REVIEW ARTICLE

Iron chelation therapy in the management of thalassemia: the Asian perspectives

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Abstract Worldwide, thalassemia is the most commonly inherited hemolytic anemia, and it is most prevalent in Asia and the Middle East. Iron overload represents a significant problem in patients with transfusion-dependent β-thalassemia. Chelation therapy with deferoxamine has traditionally been the standard therapeutic option but its usage is tempered by suboptimal patient compliance due to the discomfort and demands associated with the administration regimen. Therefore, a great deal of attention has been focused on the development of oral chelating agents. Deferiprone, even though available for nearly two decades in Asia with recent encouraging data on cardiac iron removal and long-term efficacy, has serious adverse effects including agranulocytosis and neutropenia which has impeded it from routine clinical practice. A novel oral chelator; deferasirox is effective throughout a 24 h dosing period and both preclinical and clinical data indicate that it successfully removes both hepatic and cardiac iron. In Asia, optimal management of severe thalassemia patients and the availability and access to oral iron chelators still presents a major challenge in many countries. In this regard, the development and implementation of consensus guidelines for management of Asian patients with transfusion-dependent thalassemia will be a major step towards improving and maintaining the continuity of patient care.

Keywords Thalassemia · Iron chelation therapy · Deferoxamine · Deferiprone · Deferasirox

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1 Introduction

Thalassemia is a heterogeneous group of inherited disorders characterized by the complete or partial suppression of production of normal hemoglobin due to defective synthesis of one or more globin chains [1, 2]. Thalassemia is classified according to the particular globin chain that is affected (e.g., α-, β-thalassemia). Over 250 different mutations, primarily affecting the coding sequences of either α or β globin genes, have been described [3, 4]. These mutations mainly include deletion and non-deletion mutations with few exceptions of mutations involved in the up-stream regulatory elements [3, 5].

α-thalassemia largely results from the deletion of one to four α-globin genes, and the clinical severity is dependent on the number of remaining α-globin genes. In general, individuals lacking one α gene ($\alpha\alpha$/-α) have no clinical and hematological phenotype, while the severity increases with the number of α globin genes missing. They may be present as mild hypochromic microcytosis when there is a deletion

of two α genes; (- -/αα or -α/-α), moderate anemia with possible hemolytic crisis when deletion of three α genes; (- -/-α) and hydrops fetalis or intrauterine death caused by the deletion of all four α-globin genes; (- -/- -) [6].

Inheritance of one β-thalassemia gene results in the thalassemia trait (thalassemia minor), inheritance of two defective β-globin genes, can result in a wide ranged spectrum of clinical conditions depending on the type of β-thalassemia mutation (either β^0 or β^+ thalassemia) and several other known and uncertain genetic factors [2]. Therefore, the clinical phenotype in β-thalassemia can range from mild-to-moderate anemia (thalassemia intermedia) or may result in transfusion dependence (thalassemia major). Without proper management, including adequate transfusion therapy, severe anemia can result in increased erythropoietin production, expansion of ineffective bone marrow, bone deformities, splenomegaly and growth retardation [2].

In Asian populations where both α- and β-thalassemia are highly prevalent, structural hemoglobin variants known as hemoglobinopathy are also common; these involve hemoglobins S, C and E. Individuals may inherit the gene for thalassemia from one parent and the gene for a hemoglobin variant from the other parent. The most clinically important type is hemoglobin E/β thalassemia syndrome that has a wide clinical severity ranging from mild thalassemia intermedia to transfusion dependence mimicking that of thalassemia major [2, 7–10].

Thalassemia is the most commonly inherited hemolytic anemia worldwide and due to the large population and high prevalence of thalassemia carriers, Asia and the Middle East account for 95% of overall thalassemia births [7]. Globally, it has been estimated that there are 300 million carriers of hemoglobin disorders, with the majority living in South East Asia. In Thailand alone, the frequency of α-thalassemia is 25%, and the World Health Organisation estimates that, without effective prevention and control programs, over 250,000 symptomatic patients will be diagnosed in this country over the next few decades [8]. A similar scenario is predicted to occur in India, Sri Lanka, Indonesia, the Philippines and Malaysia [1]. With a population of approximately 25 million, Malaysia has a β-thalassemia carrier rate of 4–5%. In a census done in 1998, transfusion-dependent β-thalassemia patients numbered 2,248, with a large proportion located in the state of Sabah [11]. The prevalence of various types of thalassemia in Asia is summarized in Table 1.

