IRON OVERLOAD IN ETA THALASSEMIA – A Review
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Abstract:
Due to improvements in transfusion therapy in beta-thalassemia major patients, transfusional hemosiderosis has now become the major cause of late morbidity and mortality in them. In India and other developing countries, iron chelation therapy is still not strictly adhered to in these children, mostly due to financial constraints. An orally effective and cheap iron chelator is the need of the hour in the treatment of beta-thalassemia major. With the advent of Deferasirox, there is new enthusiasm in this front. This review takes us through the mechanics of iron overload into the various therapies available at our disposal today and those that may be available tomorrow.

Key words:
Beta thalassemia major.
Iron overload.
Chelation therapy.
Deferoxamine mesylate.
Deferiprone.
Deferasirox

1. INTRODUCTION:
Beta thalassemia major was first described in 1925 by Thomas Cooley and Lee.¹ In those days, thalassemia major patients rarely used to survive the first decade of life. Following the introduction of regular transfusion regimens in the 1960’s, initially by Orsini, and later by Wolman and Piomelli, thalassemics survived into 2nd and 3rd decades.²,³,⁴,⁵ As a result of this improved survival due to transfusion therapy, the problems of transfusional hemosiderosis became conspicuous. Transfusional hemosiderosis is the major cause of late morbidity and mortality in patients with thalassemia major.⁶ Thus iron chelation therapy has a very important role in the management of a thalassemia major child. Since the late 1960’s deferoxamine (DFO) mesylate has been the “gold standard” iron chelator, improving the quality of life and prolonging the life of transfusion dependent thalassemics.⁷,⁸ But the need for daily parenteral infusions is an obvious disadvantage, decreasing compliance to therapy. Also, for patients in the developing countries, regular chelation with DFO is extremely expensive. An orally effective and cheap drug with good safety profile will be the ideal iron chelator. Deferasirox, though expensive at present, is an orally effective chelator with reasonably good safety profile, was approved by the FDA for transfusional hemosiderosis in children above 2 years of age.⁹ This and other investigational molecules like deferitrin, gives us hope regarding the effective management of iron overload in the thalassemics.

2. IRONS OVERLOAD IN ß-THALASSEMIA MAJOR- THE MAGNITUDE OF THE PROBLEM:
It is estimated that 1.5 % of the world population, i.e., 200 million people are carriers of the ß-thalassemia gene. In India, the mean prevalence of the ß-thalassemia gene is 3.3 %. 1,000 children are born with ß-thalassemia major each year in India. In these patients, iron deposition in parenchymal tissues begins within 1 year of starting the regular transfusions.¹ Most of the Government Medical College Hospitals in India give packed cell transfusions free of cost to thalassemia major patients. But there is no free supply of iron chelators and more than 80 % of the patients cannot afford regular iron chelation therapy. As each unit of
packed cells contain approximately 200 mg of iron, a patient who receives 25 units per year, accumulates 5 gram of iron per year in the absence of chelation. Add to this the increased intestinal iron absorption that is seen in these patients. By the beginning of the third decade, a thalassemia major patient in the absence of chelation would have accumulated 70 grams of iron.

The consequence of this is that vital organs like liver, heart, endocrine glands are loaded with iron and their function deteriorates progressively. Cardiac siderosis, manifesting as cardiac failure, arrhythmias, myocarditis, pericarditis, and myocardial infarction, is the leading cause of death in thalassemia major, accounting for 71 % of the deaths. Fibrosis of the liver correlates directly with the age, number of units transfused, and the liver iron concentration. Pubertal delay is seen in 55 % of the patients older than 15 years of age and stunted growth is seen in 33 % of the patients. In India, upto 42 % of the thalassemics have glucose intolerance as a consequence of transfusional hemosiderosis.

3. PATHOPHYSIOLOGY OF IRON OVERLOAD:
The iron deposits in thalassemics, who have received multiple blood transfusions, can exceed the storage and detoxification capacity of ferritin. Also the excess iron fully saturates transferrin. Consequently, "free" iron (or non-transferrin bound iron-NTBI) begins to accumulate in tissues and blood. This "free" iron can catalyze the formation of very injurious compounds, such as the hydroxyl radical (OH) from compounds such as hydrogen peroxide, which are normal metabolic byproducts (Fenton reaction). The hydroxyl radical is highly reactive, and attacks lipids, proteins and DNA. The initial reaction with each of these molecules is the formation of peroxides (e.g., lipid peroxides) that can interact with other molecules to form cross links. These cross-linked molecules perform their normal functions either poorly or not at all.

