



Overview of current chelation practices

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Iron overload in hemoglobinopathies

Disease	Iron overload	Organ damage
TM	Transfusions ²	Liver, endocrine, heart
TI	Increased GI absorption (transfusions) ³	Liver, endocrine (heart?)
SCD	Transfusions ^{4,5}	Liver (heart?)

TM; thalassemia major, TI; thalassemia intermedia, SCD; sickle cell disease

There is uncertainty if (and when) detectable cardiac iron deposition can occur in TI and SCD, and its correlation with cardiac morbidity and mortality.

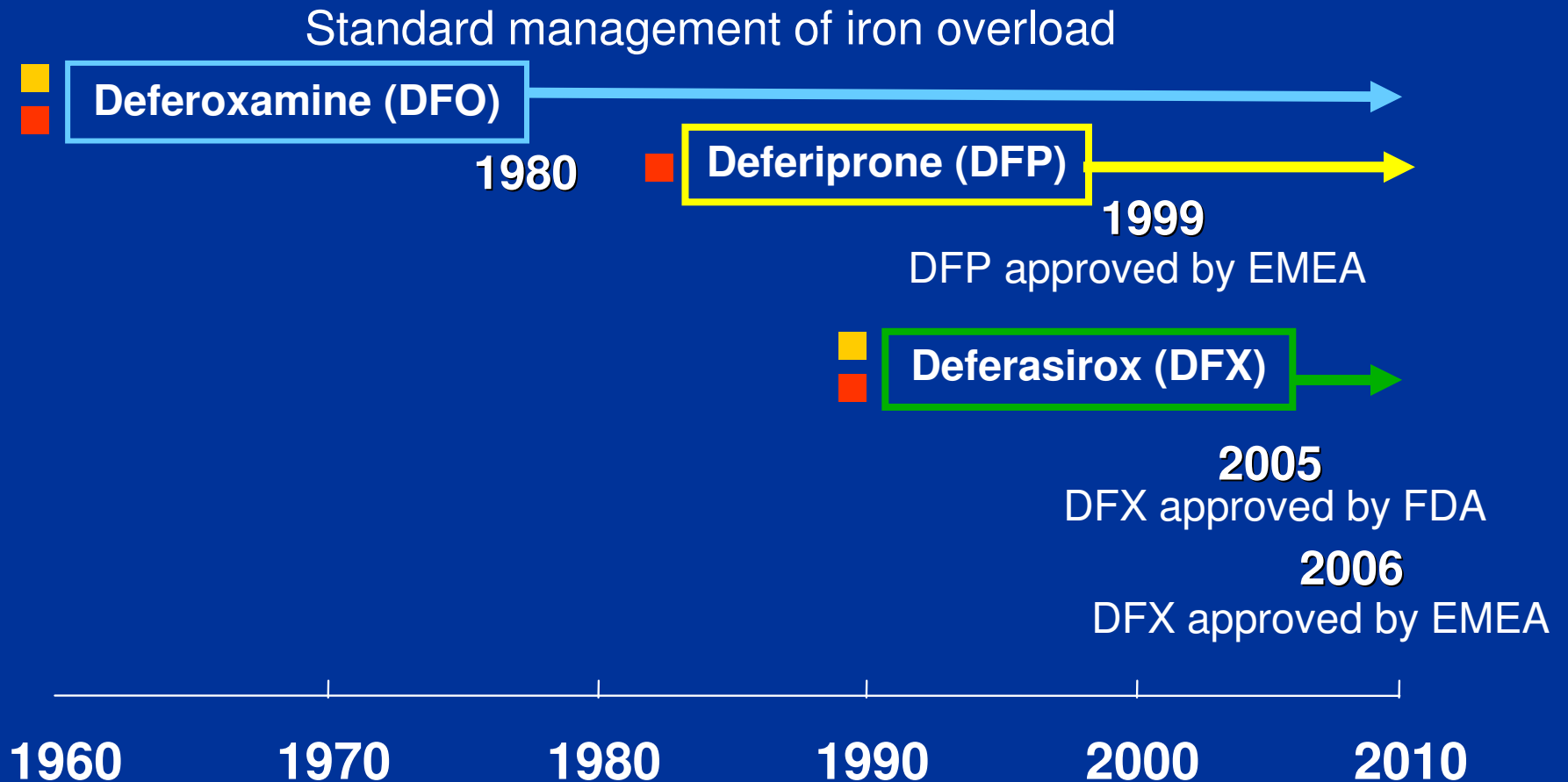
¹Modell B, *Bull World Health Organ.* 2008;86(6):480–487. ²Weatheral DJ, Clegg JB. *Thalassemia syndromes.* 2001.

³Pippard NJ, *Lancet* 1979; 2:819-21. ⁴Hulbert ML, et al. *Blood.* 2011; 117:772-9. ⁵Ware RE, Helms RW *Blood* 2010; 116: [844].

Outline

- Overview of iron chelating agents
- Primary objectives of iron chelation therapy
 - What are the safe levels of body iron burden?
 - When chelation therapy should be started?
- Secondary objectives of chelation therapy
 - What are the major influences on success of chelation therapy
 - Overview of clinical studies conducted by different chelating agents
 - improvement in hepatic & cardiac iron contents
 - prevention & reversal of endocrine complications

Evolution of iron chelation therapy



■ FDA, Food and Drug Administration, USA

■ EMEA, European Medicines Agency

Deferasirox Summary of Product Characteristics.
Deferiprone Summary of Product Characteristics.
Deferoxamine Summary of Product Characteristics.

Overview of iron chelating agents

Property	Deferoxamine	Deferiprone	Deferasirox
Chelator-iron complex	Hexadentate, 1:1	Bidentate, 3:1	Tridentate, 2:1
Usual dose	20–60 mg/kg/day	75–100 mg/kg/day	10–40 mg/kg/day
Route	s.c., i.v. 8–12 h, 5 days/week	Oral 3 times daily	Oral once daily
Half-life	20–30 min	2–3 h	8–16 h
Excretion	Urinary, fecal	Urinary	Fecal

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Overview of iron chelating agents

Property	Deferoxamine	Deferiprone	Deferasirox
MW, hydro/lipophilic	559, hydrophilic	139, lipophilic	373, lipophilic
Depletion of LPI ¹	yes (continuous infusion)	yes (rebound between doses)	yes
Removal of hepato-cellular iron	yes ²	less impressive ³	yes ⁴
Accessing LCI pool ^{5,6}	retard	rapidly penetrate and bound	rapidly penetrate and bound
Clinical data; extracting LCI pool in cardiomyocytes	benefits of 24h i.v. infusion ^{7,8}	higher than standard DFO ⁹	in comparison vs. DFO

¹Cabantchik ZI et al. *Best Pract Res Clin Hematol* 2005;18:277–287. ²De Domenico I, et.al. *Blood* 2009; 114: 4546–51.

