ORIGINAL ARTICLE

Hydroxyurea Dose Escalation for Sickle Cell Anemia in Sub-Saharan Africa

Chandy C. John, M.D., Robert O. Opoka, M.Med., Teresa S. Latham, M.A., Heather A. Hume, M.D., Catherine Nabaggala, M.B., B.S., Phillip Kasirye, M.Med., Christopher M. Ndugwa, M.Med., Adam Lane, Ph.D., and Russell E. Ware, M.D., Ph.D.

ABSTRACT

BACKGROUND

Hydroxyurea has proven safety, feasibility, and efficacy in children with sickle cell anemia in sub-Saharan Africa, with studies showing a reduced incidence of vaso-occlusive events and reduced mortality. Dosing standards remain undetermined, however, and whether escalation to the maximum tolerated dose confers clinical benefits that outweigh treatment-related toxic effects is unknown.

METHODS

In a randomized, double-blind trial, we compared hydroxyurea at a fixed dose (approximately 20 mg per kilogram of body weight per day) with dose escalation (approximately 30 mg per kilogram per day). The primary outcome was a hemoglobin level of 9.0 g or more per deciliter or a fetal hemoglobin level of 20% or more after 24 months. Secondary outcomes included the incidences of malaria, vaso-occlusive crises, and serious adverse events.

RESULTS

Children received hydroxyurea at a fixed dose (94 children; mean [±SD] age, 4.6±1.0 years) or with dose escalation (93 children; mean age, 4.8±0.9 years); the mean doses were 19.2±1.8 mg per kilogram per day and 29.5±3.6 mg per kilogram per day, respectively. The data and safety monitoring board halted the trial when the numbers of clinical events were significantly lower among children receiving escalated dosing than among those receiving a fixed dose. At trial closure, 86% of the children in the dose-escalation group had reached the primary-outcome thresholds, as compared with 37% of the children in the fixed-dose group ($P<0.001$). Children in the dose-escalation group had fewer sickle cell–related adverse events (incidence rate ratio, 0.43; 95% confidence interval [CI], 0.34 to 0.54), vaso-occlusive pain crises (incidence rate ratio, 0.43; 95% CI, 0.34 to 0.56), cases of acute chest syndrome or pneumonia (incidence rate ratio, 0.27; 95% CI, 0.11 to 0.56), transfusions (incidence rate ratio, 0.30; 95% CI, 0.20 to 0.43), and hospitalizations (incidence rate ratio, 0.21; 95% CI, 0.13 to 0.34). Laboratory-confirmed dose-limiting toxic effects were similar in the two groups, and there were no cases of severe neutropenia or thrombocytopenia.

CONCLUSIONS

Among children with sickle cell anemia in sub-Saharan Africa, hydroxyurea with dose escalation had superior clinical efficacy to that of fixed-dose hydroxyurea, with equivalent safety. (Funded by the Doris Duke Charitable Foundation and the Cincinnati Children's Research Foundation; NOHARM MTD ClinicalTrials.gov number, NCT03128515.)

From the Ryan White Center for Pediatric Infectious Diseases and Global Health, Department of Pediatrics, Indiana University, Indianapolis (C.C.J.); the Department of Pediatrics and Child Health, Makerere University (R.O.O., H.A.H., C.N., P.K., C.M.N.), Global Health Uganda (R.O.O., C.N.), and Mulago Hospital (P.K.) — all in Kampala, Uganda; the Division of Hematology, Department of Pediatrics (T.S.L., A.L., R.E.W.), and the Global Health Center (R.E.W.), Cincinnati Children's Hospital Medical Center, and the University of Cincinnati College of Medicine (A.L., R.E.W.) — all in Cincinnati; and the Department of Pediatrics, Centre Hospitalier Universitaire Sainte-Justine, University of Montreal, Montreal (H.A.H.). Address reprint requests to Dr. Ware at the Division of Hematology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., Cincinnati, OH 45229, or at russell.ware@cchmc.org.

Drs. John and Opoka contributed equally to this article.

