequent dose escalation based on blood counts. We are working to further automate the measurement of hydroxyurea in real-time and to develop an automated method of calculating recommended hydroxyurea starting dose using a web-based calculator or mobile application. We hope that this dosing strategy will soon be widely available and utilized to optimize the benefits and minimize toxicity of hydroxyurea therapy for adults and children with SCA in real-world settings across the world.

CONCLUSIONS

Hydroxyurea is a highly effective yet underutilized medication for the treatment of SCA. The attainment of optimal hydroxyurea benefits requires selection and maintenance of the proper dose, which varies widely from one patient to the next. Inadequate hydroxyurea dosing results in suboptimal clinical responses, poor medication adherence, and decreased utilization of hydroxyurea as a disease-modifying and life-saving medication. We have demonstrated that individualized hydroxyurea dosing for children with SCA results in remarkable clinical and laboratory benefits, beyond that which is seen with traditional dosing. The precision dosing process, which has been utilized for over 100 patients to date through the TREAT and HOPS clinical trials, is clinically feasible and well-received by patients and their families, as well as clinical providers (Figure 6). The increased utilization of this strategy has the capability of changing the clinical paradigm of hydroxyurea treatment from a medication that can ameliorate SCA symptoms to one that can truly prevent all complications and result in a healthy and full life for the millions of patients with SCA across the world. In an era of many new treatments for SCA, hydroxyurea must not be forgotten.

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References

1. Piel FB et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet 381, 142–151 (2013). [PubMed: 23103089]
2. Hassell KL Population estimates of sickle cell disease in the U.S. Am. J. Prev. Med 38 (4 suppl.), S512–S521 (2010). [PubMed: 20331952]
3. McGann PT, Nero AC & Ware RE Clinical features of beta-thalassemia and sickle cell disease. Adv. Exp. Med. Biol 1013, 1–26 (2017). [PubMed: 29127675]
4. Forget BG Progress in understanding the hemoglobin switch. N. Engl. J. Med 365, 852–854 (2011). [PubMed: 21879905]
5. Oneal PA et al. Fetal hemoglobin silencing in humans. Blood 108, 2081–2086 (2006). [PubMed: 16735596]
6. Benz E Anemia: pathophysiology, diagnosis, and management In Anemias, Red Cells, and the Essential Elements of Red Cell Homeostasis (eds. Benz E, Berliner N and Schiffman F) (Cambridge University Press, Cambridge 2017).
7. Sankaran VG & Orkin SH The switch from fetal to adult hemoglobin. Cold Spring Harb. Perspect. Med 3, a011643 (2013). [PubMed: 23209159]

