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Review article

Hydroxycarbamine: from an Old Drug Used in Malignant Hemopathies to a Current Standard in Sickle Cell Disease

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Abstract. While hydroxycarbamide (hydroxyurea, HU) has less and fewer indications in malignant hemopathies, it represents the only widely used drug which modifies sickle cell disease pathogenesis. Clinical experience with HU for patients with sickle cell disease has been accumulated over the past 25 years in Western countries. The review of the literature provides increasing support for safety and efficacy in both children and adults for reducing acute vaso-occlusive events including pain episodes and acute chest syndrome. No increased incidence of leukemia and teratogenicity was demonstrated. HU has become the standard-of-care for sickle cell anemia but remains underused. Barriers to its use should be identified and overcome.

Keywords: Hydroxyurea; Treatment; Sickle Cell Anemia; Clinical Management; Hemoglobinopathies; Prognosis.

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Introduction. Hydroxycarbamide (Hydroxyurea, HU) was first synthesized in Germany in 1869,[1] but its potential biologic significance was not recognized until 1928.[2] It is a simple compound of the formula, $H_2NCONHOH$, which the =C−NHOH moiety is responsible for its biological activity (**Figure 1**). HU is a potent inhibitor of DNA synthesis. It is antimitotic and cytotoxic depending upon the used concentration, the duration of exposure, and the sensitivity of the organism. HU is active mainly in the S-phase of the cell cycle. In the 1950s the drug was evaluated in a large number of experimental tumor models and was found to have broad anti-tumor activity against both leukemia and solid tumors.[3] Clinical trials began in the 1960s.[4] As an antineoplastic drug, HU has some advantages. It may be used with ambulatory patients and has relatively few side effects, which are relieved almost immediately after withdrawal of the drug. The drug is readily absorbed from the gastrointestinal tract following oral administration. Peak serum concentrations are reached in 1 to 2 hours, and the serum half-life is about 5.5 hours. It is rapidly excreted in the urine, and it is reported that up to 70% of the dose is excreted unchanged.[5] At present, HU has only a limited medical use in acute leukemia, consisting in reducing and controlling white blood cell count in patients with hyperleukocytosis. The principal use of HU has

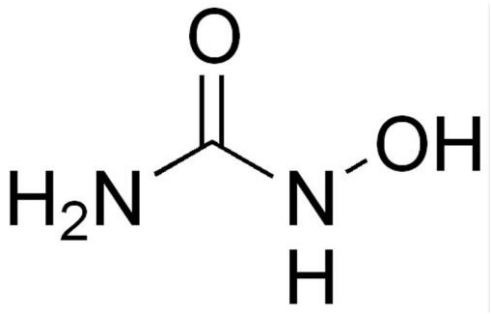

Figure 1. Structure of hydroxycarbamine (hydroxyurea, HU).

been as a myelosuppressive agent in the myeloproliferative syndromes. The efficacy of HU as initial therapy for chronic myeloid leukemia (CML) has been known for a number of years.[6] Since the introduction of tyrosine kinase inhibitors in the treatment of CML, hydroxyurea is essentially used in the *BCR-ABL1*-negative myeloproliferative neoplasms, including polycythemia vera, essential thrombocythemia, and primary myelofibrosis.[7] In high-risk patients with polycythemia vera or essential thrombocythemia, HU remains the first-line cytoreductive drug of choice, the second-line choice being represented by interferon-alpha and busulfan.[8,9] Survival is relatively long in these diseases, and risk of leukemic transformation low. Treatment with HU has not been shown to modify these favorable outcomes, while controlled clinical trials have shown increased risk of acute leukemia with the use of chlorambucil, radiophosphorus and pipobroman, and increased risk of fibrotic transformation with the use of anagrelide.[7] The introduction of new drugs should, therefore, be careful. This is particularly important when considering the use of *JAK* inhibitor ruxolitinib, which was recently approved for use in these pathologies. HU also remains the first-line drug of choice for myelofibrosis-associated splenomegaly, while hydroxyurea-refractory splenomegaly is often managed with ruxolitinib therapy or splenectomy.[10] In addition to its use as an anti-cancer agent, HU has found some marginal applications in dermatology.[11]

While HU is an old drug that can still be used to control essential thrombocythemia and polycythemia vera in patients with high-risk disease, it has emerged over the last decades as the primary disease-modifying therapy for sickle cell anemia, a non-malignant inherited disease. The purpose of this short review is to provide the reader a comprehensive understanding of HU and to reinforce the fact that HU is a safe and effective medication for the treatment of sickle cell disease.

