Iron Overload Therapies

National Patient & Parent Conference, 2011
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Conflicts of Interest: unrestricted grants from Novartis & Apotex
Iron Overload And Organ Loading

Blood saturated with iron

Toxic NTBI iron in blood

Uncontrolled iron loading of organs

- Pituitary
- Parathyroid
- Thyroid
- Heart
- Liver
- Pancreas
- Gonads

STOP

Thalassemia Foundation of Canada
Principles of Treatment

2 factors have led to improvements in survival in the past decade:
- Cardiac MRI for measurement of heart iron
- Oral iron chelators

Therapy should be tailored to the individual, according to their pattern of iron deposition.

Aim is no longer to prevent cardiac deaths, but to “normalise” body iron stores.
An Ideal Chelator

Safe
- predictable side effects
- know how to manage them

Effective
- high chelation efficacy
- 24 hour coverage
- targets all the organs

Acceptable
- oral, once a day, easy to take

Does not yet exist!
What We Do Have Available...

Deferoxamine (Desferal)

Deferiprone (Ferriprox)

Deferasirox (Exjade)
Deferoxamine (Desferal)

- In use since 1960s
- Must be given IV or subq
- Short effect means long infusion time (8-12hrs)
- 5-7 times per week
- Lots of data (longterm) showing effectiveness
- Side effects include:
  - high doses lead to deafness, retinal damage, so...
  - adjust dose based on ferritin
  - local skin reactions
  - gastrointestinal symptoms
  - high doses in children impairs bone growth
Deferoxamine (Desferal)

![Graph showing survival rate and proportion without cardiac disease over years of chelation therapy.](attachment:image.png)

**Efficacy of Deferoxamine in Preventing Complications of Iron Overload in Patients with Thalassemia Major**

Gary M. Brittenham, M.D., Patricia M. Griffith, R.N., M.S.N., Arthur W. Niemierko, M.D., Christine E. McLauren, Ph.D., Neal S. Young, M.D., Ewen E. Tucker, M.D., Christopher J. Allen, M.S., David E. Farrell, Ph.D., and John W. Harris, M.D.


**Iron-Chelating Therapy and the Treatment of Thalassemia**

By Nancy F. Grivetti and Gary M. Brittenham

*Blood* Vol 89, No 3 (February 1), 1997, pp 739-761
Deferoxamine (Desferal)

Fig 2. The effect of DFO infusion at 50 mg/kg/24 h intravenous on NTBPI is shown in a single patient with TM both on starting the DFO infusion and on stopping the infusion at 48 hours.
Deferoxamine (Desferal)

Long-term outcome of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in high-risk beta-thalassemia

Bernard A. Davis and John B. Porter

BLOOD, 15 FEBRUARY 2000 • VOLUME 95, NUMBER 4
Deferiprone (Ferriprox)

- Unlicensed in Canada
- Just approved in US and licensed in 61 countries around the World since 1990s
- 3 times a day as fairly short effect, multiple tablets (>9)
- Excellent at cardiac iron removal
- Side effects include:
  - Low WCC (infection risk) – requires weekly blood count
  - joint pains
  - Liver enzymes
Deferiprone (Ferriprox)

Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major

Caterina Borghini, Maria Domenica Cappelli, Piero De Stefano, Giovanni Carlo Del Vecchio, Gian Luca Forini, Maria Rita Gambini, Roberto Ghiardi, Antonio Piga, Maria Antonietta Ramis, Huaping Zhao, and Avital Chauan

BLOOD. 1 MAY 2006 • VOLUME 107, NUMBER 9

Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis


BLOOD. 1 MAY 2006 • VOLUME 107, NUMBER 9
Deferasirox (Exjade)

- Licensed in N. America in 2005
- Once a day, dispersion in water or juice
- “Oral version of Desferal”
- Excellent at controlling liver iron, little cardiac data
- Side effects include:
  - GI upset,
  - Kidney dysfunction
  - Rash
  - Liver enzymes
Deferasirox (Exjade)

Efficacy of deferasirox in reducing and preventing cardiac iron overload in β-thalassemia

Dudley J. Pennell,1 John B. Porter,1 Maria Domenica Cappellini,7 Amal El-Beshlawy,1 Lee Lee Chan,5 Yasmin Aydin,5 Mohsen Saleh El-Daly,5 Phoibe Safafernekhan,5 Chi-Kong Li,5 Mohamed Ebrahem,5 Vijay Varia,5 Antonios Kattanakis,6 Gillian Smith,1 Daisy Hale,1 Gabor Domokos,7 Bernadette Robert,7 and Ali Taher1

