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ORIGINAL ARTICLE **CME**

Iron Chelation Effects of Different Treatment Protocols in Thalassaemia Major: Comparison by Magnetic Resonance T2* over Two Years

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ABSTRACT

Objective: *Myocardial haemosiderosis leading to cardiac dysfunction is a major complication in transfusion-dependent thalassaemia. Our objective was to compare the iron chelation efficacy of the recently launched deferasirox (ICL670) with conventional deferoxamine (DFO) and the combined regimen of deferiprone (L1) and DFO in thalassaemia major patients, based on our local experience.*

Methods: *This was a retrospective study. Nineteen thalassaemia major patients received ICL670 for one year (as part of a therapeutic trial). All underwent magnetic resonance imaging assessment of T2* for myocardial and hepatic iron content and left ventricular ejection fraction at baseline and after one year. Twelve and 21 patients with similar T2* cardiac or liver values at baseline were selected as controls, who received DFO and combination therapy (DFO+L1), respectively. Changes in T2* values, left ventricular ejection fraction, and serum ferritin were evaluated at baseline and follow-up and the efficacy of each type of treatment was compared (analysis of variance with one factor).*

Results: *In all three treatment groups, there was significant improvement of mean myocardium T2* ($p<0.05$), and the DFO+L1 and ICL670 groups showed significant improvements in mean left ventricular ejection fraction ($p<0.05$), as well as liver T2* and ferritin levels.*

Conclusion: *This study suggests that ICL670 is as efficient as DFO and DFO+L1 for iron chelation in the heart. ICL670 is comparable to combination therapy in improving both left ventricular ejection fraction and iron chelation of the liver.*

Key Words: *Chelation therapy; Deferoxamine; Hemosiderosis; Magnetic resonance imaging; Thalassemia*

中文摘要

針對重型地中海貧血患者的不同治療方案中鐵螯合劑效果的比較：連續兩年T2加權磁共振成像的研究

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目的：對於依靠輸血的地中海貧血患者來説，心肌血鐵質沉着病引致心功能不全屬嚴重併發症。本文在香港地中海貧血患者中，比較三種療法的去鐵效果，它們分別為：最新推出的口服鐵螯合劑

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（deferasirox, ICL670）、傳統的去鐵胺（deferoxamine, DFO），以及排鐵劑deferiprone（L1）與DFO的聯合療法。

方法：本回顧研究的對象為19名重型地中海貧血患者。作為治療試驗的一部分，他們均接受ICL670已達一年。在開始治療前和接受治療一年後，用磁共振成像(MR) T2* 量度患者的心肌和肝的鐵含量，以及左心室射血分數。與此同時，安排兩組對照組，其中一組是接受DFO的12名患者，另一組是接受L1及DFO聯合療法的21名患者。在開始試驗前，兩對照組的心肌T2*值和肝的鐵含量都與實驗組相似。利用ANOVA比較三組患者在治療開始前和治療後的T2*值、左心室射血分數、及血清鐵蛋白值的轉變。並比較每種治療的效用。

結果：三組患者心肌T2*值均有顯著改善（$p<0.05$）。接受ICL670的患者及接受L1及DFO聯合療法的患者在左心室射血分數有明顯改善（$p<0.05$），而兩組在肝T2*值和鐵蛋白水平方面亦有改善。

結論：本研究顯示ICL670在心臟的鐵螯合治療方面，可媲美DFO和L1及DFO聯合療法。對於改善左心室射血分數及肝的鐵螯合治療方面，ICL670可媲美L1及DFO聯合療法。

INTRODUCTION

Thalassaemia is the commonest genetic disorder worldwide, with approximately 94 million heterozygotes for beta thalassaemia and 60,000 homozygotes born each year.[1] The estimated Hong Kong prevalence of carriers is 5% for α-thalassaemia and 3% for β-thalassaemia.[2] In last three decades, owing to an effective preventative programme (antenatal screening, antenatal diagnosis, and successful curative treatment with matched sibling haemopoietic stem cell transplantation), the total number of transfusion-dependent thalassaemia patients has not been increasing.[3] According to data from the local Red Cross Blood Transfusion Service, Hong Kong currently has about 380 such transfusion-dependent patients.[3]