³Hoffbrand A.V et al. *Blood* 2003;102: 17-24. ⁴Waldmeier F, et al. *Drug Metab Dispos.* 2010; 38:808–16.

⁵Glickstein H et al. *Blood* 2005;106:3: 242–3250. ⁶Glickstein H et al. *Blood* 2006;108:3195–3203,

⁷Davis, B.A. & Porter, J.B. *Blood* 2000; 95: 1229–1236. ⁸Anderson LJ, et al. *Br. J. Haematol* 2004; 127: 348–355

⁹Pennel DJ et al. *Blood* 2006 107: 3738-3744

The primary objective of iron chelation therapy

- Maintain body iron at safe levels at all times.
 - When chelation therapy should be started?
 - What is the safe level of body iron burden?

When chelation therapy should be started?

- Intensive DFO chelation at or close to the time of first transfusion resulted with;
 - high frequency hearing loss, retinopathy and poor growth¹
- DFO chelation has traditionally been administered;
 - patients have received 10-20 times red cell transfusion
 - serum ferritin exceeds 1000 µg/L¹
 - LIC exceeds 3.2 mg iron/g d.w.²
- A therapeutic index was implemented³

$$\text{Therapeutic index} = \frac{\text{mean daily dose of deferoxamine (mg/kg)}}{\text{serum ferritin (}\mu\text{g/L)}} \quad (\text{keep } < 0.025)$$

- It is unknown whether chelation can be safely started earlier with DFX or DFP

What is the safe level of body iron burden?

- Chelation therapy should be maintained at;
 - Serum ferritin levels 500 – 1000 $\mu\text{g/L}$
 - Liver iron concentration 3.2 – 7.0 mg/g d.w.^{1,2}
(normal liver iron =0.6-1.2 mg/g d.w.³)
- Maintenance of normal liver iron levels might decrease complications of iron overload but increase chelator toxicity.
- It is unknown whether chelator toxicity of DFP or DFX occurs as body iron levels fall to normal ranges.

¹ Cartwright GE. et al. NEJM 1979; 301:175-9 ²Olivieri NF, Brittenham GM. Blood 1997; 89: 739-61.

³ Brittenham GM. et al. NEJM 1982 307:1671,

The secondary objective of iron chelation therapy

- Reduce tissue iron to the safe levels
 - How quickly total body & tissue iron levels can be safely removed and normalized?
 - How optimal balance would be established between effectiveness in removal of excess iron and toxicity of chelator?

Major influences on success of chelation therapy

- Effectiveness of chelator in achieving iron balance
 - iron loading rate
 - prescribed dose
 - body iron burden
 - individual variability in absorption and metabolism of chelator
- Tolerability of chelator
- Compliance with chelation therapy

Negative iron balance

(impact of iron loading rate & chelator doses)

% of patients achieving negative iron balance
at different transfusional loading rates

DFO dose mg/kg X5 /w	Transfused iron (mg/kg/d)			DFX dose mg/kg o.d.	Transfused iron (mg/kg/d)		
	<0.3	0.3-0.5	>0.5		<0.3	0.3-0.5	>0.5
35-49	76%	75%	52%	10	29%	14%	0%
≥50	100%	86%	89%	20	76%	55%	47%
				30	96%	83%	82%

Negative iron balance;
excess of iron excreted over that received in form of transfused red cells

Negative iron balance

(impact of iron loading rate & chelator doses)

Transfusional iron loading = 0.3 – 0.5 mg/kg/d

Chelator	DFO ¹ (x5/week)		DFX ¹ (daily)			DFP ^{2,3} (daily)		
	35-49	>50	10	20	30	50	75	100
Dose (mg/kg)								
% of pts with negative iron balance	75	86	14	55	83	14	46	86

Higher % of patients achieved negative iron balance at greater doses of chelators
Standard doses of chelators were capable to maintain iron balance

