SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

Aspetti di ferrochelazione in eta' pediatrica

A. Barone

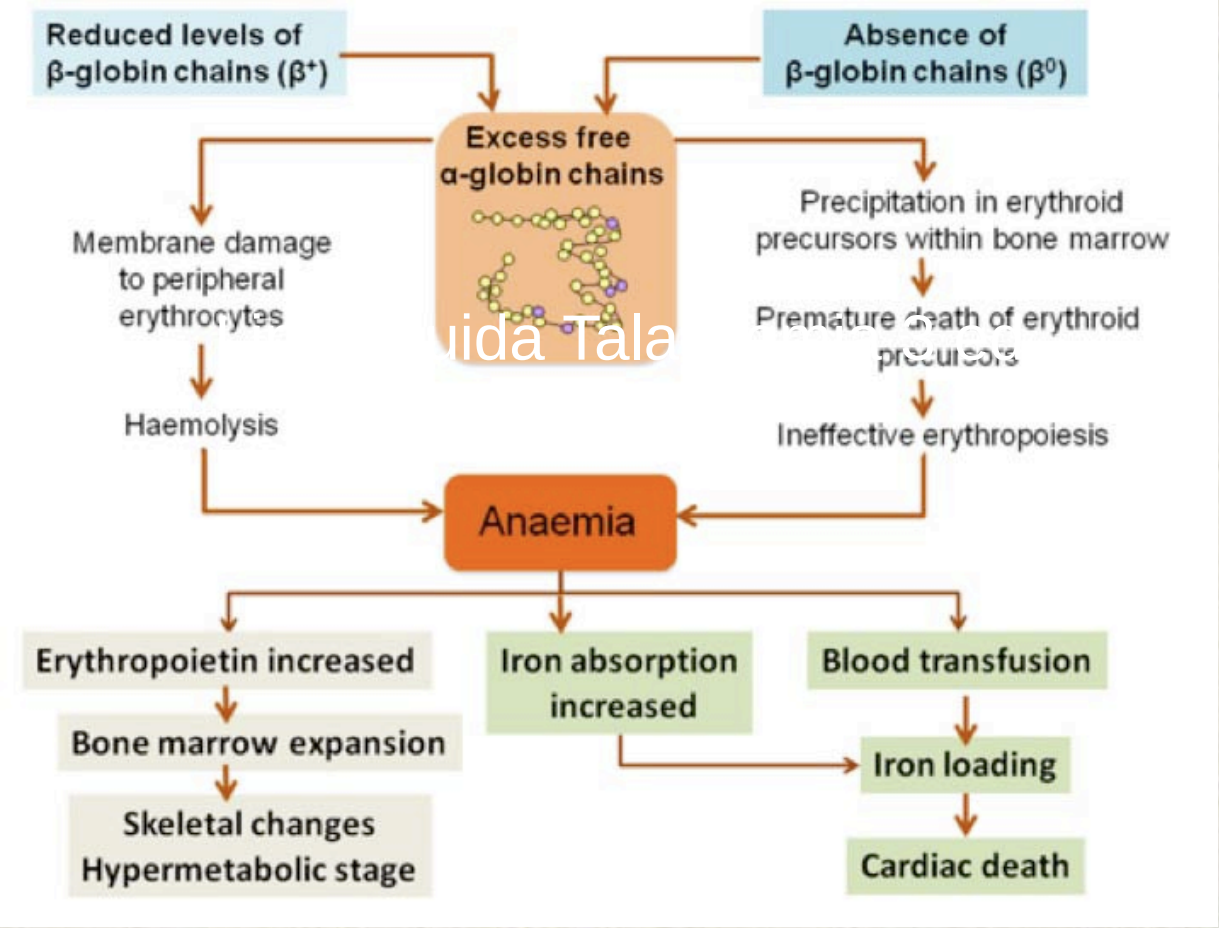
F. Savina

OSPEDALE dei BAMBINI

Cause di sovraccarico marziale

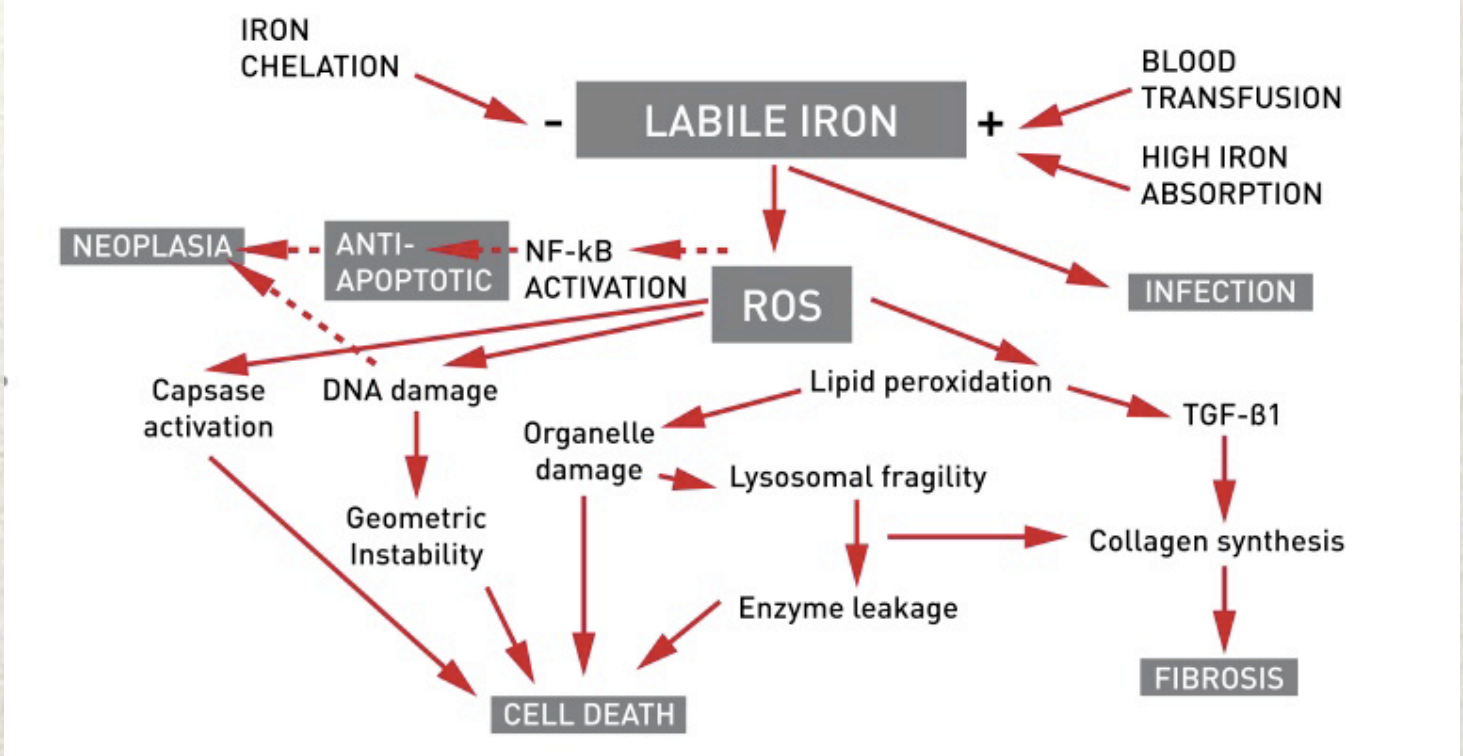
	Assorbimento	Apporto trasfusionale	Ridistribuzione
Emocromatosi	+++		
Talassemia Major	+	+++	
Talassemia intermedia	+++	+	
Anemia sideroblastica	++	++	
Anemia diseritropoietica congenita	++	++	
Aplasie		+++	
Anemie emolitiche croniche		+	
Leucemie off-therapy		+	
Mielodisplasie		++	
Trapianto di midollo		+	+
Atransferrinemia /Aceruplasminemia			+++
Sovraccarico dietetico	++		
Sovraccarico iatrogeno		++	