Cardiac failure secondary to transfusional iron overload–related cardiomyopathy remains the commonest cause of death in patients with thalassaemia major. The cardiomyopathy is reversible if intensive iron chelation treatment is instituted in time.[4-6] Serum ferritin has long been used as a clinical indicator for monitoring the effectiveness of chelation therapy. However, there is clear documentation of a discrepancy between serum ferritin levels and iron overload in the myocardium. Anderson et al[7] showed that serum ferritin level has no significant correlation with the iron load and the left ventricular ejection fraction (LVEF). Monitoring the myocardial iron load by imaging is thus prudent and essential for optimising chelation therapy and minimising cardiac-related mortality. Since 2006, the magnetic resonance imaging (MRI) scanner in our institution has been validated according to the method of Pennell,[8] and has been applied to assess iron deposition in heart and liver for all thalassaemia patients in Hong Kong.[9]

Deferoxamine mesylate (DFO) (Desferal; Novartis, Basel, Switzerland) has been the standard drug for iron chelation therapy for more than three decades. A combination regimen of deferiprone (L1) and DFO has been introduced for thalassaemia major patients who respond poorly to DFO alone. The ability of the above two drugs to decrease iron load from various organs like the liver, heart, and endocrine glands thereby reduces complications and is well-established in the literature.[3] In this study, we sought to compare the iron chelation efficacy of a recently launched chelating agent deferasirox (ICL670) with the two former drugs using MRI assessment after one year.

METHODS

Patients

From 2006 to 2007, 19 thalassaemia major patients were invited to join a therapeutic trial on ICL670 on voluntary basis. The inclusion criteria were: either T2* liver <6.3 ms or T2* heart <20 ms. Retrospectively, patients receiving chelation other than ICL670 with similar T2* heart / liver values at the above study period were also recruited. Twelve subjects received DFO and 21 subjects received combination of DFO + L1. Thus, 52 transfusion-dependent thalassaemia patients (22 females and 30 males; age range, 9-36 years; mean age, 19 years) formed the cohort for this study. They all had regular follow-up in a tertiary haematological referral centre. Since childhood, all of them had been receiving regular blood transfusion once

every three to five weeks together with iron chelation therapy.

Therapy with DFO consisted of daily subcutaneous DFO infusion five to seven days a week (50 mg/kg/day). Patients who received combination therapy continued DFO at their original dose together with L1 at 75 mg/kg/day in three divided doses. In the three groups, compliance was considered to be similar. All patients underwent baseline assessment of T2* myocardium and T2* liver. A follow-up MRI was then performed one year later. The entire study received institutional ethical approval and written informed consent was given by all patients.

Study Protocol: Magnetic Resonance Imaging and Serum Ferritin

A breath-hold MRI sequence was performed to assess T2* of the myocardial and hepatic iron contents and a short-axis cine true FISP (fast imaging with steady state free precession) sequence to cover base to apex to assess LVEF at baseline and at the one-year follow-up. The T2* measurements were made using thalassaemia tools (CMR tools, Cardiovascular Imaging Solutions, London, UK). In the heart a transmural region of interest (ROI) was drawn on the ventricular septum image, so as to avoid potential susceptibility artefacts from cardiac veins and air in the lung (Figure 1a).[10] The exponential signal decay curve (Figure 1b) was then constructed and a T2* value was calculated. Myocardium with a T2* value of more than 20 ms was taken as normal, based on previous controlled studies. The T2* evaluation of the liver was made with the same analytic tool. The largest ROI was drawn on the periphery of the liver image, avoiding the hepatic and portal veins (Figure 2a). The T2* evaluation of the liver was then made (Figure 2b). The T2* measurements were taken at least twice and a mean value was obtained. All cine true FISP images from base to apex were used to measure the LVEF.[11] At all levels, during systole and diastole the endocardium was outlined manually and the LVEF calculated using commercially available software (Argus), that is incorporated into our Syngo 2004A (Siemens) workstation.

