Effect of Hydroxyurea on Mortality and Morbidity in Adult Sickle Cell Anemia

Risks and Benefits Up to 9 Years of Treatment

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Context Hydroxyurea increases levels of fetal hemoglobin (HbF) and decreases morbidity from vaso-occlusive complications in patients with sickle cell anemia (SCA). High HbF levels reduce morbidity and mortality.

Objective To determine whether hydroxyurea attenuates mortality in patients with SCA.

Design Long-term observational follow-up study of mortality in patients with SCA who originally participated in the randomized, double-blind, placebo-controlled Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), conducted in 1992-1995, to determine if hydroxyurea reduces vaso-occlusive events. In the MSH Patients' Follow-up, conducted in 1996-2001, patients could continue, stop, or start hydroxyurea. Data were collected during the trial and in the follow-up period.

Setting Inpatients and outpatients in 21 sickle cell referral centers in the United States and Canada.

Patients Two-hundred ninety-nine adult patients with frequent painful episodes enrolled in the follow-up. Follow-up data through May 2001 were complete for 233 patients.

Intervention In the MSH, patients were randomly assigned to receive hydroxyurea (n=152) or placebo (n=147).

Main Outcome Measures Mortality, HbF levels, painful episodes, acute chest syndrome, and blood cell counts. The randomized trial was not designed to detect specified differences in mortality.

Results Seventy-five of the original 299 patients died, 28% from pulmonary disease. Patients with reticulocyte counts less than 250000/mm^3 and hemoglobin levels lower than 9 g/dL had increased mortality (P=.002). Cumulative mortality at 9 years was 28% when HbF levels were lower than 0.5 g/dL after the trial was completed compared with 15% when HbF levels were 0.5 g/dL or higher (P=.03). Individuals who had acute chest syndrome during the trial had 32% mortality compared with 18% of individuals without acute chest syndrome (P=.02). Patients with 3 or more painful episodes per year during the trial had 27% mortality compared with 17% of patients with less frequent episodes (P=.06). Taking hydroxyurea was associated with a 40% reduction in mortality (P=.04) in this observational follow-up with self-selected treatment. There were 3 cases of cancer, 1 fatal.

Conclusions Adult patients taking hydroxyurea for frequent painful sickle cell episodes appear to have reduced mortality after 9 of years follow-up. Survival was related to HbF levels and frequency of vaso-occlusive events. Whether indications for hydroxyurea treatment should be expanded is unknown.

JAMA. 2003;289:1645-1651 www.jama.com

ACUTE CHEST SYNDROME AND painful episodes are the most common precedents of death in adults with sickle cell anemia (SCA).[1] A randomized, double-blinded, placebo-controlled trial, the

For editorial comment see p 1692.

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Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), showed that, over 2.5 years, hydroxyurea diminished the morbidity of SCA in adults with frequent painful episodes by reducing the incidence of painful episodes and acute chest syndrome by nearly half.[2,3] Hydroxyurea increased fetal hemoglobin (HbF) concentration while hemolysis was diminished and neutrophil counts fell.[3,4] In SCA, HbF levels are inversely related to mortality.[1] Decreased morbidity due to hydroxyurea could be associated with reduced mortality. Following the completion of the MSH, patients enrolled in an observational follow-up study, selecting with their physicians whether to continue, start, or stop treatment with hydroxyurea. Follow-up focused on detecting potential complications of treatment such as neoplasia and cerebrovascular disease, and on ascertaining the causes of death. Cumulative mortality was analyzed according to exposure to hydroxyurea and data from the MSH on acute chest syndrome, acute painful episodes, HbF levels, reticulocyte counts, and neutrophil counts, assessed both before randomization and at the conclusion of the trial.

METHODS

The MSH Patients' Follow-up is an observational study of inpatients and outpatients in 21 sickle cell referral centers in the United States and Canada who participated from 1992 to 1995 in the MSH to test whether hydroxyurea could reduce the number of vaso-occlusive events in adults with moderate to severe SCA.[5] Requirements for MSH entry included a history of more than 3 painful episodes in the 12 months prior to enrollment and pretreatment hemoglobin levels and reticulocyte counts that would not contraindicate treatment with hydroxyurea. Definitions of painful episodes and acute chest syndrome have been published.[2] In the follow-up study, after consultation with their physicians, patients were free to continue, start, or stop treatment with hydroxyurea. From 1996 through 2001, patients were seen yearly for the purposes of the follow-up study (most patients were seen more often for medical care) when data on hydroxyurea use and reportable events including stroke, renal failure, hepatic failure, cancer, and sepsis were collected. Fatal events and serious illnesses were documented from medical records. Central review of medical records, and autopsy results when these were available, were completed to establish causes of death. Patients provided internal review board–approved written informed consent for enrollment in the follow-up study.

