

NIH State-of-the-Science Conference Statement on Hydroxyurea Treatment for Sickle Cell Disease



NIH Consensus and State-of-the-Science Statements

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The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research, and that the information provided is not a substitute for professional medical care or advice.

Reference Information

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Publications Ordering Information

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The Evidence Report prepared for this conference by the Agency for Healthcare Research and Quality is available on the Web via <http://www.ahrq.gov/clinic/tp/hydscdtp.htm>. Printed copies may be ordered from the AHRQ Publications Clearinghouse by calling 1-800-358-9295. Requestors should ask for AHRQ Publication No. 08-E007.

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Disclosure Statement

All of the panelists who participated in this conference and contributed to the writing of this statement were identified as having no financial or scientific conflict of interest, and all signed forms attesting to this fact. Unlike the expert speakers who present scientific data at the conference, the individuals invited to participate on NIH Consensus and State-of-the-Science panels are reviewed prior to selection to assure that they are not proponents of an advocacy position with regard to the topic and are not identified with research that could be used to answer the conference questions.

For more information about conference procedures, please see ***<http://consensus.nih.gov/aboutcdp.htm>***.

Archived Conference Webcast

The NIH Consensus Development Conference on Hydroxyurea for Sickle Cell Disease was webcast live February 25-27, 2008. The webcast is archived and available for viewing free of charge at ***<http://consensus.nih.gov/sicklecell.htm>***.

Abstract

Objective

To provide health care providers, patients, and the general public with a responsible assessment of currently available data on hydroxyurea treatment for sickle cell disease.

Participants

A non-DHHS, nonadvocate 14-member panel representing the fields of internal medicine, family practice, hematology, oncology, pediatrics, obstetrics, nursing, pediatric nursing, social work, pharmacology, pharmacokinetics, and pain research, mental health, epidemiology, biostatistics, public health, and health systems research, in addition to a public representative. In addition, 22 experts from pertinent fields presented data to the panel and conference audience.

Evidence

Presentations by experts and a systematic review of the literature prepared by The Johns Hopkins University Evidence-Based Practice Center, through the Agency for Healthcare Research and Quality. Scientific evidence was given precedence over anecdotal experience.

Conference Process

The panel drafted its statement based on scientific evidence presented in open forum and on published scientific literature. The draft statement was presented on the final day of the conference and circulated to the audience for comment. The panel released a revised statement later that day at <http://consensus.nih.gov>. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

Conclusions

The burden of suffering is tremendous among many patients with sickle cell disease. These patients experience disease-related pain on many days of their lives and usually do not seek medical attention until their symptoms are overwhelming. They often attempt to treat themselves and thus do not always come to the attention of the health care system. Obtaining optimal care for patients with sickle cell disease is challenging. Many patients are not in a coordinated program aimed at prevention of long-term complications and acute pain crises. They rely heavily on emergency and short-term care facilities for pain control.

Obtaining specialty care can be a substantial challenge because the number of health professionals trained to treat the disease is limited and the number of professionals specializing in the treatment of this disease is decreasing. The likelihood that patients with sickle cell disease have a principal physician is low. Transitioning from pediatric care to adult care poses particular challenges. Many children rely on public insurance for their care. Gaps in coverage occur, leading to gaps in care.

No population-based registries exist that provide good estimates of the number of people with sickle cell disease. Surveys indicate that a large proportion of patients who have sickle cell disease are poor and from underserved communities. Most U.S. patients with sickle cell disease are ethnic minorities. For many, the limited resources and lack of culturally competent care by experienced clinicians set the stage for suboptimal care.

Hydroxyurea is an important major advance in the treatment of sickle cell disease. Strong evidence supports the efficacy of hydroxyurea in adults to decrease severe painful episodes, hospitalizations, number of blood transfusions, and the acute chest syndrome. Although the evidence for efficacy of hydroxyurea treatment for children is not as strong, the emerging data are encouraging. The current data on the risks of both short- and long-term harms of hydroxyurea therapy are reassuring, and the risks of hydroxyurea use in adults are acceptable compared with the risks of untreated sickle cell disease.

