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The Economics of Iron Chelation in Developing Countries

Suthat Fucharoen M.D.

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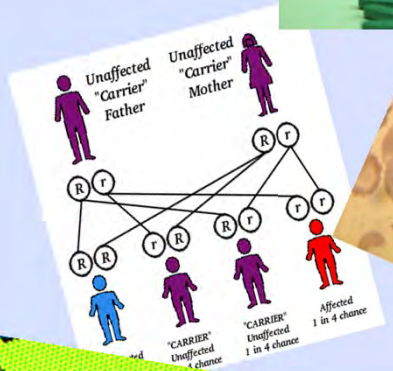
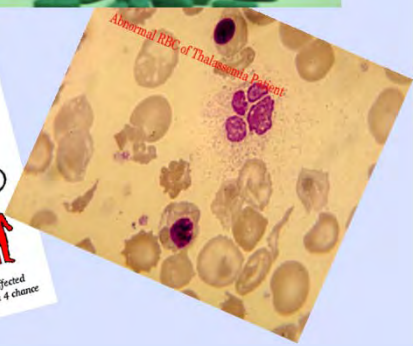
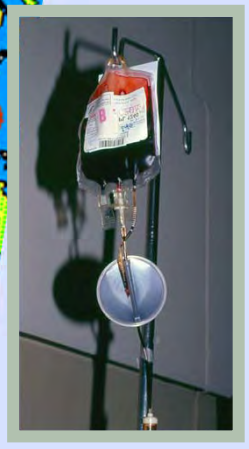
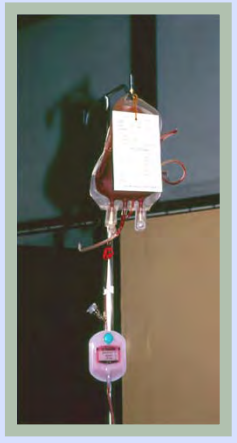
Institute of Molecular Biosciences

Mahidol University









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Pathophysiology of β–Thalassemia/Hb E Disease

Membrane damage

β-Thalassemia genes

Excess unbound α-globin chains

Inclusion bodies
Increased RBC destruction

Iron excess

Increased bilirubin production

Anemia

RE hyperplasia

Gallstones

Jaundice

Massive erythropoiesis

Hepatosplenomegaly

Extramedullary hematopoiesis

Defective development

Bone changes

Iron overload

Blood transfusion

Cardiac failure, Cirrhosis, DM

Increased infection

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Iron and thalassemia

- Healthy adult: Fe turn over 1 – 2 mg/d
- RBC 1 ml → Fe 1.16 mg
- Packed RBC 1 unit ~ Fe 200 mg
- β thal/Hb E patient → Fe absorption 0.1mg/kg/d

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Tissue Iron (autopsy)

	β-thalassemia/Hb E		Normal		
	M±SD	n	M±SD	n	P.value
Liver	6,096 ± 2,511	12	661 ± 321	25	.0001
Spleen	3,576 ± 1,269	11	1,188 ± 767	20	.0001
Pancreas	5,609 ± 3,733	6	120 ± 52	25	.02
Heart	**441 ± 335**	**8**	**166 ± 103**	**20**	**.01**
Brain	279 ± 34	5	215 ± 42	11	.07
Kidney	898 ± 495	8	329 ± 141	16	.01

- μg Fe/gm dry weight, J.Trace Elements in Exp. Med 1990;3:31-43

n = number of autopsy cases

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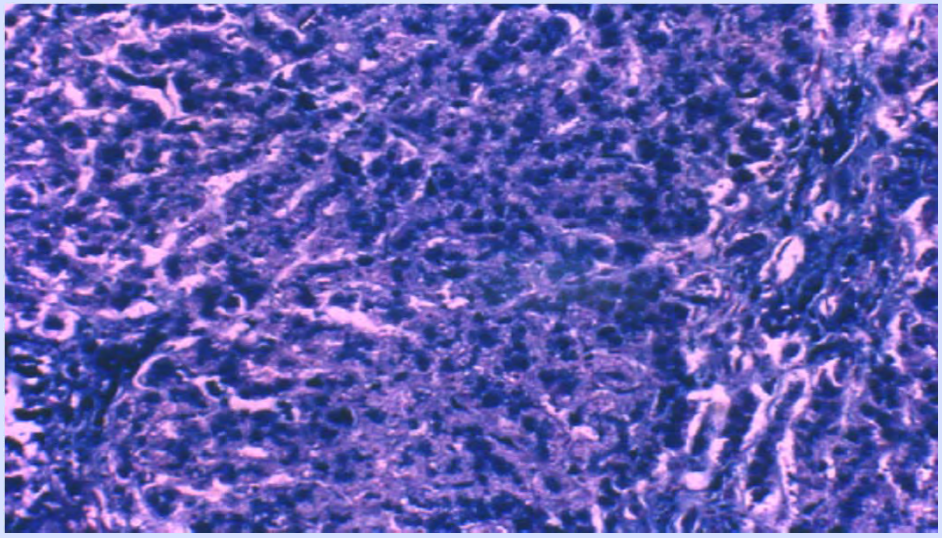

