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In this Issue... *The Role of Hydroxyurea in the Management of Sickle Cell Disease*

Sickle cell disease is a systemic disorder whose proximate cause is a single β -globin gene mutation (*HBB*, glu6val). Patients with sickle cell anemia are homozygous for this mutation. Its multifaceted pathophysiology provides the opportunity to interrupt the disease pathobiology at multiple sites. Sickle hemoglobin (HbS) polymerization is the initiating point of much of the pathophysiology of disease. The drug hydroxyurea induces an increase in fetal hemoglobin (HbF) concentration, and the presence of γ -globin reduces the polymerization tendency of deoxyHbS. While hydroxyurea lessens some of the vasoocclusive complications of sickle cell anemia, not all patients will respond to this treatment, and additional HbF-inducing agents are needed.

In this issue, we examine the role of hydroxyurea — its efficacy in adults, children, and infants, and the risks/benefits of treatment in the overall management of sickle cell disease. Two of the key interrelated events responsible for most of the clinical features of sickle cell disease - sickle vaso-occlusion and hemolytic anemia – will be discussed in depth in future issues.

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+ **Commentary and Reviews by:**
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Commentary

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Hydroxyurea, a ribonucleotide reductase inhibitor and an S-phase-specific cytotoxic agent, increases HbF levels in most, but not all, patients with sickle cell anemia. Well absorbed orally, it is a potent inhibitor of DNA synthesis. After administration, hydroxyurea reaches a peak serum concentrations in 3 to 6 hrs. However, this agent's rapid elimination makes monitoring adherence to treatment by measuring blood levels problematical, in that it is difficult to differentiate between inadequate dosing, biological resistance to treatment, and/or poor patient compliance as possible explanations for treatment failure.

In bacteria and in cell lines, resistance to hydroxyurea occurs by mechanisms that include overproduction of the B2 protein of ribonucleotide reductase, gene amplification, increased translational efficiency of mRNA, prolonged half life of enzyme subunits, and production of a resistant mutant enzyme. It is not known if resistance to the therapeutic effects of hydroxyurea occurs in patients with sickle cell disease, but, if patients continue to use the drug as directed, its hematological and clinical benefits appear to persist for at least 9-years.^{1,2} Hydroxyurea increases HbF in sickle cell anemia because its cytotoxicity causes erythroid regeneration and (it has been hypothesized) because its metabolism leads to Nitric Oxide-related increases in soluble guanylate cyclase (sGC) with an increase of cGMP that augments γ -globin gene expression.

Hydroxyurea must be taken indefinitely to be effective and is potentially mutagenic and carcinogenic. The data from the Zimmerman report, indicating no increase in T-cell gene recombination events, is reassuring with respect to chromosomal damage.² In Steinberg's follow-up of the Multicenter Trial of Hydroxyurea¹, a few patients developed malignancy, and he noted that several cases of hydroxyurea-treated sickle cell anemia patients developing acute leukemia were reported. While the importance of these cases is unclear (as the total number of patients treated is unknown), it appears that the relative risk of leukemia in hydroxyurea-treated sickle cell anemia is much less than that observed in myeloproliferative disorders. The risk of death from the complications of adult sickle cell disease appears at least 10 times greater than their incidence of leukemia, so that the risk:benefit ratio clearly favors therapy.

In patients with severe disease characterized by chronic organ damage, severe anemia, and beginning renal failure, death occurred sooner even if they received hydroxyurea.^{1,3} The impressive results of treatment with minimal adverse effects, however, beg answers to two key questions:

- How early in life can this treatment be safely started?
- Will early treatment prevent the accumulation of organ damage that appears to explain the death of hydroxyurea-treated adults?

Studies addressing these questions are underway, with results anticipated in the near future.

Hydroxyurea is the sole FDA-approved drug for treating sickle cell anemia and should be used in all adults where indications for this treatment are present. Treatment indications include: frequent painful episodes (>2 per year) requiring a visit to a medical facility and the use of opioid analgesics; severe anemia; a history of acute chest syndrome. Other possible indications are priapism, refractory leg ulcers, and a history of cerebrovascular accident. Unfortunately, for reasons that are poorly understood, less than half of all patients who might benefit from treatment actually receive it, so that a medication with proven efficacy has reduced effectiveness. While the reasons for this failure remain speculative, it could be a result of both physician hesitancy to begin the drug and escalate the dose to that needed for a therapeutic effect, and patient concerns about the potential reproductive

hazard of hydroxyurea.

