Comparison of Deferiprone to Deferasirox and Deferoxamine to Cardiac and Hepatic T2* MRI in Thalassemia Patients: Evidence-based Case Report

Pustika A. Wahidiyat, Mikhael Yosia, Teny T. Sari

Department of Child Health, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Pustika Amalia Wahidiyat, MD., PhD. Division of Pediatric Haematology - Oncology, Department of Child Health, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital. Jl. Pangeran Diponegoro no. 71, Jakarta 10430, Indonesia. email: pa.wahidiyat@gmail.com.

ABSTRAK

Latar belakang: *saat ini terdapat tiga jenis kelasi besi yang tersedia untuk pasien di Indonesia: deferiprone/ DFP (dengan merk dagang Ferriprox), deferasirox/DFX (dengan merk dagang Exjade) and deferoxamine/DFO (dengan merk dagang Desferal). Tujuan dari studi ini adalah untuk melihat kelasi besi mana yang paling efisien dalam menurunkan kelebihan besi pada miokard dan hepar yang dilihat dari hasil T2* MRI.* ***Metode:*** *pencarian jurnal dengan terminologi MeSH dilakukan di PubMed dan Scopus. Studi pada pasien thalassemia mayor di semua umur yang menggunakan monoterapi kelasi besi dan melihat efeknya pada T2* MRI liver atau miokard diikutkan ke dalam analisis. Penilaian dari studi yang digunakan dilakukan dengan metoda penilaian studi dari Oxford's CEBM dan Joana Brigs Institute.* ***Hasil:*** *total 11 studi dengan jumlah total 611 sampel diikutkan dalam analisa studi ini. Nilai rerata T2* MRI dan (jika tersedia) nilai rerata perubahan T2* MRI setelah penggunaan satu jenis kelasi besi dianalisa dari semua studi yang diikutkan. Studi komparasi maupun studi individu menemukan kontrol dan peningkatan miokardiak T2* MRI pada sampel menggunakan DFP, sedangkan penggunaan DFO yang taat lebih baik dalam mengontrol dan meningkatkan liver T2* MRI.* ***Kesimpulan:*** *DFP lebih superior dalam mengontrol dan menurunkan beban besi miokard (dibuktikan oleh miokardial T2* MRI) sedangkan DFO memiliki kemampuan lebih baik dalam mengontrol dan menurunkan beban besi pada hepar (dibuktikan oleh liver T2* MRI). Studi dengan waktu observasi lebih lama dan sampel yang lebih besar dibutuhkan untuk melihat efek signifikan DFX terhadap T2* MRI.*

Kata kunci: *besi, talasemia, T2* MRI.*

ABSTRACT

Background: *there are currently three iron chelator readily available for patients Indonesia; deferiprone/ DFP (branded as Ferriprox), deferasirox/DFX (branded as Exjade) and deferoxamine/DFO (branded as Desferal). This study aims to determine which iron chelator is the most efficient in reducing cardiac and hepatic iron overload (measured by means of T2* MRI).* ***Methods:*** *journal search with determined MeSH term was done in PubMed and Scopus. Studies that looked upon thalassemia major patient in all ages with usage of monotherapy iron chelation and its effect on myocardial T2* MRI and/or liver T2* MRI was included. Appraisal of studies was done using Oxford's CEBM appraisal tools and Joanna Brigs Institute critical appraisal tools.* ***Results:*** *total of 11 studies with grand total of 611 samples were included. Mean T2* MRI value or (when available) mean changes in T2* MRI value after usage of specific iron chelator was gained from all the studies included. Comparison study and individual studies shows better control and increase of myocardial T2* MRI in those*

with DFP, and of liver T2 in those with good adherence to DFO chelation.* ***Conclusion:*** *DFP is superior in controlling or reducing myocardial iron load (as proven by mT2* MRI) and DFO had better capabilities in controlling or reducing hepatic iron load (as proven by liver T2* MRI). Studies with longer observation and larger samples is needed to see a significant changes of T2* MRI in DFX.*

Keywords: *iron chelation, thalassemia, T2* MRI.*

INTRODUCTION

Iron overload (hemochromatosis) is a condition of excess iron accumulation in the body from any cause, one of them being repeated blood transfusions.[1] In patients who needs frequent and/or continuous blood transfusion (e.g. Sickle cell anaemia, thalassemia, aplastic anaemia, leukaemia, etc), excess iron from donor blood accumulate and in time manifest itself into transfusional hemosiderosis in which iron accumulates in the liver, heart and endocrine organs causing clinical syndromes such as cardiomyopathy, diabetes and hepatic cirrhosis.

