Chelation therapy for transfusional iron overload
a proposal for UK guidelines

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Iron Accumulation in Transfusion-dependent Anemias

- Blood Transfusion: 0.3-0.5 mg iron/kg/day
  - In a 50kg person: 15-25 mg/day

- Iron Excretion (Urine & Feces): 1-2 mg/day

- Iron Accumulation: 13-24 mg/day
Transfusional Iron Overload in Thalassemia

Transfusional Iron

Age (years)

Iron (g)

Death
Cardiac Failure
Hypoparathyroidism
Hypothyroidism
Diabetes
Hypogonadism
Cardiac arrhythmia
Hepatic Fibrosis --> Cirrhosis
Survival in TM at UCLH by 10y birth cohort

Survival probability

Years from birth

1975-2000 (n=43)
1965-74 (n=39)
1955-64 (n=21)

Porter & Davis, Best Practice & Research, 2002
Goals of iron chelation therapy

- Maintain iron balance/induce negative iron balance
- Avoid accumulation of redox-active iron
- Prevent/reverse organ dysfunction
- Prolong survival
- Avoid chelator toxicity
- Maximise adherence to prescribed therapy
- Maximize quality of life
Monitoring iron overload to manage chelation

- Serum ferritin
  - values > 2500ng/ml associated with increased risk of cardiotoxicity
  - long term trend is a useful predictor of response and prognosis
  - Unreliable, often falsely elevated

- Liver biopsy
  - good correlation with total body iron
  - good liver control at all times means cardiac loading unlikely
  - irregular distribution, invasive test.
  - not always predictive of cardiac iron on scanning (? previous poor control)

- MRI techniques (cardiac T2*, liver R2)
  - cardiac iron estimation (T2*) linked to cardiac function
  - shortened cardiac T2* can identify high risk patients
  - Liver R2 correlates best with LIC
Survival without cardiac disease according to serum ferritin measurements

Cardiac disease-free survival in patients with:
- **Orange circle**: <33% ferritin measures >2500 ng/mL
- **Green square**: 33–67% ferritin measures >2500 ng/mL
- **Light blue triangle**: >67% ferritin measures >2500 ng/mL

Liver iron and risk of complications from iron overload

Thalassemia Major

Threshold for cardiac disease and early death

Increased risk of complications

Normal

T2* MRI: emerging new standard for cardiac iron

Relationship between myocardial T2* values and left ventricular ejection fraction. Below a myocardial T2* of 20 ms, there was a progressive and significant decline in left ventricular ejection fraction ($R=0.61$, $P<0.0001$).

Cardiac T2* value of 37 in a normal heart

Cardiac T2* value of 4 in a significantly iron overloaded heart

Properties of an Ideal Iron Chelator

- Orally absorbed
- Slow rate of metabolism
- High affinity for iron
- High specificity for iron
- Ability to penetrate tissues and cells
- No re-distribution of iron
- Easily excreted
- Wide therapeutic safety margin
- Absence of toxicity
## Comparison of Currently Available Iron Chelators

<table>
<thead>
<tr>
<th>Property</th>
<th>Desferrioxamine</th>
<th>Deferiprone</th>
<th>Deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual dose</strong></td>
<td>25-60</td>
<td>75</td>
<td>20-30</td>
</tr>
<tr>
<td>(mg/kg/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>SC, IV 8-12 hr, 5 d/wk</td>
<td>Oral 3 times daily</td>
<td>Oral Once daily</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>20-30 min</td>
<td>3-4 hr</td>
<td>12-16 hr</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Urinary, faecal</td>
<td>Urinary</td>
<td>Faecal</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Licensed</td>
<td>Licensed outside US/Canada (approved in 46 countries)</td>
<td>Licensed</td>
</tr>
</tbody>
</table>
# Chelators for managing iron overload