With limited resources in most of Asian countries, it is important that a prevention and control program for severe thalassemia syndromes be implemented. A National Thalassemia Screening Program, launched in 1993, with targeted screening done in early pregnancy had resulted in a decrease in the number of β-thalassemia major births in

Table 1 Prevalence of various types of thalassemia in Asian countries where information is available

Country	Average carrier rate (%) for common thalassemia and Hb disorders			
	α^0-thalassemia	α^+-thalassemia*	β-thalassemia	Hb E
India	<1	10–13	3–4	4–30
Sri Lanka	<1	13.6	1–5	0.5
Maldives	<1	28	18	0.8
Myanmar	NA	10	1–5.3	4–48
Thailand	2.2–9	8–30	1–3	10–50
Cambodia	1	15.5	2.8	10–54
Laos	NA	11	5	>30
Vietnam	NA	3.5	4	10–20
Southern China	15	1–5	1.7	NA
Hong Kong	2.2	2.3	3.5	1–2
Taiwan	5 [70]	2.3 [70]	1.1 [70]	<1
Singapore	2–3	1–3	0.93	0.64
Malaysia	4.5	16	4.5	1–3
Indonesia	<1	3–20	3	1–33
Philippines	5	2.2	1	NA

Source Data derived from the First Meeting of Asian Network for Thalassemia Control, Bangkok, Thailand; 3–4 July 2005, or otherwise indicated

NA not available

*α^+ thalassemia included: deletional (-α) and non-deletional ($\alpha^T\alpha$ or $\alpha\alpha^T$) types

Taiwan. Approximately only 100 new cases were detected over the 10-year period from 1994 to 2003, usually due to a failure to detect parental risks [12]. In Singapore, the National Thalassemia Registry was established in 1992 with the aim of registering all individuals with thalassemia genes and offering counselling and subsidized screening for spouses and first degree relatives. As a result, there was a significant increase in the number of thalassemia carriers diagnosed and the number of thalassemia major births is now close to zero [13]. Similarly, in Hong Kong, a prenatal diagnostic screening program using DNA techniques had been established since 1982 for the diagnosis of thalassemia and other genetic disorders with significant success [14, 15].

In patients with severe β-thalassemia, although stem cell transplantation might be the treatment of choice in patients who have HLA-matched donors, such treatment has several drawbacks including limited availability of matched donors, cost of treatment, treatment related mortalities and morbidity and long-term consequences due to exposure of chemotherapy for patients' conditioning. Therefore, the

mainstay of management for most patients consists of regular blood transfusions supplemented with iron chelation therapy to prevent the effects of iron accumulation [16, 17]. Over a period of time, various transfusion regimes have been put in practice. The aim has been to promote normal growth, allow normal physical activities, minimize transfusional iron accumulation, adequately suppress bone marrow activity and reduce cardiac overload due to chronic anemia [16]. Hemoglobin levels maintained at 9–10 g/dl are thought of as optimal [18]. A higher target pre-transfusion hemoglobin level of 11–12 g/dl may be appropriate for patients with heart disease or other medical conditions [16]. Regular transfusions can be given every 3–4 weeks using leukocyte filtered, packed red blood cells with a minimum hemoglobin content of 40 g. Washed red cells may be beneficial for patients with thalassemia who have repeated severe allergic transfusion reactions. Frozen (or cryopreserved) red cells are used to maintain a supply of rare donor units for certain patients who have unusual red cell antibodies or who are missing common red cell antigens; Neocyte or young red cell transfusion may modestly reduce blood requirements, however, this approach has not been widely adopted due to several limitations [16].

2 Transfusion-dependent iron overload

As mentioned above, patients with severe β-thalassemia, particularly β-thalassemia major, require regular blood transfusions supplemented with iron chelation therapy to prevent the effects of iron accumulation [2, 19]. The Thalassemia International Federation (TIF) recommends regular blood transfusions, usually administered every 2–5 weeks, to maintain the pre-transfusion hemoglobin level above 9–10.5 g/dL [20]. Despite the judicious use of blood transfusions due to resource constraints or less dependence on transfusion therapy, many children with thalassemia may become iron loaded as a result of increased iron absorption from the diet [7].

An unfortunate consequence of transfusion therapy in transfusion dependent thalassemia is the accumulation of iron and the necessity for iron chelation therapy [21]. Excess iron can potentially penetrate cells in the liver, heart, endocrine glands and other organs, and cause progressive tissue damage by generation of hydroxyl free radicals causing oxidative stress [19, 21, 22]. The human body has a limited capacity to control iron through the tight binding of plasma iron to transferrin (Tf) protein, which will become completely saturated in heavily iron loaded patients. As a consequence, non-transferrin bound iron (NTBI) including labile plasma iron (LPI) are generated and free radical formation is accelerated in several organs and tissues [23]. Mortality in patients with β-thalassemia is primarily due to heart disease followed by infection, liver disease and malignancy [24]. The mechanism(s) by which cardiac tissue is susceptible to iron overload are not well understood.

There is a clear link between the overall iron burden and global toxicity; in patients with thalassemia the liver iron concentration (LIC) correlates with the total body iron load [22]. Serum ferritin and LIC are widely used to detect iron overload, and the latter can be measured by magnetic resonance imaging (MRI), Superconducting Quantum Interference Device (SQUID) or liver biopsy. Evidence indicates that serum ferritin is not an accurate measure of iron overload and that direct measurement of LIC via liver biopsy or MRI is more precise [25, 26]. It should be noted that the correct interpretation of LIC by liver biopsy is highly dependent on biologic, technical and analytical variability, which may be explained by factors such as the size of the biopsy sample and the possible variability in iron distribution within the liver. Alternatively, MRI offers a non-invasive option for the estimation of LIC and average iron content for the whole liver can be calculated [25].