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Sickle cell anemia is characterized by the polymerization of sickle hemoglobin to form abnormally shaped erythrocytes, which leads to severe hemolytic anemia, acute vaso-occlusive complications, chronic organ damage, and early death.[1] Sickle cell anemia is increasingly recognized as having a serious global health burden, with current estimates exceeding 300,000 affected births worldwide each year.[2] The main geographic distribution includes sub-Saharan Africa and India, where birth rates are high and the numbers of newborns with sickle cell anemia are projected to increase by 30% by 2050.[3] However, because of the lack of newborn screening programs and appropriate clinical care, the vast majority of children with sickle cell anemia do not receive a proper diagnosis and do not receive simple life-saving immunizations or antibiotic prophylaxis; an estimated 50 to 90% of these children will die before 5 years of age.[4]

Hydroxyurea is an oral therapeutic agent with proven laboratory and clinical efficacy for sickle cell anemia.[5,6] Hydroxyurea induces fetal hemoglobin, which inhibits erythrocyte sickling, but the drug also has beneficial effects on leukocytes, reticulocytes, and the endothelium. Especially when the dose is escalated to the maximum tolerated dose, hydroxyurea improves laboratory variables and reduces clinical complications.[7,8] Two trials have shown the feasibility, safety, and benefits of hydroxyurea for children with sickle cell anemia in sub-Saharan Africa. The double-blind, placebo-controlled NOHARM (Novel Use of Hydroxyurea in an African Region with Malaria) trial showed the safety of standard fixed-dose hydroxyurea (20 mg per kilogram of body weight per day) in young children with sickle cell anemia, with no increased risk of malaria and all expected treatment benefits.[9,10] The REACH (Realizing Effectiveness across Continents with Hydroxyurea) trial used open-label hydroxyurea with escalation to the maximum tolerated dose in four African countries[11]; this trial confirmed the safety and clinical benefits of hydroxyurea in children with sickle cell anemia but also showed significantly decreased incidences of malaria, transfusions, and death in this high-risk population.[12]

Although hydroxyurea has been shown to have efficacy and a good safety profile in children living in sub-Saharan Africa, dosing and monitoring regimens have not yet been determined. Several clinical trials, particularly those conducted in Europe, used hydroxyurea at a low but clinically effective dose of 15 to 20 mg per kilogram per day, which offers laboratory and clinical benefits with few hematologic toxic effects.[13-17] In contrast, most trials in the United States have used hydroxyurea with dose escalation to 25 to 30 mg per kilogram per day, a dose that confers substantial laboratory and clinical benefits, along with possibly increased laboratory-confirmed toxic effects such as neutropenia and thrombocytopenia related to serial dose escalation.[18-24]

Data from controlled trials that directly compare standard fixed-dose hydroxyurea with hydroxyurea with dose escalation to the maximum tolerated dose are lacking. The hydroxyurea dosing regimen is critical to determine, however, before implementing wider use across sub-Saharan Africa. Even if hydroxyurea dose escalation provided additional clinical benefits, the potential for increased or severe toxic effects would require frequent laboratory monitoring with dose adjustments. This is relevant for low-resource settings, where the costs of medication and routine laboratory monitoring can be prohibitive and access to medical care is limited. We conducted the NOHARM MTD trial (Optimizing Hydroxyurea Therapy in Children with Sickle Cell Anemia in Malaria Endemic Areas: The NOHARM Maximum Tolerated Dose [MTD] Study) to compare directly the risks and benefits of variable hydroxyurea dosing, with the long-term goal of determining hydroxyurea dosing standards for children with sickle cell anemia in sub-Saharan Africa.

A Quick Take is available at NEJM.org

METHODS

TRIAL DESIGN

Children with sickle cell anemia who were previously enrolled in the NOHARM trial at the Mulago Hospital Sickle Cell Clinic in Kampala, Uganda, were eligible for the NOHARM MTD trial. In the NOHARM trial, all the children received blinded treatment with hydroxyurea or placebo for 1 year, followed by open-label hydroxyurea for 1 year at a dose of 20 mg per kilogram per day, as described previously.[25] At the end of the NOHARM trial, children were prescribed commercially supplied hydroxyurea (in 500-mg capsules) at a dose of 20 mg per kilogram per

day for several months before enrollment in the NOHARM MTD trial, at which time the children were randomly assigned in a 1:1 ratio either to receive hydroxyurea (Siklos, Addmedica, in 100-mg and 1000-mg tablets) at a fixed standard dose (mean [±SD], 20±5 mg per kilogram per day) (the fixed-dose group) or to escalate hydroxyurea to the maximum tolerated dose (the dose-escalation group). For the latter group, the initial dose was 25±5 mg per kilogram per day, with further escalation allowed every 2 months if the peripheral-blood counts showed no evidence of laboratory toxic effects, to a maximum of 35 mg per kilogram per day.