<table>
<thead>
<tr>
<th>Chelator</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desferrioxamine</td>
<td>4 decades experience</td>
<td>Parenteral route</td>
</tr>
<tr>
<td></td>
<td>Survival advantage</td>
<td>Compliance problems</td>
</tr>
<tr>
<td></td>
<td>Heart failure prevented</td>
<td>Dose dependent toxicity</td>
</tr>
<tr>
<td></td>
<td>Heart failure reversed</td>
<td>-eye, ear, bone</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>Oral administration</td>
<td>3 x/day x7/week</td>
</tr>
<tr>
<td></td>
<td>Cardiac protection</td>
<td>Short plasma t 1/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unreliable control of body iron</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arthropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc deficiency</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>Oral administration</td>
<td>Short clinical experience</td>
</tr>
<tr>
<td></td>
<td>Long plasma t 1/2</td>
<td>Cardiac protection unknown</td>
</tr>
<tr>
<td></td>
<td>1/day administration</td>
<td>Changes in creatinine</td>
</tr>
<tr>
<td></td>
<td>Control of body iron</td>
<td></td>
</tr>
</tbody>
</table>
Compliance with desferrioxamine is a major issue

[Graph: Kaplan-Meier of consecutive TM according to compliance with DFO]

Gabutti & Piga, 1996
633 patients prescribed daily sc infusions of deferoxamine for 4 weeks:
• 81% of patients with AE during infusion
• 51% of infusions associated with AE

“85% of 871 patients older than 14 years have their social and/or physical activities prevented due to deferoxamine therapy.

“Compliance with Desferal® (deferoxamine) has been described by some patients and parents as a “barbaric ritual.” Even with dedication, family involvement and a positive attitude, many patients experience lapses in compliance and quality of life is diminished as a result. It is simply too difficult to undergo 8-12 hours of painful drug infusions every night of the year, for life.”
DFO or Deferiprone (L1)-induced Iron Excretion

Grady et al, Cornell University
Combination therapy with Deferiprone and Desferrioxamine

Rationale:

• Increased efficiency: additive or synergistic effect
• Fewer DFO infusions: improved adherence
• Optimize chelation from different pools: DFO for liver, deferiprone for heart
• Reduced dosage of individual chelator may minimize chelator toxicity
• Needs specialist management
Desferal and Ferriprox Combined Therapy

(43 patients; treatment 12 – 45 months)

Ferritin, ng/ml

UIE, mg/kg/die
Dose Schedule:
Ferriprox: 70-80 mg/kg/d, 7 days/week
Desferal: 20-50 mg/kg/d, 2-6 days/week
Improvement in ferritin and Cardiac ejection fraction

Figure 2. Mean ferritin levels in patients on combination therapy.
Exjade Clinical Development Program

Overview

Phase I
- Study 101
  - Single dose, safety and tolerability study
  - 24 adult β-thal patients
- Multiple dose iron Balance study
  - 24 adult β-thal patients

Phase II
- Randomized deferasirox vs DFO safety and LIC study
  - 71 adult β-thal patients
- Single arm safety and LIC study
  - 40 paediatric β-thal patients
- Single arm LIC and tolerability study
  - 184 paediatric/adult patients: β-thal, MDS, rare anaemias

Phase III
- Randomized deferasirox vs DFO safety and LIC study
  - 195 paediatric/adult SCD
- Randomized deferasirox vs DFO LIC and tolerability study
  - 586 paed./adult β-thal pts

Studies:
- Study 101
- Study 104 (12 days)
- Study 105 (48 weeks)
- Study 106 (48 weeks)
- Study 107 (1 year)
- Study 108 (1 year)
- Study 109 (1 year)
Effects of Iron Chelators on Ferritin

Desferrioxamine, deferiprone, and deferasirox all decrease ferritin

Deferasirox shown to maintain and reduce serum ferritin levels in phase 2/3 clinical trials in adult and paediatric patients (12-month efficacy—serum ferritin)

MDS: myelodysplastic syndrome; SCD: sickle cell disease.
Effects of Iron Chelators on Liver Iron Concentration (LIC)

LIC: Good control with desferrioxamine or deferasirox; inconsistent effects with deferiprone

