Iron chelation: What’s current and What’s in store?

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DISCLOSURE

Research grants and/or speaker honoraria from Novartis, Apopharma, Acceleron, Celgene, La Jolla, Bluebird Bio.
Iron chelators

deferoxamine (DFO)
deferiprone (DFP)
deferasirox (DFX)
Iron Chelators have different properties – 1

<table>
<thead>
<tr>
<th>PROPERTY</th>
<th>DFO</th>
<th>DFP</th>
<th>DFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chelator: iron binding</td>
<td>1:1</td>
<td>3:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Mol. Weight Chelator</td>
<td>560</td>
<td>139</td>
<td>373</td>
</tr>
<tr>
<td>Mol. Weight Chelator:Iron Complex</td>
<td>619</td>
<td>470</td>
<td>798</td>
</tr>
<tr>
<td>Lipophylicity (PC) Chelator</td>
<td>0.02</td>
<td>0.18</td>
<td>6.3</td>
</tr>
<tr>
<td>Binding to plasma proteins</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>99%</td>
</tr>
<tr>
<td>Charge of Chelator</td>
<td>positive</td>
<td>neutral</td>
<td>negative</td>
</tr>
<tr>
<td>Charge of Chelator:Iron Complex</td>
<td>positive</td>
<td>neutral</td>
<td>negative</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>5-10 min</td>
<td>1.5-2-5 h</td>
<td>12 -18 h</td>
</tr>
</tbody>
</table>
Overview of iron chelation therapy

- Deferasirox
- Combination
- Deferiprone
- DFO s.c. bolus
- DFO s.c. slow infusion
- DFO i.v. continuous
- DFO i.v. high dose
- DFO i.m.

Timeline from 1960 to 2020.
Search results

Items: 1 to 20 of 6586

1. Improvement of chronic hepatitis B patient with iron overload: A case report
   PMID: 29384977  Free Article

Filter your results:
- All (6586)
  - Clinical Trial (415)
  - Guideline (12)
  - Humans (6586)
  - Meta-analysis (20)
  - Randomized Controlled Trial (156)
  - Review (1304)
Overview of iron chelation therapy

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MRI T2* gradient-echo sequences
% of patients with significant iron overload

- No iron
- Liver only
- Heart only
- Liver and Heart

2003-04

Thalassemia Centre
University of Torino
deferoxamine (DFO) + deferiprone (DFP)
deferoxamine (DFO) + deferasirox (DFX)
deferiprone (DFP) + deferasirox (DFX)
% of patients with significant iron overload

- No iron
- Liver only
- Heart only
- Liver and Heart

Thalassemia Centre
University of Torino
AHA Consensus Statement

Cardiovascular Function and Treatment in β-Thalassemia Major

A Consensus Statement From the American Heart Association

Endorsed by the Thalassaemia International Federation, European Society of Cardiology Working Group on Cardiovascular Magnetic Resonance, and Society for Cardiovascular Magnetic Resonance

Dudley J. Pennell, MD, FRCP, FAHA, Co-Chair; James E. Udelson, MD, FAHA. Co-Chair; Andrew E. Arai, MD, FAHA; Biykem Bozkurt, MD, PhD, FAHA; Alan R. Cohen, MD; Renzo Galanello, MD†; Timothy M. Hoffman, MD, FAHA; Michael S. Kiernan, MD; Stamatios Lerakis, MD, FAHA; Antonio Piga, MD; John B. Porter, MD; John Malcolm Walker, MD; John Wood, MD, PhD; on behalf of the American Heart Association Committee on Heart Failure and Transplantation of the Council on Clinical Cardiology and Council on Cardiovascular Radiology and Imaging

Circulation. 2013;128:281-308 originally published online June 17, 2013;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circ.ahajournals.org/content/128/3/281
Median Serum Ferritin levels in Thalassemia Major patients at Torino Center

![Graph showing median serum ferritin levels from 1975 to 2017. The levels show a significant decrease over the years, indicating effective management or treatment strategies.](image-url)
Overview of iron chelation therapy

Achievements

- Survival
- Cardiac disease
- Cardiac iron
- Mild/moderate iron overload in most pts
Overview of iron chelation therapy

Achievements

- Survival
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- Cardiac iron
- Mild/moderate iron overload in most pts

Challenges
Overview of iron chelation therapy

Achievements
- Survival
- Cardiac disease
- Cardiac iron
- Mild/moderate iron overload in most pts

Challenges
- Tolerability
deferoxamine (DFO)
Desferal®
DFO

Allergic reaction
Yersinia enterocolitica infection
Thickening of cecal wall
deferiprone (DFP)
Ferriprox®; Kelfer®
Iron chelators that enter cells by different pathways remove iron from different subcellular compartments: deferasirox and deferiprone target cytosolic ferritin iron, and desferrioxamine mesylate targets lysosomal ferritin iron increased by stimulated autophagy, and damaged ferritin (hemosiderin) iron.

