FROM CHILD TO ADULT ON THALASSEMIA MANAGEMENT

Ali Taher

American University of Beirut, Lebanon

Introduction

Thalassemia is an inherited disorder characterized by reduced or absent hemoglobin synthesis. The pathophysiology stems from the imbalance between the alpha and beta chains. The alpha and beta chains in a normal red blood cell (RBC) should precisely match each other. The degree of mismatch produces three distinct clinical phenotypes. Beta thalassemia minor or trait is the asymptomatic, carrier form. Beta-thalassemia major is characterized by need for life-long transfusion and chelation therapy for survival. Beta-thalassemia intermedia falls in between. In beta-thalassemia, underproduction of the beta chains causes excess, unstable alpha chains to deposit in the RBC, thus producing oxidative damage to the membrane and subsequent lysis of the cells – this is ineffective erythropoiesis [1]. This will cause the bone marrow to hypertrophy, resulting in characteristic deformities of the skull and face. Cortical thinning and pathological fractures are also common [2, 3]. The primary determinant of the anemia is the degree of ineffective erythropoiesis rather than the degree of hemolysis, which only plays a secondary role [4]. Instead, hemolysis is linked to the hypercoagulable state in thalassemia [5] leading to silent infarcts [6] and pulmonary hypertension. The anemia and the ineffective erythropoiesis will increase intestinal iron absorption leading to iron overload, which causes heart failure, endocrine abnormalities and others. Thus, ineffective erythropoiesis, chronic hemolysis, and iron overload are the factors behind all the complications of thalassemia.

Iron overload

Pietrangelo [7] compared the process of iron regulation to that of glucose regulation. Even though our precise knowledge of the elements involved in iron regulation is still quite lacking, this simile holds in many aspects, with hepcidin being the counterpart of insulin. Iron is controlled by a negative feedback loop. Inflammation and excess plasma iron, just like excess glucose, is a stimulant for the transcription of hepcidin. Hepcidin interacts with ferroportin - the iron exporter - on the basolateral surfaces of hepatocytes and the intestinal epithelium and causes its internalization and degradation [8]. This traps iron inside the cells and makes it less available in the blood stream. In the hepatocytes, macrophages, and other cells of the reticuloendothelial system, it is stored in its ferritin-bound form for later use, just like glycogen. In the endothelial cells, intracellular iron is shed with the shedding of the epithelium. Hypoxia, anemia, and a demand for erythropoiesis suppress hepcidin, making more iron available for the bone marrow through increased intestinal absorption and better recycling of catabolic iron from the reticuloendothelial system [9]. In fact, the ineffective erythropoiesis is an unrelenting signal to downregulate hepcidin by increasing expression of growth differentiation factor 15 (GDF15) and hypoxia-inducible transcription factors (HIFs) [9], thus dumping more iron in the plasma through increasing intestinal absorption and depleting the macrophages of their iron stores. After all the iron saturates the transferrin stores, it is transported as the toxic non-transferrin-bound-iron. The end result is deposition in the parenchyma of the liver, heart, endocrine organs, and others. Coming back to the analogy, thalassemia intermedia is a lot like diabetes mellitus type 2. Hormonal failure, manifesting either as decreased secretion or as decreased sensitivity, is the culprit in both.

Body iron levels are usually assessed by ferritin values. However, studies have shown that ferritin underestimates the total iron burden in TI, or at least does not increase as much as TM [10]. For the same value of LIC, ferritin values in TI patients were significantly lower than TM patients. A proposed mechanism for this is that iron in transfused patients is preferentially distributed to the reticuloendothelial system, thus ferritin is more readily synthesized and exported [9]. This is in contrast to transfusion-independent TI patients, where the low hepcidin depletes the reticuloendothelial system of its iron stores, thus ferritin will be low. Other methods of evaluating body iron stores include determination of liver iron concentration by biopsy or more recently by non-invasive techniques such as R2 MRI.

Chelation therapy

There are currently three commercially available chelators. Desferrioxamine is the first one to be introduced. It is only available as infusion. It has a short half-life necessitating continues treatment via a pump to achieve good iron control. Deferiprone was the second chelator to be introduced. It is a three-times daily oral drug that has been only been approved as a second-line treatment. Particular concerns about deferiprone included the incidence of agranulocytosis among those patients using it.

Deferasirox was developed with the needs of a perfect iron chelator in mind: oral, once-daily administration, safe and efficacious. Iron excretion in DFX is through the fecal route. It was designed to have a long half-life for levels to be maintained within the therapeutic range over a 24-hour period. It can therefore provide 24-hour chelation coverage and binding of NTBI with once only daily administration.

The clinical experience of DFX included more than 7,000 patients investigated across several transfusion-dependent anemias. In a randomized phase 3 trial (EPIC) in 586 patients with TM, a DFX dose of 30 mg/kg/day was needed to significantly reduce LIC and serum ferritin. The efficacy of DFX doses of 20 or 30 mg/kg/day was comparable with that of 40-60 mg/kg/day of DFO infused 5 days/week. DFX was also shown to be effective at reducing iron burden in patients who were heavily iron overloaded at baseline and who eventually required dose escalation to >30 mg/kg/day. DFX has demonstrated long-term (5 year) dose-dependent efficacy in both adult and pediatric patients and was recently shown to be associated with improvement in iron-related hepatic pathology. DFX has been associated with greater patient satisfaction and adherence to therapy, and increased time available for normal activities when compared to DFO.

DFX has been found effective in removing iron from the heart in patients with baseline T2* 5-10 ms (severe) and T2* 10-20 ms (mild-to-moderate iron loading). Among 71 patients with varying degrees of cardiac siderosis, cardiac T2*significantly improved from a mean of 12.0 to 17.1ms over a 3 year period. LVEF in these patients was normal at the start of the study and did not change. Another study (US04), however, showed that monotherapy with DFX was effective in chelating cardiac iron in patients with mild to moderate hepatic iron stores but failed to significantly remove cardiac iron in patients with severe hepatic iron burden [11]. Effect of iron chelation of liver fibrosis has also been studied in a recent study. DFX has been to shown to stabilize or improve liver fibrosis Ishak score in 82.6% of patients [12].

Thalassemia Intermedia

Iron overload is also a problem in thalassemia intermedia. Thalassemia intermedia accumulate iron by increased absorption through their gastrointestinal tract mainly. Iron in these patients can accumulate and has been associated with multiple morbidities. Despite the lack of guidelines, one must keep a close check on iron levels in these patients and use the same methods described for thalassemia major to monitor the iron and chelate it once it reaches certain levels [13, 14]. DFX has also been studied in patients with thalassemia intermedia and has been shown to be correlated with decreased LIC with a good safety profile.

Safety monitoring

In general, DFX has shown a favorable safety profile at high doses (>30 mg/kg/day), and in patients achieving serum ferritin levels <1000 µg/l (Table 4B). Side-effects do not appear more frequent or severe at low iron levels but we recommend discontinuation when the serum ferritin is <500ug/l [11]. The main side effects are gastrointestinal and are usually mild. Other side effects include skin rash, renal changes, changes in liver transaminases and ocular and auditory changes. For that, serum creatinine should be monitored before initiating therapy, then regularly during the course of therapy and at every dose change. Liver function tests and auditory and ophthalmic functions should also be monitored at the start of therapy, then regularly thereafter.

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