8. Marcus SJ & Ware RE Physiologic decline in fetal hemoglobin parameters in infants with sickle cell disease: implications for pharmacological intervention. J. Pediatr. Hematol. Oncol 21, 407–411 (1999). [PubMed: 10524455]
9. Watson J A study of sickling of young erythrocytes in sickle cell anemia. Blood 3, 465–469 (1948). [PubMed: 18908032]
10. Ngo DA et al. Fetal haemoglobin levels and haematological characteristics of compound heterozygotes for haemoglobin S and deletional hereditary persistence of fetal haemoglobin. Br. J. Haematol 156, 259–264 (2012). [PubMed: 22017641]
11. Forget BG Molecular basis of hereditary persistence of fetal hemoglobin. Ann. N. Y. Acad. Sci 850, 38–44 (1998). [PubMed: 9668525]
12. Buchanan GR "Packaging" of fetal hemoglobin in sickle cell anemia. Blood 123, 464–465 (2014). [PubMed: 24458275]
13. Steinberg MH, Chui DH, Dover GJ, Sebastiani P & Alsultan A Fetal hemoglobin in sickle cell anemia: a glass half full? Blood 123, 481–485 (2014). [PubMed: 24222332]
14. Strouse JJ & Heeney MM Hydroxyurea for the treatment of sickle cell disease: efficacy, barriers, toxicity, and management in children. Pediatr. Blood Cancer 59, 365–371 (2012). [PubMed: 22517797]
15. Lanzkron S et al. Systematic review: hydroxyurea for the treatment of adults with sickle cell disease. Ann. Intern. Med 148, 939–955 (2008). [PubMed: 18458272]
16. Charache S et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Medicine (Baltimore) 75, 300–326 (1996). [PubMed: 8982148]
17. Steinberg MH et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: a 17.5 year follow-up. Am. J. Hematol 85, 403–408 (2010). [PubMed: 20513116]
18. McGann PT & Ware RE Hydroxyurea for sickle cell anemia: what have we learned and what questions still remain? Curr. Opin. Hematol 18, 158–165 (2011). [PubMed: 21372708]
19. Steinberg MH Treating sickle cell anemia: a new era dawns. Am. J. Hematol 10.1002/ajh.25724. [e-pub ahead of print].
20. Elford HL Effect of hydroxyurea on ribonucleotide reductase. Biochem. Biophys. Res. Commun 33, 129–135 (1968). [PubMed: 4301391]
21. Baliga BS, Pace BS, Chen HH, Shah AK & Yang YM Mechanism for fetal hemoglobin induction by hydroxyurea in sickle cell erythroid progenitors. Am. J. Hematol 65, 227–233 (2000). [PubMed: 11074540]
22. Ware RE How I use hydroxyurea to treat young patients with sickle cell anemia. Blood 115, 5300–5311 (2010). [PubMed: 20223921]
23. Platt OS Hydroxyurea for the treatment of sickle cell anemia. N. Engl. J. Med 358, 1362–1369 (2008). [PubMed: 18367739]
24. Cokic VP, Andric SA, Stojilkovic SS, Noguchi CT & Schechter AN Hydroxyurea nitrosylates and activates soluble guanylyl cyclase in human erythroid cells. Blood 111, 1117–1123 (2008). [PubMed: 17993617]
25. King SB A role for nitric oxide in hydroxyurea-mediated fetal hemoglobin induction. J. Clin. Invest 111, 171–172 (2003). [PubMed: 12531869]
26. Pule GD, Mowla S, Novitzky N & Wonkam A Hydroxyurea down-regulates BCL11A, KLF-1 and MYB through miRNA-mediated actions to induce gamma-globin expression: implications for new therapeutic approaches of sickle cell disease. Clin. Transl. Med 5, 15 (2016). [PubMed: 27056246]
27. Mnika K et al. Hydroxyurea-induced miRNA expression in sickle cell disease patients in Africa. Front. Genet 10, 509 (2019). [PubMed: 31231425]
28. Lanzkron S, Haywood C Jr, Hassell KL & Rand C Provider barriers to hydroxyurea use in adults with sickle cell disease: a survey of the Sickle Cell Disease Adult Provider Network. J. Natl. Med. Assoc 100, 968–973 (2008). [PubMed: 18717150]
29. Cabana MD et al. Barriers to pediatric sickle cell disease guideline recommendations. Glob. Pediatr. Health 6, 2333794X1984702 (2019).