Deferasirox shown to maintain and reduce LIC in phase 2/3 clinical trials in adult and paediatric patients (12-month efficacy — LIC)
Adverse events: Deferasirox

- GI events (15.2%): abdominal pain, nausea and vomiting, diarrhea, constipation
- Skin rash (10.8%)
- Mild, non progressive increases in serum creatinine. No reports of renal failure
- Increased transaminases (>5x ULN) in 5.7% Drug-induced hepatitis: Two cases both leading to discontinuation of Exjade
- Adverse effects on the ear/eye appear to be similar in frequency to those seen with DFO
- Discontinuation rates, regardless of cause, are similar in DFO (4.1%) and Exjade patients (5.7%)
Paediatric considerations

• Patients treated from as young as 2 years
• Safety profile similar to adults
• Sexual and physical development proceeded within normal parameters
• Median follow up > 2.6 years
## Effects of Iron Chelators on Heart: Desferrioxamine (DFO) and Deferiprone (DFP)

<table>
<thead>
<tr>
<th>Author</th>
<th>DFP (n)</th>
<th>DFO (n)</th>
<th>Data</th>
<th>Estimated by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piga et al.¹</td>
<td>54</td>
<td>75</td>
<td>5-year cardiac disease-free survival higher with DFP than DFO ($P &lt; .003$)</td>
<td>Clinical-survival</td>
</tr>
<tr>
<td>Anderson et al.²</td>
<td>15</td>
<td>30</td>
<td>DFP is more effective than DFO in reducing cardiac iron</td>
<td>MRI-T2*-LVEF</td>
</tr>
<tr>
<td>Maggio et al.³</td>
<td>71</td>
<td>73</td>
<td>Similar decrease in cardiac iron with each drug</td>
<td>MRI-ISR</td>
</tr>
<tr>
<td>Hoffbrand et al.⁴</td>
<td>51</td>
<td>–</td>
<td>4/51 patients died of cardiac causes</td>
<td>Clinical</td>
</tr>
<tr>
<td>Ceci et al.⁵</td>
<td>532</td>
<td>–</td>
<td>9/532 patients died of heart failure</td>
<td>Clinical</td>
</tr>
<tr>
<td>Pennell et al.⁶</td>
<td>29</td>
<td>31</td>
<td>DFP more effective in reducing cardiac iron (27% vs 13%; $P = .023$) and increasing LVEF (3.1% vs 0.3%; $P = .003$) than DFO</td>
<td>MRI-T2*-LVEF</td>
</tr>
<tr>
<td>Borgna-Pignatti et al.⁷</td>
<td>750*</td>
<td>3,610*</td>
<td>52 cardiac events on DFO; 0 on DFP</td>
<td>Clinical</td>
</tr>
</tbody>
</table>

Effects of Iron Chelators on Heart: Improved Cardiac T2* at 1 Year With Deferasirox


- **16 thalassaemia**
- **6 other anaemias**

**Dose:** 10–30 mg/kg/day

T2* geometric mean increased from 18.0 to 23.1 ms at study end (P = .013)

**Graph:**
- Pre: Median = 19.5 ms
- Post: Median = 25.7 ms

**Box Plot:**
- Pre: Lower quartile = 17.0, upper quartile = 21.0
- Post: Lower quartile = 23.0, upper quartile = 28.0
Licensed Indications for Deferasirox (Exjade)

- treatment of chronic iron overload due to frequent blood transfusions (>7ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.
- treatment of chronic iron overload due to blood transfusions when desferrioxamine therapy is contraindicated or inadequate in the following patient groups:
  - In patients with other anaemias,
  - In patients aged 2 to 5 years,
  - In patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (≤7 ml/kg/month of packed red blood cells)
UK guidelines for chelation

• Aims for a rational approach to chelation to ensure consistency across UK for patients
• Consensus view based on current evidence and UK clinical experience in 2006
• Situation is fluid and recommendations may change as more information becomes available
General considerations

- Management decisions should ideally be directed by results of:
  - ferritin levels
  - cardiac/liver iron by T2*MRI or liver biopsy (if T2* not available)

- T2* estimations are feasible and should routinely start from 10 yrs of age; below that will depend on clinical indications

- Patients need to be involved in decision making and information discussed with them should be backed up with written, impartial information.
  - if changed to deferasirox (DFX), patients need to be aware that long term safety data is not available and that they may need to revert back to alternative treatment at some point in the future if there are long term issues of safety and/or efficacy.
General considerations (cont)

• Current evidence suggests that those with current or previous cardiac loading and/or cardiac history should receive Deferiprone as part of their treatment unless this agent is not tolerated.

