Five years of experience with hydroxyurea in children and young adults with sickle cell disease

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The short-term beneficial effect of hydroxyurea (HU) in sickle cell disease (SCD) has been proven by randomized studies in children and adults. The Belgian registry of HU-treated SCD patients was created to evaluate its long-term efficacy and toxicity. The median follow-up of the 93 patients registered is 3.5 years; clinical and laboratory data have been obtained for 82 patients at 1 year, 61 at 2 years, 44 at 3 years, 33 at 4 years, and 22 after 5 years. On HU, the number of hospitalizations and days hospitalized dropped significantly. Analysis of the 22 patients with a minimum of 5 years of follow-up confirmed a significant difference in the number of hospitalizations (P = .0002) and days in the hospital (P < .01), throughout the treatment when compared to prior to HU therapy. The probabilities of not experiencing any event or any vaso-occlusive crisis requiring hospitalization during the 5 years of treatment were, respectively, 47% and 55%. On HU, the rate per 100 patient-years of severe events was estimated to be 3.5% for acute chest syndrome, 1.2% for aplastic crisis, 0.4% for splenic sequestration; it was 0% for the 9 patients with a history of stroke or transient ischemic attack followed for an average of 4 years. No important adverse effect occurred. Long-term chronic treatment with HU for patients with SCD appears feasible, effective, and devoid of any major toxicity; in patients with a history of stroke, HU may be a valid alternative to chronic transfusion support. (Blood. 2001;97:3628-3632)

Introduction

Severe sickle cell disease (SCD) remains associated with high morbidity and early mortality.1-3 Patients with 2 or more painful crises per year, stroke, or acute chest syndrome (ACS) have a reduced life expectancy.4 It has been estimated that the median age of death for men and women with SCD is, respectively, 42 years and 48 years. In addition, a high morbidity rate is related to vascular complications that induce multiple chronic organ damage affecting the brain, heart, kidneys, liver, eyes, skin, skeleton, and lungs.4,5 Until recently, no drug therapy has been able to modify the course of the disease.

In 1994, Charache and coworkers published the results of the Multicenter Study of Hydroxyurea (MSH) in sickle cell anemia, a prospective, double-blind, randomized trial with hydroxyurea (HU).6 Significant clinical improvement was observed in adult patients treated with the drug, when compared to those receiving placebo. Patients receiving HU had lower crises rates, needed fewer transfusions, and developed ACS less often.6,7

In 1996, we published the results of a pediatric randomized, crossover pilot study, which confirmed the clear benefit of HU in reducing the rate of hospitalization and the number of days hospitalized in this population.8 Although it may be a common practice currently to treat symptomatic patients with SCD with HU, unanswered questions remain concerning the long-term effects of this treatment, especially its sustained efficacy and toxicity.9 Based on the preliminary but promising observations, it was decided to propose HU treatment to all highly symptomatic patients and to evaluate their outcome under treatment.

For these reasons, it was decided to create, under the auspices of the Belgium Society of Hematology, a national registry of HU-treated SCD patients (children and young adults) under the responsibility of one of us (A.F.). This study reports the first 5 years of experience of this registry.

Patients and methods

Patients

Patients with severe SCD treated with HU were entered in the Belgian Registry of HU in SCD, which was opened in 1993. All Belgian pediatricians and adult hematologists in charge of SCD patients were requested to enter prospectively their data into this registry.

