New Chelators

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Improved survival of β-thalassaemia patients in the UK with CMR and modern iron chelation

1970: regular transfusions became the norm

1980: DFO therapy became standard practice

1999 onwards: T2* CMR introduction oral iron chelation

Deaths, n


0 5 10 15 20 25 30 35 40 45 50

Unknown Other Malignancy Iron overload Infection BMT complication Anaemia

The number of deaths in the 2000–2003 interval represents deaths during 4 years, and in all the other groups the number of deaths is over 5 years.

BMT, bone marrow transplantation; CMR, cardiac magnetic resonance; DFO, deferoxamine.

Assessment of iron loading

- Serum ferritin
  - inexpensive, frequently repeatable, good for trend recognition
  - long-term control related to survival with DFO
- LIC
  - now non-invasive, standardization improving
  - prognostically significant
  - may identify outliers where serum ferritin unrepresentative (disease, chelator, complications)
Assessment of iron loading (cont.)

● Cardiac T2*
  – prognostically significant, identifies a high-risk group
  – training and validation critical to meaningful results

● Other
  – LVEF decrements identify a very-high-risk group
  – NTBI/LPI currently a research tool, yet to identify high-risk group
  – rate of iron accumulation
  – monitoring for other iron-mediated organ (endocrine, alphafetoprotein) important
## Assessment – when?

<table>
<thead>
<tr>
<th>Observation</th>
<th>Frequency</th>
<th>Expense</th>
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</thead>
<tbody>
<tr>
<td>Iron intake rate</td>
<td>Each transfusion</td>
<td></td>
</tr>
<tr>
<td>Chelation dose and frequency</td>
<td>3 monthly</td>
<td></td>
</tr>
<tr>
<td>Growth and sexual development</td>
<td>6 monthly children</td>
<td></td>
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<tr>
<td>Liver function</td>
<td>3 monthly</td>
<td></td>
</tr>
<tr>
<td>Sequential serum ferritin</td>
<td>3 monthly</td>
<td></td>
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<tr>
<td>Glucose tolerance test, thyroid, calcium metabolism</td>
<td>Yearly in adults</td>
<td></td>
</tr>
<tr>
<td>Liver iron</td>
<td>Yearly from age 8–10 years</td>
<td></td>
</tr>
<tr>
<td>Cardiac function</td>
<td>Yearly from age 8–10 years</td>
<td></td>
</tr>
<tr>
<td>Cardiac iron (T2*)</td>
<td>Yearly from age 8–10 years</td>
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</table>
## Clinically licensed chelators (cont.)

<table>
<thead>
<tr>
<th>Property</th>
<th>DFO</th>
<th>Deferiprone</th>
<th>Deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron binding</td>
<td>1:1</td>
<td>3:1</td>
<td>2:1</td>
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<tr>
<td>Route</td>
<td>s.c., i.v.</td>
<td>Oral</td>
<td>Oral</td>
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<tr>
<td></td>
<td>(8–12 hours,</td>
<td>3 times daily</td>
<td>Once daily</td>
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<tr>
<td></td>
<td>5 days/week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>20–30 minutes</td>
<td>3–4 hours</td>
<td>8–16 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urinary, faecal</td>
<td>Urinary</td>
<td>Faecal</td>
</tr>
<tr>
<td>Usual dose (mg/kg/day)</td>
<td>25–60</td>
<td>75–100</td>
<td>20–40</td>
</tr>
<tr>
<td>Main adverse effects in PI</td>
<td>Local reactions,</td>
<td>Gastrointestinal</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td>ophthalmologic,</td>
<td>disturbances,</td>
<td>disturbances, rash,</td>
</tr>
<tr>
<td></td>
<td>auditory, growth</td>
<td>agranulocytosis/</td>
<td>mild non-progressive</td>
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<tr>
<td></td>
<td>retardation,</td>
<td>neutropenia,</td>
<td>creatinine increase,</td>
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<tr>
<td></td>
<td>allergic</td>
<td>arthralgia,</td>
<td>elevated liver</td>
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<td></td>
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<td>elevated liver</td>
<td>enzymes,</td>
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<td></td>
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<td>enzymes,</td>
<td>ophthalmologic,</td>
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<td></td>
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<td>auditory</td>
<td>auditory</td>
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</tbody>
</table>
Metodiche non invasive di misura del sovraccarico di ferro

