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Review Article

Improvement of Cardiac Function in Thalassemia Patients Using Deferiprone

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Abstract

Deferoxamine (DFO) therapy is associated with improved survival of thalassemia patients, and yet cardiac disease remains the main cause of death. Deferiprone (L1) is currently one of the orally active chelating agents used as an alternative to DFO. Both DFO and L1 have demonstrated their ability to normalize cardiac function in patients with iron-induced cardiac disease. Some evidence indicates that L1 is more effective than DFO in cardiac iron removal. Our ability to detect and manage the cardiac complications of thalassemia has also improved dramatically over the last 7 years. Noninvasive techniques of quantification of the iron burden using magnetic resonance imaging (MRI) have been validated. Using MRI and echocardiography to monitor cardiac systems, in particular the cardiac functions that are closely associated with iron overload-related complications and mortality, proved to be practical. Our increased understanding of cardiac pathophysiology and our improved ability to detect at-risk populations are yielding improved outcomes and reduced morbidity in these reported patients. The improvement in cardiac function that can be observed during L1 therapy may have several mechanisms. Due to its tiny size and physicochemical characteristics, it can readily penetrate iron-loaded myocytes where it may exert antioxidant activity or bind the excess iron and carry it out of the cell into the circulation where it is excreted, mainly in the urine. In addition, L1's cardioprotective effects may be related to its ability to mobilize citrate-bound iron or other forms of nontransferrin-bound iron. We have continued to explore the use of readily available bedside tools, such as echocardiograms and biochemical markers of cardiac dysfunction, to monitor thalassemia patients with cardiac complications. Herein, the literature and our own studies/findings are summarized. L1 chelation was found to have marginal benefits in increasing cardiac function and reducing cardiac iron accumulation. (*Tzu Chi Med J* 2007;19(4):192–199)

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1. Introduction

Heart failure due to iron overload can develop either as a result of excess dietary absorption or from repeated blood transfusions. The most striking model of cardiac iron overload is seen in thalassemia major (TM), in which heart failure remains a major cause of death, greatly exceeding deaths from infection and liver disease [1]. Despite the worldwide introduction of the iron chelating agent deferoxamine (DFO) more than 40 years ago, 50% of patients still die before the age of 35 years [2]. This high mortality is partly due to difficulties with DFO administration. This drug requires long subcutaneous or intravenous infusions at least 4 days a week; compliance with treatment is inadequate in many cases. The need for an effective alternative approach with an oral iron chelator has long been acknowledged [3] and medium-term results from prospective trials of the oral chelator deferiprone (L1) seem promising [4–6]. However, the long-term effectiveness of this drug has been questioned because liver iron content is high in some patients [7,8]. Recent studies [9,10] have suggested that L1 provides greater cardiac protection against iron-induced heart disease than DFO. The objective of iron chelation therapy is to prevent lethal cardiac complications from myocardial iron deposition. Myocardial iron and ventricular function should also be taken into account when assessing the effectiveness of chelating agents. Magnetic resonance imaging (MRI) techniques have assessed both myocardial iron and ventricular function in these reports [11]. The present article aims to summarize the information from the literature and our own studies. Only the most profound and relevant data/findings from various studies on the efficacy of DFO and/or L1 on thalassemic cardiomyopathy were considered eligible for inclusion in the analysis. Here, we also review previously published data and findings from our own studies on the same topic from 1999 to the present. All of these were focused especially on the issues of: (a) the effects of L1 and DFO on the heart; and (b) evidence and possible mechanisms of how L1 prevents cardiotoxicity. In the final section, potential future strategies for cardiomyopathy are discussed.

2. Natural history of hypertransfusion

Patients remain well for many years; symptoms are typically absent for <100 units of blood transfused and rare until over 200 units. Cardiac arrhythmias are often one of the earliest signs, ranging from isolated premature atrial and ventricular beats to complex sustained arrhythmias. Electrocardiogram (ECG) changes include conduction defects, generalized slowing, repolarization abnormalities and ventricular hypertrophy [12]. Ventricular function is typically normal until physical symptoms of congestive heart failure are noted. Stress imaging revealed a population of "subclinical patients". Clinical degeneration from the onset of clinical symptoms or ventricular function abnormalities was short, often less than 6 months [13].