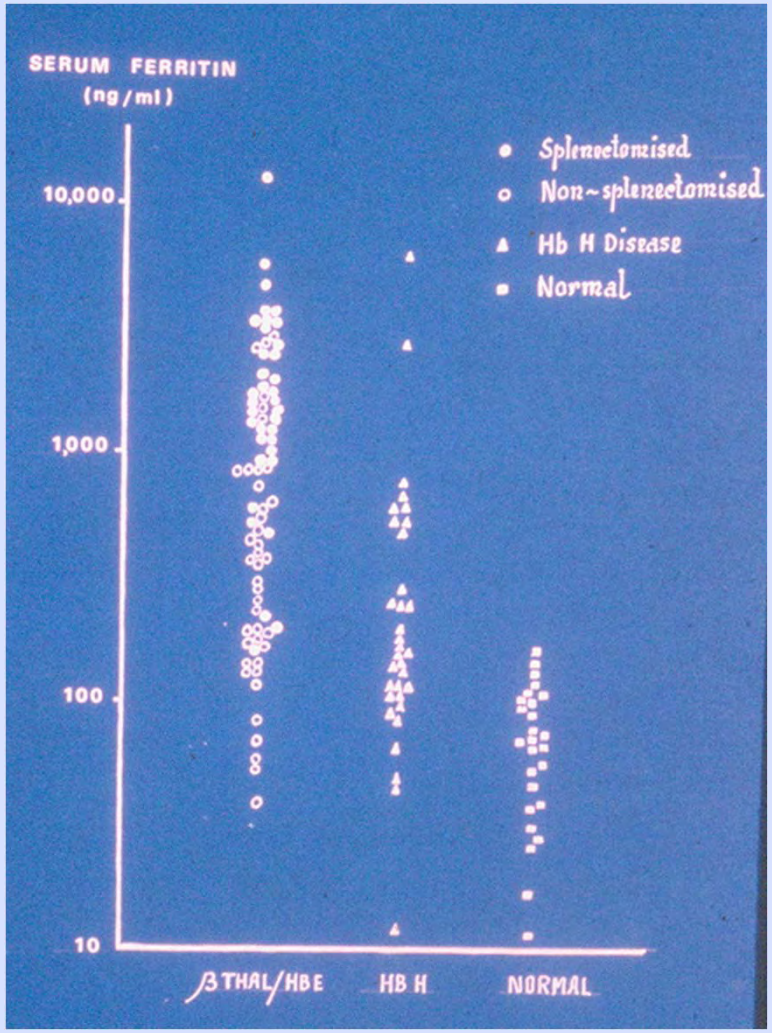

Iron Overload: Skin changes, liver iron and serum ferritin

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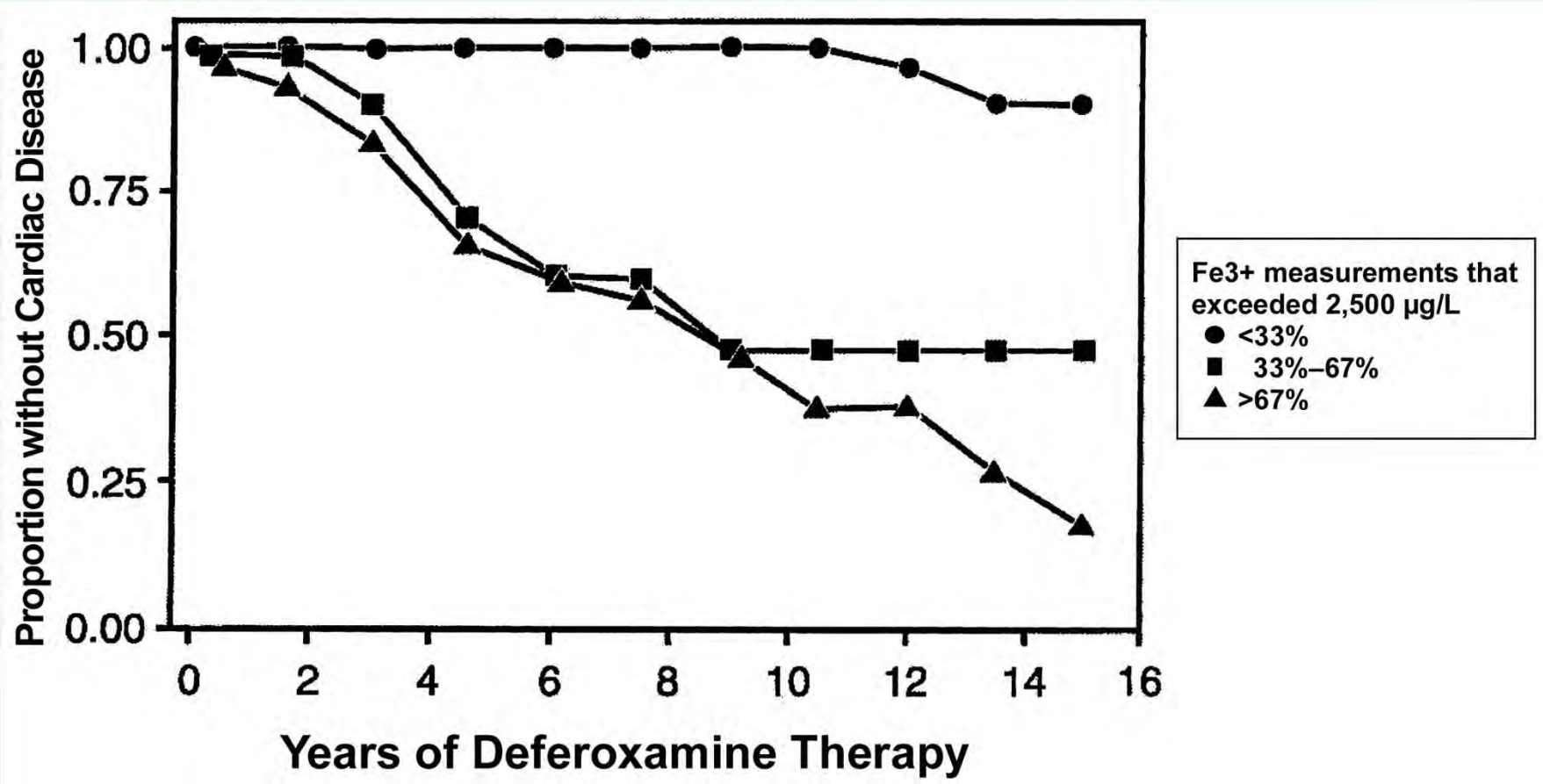
Survival a Function of Serum Ferritin



