Review article

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

Giovanna Cannas¹², Solène Poutrel¹ and Xavier Thomas³

¹ Hospices Civils de Lyon, Department of Internal Medicine, Edouard Herriot Hospital, Lyon, France.
² Claude Bernard University Lyon 1, Laboratoire Interuniversitaire de Biologie de la Motricité EA7424, Equipe ‘Vascular biology and red blood cell’, Villeurbanne, France.
³ Hospices Civils de Lyon, Hematology Department, Lyon-Sud Hospital, Pierre Bénite, France.

Competing interests: The authors have declared that no competing interests exist.

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.

Citation: Cannas G, Poutrel S and Thomas X. Hydroxycarbamine: from an old drug used in malignant hemopathies to a current standard in sickle cell disease. Mediterr J Hematol Infect Dis 2017, 9(1): e2017015, DOI: http://dx.doi.org/10.4084/MJHID.2017.015

Published: February 15, 2017 Received: December 12, 2016 Accepted: January 20, 2017

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nc/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Correspondence to: Xavier Thomas, M.D., Ph.D., Hospices Civils de Lyon, Hematology Department, Lyon-Sud Hospital, Bât. 1G, 165 chemin du Grand Revoyet, 69495 Pierre Bénite, France. Tel: +33 478862235. Fax: +33 4 72678880. E-mail: xavier.thomas@chu-lyon.fr

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, H₂NCONHOH, 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.\textsuperscript{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 thrombocytemia, and primary myelofibrosis.\textsuperscript{7} In high-risk patients with polycythemia vera or essential thrombocytemia, HU remains the first-line cytoreductive drug of choice, the second-line choice being represented by interferon-alpha and busulfan.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10} In addition to its use as an anticancer agent, HU has found some marginal applications in dermatology.\textsuperscript{11}

While HU is an old drug that can still be used to control essential thrombocytemia 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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{17} At that time, only 50% of afflicted children survived into adulthood.\textsuperscript{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.\textsuperscript{19} By the 1990s, widespread mandatory newborn screening and the routine administration of penicillin to prevent pneumococcal sepsis increased childhood survival to over 90%.\textsuperscript{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. 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 in sickle erythrocytes. 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. 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. On a chronic basis, vaso-occlusion may damage the lungs, kidney or brain accounting ultimately for most deaths in patients with sickle cell disease. Clinical studies with HU demonstrated a decreased rate of vaso-occlusive disease and acute chest syndrome, and an improved survival. 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, and a consensus conference on HU in the treatment of sickle cell disease was organized by the National Institute of Health.

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. 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. 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. 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. 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. 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. 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. 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. 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. The drug also produces nitric oxide, which stimulates soluble guanylate cyclase (an enzyme containing heme iron) resulting in the production of HbF. Some of the clinical effects
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.28 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

| 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) | (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.

Table 1. Randomized trials comparing HU with placebo.

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                    | ↓ vaso-occlusive crises                               |
| 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 Retrospective    | 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.54,50,53,56 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.52 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.52-86 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 velocities93 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
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. In Africa, one on 14 persons with sickle cell anemia is an asymptomatic carrier. One in 700 newborns is affected. 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. 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. 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. 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. In the United States, it was reported per year 113,000 hospitalizations for sickle cell disease generating total hospital costs of about $488 million. The average cost of HU was estimated at about $1,000 per year plus $400 per year for visits and tests. 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.

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. In addition to HU, a number of drugs have been proposed: histone deacetylase inhibitors, decitabine, thalidomide and related compounds, pomalidomide. Optimally efficient induction of
HbF may require combined use of drugs. 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. Sanguinate is a bovine pegylated Hb product designed to reduce sickling by delivering carbon monoxide to HbS and then carrying O2. 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) and the humanized monoclonal antibody SelG1. Heparin derivatives, such as sevuparin or tinzaparin, also have a well-known ability to inhibit adhesive interactions via P-selectin. Targeting signaling pathways that activate adhesion molecules is another potential therapeutic modality. This can be achieved via beta-blockers or through the use of MEK inhibitors that might reduce red blood cell adhesion. Poloxamer 188, a nonspecific inhibitor of adhesion is also currently being studied. 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. A humanized monoclonal antibody against invariant NKT cells has also recently shown some efficacy. 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. Intravenous γ globulin infusion can also reduce inflammation via inhibition of neutrophil adhesion. Statins that decrease endothelial inflammation have also been studied in sickle cell disease. 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. 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”. Treatment endpoints remain “less pain and improved well-being, increased HbF to 15%-20%, increased hemoglobin level, and acceptable myelotoxicity”. 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.
References:

