Review
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Role Of Iron Chelation In Thalassemia And Iron Overload

Shachi Jain Taran[1], Rakesh Taran[1]

Abstract

Beta Thalassemia major is a hereditary disease known long back in areas where malaria is endemic. In India more than 20000 children are born each year with this disease. Though regular blood transfusion is an effective treatment for the disease but has acted as double edged sword. One side it has given long term survival benefit to the patient on the other hand patient also has to face problem of iron overload. To combat this problem we already have a well-known chelating agent –Deferoxamine. Now newer agents are also being used like deferiprone, deferasirox and wheatgrass. Most of the studies for these agents are largely done in India and found satisfactory results. Deferoxamine still remains single most effective chelating agent. Studies on combination therapy are showing better results than any single agent alone.

Keywords: Iron chelation, iron overload, thalassemia

Introduction

β-Thalassemia major is a hereditary disease characterized by anemia due to ineffective erythropoiesis [1]. Its prevalence is highest in areas where malaria is (or was) endemic, confirming its role as an evolutionary protective mechanism [2]. About 5% of the world's population has a globin variant and 1.7% has α- or β-thalassemia trait. Thalassemia affects men and women equally and occurs in approximately 4.4 per 10,000 live births. In India, it is estimated that there are about 50–60 million careers of thalassemia trait and more than 20,000 children are born every year with thalassemia major [3,4]. The majority of these do not witness their first birthday. To remain alive, such patients require regular red blood cell transfusion that leads to secondary iron overload and are, in turn, dependent on proper iron chelation to maintain health. Marwah has estimated that in India, 2 million units of packed red cells are required for transfusion to thalassemic patients [5]. It is ideally recommended that iron chelation should start as soon as the first transfusion is given. The Thalassemia International Federation guidelines (2008) advise that it should be commenced after 10–15 transfusions or when the serum ferritin levels are above 1000 ng/ml [6]. Common iron overload–related complications include endocrine complications, dilated cardiomyopathy, liver fibrosis/cirrhosis and related problems [6]. The first centers for care of thalassemia were probably started in Mumbai in early 1970s in JJ Hospital and KEM Hospital. The first bone marrow transplant center in India was also established at Tata Memorial Hospital, Mumbai in 1983 [7]. The International Thalassemia Federation (ITF), Indian Red Cross Society, and parents' associations [e.g. Thalassemics India, Federation of Indian Thalassemics (FIT)] have played an important role in improving the care of thalassemics in India [3]. Today there are more than 60 such support groups (parent/patient societies) for thalassemia in India. In fact, the Government of India has specifically included the care and management of thalassemia into its 12th Five Year Plan [3]. As a result, patients with thalassemia major who receive optimal care in India now survive to adulthood [8]. In fact, several of them have even got married (Parikh PM, personal communication) and continue to enjoy a productive life in society beyond the age of 40 years. To ensure that this translates into reality for the majority of patients with thalassemia major, we need to focus on the problems and management of iron overload.

[1]Department of Pediatrics, SAIMS, Indore ,MP.
[2]Department of Medical Oncology, SAIMS, Indore , MP.

Address of Correspondence
Shachi Jain Taran,
201 Sanskriti Apartment,
44 Saketnagar,
Indore, MP, India.
Email – shachitaran@yahoo.co.in

Consequence of Untreated Iron Overload

The excess iron is processed by macrophages which digest erythrocytes and return the iron to transferrin in the plasma. When transferrin becomes saturated, iron concentrations cross the tipping point, leading to the formation of non–transferrin-bound iron (NTBI) in the plasma, which is then quickly taken up by hepatic and other specific parenchymal cells leading to their compromised function [9]. If left untreated, this iron overload will impact on physical growth, endocrine function, and bone density [9,10]. Several investigators have studied growth in thalassemic children, and several others have reported on pubertal development and endocrinal function. Abnormalities of beta-cell function and diabetes mellitus have also been explored.[11] Significant effects of the disease on growth as well as pubertal growth occur only when effective iron chelation is not provided. At this stage, it is prudent to mention that comprehensive management includes interventions beyond iron

Table 1: Comparison of serum ferritin levels in the three groups

	Serum ferritin levels (ng/ml)		
Group	*Mean before chelation*	*Mean after chelation*	*Change/difference*
I	5077.18	3718.30	Fall of 1358.87
II	2672.90	3422.65	Rise of 749.75
III	3347.78	3376.57	Rise of 28.79

desferrioxamine, deferiprone and in combination on iron chelation in thalassemic children. Indian Pediatr 2004;41:21-7
P = 0.00253 when comparing Group I with Group II
P = 0.00253 when comparing Group I with Group II

chelation. For instance, Mamtani et al. carried out a meta-analysis of bone recovery after zoledronate therapy in thalassemia-induced osteoporosis [12]. Vitamin C is also used to augment the effect of iron mobilization. To prevent toxicity of the liberated iron, vitamin C dose should be restricted to 2–3 mg/kg/day.