- Risonanza Magnetica
- Biosuscettometria: SQUID, MID
Techniques for Measurement of LIC Using MRI

● Signal intensity ratio (SIR) methods
  – Spin echo with SIR (1.5 tesla)\(^1\)
  – Gradient echo with SIR\(^2\)

● Relaxometry methods *(standard method)*
  – Gradient echo T2\(^*\)\(^3\)
    • Less accurate at levels >15 mg/g
    • Single or multiple breath holds
    • Images acquired in 10-12 seconds
  – Gradient echo R2\(^*\)=1/T2\(^*\)\(^4\)
  – Spin echo T2, R2 (FerriScan)\(^5\)
    • Linear over larger range, longer acquisition time
    • Permits free breathing

Viene misurata la variazione del campo magnetico dovuta al parziale allineamento dei momenti magnetici degli atomi di ferro ad un campo magnetico esterno
SQUID (liver susceptiometry)

- The first validated non-invasive method for liver iron measurement
- Linear relationship to iron by biopsy
- Only 4 operating machines in the world
- Expensive, but room temperature devices being developed
- Issues about comparison between centres
- Underestimated LIC in deferasirox studies by 2-fold

LIC from biopsy (µg/g wet wt)

LIC from biomagnetic liver susceptometry (µg/g wet wt)

\[ \text{LIC}_{\text{biop}} = 1.03 \times \text{LIC}_{\text{BLS}} - 33 \]

\[ R^2 = 0.96 \]
• Biosuscettometro MID:

Il MID misura le proprietà magnetiche di tutti i tessuti all’interno della sua regione di sensibilità. Il sovraccarico di ferro, espresso in grammi, è ricavato dalla differenza fra il segnale del paziente e il segnale basale attribuitogli in funzione delle sue caratteristiche antropometriche.

Limite della misura: l’apparato può misurare sovraccarichi superiori a 1 grammo di ferro. L’errore di misura (1g) è determinato dal limite del calcolo del segnale basale ricavato dalla misurazione di una coorte di individui sani.
New chelation schedules

– deferasirox
– deferiprone
– combination and sequential therapy
– iron chelator in development
Deferasirox: recent publications

- Long-term cardiac effects
- Liver effects
- Long-term efficacy and tolerability
- Safety and efficacy of dose escalation
- Tolerability at low levels of iron load
- Effect of administration regime on efficacy and tolerability
- Use in combination with other chelators
- Use in conditions other than transfusion-dependent thalassaemia
5-year follow-up in patients with β-thalassaemia major: changes in serum ferritin

N = 472 at baseline (BL)

Mean actual daily dose of DFX: 22.1 ± 6.4 mg/kg/day (range 6–37)

Median serum ferritin (μg/L)

Time (months)

Studies 105–108: 4.5-year data

Experience with serum ferritin < 1,000 μg/L

The incidence of drug-related AEs did not appear to increase during the periods after serum ferritin levels first decreased < 1,000 μg/L

174 adult and paediatric patients (out of 474) were chelated to serum ferritin levels < 1,000 μg/L

Safety profile over time in patients with β-thalassaemia major


* Reports of abdominal pain and abdominal pain are combined and presented as abdominal pain.
Cardiac iron reduction with deferasirox: continued improvement in cardiac T2*
Objective: to prospectively compare the efficacy of deferasirox to DFO in patients with a MRI-measured LVEF of ≥ 56% but with evidence of cardiac iron deposition depicted by a myocardial T2* of ≤ 20 ms

* = Patients with β-thalassaemia major or Diamond-Black anaemia or sideroblastic anaemia on chronic transfusion therapy.
82.6% of patients experienced either stabilization or improvement in fibrosis staging. Improvements in fibrosis staging were observed in patients who met the LIC response criteria and in those who did not.
Deferasirox
Iron response in specific diseases