1. Dresler WFC, Stein R. Über den hydroxyhämaturfin. Justus Liebig's Ann Chem 1869; 150:242-52. https://doi.org/10.1515/9783110019012

2. Rosenthal F, Wislicki L, Koller L. Über die beziehungen von schwersten blutgift zu abbauprodukten des eiweisses: ein beitrag zum entstehungsmechanismus der pernizösen anemia. Klin Wochenschr 1928; 7:977-8. https://doi.org/10.1002/kwy.1716922

3. Sistars B, Losee KA, Bernstein J. Hydroxyurea: a new type of potential antitumor agent. J Med Chem 1963; 6:201. https://doi.org/10.1021/jm00380a026 PMid:14188794

4. Fishbein WN, Carbone PP, Freireich EJ, et al. Clinical trials of hydroxyurea in patients with cancer and leukemia. Clin Pharmacol Ther 1964; 5:574-80. https://doi.org/10.1002/cpt196455574

5. Becloff GL. Pharmacological, metabolic and clinical experience with hydroxyurea. Clin Trials J 1967; 4:873-83.

6. Kennedy BJ. Hydroxyurea therapy in chronic myelogenous leukemia. Cancer 1972; 29:1052-6. https://doi.org/10.1002/1097-0142(19720429-4s1052-AID-CNCR2820290304543.0.CO;2-7

7. Teffert A, Paradani A. Myeloproliferative neoplasms. A contemporary review. JAMA Oncol 2015; 1:97-105. https://doi.org/10.1001/jamaoncol.2015.85 PMid:26182311

8. Cortelazzio S, Manzzi G, Specchia G, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med 1995; 332:1132-6. https://doi.org/10.1056/NEJM199504273321704 PMid:7700286

9. Fruchtman SM, Mack K, Kaplan ME, et al. From efficacy to safety: A Polycytensy Vera Study Group report on hydroxyurea in patients with polycythemia vera. Semin Hematol 1997; 34:17-23. https://doi.org/10.1056/NEJM199701293290406 PMid:9025158

10. Teffert A. Primary myelofibrosis: 2014 update on diagnosis, risk-stratification, and management. Am J Hematol 2018; 89:915-25. https://doi.org/10.1002/ajh.24303 PMid:25124131

11. Leavell UW, Yarbro JW. Hydroxyurea: A new treatment for psoriasis. Arch Dermatol 1970; 102:144-50. https://doi.org/10.1001/archderm.1970.01000080010003

12. Herrick JB. Peculiar elongated aneuploid cells: correlative study with clinical features. Am J Clin Pathol 1944; 18:687-95. https://doi.org/10.1093/ajcp/18.3.687

13. Pauling L, Itano HA. Sickle cell anaemia. Nature 1956; 178:792-5. https://doi.org/10.1038/178792a0

14. Ingram VM. A specific chemical difference between the globins of human and a peculiar form with a probable anemia. Biochem J 1938; 33:577-95. https://doi.org/10.1042/bj0330577

15. Vinson L, Itano HA. Sickle cell anaemia. Arch Intern Med 1910; 16:517-60. https://doi.org/10.1001/archinte.1910.00220400039001

16. Herrick JB. Peculiar elongated aneuploid cells: correlative study with clinical features. Am J Clin Pathol 1944; 18:687-95. https://doi.org/10.1093/ajcp/18.3.687

17. Scott RB. Health care priority and sickle cell anemia. JAMA 1970; 214:731-4. https://doi.org/10.1001/jama.1970.03380400390008 PMid:5536114

18. Benson JM, Therrell BL Jr. History and current status of newborn screening for hemoglobinopathies. Semin Perinatol 2010; 34: 134-44. https://doi.org/10.1053/j.semperi.2009.12.006 PMid:20207263

19. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood 2010; 115:347-52. https://doi.org/10.1182/blood-2009-07-233700 PMid:20198981 PMcid:PMc2867259

20. Naik RP, Derebail VK, Grams ME, et al. Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. Jama 2014; 312:2115-25. https://doi.org/10.1001/jama.2014.15063 PMid:25393378 PMcid:PMc4356116

21. Auer PL, Johnsen JM, Johnson AD, et al. Imputation of exome sequence variants into population-based samples and blood-cell-
42. Ware RE, Helms RW. Stroke with transfusions changing to hydroxyurea at SWITCH. Br J Haematol 2012; 160:225-32. https://doi.org/10.1111/j.1365-2141.2011.08392.x PMid:21879461