3. Effect of L1 and DFO on the heart

Cardiac decompensation is less precipitous than in the unchelated state but depressed ventricular function carries a very poor prognosis. Rhythm disturbances are often still the earliest sign [12]. Both arrhythmias and cardiac dysfunction are reversible with continuous DFO therapy but relapse is common unless prolonged therapy is maintained. Some patients die from iron cardiomyopathy despite apparently "adequate" iron chelation of ferritin and liver iron. Both DFO and L1 have demonstrated their ability to normalize cardiac function in patients with iron-induced cardiac disease. The improvement in cardiac function that can be observed during continuous intravenous DFO infusions in patients with iron-induced cardiac failure is limited in its removal of excess myocardial iron because DFO's molecular size argues against meaningful cellular penetration [14]. Studies of cardiac iron overload in animal models have documented the limited ability of DFO to remove cardiac iron. A possible explanation for the beneficial effect of DFO is that it may be related to extracellular events, such as the decline in the plasma concentration of nontransferrin-bound iron (NTBI), which has been reported to occur during DFO administration. The improvement in cardiac function that can be observed during L1 therapy may have several mechanisms. Its tiny size and physicochemical characteristics mean that it can readily penetrate iron-loaded myocytes, where it may exert antioxidant activity or bind the excess iron and carry it out of the cell into the circulation where it is excreted, mainly in the urine. In addition, L1's cardioprotective effects may be related to its ability to mobilize citrate-bound iron or other forms of NTBI. The need to maintain continuous levels of chelators in the plasma in order to decrease cardiac injury by toxic species of iron may explain, in part, the different cardiac protective effects observed between continuous 24-hour infusion and the standard regimen of DFO. This need to maintain continuous blood levels of chelators could also explain the difference in cardioprotection observed between standard subcutaneous DFO administration and uninterrupted L1 therapy.

4. Assessment of cardiac iron

4.1. Serum ferritin

Serum ferritin values have been the most reliable method available for prediction of iron-induced cardiac damage. It is a relatively easy test to perform and does more than simply provide an indication of body iron load: several studies have shown a correlation between serum ferritin level and cardiac mortality in thalassemia patients [15–17]. Two recent trials, both exceeding 10 years, have unequivocally demonstrated that effective long-term use of DFO in TM is associated with long-term survival that is free of the complications of iron overload [18,19]. Both studies identified the magnitude of the body iron burden as the principal determination of clinical outcome. One trial used serum ferritin levels to evaluate iron loading [18]. Over the follow-up period, patients with serum ferritin concentrations $<2500\,\mu g/L$ had an estimated cardiac disease-free survival of 91% after 15 years. In contrast, in patients with serum ferritin concentrations $>2500\,\mu g/L$, estimated cardiac disease-free survival was <20% after 15 years. However, serum ferritin is an acute phase reactant, so its levels can be influenced by other factors, such as inflammatory processes, infection and chronic disease. Thus, single measurements of serum ferritin must be interpreted with caution [20]. Furthermore, there is little evidence demonstrating that serum ferritin levels correlate with cardiac function, as determined by left ventricular ejection fraction (LVEF), or with cardiac load, as assessed by cardiac T2 or T2* values [11,13,21–23].

4.2. Liver iron

The liver is the major site of iron storage in iron overload, accounting for more than 70% of body iron stores [24,25]. However, in contrast to the situation with serum ferritin levels, there is little evidence for the value of liver iron concentrations as a predictor of myocardial iron load or of iron-induced cardiac disease in patients undergoing chelation therapy [21].

4.3. Cardiac imaging (echography, T2 and T2* MRI) [11,13,26]

Cardiac performance was monitored by ECGs, which included B-mode, M-mode and flow Doppler investigations, as determined by LVEF, etc.

The MRI T2* gradient echo technique involves measuring the decay in signal intensity (SI) as the echo time of the images is progressively increased. The rate of decay is strongly enhanced in the presence of iron deposition: increased iron levels cause reduced T2* values. Similarly, the extent of cardiac iron depositions by T2 was assessed by SI in MRI, which was defined by comparing the image signal to that of the paraspinous muscle on the same section. The MRI sequence was spino-echo T2-weighted in the axial plane. No contrast medium was given. A cardiac T2* of less than 20 ms indicates iron overload. Below this value, there is a progressive and significant decline in LVEF ($r=0.61$; $p<0.0001$). Based on this relationship, T2* values can be used as a guide to the level of cardiac risk (e.g. 0–10 ms=high risk; 10–20 ms=intermediate risk; 20+ms=low risk). Apart from iron overload, no other clinical scenarios have been found that decrease cardiac T2* below 20 ms. Importantly, T2* studies also showed that there was no significant correlation between myocardial T2* and liver T2*, or between myocardial T2* and the "traditional" measures of body iron load of serum ferritin and liver iron levels. It, therefore, seems reasonable to conclude that myocardial iron content cannot be reliably predicted from serum ferritin or liver iron levels, and that T2* is the only currently available technology that provides a reliable assessment of heart iron load.