BLOOD, 25 MARCH 2010 · VOLUME 115, NUMBER 12
Table 1. Baseline demographics and patient characteristics (N = 27)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline results</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>22.6 (10-44)</td>
<td>NA</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>19:8</td>
<td>NA</td>
</tr>
<tr>
<td>Serum ferritin, ng/mL</td>
<td>4417 ± 669 (394-16249)</td>
<td>15-300</td>
</tr>
<tr>
<td>LIC, mg Fe/g dw</td>
<td>20.3 ± 3.0 (2.5-62.3)</td>
<td>&lt; 1.8</td>
</tr>
<tr>
<td>Cardiac T2*, ms</td>
<td>8.6 ± 1.1 (1.8-16.1)</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>LVEF, percentage</td>
<td>61.4 ± 0.88 (51.9-73.3)</td>
<td>&gt; 56</td>
</tr>
</tbody>
</table>

![Graph showing cardiac T2* and LIC over time](chart)

The effect of deferasirox on cardiac iron in thalassemia major: impact of total body iron stores

John C. Wood,1 Benita P. Kang,1 Akiva Thompson,1 Patricia Gandino,1 Paul Hermatz,1 Tara Glynn,1 Carole Pally,1 and Thomas D. Coates1

BLOOD, 29 JULY 2010 - VOLUME 116, NUMBER 4
Oral Cardiac Chelation

Figure 1
Combination Therapy

167 Screened

65 Randomized

Deferoxamine + deferiprone
(combined group)
32

Completed 28
4 withdrawals
[3 adverse events, 1 patient request]

Deferoxamine + placebo
(deferoxamine group)
33

Completed 30
3 withdrawals
[1 adverse event, 2 patient requests]

Ferritin [μg/L]

Between groups: p=0.001

Change in Heart T2* [ms]

Between groups: p=0.02

Change in Ejection Fraction [%]

Between groups: p=0.05

Circulation 2007;115;1876-1884

A Randomized, Placebo-Controlled, Double-Blind Trial of the Effect of Combined Therapy With Deferoxamine and Deferiprone on Myocardial Iron in Thalassemia Major Using Cardiovascular Magnetic Resonance

M.A. Tanzer, MBChB, B. G绝ndorf, MD, C. Devi, MD, G.C. Smith, MSc, M.A. Westwood, MD, A. Agno, MD, M. Roughton, MSc, B. Scrony, MBChB, J.N. Nez, MBChB, J.M. Walker, MD, D.J. Prasad, MD.
Combination Therapy

Table 1. Evolution of thalassemia clinics in Cyprus.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Organized blood donation for transfusion</th>
<th>Desf.</th>
<th>Def.</th>
<th>New diagnosis records</th>
<th>Clinical records</th>
<th>Genotyping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-1974</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Inadequate</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>1974-1980</td>
<td>Yes</td>
<td>Clinical trial</td>
<td>No</td>
<td>Yes</td>
<td>Inadequate</td>
<td>No</td>
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<tr>
<td>1980-1995</td>
<td>Yes</td>
<td>Standard protocol</td>
<td>No</td>
<td>Yes</td>
<td>Comprehensive</td>
<td>No</td>
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<tr>
<td>1995-2000</td>
<td>Yes</td>
<td>Standard protocol</td>
<td>Clinical trial</td>
<td>Yes</td>
<td>Comprehensive</td>
<td>Yes</td>
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<tr>
<td>Post 2000</td>
<td>Yes</td>
<td>Standard protocol</td>
<td>Combination protocol</td>
<td>Yes</td>
<td>Comprehensive</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Def.: deferasiroxine; Desf.: deferoxamine.

Figure 2. Death rates per 1000 person-years during 5-year periods of follow-up. Cardiac (black) and non-cardiac (white) causes. Error bars represent upper 95% confidence limits. To simplify the illustration, error bars have been omitted from non-cardiac deaths, since there were no significant time-related trends in these data.
How We Use Chelators

Start iron chelation
- at age ~3 years old
- after receiving 15 transfusions
- once ferritin >1000

Which Drug?
- Desferal upto 6 yrs of age, then Exjade is first choice for most patients

Treatment Not Working?
- Change drug, dose, or route of administration
Other & Future Options

Ferrokin Biosciences drug FBS0701 (Phase 3 study in 2012?)
Exjade-Ferriprox combination

Limiting transfusion volumes

Better understanding of iron sensitivity of organs and its removal
Conclusion

Personalised healthcare through using knowledge of patient’s iron load and targeted therapies

Reduce morbidity as well as mortality for a normal life expectancy and quality

(Developing World issues)