From Olivieri NF, et al. *NEJM.* 1994;331:574-578. Reproduced with permission

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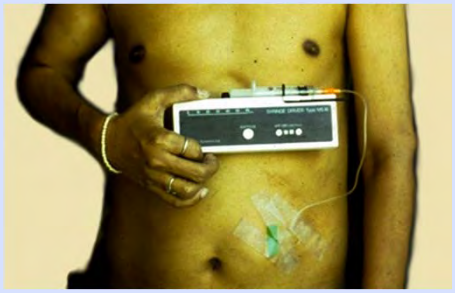
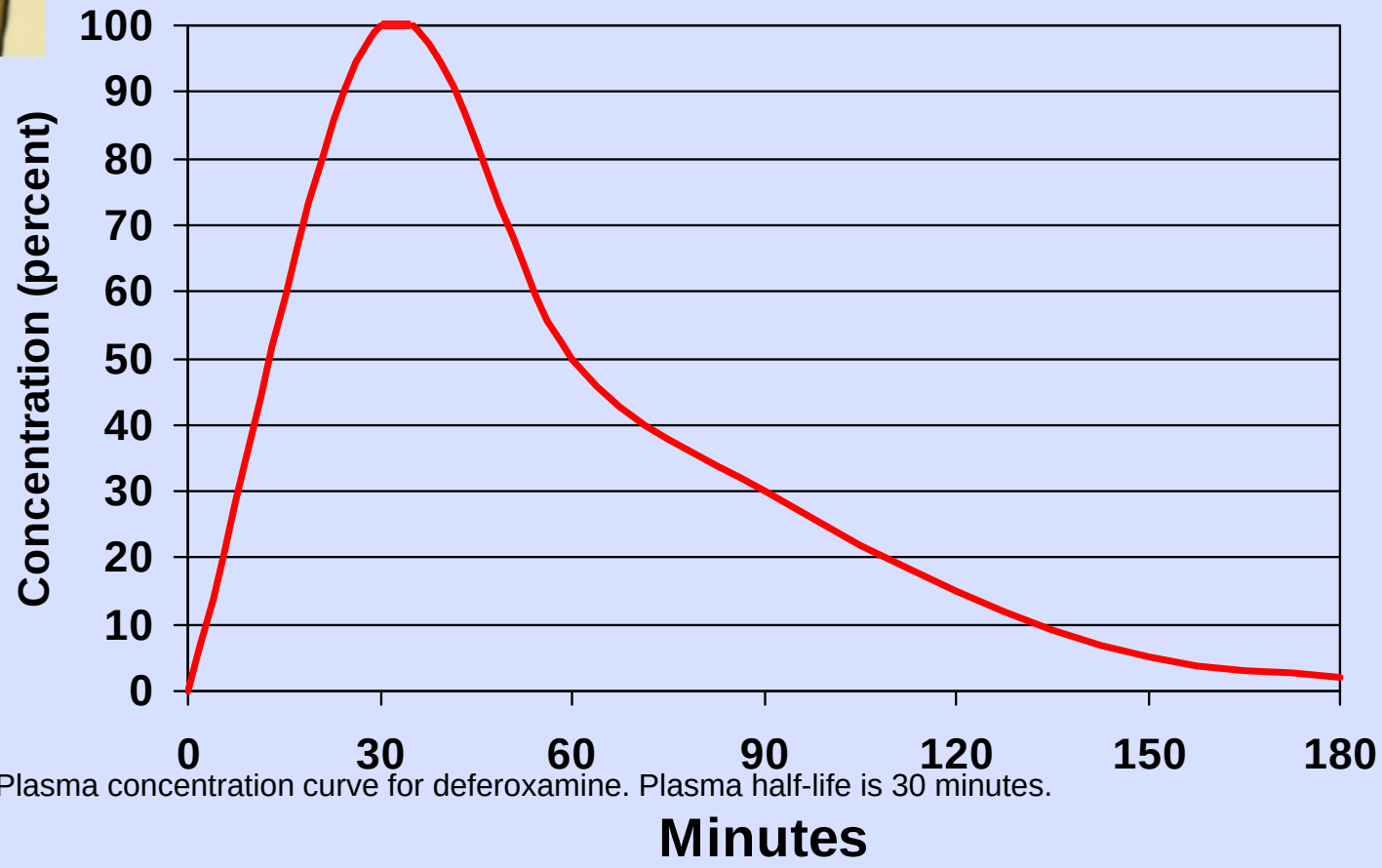
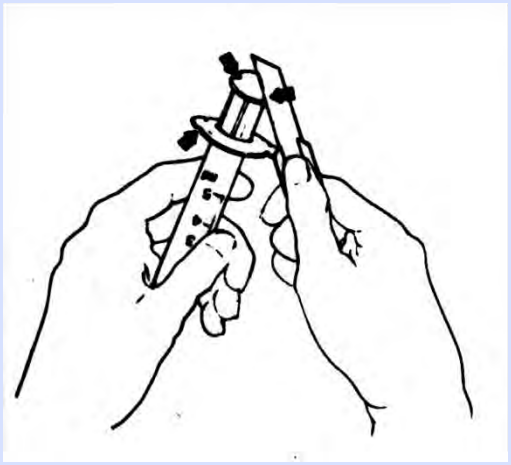