While no randomized clinical trials have specifically studied the effectiveness of hydroxyurea in HbSC disease, the second most prevalent genotype of sickle cell disease (compound heterozygosity for HbS and HbC [HBB, glu6lys]), it has been theorized that hydroxyurea might have its major effect by reducing cell density independent of increasing HbF concentration. The pathophysiology of HbSC differs from that of sickle cell anemia in that the average HbSC cell is dense, dehydrated, poorly deformable, contains less HbF, and is longer lived than the erythrocyte of sickle cell anemia. Therefore, one might expect that the response to hydroxyurea treatment might also differ. In the few patients with HbSC disease given hydroxyurea, cell density was reduced and MCV increased; in addition, there was less hemolysis as estimated by a fall in reticulocytes and increase in total hemoglobin concentration, while HbF increases were inconsistent⁴. A decision to treat patients with this genotype is a matter of clinical judgment: is a patient sick enough to warrant a trial of a potentially hazardous drug given the possibility that its use in this disorder will not be beneficial? The true test of the benefit of this drug in HbSC disease awaits the completion of ongoing clinical trials.

References

1. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A et al. [Effect of hydroxyurea on mortality](#)
2. Zimmerman SA, Schultz WH, Davis JS, Pickens CV, Mortier NA, Howard TA et al. [Sustained long-term and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment.](#) JAMA 2003; 289:1645-1651
3. Bakanay SM, Dainer E, Clair B, Adekile A, Daitch L, Wells L et al. [Hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease.](#) Blood 2004; 103:2039-2045.
3. Bakanay SM, Dainer E, Clair B, Adekile A, Daitch L, Wells L et al. [Mortality in Sickle Cell Patients on Hydroxyurea Therapy.](#) Blood 2005; 105:545-547.
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HYDROXYUREA & ACUTE PAINFUL EPISODES

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Pilot studies in the early 1990's showed that hydroxyurea had hematological effects in sickle cell anemia, which suggested that its use could beneficially effect the course of disease. Primary among these was an increase in HbF. Therefore, in 1995, Charache et al designed a multicenter, double-blinded, placebo-controlled trial of hydroxyurea in adults with sickle cell anemia and moderately severe to severe disease. Its goal was to see if maximally tolerated doses of this drug would reduce the frequency of acute painful episodes, the most common feature of disease and an indicator of premature mortality.

In this study, patients aged 18 or older with homozygous sickle cell anemia and a history of at least three medical contacts for pain in the preceding year were randomized to hydroxyurea (n=152) or placebo (n=147). The hydroxyurea dose was initiated at 15 mg/kg per day and escalated at 12 week intervals to achieve a maximally-tolerated-dose, just below that producing marrow toxicity. The mean number of vaso-occlusive crises (VOC) in the placebo group was 4.5 per year, versus only 2.5 per year in the HU treated group, a statistically significant decrease in frequency of 44%. In addition, VOC requiring hospitalization occurred at a rate of 2.4 per year in the placebo group versus 1.0 per year in the treated group (p <0.001). Additional analyses showed that the time-to-first VOC was significantly less in the treated group (1.5 months vs. 3.0 months, p <0.01).

The effect of hydroxyurea continued with ongoing treatment, as the time-to-second VOC was also significantly less in the treated group than controls (4.6 months vs. 8.8 months). Furthermore, the hydroxyurea treated group had fewer episode of the Acute Chest Syndrome, another severe morbid complication of sickle cell disease, (n=25) than controls (n=51); this decrease in the Acute Chest Syndrome was accompanied by a significant decrease in the number of patients receiving transfusion and in the number of units used during the trial. Moreover, the effect of hydroxyurea became evident at 4 to 8 weeks after initiation of therapy, before the maximum rise in HbF was achieved. Only about one half of the patients randomized to receive active drug had an increase in HbF that might be considered clinically important, (between 9.5% and 18%), while half had a increase to only 4%, what many experts would consider suboptimal.

While the therapeutic benefits of hydroxyurea are most likely a result of its ability to increase HbF, many other biological changes occurred during drug treatment. These included, among others, a reduction in red cell adherence, a reduction in circulating adherence molecules, and increased nitric oxide (NO). It is possible that these and other observations are effects secondary to increased HbF. Toxicity was primarily that of marrow suppression and resolved with temporary cessation of treatment. Some patients reported weight gain, which was attributed to the reduced energy requirements of the suppressed bone marrow.