5. Summary of literature regarding treatment for myocardial siderosis

The primary goal of chelation therapy is to prevent iron-induced organ damage and premature death. Implicit in this goal is the imperative to remove iron effectively from the heart (target lethal organ) in thalassemia [26]. DFO can improve survival and delay the complications of iron overload [16]. Standard therapy involves subcutaneous infusion of 20–40 mg/kg/day over 8–24 hours, 5–7 days per week [27] and is usually initiated in children after the first 10–20 blood transfusions. Prior to the availability of DFO, iron-induced myocardial disease was invariably fatal [28]. Continuous 24-hour parenteral infusion of DFO aimed at removing cardiac iron can reverse arrhythmias and congestive heart failure in many patients [29]. Anderson et al [14] followed thalassemia patients commencing intravenous DFO for iron-induced cardiomyopathy during a 12-month period. The data confirms that siderotic heart failure is often reversible with intravenous iron chelation by DFO. Myocardial T2* improves in concert with left ventricular volumes and function during recovery, although iron clearance from the heart is considerably slower than from the liver. In another retrospective study, Anderson et al [9] (Table 1) compared myocardial iron content and cardiac function in 15 patients receiving long-term L1 treatment with 30 matched controls on long-term

Table 1 — Studies that compare cardiac parameters from different chelation therapy styles

Order (Ref)	Patients, *n*	Length of study (mo)	Chelation treatment & dose (mg/kg/d)	SIR of T2[a] or T2*[b] MRI (estimation; a: 0.92±0.12, b: >20 ms)		LVEF (%)		Conclusions
				Initial	Final	Initial	Final	
1 (9)	30	68.4	DFO (37.4)	ND	11.4 (7.0–25.0)[b]	ND	63 (±6.9)	Excess myocardial iron significantly less common in the L1 group
	15		L1 (80.5)	ND	34.0* (18.0–56.0)[b]	ND	70* (±6.5)	
2 (10)	75	73	DFO (20–50)	ND				L1 group had significantly greater cardiac disease-free survival over 5 yr (p=0.003)
	54		L1 (25–100)					
3 (30)	32	12	DFO (43)	13.3[b]	15.0[b]	68.4	68.5	L1 had superior efficacy in reducing cardiac iron over 12 mo assessed by T2* and LVEF
	29		L1 (92)	13.0[b]	16.5*[b]	69.7	73*	
4 (31)	359	108	DFO (30–50)	ND				L1 group had 0% cardiac events over 9 yr *vs.* 14.5% with DFO group
	157		L1 (75)					
5 (22)	10	36	DFO (45.4)	0.68 (±0.23)[a]	0.69 (±0.18)[a]	63.3 (±6.3)	64.6 (±7.0)	- L1 group had a superior LVEF improvement - The improvement in LVEF was proportional to the reduction in cardiac iron deposition (SIR T2 MRI)
	11		L1 (73.8)	0.67 (±0.21)[a]	0.87* (±0.17)[a]	58.6 (±6.8)	65.2* (±7.1)	
6 (23)	Patient 1	13	DFO (50)+ L1 (80)	0.55[a]	0.88[a]	41	58	Combined therapy can successfully regress severe siderosis cardiomyopathy
	Patient 2	6	DFO (50)+ L1 (80)	0.49[a]	0.85[a]	35	64	
7 (32,38)	26	28	DFO (50)	0.67 (±0.25)[a]	0.68 (±0.18)[a]	64.3 (±6.1)	65.2 (±7.1)	- Combined chelation therapy (L1+DFO) was the most effective against thalassemic cardiomyopathy - L1-only group was the 2nd of 3 - DFO-only group was the 3rd of 3
	57	36	L1 (75)	0.68 (±0.24)[a]	0.86* (±0.19)[a]	56.6 (±6.5)	66.3* (±6.9)	
	31	24	DFO (40)+ L1 (75)	0.62 (±0.33)[a]	0.89* (±0.21)[a]	52.4 (±6.3)	70.3* (±7.0)	
8 (13)	9	132 (DFO, 84; L1, 48)	DFO (50) was switched to L1 (75) since 1999	EPSS (DFO: 8.11±3.67 to L1: 2.9±0.89*) EPSS/LVDd (DFO: 0.19±0.08 to L1: 0.06±0.02*) LA/AO (DFO: 1.27±0.15 to L1: 1.10±0.13*)				Myocardial dysfunction can be reversed by oral L1

*p<0.05, initial *vs.* final data. EPSS = E-point of a full opened mitral valve to septum separation (mm); LVEF = left ventricular ejection fraction; EPSS/LVDd = E-point to septal separation/left ventricular end-diastolic dimensions; LA/AO = left atrial dilatation was defined by the ratio between the left atrium dimension and the aorta diameter; a = T2 MRI; b = T2* MRI; ND = no data.