Iron Chelation

The Thalassemia International Federation guidelines (2008) advise that iron chelation should be commenced after 10–15 transfusions or when the serum ferritin levels are above 1000 ng/ml [6]. Establishing effective iron chelation therapy requires careful monitoring and assessment of iron overload, tailored to the individual patient's specific needs. Patients in the early transfusion period with a known transfusion history should have serum ferritin levels determined every 1–2 months in order to have a baseline value of iron load to be used for initiating iron chelation therapy. Certain subgroups need additional attention [13-15].

1. For patients <3 years of age, careful monitoring of growth and bone development is advised during iron chelation therapy.
2. Patients aged >5 years with an unknown previous transfusion history and/or inappropriate chelation therapy should have both serum ferritin and liver iron concentration (LIC) determined in order to plan iron chelation therapy. LIC should be repeated every year while receiving chelation therapy.
3. Cardiac function is usually monitored by documenting ejection fraction.
4. In patients with a poor chelation history or in whom LIC documents non-optimal chelation therapy, heart iron content should be monitored every year using cardiac magnetic resonance imaging (MRI) (T2*). This requires use of the gradient-echo T2* method wherein values <20 ms indicate increased myocardial iron and are associated with an increased chance of decreased left ventricular function [5] and development of arrhythmia. If the value of T2* falls to <10 ms, there is a high association with the development of heart failure[6].
5. A liver biopsy should be performed in case the serum ferritin levels deviate from the expected trends, if there is co-existent hepatitis, or if there is an uncertain response to chelation. The additional baseline tests required before starting iron chelation therapy are serum creatinine and creatinine clearance, serum transaminases and bilirubin, as well as auditory and ophthalmic examinations. While on iron chelation, if the serum ferritin falls consistently below 500 mcg/l, temporarily interrupting the chelation agent needs to be considered. The aim is to adjust the dose to keep the therapeutic index less than 0.025 at all times using the formula: mean daily dose (mg/kg)/ferritin (g/l), where mean daily dose = (actual dose received on each day of desferrioxamine infusion doses per day/7) [16]. Iron chelation is possible with three commercially available agents – deferoxamine (Desferal or DFO), deferiprone (L1 or Kelfer), and deferasirox (Exjade, ICL670) [17-23].

Deferoxamine

In the early years, DFO was the only one chelating agent available and has been in use since four decades. Its disadvantages are that it has to be given intravenously over many hours using a pump, is expensive, and compliance is poor. It is a hexadentate chelator that binds iron tightly, and the iron–DFO complex is excreted in both urine and stool. DFO is administered as long parenteral infusions because the plasma half-life is short (minutes) and it is not active orally. Thus, it is given as an overnight subcutaneous infusion for 5–7 nights/week. The DFO–iron chelate is charged and does not readily enter and leave cells [4]. Parenteral administration and the daily nuisance of an infusion pump hinder optimal compliance (ellis ref). Desferal is supplied as vials containing 500 mg and 2 g of DFO mesylate USP in sterile, lyophilized form [20-23]. For subcutaneous administration, a daily dose of 1000–2000 mg (20–40 mg/kg/day) should be administered over 8–24 h utilizing a small portable pump capable of providing continuous mini-infusion. The duration of infusion must be individualized. In some patients, as much iron will be excreted after a short infusion of 8–12 h as with the same dose given over 24 h. Final concentration of the solution to be injected should be 95 mg/ml. Intravenous administration is possible in patients with intravenous access. The standard dose is 20–40 mg/kg/day in children and 40–50 mg/kg/day over 8–12 h in adults for 5–7 days/week. In children, the average doses should not exceed 40 mg/kg/day until growth has ceased. In adults, the average doses should not exceed 60 mg/kg/day. The intravenous infusion rate should not exceed 15 mg/kg/h. Final concentration of the solution to be injected should be 95 mg/ml. In patients who are poorly compliant, Desferal may be administered before or following blood transfusion on the same day (e.g. 1 g over 4 h on the day of transfusion); however, the contribution of this mode of administration to iron balance is limited. Desferal should not be administered concurrently with the blood transfusion as this can lead to errors in interpreting side effects such as rash, anaphylaxis, and hypotension. For intramuscular administration, a daily dose of 500–1000 mg may be used. The total daily dose should not exceed 1000 mg. Final concentration of the solution to be injected should be 213 mg/ml.