Subsequently, the placebo group was offered therapy with hydroxyurea and follow-up of this group for late toxicity was continued by Steinberg et al. The more than 9-years of observation in 233 of the original subjects found little risk associated with treatment, no clinically important hematological toxicity, and no increase in adverse events occurred. Cumulative mortality was reduced by nearly 40%, with death rates for subjects continuing hydroxyurea reported as 1.5 ±7.9 per 3 month period vs. 2.6 ± 5.8, p <0.04). These favorable results were related to the ability of the drug to increase HbF and to reduce the frequency of both painful episodes and of the Acute Chest Syndrome.

An initial assessment of the data raised the question of whether these results could be explained by the treatment-associated fall in leukocyte count. However, further analysis showed no relationship between the decrement in neutrophil counts and mortality, and it was likely that the study design, where hydroxyurea was given at sub-toxic doses, forced a relationship between leukocyte count and clinical events.

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LONG-TERM EFFECTS OF HYDROXYUREA THERAPY IN CHILDREN

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In infants, children, and adolescents with sickle cell anemia, the HbF response to hydroxyurea is more robust than in adults. In the study by Zimmerman et al of 106 children who received maximal drug doses for a median of 11 years, HbF increased to almost 20%, and the hematological effects were sustained for 7 years without clinically important toxicity. Transient decreases in WBC, hemoglobin concentration or platelet counts were found to be readily reversible, allowing the drug to be restarted at slightly lower doses. Further, gastrointestinal upset could be mitigated by bedtime dosing. Melanonychia occurred in 10% of patients studied, but did not require discontinuation of therapy. Height and weight growth velocities improved in the majority of patients on treatment. Importantly, during 455 patient-years of observation, no episodes of the Acute Chest Syndrome severe enough to require exchange transfusion or mechanical ventilation occurred in this patient population. In 26 of the 34 subjects who were treated for at least 5 years, analysis of interlocus VDJ recombination events of the T-cell gene on chromosome 7 revealed no increase in rearrangements.

Taken together, these data support the contention that hydroxyurea at maximum tolerated dose in children with sickle cell anemia has long term hematologic efficacy. In agreement with previous studies, hydroxyurea had no adverse effect on growth in this population, was not associated with an increased incidence of DNA mutations and no cases of myelodysplasia, acute leukemia or other malignancies were observed.

1. Zimmerman SA, Schultz WH, Davis JS, Pickens CV, Mortier NA, Howard TA et al. Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. Blood 2004; 103:2039-2045.

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HYDROXYUREA & PATIENT MORTALITY

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Investigating hydroxyurea and patient mortality, Bakanay et al report on 262 adult patients, finding that those who died during treatment (compared to survivors) had had hydroxyurea treatment started later in life (35.8 ± 11.4 yr vs. 32.1 ± 10 yrs), appeared to have had more organ damage as illustrated by lower total hemoglobin levels (7.7 ± 1.3 Vs. 8.4 ± 1.3 , $p < 0.01$) and higher creatinine (0.7 ± 0.2 Vs. 0.6 ± 0.2 , $p = 0.04$), and were felt to have had more severe disease. Curiously, in those patients who died, the HbF level attained with treatment was not associated with an increase in total hemoglobin concentration, suggesting that these patients had bone marrow damage preventing a response to the decreased degree of hemolysis.

This important study identifies a subgroup of sickle cell anemia patients who are unlikely to respond to hydroxyurea therapy. The phenotype of this group is characterized by more severe anemia, homozygosity for homozygous BAN or heterozygosity for heterozygous CAM and impaired organ function. The data suggest that institution of hydroxyurea therapy earlier and at a higher dose, or the use of other agents that stimulate hemoglobin F synthesis. could be beneficial in these patients.

1. Bakanay SM, Dainer E, Clair B, Adekile A, Daitch L, Wells L et al. Mortality in Sickle Cell Patients on Hydroxyurea Therapy. Blood 2005; 105:545-547.

