

Retrospection of the effect of hydroxyurea treatment in patients with sickle cell disease

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Abstract

Sickle cell anemia (SCA) is one of the inherited hemoglobin disorders with substantial morbidity and early mortality. Hydroxyurea is the US Food and Drug Administration (FDA)-approved medication that has emerged as the primary disease-modifying therapy for SCA. Our purpose is to summarize the available evidence regarding the pharmacology, clinical efficacy, and safety of hydroxyurea therapy for the treatment of SCA. The electronic databases PubMed and Embase were searched from their starting dates to May 31, 2016. Databases were searched using the following terms: sickle cell, hydroxyurea, nitric oxide, dosing, therapeutic, and safety monitoring. Hydroxyurea therapy may cause severe myelosuppression when used in patients with SCA. SCA patients are initially treated with hydroxyurea at 10 or 20 mg/kg, and then the dose is escalated to mild myelosuppression using a standardized regimen. Routine blood monitoring should be performed while the patient receives hydroxyurea treatment. Hydroxyurea can increase fetal hemoglobin (HbF) level and ameliorate some of the vascular symptoms in patients with SCA. Hydroxyurea therapy may help to avoid frequent hospitalizations, especially in patients with vaso-occlusive crisis. Taken together, available evidence suggests that hydroxyurea represents an inexpensive and effective treatment option that should be offered to patients with SCA.

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Keywords:

sickle cell disease, hydroxyurea; HbF, NO, side effects

Introduction

Hemoglobinopathies are a group of inherited disorders of hemoglobin, which result in either structurally abnormal or abridged synthesis of beta globin subunits (Fig. 1). A single-nucleotide transversion (A>T) in the *HBB* gene causes the change of glutamic acid (Glu) to valine (Val) at the sixth position of its protein, which leads to the production of structurally abnormal hemoglobin (HbS). HbS facilitates the polymerization of hemoglobin and distorts the red blood cells (RBCs) to assume a sickle shape, especially when under low oxygen tension and this condition is known as sickle cell anemia (SCA) [1]. Abridged or absent synthesis of the beta globin chains shows variable outcomes ranging from severe anemia to clinically asymptomatic individuals, the disorders being called beta-thalassemias (β -thalassemias) [2]. Similarly, impaired production of alpha globin chains from one, two, three, or all four of the alpha globin genes is called as alpha-thalassemia (α -thalassemia). In addition to SCA, and the beta and alpha thalassemias, there are several documented regional hemoglobinopathies, such as HbC, HbD, HbE, and HbO.

The distribution of hemoglobinopathies varies from place to place, and much of the global burden of hemoglobinopathies is mainly correlated with malaria endemicity [3]. Further, hemoglobin SS disease (SCA) is the most common cause of sickle cell disease (SCD) and is most prevalent in Africa, Asia, and Mediterranean regions [4]. Beta-thalassemia is prevalent in populations of African descent and in regions of the Mediterranean, the Middle East, Transcaucasus, Central Asia, Indian subcontinent, and the Far East. Highest incidences of beta-thalassemia are found in populations of Cyprus

(14%), Sardinia (12%), and Southeast Asia [5]. Alpha-thalassemia is more common in sub-Saharan Africa, the Mediterranean Basin, the Middle East, South Asia, and Southeast Asia [6, 7, 8, 9].

In SCA, the deformed RBCs tend to get stuck in narrow blood capillaries and block the blood flow. Patients experience vaso-occlusive crisis (VOC) in their joints and bones, along with severe pain, which causes multiple organ damage (Fig. 2) in SCD patients [10]. Further, these patients – in younger age – have increased susceptibility to infections, acute chest syndrome, and stroke, while – in older age – they are susceptible to retinopathy, as well as damage to the lungs, kidney, and heart [11, 12]. In addition to VOC, sickle cell patients experience sequestration crisis (pooling of blood in an organ), aplastic crisis (reduced function of bone marrow), and hemolytic crisis (rapid breakdown of blood cells). Presence of high levels of fetal hemoglobin (HbF) inhibits polymerization in SCA patients, highlighting the role of HbF ($\alpha_2\gamma_2$) in SCD. Although the pathophysiology of SCA is well understood, its management mainly depends on supportive care. Several lines of evidence show that pharmacological induction of HbF helps in the prevention of intracellular sickling, which in turn reduces hemolysis and vaso-occlusion. Hydroxyurea (HU) is an effective and strong inducer of HbF.