treatment with DFO. MRI T2* was used to measure cardiac iron. The researchers found that the L1 group had significantly less myocardial iron than the DFO-treated group (p=0.02). The odds ratio for excess myocardial iron with DFO was 5.5 (95% confidence interval, 1.2–28.8). Cardiac function was also better in the L1 group: this group had a higher mean LVEF (p=0.004) and less left ventricle dilatation in systole (p=0.03) and diastole (p=0.01) than the DFO group. The same results were recently confirmed in a larger, prospective, randomized controlled trial by Pennell et al (30) (Table 1). In this study, 61 patients previously treated with DFO were randomized to be maintained on DFO (43 mg/kg for 5.7 days/week) or switched to L1 (92 mg/kg/day). During the 1-year period of the study, compliance was similar in the two groups (93% *vs.* 94%, respectively; p=0.023). There was significantly greater improvement in myocardial T2* for patients receiving L1 than those receiving DFO (27% *vs.* 13%; p=0.023). LVEF also increased more significantly in the L1 group (3.1% *vs.* 0.3%; p=0.0034). Baseline serum ferritin level was not significantly predictive of the improvement in T2*. The prospective trials demonstrating superior efficacy in treating cardiac siderosis and better outcome for LVEF have received some support from outcome studies looking at survival and clinical complications. The first survival data comparing L1 and DFO was reported from a recent retrospective study by Piga et al (10) (Table 1). This study compared records of 54 patients treated with L1 with that of 75 patients treated with DFO for an average of 6 years. All patients had been previously treated with DFO. The study found that cardiac disease-free survival was significantly better in the L1 group over the course of 5 years (p=0.003). Cardiac dysfunction was diagnosed in two (4%) of the

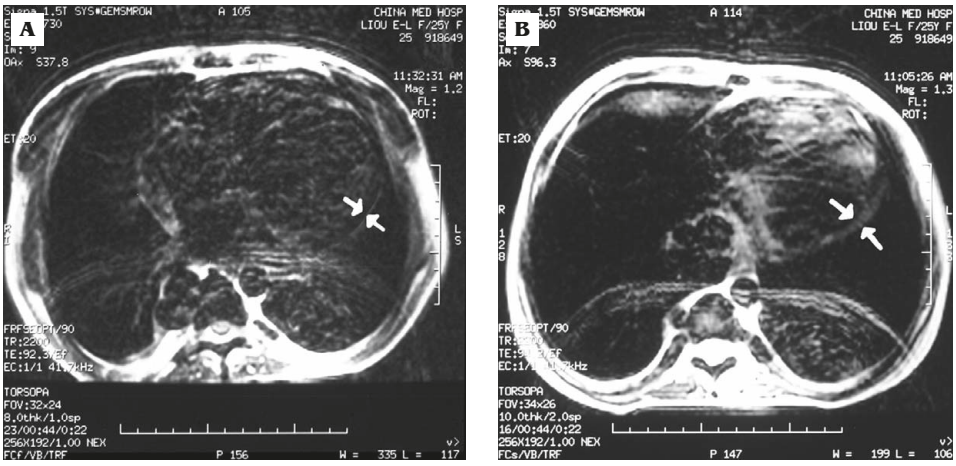

Fig. 1 — Magnetic resonance imaging of a patient's heart: (A) before combined therapy, axial view of the heart shows a decrease in signal intensity (SI) in the myocardium, suggesting substantial iron deposition (between arrows); (B) 13 months after combined therapy, marked recovery of SI suggests depletion of iron deposition (between arrows). ***Reprinted with permission from reference 23.***

L1-treated patients and in 15 (20%) of the DFO-treated patients ($p=0.007$).

A recent multicenter natural history study by Borgna-Pignatti et al [31] (Table 1) also found that cardiac disease outcome and survival were better for patients treated with L1 than with DFO. The study involved 359 patients receiving DFO (30–50 mg/kg/day, 5–6 times per week) and 157 patients who were switched to L1 (75 mg/kg/day, 3 times a day) at seven Italian centers between 31 January 1995 and 31 December 2003. There were a total of 52 cardiac events, including 15 cardiac deaths, during the 9-year period. All events occurred in the patients treated with DFO and there were no cardiac events in those receiving L1. Overall, 14.5% of the DFO patients had a cardiac event versus 0% of the L1 patients. The authors concluded that their epidemiological study "demonstrated a significant difference in cardiac morbidity and mortality between thalassemia patients treated with L1 and those treated with DFO".