Laboratory Methods

Methods for blood cell counts and measurement of HbF levels have been previously reported.[2,3,5,6] A single pretreatment value for each laboratory determination was computed by averaging all pretreatment values of that measurement for each patient. A single 2-year value was computed by averaging available data during the final 18 to 24 months of study treatment.[2] Levels of HbF were expressed as absolute levels of HbF in g/dL (HbF [g/dL] = HbF [%] × hemoglobin concentration [g/dL]) because no biological mechanism of HbF production exists that would regulate HbF as a percentage of total hemoglobin.

Statistical Methods

Patients were grouped for comparisons in a variety of ways, including the treatment group (hydroxyurea or placebo) to which they were originally assigned, and according to characteristics measured later during the MSH, such as HbF level and painful crisis rate at 2 years. For discrete variables, χ^2 tests were used to compare the frequency of patient characteristics.[7] Continuous measurements are presented as mean (SD) and compared using analysis of variance.[8]

Mortality in 3-month intervals was assessed using general estimating equation logistic models based on hydroxyurea usage (yes or no) during each interval.[9] Analyses were performed using SAS v7.6 (SAS Institute Inc, Cary, NC). Mortality is also reported as cumulative 9-year event rate from Kaplan-Meier survival curves.[10] Differences in mortality between patients randomly assigned to receive hydroxyurea and those assigned to receive placebo (ie, intention-to-treat analyses) and between post hoc groups (eg, HbF levels at 2 years) were tested with the log-rank statistic.[10] Patients were censored at the time they were last documented to be alive by clinical center staff. Hydroxyurea usage was measured as taken, not taken, or unknown for each month during the trial and follow-up period until the patient died or was censored, and was summarized as total months of taking hydroxyurea (never, <1 year, or ≥ 1 year).

The MSH was not designed to detect specified differences in mortality. Because of multiple testing that has occurred in secondary analyses of data from these patients, the strength of statistical evidence for differences between the original treatment groups was predetermined at a more stringent level than the primary end point trial design of $\alpha = .05$.[5] Observed differences carrying a nominal *P* value of less than .05 should not be taken as conclusive evidence of a difference. Because inference is not formal with the comparisons presented now—most of which are observational and not randomized—the nominal *P* values should be regarded as indicators of association, not tests of a priori hypotheses, and should be interpreted cautiously.

RESULTS

Follow-up data for up to 9 years through May 2001 were complete for 233 (77.9%) of the 299 patients enrolled in the long-term follow-up. Eight patients died during the randomized trial (2 receiving hydroxyurea, 6 receiving placebo). Hydroxyurea use in follow-up is unknown for 13 patients (4.3%) originally randomly assigned to receive hydroxyurea and for 15 patients (5.0%) assigned to receive placebo. Vital status was not entered into our database for 27 patients (9.0%).

Many patients were treated with hydroxyurea for at least 1 year since the start of the trial (TABLE 1). Ninety-six (32%) patients never received hydroxy-

Table 1. Cumulative Event Rates During MSH Follow-up (9 Years)