To be eligible for HU therapy, patients had to fulfill at least one of the following inclusion criteria: 2 or more vaso-occlusive crises (VOCs) per year requiring hospitalization defined as painful episodes probably of vascular origin (trivial causes excluded); one episode of previous ACS defined as acute chest pain with new lung infiltration and with PaO2 less than 75 mm Hg; overt stroke or transient ischemic attack (TIA), defined as transient neurologic deficit (or seizures) and confirmed by a neurologist after electroencephalography and imaging; priapism defined as persistent painful erection not associated with erotic stimulation; or the development of ischemic bone necrosis, defined as hip or shoulder pain with functional...
impairment with abnormal bone scintigraphy, magnetic resonance imaging, or abnormal radiography. At inclusion (start of HU therapy), the following minimal information was required: birth date, country of origin, electro-physiologic diagnosis, hemoglobin (Hb) level, percentage of fetal hemoglobin (HbF), mean corpuscular volume (MCV), neutrophil counts, previous major adverse events, and number of hospitalizations and days in the hospital during the last 12 months before start of HU. All participants agreed to complete, before and each year after inclusion of their patients, a pre-established registry file. Oral or written consent for HU treatment was obtained for each patient. The registry was approved and conducted under the auspices of the Belgian Society of Paediatric Haematology and the Belgian Society of Haematology. The pre-HU data were based on the actual experience at the clinical centers or on records obtained from other Belgian centers.

Patients and parents (or legal guardian) were aware of the potential risks and side effects related to HU. Adults and adolescents were also aware of the need for active contraception.

The initial dose of HU was 20 mg/kg daily; it was increased by 5 mg/kg if judged appropriate by the treating clinician. Treatment attitude was mainly based on the clinical response of each patient at the starting dose of 20 mg/kg. There were no fixed guidelines for dose escalation and dose modification as long as the patient was found to be adequately controlled by each center’s physician. There has never been any attempt to reach a “maximal tolerated dose.” All SCD patients, whether on HU or other type of treatment, were routinely seen every 2 months. In addition, patients on HU were tested for hematologic toxicity and HbF response every 2 months.

Annual clinical and biologic evaluation included the following: (1) status of the patient (alive or dead); (2) number of hospitalizations and days hospitalized each year (for whatever reason); (3) major SCD-related events (such as stroke or TIA, ACS, osteonecrosis, priapism, VOC); (4) transfusions given; (5) presence of hematologic toxicity defined by platelet count less than 100 × 10^9/L or white blood cell (WBC) count less than 3 × 10^9/L; (6) presence of an opportunistic infection; (7) development of malignant disease; and (8) other major events.

The annual biologic evaluation was limited to Hb level, HbF, MCV, and neutrophil count at the end of each year of treatment. Values within 3 months after the last transfusion were not considered. The differential WBC count was determined using a H3 Blood Cell Count Analyzer (Bayer Technology, Dublin, Ireland). The dosage of HbF was done by high-pressure liquid chromatography (HPLC). The mean HU dose per kilogram was also calculated each year.

Statistical analysis

For hematologic data and number of days hospitalized, paired t tests were performed to test for differences between means in successive years and between means from the first year and the last one. A Bonferroni adjustment was used to provide conservative confidence limits for the estimates of pairwise differences between years. Analyses of variance (ANOVA) were used to test for a global time effect from the end of the first year of treatment until the end of the fifth year of treatment (only patients with 5 years of evaluation were considered).

For the number of hospitalizations, Wilcoxon-signed tests were used to test for differences between mean in successive years. Marginal homogeneity tests (extension of the McNemar test for more than 2 categories) were performed to compare the probability distributions between 2 years.

Kaplan-Meier survival curves were estimated for the time to the first VOC and for the time to the first event of any type (stroke, acute chest syndrome, VOC, osteonecrosis, allogeneic hemopoiesis, priapism, or hospitalization for any reason). McNemar tests were used to test the equality of VOC rates (or events rates) between 2 different years of treatment.

Analyzing only those patients with 5 years of follow-up, a t test was performed to test for a difference in the hematologic results at baseline between patients who had at least one event during their treatment and for patients who had no event during their treatment.

Results

Characteristics of the patients and clinical data

Ninety-three patients with severe SCD entered the registry in Belgium. They came from 6 different centers. Among the 91 patients for whom the country of origin is known, 69 (75.8%) came from Congo-Zaire and 6 (6.6%) from Angola. Three patients came from Cameroon, 2 patients each from Burkina-Faso and Mali, and one each from Benin, Ghana, Guinea, India, Nigeria, Uganda, Senegal, Togo, and Turkey. Age at inclusion varied from 8 months to 45 years, with a median of 7 years. Seven children were younger than 2 years at the start of HU treatment, 20 were between 2 and 5 years, 33 were between 5 and 9, 27 were aged 10 to 19 years, and 6 were 20 or older.