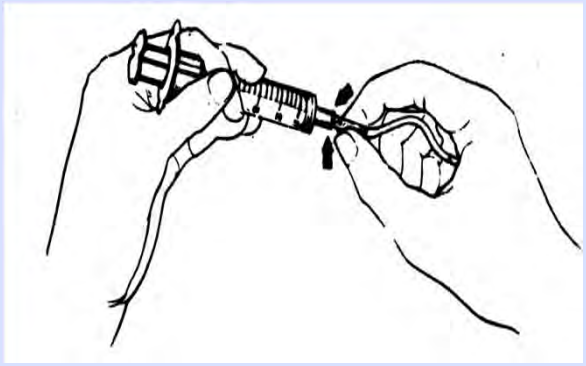
Deferoxamine: Mode and Frequency of Administration (1)



Plasma concentration curve for deferoxamine. Plasma half-life is 30 minutes.



1.



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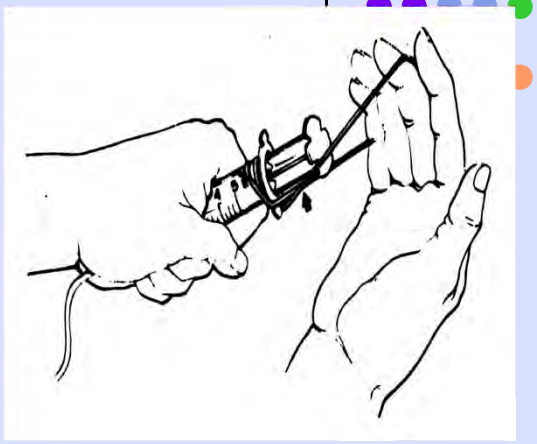

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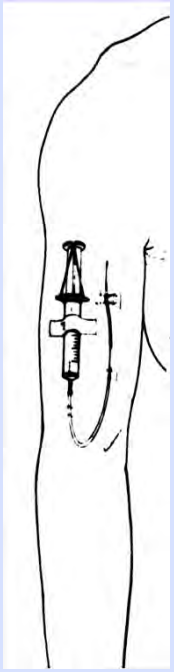

5.

. Birth Defects 1988; 24(5B):123-27.

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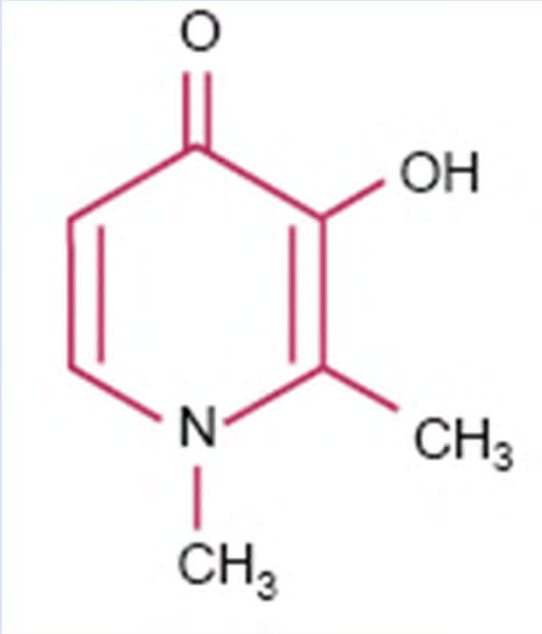
Deferiprone L1: Oral iron chelator

- 1,2-dimethyl-3-hydroxypyrid-4-one
- forms a neutral 3/1 chelator/ferric complex
- Second line therapy in thal patient
- Full marketing approval in Europe in 2002



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Chelation therapy with deferiprone

- Deferiprone has been available in various countries outside the US and Canada since the late 1990s

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Deferiprone : side effects

- Arthropathy 15 - 40 %
- Agranulocytosis 1 - 2 %
- Neutropenia 2%
- GI symptoms 10 %
- Zn deficiency
- ?progression of hepatic fibrosis

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Deferiprone Experience in Thailand

- 9 patients with β-thal/Hb E(7) and homzygous β-thal(2)
- transfusion independent
- dose 25-50 mg/kg/d, duration 17-86 wk, mean 49 wk
- serum ferritin 2,168 → 300 ng/ml
- Hepatic iron 16.3 →11.8 mg/gDW
- RBC iron 76.2 → 7.2 mmol/mg