Sickle Cell Disease: Historical Considerations. Sickle cell anemia, first described by James B Herrick in 1910,[12] is the first inherited disease identified at the molecular level. In 1949, Linus Pauling confirmed an intrinsic dissimilarity in the hemoglobin from patients with sickle cell anemia on electrophoretic mobility patterns.[13] Because of the heterozygote state, sickle cell trait, appeared to persist in some populations with prevalence as high as 20%-40% and the sickle cell trait allele frequency overlapped with malarial endemicity, AC Allison hypothesized that sickle hemoglobin (HbS) must confer a selective advantage of malarial resistance in the carrier state.[14] A recent meta-analysis confirmed a strong protective advantage of sickle cell trait for *Plasmodium falciparum* malaria, suggesting that HbS does not protect against infection itself, but rather to progression to clinical malaria and its childhood associated-mortality.[15] Although not elucidated, the suggested mechanisms involved in this epidemiologic observation comprise a protective effect through enhanced immunity, increased clearance of infected erythrocytes, and reduced parasite growth. In 1956, VM Ingram discovered a single amino acid substitution in HbS.[16] The genetic basis for the abnormal hemoglobin was a single base-pair change (A → T) in the β-globin gene, resulting in a substitution of a valine for glutamic acid at position 6. Structural changes promote polymerization into long fibrils, distorting the red cell into a sickle shape, leading to erythrocytes dehydrated, rigid and prone to hemolysis, and so to occluding the microvasculature causing acute and chronic tissue ischemia and injury. It took then until the 1970s for systematic research into the laboratory screening techniques and clinical sequelae of sickling disorders to be prioritized.[17] At that time, only 50% of afflicted children survived into adulthood.[18] As a result of the institution of the National Sickle Cell Anemia Control Act, a Hemoglobinopathy Reference Laboratory was created to standardize techniques and elaborate screening programs.[19] By the 1990s, widespread mandatory newborn screening and the routine administration of penicillin to prevent pneumococcal sepsis increased childhood survival to over 90%.[20] Currently, the most common

screening techniques include sickle solubility testing, hemoglobin electrophoresis, high-performance liquid chromatography, and isoelectric focusing, each with their own advantages and limitations. Recent advances in technology have also allowed for detection of sickle cell trait from DNA through exome sequencing.[21,22] Indeed misclassification of individuals with sickle cell trait and sickle cell disease in early case reports led to confusing series in which sickle cell disease complications were ascribed to individuals with sickle cell trait.

No specific therapy was available until the 1970s when it was recognized that patients with increased red blood cell HbF had fewer adverse clinical events. First described as a potential therapy for sickle-cell anemia in 1984, HU enhances the production of fetal hemoglobin production in sickle erythrocytes.[23] The two most common acute morbidities in sickle cell anemia are vaso-occlusive pain crises and acute chest syndrome, corresponding to the occlusion of small vessels in the bone marrow and lungs, respectively.[24,25] Other pulmonary complications of sickle cell disease include pulmonary hypertension, pulmonary artery thrombosis, and pulmonary fibrosis, with an increased prevalence of reactive airways disease, increased tricuspid regurgitant jet velocity, sleep-disordered breathing, and nocturnal hypoxemia.[26] On a chronic basis, vaso-occlusion may damage the lungs, kidney or brain accounting ultimately for most deaths in patients with sickle cell disease.[27] Clinical studies with HU demonstrated a decreased rate of vaso-occlusive disease and acute chest syndrome, and an improved survival.[28] Consequently, HU became in 1998 the only US Food and Drug Administration-approved therapy for sickle cell disease. The European Medicines Agency authorized HU in 2007 for pediatric and adult patients with sickle cell anemia. In 2008, the Agency for Healthcare Research and Quality published a comprehensive review,[29] and a consensus conference on HU in the treatment of sickle cell disease was organized by the National Institute of Health.[30]

