First Report of Reversal of Organ Dysfunction in Sickle Cell Anemia by the Use of Hydroxyurea: Splenic Regeneration

By Susan Claster and Elliott Vichinsky

Much of the morbidity associated with sickle cell anemia (SCA) is due to ongoing infarction resulting in organ dysfunction. Because the spleen is often the first organ damaged in this illness, there is a significant impairment of the immune system in these patients. Hydroxyurea (HU) has been shown to increase fetal hemoglobin (HbF) and decrease painful episodes in patients with this disease. It is unclear whether HU can prevent organ damage. We treated two SCA patients with HU for several years and found evidence of reversal of previously documented splenic dysfunction. Patient no. 1 was treated for 30 months with an increase in HbF to 30%. HU was stopped because of cytopenia.

MUCH OF THE MORBIDITY associated with sickle cell anemia (SCA) is the result of progressive organ damage due to sickling-induced infarction. One of the earliest organs to be damaged is the spleen.1 As the level of fetal hemoglobin (HbF) decreases to less than 15% to 20% during early childhood, the corresponding increase in hemoglobin S causes progressive dysfunction in this organ.2 Young children with SCA often have an enlarged but poorly functioning spleen. Eventually, the spleen completely autoinfarcts and becomes nonfunctional, resulting in significant impairment of the patient’s immune system.3,4

MATERIALS AND METHODS

There are two commonly used methods for evaluating splenic function. The first, radionuclide scanning, uses the uptake of the technetium-99m isotope, attached to a sulphur colloid particle, to show the functioning of the reticuloendothelial cells of the spleen.3 The other method measures splenic function by quantitation of pitted red blood cells (RBCs) using phase contrast microscopy to show surface pits.6 A normally functioning spleen removes these imperfections. In sickle cell disease, the level of pitted RBCs is inversely related to HbF and increases with age.7 A pit count greater than 3.5% has been determined to indicate splenic dysfunction.7 Using these techniques, previous studies have shown that transfusion therapy as well as bone marrow transplantation can reverse splenic dysfunction in certain individuals.6,8,11

Hydroxyurea (HU) has been administered to sickle cell patients because of its ability to increase HbF levels and thereby retard sickling.12 Previous studies have shown this drug has the ability to decrease the number of painful episodes in SCA patients.13 The ability of HU to sustain elevations of HbF as high as 20% to 30% in some patients suggests that the use of this drug may offer some potential reversal of organ damage without the attendant risks of transfusion. We now report the return of splenic function in two patients who were treated with long-term HU therapy. This is the first evidence this drug may, in fact, reverse organ dysfunction in some sickle cell patients.

RESULTS

Patient no. 1. Patient no. 1 is a 27-year-old woman with SCA who has had a severe clinical course. Her previous history has been characterized by multiple episodes of vaso-occlusion, acute chest syndrome, and sepsis. Her spleen remained consistently palpable until the age of 10 (1977). Between the ages of 10 and 19, she was transfused on seven occasions, beginning in May 1977. Seven months later, her spleen was no longer palpable. A liver-spleen scan performed in early 1979 showed no splenic activity. She received 5 U of blood over a 4-month period in mid 1979, and her spleen became palpable for approximately 6 months. In 1980, a pit count was 8.0%. She received transfusions again between 1984 and 1986, including a 7-U exchange transfusion in 1985; however, her spleen never again became palpable. A repeat liver-spleen scan in 1984 was unchanged. A bone scan in 1987 showed splenic activity consistent with splenic fibrosis and calcification.14

She was started on HU therapy in 1987 at the age of 20. At that time, her hemoglobin level was 6.3 g/dL and her HbF was 4.1%. Thirty months later, her HbF had increased to 30%. However, several months later, her HU therapy was discontinued because of cytopenia. Her hemoglobin level decreased to 6.0 g/dL from 9.4 g/dL. Her platelet count decreased to 35,000. Her absolute neutrophil count was 2,000. She was admitted to the hospital. During that admission, she presented with left upper quadrant pain and fever. No splenomegaly was noted on exam. A computer tomography (CT) scan of her abdomen showed an enlarged spleen with focal lesions, consistent with either nodular regeneration or abscesses. Splenectomy was performed because of the concern about the latter. Her spleen weighed 294 g. Microscopic examination showed cords filled with RBCs. Reactive germinal centers were also seen, consistent with

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active immune function. There was diffuse fibrosis. No extramedullary hematopoiesis was seen and neither was there any evidence of infection. HU therapy was not restarted.