In order to prevent manifestation of excess iron into diseases, iron chelator had long been used. There are currently three different types of iron chelator readily available for patients Indonesia; deferiprone/DFP (branded as Ferriprox), deferasirox/DFX (branded as Exjade) and deferoxamine/DFO (branded as Desferal). Each of the three chelator offers different benefits and challenges to the patients; DFP comes in tablet (500 mg/tab) or syrup (100mg/mL) which makes it easier for children to consume, DFX are also available in 250 and 500 mg/tablet form, DFO is the first iron chelator available for use in RSCM but it can only be administered via subcutaneous (sc) or intravenous (iv) injection thus explaining its unpopularity and low compliance.[2]

There are different means of assessing iron overload in patients; simple blood examination (total iron binding capacity/TIBC, serum iron/SI, transferrin saturation/TS and serum ferritin/SF) and radiology (T2* MRI). As a more reliable mean to predict iron overload in organ (especially heart and liver), T2* MRI had been meticulously used to assess hemosiderosis and whether dose adjustment or combination iron chelation therapy is needed.[2]

There are studies available that assess the benefits of all different iron chelator; Luangasanatip et al[1] and Pepe et al[2] both uses Quality Adjusted Life Years (QALY) assessment to see economic benefits of each drugs, Xia et al[3] look upon serum ferritin (SF), liver iron concentration (LIC), myocardial iron content (MIC), left ventricular ejection fraction (LVEF) and adverse events (AEs) as means of assessing effectiveness of each different iron chelator. Yet the question still remains, which iron chelator is the most efficient in regards to reducing cardiac and hepatic iron overload through assessment via T2* MRI.

CLINICAL QUESTION

11-year-old boy with beta-thalassemia major, had been receiving continuous blood transfusion. His recent T2* MRI result shows a moderate hepatic and myocardial iron load. Previous doctor prescribed DFO for the last 3 years, but compliance level had been very low due to the hassle of sc administration. Current attending doctor decided to prescribed oral DFP with hopes that compliance level may increase and his body iron load can be controlled. The patient parents become concern with the change of iron chelator and T2* MRI results, they asked whether the oral drug given is more effective compared to the sc ones their child had been using.

From the case illustration, a clinical question arises: "Which of the three iron chelator (DFP, DFX, DFO) is the most effective in reducing cardiac and hepatic iron load proven by means of T2* MRI?"

METHODS

This review will consider all in vivo studies in human subjects of any age who suffers from thalassemia. Intervention includes usage of DFP and/or DFX and/or DFO monotherapy in any dose. Those on combination iron chelator aren't

going to be included. Outcome measure wanted are T2* MRI that assess both/either hepatic or cardiac iron load. All Randomized Control Trial (RCT), prospective study, retrospective study, cross-sectional study with full text available in English or Indonesian since 20 years ago will be included.

Search Strategy

The initial search terms will be 'iron chelator', 'MRI T2*', 'thalassemia', followed by proper MeSH search (**Table 1**). Articles published in the following databases will be searched: PubMed and Scopus. Full copies of articles identified by the search, and considered to meet the inclusion criteria, based on their title, abstract and subject descriptors, will be critically appraised.

RESULTS

Summary of the literature search process and result can be seen in **Figure 1**. This study included 6 prospective studies, 1 randomized control trial, 1 prospective-comparative studies, 2 cross-sectional studies and 1 retrospective studies. In total, 11 studies are included with a total of 611 patients using different monotherapy of either DFP, DFO or DFX. All the studies used adhere to the criteria that is set by the