43. Jain DL, Sarathi V, Desai S, et al. Low fixed-dose hydroxyurea in severely affected Indian children with sickle cell disease. Hemoglobin 2012; 36:323-32. https://doi.org/10.3109/036303602021269798 PMid:22734586

44. Wang W, Brugnara C, Snyder C, et al. The effects of hydroxycarbamine and magnesium on haemoglobin SC disease: results of the multicentre CHAMPS trial. Br J Haematol 2011; 152:771-6. https://doi.org/10.1111/j.1365-2141.2010.08523.x PMid:21359585

45. Alvarez O, Yovetch NA, Scott JP, et al. Pain and other non-neurological adverse events in children with sickle cell anemia and previous stroke who received hydroxyurea and phlebotomy or chronic transfusions and chelation: results from the SWITCH clinical trial. Am J Hematol 2013; 88:932-8. https://doi.org/10.1002/ajh.23547 PMid:23861242

46. Lebensburger JD, Miller ST, Howard TH, et al. Influence of severity of anemia on clinical findings in infants with sickle cell anemia: analyses from the BABY HUG study. Pediatr Blood Cancer 2012; 59:675-8. https://doi.org/10.1002/bpc.20437 PMid:22190441 PMid:PCMCi:PMC337342

47. Thornburg CD, Files BA, Luo Z, et al. Impact of hydroxyurea on clinical events in the BABY HUG trial. Blood 2012; 120:4304-10. https://doi.org/10.1182/blood-2012-03-419870 PMid:22915643

48. Ali SB, Moosang M, King L, et al. Stroke recurrence in children with sickle cell disease treated with hydroxyurea following first clinical stroke. Am J Hematol 2011; 86:846-50. https://doi.org/10.1002/ajh.21142 PMid:21805530

49. Gilmore A, Cho G, Howard J, et al. Feasibility and benefit of hydroxy carbamidine as a long-term treatment for sickle cell disease patients: results from the North West London Sickle Cell Disease Registry. Am J Hematol 2011; 86:958-61. https://doi.org/10.1002/ajh.22146 PMid:21948113

50. Italia K, Jain DL, SWITCH, S, et al. Hydroxyurea in sickle cell disease – a study of clinic-pharmacological efficacy in the Indian haplotype. Blood Cells Mol Dis 2009; 42:425-31. https://doi.org/10.1016/j.bcmd.2008.08.003 PMid:1895999

51. Lobo CL, Pinto JP, Nascimento EM, et al. The effect of hydroxyurea therapy on survival of children with sickle cell disease. Br J Haematol 2013; 161:852-60. https://doi.org/10.1111/bjh.12333 PMid:23590693

52. Nzouakou R, Bachir D, Lavaud A, et al. Pulmonary hypertension in patients with sickle cell disease: impact on splenic function and compliance with therapy. Pediatr Hematol Oncol 1998; 15:381-90. https://doi.org/10.1080/0888001992772772 PMid:10326220

53. Olivieri NF, VichinskyEP. Hydroxyurea in children with sickle cell disease: impact on splenic function and compliance with therapy. J Pediatr Hematol Oncol 1998; 20:26-31. https://doi.org/10.1097/00008880-199801000-00004

54. Silva-Pinto AC, Angulo IL, Brunetta DM, et al. Clinical and hematological effects of hydroxyurea therapy in sickle cell patients: a single center experience in Brazil. Sao Paulo Med J 2013; 131:238-43. https://doi.org/10.1590/S1516-31802013001000047 PMid:24141294

55. Desai PC, May RC, Jones SK, et al. Longitudinal study of echocardiography-derived tricuspid regurgitant jet velocity in sickle cell disease. Br J Haematol 2013; 162:836-41. https://doi.org/10.1111/bjh.12453 PMid:23829561

56. Goede VR, Campbell A, Rana S, et al. Relationship of erythropoietin, fetal hemoglobin, and hydroxyurea treatment to tricuspid regurgitation velocity in children with sickle cell disease. Blood 2009; 114:4699-4704. https://doi.org/10.1182/blood-2009-04-218040 PMid:19724057 PMid:PCMCi:PMC2783030

57. Pashankar FD, Carbonella J, Bassy-Aasaad A, et al. Prevalence and risk factors of elevated pulmonary artery pressures in children with sickle cell disease. Pediatrics 2008; 121:777-82. https://doi.org/10.1542/peds.2007-0730 PMid:18381543