3.1. Lipids:
Peroxidation promotes cross links in membrane lipids, creating islands or domains of dysfunctional molecules. Cell membranes, which consist primarily of lipids, stiffen and acquire odd shapes. This is particularly problematic for red cells, which have no nucleus. Unlike most other cells, red cells cannot repair membrane damage. The red cells of patients with thalassemia or sickle cell disease loose the elasticity needed to pass through the microcirculation. These damaged red cells are removed by reticuloendothelial cells, most prominently in the spleen.

3.2. Proteins:
Protein cross linking can create protein clusters, particularly in membranes. Again; red cells are particularly susceptible to such damage, lacking membrane repair mechanisms. The cells of the immune system recognize these protein clusters as being abnormal. Antibodies to these clusters (termed "membrane senescence antibodies") promote removal of damaged red cells from the circulation. The result is enhanced hemolysis. Oxidation of band 3, the red cell anion transport channel, disturbs the osmotic balance of red cells and impairs their function.

3.3. DNA:
DNA cross-links can impair cell replication, leading to cell death. The degree of cross-linking produced by
reactive oxygen species in patients with iron overload generally is relatively small and probably relatively unimportant.

Red cells alone do not bear the brunt of the reactive oxygen species. Damage to cells of other organs start to accumulate within a year of commencing transfusion therapy. Hepatocytes are the major storage site for body iron. With iron overload, these cells are relentlessly bombarded by reactive oxygen species and eventually die. They are replaced by fibroblast cells. The collagen laid down by fibroblasts produces liver fibrosis and, eventually, cirrhosis. Likewise, cardiac cells are damaged with iron overload. Normal cardiac function requires the coordinate activity of all the cells in the heart. Damaged, poorly-functioning cells often fail in this regard. The clinical manifestations include congestive heart failure (due to injury to myocytes) and arrhythmias (due to damage to the cells of the cardiac conducting system).

3.4. Assessment of iron overload:
No measure of iron stores has been thoroughly and prospectively studied to establish levels predictive of iron related complications in patients with thalassemia major.

3.5. Liver iron concentration:
Liver biopsy with biochemical measurement of liver iron concentration has been the “gold standard” for assessing total body iron stores. Hepatic iron levels of 15 mg/g dry weight has been associated with a greater risk of iron induced heart disease. Ideally, a yearly testing of liver iron will give accurate estimation of total iron accumulation in a thalassemia major patient on regular transfusions and chelation therapy. However, being an invasive technique this is not practical.

3.6. Serum ferritin measurement:
This is a readily available test. But it has to be emphasized that a single estimation of serum ferritin level correlates poorly with hepatic iron concentration. Also, it is influenced by vitamin C deficiency (lowers ferritin) and hepatitis (increases ferritin), both of which are seen in thalassemics. But serial ferritin measurements are predictive of complications like iron induced heart disease.

3.7. Cardiac T2 MRI:
MRI measures tissue iron concentration indirectly via the detection of the paramagnetic influences of storage iron (ferritin and hemosiderin) on the proton resonance behavior of tissue water. MRI remains the only noninvasive modality in clinical use with the ability to detect cardiac iron deposition. T2 MRI is rapidly becoming the new standard for measuring cardiac iron levels. One study found that below a myocardial T2 of 20 ms, there was a progressive and significant decline in left ventricular ejection fraction (LVEF). In general, the lower the T2, the higher the risk of cardiac dysfunction, with a T2 <8 ms suggestive of severe iron overload.

T2 MRI can also be used to assess liver iron concentration. MRI provides a non-invasive alternative to liver biopsy, and may actually be more accurate in patients with heterogeneous liver iron deposition (such as those with cirrhosis) since it measures iron in the whole organ.