Only the pharmacist knew the actual treatment-group assignments; blinding was maintained because children in both treatment groups had periodic dose adjustments for weight gain throughout the trial. Dose-limiting toxic effects were cytopenias defined per protocol as a hemoglobin level of less than 4.0 g per deciliter (or <6.0 g per deciliter unless the absolute reticulocyte count was $>100\times10^9$ per liter), an absolute neutrophil count of less than 1.0×10^9 per liter, an absolute reticulocyte count of less than 80×10^9 per liter (unless the hemoglobin concentration was >7.0 g per deciliter), or a platelet count of less than 80×10^9 per liter. (See the protocol, available with the full text of this article at NEJM.org.) No dose escalation occurred after month 8, and laboratory monitoring for hematologic toxic effects was then performed every 2 to 3 months throughout the 24-month trial. Each scheduled visit had a 14-day window.

In both treatment groups, hydroxyurea dosing was managed with the use of an interactive online dosing application that included a safety check of peripheral-blood counts for toxic effects and a recommended daily dose at each visit, which ensured dosing accuracy and helped maintain the trial blinding. Every child who was evaluated for a history of fever or measured fever (axillary temperature, ≥37.5°C) had blood microscopy for malaria, and children with a positive blood smear for plasmodium species were treated with artemether–lumefantrine. Standard preventive care was provided according to local and national guidelines. This care included folic acid, penicillin prophylaxis for children younger than 5 years of age, pneumococcal vaccination, malaria prophylaxis, and mebendazole.

OUTCOMES

The protocol-specified primary outcome was the proportion of children with a hemoglobin level of 9.0 g or more per deciliter or a fetal hemoglobin level of 20% or more after 24 months of randomized treatment. Secondary outcomes included the incidences of malaria, vaso-occlusive crises, and serious adverse events.

TRIAL OVERSIGHT

This prospective trial was designed by the authors. It was approved in Uganda by the Makerere School of Medicine Research Ethics Committee, the Mulago Hospital Research Ethics Committee, the Uganda National Drug Authority, and the Uganda National Council of Science and Technology, and in the United States by the institutional review boards at Indiana University and Cincinnati Children's Hospital Medical Center. Caregivers of the children provided written informed consent for participation in the trial with the use of forms in English or the local language. An independent data and safety monitoring board was made up of U.S. and Ugandan experts in hematology, malaria, clinical trials, biostatistics, and patient advocacy. The data and safety monitoring board reviewed all trial results on a 6-month schedule throughout the trial. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

The Doris Duke Charitable Foundation and the Cincinnati Children's Research Foundation provided funds for the trial, and Addmedica donated hydroxyurea (Siklos) for use in the trial. None of these entities had access to the trial data, statistical analysis, or the manuscript before submission.

STATISTICAL ANALYSIS

The local trial team collected data and completed data entry into a secure OnCore database, which was monitored and analyzed by the data coordinating center, as described previously.[9] Adverse clinical events of grade 2 or higher were recorded locally according to International Conference on Harmonisation E6 guidelines for Good Clinical Practice and were categorized and scored according to the Common Terminology Criteria for Adverse Events, version 4. For all key clinical adverse events and laboratory dose-limit-