All the above measurements were taken by the same experienced radiologist who had no knowledge of the treatment arm of each patient. Serum ferritin level was checked for each subject within one week of the MRI assessment; any level of >4400 pmol/l was defined as abnormal based on categorisation from previous studies.[7,12]

Statistical analysis

Differences in cardiac T2*, liver T2* and LVEF (%) determined by MRI between the baseline and the one-year follow-up values were evaluated for all three groups. Improvements in T2* values of myocardium and liver and EF were denoted by a positive value while improvements in serum ferritin level were denoted

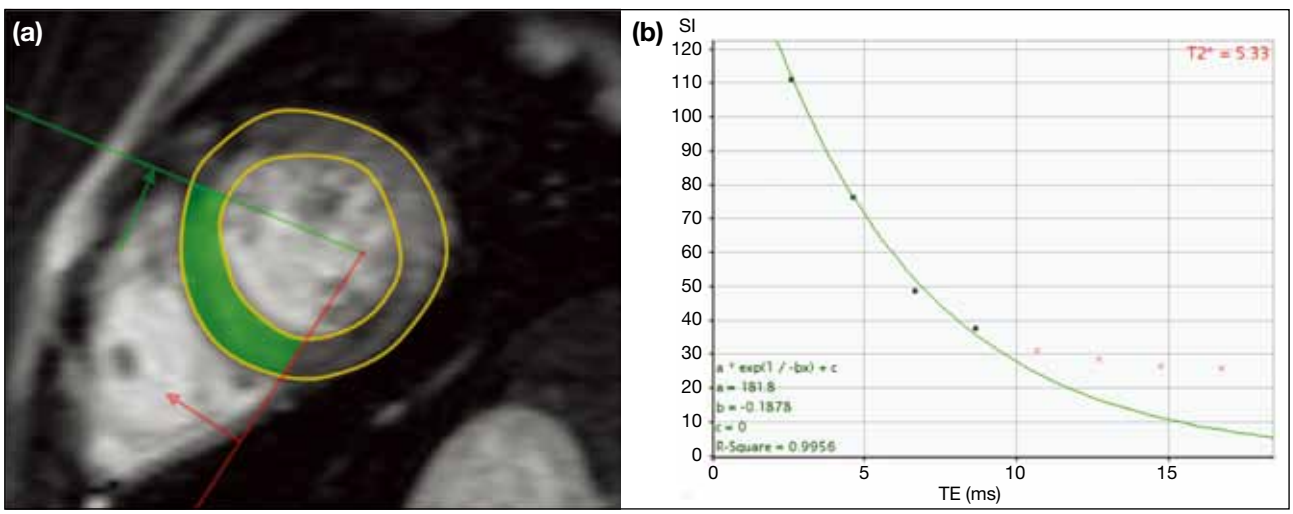

Figure 1. Magnetic resonance imaging assessment of myocardium T2* value. (a) Transmural region of interest is drawn in the ventricular septum (highlighted in green). Caution has been taken to avoid potential susceptibility artefacts from the cardiac veins and air in the lung. (b) Data analysis using thalassaemia tools (CMR tools, Cardiovascular Imaging Solutions, London, UK): the signal intensity (TE) is plotted against multiple TE values (2.6, 4.62, 6.64, 8.66, 10.68, 12.7, 14.72, 16.47 ms). The exponential signal decay curve is then constructed. T2* value is calculated automatically by the preset formula. A T2* value of less than 10 ms indicates severe iron overload in the heart.