3.8. Superconducting quantum interference device (squid):
This imaging modality uses a very low-power magnetic field with sensitive detectors that measure the interference of iron within the field. Although SQUID is
still considered investigational, linear correlations have been demonstrated between SQUID measurements and liver biopsy LIC levels. The limited availability and high cost of this test currently restrict its use to research. In addition at present, it appears to underestimate liver iron concentration (LIC) values versus liver biopsy.

3.9. Other tests:
Endomyocardial biopsy, though gives an accurate estimate of cardiac iron, is rarely ever done in clinical practice.

Various laboratory tests have been developed to assess iron overload. While not widely available, they may hold promise of providing additional clinical information; like estimation of serum ferritin iron, serum transferrin receptor concentration and labile pool iron (LPI).

4. CHELATION THERAPY FOR IRON OVERLOAD:
Iron chelation therapy is inevitable to prevent the consequences of transfusional hemosiderosis in thalassemia major patients. Four decades of experience with deferoxamine mesylate has clearly demonstrated the following benefits of iron chelation:

1. Liver iron concentrations can be maintained at normal or mildly elevated levels.
2. Hepatic fibrosis can be prevented.
3. Iron induced cardiac disease can be markedly decreased.
4. Normal growth and sexual development can be achieved.
5. Long term survival is substantially improved.

5. OPTIMUM AGE FOR STARTING CHELATION THERAPY IN THALASSEMIA MAJOR:
This has not been established with certainty. The high concentration of liver iron found in some patients with thalassemia with in the first 2-3 years of transfusion therapy provides the rationale for early initiation of chelation therapy. However iron excretion in response to deferoxamine (DFO) is relatively low during the first few years of iron accumulation. Also, deferoxamine adversely affects bone development and growth in some young patients. Chelation therapy is usually begun when one of the following criteria is met;

1. Patient has received 100ml/kg packed cells, ie, approximately 10 – 15 units for a 15 kg child.
2. Serum ferritin exceeds 1000 μg/L.
3. When the child is 3 – 5 years old as DFO related growth impairment is less and significant iron excretion can be accomplished.
4. Liver iron concentration (measured 1 year after onset of regular transfusions) exceeds 7 mg/g dry weight of liver.

6. MECHANISM OF ACTION OF IRON CHELATORS:
Chelators protect cells from iron-mediated toxicity in two ways.

6.1. Removal of excess iron.
The most readily apparent mechanism by which chelators provide protection is removal of the excess iron from the body. Once the toxic iron is gone, the body's repair mechanisms can swing into action to correct damage that may have occurred. The ability of chelators to remove excess iron depends on (at least) two factors: (a) the rate at which the chelator depletes storage iron, and (b) the rate of continued iron accumulation.
Most patients with transfusional iron overload require transfusions indefinitely. Since each unit of blood deposits about 230 mg of iron, most patients who require, for instance, 2 units of blood per month will have at most a very slightly negative iron balance with chelation therapy. The most widely used iron chelator, desferrioxamine, removes somewhere between 30 and 70 mg of iron per day. Protection of patients with ongoing transfusion requirements solely by removal of excess iron is uncommon.

6.2. Neutralization of "free" iron
The tight binding of chelators to iron blocks the ion's ability to catalyze redox reactions. Iron ions have six electrochemical coordination sites. Consequently, a chelator molecule that binds to all six sites completely inactivates the "free" iron. Such chelators are termed "hexidentate", of which deferoxamine is an example. With some chelators, a single molecule interacts with only two of the coordination sites on iron. These chelators are called, "bidentate". An example of this type of molecule is deferiprone. Three molecules coordinate with a single iron ion to produce complete chemical immobilization. Deferasirox, the newest chelator approved by the FDA, is a "tridentate" chelator.

Since neutralization of free iron is essential to protect cells, a molecule such as deferoxamine has the advantage of inactivating iron as part of a 1:1 molecular complex. On the other hand, bidentate chelators (C) can produce partial reaction products with iron (Fe):

1. Fe(C) [redox reactive]
2. FeC_2 [redox reactive]
3. FeC_3 [inactive]

With a bidentate iron chelator, a spectrum of chemical species will exist, of which a minority is inactive. A large chemical excess of chelator is needed to push the reaction toward completion, the formation of the FeC_3 (inactive) product.