Properties of HU

HU is a ribonucleotide reductase inhibitor that inhibits DNA replication in a wide variety of cells. HU is an antimetabolite cytotoxic drug. HU has excellent oral bioavailability [13], with a biological half-life of about 2-4 hours in both children and adults [14, 15]. The elimination of HU from the blood is relatively rapid and appears to have an acceptable

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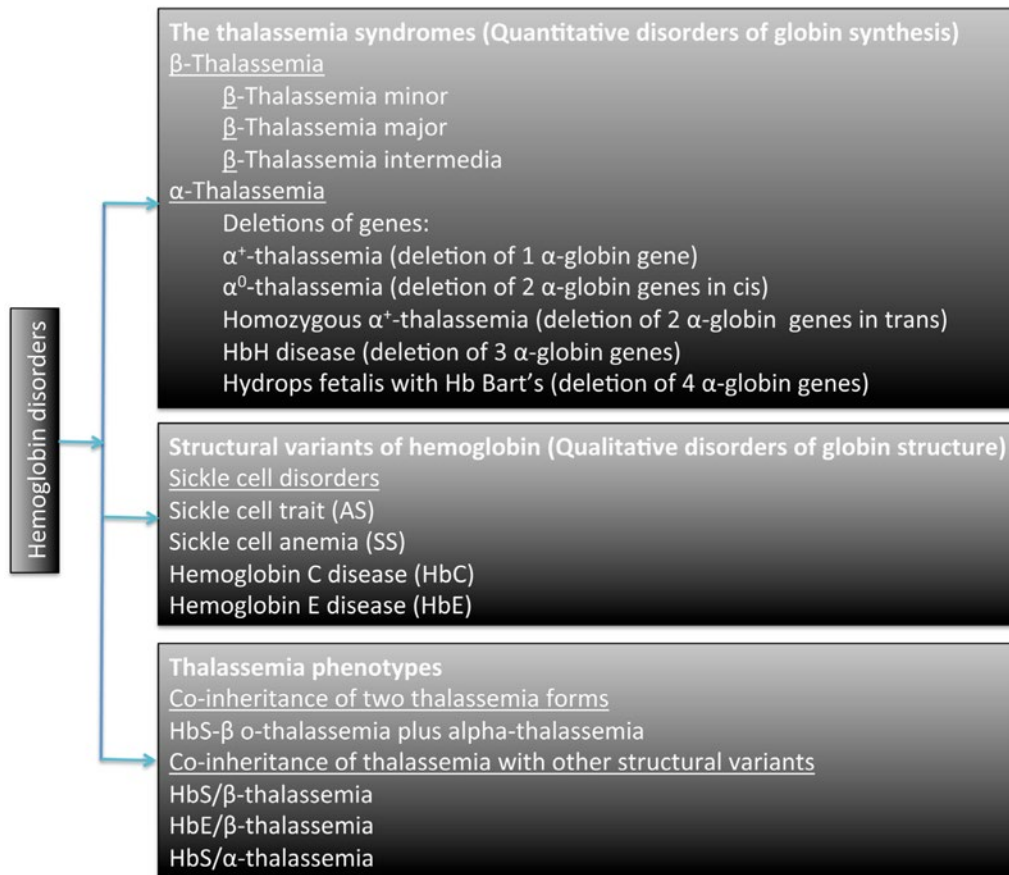