	Treatment Assigned in MSH			Time Receiving Hydroxyurea in MSH and Follow-up		
	Total	Hydroxyurea	Placebo	Never	<1 Year*	≥1 Year
Total, No.	299	152	147	47	33	219
Person-years†	2264	1174	1091	314	219	1731
Follow-up, mean (SD)	7.6 (2.0)	7.7 (1.7)	7.4 (2.1)	6.7 (2.9)	6.6 (2.7)	7.9 (1.4)
			Events			
Death, No. (%)	75 (25.1)	36 (23.7)	39 (26.5)	14 (29.8)	15 (45.5)	46 (21.0)
No. per 100 person-years	3.3	3.1	3.6	4.5	6.8	2.7
Stroke, No. (%)	14 (4.7)	8 (5.3)	6 (4.1)	1 (2.1)	2 (6.1)	11 (5.0)
No. per 100 person-years	0.6	0.7	0.5	0.3	0.9	0.6
Renal failure, No. (%)	28 (9.4)	14 (9.2)	14 (9.5)	9 (19.1)	3 (9.1)	16 (7.3)
No. per 100 person-years	1.2	1.2	1.3	2.9	1.4	0.9
Hepatic failure, No. (%)	13 (4.3)	3 (2.0)	10 (6.8)	5 (10.6)	2 (6.1)	6 (2.7)
No. per 100 person-years	0.6	0.3	0.9	1.6	0.9	0.3
Malignancy, No. (%)‡	2 (0.7)	1 (0.7)	1 (0.7)	0	0	2 (0.9)
No. per 100 person-years	0.1	0.1	0.1	0	0	0.1
Sepsis/infection, No. (%)	38 (12.7)	18 (11.8)	20 (13.6)	3 (6.4)	6 (18.2)	29 (13.2)
No. per 100 person-years	1.7	1.5	1.8	1.0	2.7	1.7

Abbreviation: MSH, Multicenter Study of Hydroxyurea in Sickle Cell Anemia.
*Includes 6 patients who took hydroxyurea for less than 3 months, counted as 0 months receiving hydroxyurea in Table 4.
†From start of the MSH to patient death or data cutoff.
‡A third malignancy in the MSH Patients' Follow-up occurred after data files were closed for this analysis and is not included in this table.

urea; 48 (16%) received hydroxyurea for less than 1 year and 156 (52%) received hydroxyurea for 1 or more years. Twenty-five percent of patients (n=75) who volunteered for the MSH died during the trial or follow-up, reflecting the severity of disease, which was a criterion for enrollment, and the high death rate in adult SCA.[1] Twenty-eight percent of these deaths were due to pulmonary complications (TABLE 2).

When analyzed according to the original assignment (regardless of the patient's choice of treatment after the randomized phase of the study was completed), mortality was similar in the original 2 treatment groups ($P=.35$; FIGURE, A). Cumulative mortality analyzed according to clinical events and laboratory measurements at the conclusion of randomized treatment is shown in the Figure (panels B-F). Of 276 patients who had HbF levels measured approximately 2 years into the MSH, patients with HbF levels lower than 0.5 g/dL had a 28% cumulative mortality through 9 years compared with 15% mortality in patients whose HbF levels were 0.5 g/dL or higher ($P=.03$ by log-rank test; Figure, B). The effect on mortality was similar when HbF levels lower than 0.75 g/dL and those 0.75 g/dL or higher were analyzed. Cumulative mortality through 9 years in the 199 patients with pretreatment HbF levels lower than 0.5 g/dL was 32% compared with 15% mortality in patients whose pretreatment HbF levels were 0.5 g/dL or higher ($P=.01$). Before treatment, 68% of patients randomly assigned to receive hydroxyurea and 65% of those assigned to receive placebo had HbF levels of lower than 0.5 g/dL. When the trial was completed, 38% of the patients assigned to receive hydroxyurea with initial HbF levels lower than 0.5 g/dL had HbF levels 0.5 g/dL or higher. In contrast, only 8% of patients receiving placebo with baseline HbF levels lower than 0.5 g/dL had final HbF levels 0.5 g/dL or higher.

Neutrophil counts before random assignment and treatment were not asso-

Table 2. Cause of Death According to Original Treatment Assignment in Patients in the MSH

	Original Treatment Assignment	
Causes of Death*	Hydroxyurea, No. (%) (n = 152)	Placebo, No. (%) (n = 147)
Total deaths	36 (23.7)	39 (26.5)
Pulmonary disease	7 (4.6)	14 (9.5)
Death during crisis	4 (2.6)	5 (3.4)
Sepsis/infection	2 (1.3)	3 (2.0)
Cardiovascular disease	1 (0.7)	2 (1.4)
Cerebrovascular	6 (3.9)	0
Hepatic disease	2 (1.3)	2 (1.4)
Gastrointestinal disease	2 (1.3)	1 (0.7)
Renal disease	1 (0.7)	3 (2.0)
Unintentional injury/homicide	3 (2.0)	4 (2.7)
Undetermined	4 (2.6)	1 (0.7)
Not yet classified	4 (2.6)	4 (2.7)