7. Properties of an ideal iron chelator:
An ideal iron chelator should have the following properties:

1. High affinity for iron in ferric form and low affinity for ferrous form and other metals.
2. High chelating efficiency - should be able to chelate a large quantity of iron and have long half life.
3. Attain negative iron balance.
4. Good tissue and cell penetration.
5. There should be no redistribution of iron.
6. Tolerability should be good.
7. Orally bioavailable.
8. Slow rate of metabolism - effective in once or twice daily doses.
9. Affordable
10. Easily available.

8. Deferoxamine mesylate : (DFO)
DFO is a hexidentate iron chelator, produced by *Streptomyces pilosus*, was first used for treatment of transfusional hemosiderosis in 1962. With four decades of clinical experience, it has been definitely proven beyond doubt that DFO when administered as prolonged parenteral infusions, either intravenously or subcutaneously can achieve negative iron balance. DFO is the
current “gold standard” chelator against which newer chelators are measured. Olivieri, et al, in 1994, demonstrated that in those with serum ferritin less than 2500 μg/L, cardiac disease free survival is 91 % after 15 years of chelation with DFO. But in those with ferritin above 2500 μg/L cardiac disease free survival is less than 20 % after 15 years. Hence chelation therapy should be initiated as soon as serum ferritin rises above 1,000 μg/L or if any of the earlier discussed criteria are met.

Long term chelation can reverse the functional complications due to iron overload like liver fibrosis, arrythmias, abnormalities detected by echocardiogram. But the complications due to extensive tissue damage, like frank diabetes, hypothyroidism and myocardial sclerosis cannot be reversed.

The continuous infusions protocols were devised in the late 1990’s. Over-night subcutaneous infusion regimen given through a battery operated infusion pump is the preferred mode of administration of DFO. The usual dose of DFO is 20-60 mg/kg/day. More intensive chelation, ie, 24 hour continuous intravenous infusions administering 100 mg/kg/day are advocated for patients presenting with arrythmias and severe left ventricular failure as a result of cardiac siderosis. Improvement in cardiac function can be demonstrated even before total iron load is significantly reduced, as a result of binding of toxic NTBI.38

As shown in Table 1, the advantages of DFO is its high affinity for ferric iron, high efficiency in attaining negative iron balance and absence of iron redistribution. Its disadvantages are that it is not orally bioavailable, fast rate of metabolism necessitating prolonged parenteral infusions, poor compliance, cheats zinc (sometimes causing clinical zinc deficiency) and high cost.

9. Toxicity of DFO:

a. The most common complication of subcutaneous therapy is inflammation and induration at the site of infusion. If local reactions persist in spite of rotating the site of needle placement, add a small amount of hydrocortisone to the infusion may help.

b. Ophthalmic toxicity: Loss of central vision, night blindness, and amourosis can occur with high dose DFO due to retinal and optic nerve disturbances.39, 40 These are reversible on drug withdrawal and resumption of therapy is well tolerated.

c. Auditory toxicity: High frequency hearing loss usually occurs in younger patients with lower serum ferritin levels.41 Yearly audiogram is recommended for patients on long term DFO. Significant improvement occurs

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Table 1. Comparison of the three chelating agents available in India.
after reduction of dose in those with a mild hearing defect, but in those with severe hearing loss, it persists even after discontinuation of the drug.42

d. Impaired growth: Cartilage dysplasia has been demonstrated in those initiated on DFO at a very young age (less than 3 years) at a dose higher than 40 mg/kg.43, 44, 45 This results in stunted growth and ricket-like bone changes. Vertebrae are relatively more affected than other bones, as a result sitting height is more affected than standing height. Cupping of radial, ulnar and tibial metaphyses also can occur. Reduction of the dose establishes normal growth velocity.

e. Acute pulmonary toxicity and renal failure occurs in those treated intensively with very high doses like 10-20 mg/kg/hour.46, 47

f. Infections: Growth of *Yersinia enterocolitica* is facilitated by hemosiderosis and presence of DFO in plasma.48 Susceptibility to mucormycosis is also increased in those on DFO.