Fig. 1. Classification of inherited hemoglobin disorders

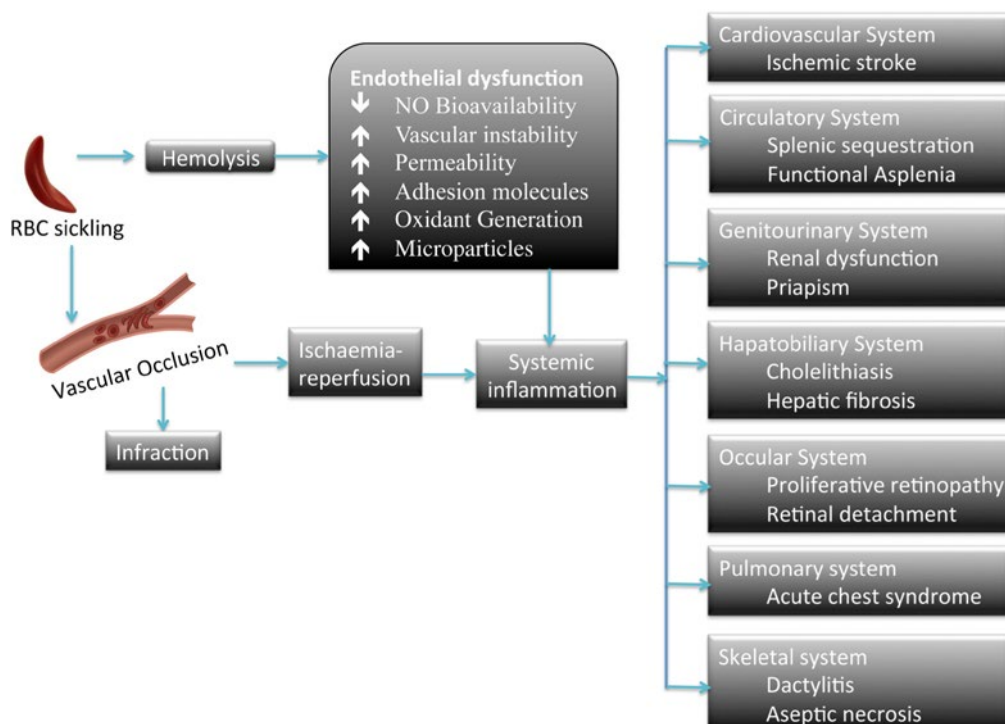


Fig. 2. Complications of sickle cell anemia

safety profile, as indicated by lower hepatic and renal toxicity [16]. Recent studies have demonstrated the involvement of drug transport proteins in the in vivo absorption, cellular distribution, and elimination of HU [17]. HU has long been utilized in both human and veterinary medicine. Although it was first synthesized in 1869, trials for testing the safety of this drug in humans started only after a century [18]. The United States Food and Drug Administration (FDA) in 1967 approved HU for the treatment of certain solid, myeloid tumors. Further, both the US FDA and, in the European Union, the European Medicines Agency (EMA) have approved HU for the treatment of SCD in 1998 and 2007, respectively. The present review focuses on the clinical benefits of HU in SCD and enhances the current understanding of the possible mechanisms of benefit for these hemoglobinopathies.

HbF induction

HU has been in use for the treatment of SCD over many years. The main rationale behind the usage of HU for the treatment of SCD is its ability to induce HbF [19]. The possible cellular and vascular effects of HU are depicted in figure 3. Several lines of evidence suggest that HU elicits HbF induction and offers clinical benefits to SCD patients through a wide range of possible mechanisms [20]. The precise mechanism of HbF induction by HU is not fully

known; however, it is mediated mainly by the redox inactivation of a tyrosyl radical on the enzyme ribonucleotide reductase [21]. The absorption, distribution, and excretion of HU vary greatly among individuals. HU causes intermittent cytotoxic suppression of erythroid progenitors and cell stress signaling, which leads to recruitment of erythroid progenitors with increased HbF levels [22, 23, 24]. HU is also involved in free radical formation, iron chelation, activation of soluble guanylyl cyclase, and direct nitric oxide (NO) production [25]. HU shows cytotoxic effects and reduces the absolute numbers of neutrophils, reticulocytes, and platelets in the bone marrow. Reduction of platelets reduces inflammation, while reduction of neutrophils and reticulocytes reduces the surface expression of adhesion receptors and alters the adhesion of RBCs to the endothelium [26].

NO production

NO plays a critical role as a molecular mediator of a variety of physiological processes, including vascular tone regulation and neurotransmission. NO synthesis results from the action of NO synthetase (NOS) on nonessential amino acids, such as arginine, and molecular oxygen [27]. Further, this free-radical gas molecule is produced in vitro by the oxidation HU by heme groups [28]. Significant