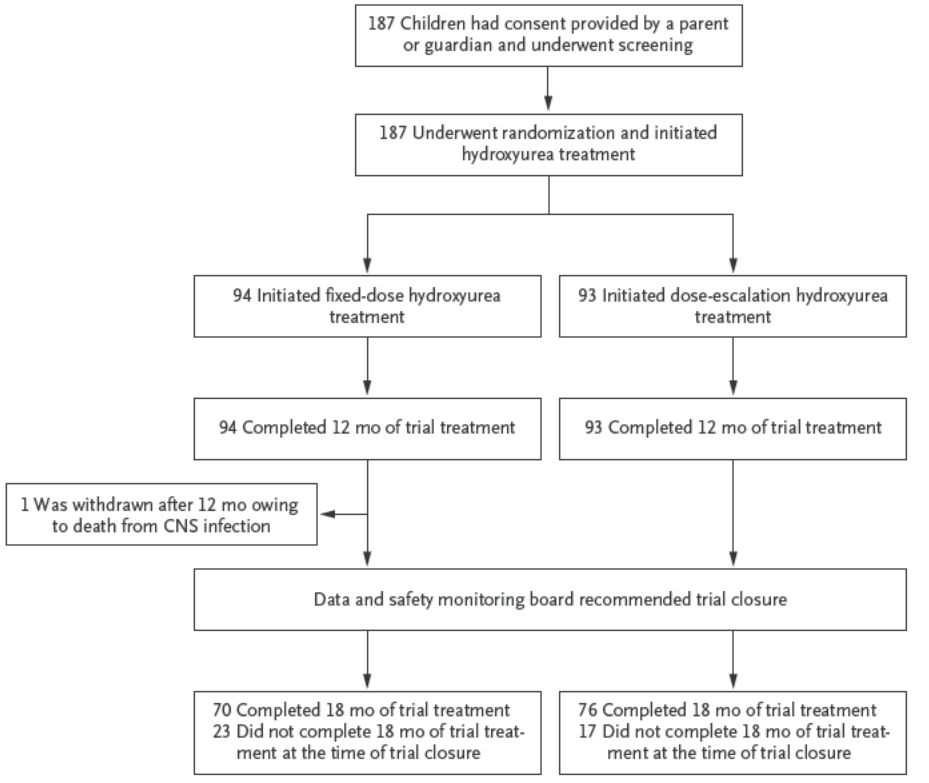

Figure 1. Randomization and Follow-up.

A total of 187 children were randomly assigned either to fixed-dose hydroxyurea (94 children) or dose escalation to the maximum tolerated dose (93 children). At the time of the recommendation by the data and safety monitoring board to halt randomized treatment, 70 and 76 children in the respective groups had completed the month 18 visit. CNS denotes central nervous system.

ing toxic effects, incidence rate ratios with 95% confidence intervals were calculated for the full randomized cohort. For the primary outcome, comparison of proportions was analyzed by two-sided chi-square analysis for the 146 children with fetal hemoglobin values at month 18. Continuous variables were reported as means and standard deviations and were compared between the groups with the use of the Wilcoxon rank-sum test. Differences in clinical events between the groups are reported as incidence rate ratios. Those rate ratios and corresponding confidence intervals were generated with the use of Poisson regression, with no adjustments for interim analysis. All statistical results were computed with the use of R software, version 3.5.1 (R Foundation for Statistical Computing).

RESULTS

ENROLLMENT AND RETENTION

A total of 187 children were enrolled in the trial and underwent randomization (Fig. 1). At the time of enrollment and randomization, the two treatment groups were matched for a variety of clinical and demographic characteristics (Table 1). Baseline laboratory characteristics were also similar and reflected previous fixed-dose hydroxyurea treatment as part of the original NOHARM trial. The retention of children was excellent throughout the trial, as was adherence to protocol-directed trial visits, with no missed clinic visits and 96% of interval visits completed within the target visit window.

Table 1. Characteristics of the Trial Population at Enrollment.*

Characteristic	Fixed-Dose Group (N=94)	Dose-Escalation Group (N=93)
Age — yr	4.6±1.0	4.8±0.9
Male sex — no. (%)	55 (59)	47 (51)
Z score for height for age	−0.80±0.96	−0.73±0.94
Hemoglobin level — g/dl	8.4±1.2	8.4±1.0
Mean corpuscular volume — fl	91±10	93±10
Fetal hemoglobin level — %	22.4±8.6	22.5±8.7
Absolute reticulocyte count — $\times 10^{-9}$/liter	232±89	224±87
White-cell count — $\times 10^{-9}$/liter	11.0±4.2	11.3±3.7
Absolute neutrophil count — $\times 10^{-9}$/liter	4.4±2.4	4.7±1.9
Platelet count — $\times 10^{-9}$/liter	353±156	383±146
Alanine aminotransferase level — IU/liter	17±6	17±7
Creatinine level — mg/dl	0.4±0.1	0.4±0.1

* Plus–minus values are means ±SD. All children were previously enrolled in the NOHARM (Novel Use of Hydroxyurea in an African Region with Malaria) trial and so have laboratory values reflecting the use of fixed-dose hydroxyurea. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