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HYDROXYUREA & CEREBROVASCULAR EVENTS

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Some investigators have proposed using hydroxyurea for secondary prevention of stroke in children. Gulbis et al report on 127 children who were treated with less than the maximally tolerated dose of hydroxyurea (20 mg/kg/d or less). Of these, 72 had transcranial Doppler (TCD) studies performed. Of the 34 patients deemed to be "at risk" for stroke on the basis of these TCD results, only one individual had a stroke during a 98 patient-years of observation. While not a controlled study, these results are similar to the prevention of a first stroke using blood transfusion.

Of 8 subjects at risk for second stroke, only 1 had stroke over 6 years of observation; this rate is substantially lower than the expected 50% recurrence rate. Moreover, the rate for Acute Chest Syndrome in this population was 3.3 per 100 pt-yrs, compared to the expected rate of 25.3 per 100 pt-yrs. However, the overall rate for stroke was 1.3 per 100 pt-yrs as compared to the expected rate of 0.61 per 100 pt-yrs reported in the Cooperative Study of Sickle Cell Disease (Ohene-Frempong, et al). In addition, the rates for Acute Chest Syndrome and VOC seemed to increase after 3 years of therapy, which the investigators felt was due to either more severe disease at baseline or a sub-maximal response due to the lower dose of hydroxyurea.

In the Ware study of 16 patients who were unable to continue transfusion for the secondary prevention of stroke, hydroxyurea was given to the maximally-tolerated-dose. Over a mean follow-up of 22 months (range 3 to 52 mos), there were no instances of the Acute Chest syndrome and only 8 VOC (two requiring hospitalization). Three of these subjects developed new CNS symptoms or findings 11 to 16 weeks after discontinuation of transfusion. Ware et al felt that this early occurrence of stroke might have been the result of the rapid return of sickle erythropoiesis prior to the cellular effects of hydroxyurea, and proposed a longer transition period of gradually decreasing transfusion while hydroxyurea is initiated.

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3. Ware RE, Zimmerman SA, Schultz WH. Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. *Blood* 1999; 94:3022-3026.



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HYDROXYUREA EFFICACY & TOXICITY IN INFANTS

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While the long-term efficacy and toxicity of hydroxyurea for infants are undefined, and this agent's role in preventing organ dysfunction when started in infancy is unknown, the short-term feasibility of hydroxyurea administration, its toxicities and hematologic effects and its effect on spleen function in infants with sickle cell anemia were investigated by Hankins et al. They studied 21 infants who had completed 2 years of hydroxyurea therapy at a fixed dose of 20 mg/kg/d; participants were offered study extension with dose escalation to 30 mg/kg/d and were monitored with laboratory tests and biannual imaging studies for splenic function and brain magnetic resonance imaging and angiography (MRI/MRA). Hematologic indices were compared with predicted age-specific values and observed event rates compared with historic rates.

All 21 subjects completing the original trial enrolled in the extension study, at a median age of 3.4 years. After 4 years, hemoglobin concentration was 9.1 g/dL compared with an expected value of 8.1 g/dL; HbF was ~24% compared with an expected level of 9%; and there was an additional increase in HbF with dose escalation of ~2%. Consistent with these observations, mean corpuscular volume (MCV) increased, while reticulocytes, white blood cell and platelet counts all decreased. Patients experienced 7.5 acute events per 100 person-years, compared with 24.5 events per 100 person-years among historic controls. Forty-three percent of treated patients had asplenia compared with an expected 94%; two patients had return of splenic function during the study; and growth rates improved to the extent that patient growth patterns approximated that of normal controls. In addition, one patient developed a silent infarct on MRI, and two patients had regression of cerebral artery stenosis.

This extension of the Hydroxyurea Safety and Organ Toxicity Study (HUSOFT) demonstrates that infants with sickle cell anemia benefit from hydroxyurea therapy at a dose of 30mg/kg/d with sustained hematologic improvement, reduced episodes of ACS, and improved growth and organ function.

1. Hankins JS, Ware RE, Rogers ZR, Wynn LW, Lane PA, Scott JP et al. Long-term hydroxyurea therapy for infants with sickle cell anemia - the Husoft extension study. *Blood* 2005; 106:2269-2275.



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Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe the indications for the use of hydroxyurea in the management of sickle cell disease.
- Identify the benefits of hydroxyurea therapy in sickle cell disease.
- Discuss the current state of knowledge regarding the risk:benefit ratio of hydroxyurea therapy in adults, children, and infants.

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