Iron Overload and Chelation Therapy in Non-Transfusion-Dependent Thalassemias (NTDT)

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Iron overload in NTDT

- **Cumulative process**
  - Positive correlations between iron overload indices and advancing age\(^1\text{-}^5\)

- **Slower than transfusional siderosis**
  - 3-4 mg/day or as much as 1,000 mg/year\(^6\)
  - Annual increase in liver iron concentration of 0.38 ± 0.49 mg Fe/g dry\(^7\)

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SF levels increased over 11 years in 52 non-chelated β-TI patients: The ORIENT study

Mean serum ferritin level and 95% CI (ng/ml)

Assessment of iron overload in NTDT

- There are several methods to assess iron overload in NTDT patients; each carrying their own advantages and disadvantages:
  - Liver iron concentration (LIC)
    - MRI
    - Biopsy
    - SQUID
  - Serum ferritin
  - Cardiac MRI
    - No evidence of cardiac siderosis in NTDT
    - May be reserved for older patients with high LIC
  - Other markers (NTBI, Transferrin Sat)
    - Few clinical studies


SQUID = superconducting quantum interfering device
NTBI = Non-transferrin-bound iron
Serum ferritin underestimates iron burden in NTDT

Which NTDT patients should receive iron chelation therapy and at what thresholds

- **Patients ≥10 years of age**
  - Increased iron-related morbidity risk beyond this age\(^1\)

- **Patients with a LIC ≥5 mg Fe/g dw**
  - Increased risk of morbidity beyond this threshold\(^2,3\)
  - Iron chelator efficacy beyond this threshold is established (THALASSA)\(^4,5\)

- **Patients with a serum ferritin ≥800 ng/ml (LIC not available)**
  - Best reflects a LIC of ≥5 (specificity/sensitivity analysis)\(^6\)
  - Increased morbidity risk beyond this threshold\(^7\)

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Patients with a LIC ≥5 have a higher prevalence of morbidities (n=168, β-TI, non-chelated)

The prevalence of any morbidity was 84.7% vs. 50% and multiple morbidity was 60.2% vs. 16.1%, in the ≥5 and <5 groups, respectively (p<0.001)
Within a clinically relevant LIC range (3-15), the LIC of 5 threshold had the highest absolute risk difference for development of a morbidity.
Patients with SF ≥ 800 μg/L have a higher incidence of morbidities over 11 years.

![Graph showing proportion of patients surviving without morbidity over time to first morbidity for different SF levels.](image)

- **SF ≤ 300 μg/L**: 8, 8, 8
- **SF > 300 to < 800 μg/L**: 17, 14, 12
- **SF ≥ 800 μg/L**: 27, 16, 1

**Chi-square** = 38.29, **p value** = 0.001


**ORIENT study**
SF >800 ng/mL is predictive of LIC >5 mg/g

- Patients with SF > 800 µg/L had a high probability of LIC ≥ 5 mg Fe/g dry wt
- SF > 2,000 µg/L was highly predictive of LIC ≥ 7 mg Fe/g dry wt
- SF ≤ 300 µg/L appears adequate to safely interrupt DFX therapy

When MRI is unavailable, SF thresholds are useful to indicate initiation of ICT, dose escalation, and/or dose interruption.

However, around 50% of patients with SF<800 could still have LIC >5

ROC, receiver operating characteristic.

Primary goals of ICT

Remove excess iron

Total body chelation

Provide protection from toxic iron effects

Achieve iron balance
Initial evidence on benefit from iron chelation in NTDT

- The OPTIMAL CARE study: 336/584 patients chelated
- In a retrospective analysis, ICT was protective against PHT, cholelithiasis, and osteoporosis

### The OPTIMAL CARE study*

<table>
<thead>
<tr>
<th>Complication</th>
<th>RR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT</td>
<td>0.53</td>
<td>0.29–0.95</td>
<td>0.032</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>0.30</td>
<td>0.18–0.51</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>2.51</td>
<td>1.48–4.26</td>
<td>0.001</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.40</td>
<td>0.24–0.68</td>
<td>0.001</td>
</tr>
</tbody>
</table>