Talassemia major



Linee guida Talassemia 3 ed - Thalassemia international Federation

Complicanze dell'accumulo di ferro



Linee guida Talassemia 3 ed

Quali sono le potenziali conseguenze

- Ritardo di crescita
- Ritardo di sviluppo puberale
- Ipogonadismo
- Cardiomiopatia e, raramente, aritmie
- Fibrosi e cirrosi epatica
- Diabete mellito
- Ipopartiroidismo
- Ipopituitarismo
- Ipocorticosurrenalismo

RITARDO DI CRESCITA

I fattori principali che determinano il rallentamento della crescita nei pazienti con talassemia sono:

- anemia cronica
- accumulo di ferro trasfusionale
- Tossicità secondaria della terapia chelante
- Deficit di GH o di IGF-1
- Ipogonadismo
- Carenze nutrizionali

HOW TO PREVENT GROWTH RETARDATION IN THALASSAEMIA MAJOR

Improve blood transfusion (correct hypoxia)	→	Improvement of nutrient and O_2 supply to liver and endocrine glands and growth plate
Improve Fe chelation theraphy	→	Prevent siderosis of liver, heart, pituitary, pancreas and growth plate
Improve nutrition (calories, vit. D, folic, zinc, carnitine)	→	Improvement of macro and micronutrient supply of liver, glands and growth plate: compensates for hypercatabolism
Correct GH-IGF-1 deficiency by GH/IGF-1 therapy	→	Stimulates endochondral frowth and bone mineral accretion + anabolic for muscle and fat
Induction of puberty at proper time/sex steroid replacement in hypogonadism	→	Stimulate GH-IGH axis + Direct stimulation of growth and protein anabolism in muscle and bones

Normal synthesis and proper function of hepatic (systemic) IGF-1 and local IGF-1 (autocrine and paracrine) on growth plate muscles and adipose tissue

Soliman 2013

SVILUPPO PUBERALE

- Ritardo puberale ed ipogonadismo sono tra le principali conseguenze del sovraccarico marziale.
- Il deposito di ferro a livello ipofisario determina alterazione della produzione di LH e FSH;
- La funzionalità gonadica, in caso di ferro-chelazione adeguata, è generalmente conservata

De Sanctis V. Growth and puberty and its management in thalassaemia. Horm Res. 2002

Anemie non trasfusione dipendenti

- Drepanocitosi
- Eterozigosi Beta-talassemia/emoglobina S e altre eterozigosi composte

Indicazioni alla terapia trasfusionale

- prevenzione dello Stroke
- trattamento di complicanze acute

I pazienti con SCD regolarmente trasfusi hanno LIC epatica aumentata. Tale dato è correlabile con:

- Durata del regime trasfusionale cronico
- Volume di sangue trasfuso
- Rischio di fibrosi epatica

(Harmatz 2000 Olivieri 2001, Brown 2009)

Esiste un'associazione tra sovraccarico di ferro e aumentata morbilità e mortalità nei pazienti con SCD

(Balas et al 2001, Darbari et al 2006, Fung et al Transfusion 2008)

Come valutare il sovraccarico marziale?

- (biopsia epatica)
- Squid
- RM T2*
- RM R2

SQUID

La suscettibilità magnetica di un tessuto è determinata dalla forza della risposta magnetica evocata nel tessuto dall'applicazione di un campo magnetico (Brittenham 1988)

In una misurazione della suscettibiità magnetica epatica in vivo, l'effetto diamagnetico del parenchima epatico e l'aumentato paramagnetismo, causato dai depositi di ferro, saranno sovrapposti.

Considerando il piccolo e pressochè costante effetto diamagnetico del tessuto epatico, la misura della suscettibilità magnetica può essere utilizzata per determinare i depositi di ferro.

(Shet S. Pediatr Radiol 2003)

Sono state dimostrate correlazioni lineari tra le misurazioni SQUID e i LIC alla biopsia epatica

(Jensen, Br J Haematol. 2004)

Apparecchi SQUID nel mondo

RM T2*

- Valutazione del sovraccarico di ferro epatico, pancreatico e cardiaco
- Metodica non invasiva
- Buona riproducibilità

Ramazzotti et al, J Magn Res Imag 2009

- Durata dell'indagine

Indicazioni all'inizio della terapia ferrochelante: thalassemia

- 10-20 trasfusioni
- ferritina > 1000 ng/ml

Guidelines for the management of TDT 3rd ed

- volume di emazie trasfuso supera 1000 g
- saturazione della transferrina superiore al 50% con volume di emazie trasfuso inferiore a 1000 g
- Età superiore a 2 anni

Indicazioni all'inizio della ferrochelazione nella drepanocitosi

- LIC ≥ 5-7 mg Fe/g peso secco
- Ferritina > 1000 ug/l
- Apporto trasfusionale cumulativo di 120 cc RBC/kg
- Almeno 20 trasfusioni

Linee guida per la gestione della malattia drepanocitina pediatrica in Italia (AIEOP II ed)
(NHLBI 2002, Sickle Cell Society 2008)