Deferiprone

This drug was discovered by George J. Kontoghiorghes and was designed and developed by academic initiatives [24]. Indian scientists and patients contributed immensely to the clinical trials with L1 [19-25]. It was finally approved for use in India in 1994 and in Europe in 1999. It is being used extensively in India and other developing countries. However, it causes joint pain in some patients. Thousands of patients are now treated with L1 worldwide. Deferiprone (Ferriprox and others) is an orally active hydroxypyridinone that was first used in humans in 1987. Deferiprone is a bidentate chelator (three molecules surround one iron ion). An advantage of this compound is that the iron (III) chelate of deferiprone carries no net charge and, therefore, can penetrate the membranes easily, allowing removal of potentially toxic iron from the tissues. Idiosyncratic side effects that are potentially severe include erosive arthritis (common in patients in South Asian countries, incidence from 5% to >20%) and neutropenia (in up to 5% of patients). Typical dosage for deferiprone is 75 mg/kg/day in three divided doses, up to 100 mg/kg daily.

Deferasirox

This belongs to the N-substituted bis-hydroxyphenyltriazole class of oral tridentate chelator [18,22,26-29]. With a plasma half-life of 8–16 h, once-daily dosing permits the circulating drug at all times to scavenge non–transferrin-bound "labile plasma iron," the chemical species responsible for tissue damage in iron-overloaded subjects by means of toxic oxygen intermediaries. Deferasirox–iron complexes are excreted in the stool. The agent is available as 125, 250, and 500 mg dispersible tablets. It is not to be chewed or taken whole. It must be dissolved in water and taken as a suspension. The recommended initial dose of Exjade for patients 2 years of age and older is 20 mg/kg body weight orally, once daily. Calculate doses (mg/kg/day) to the nearest whole tablet. This dose stabilizes serum ferritin levels and LIC. A higher dose of 30 mg/kg/day reduces serum ferritin and LIC and achieves negative iron balance. After commencing therapy, monitor serum ferritin levels monthly and adjust the dose of Exjade, if necessary, every 3–6 months based on serum ferritin trends. Make dose adjustments in steps of 5 or 10 mg/kg and tailor adjustments to the individual patient's response and therapeutic goals. In patients not adequately controlled with doses of 30 mg/kg (e.g. serum ferritin levels persistently above 2500 mcg/l and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered. Doses above 40 mg/kg are not recommended. If the serum creatinine increases by 33% or more above the average baseline measurement (all ages) or is greater than the age-appropriate upper limit of normal (in children 2–15 years of age), reduce the dose by 10 mg/kg. Discontinue therapy for serum creatinine greater than two times the age-appropriate upper limit of normal or for creatinine clearance <40 ml/min [18]. Efficacy of iron chelation has also been shown across various transfusion-dependent anemias including myelodysplastic syndromes, sickle cell disease, and other rare transfusion-dependent anemias.

Indian data

The first landmark publication on deferiprone was from India. Agarwal et al. published data on 52 patients with transfusion-dependent thalassemia major who were treated between August 1989 and May 1991 [19]. Deferiprone was given up to 21 months, with the mean fall in serum ferritin being 1465 μg/l after 5 months and 3641.2 μg/l after 20 months of therapy. Arthralgia as an adverse drug reaction was seen in 20 patients (38.5%), while minor gastrointestinal (GI) tract symptoms occurred in 7 (3.5%) cases. There was no evidence of neutropenia, thrombocytopenia, or ear or eye toxicity. Subsequently, several other Indian studies have studied the role of deferasirox in reducing the iron burden in patients with β-thalassemia who had received many blood transfusions [22,23,28,29]. One publication by Chandra et al. reported the use of deferasirox in 40 North Indian children with β-thalassemia major [22]. Previously, these patients had received deferiprone alone (37 patients) or deferiprone in combination with desferrioxamine (3 patients) before commencing deferasirox. Serum ferritin level was estimated at baseline and then every 3 months. Serum ferritin levels fell in 24 of 32 patients (75%) who received deferasirox for over 1 year, from a mean of 6323•37 μg/l to 5458•91 μg/l (P < 0•05). The therapy with deferasirox was well tolerated. Nausea, vomiting, and abdominal pain were observed in 25%, 20%, and 15% patients, respectively. Grayish-brown pigmentation of the skin seen in 4 (10%) children was their novel observation. Madan's group studied 30 thalassemic children, who had received more than 20 blood transfusions and a serum ferritin greater than 1500 ng/ml, in a randomized study [23]. These patients were divided into three groups with 10 patients each. Group I included children receiving subcutaneous DFX at a dose of 40 mg/kg/day over a period of 8–10 h for 5 days a week. Group II children were given oral deferiprone at a dose of 75 mg/kg/day in two to three divided doses daily, and Group III children received both the drugs – oral deferiprone and subcutaneous desferrioxamine (same dose and administration schedule as in groups I and II). The results are shown in Table 1. Therapy with DFO reconfirmed its efficacy as the best of the three groups of iron chelation in this study.[30,31] However, its difficult mode of administration and high cost of treatment are strong impediments to follow this therapy on a regular basis. There was a rise in serum ferritin values after 6 months of chelation with oral L1, which is in conformity with the results of few earlier workers [25,32]. This has been attributed to the rapid glucoronization of the drug in the liver, making it ineffective to chelate the stored iron in the body [14]. Deferiprone was found to only balance the iron input (due to blood transfusion) with its output (excreting urinary iron) in this study. A fall in serum ferritin values can only be expected after long-term use (at least 18 months) of the effective dose [19]. Its combination with DFO, on the other hand, results in the clearance of excess cardiac iron.