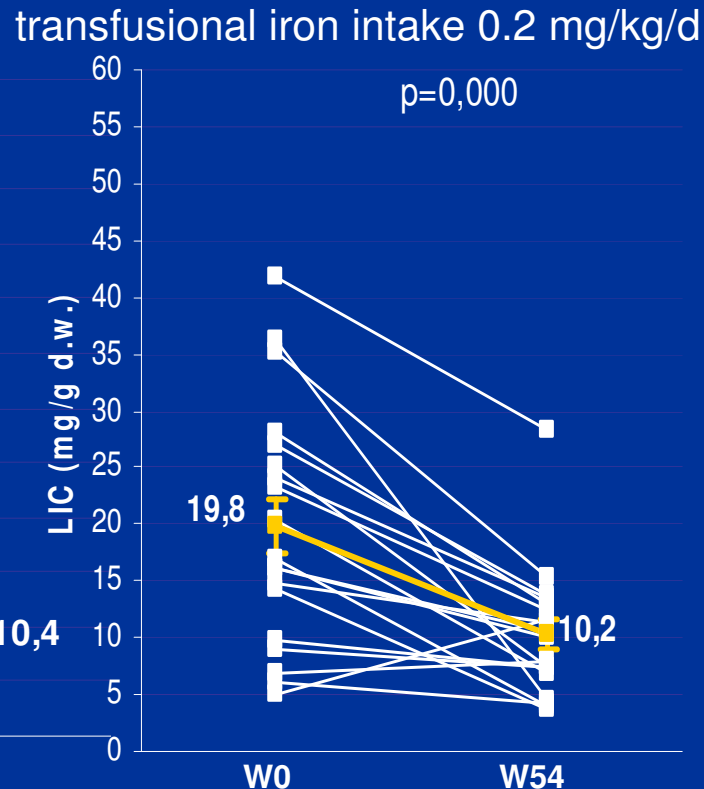
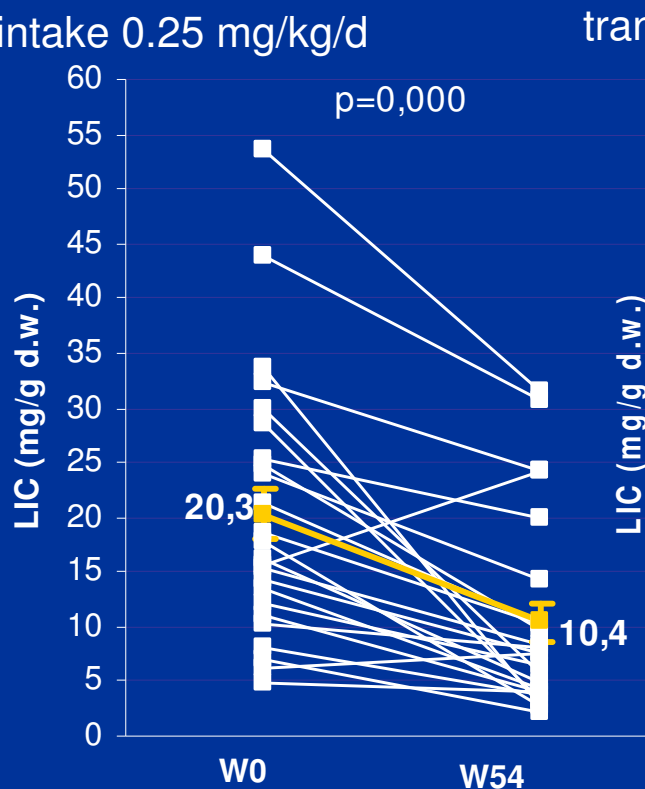
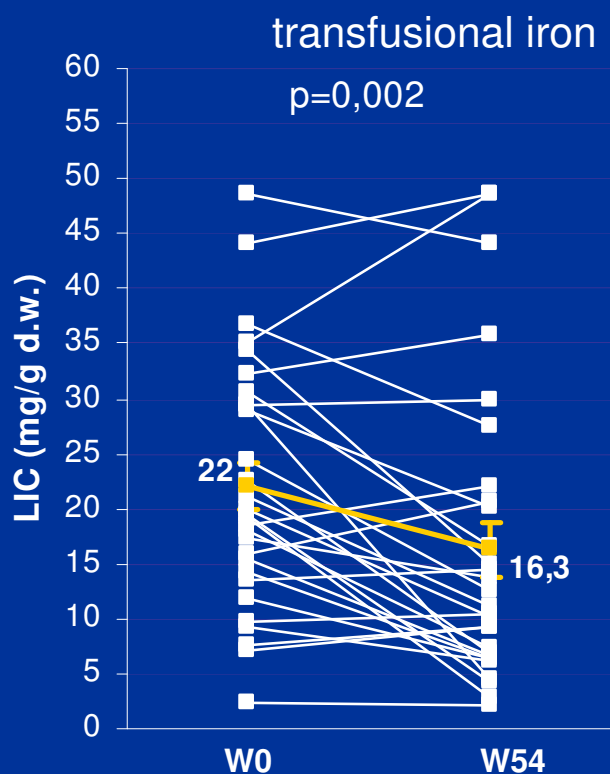
¹ Cohen AR, et al. Blood 2008; 111:583-7. ²Grady RW, et al. 11th ICOC, 2001;74–78. ³Grady RW, et al. ASH, 2002; 100:241a

Changes in LIC with different chelation regimens in thalassemia major

DFP (n=29)
 decrease in 18 (62%)
 maintained in 4* (14%)
 increase in 7 (24%)

DFP + DFO (n=24)
 decrease in 21 (87,5%)
 maintained in 2* (8,5%)
 increase in 1 (4%)

DFO (n=19)
 decrease in 17 (90%)
 maintained in 1* (5%)
 increase in 1 (5%)



*one maintained below 7mg/g d.w.

*two maintained below 7mg/g d.w.

*one maintained below 7mg/g d.w.

Changes in LIC & cardiac iron content with standard doses of DFP

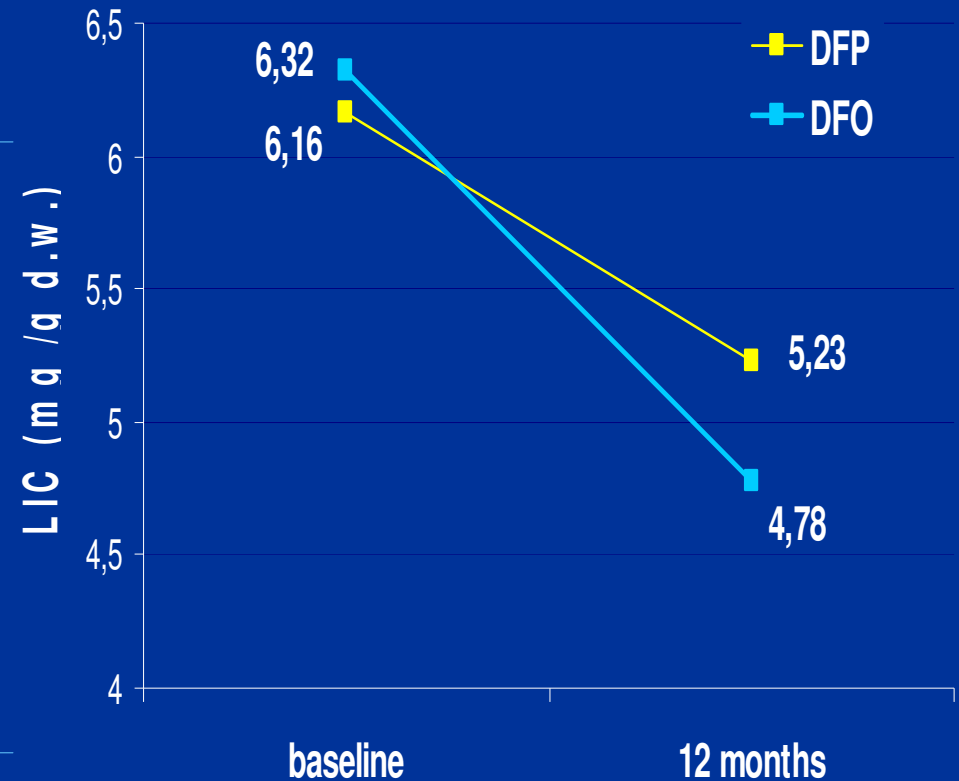
Chelators Doses	DFP group (n =60) 75 mg/kg/day			DFO group (n=66) 50 mg/kg/d x 5 days / week		
	Baseline	EOS	Difference	Baseline	EOS	Difference
Liver MRI (SIR)	0.83±0.21	0.90±0.26	-0.07±0.38	0.87±0.34	1.02±0.33	-0.15±0.27[#]
Heart MRI (SIR)	1.08±0.19	1.19±0.31	-0.11±0.33[*]	0.96±0.26	1.09±0.28	-0.13±0.31[#]