It is difficult to draw conclusions about the effectiveness of hydroxyurea in everyday practice because we lack precise estimates of the number of people with sickle cell disease in the United States and the number of people receiving hydroxyurea. Furthermore, although barriers to the use of hydroxyurea in persons with sickle cell disease seem to be extensive, little research exists on the barriers at the patient, parent/family/caregiver, provider, and system levels. More studies are required to address these issues.

The best way to achieve optimal care for patients with sickle cell disease, including preventive care, is for patients to be treated in clinics specializing in the care of this disease. All patients with sickle cell disease should have a principal health care provider, and that provider, if not a hematologist, should be in frequent consultation with one. The National Institutes of Health funds sickle cell research centers, and several states currently support sickle cell specialty clinics. Increased funding for basic, clinical, and social research on this disease is critically needed. There is an urgent need for centers specializing in the treatment of sickle cell disease to organize and network together to improve patient access to quality care.

Introduction

Sickle cell disease is an inherited blood disorder that affects 50,000 to 100,000 people in the United States. It is estimated that 2,000 babies are born with sickle cell disease in the United States each year. Sickle cell disease was the first disease for which a specific molecular defect in a gene was identified, and it is the most common genetic disease identified as part of the Newborn Screening Program in the United States. The condition is chronic and lifelong, and it is associated with a decreased lifespan. Sickle cell disease is most common in people whose families come from Africa, South or Central America, Caribbean islands, Mediterranean countries (such as Turkey, Greece, and Italy), India, and Saudi Arabia.

Sickle cell disease occurs when an infant inherits the gene for sickle hemoglobin from both parents (Hb SS, or sickle cell anemia) or the gene for sickle hemoglobin from 1 parent and another abnormal hemoglobin gene from the other parent. In addition, approximately 2 million Americans have the sickle cell trait (in which an infant inherits the gene for sickle hemoglobin from 1 parent and a normal hemoglobin gene from the other parent). Several additional sickle syndromes result from genotypes that include, but are not limited to, SCD-S β^0 , SCD-SC, SCD-SD, SCD-S β^+ , and SCD-SO_{arab}.

Erythrocytes (red blood cells) in people with sickle cell disease become deoxygenated (depleted of oxygen), dehydrated, and crescent-shaped or "sickled." The cells aggregate, or clump together, and stick to blood vessel walls. Aggregation blocks blood flow within limbs and organs. This can cause painful episodes and permanent damage to the eyes, brain, heart, lungs, kidneys, liver, bones, and spleen. Infections and lung disease are the leading causes of death in people with sickle cell disease.

Patients with sickle cell disease are frequently seen in emergency departments and hospitalized for pain

crises. Standard treatments for acute pain crises include painkilling medications, hydration, and oxygen.

Hydroxyurea was initially synthesized in Germany in 1869. Nearly 50 years ago, it was developed as an anticancer drug and has been used to treat myeloproliferative syndromes, some types of leukemia, melanoma, and ovarian cancer. It has also been used to treat psoriasis. Hydroxyurea was first tested in sickle cell disease in 1984. Initial studies show that it acts to increase the production of fetal hemoglobin-containing erythrocytes and dilute the number of sickled cells in circulation.

In the mid-1990s, investigators of a major study randomly assigned nearly 300 adults with sickle cell disease who had more than 3 severe painful crises or episodes per year to hydroxyurea or placebo. (In the past, the term pain crises has been used; currently, the term severe pain episodes is preferred.) This study was stopped early because it clearly showed that hydroxyurea reduced the number and severity of pain episodes in patients with sickle cell disease compared with placebo. Follow-up with the trial participants, including patients who were originally given placebo and were later prescribed hydroxyurea after the drug was determined to be beneficial, has shown that hydroxyurea reduces the damaging effects of sickle cell disease and improves some aspects of quality of life. The drug also may extend survival. In 1998, the U.S. Food and Drug Administration approved hydroxyurea for prevention of pain crises in adults with sickle cell anemia. Although the efficacy of hydroxyurea has been established in adults, the evidence of its efficacy in children is not as strong; however, the emerging data are supportive.

