Iron Chelation therapy in Thalassaemia Patients journey

George Constantinou
11th Annual sickle cell disease and Thalassaemia conference (ASCAT)
Why Chelation

Organ Systems Affected by Iron Overload

<table>
<thead>
<tr>
<th>Organ</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary</td>
<td>Hypogonadotrophic hypogonadism&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Hypothyroidism&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Parathyroid</td>
<td>Hypoparathyroidism&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heart</td>
<td>Cardiomyopathy&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Liver</td>
<td>Cirrhosis, carcinoma&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Diabetes&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Skin</td>
<td>Pigmentation&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gonads</td>
<td>Hypogonadotrophic hypogonadism&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Joints</td>
<td>Arthropathy&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Timeline of Patient’s Journey: Chelation Therapy

- No chelation
- Desferal: Intra-muscular injection
- Desferal: Intra-venous infusion
- Desferal: Bedside infusion pump
- Desferal: Portable infusion pump
- Desferal: Pre-Filled infuser
- Desferal: Use of port-a-cath
- Oral: L1 -- Deferiprone
- Oral: Deferiprone + Desferoxamine
- MR1 T2* & Ferri scan
- Oral: Exjade


George Constantinou ASCAT 2017
Desferrioxamine History

• The early history of desferrioxamine was described by Keberle at the 1964 Cooley's anaemia meeting. (Keberle H. The biochemistry of desferrioxamine and its relation to iron metabolism. Ann N Y Acad Sci. 1964 Oct 7;119:758-68.)

1960

• In a search for antibiotics, it was observed that a mould called Streptomyces griseus prevents the growth of bacteria, and desferrioxamine was shown to be responsible. The Streptomyces produces desferrioxamine in order to pick up iron from its surroundings: the iron complex is called ferrioxamine. The mould (re)absorbs ferrioxamine and uses it as an iron source for growth.

• Bacteria needs iron to multiply. When desferrioxamine is present it binds all available iron as ferrioxamine. Most bacteria cannot absorb ferrioxamine, and so cannot grow when Streptomyces griseus, and so desferrioxamine, is present.

• We now know of two exceptions: Yersinia and possibly Klebsiella can use ferrioxamine as an iron source.
Questions that needed an answer

Question 1. Can desferrioxamine be used as an antibiotic?
• NO

Question 2. Can the iron chelate ferrioxamine be used to treat iron deficiency?
• NO

1961
Question 3. Can desferrioxamine be used to treat ACUTE iron poisoning?
• It was found that acute iron poisoning can be successfully treated by intravenous infusion of desferrioxamine (to bind iron that has been absorbed from the gut) plus desferrioxamine by mouth (to bind free iron in the gut and stop it being absorbed).
Questions that needed an answer

Question 4. Is desferrioxamine treatment life-saving?

- In 1964 Bernadette Modell initiated a study of all thalassaemic patients in the UK that later became the UK Thalassaemia Register (1964-2003). The aim was to collect as much clinical information as possible, and relate outcomes to transfusion and desferrioxamine treatment. **By 1981 it was clear that regular intramuscular desferrioxamine is life-saving.**

1966

Question 5. Does desferrioxamine prevent liver damage?

- In 1966 GOS initiated a randomised trial, in which 10 children received 500mg DF/day and 10 did not. The end point was to be extent of iron loading in the liver and liver damage, assessed by liver biopsy. The trial, which ended in 1978, showed that treatment with desferrioxamine even in the low dose used arrested liver iron damage *(Barry M, Flynn DM, Letsky EA, Risdon RA. 1974. Long-term chelation therapy in thalassaemia major: effect on liver iron concentration, liver histology and clinical progress. BMJ ii, 16.)*


- Ciba Geigy marketed desferrioxamine for treatment of acute iron poisoning.
Desferal® Ciba Geigy

• European Pharmacopeia: deferoxamine

• PINN (Proposed International Non-Proprietary Name): deferoxamine

• British Approved Name (BAN): desferrioxamine
Desferrioxamine
Generic Desferrioxamine
Intramuscular gun for children
What next? Intravenous infusion

- This was the next step to increase the iron excretion.
- Sephton-smith 1964 & Model & Beck 1973 found that if desferrioxamin was infused slowly during the blood transfusion the urinary iron excretion will be greater.
- Propper et al 1976 after looking at the results of the GOSH trial and other observations concluded that desferrioxamine is a very effective drug but limited in the method of administrating.