In patients with thalassemia, iron overload can be prevented or treated with the use of a chelating agent capable of forming a complex with iron and promoting its excretion. The efficacy of a chelating agent will be partly determined by its ability to bind NTBI and LPI over sustained periods of time as an effective means to reduce excess cellular iron and iron loading in organs [22, 23].

2.1 Thalassemia intermedia: need for iron chelation

Thalassemia intermedia (HbE/β-thalassemia), is a heterogeneous condition with a wide variety of clinical presentations. In these patients, anemia can range from relatively mild (hemoglobin >10 g/dL) to severe (hemoglobin <4 g/dL). If not receiving adequate treatment, patients with moderate to severe HbE/β-thalassemia are at high risk of poor growth development [27]. The problem of iron overload in patients with thalassemia intermedia is significant, and increases with advancing age [7, 10].

While in thalassemia major, a significant correlation, although not absolute, has been demonstrated between the levels of serum ferritin and LIC (as assessed by MRI), in thalassemia intermedia there is limited data correlating these two parameters. Preliminary data suggested that in patients with thalassemia intermedia, there is a weaker correlation between serum ferritin levels and LIC than that observed in patients with thalassemia major. Serum ferritin levels underestimated the severity of iron overload in patients with thalassemia intermedia and therefore have little value in monitoring iron overload and iron chelation therapy in this group of patients [28–30]. Using levels of

Table 2 Characteristics of available iron chelating agents [21, 32, 67, 68, 71, 72]

Parameters	Deferasirox	Deferiprone	Deferoxamine
Route of administration	Oral	Oral	Subcutaneous or continuous intravenous infusion
Plasma half-life	8–16 h	3–4 h	20–30 min
Route of iron excretion	Primarily fecal	Primarily urinary	Urinary and some fecal
Tissue and cell penetration	Good to hepatocytes, myocytes and reticuloendothelial system	Low to hepatocytes, good to red cells and myocytes	High to hepatocytes, moderate to reticuloendothelial system and myocytes
Cardiac protective effect	Promising preclinical data. EPIC substudies showed improved/maintained myocardial T2* in 1 year	Greater than deferoxamine	Can reverse cardiac failure when given as a continuous infusion
Adverse effects	Gastrointestinal symptoms, skin rash, abdominal discomfort	Arthropathy, neutropenia, agranulocytosis, abdominal discomfort	Auditory and retinal toxicity; effects on bone growth and cartilage

serum ferritin to determine the degree of iron overload could lead to a delay in chelation therapy for these patients. In transfusion-naïve thalassemia intermedia patients, LIC from liver biopsy but not serum ferritin is a good predictor of the extent of iron overload and may be used to determine the need for chelation therapy. Alternatively, LIC assessments such as MRI should be used in these patients [28].

3 Iron chelation therapy

3.1 Deferoxamine

To date, the management of iron overload has largely consisted of chelation therapy with parenteral deferoxamine (Desferal[TM]). Deferoxamine has been the standard therapeutic option for thalassemia in the past 40 years [31–33]. A recent prospective evaluation of changes in ferritin levels and LIC in 290 thalassemia major patients [20] demonstrated that a mean daily dose of deferoxamine 42 mg/kg resulted in a decrease in serum ferritin of 364 µg/L at 1 year, whereas a mean daily dose of deferoxamine 51 mg/kg resulted in an average serum ferritin decrease of approximately 1,000 µg/L over 1 year. Deferoxamine is able to effectively maintain normal/near normal iron stores, reduce organ damage and increase life expectancy in patients with thalassemia [7]. It is therefore, still the only acceptable active comparator in clinical studies with newer iron chelators. However, patient compliance is suboptimal due to the discomfort and demands associated with the administration regimen [21, 33, 34]. Within the Asian population, there are scant data regarding deferoxamine compliance. Recently an analysis of 120 Thai patients with β-thalassemia, who had been receiving subcutaneous deferoxamine for >2 years (maximum of 12 years), demonstrated that only 14% of cases could be classified as having good compliance [35]. The major obstacles for

achieving optimal compliance included inconvenience, pain and the complexity and discomfort of deferoxamine administration [35]. These findings indicate that although deferoxamine has long been available in Asia, there are significant limitations with regard to its use and compliance for the long-term control of iron overload.