Although hydroxyurea is beneficial to some patients with sickle cell disease, several issues about use of the drug are unresolved. These include patient and health practitioner concerns about the overall safety and effectiveness of hydroxyurea, as well as a lack of providers expert in the treatment of patients with sickle cell disease.

To more closely examine this important topic, the National Heart, Lung, and Blood Institute and the Office of Medical Applications of Research of the National Institutes of Health convened a Consensus Development Conference from 25 to 27 February 2008 to assess the available scientific evidence related to the following questions:

- What is the efficacy (results from clinical studies) of hydroxyurea treatment for patients who have sickle cell disease in 3 groups: infants, preadolescents, and adolescents and adults?
- What is the effectiveness (in everyday practice) of hydroxyurea treatment for patients who have sickle cell disease?
- What are the short- and long-term harms of hydroxyurea treatment?
- What are the barriers to hydroxyurea treatment for patients who have sickle cell disease, and what are the potential solutions?
- What are the future research needs?

At the conference, invited speakers presented information pertinent to these questions, and a systematic literature review prepared under contract with the AHRQ (<http://www.ahrq.gov/clinic/tp/hydscdtp.htm>) was summarized. Conference attendees provided both oral and written statements in response to the key questions. The panel members weighed all of this evidence as they addressed the conference questions.

This consensus statement is intended to provide researchers, health care providers, patients, and other interested members of the general public with an objective assessment of what is known about hydroxyurea as a treatment for sickle cell disease, and what questions remain.

1. What Is the Efficacy (Results from Clinical Studies) of Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease in 3 Groups: Infants, Preadolescents, and Adolescents and Adults?

Efficacy is the therapeutic effect of an intervention in a controlled setting, in contrast to effectiveness, which is the therapeutic effect of an intervention in real-world situations. The spectrum of sickle cell disease includes the SCD-SS, SCD-S β^0 , SCD-SC, SCD-SD, SCD-S β^+ , and SCD-SO_{arab} genotypes. Efficacy studies have varied in their inclusion of specific genotypes, but almost all include SCD-SS. In addition, the geographic origin of sickle cell disease is associated with different haplotypes and varying degrees of clinical severity. The 3 most common and phenotypically distinct haplotypes are Senegalese, Benin, and Bantu. Other geographic areas of origin associated with sickle cell disease include Saudi Arabia and the Indian subcontinent. The Benin and Bantu haplotypes are more common among people residing in the Western Hemisphere and are associated with worse clinical outcomes. Response to hydroxyurea therapy may vary by haplotype or genotype. However, few studies of efficacy have appropriately accounted for the heterogeneity of study populations that differed by genotype and phenotype as well as by demographic factors (such as sex and age).

Although clinical experience on the use of hydroxyurea for treating sickle cell disease has been amassed over nearly 25 years, the strength of evidence supporting the efficacious use of hydroxyurea is not equivalent across age groups. Hydroxyurea is currently U.S. Food and Drug Administration-approved for use in adults and is the only treatment for sickle cell disease that modifies the disease process. Evidence is strong in adults but more

limited in children because the sole randomized clinical trial in the latter population had a weak study design, small sample, and short follow-up. Nonetheless, the evidence in children does not contradict the findings in adults that hydroxyurea improves hematologic variables and decreases hospitalization rates. Published evidence based on weaker, observational study designs, such as cohort studies, before-and-after studies, case series, and case reports, suggests that hydroxyurea is efficacious. Adding to the difficulty in reaching a consensus on the use of hydroxyurea is that published efficacy studies are difficult to interpret because diverse outcome measures have been used, including hematologic end points; reduced incidence of severe pain episodes, the acute chest syndrome, hospitalizations, strokes, and kidney and spleen damage; and need for transfusion therapy. Studies currently underway should provide more information regarding the benefit of hydroxyurea in preventing organ damage and additional sickle cell disease outcomes. Elucidating the mechanism of action of hydroxyurea should prove useful in developing new agents.