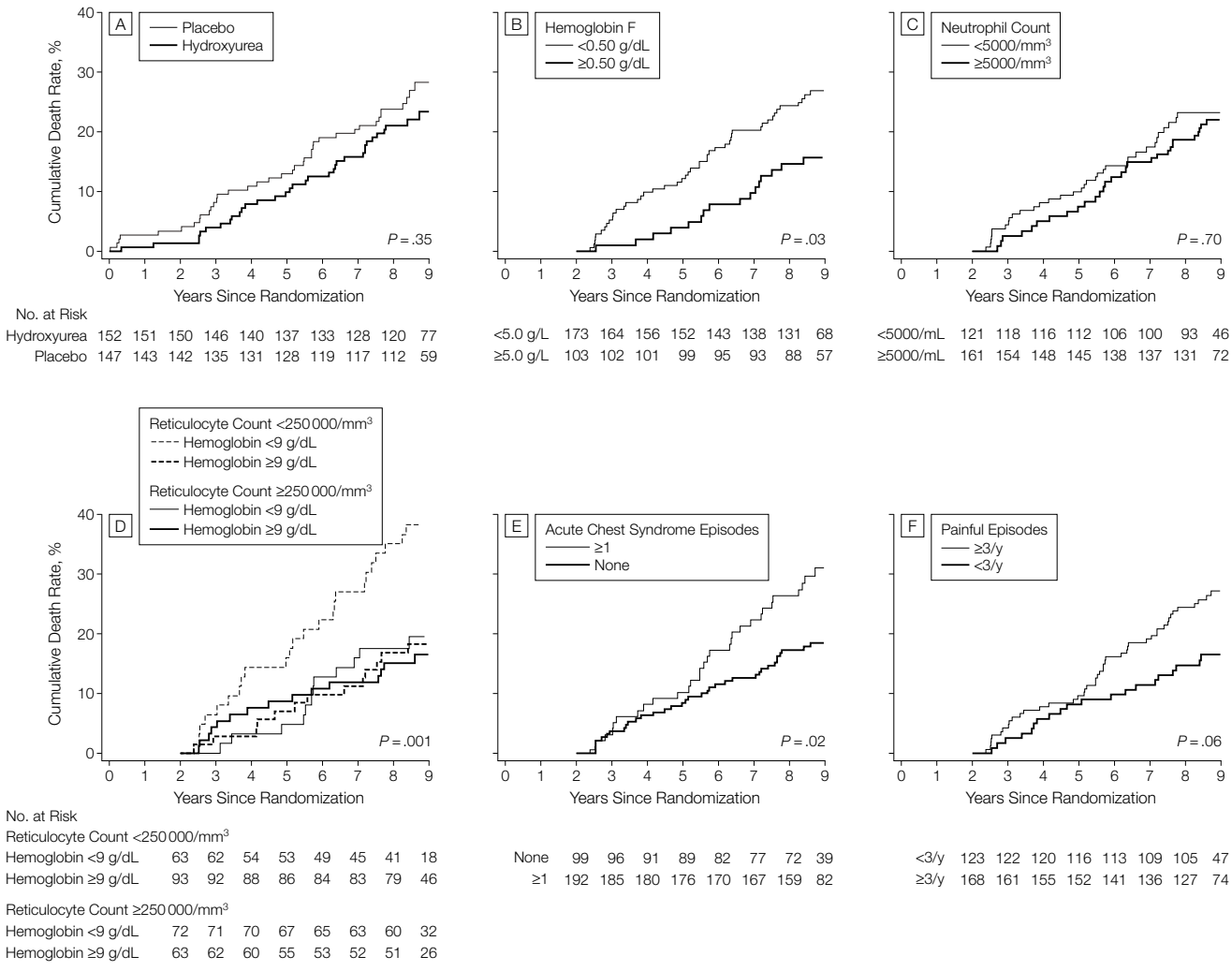
Abbreviation: MSH, Multicenter Study of Hydroxyurea in Sickle Cell Anemia.
*The single death from malignancy in the MSH Patients' Follow-up occurred after data files were closed for this analysis and is not included in this table.