Deferoxamine is associated with an increased risk of infection which necessitates suspension of treatment [17]. Dose-related complications (e.g., hearing problems, growth retardation and ocular toxicity) may also occur in patients who are not heavily iron loaded and who receive a high dosage of deferoxamine. Therefore, attention has been focused on the development of iron chelating agents that can be administered orally. Currently, oral deferiprone (L1, Ferriprox® or Kelfer®) is only licensed in Europe and Asia. Oral deferasirox (Exjade®) has however, been extensively studied in adults and children and approved in over 85 countries worldwide, including the USA and Europe, for the treatment of transfusion-induced iron overload [36]. A summary of product characteristics of the available iron chelators is provided in Table 2.

3.2 Deferiprone (L1)

Deferiprone is an orally absorbed iron chelator first licensed in India, followed by the European Union and other countries outside US and Canada, inclusive of others in Asia in the late 1990s. It is indicated mainly for use in patients with thalassemia major for whom deferoxamine therapy is contra-indicated or who present serious toxicity with deferoxamine therapy [37].

3.2.1 Clinical pharmacology

Deferiprone is a bidentate ligand which binds to iron atoms in a 3:1 molar ratio. In humans, the drug is rapidly

metabolized and inactivated in the liver by glucuronidation of one of its iron binding sites. The elimination half-life in most patients is 2–3 h. Therefore, it has to be given three times a day [37]. It is eliminated mainly via the kidneys in the forms of free deferiprone, the glucuronide metabolite and the iron-deferiprone complex [37].

According to the summary of product characteristics [37], deferiprone therapy should be initiated and maintained by a physician experienced in the treatment of patients with thalassemia. It is given as 25 mg/kg body weight three times a day for a total daily dose of 75 mg/kg body weight. Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions. It is recommended that serum ferritin concentrations be monitored monthly or at least every 2 months to access the long-term effectiveness of chelation with deferiprone. There are limited data available on the use of deferiprone in children between 6 and 10 years of age, and no data on its use in children under 6 years of age. Since deferiprone has been shown to cause neutropenia, including agranulocytosis, it is recommended that a patient's absolute neutrophil count (ANC) be monitored every week. If the patient develops an infection, the therapy should be interrupted and the neutrophil count monitored more frequently.

3.2.2 Clinical experience

Several clinical studies demonstrated that deferiprone was effective in promoting iron excretion and can prevent the progression of iron accumulation as assessed by serum ferritin, in transfusion-dependent thalassemia patients. In the recent Cochrane review of all 10 available randomized controlled trials with deferiprone, the authors however, reported that there was little consistency between outcomes of these studies and little information to fully assess the methodological quality [38]. There was also no controlled trial reporting long-term outcomes (such as mortality and end organ damage) and no consistent effect on reduction of iron overload between all treatment comparisons [38].

Recent data have shown potential benefit of deferiprone on cardiac iron removal, however most data came from uncontrolled case series and retrospective cross sectional analysis [39–41]. In an open-label, non-randomised Italian study, eighteen adult patients who received deferiprone for around 45 ± 21 months after a long period of deferoxamine treatment were matched for age and sex with another 18 adult patients who continued on deferoxamine. Overall heart T2* was measured once using a multislice multiecho T2* MRI [42]. The value was reported significantly higher in the deferiprone group versus deferoxamine group (35 ± 7 vs. 27 ± 2 ms; $p = 0.02$) and the number of segments with normal T2* (>20 ms) was significantly higher in the deferiprone group (11 ± 1 vs. 8 ± 5 with

deferoxamine; $p = 0.03$). No significant differences were found in biventricular function parameters. However, there was no baseline value available for comparison between the two groups, which may lessen the strength of the study.

The adverse events that occurred in the randomised controlled trials with deferiprone included nausea, joint pain (arthralgia) to severe arthritis, stomach upsets and low white blood count [38]. The most serious complication associated with deferiprone was agranulocytosis which occurred in 1% of patients [43]. In one trial, the risk of experiencing an adverse event with deferiprone was twice that of the risk with deferoxamine (RR = 2.24) [38]. Concerns regarding the adverse events associated with deferiprone had resulted in delays in its acceptance and regulatory approval. Its use is limited to second-line therapy for the treatment of iron overload in thalassemia major [44].

In Asia, several groups reported their experiences with deferiprone in patients with thalassemia major. An Indian retrospective study on safety profile of deferiprone in 44 children aged younger than 6 years found that 4.5% of patients experienced neutropenia and none had agranulocytosis [45]. However, they, observed thrombocytopenia in 45.45% of the study population, which occurred 3 months to 1 year after deferiprone therapy. Interruption of treatment for 2–4 weeks led to reversal of symptoms in all but two patients [45]. In Taiwan, 17 patients who received deferiprone therapy continuously for a mean period of 3.3 years and underwent liver biopsy twice were studied for hepatic toxicity of deferiprone. The researchers found no progression of hepatic fibrosis or increased liver iron stores in most patients with deferiprone treatment [46]. Another Taiwanese study group conducted a prospective 3 year study comparing cardiac and hepatic efficacy and safety of chelating treatment with deferiprone and deferoxamine [47]. Among 24 patients studied, 11 were switched from deferoxamine to deferiprone due to unwillingness or intolerability while the remaining 13 patients stayed on deferoxamine. There were no differences between the two groups in efficacy of lowering serum ferritin, serum ALT and hepatic iron levels. There was a marginal benefit in reducing cardiac iron accumulation and increasing cardiac function in the deferiprone group. The study group hence recommended the use of deferiprone in patients who failed on deferoxamine treatment [47].