Adolescents and Adults

Strong evidence supports the efficacy of hydroxyurea use in adults. The published clinical trials included adolescents; however, they were not analyzed or reported as a separate group. Outcomes were diverse and included blood markers as measures of treatment effect (for example, hemoglobin level, hemoglobin F cell count, percentage of hemoglobin F, mean corpuscular volume, leukocyte count, and platelet count). Studies used a variety of clinical outcome measures (severe pain episodes, hospitalizations, the acute chest syndrome, blood transfusion therapy, mortality, priapism [unwanted, prolonged, painful erection], strokes, and leg ulcers) and examined the effects of hydroxyurea on the spleen, kidneys, and blood flow to the brain (Table 1).

Table 1. Study Outcomes for Adults Receiving Hydroxyurea for Sickle Cell Disease

Outcome	Effect
<i>Blood markers</i>	
Hemoglobin level	Increase (high-grade evidence)
Percentage of fetal hemoglobin	Increase (high-grade evidence)
Mean corpuscular volume	Increase (high-grade evidence)
Leukocyte count	Increase (high-grade evidence)
<i>Clinical outcomes</i>	
Pain crises	Decrease (high-grade evidence)
Hospitalizations	Decrease (high-grade evidence)
Blood transfusion therapy	Decrease (high-grade evidence)
The acute chest syndrome	Decrease (high-grade evidence)
Priapism	Not evaluated
Stroke	Not evaluated
Leg ulcer	Not significantly different
Sepsis	Not evaluated
<i>Prevention of end-organ damage</i>	
Spleen	Not evaluated
Kidney	Not evaluated
Brain (cerebral blood flow)	Being evaluated
<i>Mortality</i>	Decrease (low-grade evidence)

Although a reduction in mortality with hydroxyurea therapy has been reported, the published trial was not specifically designed to assess this end point. It is therefore difficult to draw definitive conclusions about the effect of hydroxyurea on mortality.

Preadolescents

The evidence varies on whether the use of hydroxyurea improves short-term end points, especially hematologic measures, in preadolescent populations beyond infancy (Table 2).

Evidence is strong for an improvement in blood markers and reduced hospitalizations and moderate for a reduction in the incidence of pain crises. Ongoing investigations in this age group will determine the efficacy of hydroxyurea treatment for children with SCD-SS, a history of stroke, and too much iron (iron overload).

Infants

No published, well-designed clinical trials have evaluated the efficacy of hydroxyurea treatment for infants. Ongoing prospective trials and observational studies are attempting to address this gap. The end points of these studies include prevention of damage to the kidney and spleen and improvements in blood markers that predict long-term clinical outcomes.

In summary, the efficacy of hydroxyurea treatment for adults with SCD-SS is established. Although the evidence for efficacy of hydroxyurea treatment for children is not as strong, the emerging data are supportive. Future directions include evaluation of efficacy in preadolescent children and infants and further development of other therapeutic techniques, including stem-cell transplantation and gene therapy. Stem-cell transplantation can cure sickle cell anemia.

Table 2. Study Outcomes for Preadolescent Children beyond Infancy Receiving Hydroxyurea for Sickle Cell Disease

Outcome	Effect
<i>Blood markers</i>	
Hemoglobin level	Not significantly different
Percentage of fetal hemoglobin	Increase (high-grade evidence)
Mean corpuscular volume	Increase (high-grade evidence)
Leukocyte count	Decrease (high-grade evidence)
<i>Clinical outcomes</i>	
Pain crises	Decrease (moderate-grade evidence)
Hospitalizations	Decrease (high-grade evidence)
Blood transfusion therapy	Insufficient data
The acute chest syndrome	Insufficient data
Priapism	Not evaluated
Stroke	Decrease (low-grade evidence)
Leg ulcer	Not evaluated
Sepsis	Not evaluated
<i>Prevention of end-organ damage</i>	
Spleen	Being evaluated
Kidney	Being evaluated
Brain (cerebral blood flow)	Being evaluated
<i>Mortality</i>	Insufficient data