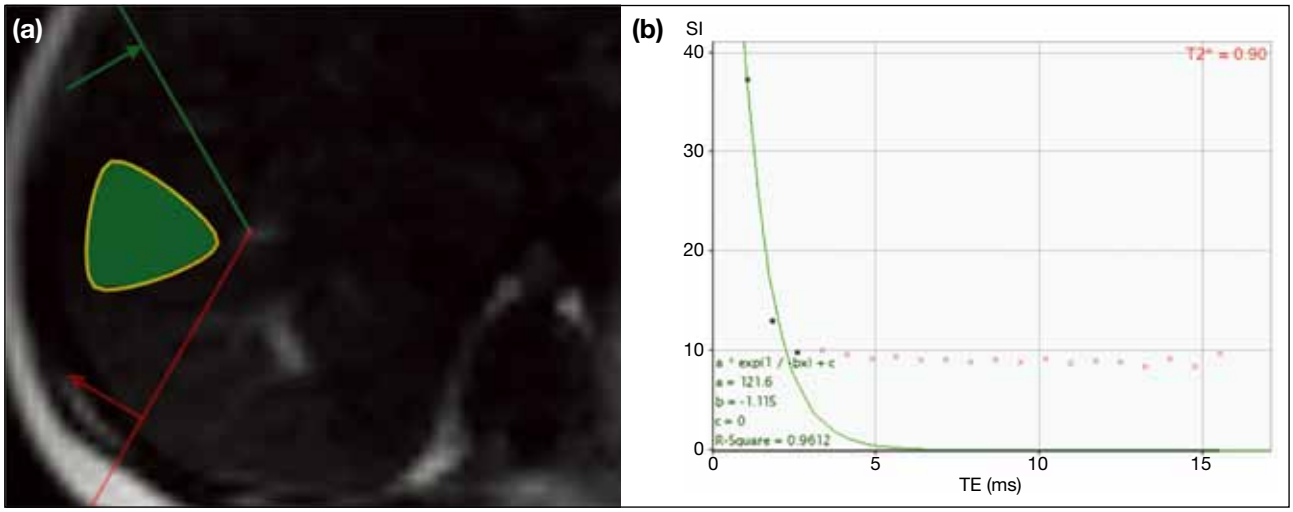

Figure 2. Magnetic resonance imaging assessment of hepatic T2* value: (a) Region of interest is drawn in the periphery of the right lobe of liver (highlighted in green), avoiding the hepatic and portal veins. (b) Data analysis using (CMR tools, Cardiovascular Imaging Solutions, London, UK): the signal intensity (TE) is plotted against multiple TE values (1.07, 1.83, 2.59, 3.35, 4.11, 4.87, 5.63, 6.39, 7.15, 7.91, 8.67, 9.43, 10.19, 10.95, 11.71, 12.47, 13.23, 13.99, 14.75, 15.51 ms). The exponential signal decay curve is then constructed. T2* value is calculated automatically by the preset formula. A T2* value of less than 1.4 indicates severe iron overload in the liver.

by a negative value. Improvements in serum ferritin levels, iron contents of the heart and liver (T2*) and LVEF with each treatment protocol were compared using paired *t* tests. Correlation analyses were carried out between T2* myocardium, T2* liver, LVEF, and serum ferritin levels. P values of <0.05 were considered significant. All the statistical analyses were performed using the Statistical Package for the Social Sciences (Windows version 17.0; SPSS Inc, Chicago [IL], US).

RESULTS

The demographic data and treatment details of all subjects at baseline are summarised in Table 1. The categorisation of T2* values was based on previous studies,[11] and the values are shown in Table 2.

Most patients in the DFO group had higher baseline T2* myocardium values and there was a significant group difference in baseline T2* myocardium values between the DFO and the other two groups (ANOVA; p = 0.016). Otherwise, there was no significant difference between the groups (for T2* liver, serum ferritin level, and LVEF).

The change of categorisation for all subjects in the three treatment groups is given in Tables 1 and 3.