Combination treatment with deferoxamine and deferiprone has been studied mainly in β-thalassemia major patients with evidence of cardiac iron overload. In a randomized, placebo-controlled, double-blind study, 65 patients with cardiac T2* between 8 and 20 ms entered the study with continuation of deferoxamine and were randomized to receive additional oral placebo or deferiprone [48]. The results of the study demonstrated that in comparison to monotherapy with deferoxamine, combination

treatment reduced myocardial iron and improved the ejection fraction and endothelial function in thalassemia major patients with mild-to-moderate cardiac iron loading. It was generally well-tolerated. However, gastrointestinal symptoms were more likely to be recurrent in the combination group compared with the deferoxamine group (19 vs. 3%; $p = 0.05$). There were 1 episode of agranulocytosis and 2 episodes of neutropenia in the combined group. All episodes resolved after interventions [48]. So far, deferiprone appears to be a practical oral chelator for Asia due to cost and acceptable efficacy. However, several adverse events associated with deferiprone including agranulocytosis (ANC < 500/mm^3), neutropenia (ANC < 1,500/mm^3) and arthropathy in which all of them can be severe, might have limited its use in routine clinical practice. In several Asian countries such as the Philippines, Maldives or Indonesia, the logistics of monitoring the recommended routine WBC weekly may not be feasible. In Thailand, although a locally-made deferiprone has been available since 2008, many clinicians remain reluctant to prescribe the drug due to its potential side effects and a national guideline on deferiprone therapy is underway.

3.3 Deferasirox: a new oral iron chelator

Deferasirox, a newer oral tridentate chelator, was approved by the US Food and Drug Administration in October 2005 for first-line use in adults and children (aged ≥2 years) with chronic iron overload due to blood transfusions [49, 50]. It was developed to overcome the obstacles associated with administration of intravenous deferoxamine [51]. Deferasirox has now been approved in most Asian countries such as Malaysia, Singapore, Taiwan, Thailand, etc.

3.3.1 Clinical pharmacology

Deferasirox mobilizes iron stores by selectively binding to the ferric form of iron (high affinity, 2:1 ratio), and promoting the excretion of iron, primarily in the feces (84% of the dose) [34, 52]. Preclinical data indicates that deferasirox was 4–5 fold more effective than deferoxamine in promoting the excretion of storage iron from parenchymal iron stores and 2 to 3 times more effective in promoting reticuloendothelial iron excretion [53].

Following once-daily oral dosing, maximum plasma concentration is reached within 1.5–4 h, and deferasirox has an absolute bioavailability of 70% compared with an intravenous dose [52]. In a phase II study of patients with β-thalassemia ($n = 71$), deferasirox accumulation occurred between single dosing and steady state but no additional accumulation occurred after repeated daily dosing [54].

Deferasirox has a long plasma half-life of 8–16 h; which means that circulating drug is continually available to scavenge non-transferrin bound LPI [33]. Deferasirox is therefore effective throughout the 24-h dosing period [55]. An evaluation of subgroup data ($n = 13$) from the ESCALATOR trial, conducted in Middle Eastern patients with β-thalassemia and iron overload despite previous treatment with monotherapy or combination therapy, confirmed that once-daily dosing with deferasirox ≥20 mg/kg/day provided sustained reduction in LPI levels, suggesting 24-h protection from LPI (0.98 vs. 0.12 μmol/L pre- vs. 2 h post-administration at baseline, $p < 0.0006$; pre-administration LPI reached the normal range at week 4 and sustained throughout the remainder of the study vs. baseline, $p \leq 0.02$) [56].

Based on Summary of Product Characteristics, treatment with deferasirox should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions. The recommended initial dose of deferasirox is 20 mg/kg/day, and treatment should be initiated after the transfusion of approximately 20 units (about 100 ml/kg) of packed red blood cells or when serum ferritin is consistently >1,000 μg/L [57]. An initial daily dose may be modified (to either 10 mg/kg/day or 30 mg/kg/day) depending on the number of transfusions the individual patient is receiving and whether the patient's therapeutic goal is to decrease or maintain body iron levels [36]. Serum ferritin should be monitored monthly and the deferasirox dose should be adjusted if necessary, every 3–6 months based on the trends in serum ferritin. Deferasirox dose adjustment should be made by 5–10 mg/kg/day and tailored to the individual patient's response and needs. It is recommended that serum creatinine be assessed in duplicate before initiating therapy and monitored monthly thereafter [57]. In patients on high doses of deferasirox or those receiving low rates of transfusion, serum creatinine should be monitored closely [36]. It is also recommended that liver function tests be performed monthly, and auditory and ophthalmic tests be performed before the start of treatment and every 12 months thereafter. As a general precautionary measure in the management of pediatric patients with transfusional iron overload, body weight, height and sexual development should be monitored at regular intervals (every 12 months) [57].