There were 47 males and 44 females; all except one were homozygous for sickle cell anemia. One patient had SD-Punjabi heterozygosity.

Before inclusion, 67 (72%) had 2 or more yearly hospitalizations for VOC; 19 (20%) had previous ACS; 17 (18%) a history of osteonecrosis; and 9 (10%) patients presented with stroke or TIA in the previous year. Among the 7 children under 2 years of age, 4 had presented with ACS, 3 had more than 2 VOCs in the 12 months preceding inclusion in the registry, and 3 had recurrent episodes of splenic sequestration; 2 of these 3 last patients had other major criteria, the third one having this sole criteria for registration. Data on hospitalizations during the year preceding inclusion in the registry were obtained from medical records in 78 patients. Fifteen patients fulfilled inclusion criteria but the exact number of hospitalizations or days hospitalized prior to HU was evaluated only on patient recall and thus not considered. The median number of hospitalizations was 2.7 (range, 0-10) and the mean duration in the hospital was 18 days per year per patient (range, 0-82).

Among these 93 patients, 82 (88%) were evaluated after 1 year, 61 (66%) after 2 years, 44 (47%) after 3 years, 33 (35%) after 4 years, 22 (24%) after 5 years, and 12 (13%) after 6 years. A total of 254 years of treatment have been assessed (“254 patient-years”).

After a median follow-up of 3.5 years, all the patients were still alive. The median number of hospitalizations dropped from 2 before the start of HU (with a median duration of hospitalization of 14 d/yr) to zero per year during subsequent years. The mean number of hospitalizations per year and number of days in the hospital dropped significantly all along the 5 years of HU treatment (Table 1). SCD-related clinical events on HU are detailed on Table 2. During the first year, 84% of patients were free of VOC events requiring hospitalization. These percentages were 79%, 81%, 90%, and 74%, respectively, for the second, third, fourth, and fifth year on HU. To evaluate if HU treatment had any sustained effect, 22 patients who had a minimum of 5 years of follow-up were analyzed by the Wilcoxon test. Using this test, a highly significant difference in terms of number of hospitalizations was observed between the year preceding the start of HU and the end of the first year of treatment ($P = .0002$). In contrast, no significant time effect on the number of hospitalizations from one year of treatment to the next one or from the first year of treatment to the last one was observed ($P > .2$). The same test applied on all patients available both at the end of the ith year and the end of the previous year (i-1), led to the same conclusions.

Considering the number of days hospitalized, no significant change was demonstrated for patients evaluated after 2 years, 3 years, and 4 years; however, analysis of the 22 patients who were
treated for 5 years revealed no difference in the number of days in the hospital at 5 years as compared to baseline values. This might be due to the limited number of patients evaluated at 5 years because ANOVA did not demonstrate any time effect all along the study period including the fifth year (P = .40). Similarly, no significant change was demonstrated concerning both the occurrence of VOC requiring hospitalization and the occurrence of any SCD event during the 5 years of treatment. The McNemar test revealed no significant difference from one year of treatment to the next one (P ≥ .05). Again the McNemar test for a difference between the occurrences of VOC or the occurrence of an event in the year before start of HU and at the end of the first year of treatment showed a significant difference (P = .001); the occurrence of VOC requiring hospitalization or an event was lower after the first year of treatment. The estimated time to the occurrence of VOC among patients receiving HU is shown in Figure 1. The cumulative probability of not experiencing a VOC during at least 5 years of treatment was 55%. The estimated time to the occurrence of an event among patients receiving HU is shown in Figure 2. The cumulative probability of not experiencing any event during at least 5 years of treatment was 47%.