T2* Myocardium and Ejection Fraction

In all three treatment arms, compared to baseline there was a significant improvement of myocardial T2* values (p<0.05) at follow-up. Most DFO patients had normal LVEF values at baseline and there was no significant improvement at follow-up. Whereas a significant proportion of DFO + L1 and ICL670 patients had suboptimal LVEF values; these two groups showed significant improvements at follow-up (p<0.05).

T2* Liver

Compared to baseline values, only DFO + L1 and ICL670 groups showed improvement in T2* liver levels at follow-up. There was no significant change in the T2* liver level in the DFO group.

Serum Ferritin

Only the ICL670 group showed an improvement in the ferritin level (p<0.05), there being no significant difference between consecutive years for DFO patients.

DISCUSSION

Blood transfusion is the prime treatment for the thalassaemia major patients. Chronic iron overload resulting from the life-saving blood transfusions is a serious complication due to iron deposition in various tissues of the body, particularly the liver, heart, and endocrine organs.[13]

Although effective in reducing iron stores in the body, DFO has some drawbacks, namely a short duration

Table 1. Distribution of T2* myocardium, T2* liver, LVEF, and serum ferritin values at baseline and FU among three treatment groups. The T2* myocardium value is lower in DFO + L1 group (p = 0.016, ANOVA); while the other parameters are not significantly different among the three groups (all p>0.05, ANOVA). Note categorisation of each parameter is based on reference by Royal Brompton Hospital[7] and Ha et al.[3]

	ICL group (n = 19)		DFO+L1 group (n = 21)		DFO group (n = 12)	
Mean age (years)	19.7		21.0		17.8	
Sex (M : F)	11 : 8		11 : 10		9 : 3	
T2* myocardium (ms)	Baseline	FU	Baseline	FU	Baseline	FU
<10	5	3	6	4	0	0
10-14	3	4	3	3	0	0
15-20	4	4	4	3	2	1
>20	7	8	8	11	10	11
T2* liver (ms)	Baseline	FU	Baseline	FU	Baseline	FU
<1.4	1	0	2	0	2	2
1.4-2.7	6	2	4	5	2	1
2.8-6.3	9	12	8	5	4	5
>6.3	3	5	7	11	4	4
LVEF	Baseline	FU	Baseline	FU	Baseline	FU
<56%	10	3	5	1	0	0
>56%	9	16	16	20	12	12
Serum ferritin (pmol/l)	Baseline	FU	Baseline	FU	Baseline	FU
<4400	1	6	13	12	3	5
>4400	18	13	8	9	9	7

Abbreviations: LVEF = left ventricular ejection fraction; DFO = deferoxamine mesylate; ICL = deferasirox; L1 = deferiprone; ANOVA = analysis of variance; FU = follow-up.

Table 2. Categorisation of T2* values based on previous studies.[11]

Iron load	T2* values (ms)			
	Severe	Moderate	Mild	Normal
In the myocardium	<10	10-14	15-20	>20
In the liver	<1.4	1.4-2.7	2.7-6.3	>6.3

of action and the need for parenteral administration. These features necessitate 10-12–hour subcutaneous or intravenous infusions by pump, daily, for five to seven days a week. Not surprisingly, there is poor compliance with this treatment regimen, particularly in adolescents.[14-16] In Hong Kong, DFO has been available since early 1980,[17] however complications due to iron overload are still common.[17] Apart from these complications, the relative inability of DFO to remove cardiac and endocrine iron in some patients is a major cause of morbidity and mortality.

L1 (an oral iron chelator) has proved to be more effective than subcutaneous DFO in removing cardiac iron. In some countries, marketing authorisation has been granted to this product (Ferriprox; Apotex Toronto [ON], Canada) in the form of solid tablets administered three times a day. In Hong Kong, it is currently approved as second-line therapy requiring weekly neutrophil count monitoring. The disadvantages of L1 are its narrow therapeutic window viz-a-viz safety including drug-related agranulocytosis and arthropathy.[18,19] L1 was confirmed to have the safety and efficacy when use in combination with DFO in the poorly chelated patients.[3,20] Ha et al[21] have demonstrated efficacy of this combined regimen (DFO + L1) based on cardiac MRI. Their study has shown better reductions in serum ferritin levels and favourable effects on cardiac and liver iron using a combined DFO + L1 regimen.