3.3.2 Clinical experience

Clinical registration and development trials with deferasirox have involved the largest number of patients ever conducted for iron chelation therapy. To date more than 1,000 patients have been enrolled [36]. A phase II randomised, open-label clinical trial in adult patients ($n = 71$) with β-thalassemia and transfusional iron overload demonstrated that deferasirox at daily dose of 20 mg/kg showed similar efficacy to deferoxamine 40 mg/kg with regard to decreases in LIC

Table 3 Efficacy of deferasirox (20–30 mg/kg) compared with deferoxamine (≥35 mg/kg) in patients (≥2 years of age) with β-thalassemia and baseline LIC ≥7 mg Fe/g dw [36]

Endpoints	Patient-baseline LIC	Deferasirox	Deferoxamine
LIC (Success rate, %)	Overall population	52.9 (dose ranged 5–30 mg/kg)	66.4 (dose ranged 20 to ≥50 mg/kg)
	≥7 mg Fe/g dw	58.6 (dose ranged 20–30 mg/kg)	58.9 (dose ≥35 mg/kg)
LIC (mean change, mg Fe/g dw)	≥7–14 mg Fe/g dw	−0.4	−1.9
	>14 mg Fe/g dw	−8.9	−6.4
Serum ferritin (mean change, μg/L)	≥7–14 mg Fe/g dw	−36	−364
	>14 mg Fe/g dw	−926	−1,003
Iron excretion-intake ratio* (mean)	≥7–14 mg Fe/g dw	1.02	1.13
	>14 mg Fe/g dw	1.67	1.44

dw dry weight; *LIC* liver iron concentration

* Values <1 denote iron intake in excess of excretion and values >1 denote iron excretion in excess of intake

[58]. Deferasirox was well tolerated at 10 and 20 mg/kg/day with no patient discontinuing treatment due to adverse events. In another phase II open-label, non-comparative trial in pediatric patients, deferasirox 10 mg/kg once daily also demonstrated good tolerability and efficacy in 39 patients aged 2 to <12 years, with transfusion-dependent β-thalassemia major [59]. It is important to note that in heavily transfused patients, particularly children, a higher dosage of 20–30 mg/kg/day seemed more efficient to reduce iron burden to a safe level and to maintain an acceptable iron balance.

Data from a comparative phase III registration study in regularly transfused patients with β-thalassemia aged 2 years or older ($n = 586$) confirmed the efficacy and safety of deferasirox (5–30 mg/kg, depending on LIC values) and its non-inferiority to deferoxamine (20 to ≥50 mg/kg, depending on LIC values) in patients with baseline liver iron concentrations (LIC) values of 7 mg Fe/g dw or higher. Both deferasirox daily doses of 20–30 mg/kg and deferoxamine doses of ≥35 mg/kg significantly and similarly reduced the LIC (Table 3) and serum ferritin levels in patients with baseline LIC of ≥7 mg Fe/g dw [60]. In the sub-analysis of the same pivotal study, the patient-reported satisfaction and convenience were significantly higher with the deferasirox therapy [61]. Among patients who had previously taken deferoxamine and were randomized to receive deferasirox during the study, 96.9% reported a preference for deferasirox over deferoxamine. The primary reasons given for preferring deferasirox were that it was more convenient to take (37.4%), did not involve the injection-site soreness associated with DFO (25.3%), was less disruptive to their day (22.8%), less disruptive to their sleep (6.2%), and less disruptive to their family (4.2%) [61].

Deferasirox has also demonstrated safety and efficacy on LIC when administered for 1 year in the ESCALATOR study in 252 patients with β-thalassemia who had high iron burden and previously unsuccessfully chelated with deferoxamine and/or deferiprone in the Middle East [62]. In the per-protocol population, deferasirox was associated with an overall success rate (defined as LIC (mg Fe/g dw) reduction ≥3 if baseline LIC ≥10 or final LIC of 1–7 if baseline LIC 2 to <10) of 57.7% ($p = 0.007$). Compliance with deferasirox remained high for the duration of the study (median 99.3%). The most common treatment-emergent adverse events were transient and mild/moderate vomiting (8.3%), nausea (7.1%) and skin rash (7.5%). Due to high baseline iron burden resulted from previous inadequate chelation, dose escalation to 25/30 mg/kg/day during the course of the study was required in 76.2% patients not achieving target reduction in iron burden. This highlighted the importance of timely dose adjustments to achieve therapeutic goals [62]. Among 247 patients who entered the extension phase of ESCALATOR study, 93% completed additional 1.7 years of treatment. Deferasirox dose increases were further performed in 56% of patients, with increases to >30 mg/kg/day in 112 patients. Mean reduction in LIC from baseline to the end of study (2.7 years) was 8.9 ± 11.7 and 7.9 ± 8.7 mg Fe/g dw in adult and pediatric patients (both $p < 0.0001$), who were heavily iron-overloaded and previously unsuccessfully chelated. More patients were able to achieve LIC <7 mg Fe/g dw with a longer course of deferasirox therapy. Despite dose increases to ≥30 mg/kg/day in many patients during the extension phase, the safety of deferasirox was maintained with a lower AE reporting rate than that in the core study phase (22 vs. 42%) [63].