1974
- The first results from UCH and GOS were presented at the 1974 Cooley's anemia meeting. *(Modell B, Beck J. Long-term desferrioxamine therapy in thalassaemia. Annals N.Y. Acad. Sci. 232: 202. 1974, and Barry et al. as above).* At this meeting David Nathan and Richard Propper agreed that desferrioxamine is an excellent drug, and identified the main problem as the mode of administration.
What happened next? Subcutaneous infusion

- The use of the bedside Pumps was used to provide the subcutaneous infusion of desferrioxamine through the night. This allowed the clinicians to start manipulating the dosage of the drug.
Bedside infuser
Portable Pump

- Proper rapidly went on to develop the concept of sub-cutaneous infusion of desferrioxamine overnight using the portable pump

Can we administer desferal in a more patient friendly way?

1976

- 1976 Modell and Berdoukas at UCH initiated a meeting of parents and Patients at the UCH with the request to form a Thalassaemia support group and as a 1st project to help raise funds for the developing of a portable infuser to replace the bed side one

- Bernadette Model and Vasili Berdoukas met with Martin Wright at Northwick Park hospital, to request the possible development of a small portable syringe driver that could be safely managed by a child of seven. The UKTS provided the funds (s£5000.00) for the development of the 20 prototypes

- Once the prototypes were shown to work, Pye Dynamics started production of "The Pump". In principle it was now possible to deliver enough desferrioxamine to every patient to successfully control their iron overload.

- We recognised that thalassaemia was the ideal disorder for testing the syringe driver, because if it accidentally stopped or delivered too much desferrioxamine, there would be no negative consequences – a risk-free study! And an example of how thalassaemia research often had far wider implications.
Portable infusers
Problems with patient compliance
We needed something better
Elastomeric Pre-filled Infuser
Elastomeric Pre-filled Infusers

• Developed in the late 1990’s in order to help patients with their compliance problems.
• It was considered that if they pump was pre filed and had an expiry day then the patients will be more prone to using them more than the pumps they had to prepare themselves.

Advantages
Light to carry
Noiseless
Ready to be used and so no waste of time
Home delivery
Easier for children
No complicated preparation needed and dosage controlled by the hospital

Disadvantages
Very expensive especially as it is home delivered
Wasted if not used by expiry day
Port-a-cath Hazards

- Body image
- Lifestyle restrictions
- Infection / septicaemia
- Blood clots (pulmonary emboli)
- Anticoagulation therapy
Desferrioxamine

- **Advantages**
  1. Removal of Iron
  2. 1st line Drug for chelation
  3. Drug used for many years so knowledge of safety
  4. When used correctly it is considered the safest of all chelators

- **Disadvantages**
  1. Pain, Swelling, itching at infusion side
  2. Abnormal bone growth or hearing loss on high dosages
  3. Long time to prepare the infusion
  4. Expense of the pump
  5. Very costly (if prefilled infusers)
  6. Needle in your body for 12-18 hours
  7. Very difficult to use during the day at school or work

- NON COMPLIANCE
Therefore needed something even better?
**Oral iron chelation: Deferiprone (L1)**

- **The 1st oral chelator:** Developed by Dr George Kontogeorgies with Prof Hofbrand, Dr B. Wonke & others with the *research funding given by the UKTS at the staggering amount of £1 million in the late 1980’s and early 1990’s*

- This development had controversial issues resulting to all kinds of problems even to a book being published!