At-risk NTDT patients who are not chelated have the greatest risk of complications


<table>
<thead>
<tr>
<th>Hydroxyurea</th>
<th>Transfusion</th>
<th>Iron chelation</th>
<th>Mean number of complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>1.31</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>2.00</td>
</tr>
<tr>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>0.85</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>N</td>
<td>2.02</td>
</tr>
<tr>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>1.54</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>2.43</td>
</tr>
</tbody>
</table>

n = 584
## Studies performed in NTDT patients with DFO

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease type</th>
<th>Regimen</th>
<th>n (patient ages, years)</th>
<th>Type of study</th>
<th>Study objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pippard MJ, Weatherall DJ, 1988</td>
<td>β-TI</td>
<td>DFO 150 mg/kg over 24 hours</td>
<td>4 (18–27)</td>
<td>Prospective, placebo-controlled</td>
<td>Effect of DFO on iron balance in β-TI patients with positive iron balance</td>
<td>All patients achieved negative iron balance after 6 days of DFO treatment</td>
</tr>
<tr>
<td>Cossu P, 1981</td>
<td></td>
<td>Each of 20, 40, 60, 80, and 100 mg/kg/day</td>
<td>10 (1.2–17.3)</td>
<td>Single-arm open-label trial</td>
<td>Urinary iron excretion over 24 hours and change in serum ferritin over 6 months</td>
<td>Significant increases in urinary iron excretion; non-significant decreases in serum ferritin</td>
</tr>
</tbody>
</table>

Treatment of IOL in NTDT patients with DFO can lead to net negative iron balance, but compliance in this patient population that was not classically iron chelated is expected to be low with a subcutaneous regimen.
Efficacy and safety of DFP in NTDT have been investigated in several studies with limited sample size

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<thead>
<tr>
<th>Study</th>
<th>Disease type</th>
<th>Regimen</th>
<th>n (patient ages, years)</th>
<th>Type of study</th>
<th>Study objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akrawinthawong K, 2011</td>
<td>HbE/β-thal</td>
<td>DFP, starting dose 50 mg/kg/day</td>
<td>30 (18–50)</td>
<td>Prospective, single-arm, open-label trial</td>
<td>Efficacy of DFP in reducing possibility of cardiac complications over 1 year in HbE/β-thal patients receiving intermittent transfusions</td>
<td>Significant decrease in mean pulmonary arterial pressure and pulmonary vascular resistance and significant decrease in SF after 1 year</td>
</tr>
<tr>
<td>Chan JC, 2006</td>
<td>HbH disease</td>
<td>DFP, starting dose 50 mg/kg/day</td>
<td>17 (29–76)</td>
<td>Prospective, control-matched, open-label trial</td>
<td>Efficacy and toxicity of DFP in HbH patients with gross IOL over 18 months, compared with age- and HbH genotype-matched controls without IOL</td>
<td>Significant reduction in SF after 6 and 18 months</td>
</tr>
<tr>
<td>Pootrakul P, 2003</td>
<td>HbE/β-thal or β-TI</td>
<td>DFP, starting dose 25 or 50 mg/kg/day</td>
<td>9 (20–48)</td>
<td>Prospective, single-arm, open-label trial</td>
<td>Efficacy and toxicity of DFP over 17–86 weeks</td>
<td>Significant decreases in SF, LIC, red cell membrane iron, and NTBI; reduced transfusion requirements in 4 patients</td>
</tr>
<tr>
<td>Rombos Y, 2000</td>
<td>β-TI</td>
<td>DFP 75 mg/kg/day</td>
<td>3 (&gt; 18)</td>
<td>Prospective, single-arm, open-label trial</td>
<td>Efficacy (change in SF and urinary iron excretion) and safety of DFP over 2 years</td>
<td>Decline in SF in all patients within 6 months, which was maintained over 24 months</td>
</tr>
<tr>
<td>Olivieri NF, 1992</td>
<td>β-TI</td>
<td>DFP 75 mg/kg/day</td>
<td>1 (29)</td>
<td>Case study</td>
<td>Change in iron status of a 29-year-old man with DFP treatment over 9 months</td>
<td>Decrease in SF from 2,174 μg/L to 251 μg/L after 6 months; decrease in LIC from 14.6 to 1.9 mg Fe/g dry wt after 9 months</td>
</tr>
</tbody>
</table>