ciated with differences in mortality. Neutrophil counts above or below 5000/mm^3 at the end of the clinical trial also did not predict mortality (P=.70 by log-rank test; Figure, C), although aggressive titration with hydroxyurea affects neutrophil counts. Similarly, neutrophil counts above or below 7000/mm^3 did not affect mortality. Reticulocyte counts before randomization did not predict mortality. Patients with absolute reticulocyte counts less than 250 000/mm^3 after 2 years of treatment had a cumulative mortality of 37% compared with 18% for individuals with 250 000/mm^3 or more (P=.001). A subgroup of 63 patients with reticulocyte counts less than 250 000/mm^3 and hemoglobin concentrations lower than 9 g/dL had increased cumulative mortality up to 9 years of observation (38% dead at 9 years, P=.002 by log-rank test; Figure, D) They also had lower HbF levels (0.42 g/dL vs 0.62 g/dL; P=.005), higher mean (SD) serum creatinine levels (1.49 [1.77] vs 0.96 [0.23] mg/dL [131.7 {156.5} vs 84.9 {20.3} µmol/L]; P=.02) and received lower doses of hydroxyurea compared with other patient groups (TABLE 3).

Patients with no episodes of acute chest syndrome during the trial had a mortality of 18% compared with 32% in patients who had 1 or more episodes (P=.02; Figure, E). Individuals with fewer than 3 annual painful episodes during the clinical trial had a mortality of 17% compared with 27% in patients with 3 or more episodes annually (P=.06; Figure 1F).

As shown in TABLE 4, total months of exposure to hydroxyurea were related to original treatment assignment, duration of survival in follow-up, and choice of treatment in follow-up. By analyzing mortality in 3-month intervals according to hydroxyurea usage in the interval, death rates were reduced 40%

Figure. Cumulative Mortality in Patients With Sickle Cell Anemia in the MSH and in Follow-up



Hemoglobin F indicates fetal hemoglobin; MSH, Multicenter Study of Hydroxyurea in Sickle Cell Anemia.

during 3-month intervals when patients were taking hydroxyurea [2.6 (5.8) deaths per 3-month period vs 1.5 (7.9) deaths per 3 months; $P = .04$)].

Three patients developed cancer. One individual who was randomly assigned to receive placebo, but who subsequently received hydroxyurea for 63 months, had carcinoma in situ of the uterine cervix at 7 years after randomization. A patient randomly assigned to hydroxyurea had 47 months of exposure to hydroxyurea in 3 periods: for less than 1 year during the MSH, after the clinical trial, and after mastectomies 3 years later. She had a history of fibrocystic disease of the breast and had had prophylactic bilateral mastectomies. Histological examination showed multifocal carcinoma in situ in the left breast. Both patients died of causes unrelated to carcinoma. A third patient randomly assigned to hydroxyurea who received long-term treatment was diagnosed with and died from endometrial carcinoma after the completion of 9 years of follow-up.

Fourteen patients had stroke; 8 in the original hydroxyurea group and 6 in the original placebo group (Table 1). Eleven of these patients had more than 1 year of exposure to hydroxyurea, 2 had less than 1 year of exposure, and one had unknown exposure prior to the event—results consistent with the number of years of hydroxyurea treatment accumulated across the MSH Patient's Follow-up.

COMMENT

The MSH was designed to test whether hydroxyurea reduced the incidence of vaso-occlusive episodes in SCA and not to detect differences in mortality between treatment groups. However, our follow-up studies suggest that adults with moderate to severe SCA who take hydroxyurea have reduced mortality compared with patients not taking this drug. Our estimated overall reduction in mortality up to 9 years of observation is 40%. These results must be interpreted cautiously. Comparisons of patients receiving and not receiving hydroxyurea were no longer randomized after the initial treatment period of the MSH, so patients who might receive more medical care and better follow-up while taking hydroxyurea might live longer for reasons other than treat-

Table 3. Characteristics of Patients With Low Reticulocyte Count (<250 000/mm^3) and Low Hemoglobin Level (<9 g/dL) After 2 Years of Treatment With Hydroxyurea or Placebo