* p>0.05, # p<0.01 compared to baseline SIR; signal intensity ratio

- A significant reduction in cardiac iron content achieved by both chelation regimens
- Iron reduction in the liver was significant in only DFO group.

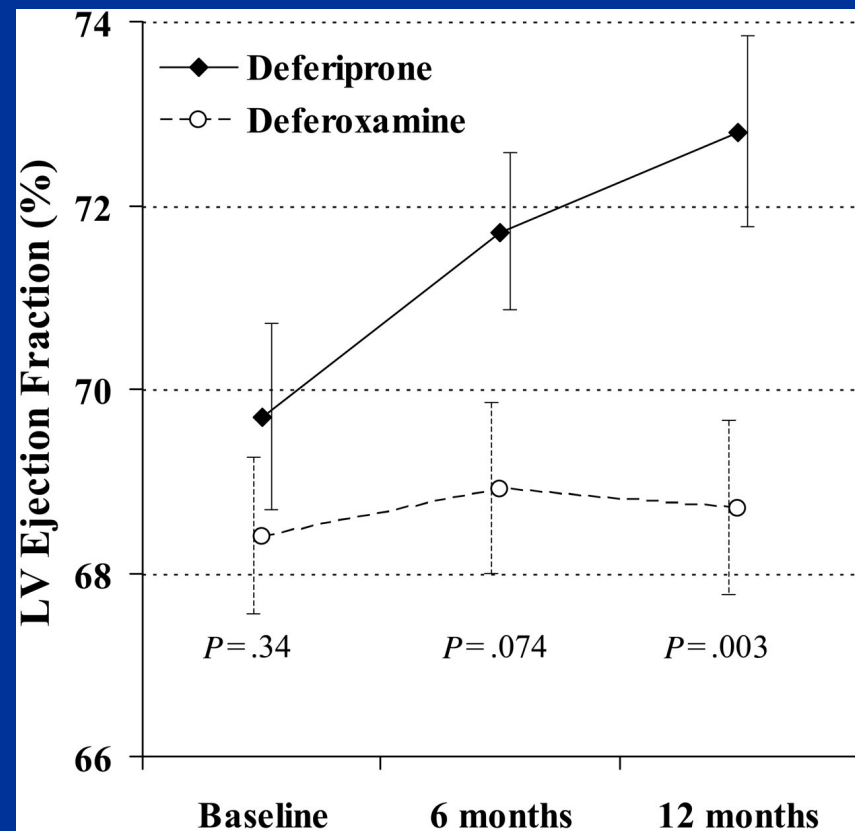
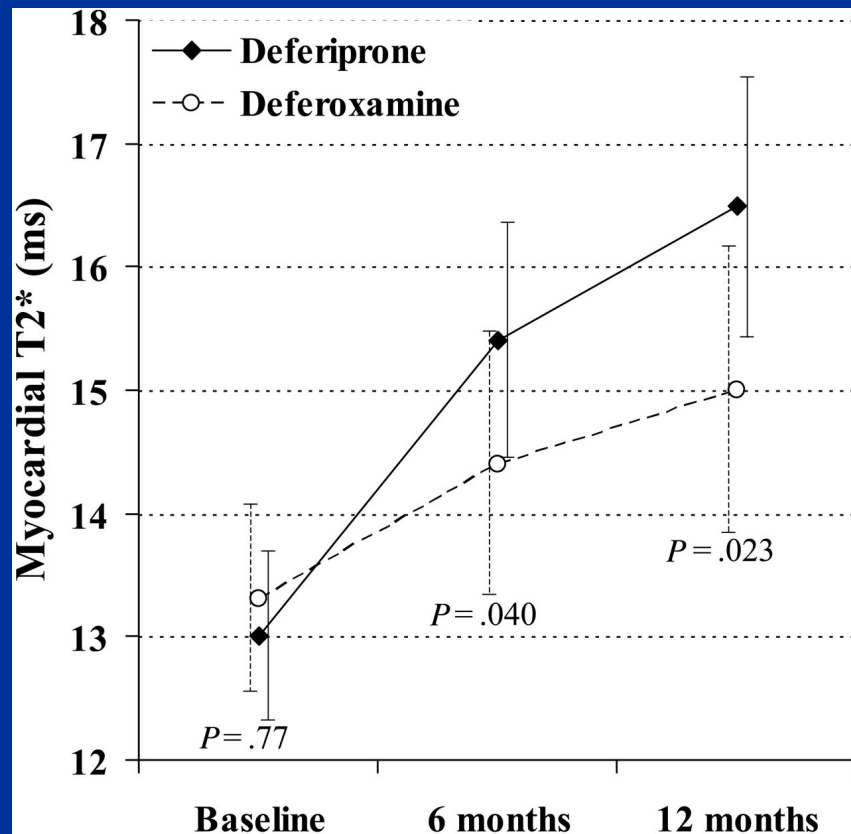
Changes in LIC with high dose of DFP in thalassemia major with cardiac siderosis

Chelators	DFP (n=29)	DFO (n=32)
Dose	92 mg/kg/d	43 mg/kg/d X5,7/w (35mg/kg/d)
Compliance (%)	94 ± 5.3	93 ± 9.7
Transfusion (ml/kg/year)	152 ± 43.4	144 ± 44.4
T2* (ms)	13	13.3