DFO and DFP in NTDT

DFO\(^1\)

- Significant decline in serum ferritin after 6 months of DFO treatment
- Significant UIE after 12 hours of continuous DFO (except in patients aged < 1 year)
  - In some patients, substantial UIE despite modest SF levels
  - SF levels of no value in predicting UIE
  - No significant differences in excretion across doses

Deferiprone\(^2\)

- Significant reductions seen in mean SF, hepatic iron, red cell membrane iron, and serum NTBI levels
  - SF ± SD: initial 2168 ± 1142 μg/L; final 418 ± 247 μg/L
- Significant mean increase in serum EPO also observed
- Increase in Hb values in 3 patients; reduction in transfusion requirements in 4 patients


NTBI, non-transferrin-bound iron; UIE, urinary iron excretion.
Deferasirox in NTDT: THALASSA study design

THALASSA study evaluated the efficacy of two deferasirox regimens (5 and 10 mg/kg/day) in NTDT patients, based on the change in LIC from baseline compared with placebo.

Randomize NTDT patients (2:1 DFX/placebo)

Screening (28 days)

Deferasirox 5 mg/kg/day

Placebo 5 mg/kg/day

Deferasirox 10 mg/kg/day

Placebo 10 mg/kg/day

24 weeks

52 weeks

LIC was measured by MRI after every 6 months
SF was measured monthly

EXTENSION

LIC < 3 mg Fe/g dry wt: interrupt
LIC 3–15 mg Fe/g dry wt: ≤ 10 mg/kg/day
LIC > 15 mg Fe/g dry wt: ≤ 20 mg/kg/day

52 weeks

104 weeks

The THALASSA study demonstrated a significant reduction in LIC in both deferasirox arms with a greater reduction in the 10 mg/kg/day group
Deferasirox continues to reduce iron burden over 2 years

Deferasirox core + extension: median dose = 9.5 mg/kg/day
Deferasirox extension: median dose = 10.8 mg/kg/day
Placebo/deferasirox: median dose = 14.0 mg/kg/day

Improvements in LIC were greater with increasing deferasirox dose

<table>
<thead>
<tr>
<th>DFX dose category (mg/kg/day)</th>
<th>Mean ± SD absolute change in LIC from extension baseline to Month 24 (mg Fe/g dry wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 0–&lt; 7.5</td>
<td>n = 5</td>
</tr>
<tr>
<td>7.5–12.5</td>
<td>n = 60</td>
</tr>
<tr>
<td>&gt; 12.5–17.5</td>
<td>n = 30</td>
</tr>
<tr>
<td>&gt; 17.5</td>
<td>n = 31</td>
</tr>
</tbody>
</table>

These results underscore the need for appropriate dose adjustments based on efficacy and safety parameters.

Deferasirox consistently reduces iron burden across all evaluated patient subgroups

Age
- Age <18 (n=21)
- Age ≥18 (n=145)

Gender
- Male (n=89)
- Female (n=77)

Race
- Caucasian (n=94)
- Asian (n=69)
- Black (n=2)
- Other (n=1)

Baseline LIC
- ≤7 (n=31)
- >7–15 (n=77)
- >15 (n=57)

Baseline SF (ng/mL)
- >300–500 (n=17)
- >500–1000 (n=67)
- >1000 (n=82)

Splenectomy
- Yes (n=88)
- No (n=78)

Underlying disease
- β TI (n=95)
- α thalassemia (n=22)
- Hb E/β thalassemia (n=49)

Least squares mean difference in absolute change in LIC from baseline (95% CI)