30. Haywood C Jr et al. Examining the characteristics and beliefs of hydroxyurea users and nonusers among adults with sickle cell disease. Am. J. Hematol 86, 85–87 (2011). [PubMed: 21117058]
31. Su ZT, Segal JB, Lanzkron S & Ogunsile FJ National trends in hydroxyurea and opioid prescribing for sickle cell disease by office-based physicians in the United States, 1997–2017. Pharmacoepidemiol. Drug Saf 28, 1246–1250 (2019). [PubMed: 31328369]
32. Brousseau DC et al. Hydroxyurea use for sickle cell disease among Medicaid-enrolled children. Pediatrics 144, e20183285 (2019). [PubMed: 31227564]
33. McGann PT & Ware RE Hydroxyurea therapy for sickle cell anemia. Expert Opin. Drug Saf 14, 1749–1758 (2015). [PubMed: 26366626]
34. Antonioli E et al. Hydroxyurea-related toxicity in 3,411 patients with Ph'-negative MPN. Am. J. Hematol 87, 552–554 (2012). [PubMed: 22473827]
35. Diav-Citrin O, Hunnisett L, Sher GD & Koren G Hydroxyurea use during pregnancy: a case report in sickle cell disease and review of the literature. Am. J. Hematol 60, 148–150 (1999). [PubMed: 9929109]
36. Ballas SK et al. Exposure to hydroxyurea and pregnancy outcomes in patients with sickle cell anemia. J. Natl. Med. Assoc 101, 1046–1051 (2009). [PubMed: 19860305]
37. Ware RE, Marahatta A, Ware JL, McElhinney K, Dong M & Vinks AA Hydroxyurea exposure in lactation: a pharmacokinetics study (HELPS). J. Pediatr 222, 236–239 (2020). [PubMed: 32171562]
38. Hankins JS et al. From infancy to adolescence: fifteen years of continuous treatment with hydroxyurea in sickle cell anemia. Medicine (Baltimore) 93, e215 (2014). [PubMed: 25526439]
39. Voskaridou E et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). Blood 115, 2354–2363 (2010). [PubMed: 19903897]
40. Rodriguez GI et al. A bioavailability and pharmacokinetic study of oral and intravenous hydroxyurea. Blood 91, 1533–1541 (1998). [PubMed: 9473217]
41. de Montalembert M et al. Pharmacokinetics of hydroxyurea 1,000 mg coated breakable tablets and 500 mg capsules in pediatric and adult patients with sickle cell disease. Haematologica 91, 1685–1688 (2006). [PubMed: 17145606]
42. Ware RE et al. Pharmacokinetics, pharmacodynamics, and pharmacogenetics of hydroxyurea treatment for children with sickle cell anemia. Blood 118, 4985–4991 (2011). [PubMed: 21876119]
43. Paule I et al. Population pharmacokinetics and pharmacodynamics of hydroxyurea in sickle cell anemia patients, a basis for optimizing the dosing regimen. Orphanet J. Rare Dis 6, 30 (2011). [PubMed: 21619673]
44. Yawn BP et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 312, 1033–1048 (2014). [PubMed: 25203083]
45. Platt OS, Orkin SH, Dover G, Beardsley GP, Miller B & Nathan DG Hydroxyurea enhances fetal hemoglobin production in sickle cell anemia. J. Clin. Invest 74, 652–656 (1984). [PubMed: 6205021]
46. Ware RE Optimizing hydroxyurea therapy for sickle cell anemia. Hematol. Am. Soc. Hematol. Educ. Prog 2015, 436–443 (2015).
47. Alvarez O et al. Effect of hydroxyurea treatment on renal function parameters: results from the multi-center placebo-controlled BABY HUG clinical trial for infants with sickle cell anemia. Pediatr. Blood Cancer 59, 668–674 (2012). [PubMed: 22294512]
48. Ware RE et al. Renal function in infants with sickle cell anemia: baseline data from the BABY HUG trial. J. Pediatr 156, 66–70 e61 (2010). [PubMed: 19880138]
49. Dong M, McGann PT, Mizuno T, Ware RE & Vinks AA Development of a pharmacokinetic-guided dose individualization strategy for hydroxyurea treatment in children with sickle cell anaemia. Br. J. Clin. Pharmacol 81, 742–752 (2016). [PubMed: 26615061]
50. Sheiner LB, Beal S, Rosenberg B & Marathe VV Forecasting individual pharmacokinetics. Clin. Pharmacol. Ther 26, 294–305 (1979). [PubMed: 466923]
51. Sheiner LB, Beal SL. NONMEM Users Guide. San Francisco: Division of Pharmacology, University of California; 1979.

52. Marahatta A, Megaraj V, McGann PT, Ware RE & Setchell KD Stable-isotope dilution HPLC-electrospray ionization tandem mass spectrometry method for quantifying hydroxyurea in dried blood samples. Clin. Chem 62, 1593–1601 (2016). [PubMed: 27694393]

53. Fuchs A, Csajka C, Thoma Y, Buclin T & Widmer N Benchmarking therapeutic drug monitoring software: a review of available computer tools. Clin. Pharmacokinet 52, 9–22 (2013). [PubMed: 23196713]

54. McGann PT et al. Robust clinical and laboratory response to hydroxyurea using pharmacokinetically guided dosing for young children with sickle cell anemia. Am. J. Hematol 94, 871–879 (2019). [PubMed: 31106898]

55. Charache S et al. Hydroxyurea: effects on hemoglobin F production in patients with sickle cell anemia. Blood 79, 2555–2565 (1992). [PubMed: 1375104]

56. Dover GJ et al. Hydroxyurea induction of hemoglobin F production in sickle cell disease: relationship between cytotoxicity and F cell production. Blood 67, 735–738 (1986). [PubMed: 2418898]

57. Charache S et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N. Engl. J. Med 332, 1317–1322 (1995). [PubMed: 7715639]

58. Creary SE & Strouse JJ Hydroxyurea and transfusion therapy for the treatment of sickle cell disease: a pocket guide for the clinician <https://www.hematology.org/Clinicians/Guidelines-Quality/Quick-Ref/3468.aspx> (2014).