Farmaci ferrochelanti

- Deferoxamina: 20-40 mg/kg sc in infusione notturna di 8-12 h per 5-7 notti/settimana
- Deferiprone: 75-100 mg/kg/die in 3 dosi
- Deferasirox: 20-30 mg/kg/die

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) •• ••–•• 1

PAEDIATRIC CLINICAL PHARMACOLOGY

Population pharmacokinetics and dosing recommendations for the use of deferiprone in children younger than 6 years

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Received 23 April 2016; **Revised** 26 August 2016; **Accepted** 11 September 2016

Francesco Bellanti[1], Giovanni C. Del Vecchio[2], Maria C. Putti[3], Aurelio Maggio[4], Aldo Filosa[5], Carlo Cosmi[6], Laura Mangiarini[7], Michael Spino[8], John Connelly[8], Adriana Ceci[7], Oscar Della Pasqua[1,9] and on behalf of the Consortium DEferiprone Evaluation in Paediatrics (DEEP)

etics in children aged <6 years.
population using a population
nded doses yield appropriate

METHODS

Data from a study in which 18 paediatric patients were enrolled were available for the purposes of this analysis. Patients were randomised to three deferiprone dose levels (8.3, 16.7 and 33.3 mg kg^{-1}). Blood samples were collected according to an optimised sampling scheme in which each patient contributed to a maximum of five samples. A population pharmacokinetic model was developed using NONMEM v.7.2. Model selection criteria were based on graphical and statistical summaries.

RESULTS

A one-compartment model with first-order absorption and first-order elimination best described the pharmacokinetics of deferiprone. Drug disposition parameters were affected by body weight, with both clearance and volume increasing allometrically with size. Simulation scenarios show that comparable systemic exposure (AUC) is achieved in children and adults after similar dose levels in mg kg^{-1}, with median (5–95th quantiles) AUC values, respectively, of 340.6 (223.2–520.0) μmol l^{-1} h and 318.5 (200.4–499.0) μmol l^{-1} h at 75 mg kg^{-1} day^{-1}, and 453.7 (297.3–693.0) μmol l^{-1} h and 424.2 (266.9–664.0) μmol l^{-1} h at 100 mg kg^{-1} day^{-1} given as three times daily (t.i.d.) doses.

CONCLUSIONS

Based on the current findings, a dosing regimen of 25 mg kg^{-1} t.i.d. is recommended in children aged <6 years, with the possibility of titration up to 33.3 mg kg^{-1} t.i.d.

Deferiprone (GPO-L-ONE®) 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

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Accessibility to iron chelators including deferoxamine and deferasirox remains obscured in many developing countries. To provide an alternative, the government pharmaceutical organization of Thailand (GPO) manufactured deferiprone which has similar bioequivalent to the standard product. Seventy-three pediatric patients with severe β thalassemias, age range 3.2–19 years, were recruited to a 1-year multicenter prospective, single arm, open label, dose escalating Phase III study of deferiprone to determine its clinical efficacy and safety. Sixty-four patients (87.6%) completed the study with good compliance (>94%). Average deferiprone dose was 79.1±4.3 mg/kg/day. Overall, mean serum ferritin (SF) levels at 1 year were not significantly changed from baseline. However, 45% of patients (response group) had SF reduced >15% from baseline at 1 year with a median reduction of 1,065 ng ml^{-1}. Baseline SF was the major factor that predicts clinical efficacy; patients with baseline SF>3,500 ng ml^{-1} had the most significant fall of SF at 1 year. A subgroup analysis by MRI-T2* confirmed that the response group had higher baseline liver iron and deferiprone could significantly reduce liver iron overload and normalize levels of ALT at 1 year. Although, gastrointestinal irritation (20.5%) was the most common drug-related adverse events (AEs) followed by transaminitis (16.4%) and neutropenia (6.8%), all patients were well tolerated. There was no mortality and agranulocytosis found in this trial. Monotherapy of deferiprone with appropriate dose adjustment and monitoring for adverse events appeared to be an effective chelation therapy in some patients with good compliance and acceptable safety profiles. Am. J. Hematol. 88:251–260, 2013.

Studi in corso

- Trial randomizzato su efficacy e safety del Deferiprone vs Deferasirox in pazienti di età tra 1 mese e 18 anni

- Trial randomizzato su safety ed efficacy di Deferiprone in bambini con nuova diagnosi di talassemia trasfusione-dipendente

(Elafty et al)

RESEARCH ARTICLE

AJH

Deferiprone-induced agranulocytosis: 20 years of clinical observations

Fernando Tricta,[1]* Jack Uetrecht,[2] Renzo Galanello,[3†] John Connelly,[1] Anna Rozova,[1] Michael Spino,[1] and Jan Palmblad[4]

Use of the iron chelator deferiprone for treatment of iron overload in thalassemia patients is associated with concerns over agranulocytosis, which requires weekly absolute neutrophil counts (ANC). Here, we analyze all episodes of agranulocytosis ($n = 161$) and neutropenia ($n = 250$) during deferiprone use in clinical trials (CT) and postmarketing surveillance programs (PMSP). Rates of agranulocytosis and neutropenia in CT were 1.5% and 5.5%, respectively. Of the agranulocytosis cases, 61% occurred during the first 6 months of therapy and 78% during the first year. These events appeared to be independent of dose, and occurred three times more often in females than males. Their duration was not significantly shortened by use of G-CSF. No patient with baseline neutropenia ($n = 12$) developed agranulocytosis during treatment, which raises questions about the validity of prior neutropenia as a contraindication to use. Only 1/7 novel neutropenia cases in CT progressed to agranulocytosis with continued treatment, indicating that neutropenia does not necessarily lead to agranulocytosis. The agranulocytosis fatality rate was 0% in CT and 15/143 (11%) in PMSP. Rechallenge with deferiprone produced agranulocytosis in 75% of patients in whom the event had already occurred, and in 10% with previous neutropenia. Weekly ANC monitoring allows early detection and interruption of therapy, but does not prevent agranulocytosis from occurring. Its relevance appears to decrease after the first year of therapy, when agranulocytosis occurs less often. Based upon analysis of data collected over the past 20 years, it appears that patient education may be the key to minimizing agranulocytosis-associated risks during deferiprone therapy.

Am. J. Hematol. 91:1026–1031, 2016.

Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up

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Table 1. Demographics and patient characteristics at the start of deferasirox treatment

Characteristic	Deferasirox cohort (n = 296)	Crossover cohort (n = 259)	All patients (n = 555)
Mean age, y (range)	17.1 (2-49)	18.3 (3-54)	17.7 (2-54)
Age group, n (%)			
2 to < 16 y	153 (51.7)	120 (46.3)	273 (49.2)
≥ 16 y	143 (48.3)	139 (53.7)	282 (50.8)
Male:female	140:156	134:125	274:281
Race (white:Oriental:other)n	263:9:24	225:10:24	488:19:48
Mean LIC ± SD, mg Fe/g dw			
Biopsy	15.5 ± 9.9	11.5 ± 7.8	13.3 ± 9.2
SQUID	6.1 ± 2.8	5.2 ± 2.9	5.7 ± 2.8
LIC category, n (%)*			
< 7 mg Fe/g dw (biopsy)	60 (20.3)	64 (24.7)	124 (22.3)
< 7 mg Fe/g dw (SQUID)	33 (11.1)	35 (13.5)	68 (12.3)
7-14 mg Fe/g dw (biopsy)	68 (23.0)	93 (35.9)	161 (29.0)
7-14 mg Fe/g dw (SQUID)	15 (5.1)	6 (2.3)	21 (3.8)
≥ 14 mg Fe/g dw (biopsy)	120 (40.5)	58 (22.4)	178 (32.1)
≥ 14 mg Fe/g dw (SQUID)	0	2 (0.8)	2 (0.4)
Median serum ferritin (range), ng/mL	2211 (321-12 646)	1758 (273-8529)	2007 (273-12 646)
Serum ferritin category, n (%)			
≤ 1000 ng/mL	21 (7.1)	48 (18.5)	69 (12.4)
> 1000-2500 ng/mL	155 (52.4)	140 (54.1)	295 (53.2)
> 2500-4000 ng/mL	64 (21.6)	50 (19.3)	114 (20.5)
> 4000 ng/mL	56 (18.9)	21 (8.1)	77 (13.9)

*LIC at start of deferasirox was not available for 1 patient in the crossover cohort.