2. What Is the Effectiveness (in Everyday Practice) of Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease?

Effectiveness is the therapeutic effect of an intervention as demonstrated or observed in patients in their usual care setting. The efficacy of hydroxyurea in treating adults with sickle cell disease is established. Data on the effectiveness of hydroxyurea are limited, but the experience of multiple physicians and clinics strongly suggests that the drug is highly effective in widespread practice. One problem in determining the effectiveness of hydroxyurea treatment is that precise estimates of the number of people with sickle cell disease in the United States and of the number of people receiving hydroxyurea treatment are lacking. Another problem is that adherence to hydroxyurea therapy substantially affects its effectiveness. The fact that it often takes 3 to 6 months of treatment for the patient to have a clinical response decreases adherence. Additional reasons for nonadherence are not fully understood.

Most people who have received hydroxyurea seem to be treated in specialty clinics. Only a fraction of patients who might benefit from hydroxyurea have received treatment. Potentially, many more patients could benefit from treatment, including patients who have been excluded from past research studies. Reasons for exclusion have been pregnancy, substance abuse problems, previous hydroxyurea therapy, HIV infection, stroke in the past 6 years, and long-term use of opioids. Therefore, some of the sickest patients with sickle cell anemia have been excluded from studies. Observational studies in both adults and children support the use of hydroxyurea in reducing the complications of sickle cell disease (including pain, hospitalizations, blood transfusions, and the acute chest syndrome) and decreasing mortality. Although data are limited regarding the effectiveness of hydroxyurea treatment for sickle cell disease, it seems to be highly effective but is currently underutilized.

3. What Are the Short- and Long-Term Harms of Hydroxyurea Treatment?

Hydroxyurea treatment has potential short- and long-term negative effects (Table 3). The known and potential side effects of this agent seem to be related to its interference with rapidly dividing cells, particularly newly formed blood cells. We have defined short-term effects as conditions that generally occur within 6 months of initiation of hydroxyurea therapy and long-term effects as conditions that are chronic or occur more than 6 months after initiation of hydroxyurea therapy.

Short-Term Effects

The blood-related, short-term effects of hydroxyurea are dose-related and can be predicted on the basis of its mechanism. These are intrinsic to the therapeutic effect of hydroxyurea. They include a decreased leukocyte count (leukopenia), decreased platelet count (thrombocytopenia), decreased erythrocyte count (anemia), and decreased reticulocyte count (fewer newly formed erythrocytes).

A decrease in leukocyte count may predispose the patient to infection, and a decrease in platelet count may predispose the patient to bleeding; these blood cells are therefore monitored regularly during therapy. The effect of hydroxyurea on blood is temporary and reversible. If leukocyte or platelet counts are too low, the dose of hydroxyurea is reduced or hydroxyurea therapy is discontinued. Careful monitoring of blood-related laboratory tests and dose adherence will usually prevent these side effects.

Another possible short-term effect among men taking hydroxyurea is decreased sperm production, which may be temporary and reversible. Data are limited. No large studies are available of sperm production among men receiving hydroxyurea for sickle cell disease. We are

Table 3. Side Effects of Hydroxyurea Treatment in People with Sickle Cell Disease

Side Effect	Comment
Short-term	
Decreased leukocyte count (leukopenia) Decreased platelet count (thrombocytopenia) Decreased erythrocyte count (anemia)	Frequent, expected, and dose-related; typically can be anticipated and prevented by temporary discontinuation of hydroxyurea or decrease in hydroxyurea dose; usually resolves within 1 to 2 weeks
Nausea (usually mild)* Skin rash Pneumonitis (lung inflammation)	Infrequent
Temporarily decreased sperm count or sperm abnormalities*	Not adequately evaluated
Long-term	
Increased risk for superficial skin cancer* Skin and nail darkening (hyperpigmentation)	Infrequent
Permanently decreased sperm count*	Not adequately evaluated
Reproductive*	When taken during pregnancy, hydroxyurea can in theory increase the risk for miscarriage, birth defects, restricted fetal growth, or postnatal development; sexually active couples should avoid pregnancy if either person is receiving hydroxyurea
* Evidence is insufficient or low that this side effect is associated with hydroxyurea.	

not aware of any reports of an increase in birth defects among the offspring of men who take hydroxyurea.