59. McGann PT Sickle cell anemia: an underappreciated and unaddressed contributor to global childhood mortality. J. Pediatr 165, 18–22 (2014). [PubMed: 24630351]

60. Opoka RO et al. Novel use of hydroxyurea in an African Region with Malaria (NOHARM): a trial for children with sickle cell anemia. Blood 130, 2585–2593 (2017). [PubMed: 29051184]

61. Tshilolo L et al. Hydroxyurea for children with sickle cell anemia in sub-Saharan Africa. N. Engl. J. Med 380, 121–131 (2019). [PubMed: 30501550]

62. John CC et al. Hydroxyurea dose escalation for sickle cell anemia in Sub-Saharan Africa. N. Engl. J. Med 382, 2524–2533 (2020). [PubMed: 32579813]

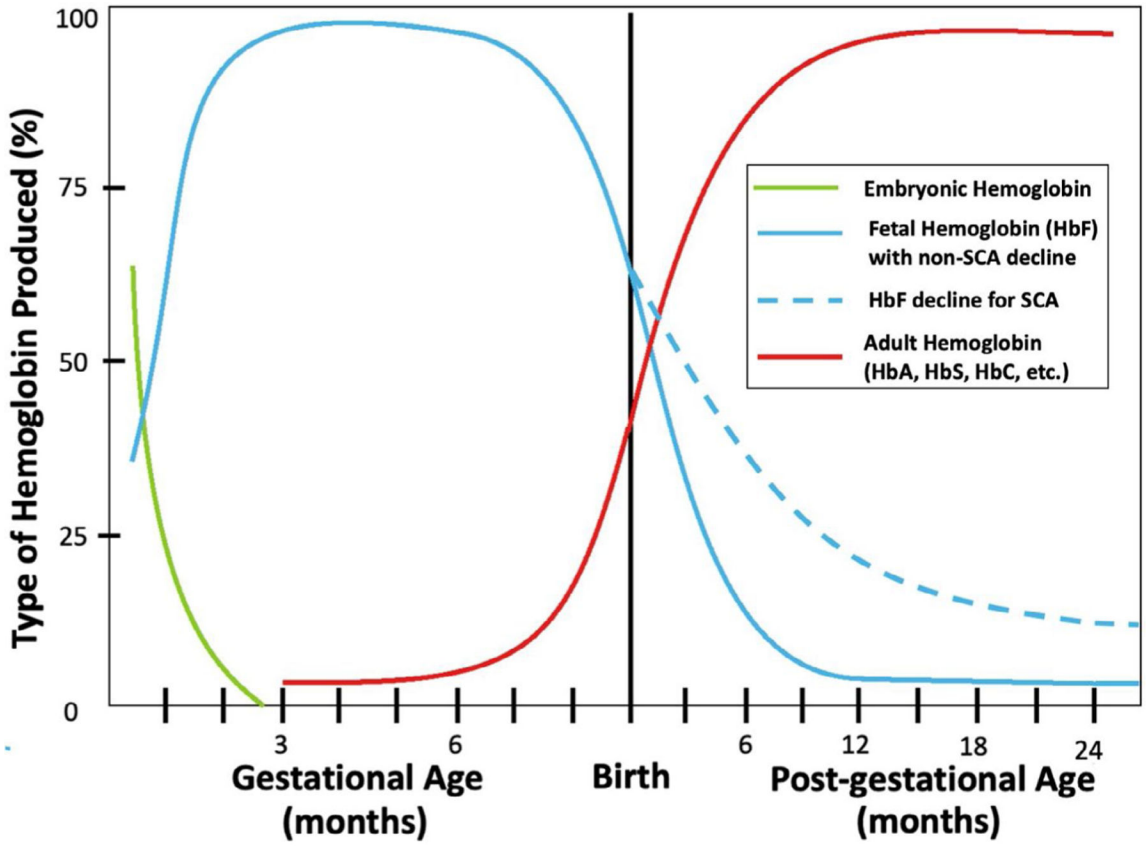

Figure 1.