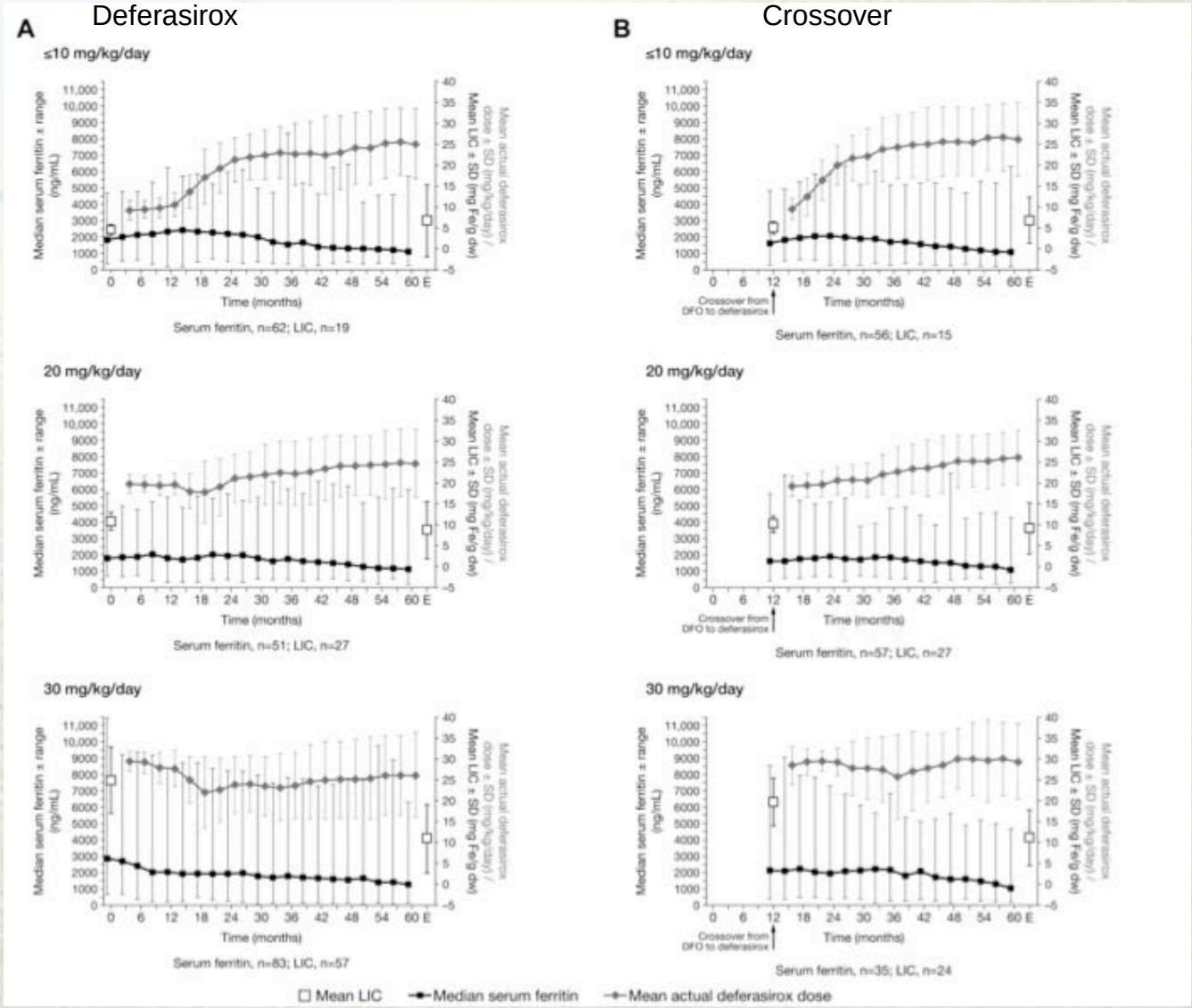
Cappellini et al Blood 2011

Table 3. Adult and pediatric patient disposition

Disposition, n (%)	Deferasirox cohort		Crossover cohort		All patients (n = 555)
	Adults (n = 143)	Pediatrics (n = 153)	Adults (n = 139)	Pediatrics (n = 120)	
Completed	74 (51.7)	107 (69.9)	88 (63.3)	102 (85.0)	371 (66.8)
Discontinued	69 (48.3)	46 (30.1)	51 (36.7)	18 (15.0)	184 (33.2)
Adverse events	14 (9.8)	13 (8.5)	10 (7.2)	6 (5.0)	43 (7.7)
Abnormal laboratory value	1 (0.7)	2 (1.3)	4 (2.9)	2 (1.7)	9 (1.6)
Abnormal test procedure result	1 (0.7)	—	—	—	1 (0.2)
Unsatisfactory therapeutic effect	11 (7.7)	4 (2.6)	7 (5.0)	4 (3.3)	26 (4.7)
Protocol violation	1 (0.7)	1 (0.7)	—	—	2 (0.4)
Withdrawal of consent*	24 (16.8)	6 (3.9)	26 (18.7)	6 (5.0)	62 (11.2)
Lost to follow-up	—	—	1 (0.7)	—	1 (0.2)
Administrative problems	1 (0.7)	—	1 (0.7)	—	2 (0.4)
Death	2 (1.4)	1 (0.7)	2 (1.4)	—	5 (0.9)
Stopped at end of core	13 (9.1)	19 (12.4)	—	—	32 (5.8)
Stopped at end of extension year 3	1 (0.7)	—	—	—	1 (0.2)

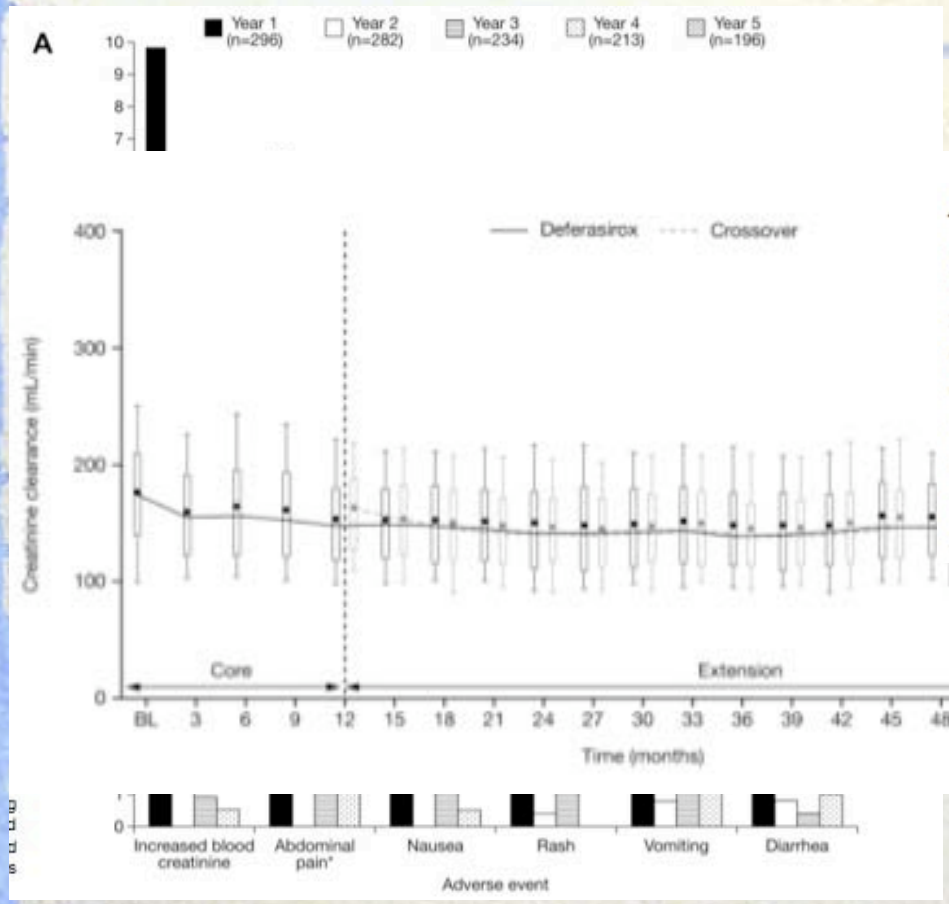
*May include patients who left the study when deferasirox became commercially available.

Cappellini et al Blood 2011



Cappellini et al Blood 2011

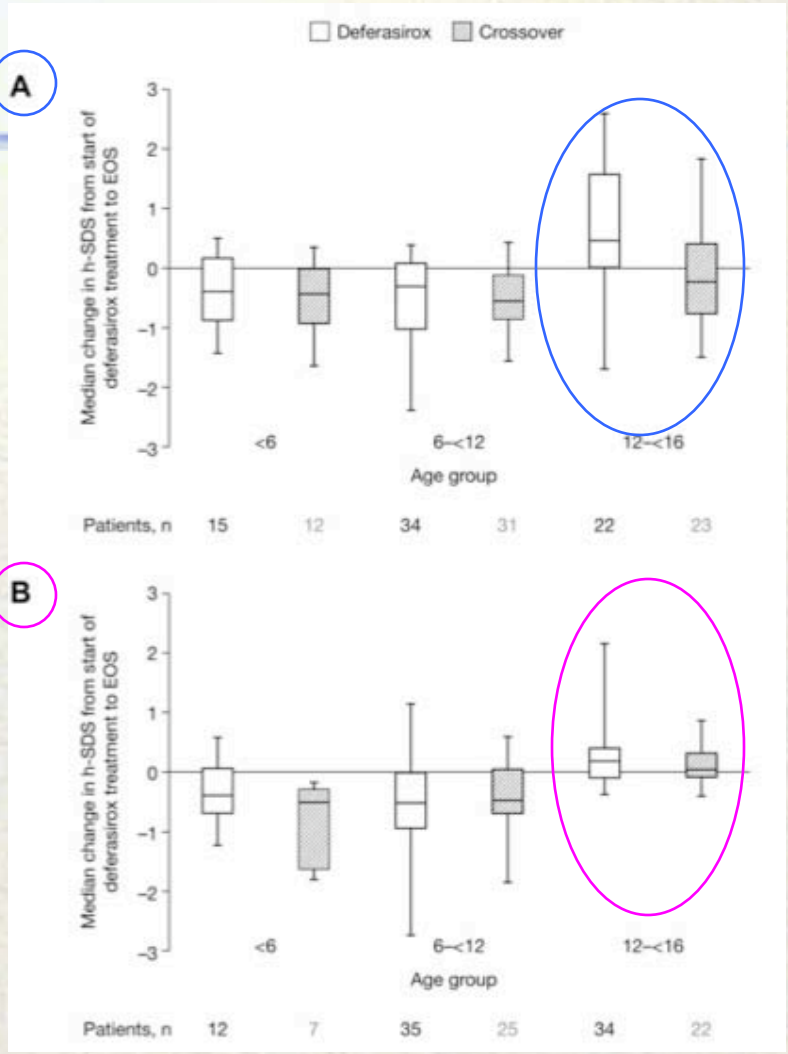
Effetti collaterali



Adverse events. The most common (≥ 5% overall) investigator-assessed deferasirox-related AEs were increased blood creatinine levels (n = 62; 11.2%), abdominal pain (including upper abdominal pain; n = 50; 9.0%), nausea (n = 41; 7.4%), rash (n = 36; 6.5%), vomiting (n = 35; 6.3%), and diarrhea (n = 28; 5.0%). Gastrointestinal disorders with a suspected relationship to deferasirox treatment were observed more frequently in patients aged ≥ 16 years (n = 82; 29.1%) than < 16 years (n = 43; 15.8%). AEs were predominantly transient and mild to moderate in nature. Their incidence generally decreased after the first year of deferasirox