• Desferrioxamine doses according to
  therapeutic index = \[
  \frac{\text{mean daily dose (mg/kg)}}{\text{serum ferritin (µg/l)}}
  \]
  - maintain at <0.025 at all times
  - consider balloon infusors to aid adherence to desferrioxamine
• DFO  Desferrioxamine 20-50 mg/kg/day
• DFP  Deferiprone 75-100 mg/kg/day
• DFX  Deferasirox 20-30 mg/kg/day

Dose Schedule: Combination

Ferriprox: 70-80 mg/kg/d, 7 days/week

Desferal: 20-50 mg/kg/d, 2-6 days/week
Recommendations
(irrespective of funding issues)

1 Previously untreated patients

Discuss options and available data with parents. If started on DFX, monitor as part of long term follow up study.

N.B. terms of license open to interpretation in young children
2 Those with stable ferritin levels (<2500ng/ml) and probably adhering to treatment:

a) no liver or cardiac loading
- Continue with present regimen unless patient expresses a desire to change to DFX. In this situation discuss options and available data with patients, document carefully. Reassess at 6-12 months

b) current or previous cardiac loading on T2*MRI or clinical history of cardiac problems, liver load low
- On current evidence, should consider adding DFP: as part of combination or as monotherapy.
c) heavy liver involvement (>7mg/kg/dw) but normal T2* cardiac iron load

- currently on DFO monotherapy - continue DFO at increased dose according to TI. Consider alternative means of DFO delivery (e.g. pre-filled infusors or iv port). If not tolerated or poor adherence consider changing to DFX

- currently on DFP monotherapy – change to DFO monotherapy, if possible, and consider alternative delivery means, as above. An alternative is combination DFO/DFP with daily DFP to a maximum of 80-100 mg daily and DFO at least three times a week. If not tolerated or poor adherence then consider changing to DFX

- currently on DFO/DFP- continue DFO at increased dose according to TI and increase DFP dosage to 80-100mg/kg/day. If not tolerated or poor adherence consider changing to DFX
d) both cardiac and liver iron load high (unlikely at this ferritin level, consider Vitamin C deficiency)

- DFO at increased doses (as tolerated and according to therapeutic index) in combination with DFP. If combination fails due to side effects, give IV DFO via port or central line
3. Patients with ferritin levels >2500ng/ml on current regimen and/or suspected poor adherence

a) no cardiac loading
• Deferiserox (DFX): try for 6-12 months and re-evaluate

B) current or previous cardiac loading on T2*MRI or clinical history of cardiac problems, liver load low
• 1st choice: combination treatment with DFO and DFP, increasing DFP to 80-100mg/kg/day, DFO to maximum tolerated dose according to TI.
• 2nd choice DFX: try for 6-12 months and re-assess with MRI
4. Patient requesting DFX
   • Discuss options and available data with patients, document carefully. Reassess at 6-12 months

5. Hepatitis C positive patients
   • Continue DFO and/or DFP according to the indications above (data too early for DFX).

6. Other patients e.g. Thalassaemia intermedia, Sickle cell disease, other chronically transfused
   If previously untreated discuss options and available data with patients. If DFX chosen, document decision and reassess after 6-12 months

   Otherwise as above
Thanks to contributors

- Kate Ryan
- Paul Telfer
- Anne Yardumian
- Farrah Shah
- Sally Kinsey
- Christine Wright
Issues for discussion

Comments?

Where do we go next with these guidelines?

What about funding?
  – postcode prescribing must be avoided