Hydroxyurea seems to cause dryness of the skin and darkening of the skin and nails (hyperpigmentation); this may also be a long-term side effect.

Leg ulcers are common in adults with sickle cell disease. In a randomized clinical trial comparing hydroxyurea and placebo, hydroxyurea did not seem to affect the development of leg ulcers in people with sickle cell disease. Gastrointestinal tract symptoms were no more common among people receiving hydroxyurea for sickle cell disease than among those not receiving hydroxyurea.

Long-Term Effects

The potential long-term effects of hydroxyurea are birth defects in the offspring of people receiving the drug, growth delays in children receiving the drug, and cancer in both children and adults who have received the drug. These long-term harms may be permanent and irreversible, but they are not yet proven.

There have been concerns about the potential for hydroxyurea to cause birth defects in humans because it has caused birth defects in experimental animals. Pregnant rats and mice given hydroxyurea in very high doses have an increased number of offspring with birth defects. However, the number of birth defects among the offspring of women who received hydroxyurea during pregnancy does not seem to be increased. The long-term effects of hydroxyurea on children exposed to the drug in utero are unknown. Nonetheless, because of concerns about the potential of hydroxyurea to cause birth defects, the drug is generally not prescribed to pregnant women. Men and women who are receiving hydroxyurea are advised to use contraception. Women who are trying to become pregnant or who do become pregnant while taking hydroxyurea should stop taking the drug.

Children 5 to 15 years of age who have sickle cell disease and receive hydroxyurea show a growth rate similar to that of peers with sickle cell disease who are not receiving hydroxyurea.

Hydroxyurea has an excellent and long-standing safety profile in the treatment of myeloproliferative disorders, although cases of leukemia and other types of cancer have been reported in patients who have received hydroxyurea for other blood conditions. Most of these conditions are blood disorders, such as polycythemia vera or essential thrombocytosis, and these conditions can progress spontaneously to leukemia. This makes it difficult to determine whether hydroxyurea itself causes leukemia. Cases of leukemia and other types of cancer also have been reported among both children and adults who have taken hydroxyurea to treat sickle cell disease. These cases are rare and seem to be no more common than among the general population. The risk for cancer does not seem to differ for people with sickle cell disease who have received hydroxyurea and those who have not.

Because both patients and providers have identified side effects as a concern that limits the use of hydroxyurea, more information on the incidence and severity of these side effects is essential for both patients and providers to make informed choices. These data could come from a registry of patients with sickle cell disease. Nevertheless, the currently available data are reassuring with respect to the risks for both short- and long-term harms of hydroxyurea.

The natural history of sickle cell disease results in frequent, severe pain episodes and permanent damage to the eyes, brain, heart, lungs, kidneys, liver, bones, and spleen. Hydroxyurea reduces the frequency and severity of pain episodes. The risks of hydroxyurea are acceptable compared with the risks of untreated sickle cell disease.

4. What Are the Barriers to Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease, and What Are the Potential Solutions?

Barriers to hydroxyurea treatment for patients with sickle cell disease can arise at 4 levels: patient, parent/family/caregiver, provider, and system (Table 4). A systematic evidence review of the barriers to hydroxyurea treatment found only 3 studies that specifically addressed this issue and none that tested interventions to overcome barriers to hydroxyurea treatment. Given this, we agreed to include evidence obtained from expert testimony and studies analyzing barriers to the delivery of quality health care to patients with sickle cell disease. These studies examined potential barriers to hydroxyurea treatment, including the receipt of routine, scheduled care; adherence to medications; and receipt of therapies, including pain control and prescriptions.