- **SCD**
  - 5-year follow-up study of safety and efficacy (n = 185)¹
  - 2-year phase II study evaluating the efficacy and safety of DFX vs DFO, including PK and safety with hydroxyurea (n = 203)²

- **NTDT**
  - THALASSA: a 1-year prospective randomized study with DFX (2 doses) vs placebo (n = 166)³

- **Rare anaemias**
  - EPIC sub-study (1 year) (n = 34)⁴

- **AA**
  - EPIC sub-study – safety and efficacy (1 year) (n = 116)⁵
  - haematological response in EPIC⁶

- **MDS**
  - EPIC sub-study (1 year) (n = 341)⁷
  - EXtend and eXjange: DFX in chelation-naïve and prechelated patients (n = 123)⁸
  - haematological response in EPIC⁹

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NTDT = non-transfusion-dependent thalassaemia.
Agenda

- deferasirox
- **deferiprone**
- combination and sequential therapy
- iron chelator in development
Deferiprone monotherapy: recent publications

- Response rate to deferiprone very variable, why?
- Pharmacokinetics and metabolism?\(^1,2\)
  - rapidly inactivated by glucuronidation of iron binding site
  - glucuronidation in liver, solely with UGT1A6\(^1\)
  - in healthy volunteers not linked to UGT1A6 genotypes\(^3\)
  - other factors affecting PK and metabolism?\(^2\)
    - splenectomy status
- Use of NTBI to predict response rate?\(^4\)
- Oral preparations, syrup – efficacy and tolerability?
  - 9 young children received syrup for 9 months up to 100 mg/kg\(^5\)
    - serum ferritin fell from 2,440 to 2,030 \(\mu g/L\)
  - 10 children < 10 years old, 25 mg/kg t.d.s. for 6 months\(^6\)
    - serum ferritin median fell from 1,598 to 1,446 \(\mu g/L\)

Pharmacokinetics of deferiprone (cont.)

Serum concentrations of non-conjugated DFP, DFP glucuronide, and DFP-chelated iron

- Non-splenectomized patients
- Splenectomized patients

Splenectomized and non-splenectomized patients with β-thalassaemia/HgE. *p<0.05; **p<0.001; AUC_{last-iron} = the total amount of DFP-chelated iron.

Combination therapies

- DFO + DFP
- DFO + DFX
- DFP + DFX
Deferoxamine alone vs combination Rx

LIC response with DFP monotherapy vs combination with DFO

DFP monotherapy
Decrease in 5/12 Non-response 68%
Baseline LIC (mg/g dry wt) 30.7 ± 3.1
EOS LIC (mg/g dry wt) 28.6 ± 3.7

Combination monotherapy
Decrease in 7/8 Non-response 13%
Baseline LIC (mg/g dry wt) 26.6 ± 5.4
EOS LIC (mg/g dry wt) 18.1 ± 4.1*

Combination therapies

- DFO + DFP
- DFO + DFX
- DFP + DFX
DFX + DFO: metabolic iron balance studies

- **Patients**
  - 6 with TM
  - 34-day metabolic iron balance study
  - each patient serving as his/her own control
  - fixed low-iron diet consisting of 4 individualized meal plans

- **Dosing**
  - DFO (40 mg/kg) on days 5–10 as an 8-hour s.c. during night
  - DFX (30 mg/kg) days 15–20, 30 minutes prior to breakfast
  - washout – then *both drugs* were given on days 25–30

- **Results**
  - Combination – mean Fe iron balance – 251% (range 206–270%)
    - Combination > additive 2 patients (35% and 57%)
    - additive in 3 patients
    - < additive in 1 patient

DFX + DFO: improvements in iron overload

Cardiac improvements (in three patients who had T2* < 20 ms at baseline)

- T2* < 20 ms at baseline (6.5–19.5 ms): improved +2.43 ms (8.8–21.3 ms) (p = 0.027)
- LVEF < 60% at baseline (47.4–58.1%): improved to 60.6–64.4%
- Median LPI decreased: 0.87 µM to 0.05 µM (p = 0.004)

LPI = labile plasma iron.