- **The biggest unfortunate issue of all, was that Thalassaemia patients were in the middle of the controversy and many DIED due to this controversy**

- However many doctors did put their patients on L1 such as Dr Wonke at the Whittington Hospital and Dr Agarwal in India:

George Constantinou ASCAT 2017
Deferiprone: Brief Development History

- ApoPharma began formal development - 1993
- Ferriprox®
  - approved by the EMEA - 1999
  - approved by the FDA - 2011 (12 YEARS LATER)
  - approved by Health Canada - 2015
  - approved in > 60 countries
Deferiprone
Deferiprone Solution
Ferriprox® (deferiprone)

4.1 Therapeutic indications
Ferriprox monotherapy is indicated for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.
Ferriprox in combination with another chelator is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction.

5.1 Pharmacodynamic properties
...FERRIPROX has comparable efficacy to deferoxamine in controlling serum ferritin and liver iron concentrations, and is superior to deferoxamine in reducing excess cardiac iron content and in improving cardiac function in patients with cardiac iron overload.
...patients with transfusion-dependent thalassemia treated long term with deferiprone have a lower incidence of iron-induced cardiac disease than patients treated long term with deferoxamine, and increased survival.

adapted from the EMA Ferriprox SmPC
Deferiprone (DFP)

• **Advantages**
  - Removal of Iron
  - Removal of Iron from the heart
  - Substantial experience in the use of this drug
  - Oral (tablets) so no needles
  - Improvement of Adherence

• **Disadvantages**
  - Can develop agranulocytosis (1.5%) hence a 1-3 weekly blood test of white cells is advisable.
  - Not as efficient in removing iron from the liver as it is from the heart
  - Dose is 3 times a day
  - Higher cost than DFO
Combination chelation therapy with desferrioxamine and deferiprone

• This was the answer for many patients that would not have survived
## Alternate chelation

<table>
<thead>
<tr>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thu</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>L1</td>
<td>L1</td>
<td>L1</td>
<td>L1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Sequential chelation

<table>
<thead>
<tr>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thu</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>L1</td>
<td>L1</td>
<td>L1</td>
<td>L1</td>
<td>L1</td>
<td>L1</td>
</tr>
</tbody>
</table>

| DFO | DFO | DFO | DFO | DFO | DFO | DFO |

George Constantinou ASCAT 2017
Rationale for Combination Chelation

• Increased efficiency: Additive or synergistic effect (Shuttle effect)
• Fewer DFO infusions: Improved adherence
• Optimize chelation from different pools: DFO for liver, Deferiprone for the heart
• Reduced dosage of individual chelator may minimize chelator toxicity
Next came another oral iron chelator
Deferasirox (Exjade)

- EXJADE is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

- EXJADE is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:
  - in paediatric patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years,
  - in adult and paediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,
  - in adult and paediatric patients with other anaemias aged 2 years and older.

- EXJADE is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.
Deferasirox (Exjade)

- Dispersible tablet
- FDA approval November 2005
- EMA Approval August 2006
- Registered in 128 countries
- Marketed in 113 countries

Exjade approval 2005
Deferasirox (Exjade)

New Formulation Exjade / jADENU

• New Formulation film coated tablet
• FDA approval 2015
• EMA approved but as the same name as before
Deferasirox

Advantages

• Removal of Iron
• Oral Once a day (12-16 hours working)
• Can be given to children
• Removal of Iron especially from the liver
• Patients felt very safe as this drug had a long periods of clinical trials
• Improvement of Adherence

Disadvantages

• Dispersible
• Terrible taste
• Skin rash
• G I symptoms
• Some hepatic failure
• Renal tubular damage
• Some increase to serum creatinine
• Most excretion from faeces so many patients can not see the iron being removed