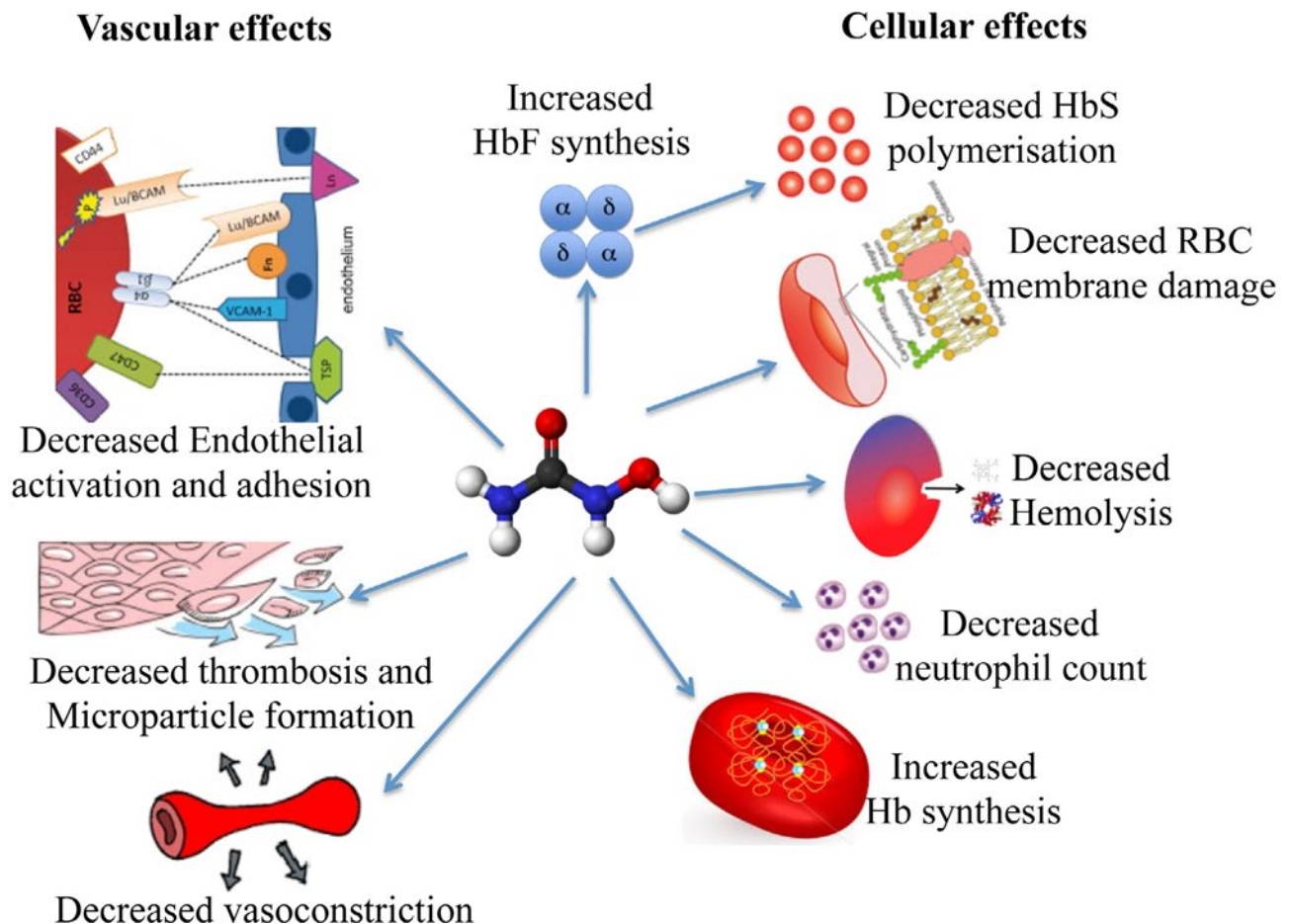


Fig. 3. Multiple effects of hydroxyurea administration in sickle cell disease patients

increase in NO-derived species after an oral dose of HU indicates NO release from HU in vivo [29]. These observations provide a strong argument for the participation of NO in the mechanism of HbF induction by HU [30]. Further, NO can promote the modification of cysteine 93 in the hemoglobin b-chain, by nitrosation [31] or transnitrosation reactions, to form glutathionyl hemoglobin [32], which inhibits HbS polymerization [33]. Downregulation of endothelial expression of vascular cell adhesion molecule (VCAM)-1 has been reported with both NO and HU therapy [34].

Modulation of RBC – endothelial cell interactions

VOCs are the acute complications of SCD and are initiated by the abnormal adhesion of circulating blood cells to the vascular endothelium of the microcirculation. Recent studies have shown that various signalling pathways activate erythroid cell adhesion molecules (CAMs) and their ligands. The intricate network of interactions involving adhesion molecules between sickle RBCs and the endothelial vascular wall has been documented [35]. Modulation of several cellular biophysical properties upon HU treatment has been demonstrated in previous studies [36, 37].