The 9 patients with stroke or TIA remained free of new clinical neurologic complications. Their median follow-up is now 4 years. During the first few months after starting HU some received blood transfusion.

Nineteen patients had a history of previous ACS. Eight subsequent episodes were documented on therapy. The overall rate of ACS on HU is estimated at 3.2% per year of treatment.

Aseptic necrosis did not occur in any patient with or without a history of bone lesions. No patient developed priapism while on therapy.

Two patients developed long-lasting severe hematuria. A diagnosis of papillary necrosis was made and the patients recovered without any renal impairment while continuing HU therapy. Two parvovirus infections with typical aplastic crisis and one splenic sequestration occurred.

Forty-two patients have received transfusions during the 254 patient-years. The main reasons for transfusions were continuation of chronic transfusion support for a few months after stroke during the first year on HU (n = 9), ACS (n = 7), surgery (n = 8), aplastic crises (n = 2), or other crises, according to each center’s policy (n = 16). One HU-treated patient presented transient hematologic toxicity that resolved after drug dosage was reduced. Neither opportunistic infection nor malignancy has occurred to date. No other major event was reported.

Treatment was interrupted in 6 cases. Two patients were successfully grafted with identical HLA siblings and remain free of SCD-related symptoms. One patient remained severely symptomatic with unchanged hospitalization rate and no increase in HbF, despite macrocytosis, and was considered to have failed treatment. Three have abandoned the treatment after few months.

At the end of the first year on HU, 55% of patients received HU 20 to 25 mg/kg daily. 41% had a dose under 20 mg/kg per day, and 4% between 25 and 30 mg/kg per day. Only one patient (1.3%) received more than 30 mg/kg per day. These proportions remained unchanged during the subsequent years.

### Laboratory data

At start of HU therapy, the mean Hb level was 8.2 g/dL (range, 5.9-12.3) and mean MCV was 83 fL (range, 60-113). Initial HbF was 7.3% (range, 0.1%-32%). Mean granulocyte count was 6.0 × 10⁹/L (range, 1.9-16).

The Hb levels, MCVs, HbF levels, and absolute neutrophil count (ANC) after each year of therapy are given in Table 3. No relevant change in the hematologic data occurred from one year of treatment to the next or from the first year of treatment to the last one. However, a significant difference was observed between the year preceding the start of HU and the end of the first year of treatment: higher Hb, higher HbF, higher MCV, and a low level

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**Table 1. Clinical outcome in sickle cell disease patients before and during hydroxyurea therapy**

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Before HU</th>
<th>After 1 y HU</th>
<th>After 2 y HU</th>
<th>After 3 y HU</th>
<th>After 4 y HU</th>
<th>After 5 y HU</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. evaluable patients</td>
<td>93*</td>
<td>82</td>
<td>61</td>
<td>44</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>No. of hospitalizations per year (mean ± SD)</td>
<td>2.76 ± 2.3</td>
<td>1.15 ± 1.9§</td>
<td>1.08 ± 1.5§</td>
<td>1.11 ± 1.5§</td>
<td>1.33 ± 2.1§</td>
<td>1.2 ± 1.5‡</td>
</tr>
<tr>
<td>No. of days in hospital (mean ± SD)</td>
<td>18.1 ± 17.3</td>
<td>7.3 ± 15.8§</td>
<td>5.4 ± 9§</td>
<td>4.9 ± 7.2§</td>
<td>9.1 ± 13.3‡</td>
<td>9.4 ± 13‡</td>
</tr>
</tbody>
</table>

*Mainly for vaso-occlusive crises, but hospitalizations for surgery or infection are also included.

ACS indicates acute chest syndrome; TIA, transient ischemic attack.

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**Table 2. Sickle cell disease-related clinical events reported in the Belgian Registry in patients on hydroxyurea**

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Adverse events (no.)</th>
<th>Rate/100 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of hospitalizations*</td>
<td>271</td>
<td>106</td>
</tr>
<tr>
<td>ACS</td>
<td>9</td>
<td>3.5</td>
</tr>
<tr>
<td>Parvovirus infection with aplastic crisis</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Papillary necrosis</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>Surgery for gallstones</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>Splenic sequestration</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>TIA or stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Priapism</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Mainly for vaso-occlusive crises, but hospitalizations for surgery or infection are also included.