More expensive than all other chelators
## Overview of available iron chelators

<table>
<thead>
<tr>
<th>Property</th>
<th>Deferoxamine (DFO)</th>
<th>Deferiprone (DFP)</th>
<th>Deferasirox (DFX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual dose</td>
<td>35–60 mg/kg/day</td>
<td>75- 100 mg/kg/day</td>
<td>20–40 mg/kg/day</td>
</tr>
<tr>
<td>Half-life</td>
<td>20–30 min</td>
<td>3–4 h</td>
<td>8–16 h</td>
</tr>
<tr>
<td>Route</td>
<td>SC/IV 8–12 h, 5-7 days/week</td>
<td>oral 3 times daily</td>
<td>oral once daily</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urinary, faecal</td>
<td>Urinary/faecal</td>
<td>Faecal</td>
</tr>
<tr>
<td>Dose related toxicity</td>
<td>Growth failure, hearing loss, visual abnormalities</td>
<td>GI, Hepatic</td>
<td>Renal, GI, Hepatic</td>
</tr>
<tr>
<td>Warnings</td>
<td></td>
<td>Agranulocytosis</td>
<td>Renal failure Liver failure GI hemorrhage</td>
</tr>
</tbody>
</table>

**Warnings**
- Agranulocytosis
- Renal failure
- Liver failure
- GI hemorrhage
# Current UK licensing indications for iron chelating drugs (UKTS STANDARD)

<table>
<thead>
<tr>
<th></th>
<th>DFO</th>
<th>DFP</th>
<th>DFX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children age 2-6</strong></td>
<td>First line</td>
<td>Insufficient information</td>
<td>Second line if DFO contra-indicated or inadequate</td>
</tr>
<tr>
<td><strong>Children age &gt; 6 and adults</strong></td>
<td>First line</td>
<td>Second line: If DFO not tolerated or ineffective</td>
<td>First line</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>s.c/ i.m or i.v injection</td>
<td>Oral, tablet or liquid</td>
<td>Oral, dispersed tablet</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>20-60 mg/kg 3-7 times per week. Children's dose up to 30 mg/kg</td>
<td>75-100 mg/kg/day</td>
<td>10-40 mg/kg/day</td>
</tr>
</tbody>
</table>
| **Contra-indications** | Hyper-sensitivity        | Previous agranulocytosis
Pregnancy-teratogenic risk | Hyper-sensitivity
Estimated creatinine clearance <60ml/min
Pregnancy |

---

George Constantinou ASCAT 2017

39
## Monitoring of chelation therapy

<table>
<thead>
<tr>
<th></th>
<th>DFO</th>
<th>DFP (or combination with DFO)</th>
<th>DFX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neutrophil count</strong></td>
<td>NR</td>
<td>Weekly during therapy</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td>NR</td>
<td>NR</td>
<td>Twice before start, then Weekly during first month after initiation and change of dose. Thereafter monthly</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>Monthly</td>
<td>Monthly</td>
<td>Twice before start, then 2 weekly for first month after initiation of therapy. Thereafter monthly</td>
</tr>
<tr>
<td><strong>Urinalysis</strong></td>
<td>NR</td>
<td>NR</td>
<td>Twice before start, then weekly during first month after initiation and change of dose. Thereafter monthly</td>
</tr>
<tr>
<td><strong>Pure tone audiometry</strong></td>
<td>Annual</td>
<td>6-12 monthly for combination DFO and DFP, not if used as single agent</td>
<td>Annual</td>
</tr>
<tr>
<td><strong>Ophthalmology</strong></td>
<td>Annual</td>
<td>6-12 monthly for combination DFO and DFP, not if used as single agent</td>
<td>Annual</td>
</tr>
</tbody>
</table>
Development and Clinical Implications of MRI T2* and FerriScan

• Accurately gauge body iron loading of the 2 most vital organs
• Monitor efficacy of treatment
• ‘Tailor-make’ individual treatment regimens
• Substantial improvement in UK mortality rate since 1999 (8 deaths – only 2 from cardiac iron)
Challenging points

• When do you start chelation?
• What chelator do you start with?
• What do you do with Thalassaemia Patients who are pregnant?
• On what bases do you alter the chelator?
• The incredible cost of the chelators?
• Use of combination thereby and what combination?
• Adherence to chelation not perfect even with oral chelators
• MR1 T2* and Ferriscan, challenging and expensive
Thank you

I would like to thank Prof Bernadette Modell for her support in the historical data of this chelation journey