Iron Chelation in Thalassemia Major

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ABSTRACT

Purpose: Iron chelation has improved survival and quality of life of patients with thalassemia major. there are currently 3 commercially available iron-chelating drugs with different pharmacokinetic and pharmacodynamic activity. The choice of adequate chelation treatment should be tailored to patient needs and based on up-to-date scientific evidence.

Methods: A review of the most recent literature was performed.

Findings: The ability of the chelators to bind the redox active component of iron, labile plasma iron, is crucial for protecting the cells. Chelation therapy should be guided by magnetic resonance imaging that permits the tailoring of therapy according to the needs of the patient because different chelators preferentially clear iron from different sites. Normal levels of body iron seem to decrease the need for hormonal and cardiac therapy.

Implications: The 3 chelators currently available have different benefits, different safety profiles, and different acceptance on the part of the patients. Good-quality, well-designed, randomized, long-term clinical trials continue to be needed. (*Clin Ther*. 2015;37:2866–2877)

Key words: Thalassemia major, iron overload, iron chelators, labile plasma iron.

INTRODUCTION

The β-thalassemia syndromes are a group of hereditary blood disorders characterized by reduced or absent β-globin synthesis, resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals. Thalassemia major (TM) is the homozygous, transfusion-dependent form. The worldwide annual incidence of symptomatic individuals is estimated at 1 in 100,000.[1]

The clinical forms of thalassemia that do not require regular transfusions for survival are the non–transfusion-dependent thalassemias, including β-thalassemia intermedia, hemoglobin E β-thalassemia, and hemoglobin H disease.

TM and Iron

The anemia of TM becomes symptomatic in early childhood, usually between 6 months and 2 years of age, and requires regular blood transfusions. A regimen maintaining pretransfusion hemoglobin concentrations of 9.5 to 10.5 g/dl prevents the main complications of the disease (delayed growth and puberty, facial anomalies, hepatosplenomegaly) at the price of a mean intake of approximately 0.40 mg/kg per day of iron. A patient who receives 25 to 30 U of blood a year, by the third decade of life, in the absence of chelation, will accumulate >70 g of iron.

In addition to the iron transfused, iron absorption from the gut contributes to the iron burden. Iron absorption is the main cause of iron overload in thalassemia intermedia. In fact, the high erythropoietic drive causes severe hepcidin deficiency that, in turn, results in hyperabsorption of dietary iron.

Non–transferrin-bound iron (NTBI), and in particular its redox active component labile plasma iron (LPI), appears in plasma when approximately 70% of transferrin is saturated. LPI is believed to be responsible for catalyzing the formation of reactive radicals in the circulation of iron overloaded individuals, inducing peroxidative injury to the phospholipids of lysosomes and mitochondria, as indicated in vitro and in experimental animal studies.[2] In addition to transfusional iron load, ineffective erythropoiesis is considered to be responsible for the generation of NTBI.

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Iron, if untreated, causes considerable morbidity in most organs and ultimately leads to death.[3] Even osteoporosis appearing in adolescents and adults is thought to be related to iron overload, and the molecular basis for this phenomenon is now unfolding.[4] Heart disease, however, is the most serious consequence of iron overload and represents the first cause of death in more than half of the patients.[5] Iron is believed to enter into cardiomyocytes via the L-type Ca2+ channels.[6]

The distribution of iron loading in various organs depends in part on differences in iron-regulatory proteins. The liver can take up iron rapidly from the circulation via both transferrin- and non–transferrin-mediated processes and, similarly, can unload it via the iron exporter ferroportin, which is abundant in liver cells. The heart and endocrine glands, like the pancreas, conversely tend to take up iron only when there is circulating NTBI, whose level increases when the liver is loaded. The unloading from the heart, which contains very little ferroportin, is 4 times slower.[7]

Other hemoglobinopathies and chronic hemolytic anemias (eg, sickle cell disease, congenital dyserythropoietic anemias, and Blackfan-Diamond anemia) may also require iron chelation.

Monitoring Iron Overload

Accurate assessment of the iron accumulated is necessary to evaluate iron overload and need and efficacy of chelation therapy. Transfusional iron intake should be monitored on an ongoing basis when trying to achieve neutral or negative iron balance. Serum ferritin testing is widely available and is the least expensive way of measuring iron stores. Despite the fact that it is an acute-phase reactant and can be influenced by inflammation, liver disease, and vitamin C status, ferritin remains a satisfactory parameter of liver iron concentration (LIC) and a good predictor of cardiac response to chelation.[8] It has recently been proven to be a predictive factor for progression to endocrine dysfunction, allowing intensification of chelation and reversal of hypothyroidism.[9]

The use of magnetic resonance imaging (MRI) to measure tissue iron has had a remarkable effect on the assessment of the efficacy of iron chelators and the understanding of the pathophysiology of iron overload. The results can be reported as R2 and R2* or as their reciprocal T2 and T2*.[10–12] T2* cardiovascular magnetic resonance provides robustly validated, reproducible measurements of myocardial iron. T2* values of the interventricular septum >20 msec are considered normal, whereas values <10 msec are considered a sign of severe accumulation.[12] A validated MRI, multisection, multiecho T2* technique for global and segmental measurement of iron overload in the heart is in use in most Italian centers.[11]

The liver represents the primary iron storage site; therefore, measurement of LIC reflects total body iron stores. Liver biopsy used to be considered the gold standard for measuring LIC. However, this is an invasive procedure, and MRI is used instead whenever possible. LIC, however, does not consistently correlate with cardiac iron and therefore cannot be the only parameter used to predict the risk of cardiac disease.[12] MRI of the pituitary gland and pancreas are now often being performed. The results are predictive of hypogonadism and, for pancreas, of β-cell toxicity and cardiac iron loading.[13,14] Other devices also based on magnetic iron detection are available in a few centers.

Chelation

To prevent hemosiderosis, iron needs to be chelated and excreted in an amount equal or greater than that introduced by transfusion. In addition, the circulating LPI needs to be bound by a chelator to prevent free radical formation and lipid peroxidation. Three iron chelating agents are currently commercially available: deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX).

DFO* is the first chelating agent that became available. It was introduced in clinical use in the 1960s and was approved by the Food and Drug Administration in 1982. It has a large molecular weight and a short plasma half-life and therefore requires subcutaneous administration by means of a portable pump or intravenous administration in case of cardiac dysfunction and gross iron overload. The suggested dose is 40 to 50 mg/kg per day at least 5 times a week for 8 to 10 hours. DFO is mainly excreted through urine, although some patients may reach a 40% fecal excretion. On cessation of DFO infusion, NTBI reappearance is rapid, and therefore the protection is incomplete.

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