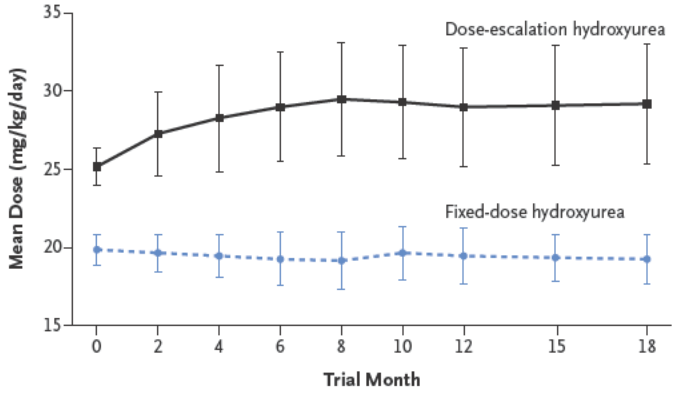

Figure 2. Hydroxyurea Dosing.
Children who were assigned to fixed-dose hydroxyurea received approximately 20 mg per kilogram of body weight per day, and those assigned to dose escalation received approximately 30 mg per kilogram per day. The I bars indicate standard deviations.

DOSE ESCALATION

Children were initially assigned to hydroxyurea at a dose of 20 mg per kilogram per day (94 children; mean [±SD] age, 4.6±1.0 years) or 25 mg per kilogram per day (93 children; mean age, 4.8±0.9 years). The dose for the latter group was then escalated over time by 5.0±2.5 mg per kilogram per day to the maximum tolerated dose with a projected mean final dose of approximately 30 mg per kilogram per day; the actual mean doses at month 8 were 19.2±1.8 mg per kilogram per day in the fixed-dose group and 29.5±3.6 mg per kilogram per day in the dose-escalation group. Figure 2 shows the hydroxyurea doses over time for the entire trial cohort and indicates stable differences between the two treatment groups.

TRIAL CLOSURE

After 146 children had completed 12 months of trial treatment, the data and safety monitoring board requested additional quarterly data analyses, with a focus on sickle cell–related events (including vaso-occlusive pain crises) as well as transfusions and hospitalizations. Six months later, the board noted significant differences between the treatment groups in clinical adverse events and medical intervention; dose escalation was superior, which led to the unanimous recommendation of the board to halt the randomized treatment groups and to offer all the children hydroxyurea treatment with dose escalation. With approval from local ethics committees, all the children and families were then offered the higher dose as an open-label observational follow-up study. At trial closure, 86% of the children assigned to hydroxyurea dose escalation met the primary-outcome threshold, as compared with 37% of the children assigned to the fixed

Table 2. Clinical and Laboratory Events, According to Treatment Group.*

Event	Fixed-Dose Group (N=94)		Dose-Escalation Group (N=93)		Incidence Rate Ratio in Dose-Escalation Group (95% CI)	P Value
	No. of Events	No. of Patients	No. of Events	No. of Patients		
Serious adverse events						
Sickle cell–related	6	4	5	2	0.84 (0.24–2.79)	0.77
Non–sickle cell–related	1	1	0	0	—	—
Clinical adverse events						
Sickle cell–related						
Any grade	245	70	105	47	0.43 (0.34–0.54)	<0.001
Grade ≥3	136	52	48	24	0.36 (0.25–0.49)	<0.001
Non–sickle cell–related						
Any grade	321	79	205	77	0.64 (0.54–0.77)	<0.001
Grade ≥3	93	45	54	35	0.59 (0.42–0.82)	0.002
Malaria infections	6	4	3	3	0.50 (0.11–1.91)	0.33
Clinical complications of sickle cell anemia						
Vaso-occlusive pain	200	65	86	46	0.43 (0.34–0.56)	<0.001
Acute chest syndrome or pneumonia	30	21	8	6	0.27 (0.11–0.56)	0.001
Acute splenic sequestration	14	8	8	1	0.58 (0.23–1.34)	0.21
Stroke or transient ischemic attack	0	0	1	1	—	—
Clinical interventions						
Transfusions	116	29	34	14	0.30 (0.20–0.43)	<0.001
Hospitalizations	90	34	19	10	0.21 (0.13–0.34)	<0.001
Laboratory dose-limiting toxic effects†						
Anemia	12	10	9	6	0.76 (0.31–1.79)	0.53
Reticulocytopenia	13	12	13	9	1.01 (0.46–2.20)	0.98
Neutropenia	4	4	8	6	2.02 (0.64–7.56)	0.25
Thrombocytopenia	14	9	13	8	0.94 (0.43–2.00)	0.86

* Clinical adverse events do not include serious adverse events or laboratory adverse events. Incidence rate ratios with 95% confidence intervals (CIs) were calculated according to follow-up time.