Pootrakul, P et: Br J Haematol 2003

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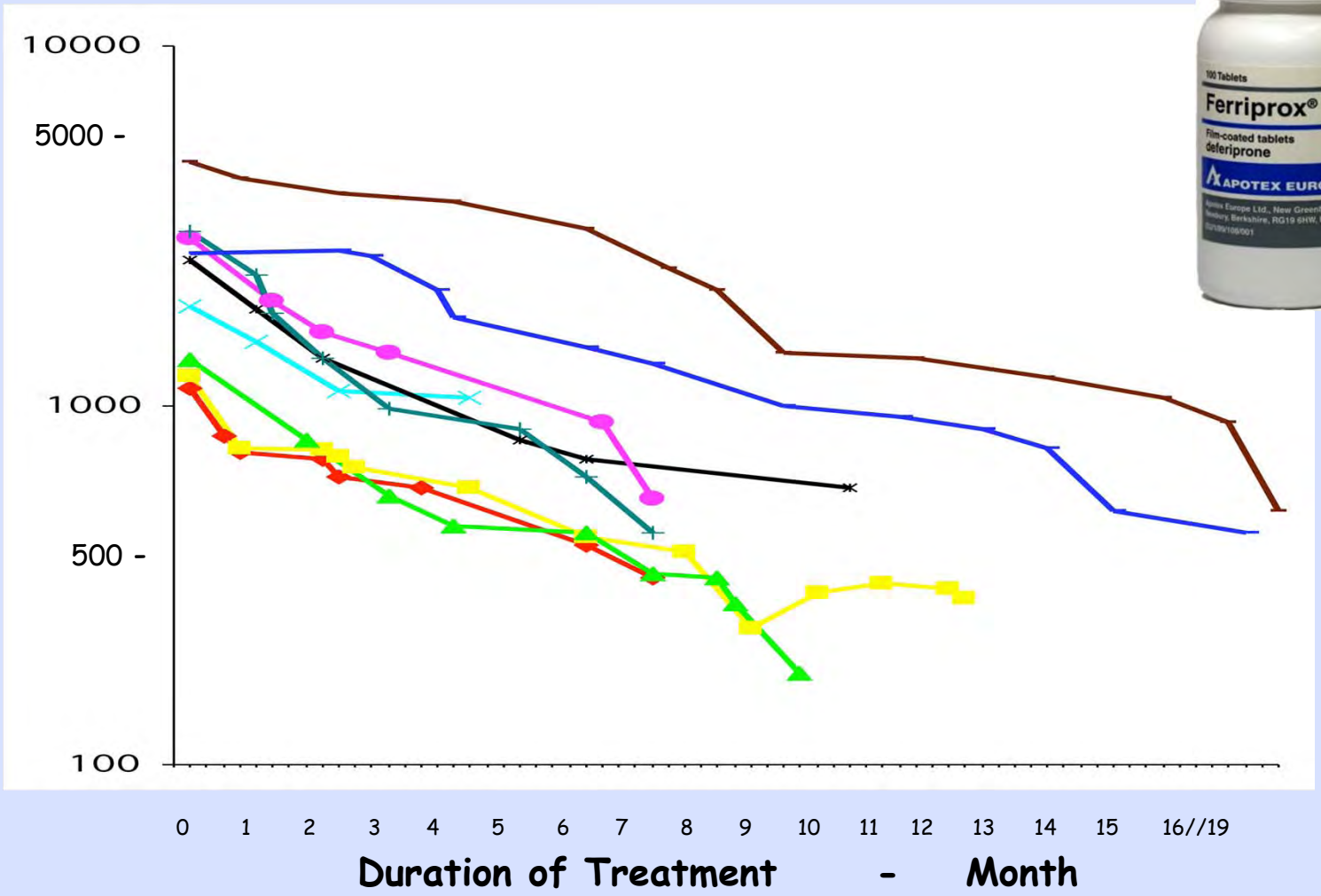
SERUM FERRITIN LEVELS DURING DEFERIPRONE TREATMENT



P.Pootrakul

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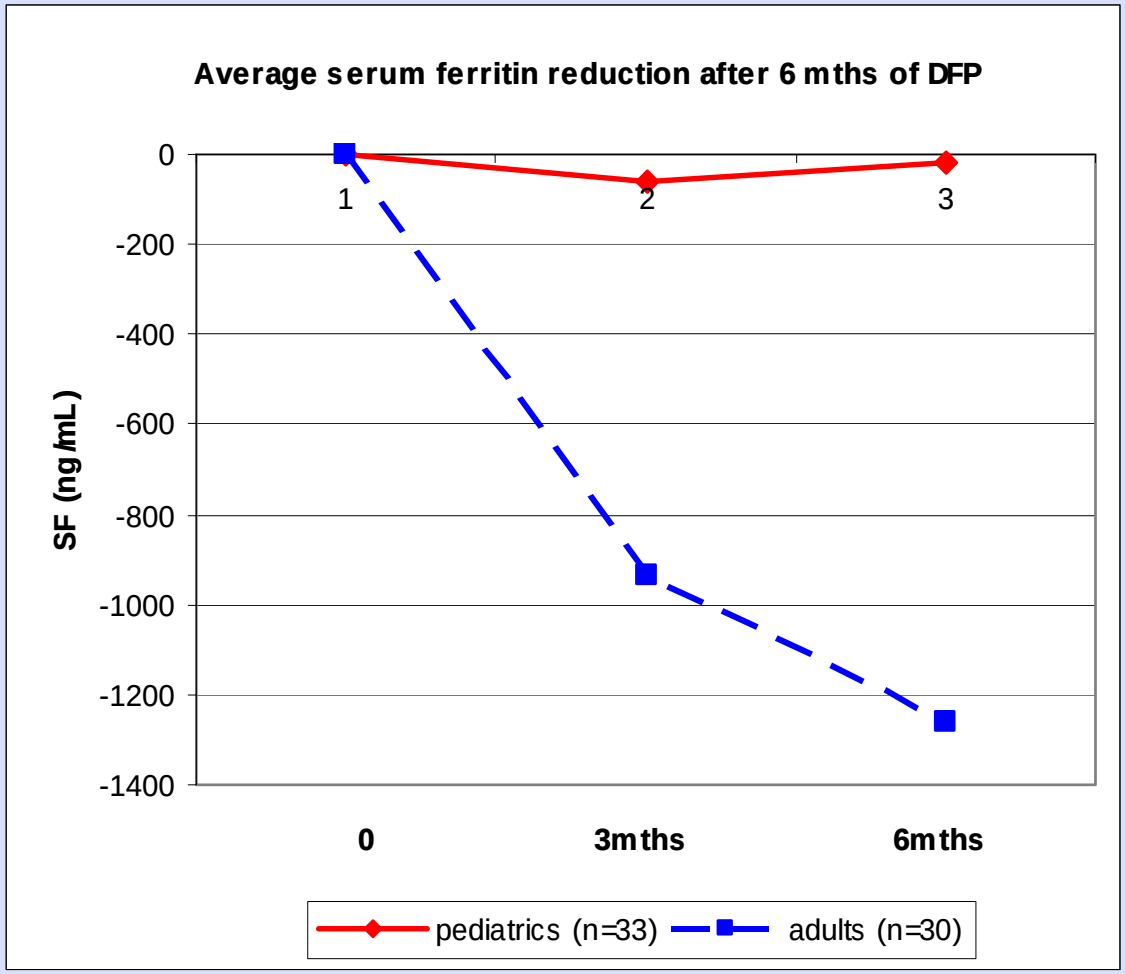
Preliminary data on serum ferritin in ADULT and pediatric patients after 6mths of GPO-L-ONE-2