Table 1. Search strategy and MeSH term used

Database	Search terms	Hits	Selected article
PubMed/Scopus	("iron"[MeSH terms] OR "iron"[All Fields]) AND ("chelating agents" [Pharmacological Action] OR "chelating agents" [MeSH Terms] OR ("chelating" [All Fields] AND "agents" [All Fields]) OR "chelating agents" [All Fields] OR "chelator" [All Fields]) AND ("thalassemia" [All Fields] OR "thalassemia" [MESH Terms] OR "thalassemia" [All Fields]) AND ("magnetic resonance imaging" [MeSH Terms] OR ("magnetic" [All Fields] AND "resonance" [All Fields] AND "imaging" [All Fields]) OR "magnetic resonance imaging" [All Fields] OR "mri" [All Fields]) and t2 [All Fields	140	10

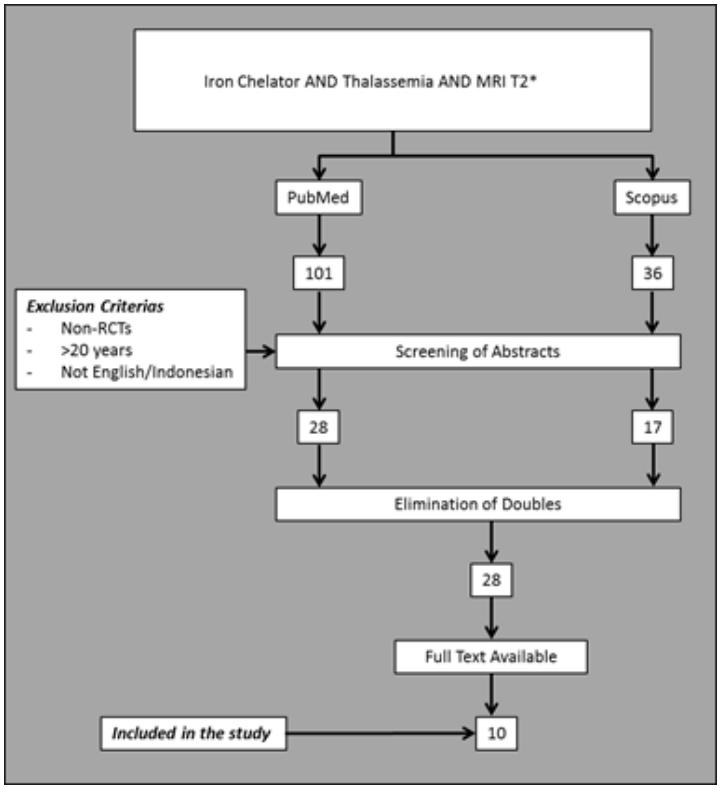

Figure 1. Flowchart of search result

Joanna Briggs Institute (JBI) critical appraisal tools (for randomized control trial, cohort and cross-sectional studies – respectively Appendix 1, Appendix 2 and Appendix 3), summary of appraisal result can be seen in **Table 3**. Breakdown for sample allocation and chelator dosage of each study present in **Table 2**. Oxford CEBM appraisal of prognosis study was used to assess all of the studies, summary of the result can be seen in **Table 4**.

DISCUSSION

The aim of this evidence based case report was to evaluate the effectiveness of DFO, DFP, and DFX alone in reducing hepatic and cardiac iron load (proven by means of MRI T2* value) in transfusion-dependent patients with thalassemia major.

Table 2. Summary of studies included with years of publication, age range of samples and type of chelator used in each study

Design	Years	Age Range (years)	Chelator Used	Samples (n)	Dose Range (mg/kgbw/day)	Author
Prospective Study	2013	6-29	DFX	30	25-35	Ahmed et al[4]
Prospective-comparative Study	2016	5-18	DFX	17	30	Gomber et al[5]
			DFP	17	75	
Prospective Study	2017	16-79	DFX	53	up to 40	Ho et al[6]
Prospective Study	2011	6-29	DFX	30	20 increased to 35	Merchant et al[7]
Prospective Study	2010	10-29	DFX	19	20	Pathare et al[8]
Prospective Study	2010	13-28	DFX	101	92	Pennell et al[9]
Randomized Control Trial	2006	25-31	DFP	29	43	Pennell et al[10]
			DFO	32	33.6 ± 9.8	
Cross-sectional study	2006	19-39	DFP	18	75	Pepe et al[11]
			DFO	18	50	
Retrospective cohort	2011	19-41	DFP	42	72 ± 10	Pepe et al[12]
			DFO	89	30 ± 9	
			DFX	24	26 ± 6.3	
Prospective Study	2013	3-19	DFP	73	79.1 ± 4.3	Viprakasit et al[13]
Cross-sectional study	2013	1-17	DFP	14	75–100	Zachariah et al[14]
			DFX	5	25–40	