LIC fell with DFP -10.1% (p=0.11) and with DFO -24.4% (p=0.02) at 12 months

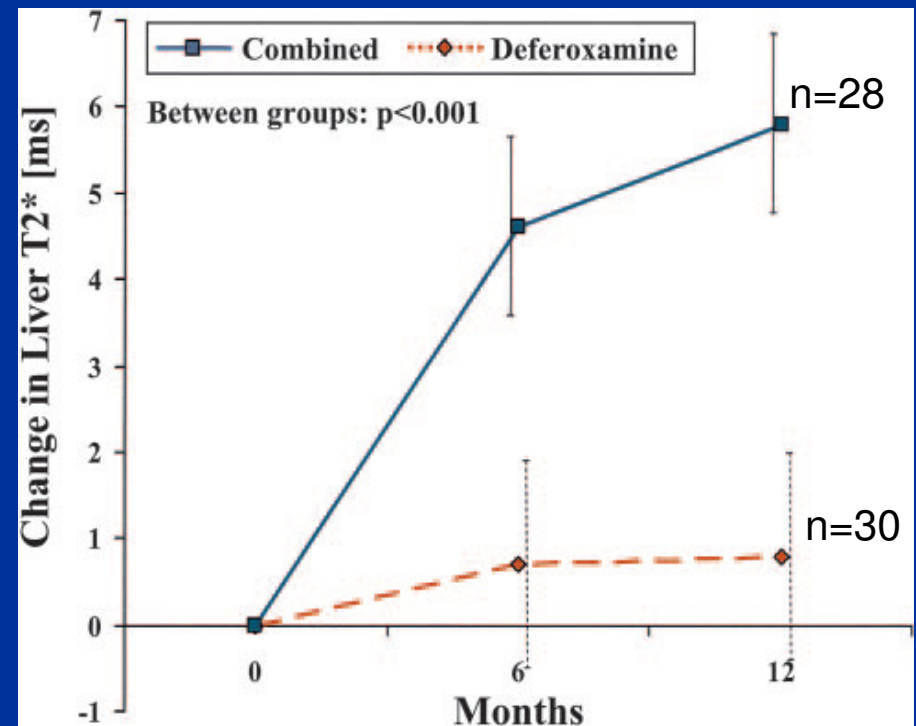
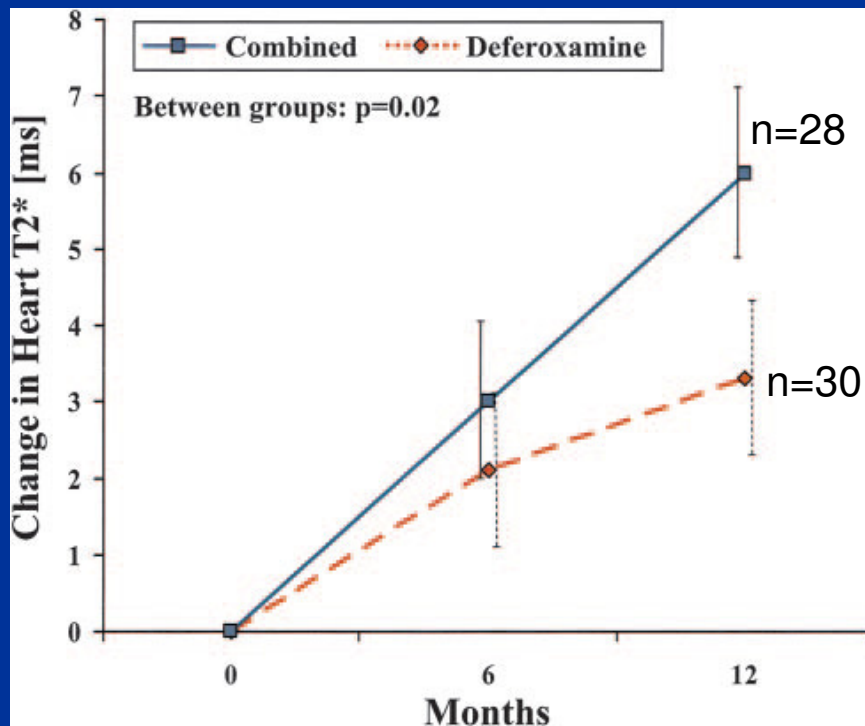
Changes in T2* with high dose of DFP in thalassemia major with cardiac siderosis



DFP; 92 mg/kg/d DFO; 43 mg/kg/d x 5.7d/w (equivalent 35mg/kg/d for 7d/w)

Changes in T2* with combined therapy of DFP & DFO in thalassemia major with moderate cardiac siderosis

Randomised placebo control study



Combined therapy: DFP; 75 mg/kg/d + DFO; 35 mg/kg/d x5d/w

DFO monotherapy: DFO; 43 mg/kg/d x 5d/w (equivalent 30mg/kg/d for 7d/w)

Tailoring iron chelation by iron intake

EPIC study (Thalassemia Major)

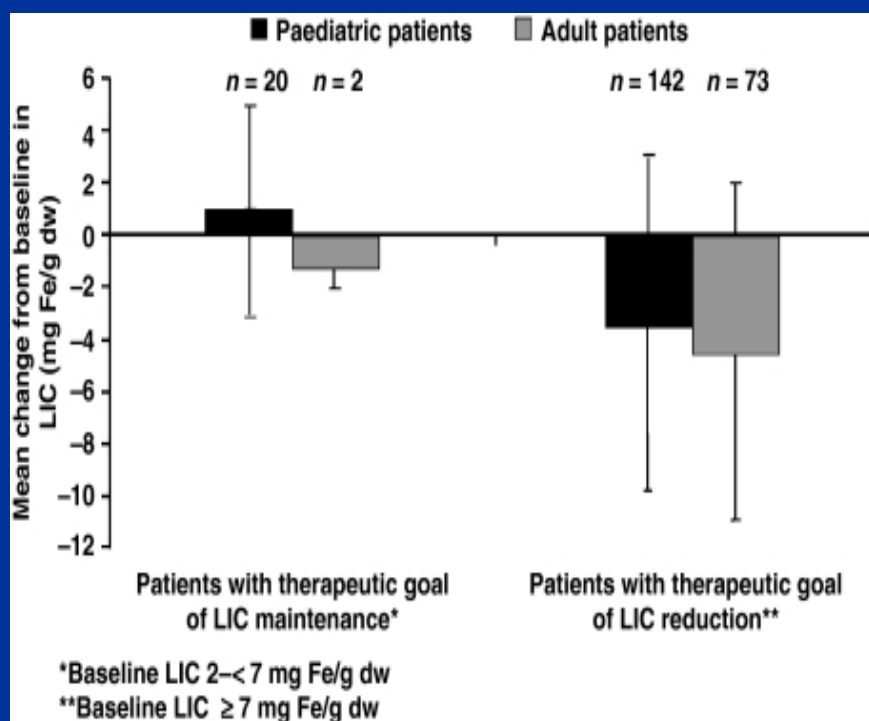
Aim: Fixed starting doses of DFX, based on transfusional iron intake, with dose titration guided by SF and safety markers, provides acceptable chelation practice in patients (aged ≥ 2 years) with transfusional iron overload