ICL 670 was developed in response to the need for an oral iron-chelating agent which could be safely administered and increase compliance in patients of all ages, and across a range of iron burdens. It has been available in our locality since 2006 and belongs to a new class of oral tridentate chelators, the N-substituted bis-hydroxyphenyl-triazoles.[22-27] Compared to DFO, ICL670 has the additional potential advantage of being able to gain access to labile cellular iron pools of cardiomyocytes via attenuating the formation of reactive oxygen species and possible restoration of myocardial contractility.[28] Furthermore, no agranulocytosis, arthropathy, or growth failure has been associated with its administration.[23] The most common reported side-effects due to repeated administration were abdominal pain, nausea, vomiting, diarrhoea, constipation, and skin rash. These symptoms were generally of mild-to-moderate severity and often resolved even when

Table 3. Absolute values of T2* myocardium, T2* liver, left ventricular ejection fraction and serum ferritin at baseline and follow-up among the three treatment groups.

	Mean ± standard deviation		
	ICL group (n = 19)	DFO+L1 group (n = 21)	DFO group (n = 12)
T2* myocardium (ms)			
Baseline (B)	21.1 ± 13.5	16.5 ± 7.3	28.1 ± 10.3
Follow up (F)	28.2 ± 19.6	26.1 ± 15.6	34.8 ± 11.2
Change (F-B)	7.1 ± 8.2*	9.6 ± 10.0†	6.8 ± 7.1*
T2* liver (ms)			
Baseline (B)	4.3 ± 2.5	5.5 ± 3.8	5.2 ± 3.9
Follow up (F)	6.8 ± 5.4	8.2 ± 6.5	6.2 ± 5.7
Change (F-B)	2.5 ± 4.6*	2.7 ± 4.2*	0.9 ± 2.6
Left ventricular ejection fraction (%)			
Baseline (B)	55.2 ± 8.6	59.8 ± 8.3	61.1 ± 6.0
Follow up (F)	61.0 ± 6.2	66.2 ± 6.5	64.8 ± 5.8
Change (F-B)	5.8 ± 7.9*	6.4 ± 7.2*	3.7 ± 8.8
Serum ferritin (pmol/l)			
Baseline (B)	7528 ± 3293	6353 ± 7216	5596 ± 1997
Follow up (F)	6167 ± 2870	6414 ± 7448	5675 ± 2446
Change (F-B)	-1362 ± 2071*	61.1 ± 1669	49.2 ± 2293

Abbreviations: DFO = deferoxamine mesylate; ICL = deferasirox; L1 = deferiprone.

* $p<0.05$, paired *t* test
† $p<0.001$, paired *t* test

the drug was continued. Preclinical evaluation and initial clinical studies have demonstrated the efficacy of ICL670 in the removal of cardiac iron.[29,30] More recently, a prospective study in a large group of patients with β-thalassaemia and a longitudinal analysis of myocardial T2* in iron-chelated patients have provided further evidence of supporting ICL670's utility in removing and preventing myocardial iron accumulation.[31-33]

Several recently published articles describe experience with ICL670 using cardiac MRI utilising T2* and/or LVEF estimation. Pathare et al[25] evaluated myocardial iron loading by T2* MRI and total body iron load using serum ferritin measurements and liver iron concentration by biopsy in 19 patients with β-thalassaemia major over an 18-month period. ICL670 therapy significantly improved mean cardiac T2* from baseline (17.2 ± 10.8 to 21.5 ± 12.8 ms). Improvements were noted in patients with various degrees of cardiac siderosis, including those with a baseline cardiac T2* of <10 ms, indicative of a high cardiac iron burden. Pennell et al[34] has tested the efficacy of ICL670 in reducing or preventing cardiac iron overload in 192 patients with β-thalassaemia in a one-year prospective, multicentre study. They found it to be effective in removing and preventing myocardial iron accumulation in patients with cardiac siderosis (T2* 5-20 ms) and even in the prevention arm patients (T2* >20 ms).