HU Mechanisms of Action in Sickle Cell Anemia. In sickle cell anemia, the red cells almost contain only HbS. Only a smaller population of red cells comes directly from immature progenitors, which contain the fetal hemoglobin (HbF). These nearly normal cells mitigate the damage caused by HbS.[31] Cells with high levels of HbS lose deformability when deoxygenated, leading to vascular obstruction and ischemia. Membrane damage shortens the life span of the cell leading to chronic intravascular and extravascular hemolysis. Damage red cells showed an increased adherence to vascular endothelium leading to vaso-occlusion and proliferative lesions involving many cells and factors underlying large-vessel stroke.[32] Shifting hemoglobin production from HbS to HbF represents then a major therapeutic approach to sickle cell anemia. Low level of HbF is one of the strongest predictors of morbidity and mortality in sickle cell disease.[27] The cytotoxic effect of HU reduces the production of red cells containing a high level of HbS, which tend to arise from rapidly dividing precursors, and favors the production of cells containing a high level of HbF.[32] The exact mechanism by which HU induces HbF remains unclear. The increase in HbF appears to interfere with HbS polymerization both by preventing contact between adjacent HbS molecules and by forming mixed hybrids with HbS that have greater solubility than HbS polymers.[33] HU may increase HbF indirectly by killing dividing late erythroid cells, causing recruitment of more primitive erythroid precursors which produce high levels of HbF, or by acting directly on the primitive precursors stimulating HbF production.[34] However, induction of HbF was unlikely to explain all the clinical effects of HU. Prior to any rise in HbF, sickle erythrocytes show reduced adhesion to endothelial cells. HU reduces adhesion molecule expression on sickle erythrocytes, including very late activation antigen-4 and CD36.[35] Other rheological properties of sickle erythrocytes, including erythrocyte hydration status and whole cell deformability, can be increased by HU. HU also reduces white blood cells and platelets reducing their roles in vascular injury. Neutrophilia has long been identified as a marker of severity in sickle cell disease.[27] Neutrophils release pro-inflammatory mediators involved in endothelial damage and cytokine release, which trigger sickling, and contribute to slow transit time via their adhesive properties and an increase in blood viscosity.[36] The drug also produces nitric oxide, which stimulates soluble guanylate cyclase (an enzyme containing heme iron) resulting in the production of HbF.[37] Some of the clinical effects

Table 1. Randomized trials comparing HU with placebo.

Study	Age Median (range)	Patients (HU/no HU)	Outcome for HU
Charache et al. [28]	30 years (18 – 59)	152/147 (HU/placebo)	↓ vaso-occlusive crises ↓ acute chest syndrome ↓ transfusions
Wang et al. [41]	13.5 months	96/97 (HU/placebo)	↓ vaso-occlusive crises ↓ acute chest syndrome ↓ dactylitis
Wang et al. [44]	13.6 years (5 – 53)	22/22 (HU/placebo)	No difference
Jain et al. [43]	12.2 years (5 – 18)	30/30 (HU/placebo)	↓ vaso-occlusive crises ↓hospitalizations ↓ transfusions
Ware et al. [42]	13 years (5 – 18)	67/66 (HU/placebo)	No difference
Lebensburger et al. [46]	(0.75 – 1.5 years)	21/25 (HU/phlebotomy with chronic transfusions and chelation)	↓ vaso-occlusive crises
Thornburg et al. [47]	(0.75 – 1.5 years)	96/97 (HU/phlebotomy with chronic transfusions and chelation)	↓ acute chest syndrome
Alvarez et al. [45]	(5 – 19 years)	67/66 (HU/phlebotomy with chronic transfusions and chelation)	No difference in vaso-occlusive crises and in acute chest syndrome

Abbreviation: HU, hydroxyurea.

are mediated by nitric oxide-induced vasodilatation or reduced platelet activation.