Table 3. Summary of study appraisal based on JBI appraisal checklist

Author	Design	Score based on appropriate JBI appraisal*													Overal appraisal
		1	2	3	4	5	6	7	8	9	10	11	12	13	
Ahmed et al[4]	Prospective study	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	NA	Included
Gomber et al[5]	Prospective study	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	NA	NA	Included
Ho et al[6]	Prospective study	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	NA	NA	Included
Merchant et al[7]	Prospective study	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	NA	Included
Pathare et al[8]	Prospective study	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NA	NA	Included
Pennell et al[9]	RCT	U	U	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	Included
Pennell et al[10]	Prospective study	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Included
Pepe et al[11]	Cross-section	Y	Y	Y	Y	N	N	Y	Y	NA	NA	NA	NA	NA	Included
Pepe et al[12]	Retrospective	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	NA	NA	Included
Viprakasit et al[13]	Prospective study	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Included
Zachariah et al[14]	Cross-section	Y	Y	Y	Y	Y	N	N	Y	NA	NA	NA	NA	NA	Included

*Scored gained/maximum score, appropriate appraisal for either RCT, cohort (prospective or retrospective) or cross-sectional study was used. RCT - 13 criteria, cohort - 11 criteria, cross-section - 8 criteria.
Y=yes; N=no; U=unclear; NA=not applicable.

Table 4. Breakdown of sample allocation followed by validity criteria fulfilment and study importance; being represented by mean liver and cardiac MRI T2* results pre and post chelation. 95%CI are included when the data is available. Change describes the number of decrease or increase of MRI T2* result

	Study	Ahmed et al[4]	Gomber et al[5]		Ho et al[6]	Merchant et al[7]	Pathare et al[8]	Pennell et al[9]		Pennell et al[10]	Pepe et al[11]		Pepe et al[12]			Viprakasit et al[13]	Zachariah et al[14]	
Subject	Total (n)	30	34		53	30	19	61		101	36		155			73	19	
	Control/placebo	0	0		0	0	0	0		0	0		0			0	0	
	DFP (n)	0	17		0	0	0	29		0	18		42			73	14	
	DFO (n)	0	0		0	0	0	32		0	18		89			0	0	
	DFX (n)	30	17		53	30	19	0		101	0		24			0	5	
Validity	Common point[a]	Yes	Yes		Yes	Yes	Yes	Yes		Yes	Yes		Yes			Yes	Yes	
	Sufficient follow up[b]	Yes	Yes		Yes	Yes	Yes	Yes		Yes	Yes		Yes			Yes	Yes	
	Blinded/ objectivity[c]	Yes	Yes		Yes	Yes	Yes	Yes		Yes	Yes		Yes			Yes	Yes	
	Time follow up	18 mo	12 mo		12 mo	18 mo	18 mo	12 mo		24 mo	cross-section		retrospective			12 mo	cross-section	
	Chelator used	DFX	DFP	DFX	DFX	DFX	DFX	DFP	DFO	DFX	DFP	DFO	DFP	DFO	DFX	DFP	DFP	DFX
Importance	Mean MRI T2* cardiac (ms)																	
	- Pre		33.30	32.00	21.92	23.80	17.20	13.00	13.30	11.20								
	- 95% CI		31.86-34.74	30.00-34.00														
	- Post		32.30	31.70	24.10	24.20	21.50	16.50	15.00	14.80	35.00	27.00	34.00	27.00	21.00		37.10	31.70
	- 95% CI		30.64-33.96	29.05-34.35														
	Change (ms)		-1.00	-0.30	2.18	0.40	4.30	3.50	2.70	3.60								
	p-value		>0.05	>0.05	<0.05	>0.05	>0.05	<0.05	<0.05	<0.05	<0.05		<0.05				>0.05	
	Mean MRI T2* liver (ms)																	
	- Pre	1.74	5.40	5.10												2.58		
	- 95% CI	1.41-2.19	5.20-5.60	4.58-5.62														
	- Post	1.76	5.60	5.40							3.70	12.00	6.60	10.90	5.50	2.93		
	- 95% CI	1.37-2.25	5.34-5.86	4.82-5.98														
	Change (ms)	0.02	0.20	0.30												0.35		
	p-value	>0.05	>0.05	>0.05							<0.05		<0.05			<0.05		
	Applicable	Yes	Yes		Yes	Yes	Yes	Yes		Yes	Yes		Yes			Yes	Yes	
	Level of evidence	2b	2b		2b	2b	2b	1b		2b	2b		2b			2b	2b	