Between January 1999 and the present, there have been five reports from the Pediatric Hematology Division, China Medical University Hospital, Taichung, Taiwan. Four reports on β-TM patients, who received regular blood transfusions and various types of chelation therapy, compare the incidence of iron-induced cardiac disease and the recovery rates in the different treatment modalities (Table 1). The other report compared cardiac function differences between normal people and TM patients [12]. Our first prospective report [22] compared cardiac iron and LVEF over 3 years between 10 patients allocated to DFO (50 mg/kg/day) at least 5 days per week and 11 patients receiving L1 (75 mg/kg/day) orally every 8 hours. Cardiac iron levels, estimated by SI of T2 MRI, were markedly improved in five of the 11 patients in the L1 group, whereas in the DFO group only slight improvement was seen in only two of the 10 patients. Mean LVEF significantly improved in the patients receiving L1, from 58.6±6.8% to 65.2±7.1%, whereas there was no significant change in the DFO group (63.3±6.3% to 64.6±7.0%). The two drugs had equivalent effects on serum ferritin and hepatic iron levels, again indicating that these two parameters do not reflect cardiac iron levels.

We reported on the successful treatment of severe heart failure in two patients with β-TM with combined therapy in 2003 [23]. The T2 MRI showed a marked recovery of SI in the heart, indicating a significant reduction of iron load in the heart (Fig. 1). Therefore, combined therapy of L1 and DFO has been suggested in patients with β-TM and cardiac complications. We also reported on nine patients with TM complicated by some degree of myocardial dysfunction in the journal *Hemoglobin* in 2006 [13]. These patients, recipients of >10 years of DFO injection therapy, were switched from DFO to L1. Echocardiographic measures of left ventricular systolic, diastolic and global function were assessed regularly every 6 months. Global cardiac function improved significantly: E-point-to-septal separation (EPSS) (8.11±3.67 mm *vs.* 2.9±0.89 mm, $p<0.01$), EPSS/left ventricle diastolic dimension (LVDd) ratio (0.19±0.08 *vs.* 0.06±0.02, $p<0.01$) and left atrium/aorta (LA/AO) ratio (1.27±0.15 *vs.* 1.10±0.13, $p=0.02$) all decreased. We concluded that myocardial dysfunction in patients with TM can be reversed by regular use of oral iron chelator L1. That same year, we conducted a case study, enrolling 136 patients with transfusion-dependent TM from five medical centers in Taiwan [32]. Combined therapy was the

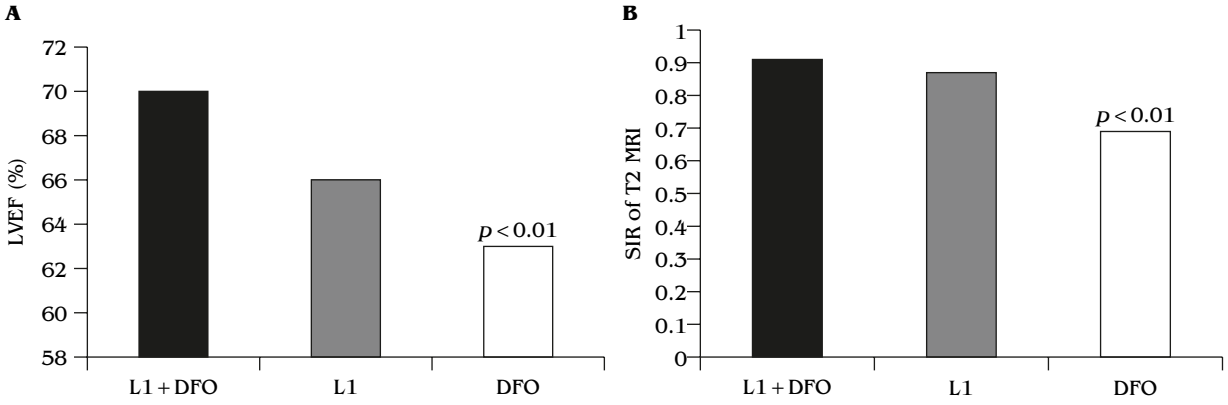

Fig. 2 — Difference in effectiveness of different chelation therapy styles in: (A) left ventricular ejection fraction (LVEF); (B) signal intensity of T2 magnetic resonance imaging. Deferiprone (L1) + deferoxamine (DFO) was most effective, L1-only was the second most effective, and DFO-only was the least effective. *Reprinted with permission from reference 38.*