The Use of HU in Sickle Cell Disease. HU was initially tested in anemic baboons.[38] The first patients were tested in 1984 showing a response within 72 hours after therapy with an elevated level of HbF.[23] Subsequent prospective studies confirmed the efficacy and tolerability of HU in this setting. Recent reviews of the literature on HU therapy in sickle cell disease showed that HU was consistently associated with overall increases in HbF, a reduction of vaso-occlusive crises, decreased rates of hospitalization, and prevention of pulmonary complications.[39,40] The benefit of HU regarding the frequency of acute clinical events was demonstrated in randomized studies (**Table 1**),[28,41-47] but also in observational studies (uncontrolled longitudinal studies, retrospective case series, or prospective cohort studies using historical controls) (**Table 2**).[48-64]

Treatment with HU in adults: Most studies included both children and adults. Among specific studies for adult patients, the most important was a multicenter, double-blind, randomized controlled study that ran from 1992 to 1994 and that was stopped early after inclusion of 299 patients, because of a significant reduction of events in the Hu arm.[28] HU improved the clinical course of sickle cell disease by significantly reducing the annual rate of crises, increasing the median time to the first and second crisis, reducing the incidence of acute chest syndrome, and reducing transfusion requirements. Furthermore, the recommended dose of HU was not always needed to achieve a clinical response. Among the other randomized studies, no difference was noted in terms of frequency of vaso-occlusive crises in three studies.[42,44,45] In one study, there were equivalent liver iron contents and similar rates of stroke in both arms.[42] However, two of these three trials terminated earlier due to poor accrual. In the third study (SWiTCH trial), given the low rates of acute chest syndrome observed in the trial, the number of patients was not sufficient to determine whether there was a true difference between acute chest syndrome in the two arms.[45] Although studies of various designs showed that HU decreased the occurrence of acute chest disease, most studies provided lower-quality evidence for such effect.[49,58,62-64] Regarding pulmonary hypertension and tricuspid regurgitant velocity, the lack of randomization and prospective follow-up makes interpretation of results difficult. If most studies showed no difference among groups[26,65-70] or even higher proportion of patients with prior exposure to HU in a group with increased tricuspid regurgitant velocity,[71] some studies tended to provide evidence of HU effect.[72,73] Evidence for primary stroke prevention was limited to observational data.[50,58] While current evidence

Table 2. Observational studies addressing acute clinical events with HU in sickle cell anemia.

Study	Population Study design	Patients receiving HU	Outcome for HU
Italia et al. [50]	Children/Adults Prospective	77	↓ vaso-occlusive crises ↓ acute chest syndrome ↓ transfusions ↓ hospitalizations
Olivieri et al. [63]	Children/Adolescents Retrospective	17	↓ acute chest syndrome
Koren et al. [62]	Children/Adults Retrospective	18	↓ acute chest syndrome
Nzouakou et al. [52]	Adolescents/Adults Retrospective	123	↓ acute chest syndrome ↓ stroke ↓ hospitalizations ↓ mortality
Singh et al. [56]	Adults Prospective	24	↓ vaso-occlusive crises ↓ hospitalizations
Gulbis et al. [59]	Children/Adolescents Retrospective	32	↓ acute chest syndrome
Hankins et al. [60]	Children Retrospective	21	↓ acute chest syndrome
Steinberg et al. [57]	Adults Prospective	255	No difference for stroke ↓ mortality if HU for at least 5 years ↓ pulmonary complications
Voskaridou et al. [58]	Adults Prospective	131	↓ vaso-occlusive crises ↓ acute chest syndrome ↓ transfusions ↓ hospitalizations ↓ mortality
Jain et al. [61]	Children/Adolescents Retrospective	144	↓ acute chest syndrome
Ali et al. [48]	Children Retrospective	10	↓ stroke
Gilmore et al. [49]	Children/Adults Retrospective	62	↓ vaso-occlusive crises ↓ acute chest syndrome ↓ transfusions ↓ hospitalizations
Patel et al. [53]	Children/Adults Prospective	118	↓ vaso-occlusive crises ↓ transfusions
Lobo et al. [51]	Children Retrospective	267	↓ acute chest syndrome ↓ hospitalizations ↓ mortality
Silva-Pinto et al. [64]	Children/Adults Retrospective	37	↓ acute chest syndrome
Rigano et al. [54]	Adults Retrospective	104	↓ vaso-occlusive crises ↓ hospitalizations
Sharef et al. [55]	Children Retrospective/Prospective	142	↓ acute chest syndrome ↓ hospitalizations
Jayabose et al. [87]	Children Prospective	15	↓ vaso-occlusive crises
Ferster et al. [89]	Children Retrospective	93	↓ hospitalizations ↓ days in hospital

Abbreviation: HU, hydroxyurea.