	Reticulocytes <250 000/mm^3; Hemoglobin Level <9 g/dL		Others*		
Characteristic	No.	Mean (SD)	No.	Mean (SD)	*P* Value
White blood cell count, $\times 10^3/\mu L$	61	10.0 (3.6)	221	11.4 (3.9)	.40
Neutrophils, $\times 10^3/L$	61	5.5 (2.7)	221	5.8 (2.9)	.47
Hemoglobin F, g/dL	61	0.42 (0.43)	215	0.62 (0.63)	.005
Platelets, $\times 10^3/\mu L$	61	401.7 (146.9)	221	420.8 (143.6)	.37
Total bilirubin, mg/dL	61	3.04 (2.38)	221	3.61 (4.50)	.19
Creatinine, mg/dL	61	1.49 (1.77)	221	0.96 (0.23)	.02
Last hydroxyurea dose, mg/kg per day	63	18.3 (10.1)	228	22.4 (9.7)	.004
Crisis rate	63	7.5 (10.5)	228	6.0 (7.5)	.31

SI conversion factors: To convert bilirubin and creatinine levels to µmol/L, multiply bilirubin levels by 17.1 and creatinine levels by 88.4.
*Those with reticulocyte counts of less than 250 000/mm^3 and hemoglobin levels of 9 g/dL or greater, reticulocyte counts of 250 000/mm^3 or greater and hemoglobin levels of less than 9 g/dL, and reticulocyte counts of 250 000/mm^3 or greater and hemoglobin levels of 9 g/dL or greater.

Table 4. Total Months That All Patients Randomly Assigned in the MSH Actually Received Hydroxyurea

	No./Deaths*							
		Randomized to Receive Placebo, No./Deaths		Randomized to Receive Hydroxyurea		Hydroxyurea Use in Follow-up Period Unknown or Incompletely Documented		
Receiving Hydroxyurea, mo	Total	Never Received Hydroxyurea	Subsequently Received Hydroxyurea	Stopped Taking Hydroxyurea	Continued Hydroxyurea	Total	Placebo	Hydroxyurea
<3†	53/15	36/13	. . .	1/0	. . .	16/2	15/2	1/0
3-11	27/14	. . .	19/9	6/5	. . .	2/0	. . .	2/0
12-17	13/5	. . .	9/4	3/0	. . .	1/1	. . .	1/1
18-23	10/4	. . .	4/1	5/3	. . .	1/0	. . .	1/0
24-36	48/14	. . .	15/4	17/4	8/4	8/2	. . .	8/2
36-45	31/8	. . .	13/3	1/0	17/5	. . .	. . .	. . .
48-59	23/6	. . .	12/2	. . .	11/4	. . .	. . .	. . .
60-71	32/3	. . .	22/1	. . .	10/2	. . .	. . .	. . .
72-83	22/5	. . .	2/0	. . .	20/5	. . .	. . .	. . .
84-95	17/0	. . .	. . .	. . .	17/0	. . .	. . .	. . .
96-107	23/1	. . .	. . .	. . .	23/1	. . .	. . .	. . .
Total	**299/75**	**36/13**	**96/24**	**33/12**	**106/21**	**28/5**	**15/2**	**13/3**

*Ellipses indicate not applicable.
†Counted as 0.

ment. Moreover, assessment of the effect of hydroxyurea on mortality in an observational study is complex. The ability to take hydroxyurea (a predictor) is dependent on being alive (an outcome). Also, patients in the MSH were not typical of all adults with SCA; their average age was 32 years and they were selected for the trial because of frequent painful episodes, a predictor of mortality.[1,5] However, it is compelling that patients who had marked clinical benefit, reduced crises, reduced chest syndrome, and a good bone marrow reserve after 2 years of receiving hydroxyurea as randomized were the ones with reduced mortality in follow-up (Figure). This, coupled with the more direct, albeit observational, comparison of 3 months receiving hydroxyurea vs 3 months not receiving the drug is consistent with a long-term salutary effect of hydroxyurea on mortality.