Deferasirox doses	<20 mg/kg (n=231)	≥ 20 –<30 mg/kg (n=732)	≥ 30 mg/kg (n=141)	All patients (n=1104)
Median SF at baseline	(462-20788) 2356	(480-22320) 3160	(1326-16944) 5093	(462-22320) 3188
at EOS	2311	3067	4167	3025
Change in SF	–45	–93	–926	–163
<i>P</i> -value	0.67	0.56	<0.0001	0.0001
Mean iron intake (mg/kg/day)	0.38	0.46	0.35	0.43

Patients receiving higher DFX dose at lower transfusional iron intake reflected in significant reduction in SF, whereas lower DFX doses at higher transfusional iron intake was consistent with maintenance of SF levels

Heavily iron loaded patients with thalassemia major (ESCALATOR study)

All patients started on DFX 20 mg/kg/d, dose adjusted based on serum ferritin up to 30 mg/kg/d, during 1 year study



Baseline demographic	Pediatric (n=162)	Adult (n=75)
Mean age (years)	9.5 (2-15)	21.4 (16-42)
Iron intake (mg/kg/d)	0.39	0.28
Mean LIC (mg/g d.w.)	17.0±8.5	20.1±10.1
Median SF (ng/ml)	3326 (914-13338)	3356 (956-25008)

These data highlight the importance of timely DFX dose adjustments based on serum ferritin levels and transfusional iron intake for achieving their therapeutic targets of maintenance or reduction in iron LIC.

Longterm efficacy and safety of DFX (ICL670E; at least 4 years DFX)

Patients aged ≥ 2 years who completed a 1-year, Phase III, randomized trial¹ entered a 4-year extension study, either continuing on DFX (deferasirox cohort) or switching from DFO to DFX (crossover cohort).

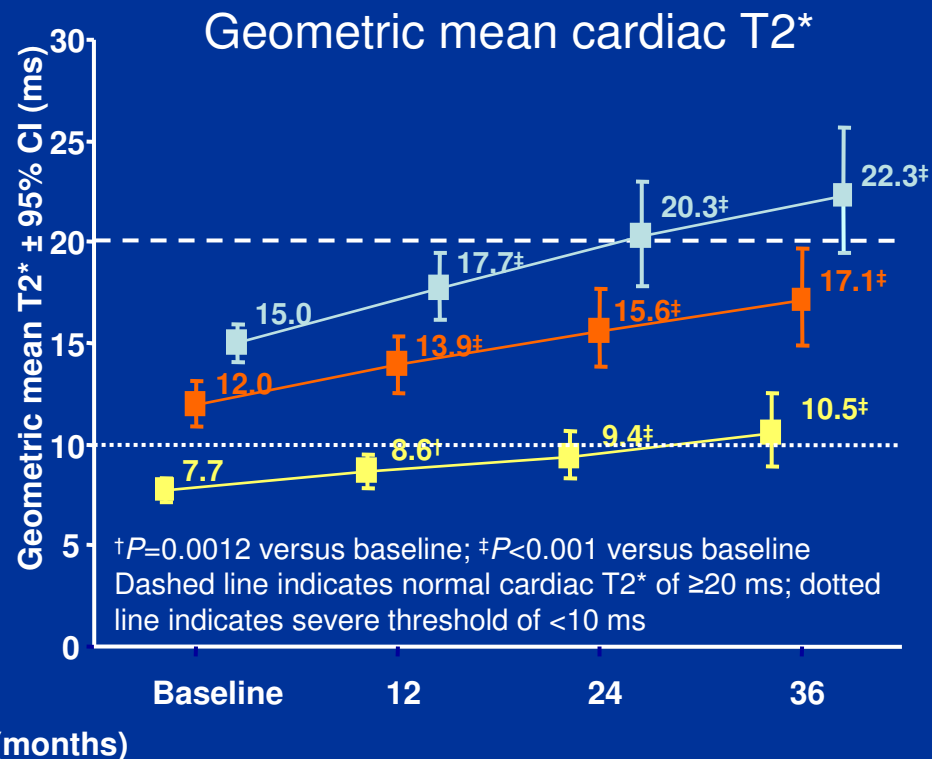
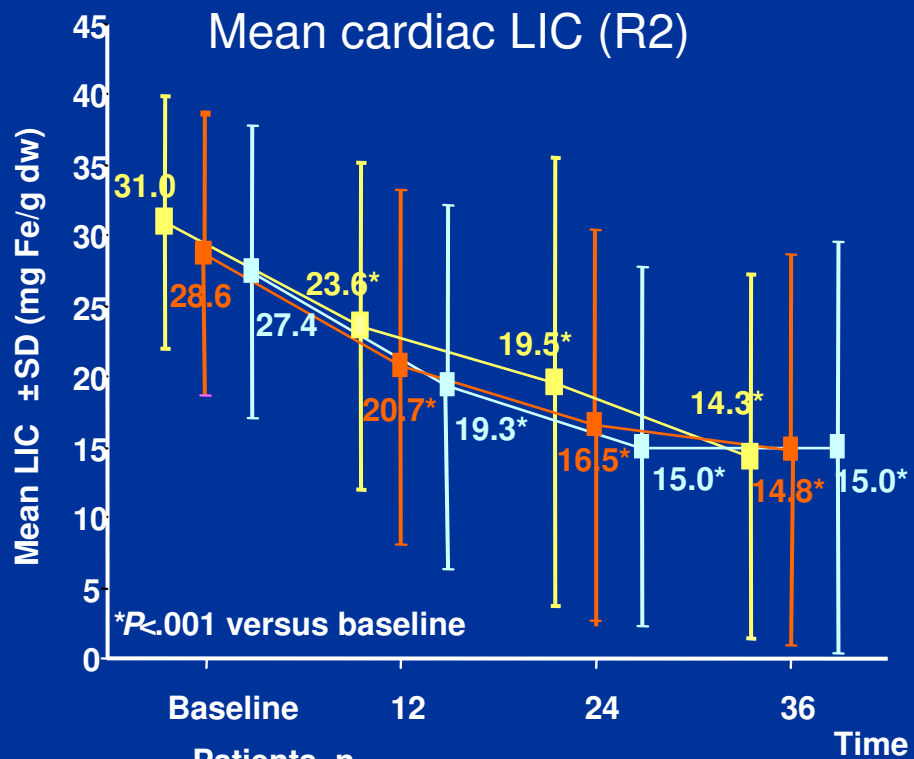
	%of patients with SF < 1000 $\mu\text{g/l}$		Starting dose (mg/kg/d)	Mean absolute change in LIC \pm SD (<i>P</i> value)	
	Deferasirox (n=181)	Crossover (n=190)		Deferasirox	Crossover
baseline	13	17	≤ 10	2.3 \pm 8.6	1.7 \pm 5.8
EOS	51	42.4	20	-2.1 \pm 6.8 (0.058)	-1.1 \pm 6.2 (0.175)
Iron intake (mg/kg/d)	0.37 \pm 0.1	0.38 \pm 0.1	30	-13.8 \pm 9.9 (<0.001)	-8.5 \pm 7.5