supports the use of chronic blood transfusions to prevent progressive disease and especially clinical stroke, HU represents an attractive alternative treatment option in order to avoid indefinite blood transfusion therapy which can lead to serious complications such as infections, iron overload, transfusion reactions, and erythrocyte allo- and auto-antibody formation.[74] The therapeutic switch from transfusions to HU should follow an overlap period of dual therapy because the benefits of HU have a slow onset and treatment should reach a stable maximum tolerated dose. After the switch, the problem of hemosiderosis persists. Despite effective oral chelators, the greatest challenge of serial phlebotomy in patients with sickle cell anemia is the underlying anemia, but HU therapy at a stable maximum tolerated dose typically raises the hemoglobin concentration, allowing a safe procedure.[75] Before the era of HU, the average life expectancy was in the 40s.[27] HU was associated

with decreased mortality in symptomatic patients compared with those receiving only short-term HU or no HU.[57] It typically takes less than 6 months for patients to be stabilized on a dose that defines their maximal tolerated dose. Before the maximal tolerated dose is established, the number of cells with high HbF levels increases.[44,50,53,56] At 6 months, the HbF level is typically doubled, the hemoglobin level is increased, and the absolute reticulocyte count, bilirubin level, and lactate dehydrogenase level are reduced.[32] Patients should receive HU therapy as a continuous treatment unless adverse events occur. The optimal dose is still a source of debate. Dose escalation has been suggested toward the maximum tolerated dose (MTD). However, the stepwise approach of dose escalation generally requires several months and patients receiving HU have variable pharmacokinetics and pharmacodynamics.[76] Creatinine, reticulocyte count, and body mass index are among the simplest parameters that best predicted the HU maximum tolerated dose. It has been demonstrated a near linear dose response to HU. The treatment dose correlated positively with both the plasma drug concentration and the percentage of HbF response.[77] However, the dose does not need to be titrated to a particular HbF threshold. The dose can be escalated simply to reach an acceptable nontoxic degree of marrow suppression with target counts for both neutrophils and reticulocytes.[78] It has been suggested that HU may have benefits for the less common genotypes, especially HbSC or HbS/β^+ thalassemia.[79] Because the primary effect of HU is damaging DNA replication by inhibiting ribonucleotide reductase, concerns have been raised about an oncogenic potential, especially after prolonged use. Although fears have been amplified by its original use as chemotherapy for chronic myeloproliferative diseases, which could evolve to acute leukemia, oncogenicity of HU is probably quite low or non-existent. Only a few cases of acute leukemia have been reported, but do not appear more frequent than in the untreated population.[80] Similarly, the benefits and harms of HU therapy in women with sickle cell disease during pregnancy and lactation represent a relevant issue.[79] No clear teratogenic phenotype exists for HU, but more data should be collected. Women with sickle cell anemia receiving HU have had successful normal pregnancies.[81] A variety of factors can lead to treatment failure. Poor adherence is recognized as a common problem and seems in part related to adverse events of the drug and inconvenience associated with monitoring.

Treatment with HU in children: The use of HU in children brings theoretically the best satisfactions regarding prevention of end-organ damage. However, it also carries potential risks in terms of growth and development and remains questionable for the risk of secondary malignancy after exposure to the drug for long periods. Observational studies in children have noted significant improvements in splenic uptake, glomerular filtration rate, renal hypertrophy, the ability to concentrate urine, microalbuminuria, and retinopathy.[82-86] As in adults studies, beneficial results with HU were reported showing a reduction in hospital admissions and days spent in the hospital, and potentially a reduced frequency of acute chest syndrome.[62,87-89] Evidence on benefits of HU use in children below 5 years is that it is associated with decreased pain crises and dactylitis.[41,90] However, most studies provided lower-quality evidence for the occurrence of acute chest syndrome.[46,47,60,61] There were few pieces of evidence that HU prevents stroke or the recurrence of stroke in children.[91] As in adults, evidence for primary stroke prevention was limited to observational data.[51] HU treatment was shown to lower secondary stroke rates in children with previous stroke.[92] Transcranial Doppler screening is used for primary stroke prevention. Abnormal velocities are the most common indication to commence chronic transfusion therapy in children. HU can lower transcranial Doppler velocities[93] and its utility in this setting is under investigations.[94] Although case reports have shown a reversal of splenic dysfunction after HU therapy, larger studies demonstrated that HU is clearly not enough to completely prevent the major complications of the disease.[95] Growth and development appeared to be unaffected in all studies.[95,96] HU should, therefore, be offered early and routinely as a preventive treatment for sickle cell anemia in children.