**Patient no. 2.** Patient no. 2 is a 21-year-old man with SCA who was first seen at our institution at the age of 5. At that time, a 3-cm spleen was noted on physical exam. HbF was measured at the age of 7 and found to be 13.6%. Pit counts performed at this time were 4.7%. In 1981, at the age of 8, the HbF was noted to be 10.4% and a liver-spleen scan showed absent uptake of tracer. He received his first transfusion that same year and his spleen became somewhat smaller. He underwent two exchange transfusions in 1983 for priapism without significant change in his splenomegaly. His splenomegaly persisted until late 1988 (age 15). By January 1989, his spleen was no longer palpable. He received transfusions from January through May 1989 for priapism, as well as exchange transfusions in 1990 and 1991 for acute chest syndrome. His last course of transfusions was from May through November 1991 for aseptic necrosis of his hips. Despite these transfusions, his spleen remained undetectable by physical exam. A bone scan performed in 1991 showed minimal splenic activity, consistent with splenic fibrosis and calcification.¹⁴

In January 1992, he was started on HU therapy. His pretreatment hemoglobin level was 7.0 g/dL and his HbF was 7.0%. Within 6 months, his total hemoglobin level had increased to 11.0 g/dL and his HbF had increased to 25% to 30%. He was maintained on a dose of 17.0 mg/kg. His spleen was not palpable on multiple occasions. Twenty-four months after starting therapy, he was noted to have palpable splenomegaly, which has persisted for 36 months. Liver-spleen scans have shown splenic uptake, and pit counts have averaged 2.0%.

**DISCUSSION**

The morbidity associated with splenic autoinfarction is of great concern to providers who care for young patients with SCA. Although the use of prophylactic penicillin decreases the risk of overwhelming sepsis from encapsulated organisms,⁵ there are now ominous reports of prophylaxis failures due to penicillin-resistant strains.⁶

Splenectomy in SCA patients has previously been reported to be reversible. Pearson showed that five children with splenomegaly showed uptake on spleen scans after the level of hemoglobin S was reduced to less than 50% by transfusions.⁸ Wethers and Grover⁹ reported two young adults with elevated pit counts that transiently normalized after transfusions. Buchanan et al⁹ found that patients on an intensive hypertransfusion regimen had normal or only slightly increased pit counts and evidence of uptake on spleen scans. Recently, correction of splenic dysfunction in three sickle cell patients who underwent successful bone marrow transplantation has also been shown.¹¹

The exact mechanism of the HU-induced effect on the spleen is unclear. It is probably related to the chronic elevation of HbF and the resultant inhibition of sickling. This mechanism is also seen in these patients with SCA who have genetically elevated levels of HbF and who have splenomegaly as adults.¹⁷ It is unclear what duration of HU therapy might be required to improve splenic function. Patient no. 2 clearly developed splenomegaly after 24 months on therapy, and patient no. 1 developed splenic abnormalities on CT scan 29 months after the initiation of HU. However, pit counts and spleen scans were not prospectively obtained in these patients. Those patients with ongoing functional hyposplenism who receive this drug may require a shorter period of time to show improvement. It is also possible that patients with severely fibrosed spleens will not respond at all to this drug. A prospective study involving a larger group of patients is clearly warranted to answer these questions.

Transfusions have been the traditional modality for treatment of chronic complications of sickle cell disease. However, it is well known that the use of transfusions is fraught with problems, including iron overload, alloantibody formation, and infection.¹⁰ HU has now been used to treat complications such as leg ulcers and stroke when transfusions were unable to be administered.¹⁹,²⁰ The improvement in splenic function in response to this drug suggests that other organ systems that are damaged by the effects of SCA may also respond favorably to the effects of prolonged elevations in HbF.

The reversal of splenic dysfunction induced by HU in young adults suggests that serious consideration should be given to administering this drug to young children. As in previous studies with transfusions, these are the patients with the greatest chance of reconstitution of splenic function. In fact, early HU therapy might potentially prevent functional hyposplenism in this group of patients. If this were the case, it might obviate the need for prophylactic antibiotics. Further studies of this drug would also be aided by measurements of immune function before and after therapy.

Finally, as HU use increases in SCA, more patients will receive the drug chronically. This may result in an increased incidence of splenomegaly and functional hyposplenism. Therefore, it is important for providers who care for these patients to evaluate the possibility of splenic infarct or sequestration in those patients who present with left upper quadrant pain. This is especially important in those older patients who have been on long-term therapy and who would otherwise not be at risk for this complication.

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