58. Voskandou F, Tsetson G, Tsoukias A, et al. Pulmonary hypertension in patients with sickle cell/beta thalassemia: incidence and correlation with serum N-terminal pro brain natriuretic peptide concentrations. Haematologica 2007; 92:738-43. https://doi.org/10.3324/haematol.2010.11136 PMid:17550645

59. Fonseca GH, Souza R, Salesi VM, et al. Pulmonary hypertension diagnosed by right heart catheterization in sickle cell disease. Eur Respir J 2012; 39:112-8. https://doi.org/10.1183/09031994.00134110 PMid:21778170

60. Parent F, Bachir D, Inamo J, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. N Engl J Med 2011; 365:44-53. https://doi.org/10.1056/NEJMoai1005565 PMid:21723836

61. Dahoui HA, Hayek MN, Nietert PJ, et al. Pulmonary hypertension in children and young adults with sickle cell disease: evidence for familial clustering. Pediatr Blood Cancer 2007; 51:398-402. https://doi.org/10.1002/bc.20206 PMid:17827138

62. Ataga KI, Moore CG, Jones S, et al. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. Br J Haematol 2006; 134:109-15. https://doi.org/10.1111/j.1365-2141.2006.06110.x PMid:16803576

63. De Castro LM, Jonassaint JC, Graham FL, et al. Pulmonary hypertension associated with sickle cell disease: clinical and laboratory endpoints and disease outcomes. Am J Hematol 2008; 83:19-25. https://doi.org/10.1002/ajh.21028 PMid:17724699

64. Chou ST, Jackson T, Vege S, et al. High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors. Blood 2013; 122:1062-71. https://doi.org/10.1182/blood-2013-03-490623 PMid:23723452

65. Aygun B, Mortier NA, Kessler K, et al. Therapeutic phlebotomy is safe in children with sickle cell anaemia and can be effective treatment for transfusional iron overload. Br J Haematol 2015; 169:262-6. https://doi.org/10.1111/bjh.13380 PMid:25612463 PMid:PCMCi:PMC4631316

66. Ware RE, Despotovic JM, Mortier NA, et al. Pharmacokinetics, pharmacodynamics, and pharmacogenetics of hydroxyurea treatment for children with sickle cell anemia. Blood 2011; 118:4985-91. https://doi.org/10.1182/blood-2011-07-361409 PMid:21876119 PMid:PCMCi:PMC3208303

67. Charache S, Dover GJ, Moore RD, et al. Hydroxyurea. Effects on
93. Wang WC, Helms RW, Lynn HS, et al. Effects of hydroxyurea on growth in children with sickle cell anemia: Results of the HUG-KIDS study. J Pediatr 2002; 140:225-9. https://doi.org/10.1016/S0022-3476(01)01238-3 PMid:11865275

94. Andree Y, Bigelow NC, Davis BH, Porter JB. Flow cytometric method for simultaneous assay of fetal haemoglobin containing red cells, reticulocytes and foetal haemoglobin containing reticulocytes. Clin Lab Haematol 2001; 23:149-54. https://doi.org/10.1046/j.1365-2257.2001.00344.x PMid:11553054

95. Dver GI, Boyer SH. Quantitation of hemoglobinins within individual red cells: asynchronous biosynthesis of fetal and adult hemoglobin during erythroid maturation in normal subjects. Blood 1980; 56:1082-91. PMid:6159933

96. Steinberg MH, Chui DHK, Dver GI, et al. Fetal hemoglobin in sickle cell anemia: a glass half full? Blood 2014; 123:481-5. https://doi.org/10.1182/blood-2013-09-528067 PMid:24222332

97. Ngo DA, Aygun B, Akinsheye I, et al. Fetal haemoglobin levels and haematological characteristics of compound heterozygotes for hemoglobin S and deletional hereditary persistence of fetal haemoglobin. Br J Haematol 2012; 156:259-64. https://doi.org/10.1111/j.1365-2141.2011.08916.x PMid:22017641

98. Horiiuchi K, Osterhout ML, Kamma H, et al. Estimation of fetal hemoglobin levels in individual red cells via fluorescence image cytometry in a model system. Blood 2005; 106:2547-54. https://doi.org/10.1182/blood-2005-08-2950 PMid:16124653

99. Steinberg MH, Lu ZH, Barton FB, et al. Multicenter study of hydroxyurea. Fetal hemoglobin in sickle cell anemia: determinants of response to hydroxyurea. Blood 1997; 89:1078-88. PMid:9028341