dose adjustments were allowed based on SF levels

EPIC cardiac substudy over 3 year

(DFX >30 mg/kg/d are required for cardiac iron removal)

■ >5-<10 ms ■ 10-<20 ms ■ All patients



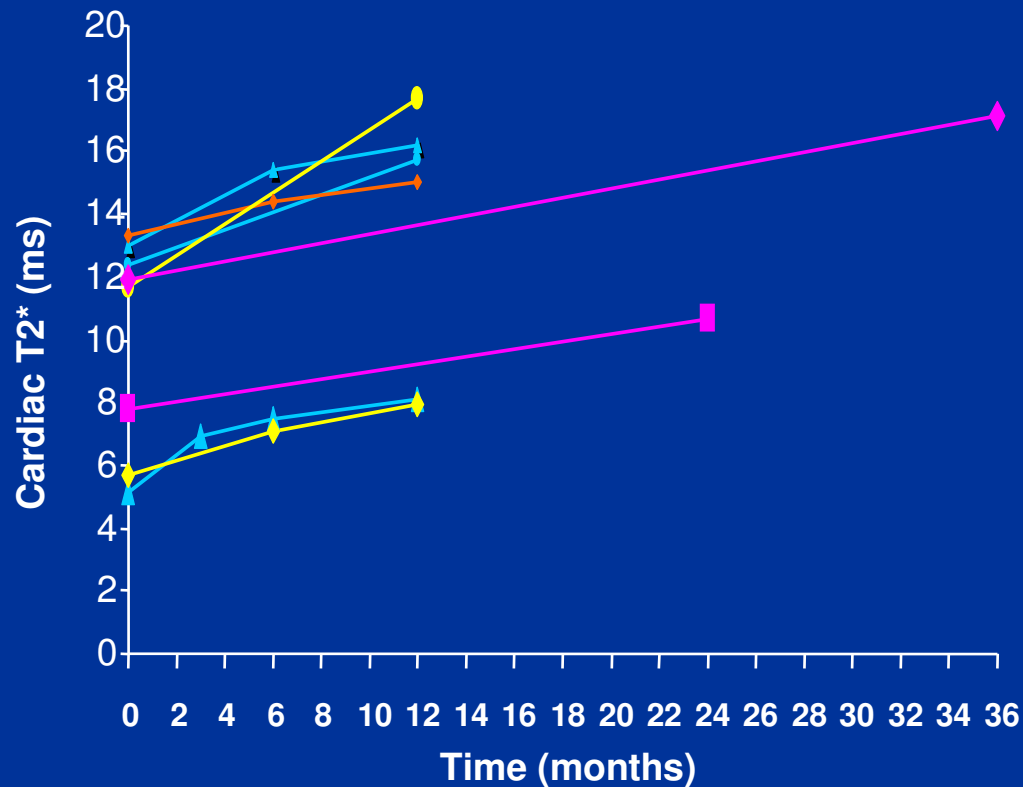
Patients, n

>5-<10 ms	24	24	24	24
10-<20 ms	47	47	47	44
All patients	71	71	71	68

The mean actual deferasirox dose throughout the study was 34.2 mg/kg/day

There were no deaths during the 3 year study

How quickly cardiac iron can be safely removed and normalized?



Improvement/month

4.3%, Tanner 2007 (DFO sc, DFP)

2.2%, Tanner 2007 (DFO sc)

1.1%, Pennell 2006 (DFO sc)

2.2%, Pennell 2006 (DFP)

1.2%, Pennell 2010 (DFX)

1.5%, Wood 2010 (DFX)

4.9%, Anderson 2004 (DFO iv, 24/7)

3.2%, Tanner 2008 (DFO sc, DFP)

DFO = deferoxamine;
DFP = deferiprone;
DFX = deferasirox.