† Anemia was defined as a hemoglobin level of less than 4 g per deciliter, reticulocytopenia as an absolute reticulocyte count of less than 80×10^9 per liter, neutropenia as an absolute neutrophil count of less than 1.0×10^9 per liter, and thrombocytopenia as a platelet count of less than 80×10^9 per liter.

dose (P<0.001); this difference was mostly due to meeting the fetal hemoglobin threshold (84% vs. 34%).

CLINICAL EFFECTS

Table 2 shows that children assigned to the dose-escalation group had fewer clinical adverse events than those assigned to the fixed-dose group, including all sickle cell–related events (105 vs. 245; incidence rate ratio, 0.43; 95% confidence interval [CI], 0.34 to 0.54) and specific events: vaso-occlusive pain crisis (86 vs. 200; incidence rate ratio, 0.43; 95% CI, 0.34 to 0.56) and acute chest syndrome or pneumonia (8 vs. 30; incidence rate ratio, 0.27; 95% CI, 0.11 to 0.56). The numbers of key medical interventions were also fewer in the dose-escalation group than in the fixed-dose group, both for transfusions (34 vs. 116; incidence rate ratio, 0.30; 95% CI, 0.20 to 0.43) and hospitalizations (19 vs. 90; incidence rate ratio, 0.21; 95% CI, 0.13 to 0.34). Serious adverse events were uncommon and oc-