Some social, economic, and cultural characteristics of patients with sickle cell disease are important in reviewing both barriers and solutions to access to hydroxyurea. Patients with sickle cell disease are often poorer than the national average and are more often covered by Medicaid. They also may be immigrants who cannot obtain insurance. The care of children and adults with sickle cell disease and the barriers to their care must be viewed in the context of their families, communities, and the U.S. health care system. The care of patients with sickle cell disease must be longitudinal across the life span, and the difficulties in transitioning care from pediatric to adult settings remain a challenge.

System-level barriers to hydroxyurea treatment for sickle cell disease include 1) financing (lack of insurance, type of insurance, underinsurance, scope of coverage, co-pays, reimbursement, payment structures); 2) geographic isolation; 3) lack of coordination between academic centers and community-based clinicians; 4) limited

Table 4. Barriers to Hydroxyurea Treatment in Persons with Sickle Cell Disease

Barrier	Level		
	<i>Patient</i>	<i>Parent/ Family/ Caregiver</i>	<i>Provider</i>
Fears or concerns about cancer, birth defects, infertility, and the uncertainty of long-term risks		✓	✓
Lack of knowledge about hydroxyurea as a therapeutic option	✓	✓	✓
Lack of perception that hydroxyurea is currently the only therapy that directly modifies the disease process	✓	✓	✓
Concern that the nonapproved status of hydroxyurea for children means that hydroxyurea is an experimental drug	✓	✓	
Difficulty in communication between patients and their caregivers regarding the use of hydroxyurea and other therapeutic options		✓	
Need for frequent monitoring of response to hydroxyurea	✓		
Lack of adherence to treatment regimen	✓		
Provider bias and negative attitudes toward patients with sickle cell disease and their treatment			✓
Lack of clarity of hydroxyurea treatment regimens and undertreatment in adults			✓
Limited number of physicians who have expertise in the use of hydroxyurea for sickle cell disease			✓
Failure to engage patients/caregivers in treatment decisionmaking in a developmentally appropriate manner			✓

access to comprehensive care centers and comprehensive care models; 5) problems in transitioning from pediatric to adult care; 6) limited access (for example, geographic distribution, recruitment, and retention of clinicians competent in the provision of comprehensive care to patients who have sickle cell disease); 7) inadequate government, industry, and philanthropic support for the care of patients with sickle cell disease; 8) slow development and promotion of hydroxyurea because of lack of commercial interest; 9) lack of visibility and empowerment of sickle cell disease advocacy groups; 10) cultural and language barriers to the provision of appropriate care; and 11) inadequate information technology systems to support the long-term care of patients with sickle cell disease.

We propose the following solutions to these barriers.

1. Promote models of care (such as comprehensive care, medical home, family-centered) across the lifespan that support quality of care and improved access to evidence-based treatment, including hydroxyurea.
2. Provide multidisciplinary care (for example, from health educators, social workers, case managers, physicians, and nurses) to improve the physical and mental health of patients with sickle cell disease and the financing structures to support such care.
3. Provide support for community health worker models (such as patient navigators, patient advocates, and peer advocates).
4. Provide support for coordination and comanagement of patients with the use of telemedicine.
5. Ensure better translation of findings to the patient and caregiver populations by using culturally or language-appropriate written and visual materials.

6. Implement health promotion models in educational interventions for adherence to therapies.
7. Engage and support community-based efforts to improve knowledge of the benefits and risks of hydroxyurea.
8. Improve federal, state, and local coordination of activities regarding sickle cell disease.
9. Provide support for cultural competency training across the interdisciplinary team regarding care for sickle cell disease.
10. Improve insurance coverage of sickle cell disease (for example, extend Medicare coverage to adults with sickle cell disease who are younger than 65 years).
11. Eliminate barriers that restrict access to public insurance.
12. Support ongoing training of health professionals to achieve and maintain competence in the care of patients with sickle cell disease, including hydroxyurea treatment.
13. Increase funding by government, industry, and philanthropic organizations for patients with sickle cell disease.
14. Encourage partnership and support of advocacy groups for sickle cell disease.
15. Develop enhanced information systems to better coordinate delivery of care in the health care system.

5. What Are the Future Research Needs?

We support the use of hydroxyurea for the treatment of sickle cell disease but recognize that additional research is required to provide information that will ensure the most appropriate application of this therapy.