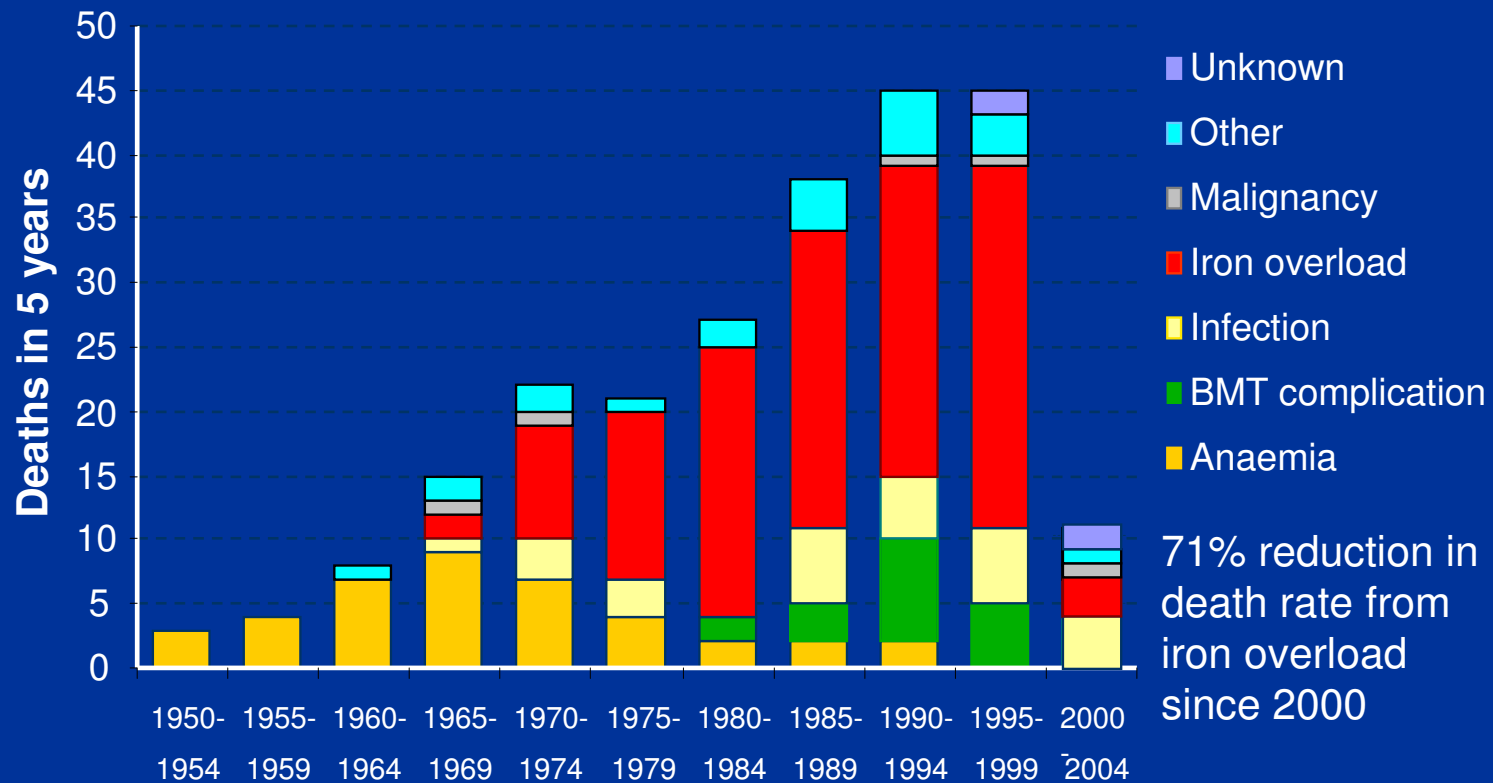
Anderson LJ, et al. Br J Haematol. 2004;127:348-55.
Pennell DJ, et al. Blood. 2006;107:3738-44.
Pennell DJ, et al. Blood. 2010;116:[abstract 4276].
Tanner MA, et al. Circulation. 2007;115:1876-84.
Tanner MA, et al. J Cardiovasc Magn Reson. 2008;10:12.
Wood JC, et al. Am J Hem 2010;85:818-19.

How quickly cardiac iron levels can be safely removed and normalized?

- 24h DFO infusion 7days/week or combined therapy of daily DFP & DFO 5 days/week may rapidly decrease cardiac iron burden, thereby reducing their risk status quicker
- The shuttle mechanism between DFP and DFO¹ is also likely to occur for the combination of Deferasirox and DFO
- Preliminary data obtained from US24 and Greece studies showed that Deferasirox-DFO combination therapy is well tolerated^{2,3}
- A prospective study combining Deferasirox & DFO in patients with severe cardiac siderosis has been started.
- The tolerability and efficacy of Deferasirox & DFP ? ^{4,5}

¹Link G *et al. J Lab Clin Med* 2001;138:130–138; ²Lal A *et al. Blood* 2009;114(22):abst 2021, ³Ladis V *et al. Haematologica* 2010;95 (Suppl 2):abst 1818 ⁴Berdoukas V, *et al. Blood* 2010; 116:2064, ⁵Balocco M, *et al. Am J Hematol*, 2010:460-1.

Deaths in thalassaemia patients in the UK



As late as, 1999;

- 50% of UK patients died before the age of 35 years
- heart disease was responsible for 71% of the deaths

Prevention and reversal of endocrine complications

- Endocrine complications remained as the most common cause of significant morbidity and impaired quality of life
- In pediatric patients, Deferasirox treatment for up to 5 years was effective in maintaining normal growth progression and sexual development^{1,2}
- Intensified chelation with DFP & DFO may prevent or reverse cardiac & endocrine complications with a positive impact on patients' quality of life³

¹Aydinok Y, et al. Haematologica. 2010;95 Suppl 2:429[abstract 1040]., ²Aydinok Y, et al. TIF 2011, OP-053, FPS-5

³Farmaki K, et al. Br J Haematol, 2009; 148, 466–475

Safety profile of chelators

DFO

- Local reactions
- HF hearing loss*
- Retinopathy*
- Allergy
- Poor growth*
- GI symptoms
- Yersinia infections

DFP

- GI symptoms
- Arthropathy
- Agranulocytosis
- Increased ALT/AST
- Low plasma Zn
- Increased appetite

DFX

- GI symptoms
- Skin rash
- Increase in serum creatinine
- Increased ALT/AST
- HF hearing loss and lenticular opacities

*keep the therapeutic index
< 0.025 at all times.

monitoring neutrophil count
weekly

monitoring serum creatinine
levels monthly

Conclusions

- Current chelation practices in thalassemia major are mainly based on;
 - Transfusional iron loading rate
 - Existing body iron burden
 - Tolerability of chelator and dosing regimen
 - Maintain body iron at or reduce to the safe levels by monitoring iron measures
- How low sustained levels of body iron should be maintained since the beginning to guarantee a lifelong complications free survival?
- How far body iron levels can be reduced without increasing chelator toxicity?
 - In patients whose liver iron and ferritin have been depleted while cardiac siderosis remains.

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