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

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ABSTRACT

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.)
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. Sickle cell anemia is increasingly recognized as having a serious global health burden, with current estimates exceeding 300,000 affected births worldwide each year. 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. 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.

Hydroxyurea is an oral therapeutic agent with proven laboratory and clinical efficacy for sickle cell anemia. 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. 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 per day) in young children with sickle cell anemia, with no increased risk of malaria and all expected treatment benefits. 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, as described previously. 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, as described previously.

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.

**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. 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.
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 >100×10^9 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. 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.

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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fixed-Dose Group (N = 94)</th>
<th>Dose-Escalation Group (N = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>4.6±1.0</td>
<td>4.8±0.9</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>55 (59)</td>
<td>47 (51)</td>
</tr>
<tr>
<td>Z score for height for age</td>
<td>-0.80±0.96</td>
<td>-0.73±0.94</td>
</tr>
<tr>
<td>Hemoglobin level — g/dl</td>
<td>8.4±1.2</td>
<td>8.4±1.0</td>
</tr>
<tr>
<td>Mean corpuscular volume — fl</td>
<td>91±10</td>
<td>93±10</td>
</tr>
<tr>
<td>Fetal hemoglobin level — %</td>
<td>22.4±8.6</td>
<td>22.5±8.7</td>
</tr>
<tr>
<td>Absolute reticulocyte count — x10^9/liter</td>
<td>232±89</td>
<td>224±87</td>
</tr>
<tr>
<td>White-cell count — x10^9/liter</td>
<td>11.0±4.2</td>
<td>11.3±3.7</td>
</tr>
<tr>
<td>Absolute neutrophil count — x10^9/liter</td>
<td>4.4±2.4</td>
<td>4.7±1.9</td>
</tr>
<tr>
<td>Platelet count — x10^9/liter</td>
<td>353±156</td>
<td>383±146</td>
</tr>
<tr>
<td>Alanine aminotransferase level — IU/liter</td>
<td>17±6</td>
<td>17±7</td>
</tr>
<tr>
<td>Creatinine level — mg/dl</td>
<td>0.4±0.1</td>
<td>0.4±0.1</td>
</tr>
</tbody>
</table>

* 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 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...
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-

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Fixed-Dose Group (N = 94)</th>
<th>Dose-Escalation Group (N = 93)</th>
<th>Incidence Rate Ratio in Dose-Escalation Group (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell–related</td>
<td>6</td>
<td>5</td>
<td>0.84 (0.24–2.79)</td>
<td>0.77</td>
</tr>
<tr>
<td>Non–sickle cell–related</td>
<td>1</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Clinical adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell–related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>245</td>
<td>105</td>
<td>0.43 (0.34–0.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>136</td>
<td>48</td>
<td>0.36 (0.25–0.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non–sickle cell–related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>321</td>
<td>205</td>
<td>0.64 (0.54–0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>93</td>
<td>54</td>
<td>0.59 (0.42–0.82)</td>
<td>0.002</td>
</tr>
<tr>
<td>Malaria infections</td>
<td>6</td>
<td>3</td>
<td>0.50 (0.11–1.91)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Clinical complications of sickle cell anemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaso-occlusive pain</td>
<td>200</td>
<td>86</td>
<td>0.43 (0.34–0.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute chest syndrome or pneumonia</td>
<td>30</td>
<td>8</td>
<td>0.27 (0.11–0.56)</td>
<td>0.001</td>
</tr>
<tr>
<td>Acute splenic sequestration</td>
<td>14</td>
<td>8</td>
<td>0.58 (0.23–1.34)</td>
<td>0.21</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>0</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Clinical interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusions</td>
<td>116</td>
<td>34</td>
<td>0.30 (0.20–0.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>90</td>
<td>19</td>
<td>0.21 (0.13–0.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Laboratory dose-limiting toxic effects</strong>†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>12</td>
<td>9</td>
<td>0.76 (0.31–1.79)</td>
<td>0.53</td>
</tr>
<tr>
<td>Reticulocytopenia</td>
<td>13</td>
<td>13</td>
<td>1.01 (0.46–2.20)</td>
<td>0.98</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>8</td>
<td>2.02 (0.64–7.56)</td>
<td>0.25</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14</td>
<td>13</td>
<td>0.94 (0.43–2.00)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

* 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 80×10⁹ per liter, neutropenia as an absolute neutrophil count of less than 1.0×10⁹ per liter, and thrombocytopenia as a platelet count of less than 80×10⁹ per liter.
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, <0.5×10^9 per liter) or severe thrombocytopenia (platelet count, <50×10^9 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,29 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,30 human immunodeficiency virus infection,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, $2.0 \times 10^9$ to $4.0 \times 10^9$ 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. 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, 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. 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, personalized dosing based on pharmacokinetics is the ideal way to determine an individual patient’s appropriate dose. 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.

Supported by a grant (ICRA 2016156, to Dr. John) from the Doris Duke Charitable Foundation and by the Cincinnati Children’s Research Foundation.

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

We thank all the children who participated in this trial and their caregivers; the staff of the Mulago Hospital Sickle Cell Clinic and Global Health Uganda for conducting trial work; and the staff of the data coordinating center at Cincinnati Children’s Hospital Medical Center for building the trial database and monitoring and analyzing all trial data.
References

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