[a] Samples are recruited at the same point of the disease progression; [b] Samples' follow up were sufficient and complete; [c] Outcome measures are blinded and/or objective; mo=months

Based upon study by Saggar et al[15], normal MRI T2* range for iron deposition in several organs (namely pancreas, liver and myocardial) can be defined. In regards to myocardial T2* value; normal range is defined as >20 ms, mild to moderate as 10-20 ms while severe as <10 ms. Value for hepatic iron load is defined as; normal T2* value would be >6.3 ms, mild is defined as 6.3-2.7 ms, moderate as 2.7-1.4 ms and severe <1.4 ms. These values would be used when talking about severity of siderosis for the sake of discussion in this study.

Myocardial T2* MRI

Looking upon usage of DFO alone, mean mT2* value from two studies (both by Pepe et al[2]) similarly shows 27.00 ms which can be defined as normal range of cardiac iron load. This result is very promising, considering that both study looked upon patients aged 19-41 years old where cardiac siderosis is usually already present (though not always as cardiac siderosis may be present at earlier age).[16] Other study that looked upon DFO is Pennell's randomized control trial, patient in this study had mild to moderate cardiac siderosis yet in the end of the study mean increase of 2.70 ms is observed in those treated with DFO. This result is in line with previous studies, namely by Borna-Pignatti et al[17] that shows how iron-related heart disease had decreased after the introduction of DFO (with earlier therapy commencement being an important aspect). Anderson et al[18] shows that 3 months of continuous DFO (50-60mg/kgbw/day) iv administration are able to normalize LVEF. Porter et al[19], however, mentioned also that if mT2* <10 ms it would take a few years to normalize mT2* with continuous DFO infusion.

DFP uses had somewhat been more preferable in many patients due to its ease of administration in oral form. Five studies (Gomber et al[5], two of Pepe et al[2] studies, Zachariah et al[14] and Pennell et al[10]) looked upon the effectiveness of DFP in improving mT2*. Two of Pepe's studies and Zachariah et al only had mean mT2* value; 35.00 ms (Pepe's cross-section), 34.00 ms (Pepe's retrospective), 37.10 ms (Zachariah et al[14]). All of the results shows normal mT2* value, it should be noted that Pepe's studies had patient from 19 years of age – 41 years of age with pretty large sample size. Zachariah had noted that his study had a limitation of low sample (with only 14 samples in DFP group). Gomber et al[5], curiously, saw a decrease in mT2* by -1.00 ms, though the study found that this changes is insignificant and blame this unusual result to small sample size combined with relatively short follow up time (12 months). Pennell's[9] study had measurements of mT2* before and after iron chelation therapy; his sample includes patient with mild to moderate cardiac siderosis (13.00 ms) and after one year of DFP consumption significant (p-value <0.05) increase of 3.50 ms is observed. The benefits that DFP has on myocardium and cardiac function in general is in concordance with Maggio et al's[20] study in which an improvement of left ventricular ejection fraction was observed in patients with DFP monotherapy.

There are seven studies that looked upon the effect of DFX on mT2*, these are studies by Gomber et al[5], Ho et al[6], Merchant et al[7], Pathare et al[8], Pennel et al[9] (prospective study), Pepe et al[11] (retrospective study) and Zachariah et al[14]. Gomber et al[5] looked upon those with good cardiac iron load and saw an insignificant decrease of 0.30 ms in mT2*, similar to what had been previously explained he blamed this odd results to sample size and follow up time. Ho et al also looked upon patient with good cardiac iron load and saw a significant increase of 2.18 ms after 12 months of DFX. Merchant et al saw an insignificant increase of 0.40 ms in patient with normal mT2*. Pathare et al[8] saw an insignificant increase of 4.30 ms in patient with mild-moderate mT2*, the study mentioned that more sample would probably resulted in a statistically significant value. Pennel et al[9,10] looked upon patient with mild-moderate mT2* and found a significant increase of 3.60 ms. Pepe et al[11] and Zachariah et al[14] only had mean mT2* value of those with DFX chelator (respectively, 21.00 ms and 31.70 ms), both studies found good mT2* MRI value in all patients with DFX chelator.