ACS indicates acute chest syndrome; TIA, transient ischemic attack.
of polychromatophilic erythroblasts was observed after the first year of treatment.

A significant change in Hb, MCV, HbF, and ANC was observed after 1 year in the 22 patients who received at least 5 years of treatment. The global time effect tested on these 22 patients who were evaluated for 5 years did not reveal any change in the hematologic results during the 5 years of treatment. Evaluation of these 22 patients did not show any significant difference in the hematologic results at baseline between patients who suffered at least one event during their 5 years of treatment and patients who did not suffer any event during the 5 years.

### Discussion

Allogenic bone marrow transplantation (BMT) remains the only curative therapy in severe SCD. The last survey of the Belgian experience in BMT for SCD, which included 50 patients, showed an event-free survival of 85% with an overall survival rate of 93%. In patients lacking an HLA-identical sibling, refusing the BMT procedure, too old for BMT, or in whom a contraindication exists, HU is the only drug that has been proven to modify the disease at short or middle term,2-6,8,14 with acceptable toxicity. However, the favorable and unfavorable long-term effects of HU, especially in young patients, remain unknown. These questions can only be addressed by establishing large-scale prospective registries or trials.

In our prospective registry, patients with severe SCD had markedly milder disease on HU with a significant reduction of the number of hospitalizations or days hospitalized per year, than before they started HU. Our results indicate that the effect of HU has been fairly constant over the 5 years of treatment. Because our conclusions are deduced from registry data and not from a standardized prospective study, there are biases that we have to consider including placebo effect in patients or unconscious bias in physicians taking care of these patients. Furthermore, some heterogeneity may exist between centers in criteria for hospitalization; it is also possible that patients presented themselves to medical care less often because they relied on the drug and it is also possible that physicians admitted the patients less often or kept them in the hospital for fewer days because they trusted the drug. However, the difference between baseline values and values under treatment are important and they can probably not only be explained by these bias. In addition, a 5-year placebo-controlled study would now be considered unethical.

The data collected from such a registry give us reliable information concerning the rate of occurrence of sickle cell Hb-related events on therapy, the lack of toxicity of this treatment, the effects on blood parameters, and the overall clinical constancy over years of therapy. Thus clinical improvement observed by many authors in the short term was maintained until the fifth year. Of interest, no patient with previous stroke or TIA had a recurrence, even after arrest of chronic transfusion support, whereas in this population, the relapse rate is usually estimated to be more than 50% in patients without transfusion and 13% in those having transfusion.17 Ware and colleagues recently reported a cohort of 16 children with SCD and stroke in whom transfusion therapy was stopped and HU started. After a mean follow-up of 22 months, only 3 patients had recurrent strokes, 3 to 4 months after discontinuing transfusion, when HU effects were not maximal. Nevertheless, these very limited data are still insufficient to modify the usual guidelines including chronic transfusions in SCD children with neurologic problems. Only prospective randomized studies will answer the question whether HU is effective for prevention of stroke or TIA.

The frequency of ACS was particularly low with 8 episodes for 254 patient-years. In the randomized prospective study of Charache and coworkers (MSH study), 25 episodes occurred among the 152 patients receiving HU for 2 years or more. The low ACS rate in our population might be due to the fact that the doses at start of HU were higher than in the MSH study and that more stringent criteria for hematologic toxicity requiring drug modification was used in the MSH study. However, the ANC after 2 years were similar between MSH patients on HU and patients registered in the Belgian study. Furthermore, most of the patients are older than 4 years, and above this age, it is well known that the incidence of ACS decreases gradually. Nevertheless, prospective studies are mandatory to assess the decreased rate of ACS on HU and the possible reduction in the occurrence of chronic lung disease.