Ruffo et al[35] reported the long-term effects of ICL670 in a case series of five transfusion-dependent β-thalassaemia major patients who underwent up to five years of chelation therapy. It was concluded that ICL670 might decrease cardiac iron overload and maintain a stable LVEF in the long term.

A study by Berdoukas et al[36] with 232 patients compared the efficacy of DFO, combination regimen of DFO + L1, and ICL670. It concluded that combination therapy (DFO + L1) was the best in reducing both cardiac and hepatic iron, while monotherapy with L1 or ICL670 were nevertheless effective for the heart and liver, respectively. In our study, monotherapy with ICL670 and combination therapy of DFO + L1 were both more effective in reducing body iron loading than DFO alone, in terms of improving serum ferritin levels.

One limitation of our present study was that selection of subjects into different treatment arms was not randomised. Subjects with stable T2* myocardium values were treated with DFO only, while those with high serum ferritin and / or low T2* myocardium values were given the choice of combination treatment (DFO + L1) or ICL670. Furthermore a number of our patients were also invited to the therapeutic trial of ICL670 regardless of their T2* myocardium levels. Thus, there was an uneven distribution of patients with different degree of myocardial iron loading in each group. For

similar reasons, baseline liver iron load and serum ferritin varied between the three groups. Such selection bias was unavoidable in the course of optimising patient management.

Another limitation was that those taking DFO only had normal LVEF values at the start of the study, so in this group a marked improvement after treatment was not expected. Whereas the DFO + L1 and ICL670 groups had significant proportions of patients with suboptimal LVEF, for whom effective chelation was expected to achieve benefits. Furthermore, the overall compliance in both patient groups improved during the study period, which may have resulted from information provided to participants in this study.

The large range of standard deviations for each measured parameter also made the statistical analysis difficult to interpret. However, Table 3 shows that a significant number of subjects in the ICL670 and DFO + L1 groups changed from being the most severe affected (T2* myocardium value <10 ms or T2* liver value <1.4 ms) to becoming less severely affected. For the DFO + L1 group, the mean baseline T2* myocardium of 16.5 changed to 26.1 post-treatment ($p<0.001$, paired *t* test). Similarly, mean baseline T2* liver of 5.5 changed to 8.2 post-treatment ($p<0.05$, paired *t* test), while the mean baseline LVEF of 59.8 changed to 66.2 ($p<0.05$, paired *t* test). For ICL670 group, the corresponding changes were from 21.1 to 28.2 ($p<0.05$, paired *t* test), 4.3 to 6.8 ($p<0.05$, paired *t* test), and 55.2 to 61.0 ($p<0.05$, paired *t* test), respectively. There was also an improvement in mean ferritin levels from 7528 to 6171 pmol/l post-treatment ($p<0.05$, paired *t* test). The number of patients with suboptimal LVEF (< 56%) also decreased (from 5 to 1 for the DFO + L1 group and from 10 to 3 for ICL670 group). Finally, the small sample size compared to previous similar studies was another limitation.

CONCLUSION

The present study compares different treatment arms by testing the response of newer chelating agent ICL670 with conventional DFO and combined regimen of DFO + L1 on the iron chelation in transfusion-dependent thalassaemia patients in Hong Kong. The preliminary data from the present study suggest that ICL670 showed significant improvement in LVEF, serum ferritin, and iron chelation of the heart and liver, and was more efficient in improving T2* of liver and ferritin levels than the DFO alone regimen. Its efficacy was also comparable to traditional combined regimen of DFO + L1, while sparing patients from the risk of agranulocytosis and other significant toxicities. Further studies with larger patient groups are warranted to substantiate these observations.

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DISCLAIMER

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