

# Use of Hydroxyurea and Recombinant Erythropoietin In Management of Homozygous $\beta^0$ Thalassemia

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**Summary:** This report describes the sustained response of an Iranian girl with homozygous  $\beta^0$  thalassemia (IVS-II-IG→A) to hydroxyurea (HU) and recombinant erythropoietin (rEPO). Since the start of this regimen 7 years ago, she has been transfusion-independent and her hemoglobin is maintained between 9.5–11.0 gm/dL. She is maintaining consistent growth around the 10th percentile for age and enjoys a good quality of life. She has not had any therapy-related adverse effects. This experience suggests that therapy with HU and rEPO may be useful long-term in some patients with  $\beta$  thalassemia.

**Key Words:** Thalassemia—Hydroxyurea—Erythropoietin.

We report a 12-year-old patient with homozygous  $\beta^0$  thalassemia who is transfusion independent for the last 7 years since being treated with hydroxyurea (HU) and recombinant erythropoietin (rEPO).

## CASE REPORT

The patient, born in 1989 in Iran to maternal first cousins, was diagnosed to have thalassemia at the age of 14 months and was started on regular blood transfusions and chelation therapy. Her family moved to the United States when she was 5 years old. On initial examination, the patient was jaundiced and below the 5th percentile for height and in the 25th percentile for weight. She had moderate hepatosplenomegaly, spleen extending 6 centimeters and liver 4 centimeters below the costal margin. Because limited information was available to confirm her diagnosis and transfusion dependence, the transfusions were stopped. After 10 weeks, hemoglobin dropped to 6.4 g/dL (from over 9 g/dL while receiving red cell transfusions) with mean corpuscular volume (MCV) 70 fl. Hemoglobin electrophoresis showed Hb F 99%, HbA<sub>2</sub> 1%, and Hb A 0%, consistent with the diagnosis of thalassemia major. Ferritin level was 1338 ng/mL. She was started back on blood transfusions and chelation therapy with a target hemoglobin level of around 10 gm/dL.

Due to progressive splenomegaly (12 centimeters below costal margin) she underwent splenectomy in 1995. A liver

biopsy performed at the same time revealed an iron level of 18,140  $\mu\text{g/g}$  of dry weight. She was started on HU 500 mg (30 mg/kg) twice per week and rEPO 400 units/kg three times per week subcutaneously. Within 3 months after initiation of this therapy and without any further transfusions, her hemoglobin increased to over 10 gm/dL with a reticulocyte count between 6% to 10%, and MCV in the mid-80 fl range.

The patient's height and weight curve has been parallel and just under the 10th percentile on the standard growth chart. She is SMR stage 1. She is gradually developing coarsening of facial features and prominence of her forehead. She attends school regularly, is an honor student, and participates in sports. She has not received any red cell transfusions since the start of HU and rEPO more than 7 years ago. A year after the initiation of therapy, the frequency of rEPO was decreased from three times to two times per week. HU continues at the same total dosage of 500 mg twice a week and has not been adjusted despite an increase in her weight (currently 14 mg/kg).

Her hemoglobin has been maintained between 9.5 to 11.0 gm/dL. The latest blood studies show white blood cell count  $18.7 \times 10^9$ , Hb 10.9 g/dL, Hct 33.9%, platelets  $704 \times 10^9/\text{L}$ , MCV 87 fl, MCH 27.8 pg, MCHC 32, RDW 24.5, reticulocyte count 7.8%, and ferritin 1464 ng/mL. Electrophoresis shows Hb F 97.9%, HbA<sub>2</sub> 2.1%. The patient experienced two brief episodes of mild neutropenia at the beginning of HU therapy (absolute neutrophil count 960 and 806). Each time there was prompt recovery after 2 weeks of withholding HU. A recent liver biopsy shows iron deposition but no fibrosis or cirrhosis. However, despite no additional red cell transfusions, quantitative analysis determines the liver iron to be 21,244  $\mu\text{g/g}$  dry weight, higher than noted 7 years ago.

Bone marrow examination done at the same time reveals an erythroid hyperplasia with some foamy cells. Cytogenetic studies did not reveal any chromosomal abnormality (46XX). Measures to decrease iron overload (chelation, phlebotomy) are being considered by the family. Endocrine evaluation shows her to be prepubertal with normal thyroid and growth hormone screening studies.

Genetic analysis done recently using automated fluorescence-based DNA sequence analysis of a PCR-amplified fragment containing the  $\beta$ -globin gene with  $\beta$ -globin specific primers on an ABI 3100 (Applied Biosystems, Inc., Foster City, CA) revealed that she is homozygous for a

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G→A mutation in intervening segment two; position one (IVS II-1) of the  $\beta$ -globin gene. Her parents have elevated hemoglobin A2 levels (mother 6.8%, father 6.1%) and are heterozygous for the same mutation. Recently an HLA-matched umbilical cord blood has become available from a sibling. Patient is being considered for a stem cell transplant.

### DISCUSSION

The sustained de novo erythropoiesis and the transfusion independence of the patient for 7 years now, along with the ability to lead a relatively normal life and activity, reflects the success of HU and rEPO in homozygous  $\beta^0$  thalassemia. In previous reports, splenectomy did not appear to influence the response of HU in thalassemia intermedia patients (10). HU therapy replaces the poorly hemoglobinized, short-lived erythroid cell population with a new cohort of precursors with active Hb F synthesis and improved function and longer life span (11,12). The benefit of rEPO is believed to be its ability to cause prolongation of RBC survival and prevent programmed cell death (9).

The patient is homozygous for the IVS-II-1 (G→A) mutation, which is a common  $\beta$  thalassemia mutation in the Iranian population (13–15). This mutation abolishes the 5' splice site and results in no globin production from this allele. Severity of the disease is largely affected by the ability to produce large amounts of Hb F (8,13–15). Hematologic parameters in the patient correlate with published values for 5 patients homozygous for IVS-II-1 (G→A) (Hb 4.3–12.2; Hb F 97.4–98.9; Hb A 0%; Hb A2 1.1–2.6) (16).

Although effectiveness of HU and rEPO in patients with severe thalassemia intermedia and thalassemia major has been reported, most have been adults with mild disease and treatment has been for shorter periods of time (1–10). Hoppe et al. (7) reported no tachyphylaxis with the use of HU on 3-year follow-up. As in their study, our patient has done well with lower doses of HU than used conventionally. Because the  $\beta$  thalassemia syndromes are the result of many different mutations in the  $\beta$  globin gene, it is not unexpected that modulation of Hb F and erythropoietin production by various agents has shown heterogeneous and varied results (1–10).

This report illustrates that a sustained long-term response can be obtained with HU and rEPO in certain homozygous

$\beta$  thalassemia genotypes. Unfortunately, although not unexpectedly, our patient has continued to accumulate iron in her body despite no further blood transfusions (17). Clinical trials involving a large group of similar patients are needed to further clarify and establish the role of such therapy in thalassemia. Future efforts should be directed towards optimum patient selection and tailoring of pharmacologic therapy based on genotype and other clinical predictors of response.

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