

Indications for Successful Iron Overload Treatment and Monitoring: Sickle Cell Disease

Mariane de Montalembert, MD

Patients with sickle cell disease often require episodic or chronic blood transfusions starting in childhood to increase oxygen-carrying capacity in severely anaemic patients and/or to restore blood flow by replacing sickle red cells with normal cells. Episodic transfusions treat disease complications such as acute splenic sequestration, hyperhaemolysis due to acute infection, stroke, and multiorgan failure. Chronic transfusion are mostly used in children to prevent primary and recurrent strokes, and in adults to prevent chronic organ damage and recurrent painful crises.

Although the transfused red blood cells reduce morbidity and mortality in patients with sickle cell disease, each unit transfused increases the total iron load of these patients. A 2001 study found that 62% of enrolled adults with sickle cell disease received transfusions and at a rate of 10 units of red blood cells per year, adding 2 g of iron to their total iron load.

The pathophysiology of iron overload in sickle cell disease is not well known. Whereas there are many studies of the cardiac, hepatic, and endocrine morbidity and mortality of iron overload in the setting of thalassaemia, there are little data on the clinical consequences of iron overload in sickle cell disease. Few studies performed in the setting of sickle cell disease have study patients who have been transfused for more than 10 years. Lacking more data, it is difficult to conclude whether iron overload has the same consequences in patients with sickle cell disease as in patients with thalassaemia, but there is no reason to assume the consequences would not be the same. In the near future, we will likely be better positioned to address this question, as up to 10% of children with sickle cell disease will be chronically transfused to prevent neurologic complication, due to the findings of the Stroke Prevention Trial in Sickle Cell Anemia (STOP).

The evaluation of iron overload is challenging. Liver biopsy is an invasive technique, and, furthermore, it has been shown that multiple ferritin measurements are more

valuable in predicting complications of iron overload than a single liver biopsy. A single ferritin measurement is influenced by any concomitant inflammatory or infectious episode, however. The magnetic resonance imaging (MRI) relaxation parameters T2 and T2* have been shown to correlate with iron overload (a low cardiac T2* value means a high cardiac iron) and with left ventricular ejection fraction. Most probably, MRI assessment of hepatic and cardiac iron will become the next gold standards for the evaluation of iron burden in transfused patients.

Options for iron chelation for patients with sickle cell disease include desferrioxamine and deferasirox. Desferrioxamine is administered via subcutaneous injection. Due to its short half-life, infusion over 8 to 12 hours, 5 to 7 days a week is necessary. In contrast, deferasirox is a once-daily oral agent. Deferasirox is indicated for patients older than 2 years of age when desferrioxamine is inadequate or contraindicated. Chelation therapy typically begins after 20 units of packed red blood cells have been transfused or when serum ferritin equals or exceeds 1000 ng/mL.

In an open-label phase II trial comparing desferrioxamine and deferasirox, 195 adult and paediatric patients were randomized 2:1 to deferasirox and desferrioxamine, respectively. At 1 year, dose-dependent reductions in liver iron concentration were similar between the two groups. Discontinuations also were similar. Deferasirox is generally well tolerated, with mild to moderate transient gastrointestinal disturbance and rash among the common adverse events. Postmarketing safety reports, however, warn about the potential for renal, hepatic, and haematologic toxicity. Clinicians should monitor serum ferritin, as well as renal and hepatic function, during therapy.

Suggested Readings

Adams RJ, Brambilla D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. *N Engl J Med.* 2005;353:2769-2778.

Adams RJ, McKie VC, Brambilla D, et al. Stroke prevention trial in sickle cell anemia. *Control Clin Trials.* 1998;19:110-129.

Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med.* 1998;339:5-11.

- Ballas SK. Iron overload is a determinant of morbidity and mortality in adult patients with sickle cell disease. *Semin Hematol.* 2001;38(1 suppl 1):30-6.
- Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. *Blood.* 2006;107:3455-3462.
- Fung EB, Harmatz PR, Lee PD, et al. Increased prevalence of iron-overload associated endocrinopathy in thalassaemia versus sickle-cell disease. *Br J Haematol.* 2006;135:574-582.
- Ohene-Frempong K. Indications for red cell transfusion in sickle cell disease. *Semin Hematol.* 2001;38(1 suppl 1):5-13.
- Porter JB. Concepts and goals in the management of transfusional iron overload. *Am J Hematol.* 2007;82(12 suppl):1136-1139.
- Rosse WF, Gallagher D, Kinney TR, et al. Transfusion and alloimmunization in sickle cell disease. The Cooperative Study of Sickle Cell Disease. *Blood.* 1990;76:1431-1437.
- Telfer PT, Prestcott E, Holden S, Walker M, Hoffbrand AV, Wonke B. Hepatic iron concentration combined with long-term monitoring of serum ferritin to predict complications of iron overload in thalassaemia major. *Br J Haematol.* 2000;110:971-977.
- Vichinsky E, Butensky E, Fung E, et al. Comparison of organ dysfunction in transfused patients with SCD or beta thalassemia. *Am J Hematol.* 2005;80:70-74.
- Vichinsky E, Onyekwere O, Porter J, et al. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. *Br J Haematol.* 2007;136:501-508.
- Wood JC, Tyszka JM, Carson S, Nelson MD, Coates TD. Myocardial iron loading in transfusion-dependent thalassemia and sickle cell disease. *Blood.* 2004;103:1934-1936.