Developmental hemoglobin switching. This illustrates the developmental hemoglobin switching that occurs during and after gestation. Embryonic hemoglobins are rapidly silenced in the first weeks of gestation and fetal hemoglobin predominates until late in the third trimester, when adult forms of hemoglobin begin to be produced. For infants without sickle cell anemia (SCA), this fetal hemoglobin (HbF) silencing is rapid with very little residual HbF by 6–12 months of age. For infants with SCA, HbF silencing is more gradual and children have a variable degree of residual HbF with further reductions in HbF levels through approximately the first 5 years of life. Figure adapted from multiple sources.[6–9]

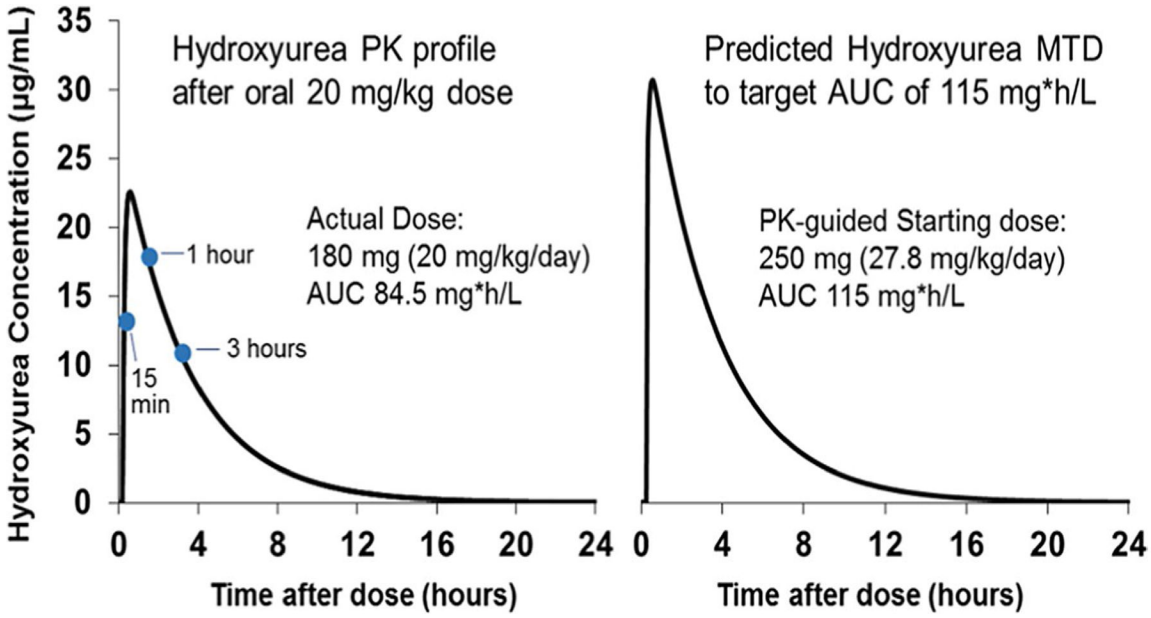

Figure 2.

Individualized, pharmacokinetic (PK)-guided hydroxyurea dose selection using sparse sampling. For the determination of an individualized, PK-guided hydroxyurea dose, patients take a single oral 20 mg/kg dose, followed by the collection of blood samples 15, 60, and 180 minutes after the dose. The left side of the figure demonstrates how hydroxyurea concentrations at these timepoints are incorporated into a population PK model to determine the hydroxyurea PK profile and to estimate hydroxyurea exposure, as defined by area under the concentration-time curve (AUC). The right side of the figure illustrates how the individualized PK profile is used to determine the required dose to target an AUC of 115 mg*hour/L, demonstrated to be the mean AUC for a cohort of patients who had achieved the optimal, maximum tolerated dose (MTD). This target dose is then selected as the starting dose.