Overall, the various clinical trials showed that deferasirox has a defined safety profile that is clinically manageable with regular monitoring in adult and pediatric patients. The most frequent adverse events reported over a median 3.5 years' treatment with deferasirox include transient, mild-to-moderate gastrointestinal disturbances (5–10%) and skin rash (5.2%) [36]. An independent post-marketing analysis in Thailand revealed that a mild transient

maculopapular rash, mainly occurring within 7–10 days after start of the drug, is the most common side effect observed in Asian population who received deferasirox which is with a higher incidence than Western studies (17.7%). Other safety parameters seemed to be similar to those of previous studies, however this preliminary finding needs further confirmation [64]. Mild, non-progressive increases in serum creatinine (generally within the upper limit of normal) were observed in approximately one-third of patients in the pivotal studies of deferasirox. The levels returned spontaneously to baseline in more than two-thirds of these patients. No cases of moderate-to-severe renal insufficiency or renal failure were reported, and no patients permanently discontinued therapy due to creatinine rises, based on data collected from up to 3.5 years of treatment in 1,034 patients in the pivotal trials [36]. Deferasirox treatment had also shown no negative impact on growth measured by height and sexual development in pediatric patients followed in extension studies up to 5 years [65, 66].

Most recently, the largest Evaluating Patients' Iron Chelation (EPIC) multi-center, 12-months trial was initiated to evaluate whether fixed starting doses of deferasirox (based on iron intake from ongoing blood transfusions) with subsequent dose titration (up to 40 mg/kg/day) every 3 months based on serum ferritin trends and safety markers can provide clinically acceptable chelation. The results were recently presented in the 50th ASH meeting in December 2008. The study confirmed that with fixed starting dose based on transfusional iron intake and subsequent dose titration, deferasirox is effective in reducing iron burden measured by serum ferritin in iron-overloaded, regularly-transfused patients with a wide range of underlying anemias including thalassemia. In fact, among 1,744 adult and pediatric patients enrolled from 21 countries (including China, Hong Kong, Malaysia, Taiwan, South Korea and Thailand in Asia), 937 patients were with β-thalassemia major heavily transfused and pre-treated with other iron chelation therapies. In those patients, after 1 year treatment of deferasirox at an average actual dose of 24.2 ± 5.6 mg/kg/day, median serum ferritin level decreased by 129 ng/mL ($P = 0.0007$ vs. baseline) [52]. The safety profile and discontinuation rates were consistent with previously reported data in thalassemia patients [52]. Two sub-studies of the EPIC trial prospectively evaluated for the first time in a multicenter setting the efficacy of deferasirox in reducing cardiac iron in β-thalassemia patients with myocardial siderosis ($n = 114$) and in preventing cardiac iron accumulation in those with normal cardiac iron level at baseline ($n = 78$). After 1-year treatment of deferasirox at mean dose of 32.6 mg/kg/day, the myocardial T2* improved significantly ($P < 0.0001$) from baseline (geometric mean at 11.2 ms) to 12.9 ms in patients with myocardial siderosis, whose cardiac function

measured by left ventricular ejection fraction (LVEF) also remained stable throughout the study [67]. In patients with normal cardiac iron level at baseline (32.0 ms), the cardiac T2* remained stable at 32.5 ms ($P = $ ns vs. baseline) after 1-year treatment of deferasirox at mean dose of 27.6 mg/kg/day, with LVEF increased significantly from 67.7 to 69.6% ($P < 0.0001$) [68]. Both data showed that deferasirox at optimal doses, removed cardiac iron and potentially prevents long-term iron accumulation in the heart.

4 Current guidelines for the treatment of iron overload

The principles of treatment for thalassemia are now fairly well established. However, there are still some areas which are subject to continuing modification; these include adequate transfusion and chelation therapy, prevention and management of complications, and monitoring for new unexpected complications. Early detection of other unrelated chronic illness, especially in an ageing population of thalassemia patients, is also an important issue.

The primary goal of treatment in patients with iron overload is to achieve safe iron levels. The recent TIF guideline [20] recommends screening for iron overload at the onset of transfusions. Serum ferritin is a well established prognostic test which should be performed every 3 months, preferably in conjunction with other measures. Liver iron concentration is the reference standard for estimating iron loading and can be determined via liver biopsy or non-invasive MRI/biomagnetic susceptometry. Newer technique like T2* imaging of the cardiac tissue is increasingly being used to assess the cardiac function of patients around the world.