Myelosuppressive effect

Myelosuppression is the dose-limiting effect of HU. Although, HU therapy results in limited myelotoxicity in SCD patients [38], it decreases the level of reticulocytes, neutrophil count, and the rate of crisis [39]. Neutrophils release powerful proinflammatory mediators that play an important role in endothelial damage and release of cytokines, both of which trigger sickling activity [40]. Hence, both neutropenia and neutrophilia have long been reported as markers of severity in SCD [41]. Comparison of polymorphonuclear leukocytes (PMNs) or neutrophils from normal individuals and sickle cell patients has revealed that these cells are less deformable and more rigid in sickle cell patients [42]. HU treatment corrected the dysregulated neutrophil L-selectin expression in SCD patients [43].

Proof of efficacy

In adults, HU increases the amount of total hemoglobin as well as HbF and thereby reduces acute complications, in terms of both number and severity [44]. After studying the safety and efficacy of HU therapy in patients with SCA, HU has been approved for the treatment of adult sickle cell patients [45]. Furthermore, prolonged HU therapy in infants with SCA showed sustained hematologic benefits, reduced acute coronary syndrome (ACS) events, improved growth, and preserved organ function. The Hydroxyurea Safety and Organ Toxicity (HUSOFT) extension study revealed that patients who continued the HU therapy showed better spleen function than expected and improved growth rates [46]. Regeneration of splenic function was also demonstrated in adult patients with severe hemoglobin SC disease [47]. Many studies used level of HbF induction as a predictor of HU therapy. A substantial increase in serum erythropoietin levels has been noted, 2–3 weeks after initiation of HU treatment in SCA and HbS/beta-thalassemia patients [48].

Attenuation of organ dysfunction

Although there was a great improvement in survival for children with SCD, the failure of two or more organ systems is associated with morbidity in SCD. Sickle cell patients develop splenic dysfunction early (4-6 months of age) in the course of their disease [49]. This raises the possibility that HU therapy might be able to exert a significant disease-modifying effect in young children with SCD. The efficacy of HU in preventing acute complications and organ damage in children with SCA was assessed in a Phase III multicenter randomized controlled trial of HU (BABY HUG trial). During this trial, 20 mg HU/kg/day was given to 9- to 18-month-old children with HbSS or sickle b0-thalassemia for a period of 2 years [50]. The Stroke With Transfusions Changing to Hydroxyurea (SWITCH) trial compared 30 months of alternative therapy (hydroxyurea and phlebotomy) with standard therapy (transfusions and chelation) in the prevention of secondary stroke and reduction of transfusional iron overload [51]. Subsequent reports suggest that HU treatment showed clinical efficacy in children with variable sickle-related organ damage, including proteinuria [26], spleen dysfunction [42], hypoxemia [52], pulmonary hypertension [53], glomerular hyperfiltration [54], neurocognitive delay [53], silent brain infarcts [41], elevated transcranial Doppler (TCD) velocities, and primary stroke [55, 56]. Furthermore, a Belgian multicenter study showed a mean hospital stay of 5.3 days in the HU-treated group and 15.2 days in the placebo group [57].

SCD management with HU

Although there is no cure for SCD, the oral chemotherapeutic drug HU is used for ameliorating the disease and improving life expectancy for most patients. The randomized BABY HUG trial has demonstrated that HU significantly reduces the incidence of VOC and dactylitis in young children [50]. There are no universally agreed indications for the initiation HU therapy in SCD patients. However, team members must review the medical history and discuss the recommendation openly with patients and families before initiating HU therapy. The initial dosage of HU for adults is 15 mg/kg/day; the dose may be reduced further to 10 mg/kg/day in patients with impaired renal function. The HUSOFT and BABY HUG trials demonstrated that 20 mg/kg/day improved hematologic parameters, provided substantial clinical benefits, and had an excellent safety profile [58, 59]. Several clinical trials have reported good clinical outcomes by using a “clinically effective dose” of 15–20 mg/kg/day [60, 61]. The positive effects of HU can be seen within weeks of commencing therapy [62]. The primary toxicity observed was neutropenia. When adjusting dosage, continuous monitoring of complete blood count (CBC) and absolute reticulocyte count (ARC) should be adopted at least every 4 weeks [63].