Wheatgrass

There are three studies of relevance to its use in thalassemia major [33-35]. In the study by Marwah et al., daily use of 100 ml of wheatgrass juice showed fall in transfusion requirement by >25% in 8/16 (50%) patients [33]. Singh et al. treated 40 patients of thalassemia major with wheatgrass tablets wherein the blood transfusion requirements fell by 25% or

more in 60% [34]. The mean interval between the consecutive blood transfusions also increased from 18.78 to 24.16 days. In contrast, the third study by Choudhary and colleagues did not find any significant benefit [35]. Unfortunately, no randomized studies have been conducted.

Iron chelation in non–transfusion-dependent thalassemia

Even in non–transfusion-dependent thalassemia (NTDT), iron overload is a problem. Ineffective erythropoiesis leads to very low hepcidin levels and significant increase in intestinal iron absorption and increased release of recycled iron from the reticuloendothelial cells [36]. This iron overload is typically slower than in patients who are dependent on transfusions. It results in accumulation of iron at the rate of 3–4 mg/day up to 100 mg/year. This is the equivalent of LIC of >5 mg Fe/g of dry weight and serum ferritin of >800 mg. Hence, chelation is required later, usually after the age of 10 years. Assessment of this iron overload is identical to that for thalassemia major dependent on transfusions for life. Fortunately, since the iron accumulation is lower and slower, use of deferasirox is more effective, as shown in a prospective study of 166 patients [37] Even its required dose is smaller. Treatment with other iron chelators in patients with NTDT has not been evaluated and cannot be recommended at present.

Systemic review

The German Cochrane group conducted randomized controlled trials comparing deferasirox with no therapy or another iron chelating treatment [38]. The placebo control showed that deferasirox leads to net iron excretion in transfusion-dependent thalassemia patients. Studies comparing deferasirox to standard treatment with DFO (one phase II study of 71 patients and another phase III study of 586 cases) confirmed the efficacy. Patient satisfaction was significantly better with deferasirox. The very next year, this data was updated to include 22 trials involving 2187 participants (range 11–586 people).[39] Efficacy evaluation showed that all three – desferrioxamine, deferiprone, and deferasirox – produced significant reduction in iron stores in transfusion-dependent, iron-overloaded people. The results also suggested an advantage of combined therapy with desferrioxamine and deferiprone over monotherapy. There was also a greater improvement in left ventricular ejection fraction (LVEF) than when desferrioxamine was used alone. If used in combination, the usually recommended ratio is 1 mg of deferasirox to 2 mg of DFO. Regular monitoring of white cell counts and liver and renal functions is recommended in patients on iron chelation. Patients on deferiprone should be specifically evaluated for joint pain, GI disturbance, increases in liver enzymes, and neutropenia. On the other hand, when deferasirox is used, increases in liver enzymes and renal impairment are the main concerns.

Conclusion

Thus, desferrioxamine remains the well-tested and most effective single agent first-line therapy for iron overload in people with thalassemia major. Deferiprone or deferasirox is indicated when desferrioxamine is contraindicated, inadequate, or rejected by the patients. Deferiprone alone is not a good chelator of iron, unless used for more than 18 months in ideal doses. Combination therapy is an effective, acceptable, and cheaper mode of chelation therapy, which may be utilized as a method of chelation in developing countries like India. People treated with all chelators must be kept under close medical supervision and regular monitoring. Cappellini et al. showed that a dose of 20–30 mg/kg/day of deferasirox can help most, but not all patients and maintain even or negative iron balance similar to that achieved by moderate doses of DFO [40]. Pennell et al. reported that deferiprone was able to improve the LVEF even in subclinical disease (with LVEF within normal ranges) [41]. Borgna-Pignatti et al. showed evidence that deferiprone is cardioprotective [42]. Subsets of patients with high iron intake will benefit from higher daily doses or twice-daily dosing of deferasirox. Deferiprone plus DFO appears to be the emerging "treatment of choice" for significant cardiac dysfunction from iron overload, as in vivo and in vitro evidences support the biochemical rationale [27,29,43].

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