100. Steinberg MH, Sebastiani P. Genetic modifiers of sickle cell disease. Am J Hum Genet 2012; 87:795-803. https://doi.org/10.1016/j.ajhg.2012.03.002 PMid:22641398 PMid:PMCID:PMC4562292

101. Elion J, Berg PE, Lapoumeroulie C, et al. DNA sequence variation in a negative control region S' to the beta-globin gene correlates with the phenotypic expression of the beta S mutation. Blood 1992; 79:787-92. PMid:13462531

102. Lorye FW, Arnpitt J, Cunningham GC. Distribution of hemoglobinopathy variants by ethnicity in a multietnic state. Genet Epidemiol 1996; 13:501-12. https://doi.org/10.1002/GEPI.1240130306 PMid:9086257

103. Treadwell MJ, McCough L, Vichinsky E. Using qualitative and quantitative strategies to evaluate knowledge and perceptions about sickle cell disease and sickle cell trait. J Natl Med Assoc 2006; 98:794-10. PMid:16749065 PMid:PMCID:PMC2590269

104. Kavanagh PL, Wang CJ, Therrell BL, et al. Communication of information on sickle cell disease: a strategy for the KIDS study. J Pediatr 2002; 140:225-9. PMid:11865275

105. Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. Blood 2010; 115:4331-6. https://doi.org/10.1182/blood-2010-01-251348 PMid:20233970 PMid:PMCID:PMC2881491

106. Pel FB, Hay SI, Gupta S, et al. Global burden of sickle cell anaemia in children under five, 2010-2050: modeling based on demographics, excess mortality, and interventions. PLoS Med 2013; 10:e1001484. https://doi.org/10.1371/journal.pmed.1001484 PMid:23874164 PMid:PMCID:PMC3712914

107. World Health Organization. Sickle cell disease: a strategy for the WHO African Region. Report AFR/RC60/8. Geneva, Switzerland: World Health Organization; 2010.

108. Yawn BP, Buchanan GR, Afeyeni-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014; 12:1033-48. https://doi.org/10.1001/jama.2014.10517 PMid:25203083

109. Cunningham-Myrie C, Abdullahi A, Waugh A, et al. Hydroxyurea use in prevention of stroke recurrence in children with sickle cell disease in a developing country: a cost-effectiveness analysis. Pediatr Blood Cancer 2015; 62:1862-4. https://doi.org/10.1002/pbc.25563 PMid:25929458

110. Steiner CA, Miller JL. Sickle cell disease patients in U.S. hospitals, 2004. Statistical brief. No.21. Rockville, Md: Agency for...
Healthcare Research and Quality, December 2006.

114. Moore RD, Charache S, Terrin ML, et al. Cost-effectiveness of hydroxyurea in sickle cell anemia. Am J Hematol 2000; 64:26-31. 
https://doi.org/10.1002/(SICI)1096-8652(20000516)1:26::AID-AJH5>3.0.CO;2-F

115. Telen MJ. Beyond hydroxyurea: new and old drugs in the pipeline for sickle cell disease. Blood 2016; 127:810-9. 
https://doi.org/10.1182/blood-2015-09-618553 PMid:26758919

116. Awteh GF, Sutton M, Nassif I, et al. Sustained induction of fetal hemoglobin by pulse butyrate therapy in sickle cell disease. Blood 1999; 93:1790-7. PMid:10068649 PMcid:PMC4269326

117. Saunthararajah Y, Molokie R, Saraf S, et al. Clinical effectiveness of decitabine in severe sickle cell disease. Br J Haematol 2008; 141:126-9. 
https://doi.org/10.1111/j.1365-2141.2008.07027.x PMid:18324975

118. Dos Santos JL, Lanaro C, Lima LM, et al. Design, synthesis, and pharmacological evaluation of novel hydrid compounds to treat sickle cell disease symptoms. J Med Chem 2011; 54:5811-9. 
https://doi.org/10.1021/jm200531f PMid:21766854

119. Meiler SE, Wade M, Kuttar F, et al. Pomalidomide augments fetal hemoglobin production without the myelosuppressive effects of hydroxyurea in transgenic sickle cell mice. Blood 2011; 118:248-58. 
https://doi.org/10.1182/blood-2010-11-319137 PMid:21535962 PMcid:PMC3148160

