Special article

Consensus of the Brazilian Association of Hematology, Hemotherapy and Cellular Therapy (ABHH) and the Brazilian Ministry of Health - General management of blood and blood products on the tests necessary for the release of exceptional medicines for sickle cell disease

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2531-1379/© 2024 Published by Elsevier España, S.L.U. on behalf of Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

Hydroxyurea (HU) is a medicine drug with many beneficial effects in the treatment of sickle cell disease (SCD), including: increasing the concentration of fetal hemoglobin (Hb) in red blood cells, improving nitric oxide metabolism, and reducing cell adhesion between reticulocytes and sickled red blood cells, leukocytes and platelets and endothelial cells, in addition to reducing the concentration of leukocytes and platelets. HU was approved in the United States of America for the treatment of people with SCD in 1998 and in Brazil in 2002.

The therapeutic success of HU is directly related to three main aspects: access to the drug, the dose used and adherence to treatment, which, in part, is correlated to the availability of HU. Access to HU, in Brazil, is a process that involves a list of mandatory laboratory tests and the resubmitting a renewal form with updated information. If one single test is missing, the patient will not receive the medication, increasing the risk of deteriorating health within a few days. Thus, the availability of HU, especially when the supply is interrupted, a situation that is not uncommon in several Brazilian states, is an important barrier and can cause a deterioration of the health. This consensus aims to reduce the number of mandatory exams needed to access the drug without affecting patient safety, prioritizing the requesting physician’s report as the fundamental document that details the reason for indication, clinical conditions and results of the patient’s exams, thereby reducing difficulties in accessing HU for people with SCD in Brazil.

HU should be the initial therapy for individuals with SCD, notably those with the Hb SS and Hb SB0 thalassemia subtypes. There is much experience in its use demonstrating its effectiveness in reducing vaso-occlusive pain and other complications with consistent safety data with improved patient survival. Today in Brazil, many individuals who would benefit are not treated with HU and many who are treated are not receiving the ideal dose and have suffered from interruptions in the medication supply.

Sickle cell disease and hydroxyurea

SCD is a chronic vasculopathy in which premature destruction of red blood cells causes chronic anemia. Vaso-occlusive phenomena and hemolysis are the clinical characteristics of SCD. Vaso-occlusion results in recurrent painful episodes (called sickling crises) and a variety of serious systemic complications that can cause progressive damage and lead to early death.

Individuals with SCD should be seen regularly by their physician and a multidisciplinary team as part of a comprehensive health care maintenance program. Routine office visits are necessary to educate the affected individual and family/caregivers about SCD, infection prevention, pain management strategies and anticipatory guidance for possible complications (e.g., splenic sequestration, avascular necrosis of the femoral head, cerebral stroke and leg ulcers). Education
about the nature of the disease, genetic counseling and psychosocial assessments of individuals and their families/caregivers are also best carried out during these visits.  

The use of HU is a pillar in the global treatment of individuals with SCD as it reduces the incidence of acute pain episodes and other vaso-occlusive events, including acute chest syndrome and stroke, reduces hospitalization rates and increases survival.  

There are several publications that inform which tests are recommended for doctors to prescribe and which to monitor patients using HU. Some of these follow-up suggestions were taken from clinical research that took place >30 years ago, when there was still little research on the safety of the medication.  

Obtaining laboratory values before initiating HU treatment (e.g., hemoglobin level, reticulocyte count, leukocyte count) and during routine visits will provide standards for comparison during clinical exacerbations because these values are often abnormal early in the follow-up.  

The exams included in the Clinical Protocol and Therapeutic Guidelines of the Ministry of Health for the use of HU are related to the early publications, mentioned above, and guide the patient’s medical monitoring. These laboratory tests, as well as transcranial Doppler (TCD) from two to 16 years of age, echocardiogram, abdominal ultrasound and fundoscopy examination should be performed for the early detection of complications, but should not guide the release of medication. Such recommendations are being used by healthcare managers to request the release of HU, which has been identified as a barrier to the use of the medicine, the only modifier of the natural history of SCD available in Brazil.  

This document was formulated by a group of experts and aims to update the tests that should be managed by doctors to request the release of HU for people with SCD. We divide usage situations into four categories:  

1. First-time Exceptional Medicines Request (EMR)  
2. Subsequent EMR with dose escalation  
3. Subsequent EMR with dose maintenance per Kg of weight  
4. EMR for reinsertion into the public system  

To prepare the EMR, the healthcare manager needs to present:  

1. To start treatment: First-time EMR:  
   - Medical report containing the reason for the request  
   - Result of a blood count performed within the last 3 months  
   - Hemoglobin fractionation test (e.g., high-performance liquid chromatography [HPLC] fractionation, hemoglobin agar gel electrophoresis, IEF) performed at any time after six months of age  
   - For women of childbearing age beta-HCG or a rapid pregnancy test from the last 30 days.  