g. Long term toxicities of DFO like auditory and ophthalmic toxicities are increased with decreasing serum ferritin and increasing DFO level. The ratio of DFO /kg weight to the serum ferritin has to be maintained less than 0.025 to decrease long term toxicities.49

10. Deferiprone (L1):

It is a less efficient orally active alternative to DFO in the treatment of transfusional hemosiderosis. It is a bidentate chelator and due to its smaller size, it is able to pass through membranes and can “shuttle” iron from tissues to blood stream.50 At a dose of 75 mg/kg/day it has been shown to be as effective as 40 mg/kg/day of DFO to induce urinary iron excretion.51 Its efficacy in removing cardiac iron equals or betters DFO as shown by Peng (2003) and Piga (2003) respectively. Its ability to decrease liver iron concentration is inferior to that of DFO. A metaanalysis of nine clinical trials, including 129 patients, concluded that the effectiveness of deferiprone in reducing total body iron levels in hemosiderosis patients.52

Deferiprone is licensed for use in India and Europe at a dose of 75 mg/kg in 3 divided doses given 1 hour before meals. Its advantage is that better compliance can be ensured as there is no need of parenteral injections and its low cost compared to DFO.

10.1. Toxicity:

1. Agranulocytosis (0.5 – 2 %) and neutropenia (4 %) 53, 54: Can occur any time after one month of initiation of therapy. Once agranulocytosis has occurred, then rechallenge of the drug is contraindicated.

2. Arthropathy: More frequent in those with more severe iron overload.53, 55, 56 It is hypothesized that formation partially redox reactive complexes of deferiprone and iron, ie, 1:1 or 1:2 iron: deferiprone complexes induce inflammatory changes, possibly mediated by free radicals.

3. Other: Fluctuation in liver enzymes, anorexia, zinc deficiency.

11. “Shuttle hypothesis”: Combination of DFO & deferiprone

This concept was first explained in Herschko in 2000.57 Deferiprone, though a weaker chelator is a relatively small uncharged molecule capable of entering cardiac cells more easily than DFO. Deferiprone transfers the intracellular chelated cardiac iron to the stronger chelator, DFO in the plasma. Thus combined therapy significantly decreases
cardiac iron load. Cabantchik in 2005 demonstrated that Labile Pool of Iron (LPI) is significantly lower during entire 24 hours with combined therapy with DFO and deferiprone than with either drug alone.\textsuperscript{58} The dose used is DFO at 50 mg/kg/day as overnight subcutaneous infusions through pump for 2 days a week and deferiprone at 50 mg/kg/day orally in 3 divided doses for rest of the 5 days of the week.

12. Role of ascorbate supplementation during chelation:
Low ascorbic acid levels have been found in iron-loaded thalassemic patients\textsuperscript{59, 60, 61} in whom ascorbate supplementation results in a marked improvement in deferoxamine-induced iron excretion\textsuperscript{62} by expansion of the chelatable iron pool to which deferoxamine has access. In parallel, ascorbate-induced expansion of this pool may enhance free radical formation, and aggravate the toxicity of iron \textit{in vivo}.\textsuperscript{63, 64, 65, 66} Although routine ascorbate supplementation has been therefore discouraged in patients with thalassemia, observation of loss of sustained efficacy of deferoxamine in an unsupplemented patient should prompt determination of tissue ascorbate concentrations. If these are reduced, 100 mg ascorbic acid per day should be administered. If possible, patients should administer ascorbic acid approximately 30 minutes to 1 hour after the start of an infusion of deferoxamine, only on days during which deferoxamine is administered. No effect of ascorbate has been found on iron excretion in response to deferiprone.