	3 mths	6mths
Pediatrics	- 57.6	- 20.6
Adults	- 934	-1260

Average dose in ped. = 75-80 MKD

Average dose in adult = 50-55 MKD

Summary of Adverse Events of Deferiprone (Kelfer) at Siriraj Hospital (July 2006 - April 2008)

Adverse events	N	%
Rash	0	
Abdominal pain	11	18.3
Nausea/Vomiting	8	13.3
Arthralgia	5	8.3
Neutropenia/Agranulocytosis	5	8.3
Transaminitis	8	13.3
Increase appetite	2	3.3
Dizziness	2	3.3
Increase stool frequency	2	3.3
Fatique	1	
Thrombocytopenia	1	1.6
Hematuria	1	

Pornpun Sripornsawan, Bunchoo Pongtanakul and Vip Viprakrasit 2008

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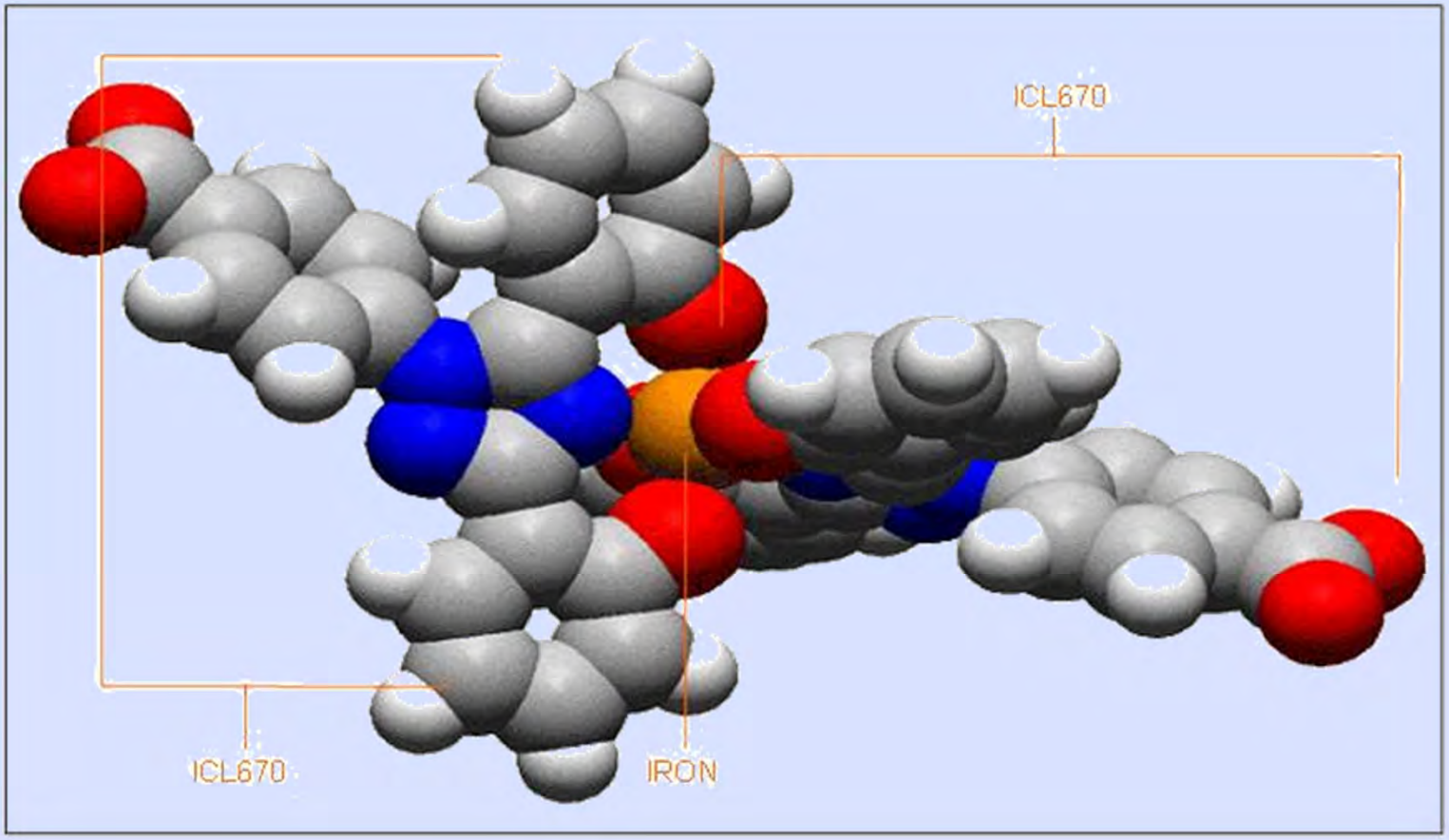
ICL670: EXJADE