A surveillance system is needed for patients with sickle cell disease who will be followed prospectively. This system should contain demographic, laboratory, clinical, treatment, and outcome information.

Additional efficacy studies of hydroxyurea are required. These studies should evaluate the efficacy of hydroxyurea, as measured in terms of clinical and laboratory outcomes, and define the mechanisms of action of hydroxyurea in a clinical setting; use pharmacokinetic and clinical measures to determine optimal dosing, dose titration, and clinical efficacy; identify the factors that predict clinical response and nonresponse to hydroxyurea; and confirm the validity of hemoglobin F as a surrogate measure of benefit.

Additional effectiveness studies are also required. These studies should determine the number of patients with sickle cell disease and those who will benefit from hydroxyurea. They should also determine when to begin the use of hydroxyurea to treat or prevent complications of sickle cell disease and how long to continue its use. These studies should complement those currently in progress.

Although we believe hydroxyurea to be safe and effective, additional studies of its safety, clinical effectiveness, and cost-effectiveness are required. Appropriate studies are needed to provide more information about developmental and reproductive adverse effects; carcinogenic risk; long-term clinical outcomes, including quality of life; the utility and cost-effectiveness of the comprehensive care and medical home models for the delivery of hydroxyurea treatment; the role of the case manager in delivery of hydroxyurea treatment; and interventions aimed at reducing parent/caregiver, provider, and health care system barriers to hydroxyurea treatment.

Conclusions

The burden of suffering is tremendous among many patients with sickle cell disease. These patients experience disease-related pain on many days of their lives and usually do not seek medical attention until their symptoms are overwhelming. They often attempt to treat themselves and thus do not always come to the attention of the health care system. Obtaining optimal care for patients with sickle cell disease is challenging. Many patients are not in a coordinated program aimed at prevention of long-term complications and acute pain crises. They rely heavily on emergency and short-term care facilities for pain control.

Obtaining specialty care can be a substantial challenge because the number of health professionals trained to treat the disease is limited and the number of professionals specializing in the treatment of this disease is decreasing. The likelihood that patients with sickle cell disease have a principal physician is low. Transitioning from pediatric care to adult care poses particular challenges. Many children rely on public insurance for their care. Gaps in coverage occur, leading to gaps in care.

No population-based registries exist that provide good estimates of the number of people with sickle cell disease. Surveys indicate that a large proportion of patients who have sickle cell disease are poor and from underserved communities. Most U.S. patients with sickle cell disease are ethnic minorities. For many, the limited resources and lack of culturally competent care by experienced clinicians set the stage for suboptimal care.

Hydroxyurea is an important major advance in the treatment of sickle cell disease. Strong evidence supports the efficacy of hydroxyurea in adults to decrease severe painful episodes, hospitalizations, number of blood transfusions, and the acute chest syndrome. Although the evidence for efficacy of hydroxyurea treatment for children is not as strong, the emerging data are encouraging. The current data on the risks of both short- and long-term harms of hydroxyurea therapy are reassuring, and the risks of hydroxyurea use in adults are acceptable compared with the risks of untreated sickle cell disease.

It is difficult to draw conclusions about the effectiveness of hydroxyurea in everyday practice because we lack precise estimates of the number of people with sickle cell disease in the United States and the number of people receiving hydroxyurea. Furthermore, although barriers to the use of hydroxyurea in persons with sickle cell disease seem to be extensive, little research exists on the barriers at the patient, parent/family/caregiver, provider, and system levels. More studies are required to address these issues.

The best way to achieve optimal care for patients with sickle cell disease, including preventive care, is for patients to be treated in clinics specializing in the care of this disease. All patients with sickle cell disease should have a principal health care provider, and that provider, if not a hematologist, should be in frequent consultation with one. The National Institutes of Health funds sickle cell research centers, and several states currently support sickle cell specialty clinics. Increased funding for basic, clinical, and social research on this disease is critically needed. There is an urgent need for centers specializing in the treatment of sickle cell disease to organize and network together to improve patient access to quality care.

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