most effective at reducing iron burden, as assessed by serum ferritin levels, SI of T2 MRI and M-mode echocardiography (LVEF). The L1-only group had the second best improvement, followed lastly by the DFO-only group (Fig. 2). In 2004, we performed ECGs in 39 patients with β-TM and 35 aged-matched controls [12]. Gender, age, heart rate, blood pressure, LVEF, acceleration time (AcT) of right ventricular outflow and right ventricular ejection time (RVET), AcT/RVET and the presence of tricuspid regurgitation (TR) were compared between the two groups. The incidence of TR in thalassemic patients was significantly higher than that in the control group (30.8% *vs.* 11.4%, $p=0.03$). The incidences of splenectomy ($p=0.03$), platelet counts ($p=0.01$) and SI ratio of myocardial MRI ($p=0.03$) in thalassemic patients with TR were significantly higher than in those without TR. Also, the AcT was shorter and AcT/RVET ratio was smaller, suggesting higher pulmonary pressure in the thalassemic patients with TR. Occurrence of TR in patients with β-TM may be a consequence of cardiac iron deposit, thrombocytosis, splenectomy or pulmonary hypertension.

6. Discussion

These studies provide strong evidence of the apparent superiority of L1 in preventing cardiac complications as the patients included are more likely to represent the disease population as a whole. L1 (1,2-dimethyl-3-hydroxypyrid-4-one) is an orally active chelator from the bidentate hydroxypyridinones family. It was synthesized in 1982 but development did not follow a systematic design. Toxic effects include arthropathy, neutropenia and agranulocytosis, which demand close monitoring. In comparison with standard DFO treatment, doses of L1 of 75 mg/kg of body weight/day give comparable urinary iron excretion levels. The effect on liver iron concentration may vary among patients. Several aspects of its safety and efficacy, as well as development, have been matters of serious discussions and controversies. The basic molecular mechanism of thalassemic syndrome is the reduced synthesis of the β-globin chains [33]. The consequences of the resulting chronic anemia are common, and include growth retardation, bone marrow expansion, extramedullary hematopoiesis, splenomegaly, increased intestinal iron absorption, susceptibility to infections and hypercoagulability [33,34]. What differentiates the major and intermediate forms of β-thalassemia is the severity of the clinical phenotype, which depends on a particularly heterogeneous molecular background and is mainly determined by the balance between α- and β-globin chains and the quantity of γ-globin chains [33]. The diverse clinical severity has led, in turn, to totally different therapeutic approaches. In these studies, TM patients have universally been on an intensive transfusion regimen that has maintained their hemoglobin level close to normal, hence allowing adequate tissue oxygen delivery. Before the introduction of regular treatment for TM, most patients died of high-output heart failure, usually by the end of the first decade of life. Regular therapy, which has been gradually introduced, modified the form and severity of thalassemia heart disease. At the same time, the heterogeneous cardiac outcome reflected the treatment variability with respect to frequency of transfusions and intensity of iron chelation. Left ventricular dysfunction was the only notable abnormality in TM and, in accordance with existing knowledge, was the cause of congestive heart failure in these patients. In TM patients with evident heart disease, end-systolic stress and relative wall thickness were affected following left ventricular dysfunction. Systolic left ventricular dysfunction, however, was not observed in patients less than 23 years

old. Chelation therapy reduces pulmonary and cardiac iron deposition, and their contribution to the elevation of pulmonary vascular resistance [35]. However, aside from restricting the negative effects of hemolysis on nitric oxide and arginine availability, regular transfusion therapy also prevents chronic tissue hypoxia and its consequences that have been implicated in the pathogenesis of pulmonary hypertension [35,36]. Cardiac death due to iron overload still accounts for two thirds of mortality due to TM, despite the availability of DFO for almost three decades. Without adequate iron chelation therapy, myocardial siderosis develops within the first decade of life and leads, inexorably, to heart failure. Monitoring of cardiac involvement in iron overload presents major challenges, since neither serum ferritin nor liver iron levels are reliable indicators of cardiac iron, and clinical symptoms only appear late in the course of the disease. Measurement of heart iron load by MRI T2 and T2* technique is providing useful insights into both the course of myocardial siderosis and the relative benefits of iron chelators. However, substantial evidence continues to accumulate, which is independent of treatment compliance, that the oral iron chelator L1 possesses cardiac benefits when compared with DFO [30,31]. The available data appear to demonstrate that L1 may have greater cardiac benefits than DFO. A possible explanation for the apparent superiority of L1 over DFO in removing excess cardiac iron is that L1 has a superior ability to penetrate myocardial cells due to its lower molecular weight, neutral charge and greater lipophilicity [37].