Treatment for iron overload should be initiated when serum ferritin levels reach approximately 1,000 μg/L or after the first 10–20 transfusions. The TIF recommends that initiation of chelation therapy should be accompanied by regular monitoring for efficacy, side effects and complications of excessive chelation, particularly with regard to auditory and ocular toxicities in cases with deferoxamine [20]. In thalassemia patients who receive deferasirox, the TIF recommends starting dose at 20 mg/kg/day (iron intake 0.3–0.5 mg/kg/day) but the dosage could be increased up to 30 mg/kg/day in patients who already have pre-existing iron overload (iron intake > 0.5 mg/kg/day). Regular monitoring of renal function is required and Deferasirox is contraindicated in patients with renal failure or significant renal dysfunction [20]. The TIF states that the majority of experience with deferiprone is with 75 mg/kg/day in 3 divided doses (up to 100 mg/kg/day with limited information), although following long-term therapy at this dose only a proportion of patients achieve the desired liver iron levels [20]. Careful monitoring of the patient's clinical

condition and laboratory testing is essential given the possibility of serious adverse effects including agranulocytosis and neutropenia. Until there are more data on the safety of deferiprone, weekly blood counts are advised, as are liver biopsies before and during therapy. At present, there is limited data on the efficacy of this agent in patients aged <10 years [20].

Within Asia, there are regional variations in thalassemia management protocols and guidelines, although most recommendations are in line with those of the TIF. In Taiwan, transfusion therapy is usually given every 2–4 weeks with the aim of maintaining pre-transfusion hemoglobin levels above 10 g/dL. Deferoxamine is administered in accordance with the TIF guidelines, and oral deferiprone three times daily and oral deferasirox once daily are also available. The treatment of thalassemia in Malaysia is largely the domain of individual clinicians although clinical practice guidelines have been available since 1998, and these were updated in 2005. In these guidelines, deferoxamine is recommended as the standard treatment and should be administered as per the TIF recommendations. Deferiprone is recommended in patients with ferritin levels >2,500 μg/L, when there is no response to deferoxamine or there are deferoxamine-related adverse effects. With the introduction of deferasirox, updated guidelines are in preparation, although the specific role of this chelator remains to be determined. In Thailand, all three chelating agents are available: deferoxamine (20–60 mg/kg/day given as subcutaneous infusion over 8–12 h, 5–6 times per week); deferiprone (50–100 mg/kg/day), and deferasirox (20–30 mg/kg/day). While in Singapore, the incidence of thalassemia intermedia is very low, the decision to transfuse is often more problematic in these patients. Iron chelation therapy is offered to all patients with β-thalassemia major and usually commence at the age of 3 years or when serum ferritin is >2,000 ng/mL. Deferoxamine, deferiprone and deferasirox are all available, although the latter has only been used recently.

5 Discussion

Despite recommendations from the TIF, adequate management of thalassemia still presents a major challenge, and difficulties arise with regards to the optimal time to commence chelation therapy, the determination of a safe ferritin level, and the accurate assessment of body iron. Furthermore, evidence from Hong Kong indicates that despite the use of iron chelation therapy with deferoxamine, severe complications still occur. In a cohort of 232 patients, the probability of survival beyond age 20 years was only 86.7%; cardiomyopathy was the leading cause of death in these patients [69].

It is anticipated that the development of new oral iron chelators, such as deferasirox, will have a major impact on the treatment of patients with thalassemia. The availability of three agents for the treatment of thalassemia will enable physicians to tailor treatment regimens to the individual patient, leading to improved life expectancy and quality of life.

In view of the increasing availability and use of deferiprone and deferasirox in the management of iron overload, there is a need for clearly defined management protocols that can be easily implemented within Asia. The development of such protocols for chelation therapy will be integral in ensuring that patients receive timely and effective treatment while minimizing adverse effects and potentially improving their compliance to treatment regimen. A clear definition of therapeutic goals and monitoring strategies will minimize the time required to find the optimal dose for each patient. Ideally, chelation therapy should be tailored to each patient, based on their baseline condition, with monitoring and dose adjustments, to achieve and maintain optimal chelation. Appropriate patient selection may further improve the effectiveness of chelation therapy.

6 Conclusion

Transfusion-dependent thalassemia represents a major healthcare burden in Asia and the development of oral iron chelators such as deferasirox represents a significant advance in iron chelation therapy. The development and implementation of consensus guidelines for management of Asian patients with transfusion-dependent thalassemia will be a major step towards improving and maintaining the continuity of patient care. However, due to a significant difference of socio-economic and medical standards among Asian countries which differ vastly from that of European or North-American standards, it is important that experts from Asian countries discuss and identify the best possible recommendations for iron chelation therapy and draw a consensus that could be used as clinical practice guidelines for optimal and appropriate management for thalassemia. There is no doubt that such a recommendation will play an important role in improving clinical management of thalassemia in Asia where many lives are affected.

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