There are five studies present with direct comparison between two or more chelators and these are studies done by Gomber et al[5], Pennell et al[9,10], both studies by Pepe et al[11,12], and Zachariah et al[14]. Gomber et al[5] compares DFP and DFX, results of his studies shows an

insignificant decrease (increase in iron load) in mT2* MRI for both DFP and DFX group (-1.00 ms and -0.30 ms respectively), though this study mentioned a somewhat lower decrease in DFX group, the result is insignificant due to very small sample size. Pennell et al[9,10] randomized control trial looked upon DFP and DFO use for 12 months and found a significant increase more favourable in those with DFP (increase of 3.50 ms compared to 2.70 ms), the study recommended a dose of around 90-100 mg/kgbw/day in order to continually improve cardiac function (judged by increase in T2* MRI). Pepe et al[9] cross sectional study found that mean T2* MRI is more favourable in those with continuous DFP usage (35.00 ms) compared to those with DFO infusion (27.00 ms). This result is similar to mechanism of DFP that is mentioned by Piga et al[21], in this study DFP is deemed to be more effective in removing myocardial iron load due to its 10 fold higher capabilities in removing citrate bound iron (an important component of Non-transferin-bound iron/NTBI, a major contributor of iron damage). Previous effect is compounded by the fact that DFP has longer half-life and more frequent dosing (3 times/day, 7 day/week) resulting in more iron protection compared to DFO (8-12 hour/day, 5-7 times per week). Pepe et al[12] retrospective study looked upon mean mT2* MRI result on patients with all three different chelators with DFP having significantly higher mean mT2* value (34.00 ms) followed by DFO (27.00 ms) and DFX (21.00 ms) resonating the results of previous studies. Zachariah et al[14] further support the trend that DFP patients seems to have higher mT2* (37.10 ms compared to 31.70 ms in DFX patient) which correlates with increase in patient's cardiac function. In comparison to both DFX and DFO, DFP seems to be superior in removing iron from the myocardium due to several possible reasons; its higher capability to mobilize NTBI, longer time available in the blood stream. As studied and mentioned by Anderson et al[18], DFP also had a smaller molecular weight, though this means that the iron-chelator complex is somewhat less stable, it allows DFP to penetrates easier into cells thus allowing removal of more iron from the myocardium.

Liver T2* MRI

Two studies both by Pepe et al looked upon the effect of DFO on liver T2* MRI value, with both study showing good mean MRI T2* value (12.00 ms and 10.90 ms). These observations are resonated by several studies, such as those by Brittenham et al and Cappelini et al[24], in which usage of DFO infusion at a dose of around 37 mg/kgbb/day is enough to stabilize or even reduced LIC (liver iron content).

Three studies, two by Pepe et al[12] and one by Viprakasit et al[13], looked upon the mean liver T2* in patient with DFP chelator. Both study done by Pepe et al[12] only presented mean liver T2* at one point in time with both showing mild siderosis in group with DFP chelation (3.70 ms in the cross-sectional study and 6.00 ms in the retrospective study). Viprakasit et al[13] study showed more favourable result with an increase 0.35 ms after one year of DFP consumption in patient with moderate hepatic siderosis. An older study by Fischer et al[25] shows also that negative iron balance by means of LIC can only be achieved in 1/3 of the patient using 75 mg/kgbw/day of DFP.

Three studies by Ahmed et al[4], Gomber et al[5] and Pepe et al[11] looked upon DFX effect on liver T2* value. Ahmed et al[4] looked upon patient with moderate to severe liver T2* MRI and found an insignificant increase of 0.02 ms after 18 months of DFX administration. Gomber et al[5] looked upon patient with mild liver T2* MRI and also found and insignificant increase of 0.30 after 12 months of DFX administration. Pepe et al[11] on the other hand looked upon mean liver T2* MRI in patient that had been consuming DFX and found a value of 5.50 (mild liver T2* MRI). This results resonates previous studies by Cappellini et al[24] who mentioned that only moderate reduction of LIC present in children under 6 years with average dose of 21.9 mg/kgbw/day.