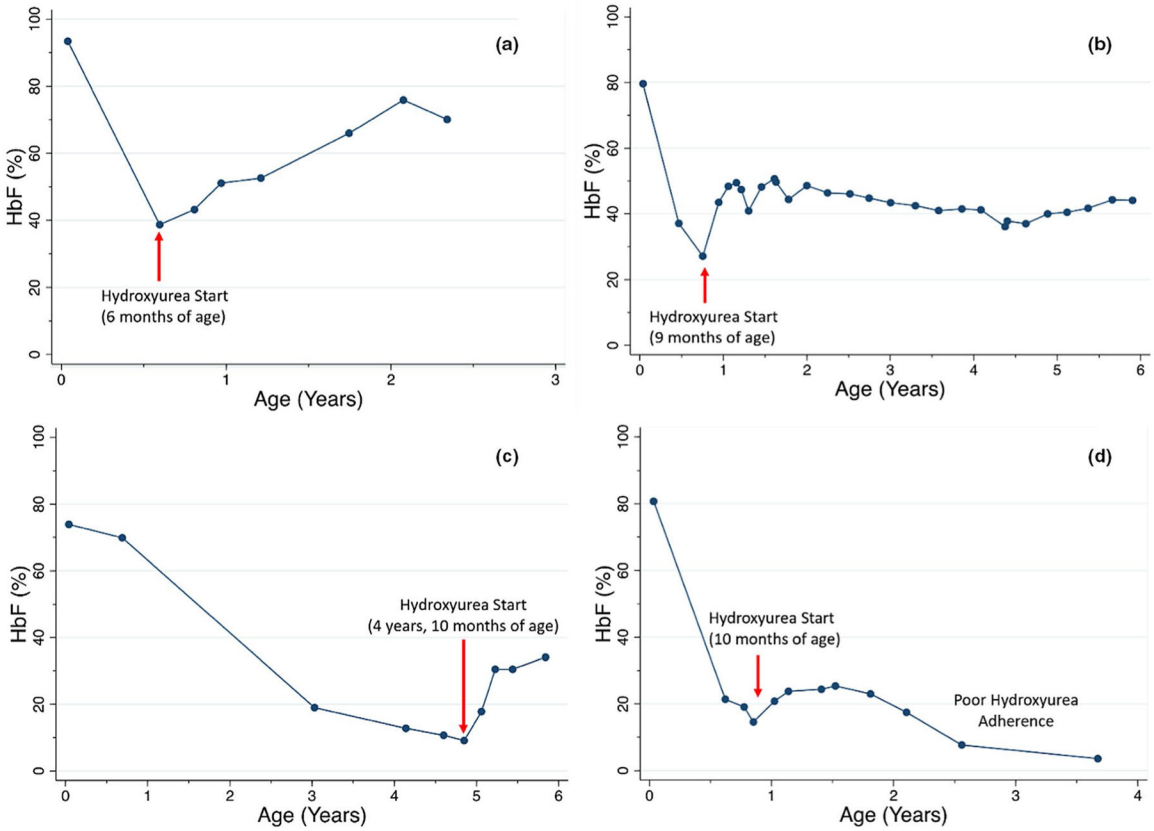

Figure 3.

Fetal hemoglobin (HbF) induction with individualized hydroxyurea dosing. With individualized, pharmacokinetic-guided dosing, participants enrolled in the Therapeutic Response Evaluation and Adherence Trial (TREAT) study achieved and sustained HbF levels beyond 30–40% for children initiating hydroxyurea at young ages (**a, b**) and older ages, beyond the expected time of HbF silencing (**c**). For infants beginning hydroxyurea as early as 6 months of age, HbF levels increased to >70% **a**. Medication nonadherence is an important factor, as HbF levels sharply decline when hydroxyurea is not taken as prescribed (**d**).