Further study is needed to evaluate the long-term treatment effects on growth and development, as well as on kidney, lung, and central nervous system function. A randomized, placebo-controlled trial in adults did not demonstrate a significant improvement in the time to resolution of VOC [64]. Adults with SCD should be evaluated for known stroke risk factors and managed according to the 2011 American Heart Association/American Stroke Association (AHA/ASA) primary stroke prevention guidelines. HU or bone marrow

transplantation is the only option for children at high risk for stroke in whom RBC transfusion is contraindicated [65]. HU therapy decreases TCD flow velocities [66], and this decrease may be associated with decreased turbulent flow and the consequent endothelial damage around the stenosis. An open-label pilot study revealed that long-term HU therapy improved cerebral oxygen saturation [67]. However, this improved oxygen saturation may raise the threshold for infarction by augmenting the oxygen reservoir [68]. The BABY HUG trial reported that cerebrovascular events occur only in about 10% of SCD children taking HU therapy [50]. Hence, HU seems to be a highly useful alternative and is relatively free of serious side effects.

Adverse effects of HU

Results of the BABY HUG Trial revealed that HU has an excellent safety profile, and side effects of HU therapy in young patients with SCD are usually low. As HU causes severe myelosuppression, patients should be monitored during treatment for cytopenias very carefully, particularly while seeking the maximum tolerated dose [69]. In children receiving HU therapy, kidney and liver toxicity was not statistically significant compared to the placebo group [70]. Further, these groups showed similar rates of cytopenia, including severe neutropenia, thrombocytopenia, and anemia with reticulocytopenia. Furthermore, a MSH study reported hair loss, skin rash, gastrointestinal disturbance, and fever in the HU-treated group, but it was not statistically significant compared to the placebo group [71]. Cutaneous side effects include nail hyperpigmentation, as well as increased skin pigmentation on the palms and soles [72]. Further, leg ulceration has been reported as a rare cutaneous manifestation of HU therapy in a few studies [73, 74, 75]. Assessment of renal function and the pharmacokinetics of HU indicate that the renal impairment results in increased systemic exposure and decreased urinary recovery of the drug [16]. Some patients receiving HU therapy showed mild albuminuria, with an increase in white cells and granular casts, as well as occasional red cells, in the urine [76]. However, the BABY HUG trial demonstrated that HU is associated with better urine-concentrating ability and less renal enlargement, in addition to improvement in overall renal function [58]. Studies in animal models revealed that HU therapy inhibits spermatogenesis and results in hypogonadism [77]. Semen analysis of SCD patients demonstrated impaired sperm count, motility, and morphology while taking HU therapy [78].

There is increasing concern about the occurrence of malignancy or myelodysplasia in patients with SCD on HU therapy [79, 80].

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Several scattered reports document the malignancy that occurs in both children and adults with SCD but do not provide complete information on the incidence of various cancer types [81, 82, 83, 84, 85]. Furthermore, a multicenter study that assessed the risks and benefits for up to 9 years of HU treatment did not show development of secondary leukemia in adults [86]. This indicates that the carcinogenic potential of HU in clinical settings is much less influential. HU is a potent teratogen in all animal species yet tested and thus qualifies as a universal teratogen [87]. The teratogenicity of HU was demonstrated by documenting various anomalies in the central nervous system, palate, as well as the genitourinary, cardiac, ocular, and multiple skeletal systems [88, 89, 90]. As very large doses (> 250 mg/kg per 24 hours) have been reported as teratogenic, the safety of HU therapy in pregnancy remains unclear. Outcome of pregnancy with HU treatment in 31 cases revealed that there was no major malformation in the case series with exposure to HU [91]. However, this study documented significant rates of intrauterine growth retardation (IUGR), fetal death, and prematurity; hence, careful follow-ups with physical, biological, and sonographic examination are warranted. A follow-up study of the original MSH trial revealed that exposure of the fetus to HU does not cause teratogenic changes [92].

Conclusions

HU is available by prescription in oral tablet, capsule, or oral syrup form. Dose concentrations of HU vary greatly in sickle cell patients, so it is critical to follow the prescription as directed by the doctor in order to see assured treatment results. Hence, SCD patients are initially treated with HU at 10 or 20 mg/kg and then dose-escalated to mild myelosuppression using a standardized regimen. Routine blood monitoring should be performed while the patient receives HU treatment. Treatment with HU should not be initiated if bone marrow function is markedly depressed. Despite the continued and growing clinical experience with HU therapy, several important areas call for further research to overcome the barriers to HU utilization among SCD patients.

Conflict of interest

There are no conflicts of interests.

Authors' contributions

All authors have contributed equally and approve the manuscript.

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