THALASSA: most common (≥ 3 patients overall) drug-related adverse events

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Deferasirox 5 mg/kg/day (n = 55)</th>
<th>Deferasirox 10 mg/kg/day (n = 55)</th>
<th>Placebo 5 mg/kg/day (n = 28)</th>
<th>Placebo 10 mg/kg/day (n = 28)</th>
<th>Total (N = 166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3 (5.5)</td>
<td>4 (7.3)</td>
<td>1 (3.6)</td>
<td>3 (10.7)</td>
<td>11 (6.6)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>2 (3.6)</td>
<td>5 (9.1)</td>
<td>0</td>
<td>1 (3.6)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>5 (9.1)</td>
<td>0</td>
<td>1 (3.6)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3.6)</td>
<td>1 (1.8)</td>
<td>0</td>
<td>2 (7.2)</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>2 (3.6)</td>
<td>1 (1.8)</td>
<td>0</td>
<td>0</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (1.8)</td>
<td>1 (1.8)</td>
<td>1 (3.6)</td>
<td>0</td>
<td>3 (1.8)</td>
</tr>
</tbody>
</table>

Overall incidence of AEs was comparable between deferasirox and placebo

Most drug-related AEs were of mild-to-moderate severity and resolved without discontinuation of treatment

There were no progressive changes in ALT, creatinine or UPCR in patients treated with deferasirox or placebo.

3 patients had 2 consecutive serum creatinine increases >33% above baseline and > ULN

ALT, alanine aminotransferase; UPCR, urine protein/creatinine ratio

THALASSA: safety profile of deferasirox remains consistent as NTDT patients approach target LIC < 3 for interrupting chelation

Laboratory parameters at baseline and before reaching LIC < 3 mg Fe/g dry wt

<table>
<thead>
<tr>
<th>Parameter (mean ± SD)</th>
<th>Baseline</th>
<th>End of Period 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>End of Period 2&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, μmol/L</td>
<td>51.8 ± 14.6</td>
<td>62.0 ± 21.9</td>
<td>61.0 ± 19.9</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>144.8 ± 42.3</td>
<td>129.8 ± 53.9</td>
<td>129.5 ± 52.3</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>31.4 ± 20.4</td>
<td>16.9 ± 7.4</td>
<td>16.4 ± 6.8</td>
</tr>
<tr>
<td>Urinary protein/creatinine ratio, mg/mg</td>
<td>0.2 ± 0.1</td>
<td>0.3 ± 0.2</td>
<td>0.2 ± 0.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Last available assessment.
THETIS was an open-label, single-arm, multicenter Phase IV study to evaluate the efficacy and safety of deferasirox in NTDT patients with iron overload.

- Results from THALASSA have demonstrated that more aggressive chelation should be initiated earlier in the course of treatment.

- Primary objective of THETIS is to assess the efficacy of deferasirox in patients with NTDT based on change in LIC from baseline after 52 weeks of treatment.

**Diagrams:****

**Screening (4 weeks) to determine patient eligibility**

**Open-label treatment (52 weeks) with deferasirox:**

**Starting dose 10 mg/kg/day for 4 weeks**

**At Week 4, dose adjustments according to baseline LIC**

- 15 mg/kg/day for patients with baseline LIC >7 but ≤15 mg Fe/g dw
- 20 mg/kg/day for patients with baseline LIC >15 mg Fe/g dw
- 10 mg/kg/day for patients with baseline LIC ≥5 but ≤7 mg Fe/g dw

**At Week 24, dose adjustments according to Week 24 LIC**

- Increase dose by 5–10 mg/kg/day if Week 24 LIC >15 mg Fe/g dw
- Increase dose by 5 mg/kg/day if Week 24 LIC >7 but ≤15 mg Fe/g dw and Week 24 LIC reduction from baseline <15%
- Increase dose by 5–10 mg/kg/day if Week 24 LIC increased from baseline to the next category
- Same dose if Week 24 LIC remained in the same baseline LIC category
- Decrease dose by 5–10 mg/kg/day if Week 24 LIC decreased from baseline to the next category
With significant and clinically relevant reductions in iron burden alongside a safety profile similar to that in THALASSA, these data support earlier escalation with higher deferasirox doses in iron-overloaded non-transfusion-dependent anaemia patients.
Algorithm for Iron Overload Assessment and Chelation Therapy in NTDT