How hydroxyurea affects morbidity and mortality in young children or individuals with less severe disease is unknown. Clinical trials of hydroxyurea have not been conducted in patients with HbSC disease, another clinically important sickle hemoglobinopathy.[11]

There were no appreciable differences for mortality or the clinical events reported here in follow-up between the 2 initial treatment groups. The clearest test of whether hydroxyurea has an impact on mortality in SCA would be a controlled study in children that could provide definitive data on long-term mortality effects. However, the death rate in children is lower than in older adults. Since hydroxyurea is likely to have similar short-term beneficial effects in children and adults, prolonged follow-up of a group of children receiving placebo may not be acceptable to families. In 93 patients with SCA, 87 of whom were younger than 20 years at the start of treatment, no severe adverse effects of treatment were found after a median of 3.5 years of observation.[12]

Hydroxyurea reduces some vaso-occlusive complications of SCA.[2] While its mechanism of action is incompletely understood, hydroxyurea is associated with increased levels of HbF in SCA; increased levels of HbF are known to improve survival.[1] In the MSH and other studies, hydroxyurea reduced the incidence of acute chest syndrome and acute painful episodes, events associated with increased mortality and influenced by HbF concentrations.[13-16] Levels of HbF 0.5 g/dL or higher, absence of acute chest syndrome, and fewer than 3 painful episodes annually during the trial were each associated with nearly a 50% reduction in mortality. Almost half of the classified deaths in our study were due to pulmonary disease or sudden death during a painful episode. Our observation of reduced mortality associated with hydroxyurea is consistent with hydroxyurea reducing the incidence of these morbid events by nearly half in the MSH.[2] These observations also confirm the link of HbF to mortality in sickle cell disease[1] and suggest that the ability of hydroxyurea to increase levels of HbF may be associated with reduced mortality.

Besides HbF, proposed mediators of the clinical effectiveness of hydroxyurea include reductions in adherent reticulocytes that may help initiate vaso-occlusion and in leukocytes that might release proinflammatory cytokines.[3,17] Neutrophil counts have been associated with mortality in other diseases besides sickle cell disease. Leukocytosis is a predictor of the extent of and sudden death from coronary artery disease.[18,19] Some beneficial effects of hydroxyurea in SCA have been associated with reduction in neutrophil counts during treatment.[1,3] We found no relationship between decrements in neutrophil counts—also a predictor of HbF concentration in patients treated with hydroxyurea[6]—and mortality, but the Cooperative Study of Sickle Cell Disease (CSSCD) found that lower leukocyte counts were associated with longevity.[1] In the MSH, hydroxyurea was titrated to maximum tolerated doses that most often were the largest doses that could be taken without neutropenia. Consequently, most patients taking hydroxyurea developed some level of potentially dangerous neutropenia. Since hydroxyurea was associated with a strong beneficial effect on painful crisis frequency in the MSH, this design forced an association between neutropenia and painful crisis frequency—low white blood cell counts being associated with fewer crises. Since neutrophils are acute-phase reactants, the association in the MSH is in the same direction as the association of neutrophil counts with mortality in the CSSCD, but for a different reason. In the follow-up study, doses of hydroxyurea used by the patients' physicians were less than the maximum tolerated doses in the MSH. During the follow-up, hydroxyurea effects, like increases in concentrations of HbF and total hemoglobin and decreases in bilirubin levels, were observed without notable effects on leukocyte counts (F.B., unpublished data). Although induction of neutropenia may play some role in the beneficial effects of hydroxyurea for SCA, the follow-up study data suggest that neutropenia is not a main mechanism of action.

Patients with reticulocyte counts less than 250 000/mm^3 and hemoglobin concentrations lower than 9 g/dL had increased mortality. These individuals also had lower HbF levels, higher serum creatinine levels, and received lower doses of hydroxyurea.[20] This combination of findings suggests that these patients had more severe disease and perhaps reduced marrow reserve and that, as a result, they were unable to tolerate sufficient hydroxyurea treatment to increase HbF levels.[6] Anemia and reticulocytopenia may also be indications of early renal failure that is associated with a poor prognosis.[20]

During the 9-year observation period we found little risk associated with the careful use of hydroxyurea in SCA. Yet, hydroxyurea must be taken indefinitely to be effective and is potentially mutagenic and carcinogenic. Other investigators have reported that 5% to 10% of patients with polycythemia vera and essential thrombocythemia, both preneoplastic myeloproliferative diseases, who received hydroxyurea developed acute leukemia.[21-28] Whether or not this risk can be extrapolated to patients with SCA is uncertain. Three reports of patients with SCA treated with hydroxy-

urea who developed acute leukemia have been published, but the total number of patients treated is unknown.[29-31] Our data suggest that the risk of leukemia in patients with SCA treated with hydroxyurea is much less than that observed in myeloproliferative disorders and that the risk of death from the complications of sickle cell disease is at least 10 times greater than the incidence of leukemia in these patients.