No patient developed leg ulcers, although an occurrence of 8.5% is found in patients on continuous HU for chronic myelogenous leukemia or other myeloproliferative disorder.20,21 Transfusion requirement is difficult to analyze because some patients, mostly those suffering from stroke or TIA, continued to be on a chronic transfusion program for a few months after starting HU; transfusions were also given to some patients prior to surgery.

### Table 3. Biologic modifications during hydroxyurea therapy

<table>
<thead>
<tr>
<th></th>
<th>At start HU (n = 93)</th>
<th>After 1 y (n = 83)</th>
<th>After 2 y (n = 61)</th>
<th>After 3 y (n = 44)</th>
<th>After 4 y (n = 33)</th>
<th>After 5 y (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hb (g/dL) (mean ± SE)</strong></td>
<td>8.2 ± 1.1</td>
<td>8.8 ± 1.2†</td>
<td>9 ± 1.5‡</td>
<td>8.7 ± 1.2‡</td>
<td>8.2 ± 1.4*</td>
<td>8.7 ± 1.3†</td>
</tr>
<tr>
<td>% HbF (mean ± SE)</td>
<td>7.3 ± 6.8</td>
<td>16.7 ± 10.6‡</td>
<td>16.1 ± 9.7‡</td>
<td>15.6 ± 8.7‡</td>
<td>15.3 ± 8.1‡</td>
<td>12.9 ± 6.7‡</td>
</tr>
<tr>
<td><strong>MCV (fL) (mean ± SE)</strong></td>
<td>83 ± 8.9</td>
<td>93.5 ± 11‡</td>
<td>93.4 ± 11‡</td>
<td>94.6 ± 12‡</td>
<td>95.8 ± 12‡</td>
<td>96.9 ± 15‡</td>
</tr>
<tr>
<td><strong>ANC (10⁹/L) (mean ± SE)</strong></td>
<td>6.0 ± 2.6</td>
<td>3.9 ± 14‡</td>
<td>4.5 ± 2.5†</td>
<td>4.2 ± 2.5†</td>
<td>4.2 ± 2‡</td>
<td>4.0 ± 2.3‡</td>
</tr>
</tbody>
</table>

HU indicates hydroxyurea; HbF, fetal hemoglobin; MCV, mean corpuscular volume; fL, femtoliter; ANC, absolute neutrophil count.

*P value not significant, when compared to baseline.
†P < .05, when compared to baseline.
‡P < .01, when compared to baseline.
and the local policy for transfusion during VOC was quite different from center to center. Of interest, 55% of severely affected patients may expect to remain free of VOC at 5 years. The probability to remain free of any event at 5 years was 47%. Furthermore, of the 22 patients who were observed on HU during at least 5 years, the clinical benefit of HU was clearly maintained over the years with fewer hospitalizations, fewer days in the hospital, and fewer VOC or other events.

In our experience, HU therapy was safe with no clinically significant hematopoietic depression requiring cessation of drug therapy. Most of the patients were maintained on doses less than 20 to 25 mg/kg per day throughout the entire follow-up without any evidence of loss of efficacy, as assessed by annual hospitalization rate and duration of hospitalization. Increasing doses to reach the maximal tolerated doses was not an usual practice among clinicians who took care of patients with SCD but this attitude did not reduce the clinical efficacy of the drug.

No other severe toxicity occurred. Nail, skin, or hair modifications were not prospectively analyzed and, if present, were considered by the physician as a minor event and not reported; the treatment was never stopped by the patient or the physician on the sole basis of these events.

Malignancy has been reported in one SCD patient on HU,22 but its incidence may be no higher than in the general population. In our study, no malignancy occurred on HU after a mean 3 years of follow-up, but the question of a possible risk of leukemogenesis in SCD patients on HU can only be answered by long-term follow-up of these patients.

We conclude that there is presently evidence that prolonged HU treatment of young patients with SCD appears efficacious, safe, and cost-effective in view of the low cost of the drug and the reduction in both the number of admissions and the number of days of hospitalization.

References

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