Theil EC, 2009, Blood
D.F., thal. major, 34 yrs old, splenectomized

DFP
Neutropenia and agranulocytosis during DFP therapy

ANC
DEFERIPRONE
G - CSF 10 mcg/Kg/9d

Predictive trend !?
deferasirox (DFX) Exjade®

New FCT formulation
Multiple dosing with deferasirox 20 mg/kg/day

Mean ± SEM deferasirox concentration (μmol/L)

Time (hours)

24 hours coverage with a single dose

Piga A et al Haematologica 2006; 91:873-880
DFX
Skin rash
Renal function in thalassemia on deferasirox

Serum Creatinine

![Graph showing serum creatinine levels over time with washout periods for long and short term patients.]
Renal function in thalassemia on deferasirox

**Glomerular Filtration Rate (GFR)**

![Graph showing the Glomerular Filtration Rate (GFR) for long term and short term patients over time.](image)

- **Long term patients**
- **Short term patients**

*Piga A, Brit J Hematol, 2015*
Exceptional Cases

Acute renal failure and Fanconi syndrome due to deferasirox

Steven Grangé¹, Dominique M. Bertrand¹, Dominique Guerrot¹, Florence Eas² and Michel Godin¹

¹Nephrology Department and ²Endocrinology Department, Rouen University Hospital, 1 Avenue de Germont, 76031 Rouen Cedex, Rouen, France

Correspondence and offprint requests to: Steven Grangé; E-mail: stevengrange@gmail.com

Abstract
Deferasirox is the first oral iron chelator and, as such, is widely used for the treatment of chronic iron overload. However, recent data from large studies confirmed the renal toxicity of deferasirox. We report a case of Fanconi syndrome associated with acute renal failure in a patient receiving deferasirox. In particular, new insights regarding the pathophysiology of the renal disease due to this treatment are discussed. This case highlights the importance of a careful monitoring of kidney function, markers of proximal tubulopathy and ferritinaemia in patients receiving deferasirox.

Successful evolution, deferasirox was initiated 1 month before the admission (1500 mg/day). Medical history recorded mild hypertension for over 20 years. No pre-existing malignancy or immunological disorder was reported. The anamnesis revealed no unusual risk of exposure to heavy metals or environmental toxic agents. Ongoing medications included irbesartan 150 mg/day, hydrochlorothiazide 12.5 mg/day and ursodesoxycholic acid.

Asthenia and anorexia, associated with constipation and epigastralgia, appeared 15 days before admission. Laboratory examinations prescribed by the general practitioner showed an increase in serum creatinine and profound hypokalaemia (2.1 mmol/L). Table 1 lists the standard laboratory tests performed during the 5-day hospitalization. At admission, the patient presented with renal failure [Modification of Diet in Renal Disease (MDRD)
DEFERASIROX DT vs FCT

DISPERCIBLE TABLETS
(DT)

125mg 250mg 500mg

DOSE - 30%

FILM COATED TABLETS
(FCT)

90mg 180mg 360mg

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Deferasirox PK curve

Patient's 5 Points Curve
Blood samples at 0h, 2h, 4h, 6h, 24h

Thalassemia Centre
University of Torino
Thalassemia Centre 
University of Torino
## PATIENT B

<table>
<thead>
<tr>
<th>SURNAME</th>
<th>NAME</th>
<th>Birth</th>
<th>Date of PK curve</th>
<th>Weight (Kg)</th>
<th>Naive to DFX</th>
<th>DFX formulation at PK curve</th>
<th>DFX dose (mg) at PK curve</th>
<th>DFX dose (mg/kg) at PK curve</th>
<th>DFX dose (mg/kg) (converted to old formulation)</th>
<th>Washout period (h)</th>
<th>Plasma DFX (µMol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>25/07/2017</td>
<td>71.0</td>
<td>NO</td>
<td>2000 NEW</td>
<td>1440</td>
<td>20.3</td>
<td>29.0</td>
<td>48</td>
<td>9 41 47 26 7.9</td>
</tr>
</tbody>
</table>

**Graph:**

- Reference PK at 30 mg/kg (N=54)
- Reference PK at 20 mg/kg (N=56)
- Patient curve

**Patient AUC:** 518.4

**Delta from ref values (OLD):** -34%
Overview of iron chelation therapy

Achievements

- Survival
- Cardiac disease
- Cardiac iron
- Mild/moderate iron overload in most pts

Challenges

- Tolerability
Overview of iron chelation therapy

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Challenges
- Tolerability
- Full prevention of complications (hypogonadism)
WHEN TO START

➢ forget serum ferritin
➢ Thalassemia Intermedia → Transferrin saturation >70%
➢ Thalassemia Major → ASAP (10-20 transfusions)

WHEN TO STOP

➢ forget serum ferritin
➢ Thalassemia Major → never
➢ Thalassemia Intermedia → LIC < 1,5 mg/g dw
Cardiac Iron loading

Cardiac Iron clearing
Trend of iron overload during 16 pregnancies in thalassemic woman (→ iron chelation)
CLINICAL TRIALS AND OBSERVATIONS

A randomized trial of amlodipine in addition to standard chelation therapy in patients with thalassemia major