- **NTDT ≥ 10 years** (≥ 15 years in deletional HbH disease)
  - LIC Q 1–2 years
  - SF Q 3 months
  - LIC ≥ 5 mg Fe/g dry wt (SF ≥ 800 μg/L)
    - Yes
    - DFX 10 mg/kg/day
  - Yes
  - LIC Q 6–12 months (SF Q 3 months)
    - LIC ≤ 3 mg Fe/g dry wt (SF ≤ 300 μg/L)
      - Discontinue DFX
    - LIC after 6 months > 7 mg Fe/g dry wt (SF > 1 500–2,000 μg/L) and < 15% decrease from baseline
      - DFX 20 mg/kg/day

When MRI is not available

- **NTDT in patients ≥10 years (≥15 years for deletional HbH)**
  - SF ≥800 ng/ml
  - SF ≤300 ng/ml
  - SF >300 to <800 ng/ml
    - Q1 yr
      - MRI
        - LIC <5 mg/g
        - LIC ≥5 mg/g
      - MRI unavailable
        - Other measures supportive of iron overload state
        - No other measure supportive of iron overload

- **SF Q3 mo**

- **Initiate iron chelation therapy with Deferasirox at 10 mg/kg/d**
  - Monitor LIC Q6-12 mo or SF Q3 mo
  - Escalate dose to 20 mg/kg/d after 6 months if LIC >7 mg/g or SF >1500-2000 ng/ml
  - Interrupt dose if LIC is 3 mg/g or SF is 300 ng/ml and monitor LIC Q1-2 yr or SF Q3 mo

Essential tools in helping thalassemia patients:
new DSSI and guidelines for management

DSSI, disease severity scoring index.


Being updated!
NTDT disease severity scoring index: why do we need it?

- NTDT management cannot be standardized and patients should be evaluated individually
  - monitoring and early intervention are KEY to prevent complications

- The goal of the NTDT disease severity scoring index (DSSI) is to provide a simple and reliable method to
  - assess disease severity (i.e. patient status)
  - guide management decisions in clinical practice
    - therapy initiation
    - evaluation of disease progression and treatment response
    - comparison of outcomes among patients

Proposed DSSI

Disease severity score index

- NTDT patients > 16 years old
- NTDT patients ≤ 16 years of age

20 domains

+ 6 extra domains (growth & development)

Total score
- Sum of domains
- Adults (max. 52 points)
- Paediatric (52 + 10 = 62 points)

Validation

Summary

- IOL in NTDT cumulative process with advancing age, and concern with increasing morbidities starts beyond the age of 10 years, as shown by the OPTIMAL CARE study.
- ICT is currently the cornerstone of managing NTDT patients is indicated in patients ≥10 years of age, if their LIC ≥5 mg Fe/g dw or when their SF level is ≥ 800 μg/l.
- Three iron chelators are currently available for the treatment of IOL: deferoxamine (DFO) in subcutaneous or intravenous injection, oral deferiprone (DFP) in tablet or solution form, and oral deferasirox (DFX) in dispersible tablet (DT) and more recently film-coated tablet (FCT) forms.
Summary

- DFX treatment in NTDT patients >10 years was found to decrease LIC (THALASSA). Reduction in LIC with DFX 5 and 10 mg/kg/day starting dose groups is consistent irrespective of baseline LIC/SF, age, gender, race, and splenectomy status.
- Greater reductions in LIC were achieved in patients dose-escalated at 6 months from DFX 10 mg/kg/day starting dose to 20 mg/kg/day.
- The THETIS study further showed that DFX is effective in reducing IOL in NTDT at a starting dose of 10 mg/kg/day, with dose escalations starting at week 4 up to 30 mg/kg/day according to the LIC response.
THANK YOU