If the indication for HU is chronic organ damage, the medical report must also include the relevant test results. Attention: for under two-year-old patients and for the same patient following treatment from two years old, the reason is to have Hb SS, Hb S/β or Hb SD (Punjab)  

2. For dose escalation:  
   It is necessary to send a medical report containing: weight, dose per Kg, blood count results and reticulocyte count performed within the last 3 months.  

3. To maintain the same dose per Kg of weight  
   It is necessary to send a medical report containing: weight, dose per Kg, blood count results and reticulocyte count performed within the last 6 months.  

4. For the patient to be reinserted into the public system  
   It is necessary to send a report with weight and dose per Kg, blood count and reticulocyte count performed within the last 3 months as well as a hemoglobin fractionation test (for example, HPLC, hemoglobin agar gel electrophoresis, IEF) performed at any time after 6 months of age  

In this case, it will be clear in the report that the patient has already been in the public system and may have interrupted it due to pregnancy or taken the medication privately. The patient re-enters the public system with the dose they have been taking; it is not necessary to start with a dose of 15-20 mg/Kg/day.  

OBS: For number 4 also needed for women of childbearing age beta-HCG or a rapid pregnancy test from the last 30 days.  

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Suggested information to be included in the medical report  

PATIENT NAME: _____________________________  
BIRTH DATE: _____________________________  
Weight: ___________ Height: ___________  
SICKLE CELL DISEASE SUBTYPE:  
() Hb SS () Hb S/THALASSEMIA () Hb SC () Hb SD  
() Others - specify: _____________________________  
DIAGNOSIS DATE: _____________________________  
INSTITUTION OF ORIGIN: _____________________________  
REASON FOR INDICATION TO USE HYDROXYUREA:  
____________________________________  
____________________________________  
____________________________________  
COMPLETE BLOOD COUNT RESULT:  
____________________________________  
____________________________________  
____________________________________  
PRESCRIBED DOSE PER KG: _____________________________  
TOTAL DAILY DOSE: _____________________________  
FULL NAME OF THE PRESCRIBING DOCTOR:  
____________________________________  
____________________________________  
____________________________________  
COUNCIL OF MEDICINE NUMBER (CRM):  
____________________________________  
REQUEST DATE: _____________________________  
SIGNATURE AND MEDICAL STAMP:  
Contraindications for taking HU:  
- neutrophils below 1000 cells/μL in babies up to one year of age and below 1500 cells/μL in over one-year-old patients  
- Hb below 4.5 g/dL  
- Reticulocyte count below 80,000/mm^3 (when Hb is <8 g/dL)  
- Platelet count below 80,000/mm^3 or  
- Pregnancy
The above values for each patient must be informed in the medical report to be sent together with the EMR.

An important point to note is that the presence of the HIV virus no longer contraindicates the use of HU and is even used in some series to control the virus.\(^{11-17}\)

**NOTE:** Patients who are already using the drug and who have experienced toxicity (see above) should have the dose reduced until the safety level is reached. Values for dose adjustment are not considered for first-time patients. In case of toxicity (according to test results mentioned above), the use of HU must be interrupted until the value returns to above acceptable levels. Treatment is then restarted with a dose 5 mg/Kg/day lower than the last dose used, following the same progressive increase scale every 4 weeks. If toxicity occurs twice for the same dose, the previous dose (5 mg/Kg lower) is considered the maximum tolerated dose. Reticulocyte counts are necessary until Hb reaches a value greater than 9 g/dL.\(^{18}\)

**NOTE:** HU should be stopped as soon as pregnancy is suspected or confirmed\(^{19}\) and ideally should be discontinued before attempting conception (six months for men and three months for women) and should not be used during pregnancy or breastfeeding.\(^{20}\)

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**Recommendation**

The request and maintenance of hydroxyurea use by way of an Exceptional Medication Request is fundamentally based on the requesting doctor’s report, which must contain in detail the patient’s clinical condition and the results of the tests indicated above, without requiring additional test reports.

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**Conclusion**

This consensus aims to make recommendations available on the content required for the EMR for dispensing HU, without reducing patient safety and, above all, to reduce the difficulties in accessing HU of people with SCD in Brazil. These recommendations should serve as a tool for doctors and patients. The other laboratory tests necessary for the follow-up of people with SCD must be maintained, but are not necessary for the release of HU.

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**Conflicts of interest**

None.

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**References**