Intracerebral hemorrhage, the main cause of stroke in adult SCA, occurs at a rate of about 1 per 400 patient-years.[32,33] Given our number of patients under observation, we should have been able to detect a doubling in the incidence of intracerebral hemorrhage, but no association of stroke with hydroxyurea was found. Cerebrovascular mortality occurred more frequently among patients originally assigned to hydroxyurea than placebo, but was not related to use of hydroxyurea in follow-up.

Hydroxyurea increased HbF concentrations and diminished vaso-occlusive complications in adults with moderate to severe SCA and these effects were associated with decreased mortality. After up to 9 years of follow-up, unexpected serious adverse effects of this treatment were not observed. Whether hydroxyurea should be given to patients with SCA and fewer vaso-occlusive events or to patients with HbSC disease remains to be determined. We conclude that underlying disease severity remains critical to determining the prognosis of adult SCA, but hydroxyurea may mitigate disease severity.

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Funding/Support: This study was supported by National Heart, Lung, and Blood Institute contract NO1-HB-67129.
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209 were from academic books and official reports. The most cited journal was *JAMA* with 135 citations, followed by the *American Journal of Preventive Medicine* (102), *BMJ* (77), and *The Lancet* (70). Fifty-six journals had articles cited more than 5 times, comprising a total of 1185 citations. Of these 56 journals, 6 (11%) had an impact factor of more than 10.0; 10 (18%) had an impact factor of 5.0 to 10.0; 11 (20%) had an impact factor of 3.0 to 5.0; and 28 (51%) had impact factors of less than 3.0. Of this latter group, 11 (20%) had impact factors of less than 2.0. Only 7 journals (13%) appeared in the top 100 journals ranked by impact factors (2001). The median impact factor of these 56 journals was 2.76. There was a significant correlation between impact factors and times cited in the USPSTF guidelines (Kendall $r=0.26$, $P=.005$).

Comment. We found that the number of citations by the USPSTF guidelines roughly parallels the impact factors for the respective journals. Journals with low impact factors, however, were also cited frequently as providing important evidence. This finding may reflect the fact that journals that focus on preventive services tend to have lower impact factors than do journals in other scientific disciplines.

Some of the possible domains of impact of journal articles that cannot be measured by impact factors are changes in readers' knowledge, practice, clinical outcomes, funding priorities for research, and prompting of further learning. Overreliance on impact factors may undervalue the unique contributions of individual areas of research. In the field of clinical or preventive medicine, in particular, citation analyses on evidence-based practice guidelines may be a more accurate assessment of the contributions of individual journals and researchers. Although we only assessed the area of preventive health services, we suspect that this general conclusion may extend to other areas of scientific inquiry.

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Acknowledgment: We thank Ms Akiko Yoshida for assistance in editing the manuscript.

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CORRECTIONS

Incorrect Author Name: In the Special Communication entitled "The Health of Latino Children: Urgent Priorities, Unanswered Questions, and a Research Agenda" published in the July 3, 2002, issue of THE JOURNAL (2002;288:82-90), author Francisco Ramos Gomez should appear Francisco J. Ramos-Gomez.

Incorrect Sentence: In the Original Contribution entitled "Effect of Hydroxyurea on Mortality and Morbidity in Adult Sickle Cell Anemia: Risks and Benefits Up to 9 Years of Treatment" published in the April 2, 2003, issue of THE JOURNAL (2003;289:1645-1651), there was an incorrect sentence on pages 1646 and 1647. The sentence that read "Ninety-six (32%) patients never received hydroxyurea; 48 (16%) received hydroxyurea for less than year and 156 (52%) received hydroxyurea for 1 or more years" should have read "Thirty-two percent of patients randomly assigned to placebo never received hydroxyurea; 16% received hydroxyurea for less than 1 year and 52% received hydroxyurea for one or more years."