Studies done by Gomber et al[5], and two studies by Pepe et al[11] compares mean liver T2* value between different chelators. Gomber et al[5] compares liver T2* value after 12 months of DFP or DFX, the study found insignificant change of 0.20 ms and 0.30 ms respectively in patient with mild liver siderosis. In Pepe et al's cross-sectional present only mean liver T2* value,

3.70 ms (mild siderosis) in group with DFP and 12.00 ms (normal) in those with DFO. Pepe et al's retrospective study resonates similar result (in regards to effectiveness and normal liver T2* in those with DFP); patient with DFO had mean liver T2* value of 10.90 ms (normal liver T2*), those with DFP had 6.60 ms (borderline normal T2*), and patient with DFX with 5.50 ms (mild siderosis). Through these comparisons alone, it can be seen that patient with treatment of DFO had better mean liver T2* MRI and good improvement after continuous administration of either intravenous or subcutaneous DFO. Looking back upon the aforementioned studies by Cappellini et al[24] and Britenham et al[23], it can be seen that DFO do have superior capability of controlling and even reducing liver iron. Though it should always be taken into consideration that adherence to DFO therapy can sometimes be challenging to patient; as had been mentioned by Viprakasit et al[13], Pennell et al[10] whilst Olivieri et al[26] found that compliance of oral chelation (DFP) can reach 95% while those with intravenous chelation (DFO) can only reach 72% compliance rate.

CONCLUSION

Through analysis done in this study it can be seen that DFP is superior in controlling or reducing myocardial iron load (as proven by mT2* MRI) and DFO had better capabilities in controlling hepatic iron load (as proven by liver T2* MRI). Usage of DFP or DFX, as oral chelator) is more preferable due to its ease of use, with several studies presenting higher compliance rate in patient with oral chelator compared to injection (sc or iv) chelator. Studies with longer observation and larger samples is needed to see a significant changes of T2* MRI in DFX.

ACKNOWLEDGMENTS

Authors of these study would like to thank fellow doctors and Faculty of Medicine – Cipto Mangunkusumo Hospital for their support.

REFERENCES

1. Luangasanatip N, Chaiyakunapruk N, Upakdee N, Wong P. Iron-chelating therapies in a transfusion-dependent thalassaemia population in Thailand: a cost-effectiveness study. Clin Drug Investig. 2011;31(7):493-505.
2. Pepe A, Rossi G, Bentley A, et al. Cost-utility analysis of three iron chelators used in monotherapy for the treatment of chronic iron overload in beta-thalassaemia major patients: An Italian perspective. Clin Drug Investig; 2017.
3. Xia S, Zhang W, Huang L, Jiang H. Comparative efficacy and safety of deferoxamine, deferiprone and deferasirox on severe thalassemia: a meta-analysis of 16 randomized controlled trials. PLoS One. 2013;8(12):e82662.
4. Ahmed J, Ahmad N, Jankharia B, Krishnan P, Merchant RH. Effect of deferasirox chelation on liver iron and total body iron concentration. Indian J Pediatrics. 2013;80(8):655-8.
5. Gomber S, Jain P, Sharma S, Narang M. Comparative efficacy and safety of oral iron chelators and their novel combination in children with thalassemia. Indian J Pediatrics. 2016;53(3):207-10.
6. Ho PJ, Tay L, Teo J, et al. Cardiac iron load and function in transfused patients treated with deferasirox (the MILE study). Eur J Haematol. 2017;98(2):97-105.
7. Merchant R, Ahmed J, Krishnan P, Jankharia B. Efficacy and safety of deferasirox for reducing total body and cardiac iron in thalassemia. Indian J Pediatrics. 2012;49(4):281-5.
8. Pathare A, Taher A, Daar S. Deferasirox (Exjade) significantly improves cardiac T2* in heavily iron-overloaded patients with beta-thalassemia major. Ann Hematol. 2010;89(4):405-9.
9. Pennell DJ, Porter JB, Cappellini MD, et al. Continued improvement in myocardial T2* over two years of deferasirox therapy in beta-thalassemia major patients with cardiac iron overload. Haematologica. 2011;96(1):48-54.
10. Pennell DJ, Berdoukas V, Karagiorga M, Ladis V, Piga A, Aessopos A, Gotsis ED, Tanner MA, Smith GC, Westwood MA, Wonke B. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. Blood. 2006;107(9):3738-44.
11. Pepe A, Lombardi M, Positano V, et al. Evaluation of the efficacy of oral deferiprone in beta-thalassemia major by multislice multiecho T2*. Eur J Haematol. 2006;76(3):183-92.
12. Pepe A, Meloni A, Capra M, et al. Deferasirox, deferiprone and desferrioxamine treatment in thalassemia major patients: cardiac iron and function comparison determined by quantitative magnetic resonance imaging. Haematologica. 2011;96(1):41-7.