Distribution of HbF. More than 75% of the hemoglobin of the newborn is HbF. It diminishes over a period of several months to adult levels. HbF is becoming <2% by one year-of-age and <1% by 2 years. In most patients with sickle cell disease, HbF levels are increased. HbF is produced

by a small number of erythroid precursors: the F-cells. Both HbF concentration and its distribution among erythrocytes are heritable. A correlation has been demonstrated between the number of F-cells and the percent of HbF in the hemolysate.[97] The concentration of HbF in each F-cell (HbF/F-cell) is changing during maturation.[98] However, quantitative methods for measuring this amount and plotting the distribution of HbF among F-cells are not available. The distribution of HbF concentrations among F-cells is the most critical element in the physiopathology of sickle cell anemia.[99] Compound heterozygosity for HbS and gene deletion hereditary persistence of HbF (HPFH) represents a condition in which the typical HbF level is 30%.[100] In this setting, HbF is distributed among all erythrocytes, each cell containing about 10 pg of HbF. Patients with sickle cell anemia have individually characteristic distributions of HbF/F-cell regardless of their total HbF level.[101] HU can induce HbF in most patients, but the HbF response to HU is highly variable.[102] Higher HbF levels were associated with a reduced rate of painful episodes, fewer leg ulcers, less osteonecrosis, and less frequent acute chest syndromes. However, HbF level had a weak or no clear association with priapism, urine albumin excretion, stroke and silent cerebral infarction, systemic blood pressure, and tricuspid regurgitant velocity.[103] HbF is unevenly distributed when high levels are successfully induced with HU. Total HbF and F-cell percentages are generally not good predictors of disease severity since they provide no information on F-cells with sufficient levels of HbF to protect against polymer-induced damage. Very few protected F-cells are present when HbF levels are about 5%, but more cells are possible when they reach 10%.[99] The calculated mean HbF/F-cell in HU-treated sickle cell anemia is about 8 pg. Early starting treatment seems to retard the fall in HbF, but many F-cells will continue to be poorly protected from polymer-induced damage even with 20% HbF.[99]

A Clinical and Economic Problem. It is estimated that 7% of the world population are carriers for hemoglobin disorders. Sickle cell disease is the most important potentially devastating, recessively inherited condition. The β-globin gene point mutation resulting in HbS has undergone evolutionary selection in the world because of its overwhelming malaria protective effects. High prevalence areas include Africa, the Middle-East, and Indian subcontinent with sickle cell trait affecting up to 300 million individuals worldwide.[104] In Africa, one on 14 persons with sickle cell anemia is an asymptomatic carrier.[32] One in 700 newborns is affected.[105] However, recent studies suggest that only 16% of polled individuals are aware of their sickle cell trait status, and only 37% of parents report having received notification of the sickle cell trait status of their children.[106,107] Sickle cell disease represents then an emerging global health burden in limited-resource countries, in which the development of sickle cell disease strategies should include sickle cell awareness, early detection, and the development of care and treatment programs.[108-110] The main recommendation is to educate all patients and their families about HU therapy. Although Food and Drug administration-label recommends treatment only for adults with sickle cell anemia severely affected with at least 3 painful crises over the prior 12 months, there are strong recommendations to treat adults with common clinical symptoms and to offer HU to children after age 9 months, regardless of clinical symptoms.[111] HU is relatively cheap. Especially in limited-resource countries without a safe and adequate blood supply, HU may represent a clinically useful and cost-effective therapeutic strategy for preventing cerebrovascular disease.[112] In the United States, it was reported per year 113,000 hospitalizations for sickle cell disease generating total hospital costs of about $488 million.[113] The average cost of HU was estimated at about $1,000 per year plus $400 per year for visits and tests.[28] This cost was offset by reduced costs for hospitalization, emergency room visits, and transfusions. The net savings was estimated at about $5,000 per patient per year.[114]

Beyond HU Therapy. HU is currently the only US Food and Drug Administration-approved medication to modify the disease course in sickle cell disease. However, elucidation of the multiple pathophysiologic mechanisms leading to vaso-occlusion and tissue injury in sickle cell disease is currently resulting in the identification of new treatment modalities.[115] In addition to HU, a number of drugs have been proposed: histone deacetylase inhibitors,[116] decitabine,[117] thalidomide and related compounds,[118] pomalidomide.[119] Optimally efficient induction of