Combination therapies

- DFO + DFP
- DFO + DFX
- DFP + DFX
DFP + DFX?
A patient case

- 34-year-old female with TM, 2 units of packed red blood cells, every 20 days
- Deferoxamine – failed to comply
  - T2* liver 1.1 ms, cardiac T2* 9.4 ms
  - serum ferritin > 2,800 µg/L
- Deferasirox, 20 mg/kg for 12 months
  - liver T2* 3.33 ms, cardiac T2* 10.6 ms
- Deferasirox 30 mg/kg for 24 months
  - liver 7.81 ms, cardiac T2* 13.8 ms
  - serum ferritin 2,080 µg/L
- Deferasirox 30 mg/kg/day + deferiprone 75 mg/kg/day
  for 12 months
  - serum ferritin 397 µg/L
  - liver T2* 15.3 ms, cardiac T2* 21.1 ms

**Patient selection**

- 16 TM > 20 years old
- Either intolerance to DFO or ‘inconvenience to DFO’
- Serum ferritin > 500 µg/L
- > 1 iron overload complication (clinical or laboratory)

**Treatment:** up to 2 years of

- DFX (20–25 mg/kg/day)
  + DFP (75–100 mg/kg/day)

**Outcome**

- Reversal of cardiac dysfunction in 2/4
- Mean LVEF increased significantly
- GTT improved in 2/8 with impaired GTT
- Improvement in gonadal function

**Tolerability**

- No serum creatinine > ULN
- No agranulocytosis, neutropenia, thrombocytopenia
- 3/15 (20%) minor GI disturbance

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<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After</th>
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<tbody>
<tr>
<td>Serum ferritin (µg/L)</td>
<td>581±346</td>
<td>103±60</td>
</tr>
<tr>
<td>LIC (mg/g dry wt)</td>
<td>1.6±1.1</td>
<td>1.0±0.2</td>
</tr>
<tr>
<td>Cardiac T2* (ms)</td>
<td>34.1±5.8</td>
<td>36.9±5.6*</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61±6.0</td>
<td>65±7.6*</td>
</tr>
<tr>
<td>2-hour GTT (mg/dL)</td>
<td>150±87</td>
<td>111±24</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

GTT = glucose tolerance test.

* p < 0.001
Agenda

– deferoxamine
– deferasirox
– deferiprone
– combination and sequential therapy
– iron chelator in development
Clinical studies with a desferrithiocin derivative FBS0701

- Phase 1b dose-escalation study: safety, tolerability, and pharmacokinetics
- 16 adult patients with transfusional overloaded
- Once daily for 7 days at doses up to 32 mg/kg
- Well tolerated at all dose levels
- Pharmacokinetics showed dose-proportionality
- $C_{\text{max}}$ at 60–90 min
- Rapidly distributed at the predicted therapeutic doses
- Plasma $t_{1/2}$ – approximately 19 hours

24-week multicentre phase 2 study with FBS0701

- 51 patients, stratified by transfusional iron intake
- FBS0701 at 14.5 or 29 mg/kg/day p.o. once daily
- 49 patients (96%) completed the study
- No AEs showed dose-dependency
- Commonest AE was increased transaminases (16%, n = 8)
- Mean serum creatinine did not change significantly
- ΔLIC mean at 14.5 mg/kg/day was +3.1 mg/g (dry wt)
  - 29% achieved a decrease in LIC
- ΔLIC mean at 29 mg/kg/day was −0.3 mg/g (dry wt)
  - 44% achieved a decrease in LIC

Conclusions

- Large scale prospective trials of iron chelation therapy now available with clinically relevant endpoints
  - ferritin, LIC, cardiac T2*, and function

- Tailored management of iron overload with new chelators and monitoring is positively impacting outcome

- Challenges for future
  - prospective studies of iron chelation safety at low iron levels
  - prospective studies assessing endocrine function required
  - prevalence of liver disease in transfusional iron overload understudied
  - systematic studies on morbidity and mortality with or without iron chelation therapy in diseases other than TM