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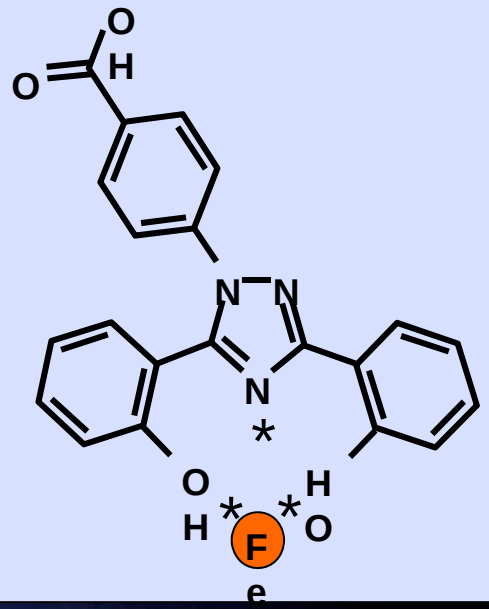
EXJADE: General Characteristics

- Oral, dispersible tablet
- Taken once daily
- Highly specific for iron
- Chelated iron excreted mainly in feces
- Less than 10% excreted in the urine



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Significant Reduction in Absolute LIC

	EXJADE **All patients** **n = 268**	**Deferoxamine** **All patients** **n = 273**
Overall population **Mean ± SD** **P value**	n = 268 -2.4 ± 8.2 p<0.001	n = 273 -2.9 ± 5.4 p<0.001
LIC <7 mg Fe/g dw **Mean ± SD**	n = 83 4.0 ± 3.8	n = 87 0.13 ± 2.2
LIC ≥7 mg Fe/g dw **Mean ± SD** **P value**	n = 185 -5.3 ± 8.0 p<0.001	n = 186 -4.3 ± 5.8 p<0.001

Reduction in liver iron content achieved was both statistically significant and clinically relevant with ICL670 at 20 and 30 mg/kg/day

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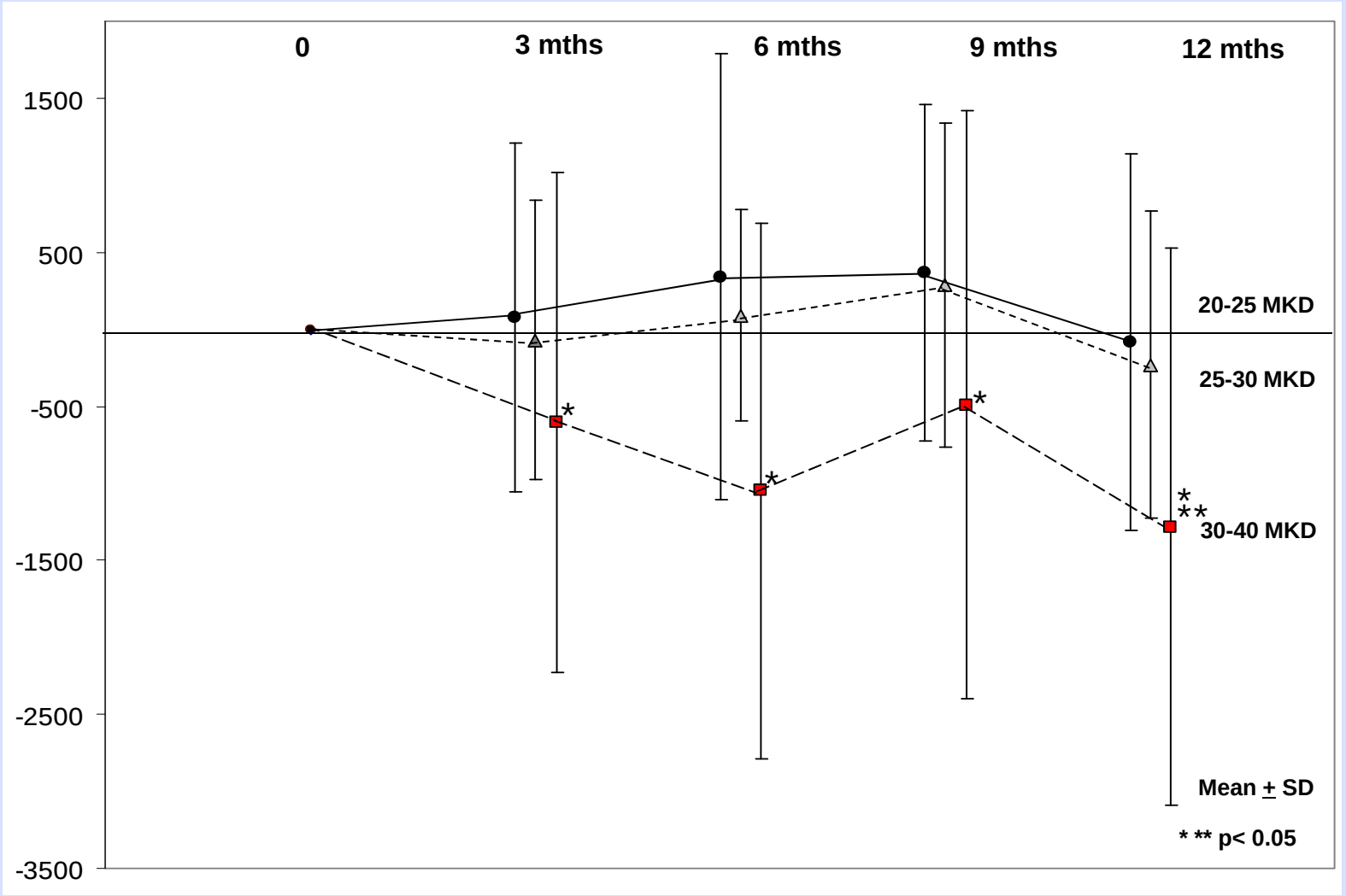
One –year-effects of deferasirox on serum ferritin in different dose groups in 54 Thai Thalassaemia patients