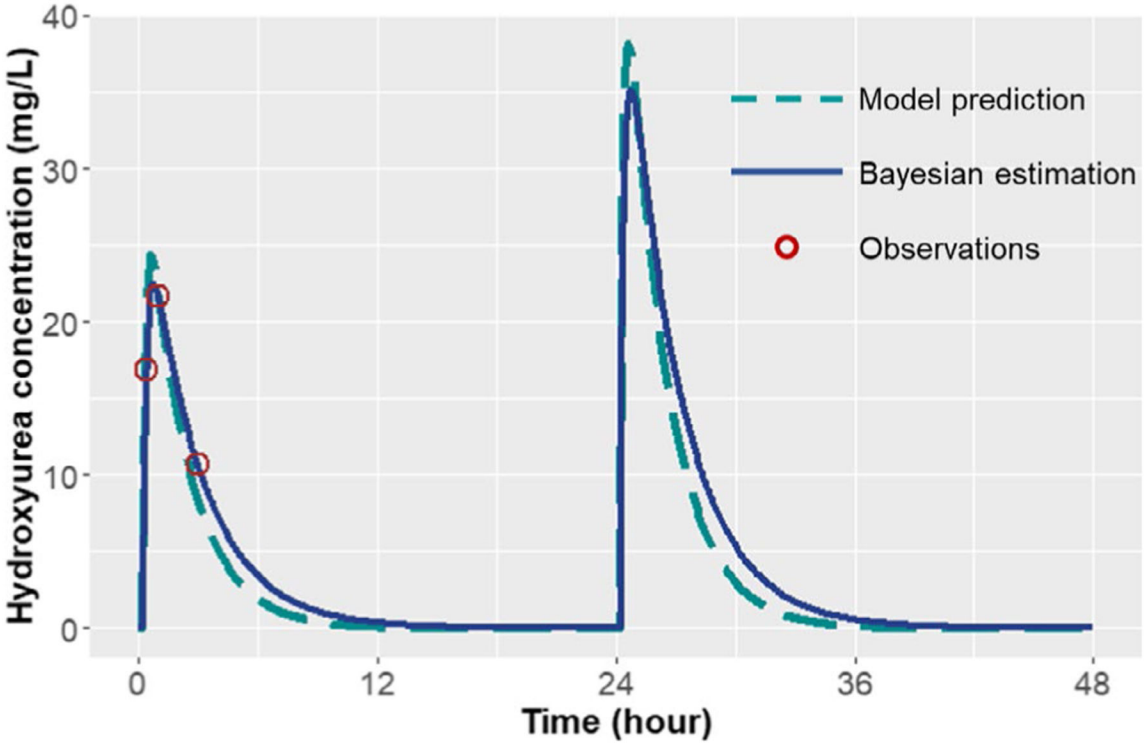

Figure 4.

Bayesian estimation of hydroxyurea pharmacokinetic (PK) profile. The figure illustrates a representative hydroxyurea PK profile re-constructed using Bayesian approach (blue line) vs. population model prediction (teal dashed line). In this young child of 7 months old, Bayesian algorithm generated an area under the concentration-time curve (AUC) prediction of 75 mg*hour/L (blue line), which is slightly different from model prediction (teal dashed line). Based on the exposure target of 115 mg*hour/L, an optimal starting dose of 30.2 mg/kg was selected to achieve the target.