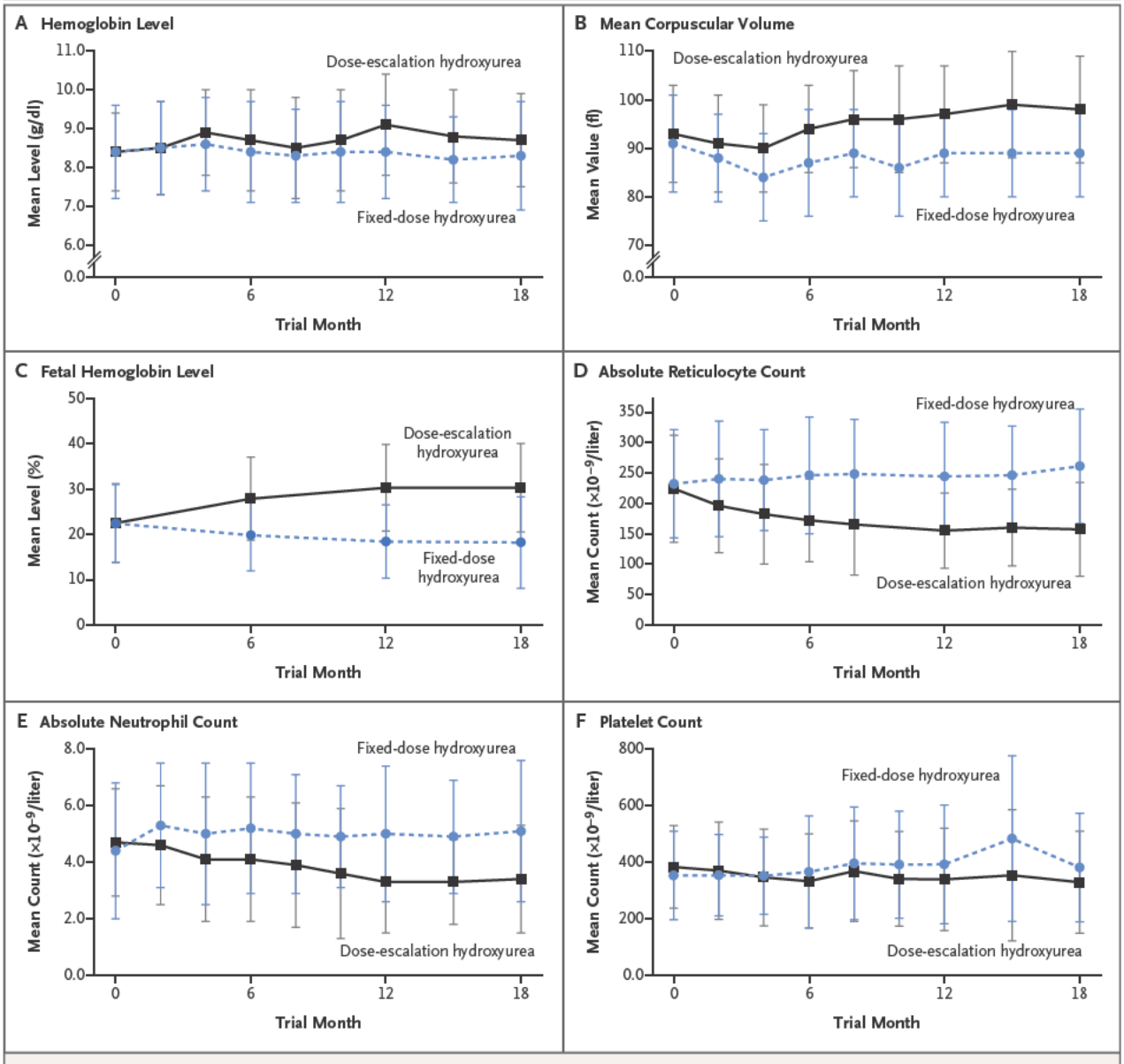

Figure 3. Changes in Laboratory Values.
The I bars indicate standard deviations.

curred in both treatment groups. Cases of malaria (all *Plasmodium falciparum*) were not common in either group (Table 2).

LABORATORY EFFECTS

Expected treatment effects of hydroxyurea included increases in the hemoglobin level, the fetal hemoglobin level, and the mean corpuscular volume as well as decreases in counts of leukocytes, neutrophils, reticulocytes, and platelets. Benefits conferred by higher doses of hydroxyurea were observable early in the trial, then continued to improve, and were maintained once a stable dose was reached. Figure 3 shows that laboratory treatment effects differed according to trial group, with significantly greater effects observed with dose escalation for most variables at month 12 and month 18. At trial closure, the dose-limiting toxic effects were similar in the two treatment groups (43 per group), with no

significant differences in individual cytopenias and no episodes of severe neutropenia (absolute neutrophil count, $<0.5\times10^9$ per liter) or severe thrombocytopenia (platelet count, $<50\times10^9$ per liter) (Table 2).

DISCUSSION

Our trial was designed to compare the relative risks and benefits of standard fixed-dose hydroxyurea as compared with hydroxyurea with dose escalation in children with sickle cell anemia. Previous studies have shown the laboratory and clinical efficacy of hydroxyurea when increased to the maximum tolerated dose,[5,6,12,20,24] but data are lacking from controlled trials that directly compare these two dosing regimens. Our prospective, double-blind randomization strategy used a composite primary outcome that included clinically meaningful values of both hemoglobin and fetal hemoglobin, and we also closely recorded important clinical outcomes such as sickle cell–related adverse events, medical interventions, and laboratory dose-limiting toxic effects. After approximately 18 months of trial treatment, the data and safety monitoring board recommended halting the trial because of safety and ethical concerns, specifically noting significantly fewer clinical complications among children assigned to dose escalation, with no increase in toxic effects. At trial closure, a significantly higher percentage of children in the dose-escalation group than in the fixed-dose group had met the primary-outcome threshold. The numbers of sickle cell–related adverse events (including vaso-occlusive pain crises and cases of acute chest syndrome or pneumonia), as well as transfusions and hospitalizations, were more than 50% lower among children in the dose-escalation group than among those in the fixed-dose group, with similar safety and toxicity profiles.

Hydroxyurea is a potent disease-modifying treatment for sickle cell anemia but has a documented dose effect and relatively narrow therapeutic window.[26] The argument regarding hydroxyurea dosing hinges, therefore, on the question of whether the potential benefits of dose escalation outweigh the predictable risks of hematologic toxic effects and the resources needed to manage variable dosing over time.[27] Even if hydroxyurea dose escalation were to confer additional clinical benefits, these might not justify greater toxic effects or the need to monitor blood counts frequently. Particularly in low-resource settings such as sub-Saharan Africa, hydroxyurea therapy and periodic laboratory testing are often neither affordable nor feasible for most patients with sickle cell anemia and their families,[28] so a simplified strategy for hydroxyurea dosing with minimal monitoring would be ideal.

Weight- or age-band medication dosing is straightforward and therefore attractive for low-resource settings. These dosing strategies are particularly suitable for medications with a large therapeutic window and are commonly used in Africa in treatments for tuberculosis,[29] human immunodeficiency virus infection,[30] and malaria.[31,32] Although individual doses are sometimes above or below the recommended target, differences in the treatment effects and toxic effects are minimal, which justifies the dosing scheme. Simplified drug-dosing regimens are also popular in the United States; for example, children with sickle cell anemia typically receive pneumococcal prophylaxis with oral penicillin at a dose of 125 mg twice daily until 3 years of age; the dose is then increased to 250 mg twice daily until 5 years of age, without adjustment for weight.[33]