DFO is administered parenterally and L1 is an oral therapy, so it is important to consider whether the apparent superiority of L1 in controlling cardiac iron might be due to superior compliance alone. This does not appear to be the case. Anderson et al [9] found excess cardiac iron, as assessed by a T2* of <20 ms, in DFO-treated patients who appeared to be complying with their drug regimen. In the study by Piga et al [10], in which cardiac disease-free survival was superior in the L1 group, the compliance rates were not significantly different for L1 and DFO. The authors speculated that the good compliance rate in the DFO group was due to the "regular and greater intensive attention" given to chelation therapy at the center. The same findings were also noted in our own studies [13,30,31] (Table 1). So, compliance was not the only variable but unarguably increased the treatments' effectiveness.

In a previous International Conference on Oral Chelation (ICOC) symposium [38], the ICOC committee recommended the following combination dose protocol for a universally effective chelation therapy in thalassemia patients: L1 at 80–110 mg/kg/day during the day and DFO 40–60 mg/kg/day, at least 3 days per week, during the night. The combination therapy can also be carried out in a simultaneous or sequential way as follows: DFO 20–50 mg/kg/day for 2–6 days (depending on the degree of iron overload) and L1 70–80 mg/kg/day for 7 days a week [39].

Results of large and controlled studies in humans became available in the 1990s and this allowed the approval of L1 in many countries, often as a second-line treatment for iron overload, although some put it in the first line in the late 1990s and 2000s. In recent years, data from several trials provided new evidence for the efficacy of L1 in the treatment of iron overload and its tolerability profile. Unfortunately, this drug has become an example, rightly or wrongly, of how difficult the academic–industry relationship can be today. Up to now (January 2007), L1 has not been approved in the United States or Canada.

7. Future strategies

Many clinical challenges remain. Cardiac complications still start too early in a patient's life and an ideal management strategy to prevent cardiac siderosis is still unclear. The role of the prophylactic use of L1, alone or in combination, needs to be determined. Combined therapy of L1 and DFO does not show any increased incidence of toxicity, and may be the best method in many transfusion-dependent patients for achieving satisfactory iron chelation therapy with good long-term patient compliance, especially in patients with cardiac complications [31]. It is possible that more frequent doses of DFO than those stated in the previously reported data, combined with L1 intake, will greatly augment the efficacy of this combined therapy. The optimal timing of MRI T2 or T2* assessments and the frequency of follow-up scans is still empirical. The role of conventional cardiovascular therapies, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and β-blockers, also needs to be fully defined. As one monograph has shown, the clinical evidence of an iron chelator's cardiac benefits takes years to demonstrate, and currently there exists only preliminary data on the ability of deferasirox to remove iron from the heart [40].

References

1. Zurlo MG, De Stefano P, Borgna-Pignatti C, et al. Survival and causes of death in thalassaemia major. *Lancet* 1989;2: 27–30.
2. Modell B, Khan M, Darlison M. Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register. *Lancet* 2000;355:2051–2.
3. Weatherall DJ, Pippard MJ, Callender ST. Editorial retrospective. Iron loading in thalassemia—five years with the pump. *N Engl J Med* 1983;308:456–8.
4. Olivieri NF, Brittenham GM, Matsui D, et al. Iron-chelation therapy with oral deferiprone in patients with thalassemia major. *N Engl J Med* 1995;332:918–22.