13. Viprakasit V, Nuchprayoon I, Chuansumrit A, et al. Deferiprone (GPO-L-ONE((R))) monotherapy reduces iron overload in transfusion-dependent thalassemias: 1-year results from a multicenter prospective, single arm, open label, dose escalating phase III pediatric study (GPO-L-ONE; A001) from Thailand. Am J Hematol. 2013;88(4):251-60.
14. Zachariah M, Tony S, Bashir W, Al Rawas A, Wali Y, Pathare A. Comparative assessment of deferiprone and deferasirox in thalassemia major patients in the first two decades-single centre experience. Pediatric Hematol Oncol. 2013;30(2):104-12.
15. Saggar K, Sobti P. MRI Assessment of iron overload in thalassemia: an overview. Rivista Italiana di Medicina dell'Adolescenza-Volume. 2013;11(1).
16. Ambati SR, Randolph R, Mennitt K, Kleinert DA, Giardina P. Monitoring cardiac siderosis in patients with beta-thalassemia major on various chelation regimens. Blood. 2011;118(21):3177.
17. Borgna-Pignatti CA, Rugolotto SI, De Stefano P, Zhao HU, Cappellini MD, Del Vecchio GC, Romeo MA, Forni GL, Gamberini MR, Ghilardi RO, Piga AN. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica. 2004;89(10):1187-93.
18. Anderson LJ, Westwood MA, Holden S, Davis B, Prescott E, Wonke B, Porter JB, Malcolm Walker J, Pennell DJ. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. British J Haematol. 2004;127(3):348-55.
19. Porter JB, Tanner MA, Pennell DJ, Eleftheriou P. Improved myocardial T2* in transfusion dependent anemias receiving ICL670 (Deferasirox). Blood. 2005;106(11):3600.
20. Maggio A, Vitrano A, Lucania G, Capra M, Cuccia L, Gagliardotto F, Pitrolo L, Prossomariti L, Filosa A, Caruso V, Gerardi C. Long-term use of deferiprone significantly enhances left-ventricular ejection function in thalassemia major patients. Am J Hematol. 2012;87(7):732-3.
21. Piga A, Gaglioti C, Fogliacco E, Tricta F. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. Haematologica. 2003;88(5):489-96.
22. 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-thalassaemia. Lancet. 2002;360(9332):516-20.
23. Brittenham GM, Cohen AR, McLaren CE, Martin MB, Griffith PM, Nienhuis AW, Young NS, Allen CJ, Farrell DE, Harris JW. Hepatic iron stores and plasma ferritin concentration in patients with sickle cell anemia and thalassemia major. Am J Hematol. 1993;42(1):81-5.
24. Cappellini MD, Bejaoui M, Agaoglu L, Porter J, Coates T, Jeng M, Lai ME, Mangiagli A, Strauss G, Girot R, Watman N. Prospective evaluation of patient-reported outcomes during treatment with deferasirox or deferoxamine for iron overload in patients with β-thalassemia. Clinical Therapeutics. 2007;29(5):909-17.
25. Fisher R. Large-scale study in thalassemia using biomagnetic liver susceptometry. InProc. 11th Int. Conf/Biomagnetism 1998.
26. Olivieri NF, Brittenham GM. Final results of the randomized trial of deferiprone (L1) and deferoxamine (DFO). InBlood 1997;90(10):1161.