13. Deferasirox:
It is a tridentate synthetic orally active iron chelator developed by computer modeling.\textsuperscript{67} It is an n-substituted bis-hydroxyphenyl-triazole selected from more than 700 compounds as a part of rational drug development programme. It is highly selective for iron and does not induce zinc or copper excretion.\textsuperscript{68} Pigo Antonio et al\textsuperscript{69} presented results of their open label, randomized, multicentre phase-II study evaluating safety, tolerability and effects on liver iron concentration (LIC) of 12 months administration of deferasirox at 10 mg/kg/day and 20 mg/kg/day vs. DFO 40 mg/kg/day subcutaneously 5 days a week. LIC measured every 3 weeks by SQUID showed maximum reduction with 20 mg/kg/day dose of deferasirox than 10 mg/kg/day dose or DFO. This and other studies\textsuperscript{70} showed deferasirox is an extremely effective once a day chelator with no significant toxicities requiring reduction of dose or withdrawal of the drug. A phase III study was completed in 2004 again proved the effectiveness of deferasirox in 586 \(\beta\)-thalassemia major patients who were poorly chelated with DFO. Deferasirox at doses of 20 or 30 mg/kg/day resulted in overall maintenance or reduction of LIC, respectively.\textsuperscript{71} Deferasirox tablet has to be taken dispersed in water or orange juice, at least 30 minutes before food. After swallowing the suspension, any residue should be resuspended in a small volume of the liquid and swallowed. Recommended initial daily dose is 20 mg/kg/day. The drug may be started at 30 mg/kg/day for those who are receiving more than 4 units of packed cells per month and at 10 mg/kg/day for those receiving less than 2 units packed cells per month. Maximum daily dose studied is 30 mg/kg/day. In practice those who are on DFO, the dictum is to start deferasirox at half the dose of DFO, ie, a patient on do mg/kg/day of DFO, start deferasirox at 20 mg/kg/day. The elimination half life of the drug ranges from 11 – 16 hours, making it feasible to give once a day. The drug is excreted through the feces. As deferasirox
is a new drug, it is recommended that serum ferritin be measured monthly until more information about its long term efficacy becomes available.

14. Precautions and toxicities:
   a. Renal toxicity: In animal studies deferasirox has been shown to cause renal tubular epithelial cell damage. It is recommended that serum creatinine be checked in duplicate prior to initiating therapy with deferasirox, and then monthly. A non progressive increase in serum creatinine has been noted in 33% of patients on deferasirox. These were not accompanied by clinical or biochemical evidence of progressive renal disease. In those with well controlled iron stores, a chance of renal toxicity is more as their liver iron concentration is less. The drug should be withdrawn if there is a progressive increase in serum creatinine.
   
   b. Increase in serum transaminases: Elevations in SGPT have occurred in few patients. But it rarely leads to drug withdrawal. Monthly monitoring of transaminases is recommended. Increasing liver iron concentration and hepatitis C infection can also lead to increase in transaminases.
   
   c. Skin rashes: Discontinue in case of severe hypersensitivity reaction.
   
   d. Annual ophthalmological and audiological examination is recommended as with other chelators.
   
   e. Patients with hereditary lactose intolerance will develop diarrhea as the drug product contains lactose.

15. Combination of deferasirox and DFO:
Studies have been done to assess the efficacy of combining DFO with deferasirox. The effect appears additive and the combination allows decreasing the dose of both the drugs and thus improves compliance by decreasing the need for DFO administration. The “shuttle effect” is applicable with this combination also as deferasirox acts as an intracellular chelator and DFO as a powerful extracellular chelator. However, such combination of deferasirox is not yet approved.

16. Newer chelators in clinical trials:
   a. HES-DFO: Attaching hydroxyl ethyl starch (HES) to deferoxamine increases the molecular weight of the compound thereby increasing the circulation time. Dose finding studies are underway.
   
   b. Deferitrin: An orally active tridentate chelator belonging to ferrothiocin class. Studies have not shown any evidence of renal toxicity which is seen with other ferrothiocin compounds. A dose escalation study is underway to find appropriate dose for a pivotal trial.

17. CONCLUSION:
The emergence of new orally effective iron chelators gives hope to both patients as well as physicians caring for thalassemia patients. Though the current “gold standard” iron chelator, DFO, is effective in attaining negative iron balance, majority of the thalassemia major patients on transfusion therapy in India suffer from consequences of iron overload. Though the long term efficacy of newer chelators remains to be proven, the ease of administration and reduced toxicities, will surely improve the compliance. Also combining them with DFO, will reduce the number of days of DFO required and thus improve compliance to DFO. A government funded programme for supplying chelating agents to these patients will help to improve the survival and quality of life of thalassemia major patients.
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