5. Kontoghiorghes GJ, Bartlett AN, Hoffbrand AV, et al. Long-term trial with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1). I. Iron chelation and metabolic studies. *Br J Haematol* 1990;76:295–300.
6. Agarwal MB, Gupte SS, Viswanathan C, et al. Long-term assessment of efficacy and safety of L1, an oral iron chelator, in transfusion dependent thalassaemia: Indian trial. *Br J Haematol* 1992;82:460–6.
7. Olivieri NF, Brittenham GM, McLaren CE, et al. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *N Engl J Med* 1998;339:417–23.
8. Hoffbrand AV, AL-Refaie F, Davis B, et al. Long term trial of deferiprone in 51 transfusion dependent iron overloaded patients. *Blood* 1998;91:295–300.
9. Anderson LJ, Wonke B, Prescott E, Holden S, Walker JM, Pennell DJ. Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassemia. *Lancet* 2002;360:516–20.
10. Piga A, Gagliotic C, Fogliacco E, Tricta F. Comparative effects of deferioprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. *Haematologica* 2003;88:489–96.
11. Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J* 2001;22:2171–9.
12. Wu KH, Chang JS, Su BH, Peng CT. Tricuspid regurgitation in patients with beta-thalassemia major. *Ann Hematol* 2004;83:779–83.
13. Huang YC, Chang JS, Wu KH, Peng CT. Regression of myocardial dysfunction after switching from deferoxamine to deferiprone in beta-thalassemia major patients. *Hemoglobin* 2006;30:229–38.
14. Anderson LJ, Westwood MA, Holden S, et al. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. *Br J Haematol* 2004;127:348–55.
15. Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Hematologica* 2004;89:1187–93.
16. Gabutti V, Piga A. Results of long-term iron-chelating therapy. *Acta Haematol* 1996;95:26–36.
17. Telfer PT, Prestcott E, Holden S, Walker M, Hoffbrand AV, Wonke B. Hepatic iron concentration combined with long-term monitoring of serum ferritin to predict complications of iron overload in thalassemia major. *Br J Haematol* 2000;110:971–7.
18. Olivieri NF, Nathan DG, MacMillan JH, et al. Survival in medically treated patients with homozygous beta-thalassemia. *N Engl J Med* 1994;331:574–8.
19. Brittenham GM, Griffith PM, Nienhuis AW, et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. *N Engl J Med* 1994;331:567–73.
20. Worwood M, Cragg SJ, Jacobs A, McLaren C, Ricketts C, Economidou J. Binding of serum ferritin to concanavalin A: patients with homozygous beta-thalassemia and transfusional iron overload. *Br J Haematol* 1980;46:409–16.
21. Wood JC, Tyszka JM, Carson S, Nelson MD, Coates TD. Myocardial iron loading in transfusion-dependent thalassemia and sickle cell disease. *Blood* 2004;103:1934–6.
22. Peng CT, Chow KC, Chen JH, Chiang YP, Lin TY, Tsai CH. Safety monitoring of cardiac and hepatic systems in beta-thalassemia patients with chelating treatment in Taiwan. *Eur J Haematol* 2003;70:392–7.
23. Wu KH, Chang JS, Tsai CH, Peng CT. Combined therapy with deferiprone and desferrioxamine successfully regresses severe heart failure in patients with beta-thalassemia major. *Ann Hematol* 2004;83:471–3.
24. Pippard MJ, Callender ST, Warner GT, Warner GT, Weatherall DJ. Iron absorption and loading in beta-thalassemia intermedia. *Lancet* 1979;2:819–21.
25. Angelucci E, Brittenham GM, McLaren CE, et al. Hepatic iron concentration and total body iron stores in thalassemia major. *N Engl J Med* 2000;343:327–31.
26. Cohen AR, Galanello R, Pennell DJ, Cunningham MJ, Vichinsky E. Thalassemia. *Hematology Am Soc Hematol Educ Program* 2004:14–34.
27. *Desferal R Product Monograph.* Novartis Inc.
28. Engle MA, Erlandson M, Smith CH. Late cardiac complications of chronic, severe refractory anemia with hemochromatosis. *Circulation* 1964;30:698–705.
29. Davis BA, O'Sullivan C, Jarritt PH, Porter JB. Value of sequential monitoring of left ventricular ejection fraction in the management of thalassemia major. *Blood* 2004;104:263–9.
30. Pennell DJ, Berdoukas V, Karagiorga M, et al. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. *Blood* 2006;107:3738–44.
31. Borgna-Pignatti C, Cappellini MD, De Stefano P, et al. Cardiac morbidity and mortality deferozamine- or deferiprone-treated patients with thalassemia major. *Blood* 2006;107:3733–7.
32. Peng CT, Wu KH, Wu SF, et al. Deferiprone or deferoxamine vs. combination therapy in patients with beta-thalassemia major: a case study in Taiwan. *Hemoglobin* 2006;30:125–30.
33. Olivieri NF. The beta-thalassemias. *N Engl J Med* 1999;341:99–109.
34. Eldor A, Rachmilewitz EA. The hypercoagulable state in thalassemia. *Blood* 2002;99:36–43.
35. Aessopos A, Farmakis D, Karagiorga M, et al. Cardiac involvement in thalassemia intermedia: a multicenter study. *Blood* 2001;97:3411–6.
36. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med* 2004;350:886–95.
37. Shalev O, Repka T, Goldfarb A, et al. Deferiprone (L1) chelates pathologic iron deposits from membranes of intact thalassemic and sickle red blood cells both *in vitro* and *in vivo*. *Blood* 1995;86:2008–13.
38. Abstract Book: 15th International Conference on Oral Chelation (ICOC) in the Treatment of Thalassemia and Other Diseases, Taichung, Taiwan, April 22–26, 2005.
39. Peng CT, Fucharoen S, Kontoghiorghes GJ, Tsai CH. Report on the proceedings of the 15th International Conference on Oral Chelation (ICOC) in the Treatment of Thalassemia and Other Diseases at Taichung, Taiwan, April 22–26, 2005. *Hemoglobin* 2006;30:63–8.
40. Porter JB, Tanner MA, Pennell DJ, Eleftheriou P. Improved myocardial T2* in transfusion dependent anemias receiving ICL670 (deferasirox). *Blood* 2005;106:3600. (ASH Annual Meeting Abstracts)