Cappellini et al Blood 2011

Ferrochelazione e crescita



Cappellini et al Blood 2011

	Serum Ferritin levels Geometric Mean (95% CI of GM) (ng/mL)		
Time Points	*Deferiprone monotherapy (n=17)*	*Deferasirox monotherapy (n=17)*	*Combination therapy* (n=15)*
At start	3140.5 (2617.5-3767.9)	3859.2 (3168.8-4700.0)	3696.5 (3079.6-4438.1)
At 6 months	3010.9 (2548.5-3557.1)	3671.1 (3098.1-4350.1)	2977.1 (2384.5-3717.1)
At 12 months	2910.0 (2220.7-3812.4)	3417.4 (2734.6-4270.7)	2572.1 (2138.9-3093.1)

P=0.008 for comparison by ANOVA; Multiple comparison (using Tukey's Test) found no pairs of two time points to be significant in both monotheraphy groups; however, baseline S. ferritin was significantly different with 6 month and 12 month S. ferritin value.

48 bambini di Età media 11,6 anni
Deferiprone 75 mg/kg/die
Deferasirox 30 mg kg/die
Deferiprone 75 mg/kg/die +Deferasirox 30 mg kg/die

La terapia combinata era più efficace nella riduzione dei livelli di ferritina rispetto a ciascuno dei singoli agenti.

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 Pediatr. 2016 Mar;53(3):207-10.

bjh research paper

Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major

Summary

Cardiac and endocrine disorders are common sequelae of iron overload in transfused thalassaemia patients. Combined chelation with desferrioxamine (DFO) and deferiprone (DFP) is well tolerated and produces an additive/synergistic effect superior to either drug alone. 52 thalassaemia major patients were transitioned from DFO to combined chelation with DFO and DFP. Serum ferritin, cardiac and hepatic iron levels were monitored regularly for up to 7 years, as were cardiac and endocrine function. Patients' iron load normalized, as judged by ferritin and cardiac and hepatic magnetic resonance imaging findings. In all 12 patients receiving treatment for cardiac dysfunction, symptoms reversed following combined chelation, enabling nine patients to discontinue heart medications. In the 39 patients with abnormal glucose metabolism, 44% normalized. In 18 requiring thyroxine supplementation for hypothyroidism, 10 were able to discontinue, and four reduced their thyroxine dose. In 14 hypogonadal males on testosterone therapy, seven stopped treatment. Of the 19 females, who were hypogonadal on DFO monotherapy, six were able to conceive. Moreover, no patients developed *de novo* cardiac or endocrine complications. These results suggest that intensive combined chelation normalized patients' iron load and thereby prevented and reversed cardiac and multiple endocrine complications associated with transfusion iron overload.

Terapie combinate: DFO + DFP

Farmaki et al BJh 2009

Terapie combinate: Deferiprone + Deferasirox

The Deferiprone and Deferasirox Combination Is Efficacious in Iron Overloaded Patients With β-Thalassemia Major: A Prospective, Single Center, Open-Label Study

Sidharth Totadri, MD, **Deepak Bansal,** MD, DNB, MAMS,* **Prateek Bhatia,** MD, **Savita V. Attri,** PhD, **Amita Trehan,** MD, and **R. K. Marwaha,** MD, MNAMS, FIAP, FRCPCH

Background. The high cost, coupled with the need for continuous infusion, renders Desferrioxamine (DFO), a non-feasible option for iron-chelation in a large majority of patients with β-thalassemia major in developing countries. Monotherapy with deferiprone (DFP) or deferasirox (DFX) may not always attain optimal control, particularly in heavily iron-loaded patients. Combination of DFP and DFX is a potential alternative. ***Procedure.*** A prospective, single-center, open-label, uncontrolled study was conducted to evaluate the safety and efficacy of the combination in patients with β-thalassemia major. Patients who had received either DFP or DFX for >1 year and a serum ferritin >2,000 μg/L were enrolled. Blood counts, liver/renal functions, and serum ferritin were monitored during the 1-year study period. Facilities for cardiac T2*-MRI were unavailable. ***Results.*** Thirty-six patients with a mean age of 13 ± 6.9 years (range: 4–29) and a ferritin of 6,768 ± 4,145 μg/L formed the study cohort. Eight (22%) patients had transient gastrointestinal adverse effects. DFX was discontinued in one patient for persistent abdominal pain/diarrhea. Eight (22%) had joint symptoms; DFP was discontinued in two. Four (11%) patients had elevation in AST/ALT levels, managed with temporary interruption of DFX. Nine (25%) had an inconsistent elevation of creatinine to >33% of baseline; no intervention was done. One had transient proteinuria. None had neutropenia. At the end of 1 year, the serum ferritin reduced by a mean value of 3,275.3 ± 618.2 μg/L ($P < 0.001$). ***Conclusions.*** The oral combination was found to be safe, efficacious, and a feasible option in patients with suboptimal response to monotherapy. Pediatr Blood Cancer 2015;62:1592–1596.