HbF may require combined use of drugs.[120] Carbon monoxide is also a potent antisickling agent that attaches to Hb and therefore reverse HbS polymerization. Shifting the oxyhemoglobin to the left or preventing cell dehydration can ameliorate sickling.[121] Sanguinate is a bovine pegylated Hb product designed to reduce sickling by delivering carbon monoxide to HbS and then carrying O_2.[122] Because adhesive cell interactions contribute to vaso-occlusion, drugs targeting either red blood cell or leukocyte adhesion appear as attractive therapeutic modalities. Drugs targeting selectin-mediated adhesion are being especially investigated including the selectin inhibitors GMI-1070 (rivipansel)[123] and the humanized monoclonal antibody SelG1.[124] Heparin derivatives, such as sevuparin or tinzaparin, also have a well-known ability to inhibit adhesive interactions via P-selectin.[125,126] Targeting signaling pathways that activate adhesion molecules is another potential therapeutic modality. This can be achieved via beta-blockers administration[127] or through the use of MEK inhibitors[128] that might reduce red blood cell adhesion. Poloxamer 188, a nonspecific inhibitor of adhesion is also currently being studied.[129] Vaso-occlusion can engender an inflammatory response typical of hypoxia/reperfusion injury. Down-regulation of inflammatory pathways can, therefore, represent another approach to ameliorate sickle cell disease. Invariant NKT cells are involved in this pathogenesis. Their activation can be down-regulated by activation of the adenosine A2A receptor. Regadenoson is a partially selective adenosine A2A receptor agonist. It has been proposed in the treatment of vaso-occlusive crisis, which involves invariant NKT cells as contributors to the inflammatory component.[130] A humanized monoclonal antibody against invariant NKT cells has also recently shown some efficacy.[131] Because inflammatory pathways are important to both vaso-occlusion and tissue injury, targeting inflammatory mediators, such as leukotrienes, has also been proposed as a promising approach for the development of novel therapies in sickle cell disease.[132] Intravenous γ globulin infusion can also reduce inflammation via inhibition of neutrophil adhesion.[133] Statins that decrease endothelial inflammation have also been studied in sickle cell disease.[134] Drugs that increase HbF levels are the archetypal antisickling agents, because HbF interferes with polymerization of HbS, thereby lessening hemolytic rate and resulting in total Hb levels seen with HU therapy. The interference lengthens the delay time, allowing cells to avoid getting stuck in the microvasculature, even if hemolysis does not happen. Despite promising results, high mortality rates in patients older than 16 years and a paucity of suitable HLA-identical donors have limited the implementation of allogeneic stem cell transplantation in this patient population.[135] In the future, correction of the β-globin gene may be the ideal approach to curing sickle cell disease. However, there are still many concerns regarding this approach.

Despite the development of these many new treatment modalities and the promising results of the initial trials, HU remains a well-tolerated, safe, cheap, and efficacious for most patients with sickle cell disease, and should currently be considered standard-of-care for this disease.

Conclusions. HU is a remarkably effective drug for a large proportion of patients with sickle cell disease and appears to be the best currently available treatment option in this setting. Treatment is indicated for patients with "frequent pain episodes, history of acute chest syndrome, other severe vaso-occlusive events, or severe symptomatic anemia".[32] Treatment endpoints remain "less pain and improved well-being, increased HbF to 15%-20%, increased hemoglobin level, and acceptable myelotoxicity".[32] However, studies regarding a better understanding of HU effects, the ability to predict individual response, and the clinical applications for modifying disease effects are still ongoing. Two decades after the approval of HU, most patients with sickle cell disease are suboptimally treated with it, or not treated at all since this disease has continued to be treated with analgesics for pain relief. HU remains underutilized for a variety of reasons. It is likely that optimal therapy will only be achieved with a multi-targeted approach. However, any of the new therapies may be similarly underused, which may be the most difficult problem. HU is currently prescribed only sparingly and therefore has only limited effectiveness. Early initiation and broader use of HU should alter the natural history of sickle cell anemia. HU should be extended to low-resource settings, where the burden of the disease and the need for such a drug is the greatest.

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