

Indications for Successful Iron Overload Treatment and Monitoring: Thalassaemia

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Patients with thalassaemia major require chronic transfusions from an early age in order to prevent the complications of anaemia and dysfunctional erythropoiesis. Although these transfusions are lifesaving, each unit of red blood cells contains 200 mg iron and this increased iron becomes iron overload after 10 to 20 transfusions. In patients with thalassaemia intermedia, for whom the need for transfusion is much less frequent compared with patients with thalassaemia major, iron overload occurs primarily due to increased gastrointestinal absorption of iron. Iron stores in these patients increase slowly over time, and consequences to overload may not be noted until late in life.

The goals of chelation therapy in patients with thalassaemia are to prevent accumulation of harmful levels of body iron, prevent tissue damage, remove stores of present iron overload, and minimize toxicity from excess chelation. The increasing efficacy of chelation therapy has significantly improved patient survival. Survival data from six birth cohorts followed chronologically since 1960 demonstrate decreasing mortality rates over time, primarily due to better management of iron overload.

Chelation therapy should be started before iron accumulation is excessive. For patients with thalassaemia major, this is typically after 10 transfusions, when serum ferritin levels exceed 1000 ng/mL, or when liver iron concentration (LIC) exceeds the normal range of the methods used. For patients with thalassaemia intermedia who receive 0 to 4 units per year, iron overload should be assessed with serum ferritin, transferrin saturation, and LIC. Urinary iron excretion (UIE) may be used if LIC is not available. Patients with transferrin saturation constantly greater than 60% and LIC greater than 4 mg/g dry weight (or UIE greater than 3 mg/24 h) should start iron chelation therapy.

Three agents are indicated for the treatment of thalassaemia: desferrioxamine (subcutaneous, 8- to 12-hour infusion, 5–7 days/week), deferasirox (once-daily oral dosing), and deferiprone (thrice-daily oral dosing). In cases of iron overload due to infrequent transfusion, deferasirox may be used only if desferrioxamine is inadequate or contraindicated. Likewise, deferiprone is also indicated only if desferrioxamine is inadequate or contraindicated.

Chelation therapy should aim for iron balance, in which the iron loaded via transfusions equals iron excreted via chelation. Too much iron results in uncoordinated iron, free-radical generation, organ damage, growth failure, organ failure, and cardiac death. Too much chelator results in uncoordinated chelator, inhibition of metalloenzymes, neurotoxicity, organ failure, and bone marrow toxicity. To ensure iron balance, patients must be monitored throughout therapy by ferritin, transferrin saturation (for thalassaemia intermedia), and LIC measurements.

Aggressive chelation therapy is indicated for patients with serum ferritin values persistently greater than 2500 ng/mL, LIC levels greater than 15 mg/g dry weight, significant cardiac disease, or active hepatitis C, and for patients planning a pregnancy or bone marrow transplant.

Various recommendations, standards, and guidelines on managing iron overload are currently in existence. Most are based on transfusion-dependent thalassaemia. No single comprehensive guideline exists, however, for managing iron overload in thalassaemia, sickle cell disease, or myelodysplastic syndromes. A growing number of health authorities are using guidelines and evidence-based data to determine reimbursement of drug costs. Thus, there is a need to produce guidelines, which include recommendations on oral chelation therapy.

Suggested Readings

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