Key words: arthropathy; chelation; desferal; exjade; India

Blood Cells, Molecules and Diseases 53 (2014) 265–271

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

Deferiprone versus Deferoxamine in Sickle Cell Disease: Results from a 5-year long-term Italian multi-center randomized clinical trial

Giusi Calvaruso [a], Angela Vitrano [b], Rosario Di Maggio [a], Samir Ballas [c], Martin H. Steinberg [d], Paolo Rigano [a], Massimiliano Sacco [a], Paul Telfer [e], Disma Renda [a], Rita Barone [a], Aurelio Maggio [a,*], The Investigators of the Multicenter Randomized Clinical Trial of Deferiprone versus Deferoxamine in Sickle-Cell-Disease

Findings	DFP	DFO	*p*-Value
N° pts	30	30	–
Females (%)	46.67	53.33	0.7970
Age, years	36.433 ± 13.92	35.83 ± 11.56	0.8565
Age at first transfusion, years	6.95 ± 8.03	7.81 ± 11.94	0.7605
Mean age at DFO starting, years	29.09 ± 14.75	29.77 ± 12.03	0.8593
Hgb, gr/dl*	9.59 ± 1.68	9.26 ± 1.27	0.4042
ALT, IU/l*	37.51 ± 22.24	45.97 ± 41.67	0.3395
Total blood transfusion, (ml/year)	2055.05 ± 1282.01	2797.15 ± 2018.08	0.1901
Mean Hb pre-Tx, gr/dl	8.99 ± 1.32	8.65 ± 0.99	0.2955
Mean basal ferritin, ng/ml	1440.14 ± 712.7	1726.03 ± 694.01	0.1274
Mean basal EF (%)	59.91 ± 6.65	60.83 ± 8.52	0.7731
Splenectomy (%)	45.4	70.6	0.1910
Cirrhosis (%)	13.3	11.5	1.000
Arrhythmia (%)	10.0	15.4	0.693
HCV-RNA positive (%)	18.52	12.00	0.705

Years	DFP mean ± sd (n)	DFO mean ± sd (n)
Baseline	1440.13 ± 712.80 (29)	1726.03 ± 694.01 (29)
1	1033.00 ± 737.41 (19)	1522.64 ± 954.98 (22)
2	1076.80 ± 897.51 (15)	1100.05 ± 798.61 (19)
3	580.10 ± 581.56 (10)	1127.68 ± 516.42 (16)
4	438.22 ± 320.81 (9)	1078.26 ± 356.31 (15)
5	695.00 ± 597.74 (7)	1333.85 ± 871.74 (14)

Deferiprone non è inferiore di Deferoxamina nel trattamento del sovraccarico marziale in pazienti con SCD.

bjh research paper

Long-term safety and efficacy of deferasirox (Exjade®) for up to 5 years in transfusional iron-overloaded patients with sickle cell disease

Table I. Patient demographics at the start of deferasirox treatment.

Characteristic	All patients (n = 185)
Mean age (range), years	19·2 (3·0–54·0)
Age group, n (%)	
<6 years	5 (2·7)
6–<12 years	42 (22·7)
12–<16 years	43 (23·2)
16–<50 years	91 (49·2)
50–<65 years	4 (2·2)
Male:female, n	74:111
Caucasian:black:other, n	11:167:7
History of splenectomy, n (%)	24 (13·0)
Median serum ferritin (range), µg/l	3329 (405–12,901)
Serum ferritin, n (%)	
500–1000 µg/l	3 (1·6)
>1000–2500 µg/l	61 (33·0)
>2500–4000 µg/l	48 (25·9)
>4000 µg/l	73 (39·5)

Table II. Patient disposition after the start of deferasirox treatment.

Disposition, n (%)	Patients (n = 185)
Completed	62 (33·5)
Discontinued	123 (66·5)
Adverse events	14 (7·6)
Abnormal laboratory value/test procedure	6 (3·2)
Unsatisfactory therapeutic effect	6 (3·2)
No longer requires study drug	9 (4·9)
Protocol violation	3 (1·6)
Subject withdrew consent	44 (23·8)
Lost to follow-up	17 (9·2)
Administrative problems	10 (5·4)
Death	3 (1·6)
Stopped at end of core	7 (3·8)
Stopped at end of extension 1*	4 (2·2)

*Completed 3-year extension study before extension was prolonged to 4 years by protocol amendment

Vichinsky et al BJH 2011

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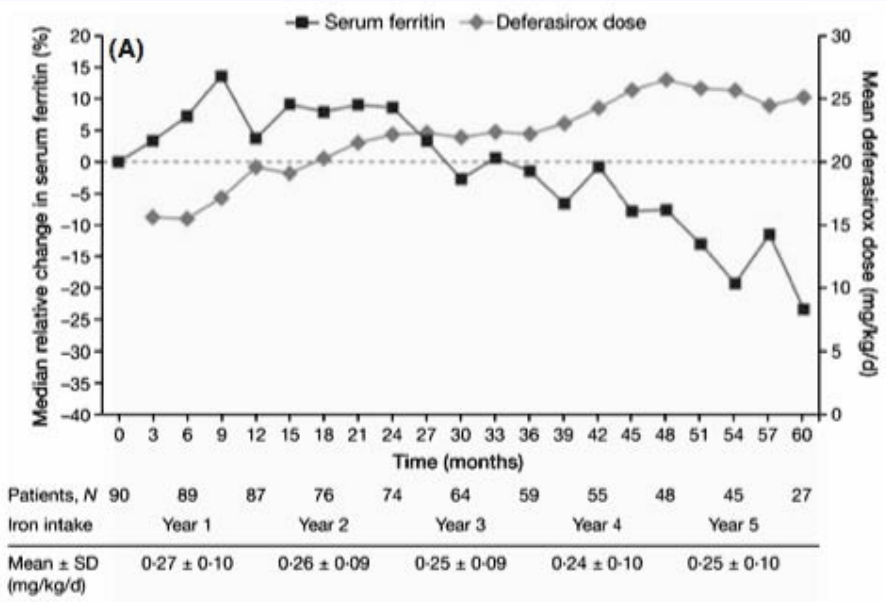


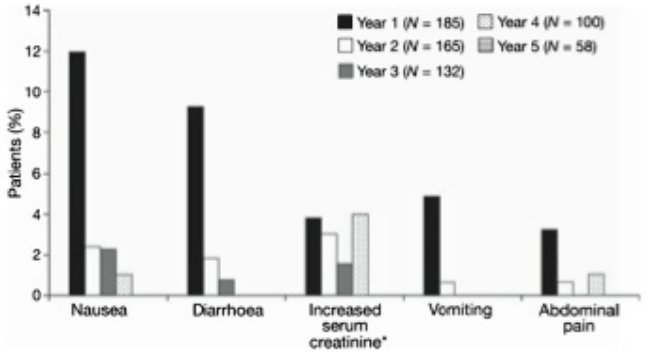


Fig 1. Yearly frequency of most common (≥5% overall) investigator-assessed drug-related AEs after the start of deferasirox. *Reported as an AE by the investigator.