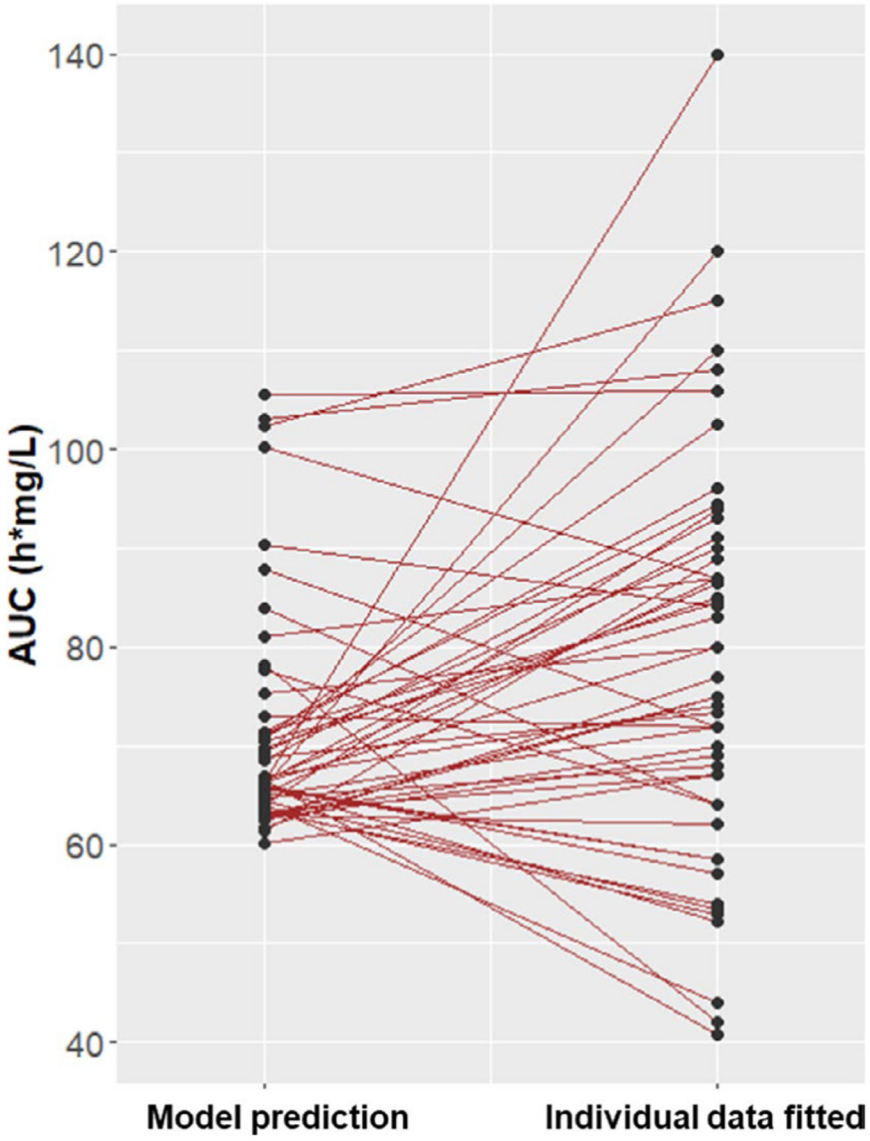

Figure 5.

Interpatient variability in hydroxyurea pharmacokinetics (PKs) and benefits of Bayesian adaptive control. There is significant interpatient variability in hydroxyurea PKs with individual area under the concentration-time curves (AUCs) ranging from 40 to 140 mg*hour/L. Bayesian estimation of AUC for individual patients demonstrates a more accurate estimation of individual hydroxyurea exposure than the population model alone.

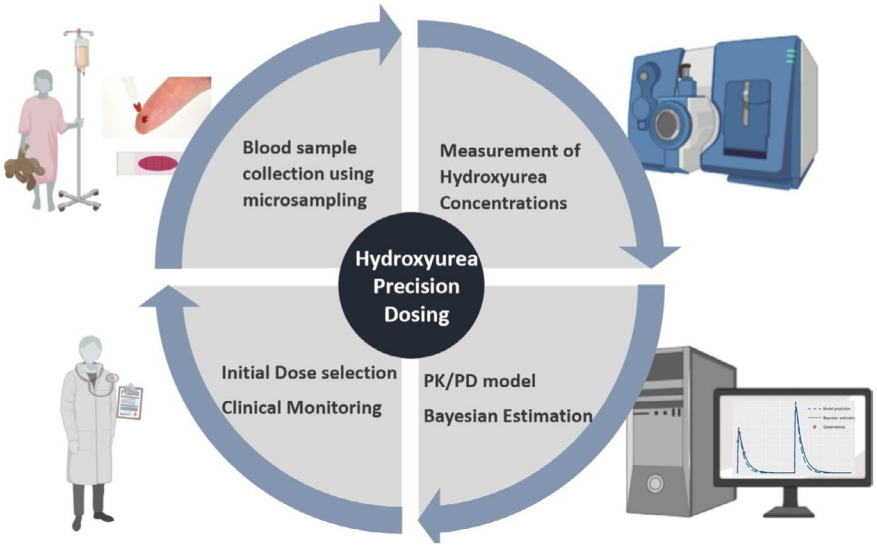

Figure 6.

Precision dosing process. The figure illustrates the process of hydroxyurea precision dosing, from blood collection through initial dose selection. We have performed this process for more than 100 patients through the Therapeutic Response Evaluation and Adherence Trial (TREAT) and Hydroxyurea Optimization through Precision Study (HOPS) trials with satisfaction by both patient and providers.