The current trial included one treatment group receiving standard fixed-dose hydroxyurea, which is suitable for weight- or age-banded dosing regimens. However, with excellent follow-up and rigorous documentation of sickle cell–related complications and toxic effects of hydroxyurea, hydroxyurea with dose escalation (mean dose, approximately 30 mg per kilogram per day) was superior to fixed-dose hydroxyurea (mean dose, approximately 20 mg per kilogram per day) in several ways. First, children receiving the higher daily dose had better clinically meaningful laboratory measures, including hemoglobin and fetal hemoglobin levels, which composed the primary outcome. Second, they had fewer overall sickle cell–related clinical adverse events, including vaso-occlusive painful crises and cases of acute chest syndrome or pneumonia, with differences similar to those observed with hydroxyurea as compared with placebo.[5,6,9] Third, medical interventions such as transfusions and hospitalizations were also less frequent in the dose-escalation group than in the fixed-dose group. Fourth, despite the higher daily dose, dose-limiting toxic effects were similar in the two treatment groups, which indicates that dose escalation is

not more toxic and does not require frequent monitoring after a stable dose is reached. This absence of severe toxic effects can be explained partly by our dose-adjustment algorithm that uses a target of mild myelosuppression (absolute neutrophil count, 2.0×10^9 to 4.0×10^9 per liter), which is unlikely to cause severe cytopenia or clinical toxic effects. In this context, we propose that adjustment to the appropriate hydroxyurea dose is a more accurate term than the maximum tolerated dose.

With direct comparison of fixed-dose hydroxyurea with dose escalation, our data provide strong evidence that dose escalation is safe and provides considerably greater clinical benefits than standard dosing. Although the children had previous hydroxyurea exposure, these effects might be extrapolated to initiation of hydroxyurea treatment. Moreover, the absence of additional toxic effects supports the suggestion that only periodic monitoring, perhaps every 2 to 3 months, may be sufficient.[34] Our findings have even broader global implications for hydroxyurea treatment and suggest that all children with sickle cell anemia, whether living in low-resource sub-Saharan Africa or high-resource Europe, might benefit from dose escalation, rather than using low-dose or fixed-dose treatment. Our findings are also relevant for the interpretation of results from current clinical trials in Africa that offer hydroxyurea at a low dose (10 mg per kilogram per day) or standard dose (20 mg per kilogram per day) to children with sickle cell anemia (ClinicalTrials.gov numbers, NCT02560935 and NCT02675790).

The public health implications of these findings for sub-Saharan Africa and other low-resource settings are important to consider. Hydroxyurea is on the World Health Organization Model List of Essential Medicines for children with sickle cell anemia[35] yet is not routinely available to most patients living in sub-Saharan Africa. Hydroxyurea with dose escalation will require an increased drug supply and some laboratory monitoring, yet those costs are likely to be offset by fewer clinical adverse events, transfusions, and hospitalizations. Formal cost-effectiveness analysis of hydroxyurea therapy with the use of dose escalation and limited monitoring is warranted for low-resource settings, as well as implementation studies that reflect thoughtful research collaborations and incorporate fair ethical principles.[36] The potential risks of infertility or teratogenicity with extended hydroxyurea exposure should also be investigated in long-term cohort studies. However, existing data on long-term follow-up of patients receiving hydroxyurea suggest that these risks are more theoretical than actual.

Initial dosing at 25 mg per kilogram per day with stepwise escalation to 30 mg per kilogram per day was used in our trial, but simple weight-based dosing at 30 mg per kilogram per day would not be appropriate, since some children would have hematologic dose-limiting toxic effects. With recognition of the known differences in hydroxyurea pharmacokinetics and pharmacodynamics,[22,37] personalized dosing based on pharmacokinetics is the ideal way to determine an individual patient's appropriate dose.[38,39] Until this approach is feasible in low-resource settings, our findings strongly support the development of accessible stepwise hydroxyurea dose-escalation algorithms, which factor in individual laboratory values, weight, and the most recent dose. With such tools, health care providers in low-resource settings could safely and effectively administer this important disease-modifying therapy at the appropriate dose and for the greatest clinical benefit to patients. The development and implementation of these tools and evaluation of their feasibility in rural clinic settings are important next steps toward the goal of universal hydroxyurea treatment for all African children with sickle cell anemia.

In this trial, hydroxyurea dose escalation led to better control of the complications of sickle cell anemia than lower-dose therapy, with a similar safety profile.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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