Richiesta trasfusionale	Intake Fe (mg/kg/die)	Obiettivo Tp	Dose iniziale Deferasirox
Bassa	<0,3	Mantenimento bilancio netto del ferro	10-15 mg/kg/die
		Riduzione bilancio del ferro	20 mg/kg/die
Intermedia	0,3-0,5	Mantenimento bilancio netto del ferro	20 mg/kg/die
		Riduzione bilancio del ferro	30 mg/kg/die
Alta	>0,5	Mantenimento bilancio netto del ferro	30 mg/kg/die
		Riduzione bilancio del ferro	>30 mg/kg/die

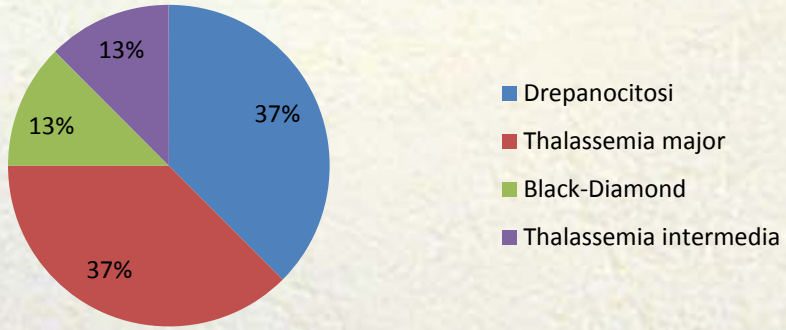
Tratto da Linee guida per la gestione della malattia drepanocitina pediatrica in Italia (AIEOP II ed)

Problema della compliance

- Nella gestione del sovraccarico di ferro la prognosi è largamente condizionata dall'aderenza al trattamento
- La scarsa compliance rappresenta la prima causa di insuccesso terapeutico della terapia ferrochelante

La nostra casistica

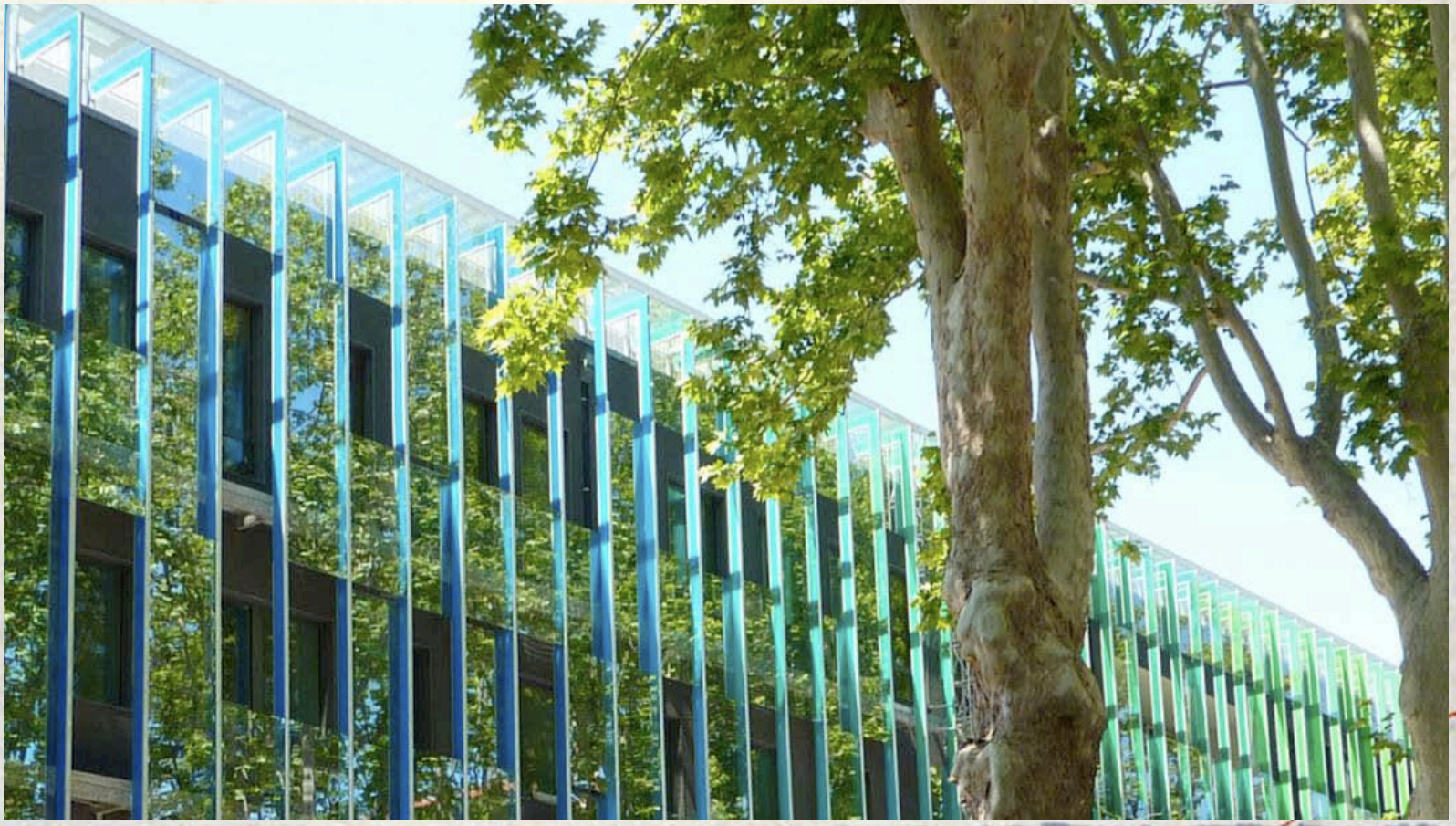
Pazienti pediatrici in tp ferrochelante negli ultimi 5 anni



Patologia	Trattati	Totale
Thalassemia major	3	4
Thalassemia intermedia	1	1
Drepanocitosi	3	3/45
Black-Diamond	1	1/5

U.O.Pediatria e Oncoematologia A.O.U.Parma
Centro Spoke della rete regionale Hub & Spoke per talassemie ed emoglobinopatie

GRAZIE PER L'ATTENZIONE



Calcolo intake trasfusionale

- Ferro (mg/kg/die): quantità di sangue trasfuso in un anno (ml) x ematocrito della sacca x 1,08 /365 (giorni dell'anno) / peso del paziente
- Depositi di ferro corporeo totale in mg/kg = 10,6 x la LIC (in mg/g di peso secco)