Vip Viprakasit, unpublished data, 2008 (permission required)

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Cost effective analyses of iron chelating therapy In transfusion dependent thalassemia population in Thailand

Luangasanatip N, Chaiyakunapruk N,
Upakdee N, Wong P

Department of Economics, School of Social Sciences, City University, London, UK
Center of Pharmaceutical Outcomes Research, Faculty of Pharmaceutical Sciences, Naresuan University
Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University
School of Pharmacy, University of Wisconsin, Madison, USA
School of Population Health, University of Queensland, Brisbane, Australia
Department of Medicine, Faculty of Medicine, Naresuan University

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Objective:

This study aims to evaluate the cost-effectiveness of deferoxamine (DFO), deferiprone (DFP), and desferasirox (DFX) in transfusion-dependent thalassaemia patients from the societal perspective.

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METHODS:

A Markov model was used to project the life time costs and outcomes represented as quality-adjusted life years (QALYs).

Clinical efficacy and safety of all therapeutic options were obtained from a systematic review and clinical trials.

Transition probabilities were derived from literatures while costs were obtained from Thai Drug and Medical Supply Information Center, Diagnostic Related Group (DRG) and other Thai literatures.
Discounting rate of 3 percent was used.
Incremental cost-effectiveness ratios were presented as values of year 2009.
A series of sensitivity analysis and cost effectiveness analysis curve (CEAC) were performed.

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Drug and Medical Supply Information Center (DMSIC).

Cost of DFO (Desferal®) was 371.06 baht ($US 10.77) per gram,

Cost of DFP (Kelfer®) was 72.00 baht ($US 2.09) per gram and

Cost of DFX (Exjade®) was 2,017.72 baht ($US 58.56) per gram.

Cost of injection set was estimated as 15.48 baht ($US 0.45) per injection,
Cost of infusion pump was 12,500 baht ($US 363), the value directly obtained from the sole supplier in Thailand (lifetime of the infusion pump was assumed as 10 years).
Cost of medical visit and CBC were 50.70 ($US 1.47) and 91.27 ($US 2.65) baht

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Table II: Results from Base-case Analyses

Outcome measure	*Deferoxamine*	*Deferiprone*	*Desferasirox*
Costs			
Direct Medical Care Cost			
Drug Cost	5,072,401.10	2,072,363.36	19,358,368.31
Other Costs	246,602.87	121,176.42	119,830.96
Direct Non Medical Care Cost	94,573.20	80,603.47	78,964.47
Indirect Cost	28,258.16	28,258.16	28,258.16
Total	5,441,835.33	2,302,401.42	19,585,421.91
Quality Adjusted Life Years (QALYs)	14.04	14.04	19.81

(US$ 1 = 34 Thai Baht)

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Outcome measure	Differences		
	DFO vs DFP	*DFO vs DFX*	*DFP vs DFX*
Costs			
Direct Medical Care Cost			
Drug Cost	-3,000,037.74	14,285,967.21	17,286,004.95
Other Costs	-125,426.45	-126,771.91	-1,345.46
Direct Non Medical Care Cost	-13,969.73	-15,608.73	-1,639.00
Indirect Cost			
Total	-3,139,433.92	14,143,586.57	17,283,020.49
Quality Adjusted Life Years gained (QALYs gained)	0	5.77	5.77
Cost per QALY gained (baht)	**DFP dominate**	**2,452,061.05**	**2,996,341.92**

DFP vs DFO: DFP is dominant with cost-savings of 3,139,434 baht (US$ 91,117);

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…When compared to DFP, DFX is cost-effective only if DFX cost was lowered from 504 baht (US$ 14.6) to 69 baht (US$ 2) per 250mg tablet.

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Conclusion:

Our findings suggest that using DFP is cost-saving when compared with the conventional therapy, while using DFX is not cost-effective compared with both DFO and DFP.

Policy makers and clinicians may consider using such information for aiding policy decision making process in Thailand.

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Properties of an Ideal Chelator

- High and specific affinity for Fe3+
- High chelating efficiency
- Achievement of negative iron balance
- Tissue and cell penetration
- No iron redistribution
- Oral bioavailability
- Slow rate of metabolism (i.e. long half-life)
- Relatively non-toxic

Adapted from Galanello R, ASH Educational Session, 2004