1Jose Michel Kalaf Research Institute, Campinas, Brazil; 2Centro de Hematologia de São Paulo, São Paulo, Brazil; 3Centro Infantil de Investigações Hematológicas Dr Domingos A Boldrini, Campinas, Brazil; 4University of Campinas, Campinas, Brazil; 5Centro de Hematologia e Hemoterapia do Paraná, Curitiba, Brazil; 6Marilia Medical School, Marilia, Brazil; 7Maringa State University, Maringa, Brazil; 8Londrina State University, Londrina, Brazil; and 9University of Torino, Turin, Italy

Key Points

- In thalassemia patients with cardiac siderosis, amlodipine combined with iron chelation resulted in more effective reduction of cardiac iron.
- The combined treatment did

Cardiovascular disease resulting from iron accumulation is still a major cause of death in patients with thalassemia major (TM). Voltage-gated calcium-channel blockade prevents iron entry into cardiomyocytes and may provide an adjuvant treatment to chelation, reducing myocardial iron uptake. We evaluated whether addition of amlodipine to chelation strategies would reduce myocardial iron overload in TM patients compared with placebo. In a multicenter, double-blind, randomized, placebo-controlled trial, 62 patients were allocated to receive oral amlodipine 5 mg/day or placebo in addition to their current chelation regimen. The main outcome was change in myocardial iron concentration (MIC)
Overview of iron chelation therapy

Achievements

- Survival
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Challenges

- Tolerability
- Full prevention of complications (hypogonadism)
- Prevention of cardiac iron loading
- Novel iron chelators
A phase 2 study of the safety, tolerability and pharmacodynamics of FBS0701, a novel oral iron chelator, in transfusional iron overload

Safety and pharmacokinetics of the oral iron chelator SP-420 in β-thalassemia.


Abstract
Our phase I, open-label, multi-center, dose-escalation study evaluated the pharmacokinetics (PK) of SP-420, a tridentate oral iron chelating agent of the desferrithiocin class, in patients with transfusion dependent β-thalassemia. SP-420 was administered as a single dose of 1.5 (n = 3), 3 (n = 3), 6 (n = 3), 12 (n = 3), and 24 (n = 6) mg/kg or as a twice-daily dose of 9 mg/kg...
Desferrithiocins – A New Generation of Oral Iron Chelators

Class of potent microbial iron chelators developed Prof. Ray Bergeron (University of Florida). DFT has significant kidney toxicity. DFT skeleton modified to produce low toxicity, orally available NCEs:

Deferitrin  
(Generzyme, 2003-2007)

SP-420

FBS0701  
(Ferrokin/Shire, 2007-)
Dendrimers iron chelator

Zhou T, *Bioorganic & Medicinal Chemistry Letters, 2018*
# Regional Siderosis

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Iron load</th>
<th>Type</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial siderosis</td>
<td>Brain, spinal cord</td>
<td>Acquired</td>
<td></td>
</tr>
<tr>
<td>Friedreich’s Ataxia (FRDA)</td>
<td>Mitochondria</td>
<td>Genetic</td>
<td>Frataxin</td>
</tr>
<tr>
<td>Neurodegeneration with brain iron accumulation (NBIA)</td>
<td>Basal ganglia</td>
<td>Genetic</td>
<td>PANK2, PLA2G6, FA2H, ATP13A2, DCAF17</td>
</tr>
<tr>
<td>Neuroferritinopathy</td>
<td>Basal ganglia</td>
<td>Genetic</td>
<td>L ferritin</td>
</tr>
<tr>
<td>Aceruloplasminemia</td>
<td>Brain</td>
<td>Genetic</td>
<td>CP</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>Substantia nigra</td>
<td>Acquired</td>
<td></td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>Brain</td>
<td>Acquired</td>
<td></td>
</tr>
<tr>
<td>Sideroblastic anemias</td>
<td>Erythroblasts</td>
<td>Genetic</td>
<td>ALAS2, SLC25A38, GLRX5, ABCB7</td>
</tr>
<tr>
<td>Anemia of chronic disease (ACD)</td>
<td>Macrophages</td>
<td>Acquired</td>
<td></td>
</tr>
<tr>
<td>Iron-refractory-iron-deficiency-anemia (IRIDA)</td>
<td>Macrophages</td>
<td>Genetic</td>
<td>TMPRSS6</td>
</tr>
<tr>
<td>Chronic liver disease (CHC, CHB, ALD, NAFLD, Porphyria Cutanea Tarda)</td>
<td>Liver</td>
<td>Acquired</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathies</td>
<td>Heart</td>
<td>Both</td>
<td></td>
</tr>
</tbody>
</table>
Mitochondrial iron overload from frataxin deficiency
Mitochondrial iron overload from frataxin deficiency
No systemic iron overload but mitochondrial iron overload in Friedreich’s ataxia

Michael S, Cerebellum, 2006
Lowering HCM severity in Friedreich's Ataxia with iron chelation by Deferiprone

N=21 mean=5,7 years (0,4-8,9)
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- Deferasirox
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- DFO i.v. high dose
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Thalassemia Centre
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Silymarin
from milk thistle
Luspatercept (ACE-536)
Hepcidin
Life Is A Balance Between Risks & Benefits