120. Fard AD, Hosseini SA, Shahjahan M, et al. Evaluation of novel fetal hemoglobin inducer drugs in treatment of β-hemoglobinopathy disorders. Int J Hematol Oncol Stem Cell Res 2013; 7:47-54. PMid:24505535 PMcid:PMC3913144

121. Ataga KI, Stoker J, Sencicap (I-CA-17043): a potential therapy for the prevention and treatment of hemolysis-associated complications in sickle cell anemia. Expert Opin Investig Drugs 2009; 18:231-9. 
https://doi.org/10.1517/13543780802708011 PMid:19236269

122. Misra H, Licklider J, Kazo F, Abuchowski A. PEGylated carboxyhemoglobin bovine (SANGUINATE): result of a phase I clinical trial. Artif Organs 2014; 38:702-7. 
https://doi.org/10.1111/aor.12341 PMid:25113835

123. Chang J, Patton JT, Sarkar A, et al. GMl-1070, a novel pan-selectin antagonist, reverses acute vascular occlusions in sickle cell mice. Blood 2010; 116:1779-86. 
https://doi.org/10.1182/blood-2009-12-260513 PMid:20508165 PMcid:PMC2947397

124. Mandarino D, Kawar Z, Alvarez R, et al. Placebo-controlled, double-blind, first-in-human, ascending single dose, healthy subject study of intravenous-administered SelG1, a humanized anti-P-selectin antibody in development for sickle cell disease. Blood 2013; 122:abstract 970.

125. Batchvarova M, Shan S, Zennadi R, et al. Sevuparin reduces adhesion of both sickle red cells and leukocytes to endothelial cells in vitro and inhibits vaso-occlusion in vivo. Blood 2013;122:abstract 182.

126. Qari MH, Aljaouni SK, Alardawi MS, et al. Reduction of painful vaso-occlusive crisis of sickle cell anemia by tinzaparin in a double-blind randomized trial. Thromb Haemost 2007; 98:392-6. 
https://doi.org/10.1111/j.1365-2095.2007.07181.x

127. De Castro LM, Zennadi R, Jonassaint JC, et al. Effect of prapranolol as anti-adhesive therapy in sickle cell disease. Clin Transl Sci 2012; 5:437-44. 
https://doi.org/10.1111/j.1752-8188.2011.00180.x PMid:23253664 PMcid:PMC3756278

128. Zennadi R. MEK inhibitors, novel anti-adhesive molecules, reduce sickle red blood cell adhesion in vitro and in vivo, and vasoocclusion in vivo. PLoS One 2014; 9:e110306.

129. Cheung AT, Chan MS, Ramanujam S, et al. Effects of poloxamer 188 treatment on sickle cell vaso-occlusive crisis: computer-assisted intravital microscopy study. J Invest Med 2004; 52:402-6. 
https://doi.org/10.1136/jim-52-06-35 PMid:15612454

130. Field JJ, Lin G, Okam MM, et al. Sickle cell vaso-occlusion causes activation of iNKT cells that is decreased by the adenosine A2A receptor agonist ragedenoson. Blood 2013; 121:3293-34. 
https://doi.org/10.1182/blood-2012-11-465963 PMid:23777438 PMcid:PMC3637009

131. Field JJ, Ataga KL, Majerus E, et al. A phase I single ascending dose study of NKTT120 in stable adult sickle cell patients. Blood 2013; 122:abstract 977.

132. Knight-Perry J, DeBaun MR, Strunk RC, Field JJ. Leukotriene pathway in sickle cell disease: a potential target for directed therapy. Expert Rev Hematol 2009; 2:57-68. 
https://doi.org/10.1586/17474086.2.1.57 PMid:21082995

133. Chang J, Shi PA, Chiang EY, Fenetree PS. Intravenous immunoglobulins reverse acute vaso-occlusive crises in sickle cell mice through rapid inhibition of neutrophil adhesion. Blood 2008; 111:915-23. 
https://doi.org/10.1182/blood-2007-04-084061 PMid:17932253 PMcid:PMC200843

134. Hoppe C, Kuyppers F, Larkin S, et al. A pilot study of the short-term use of simvastatin in sickle cell disease: effects on markers of vascular dysfunction. Br J Haematol 2011; 153:655-63. 
https://doi.org/10.1111/j.1365-2141.2010.08480.x PMid:21477202 PMcid:PMC3601917

135. Bhatia M, Walters MC. Hematopoietic cell transplantation for thalassemia and sickle cell disease: past, present and future. Bone Marrow Transplant 2008; 41:109-17. 
https://doi.org/10.1038/sj.bmt.1705943 PMid:18059330