# Chelation for Transfused and Non-Transfused Patients

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Patient-Family Conference
July 8, 2017

# Disclosures

- Consultant:  Agios, Ionis pharmaceuticals
- Research support to my institution:  Apopharma, Novartis, Shire, bluebird bio

# Overview

- The problem of iron overload
- Overview of chelators
- Using chelation
  - Transfusion dependent
  - Non transfusion dependent
- Future directions

# What Causes Iron Overload?


**Transfusion Dependent**

**18-30 mg/day**

**Usual**

**1-2 mg/day**

**5 mg/day**

**Thalassemia intermedia**

**Skin loss**

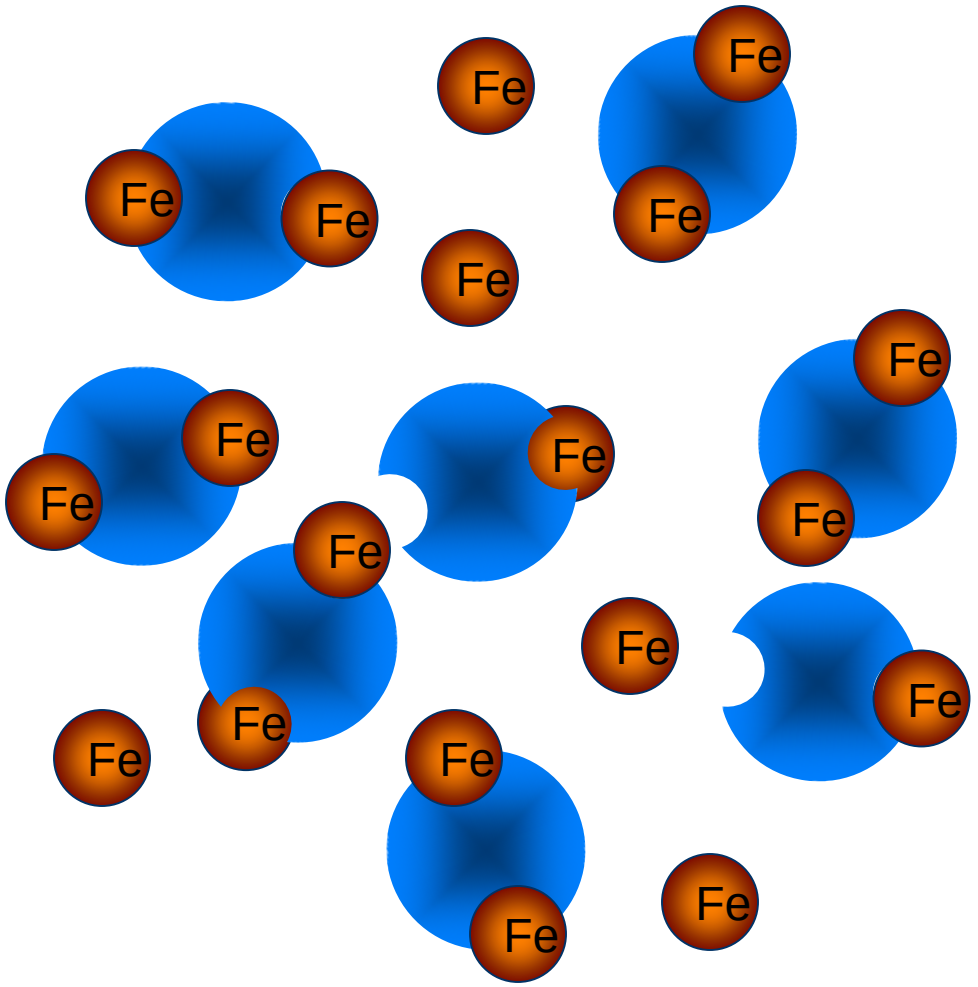
**Blood loss**

**1–2 mg/day**

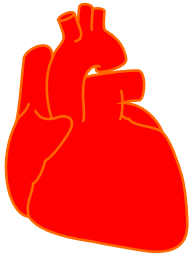
**Urinary loss**

**Stool loss**

# Why is Iron Overload a Problem?




Injures Tissues



↑ NTBI
↑ LPI
↑ LIP

Endocrine Organs

Increased iron stores

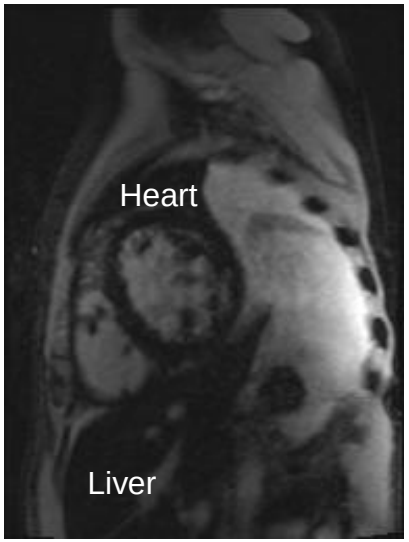
# Goals of Chelation

- Maintain a “safe” level of iron
  - **Prevent** iron build up and iron related organ injury
  - **Remove** iron build up and **reverse** iron related organ injury
- Bind to free iron and make it less toxic
  - Continuous exposure to chelator is optimal

# Monitoring Iron Levels

- **Ferritin**
  - Trends

- **Liver iron**
  - Magnetic resonance imaging (MRI)
  - SQUID
  - Liver biopsy




- **Heart iron**
  - MRI

# The Ideal Iron Chelator

- Safe
  - Few side effects
- Effective
  - Targets all organs
  - 24 hour coverage
- Acceptable
  - Once a day
  - Oral
  - Easy to take

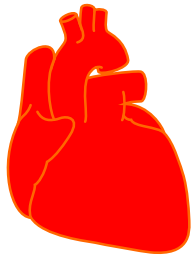
# Chelator Options

- 3 drugs are approved for iron chelation in the United States
  - Deferoxamine (Desferal)
  - Deferasirox (Exjade, Jadenu) – transfusion and non-transfusion dependent
  - Deferiprone (Ferriprox) – second line agent

# Deferoxamine (Desferal)

- Over 40 years of experience with the drug
  - The only chelator available for over 30 years
- Given as an infusion – under skin or IV over 8 to 10 hours, 5 to 7 nights/week

# How Well Does Deferoxamine Work?

| Ferritin | Liver Iron | Heart Iron |
| --- | --- | --- |
|  |  |  |
| ↓ | ↓ | ↓ Continuous IV infusion |

Very effective at reducing liver iron; may be less effective at removing heart iron (better with continuous infusion)

# Deferoxamine – Side Effects

- Local skin reactions
- Allergic reactions
- Ears: hearing loss, ringing in the ears
- Eyes: night blindness, color vision problems
- Bones/Growth: especially < 3yo and high doses

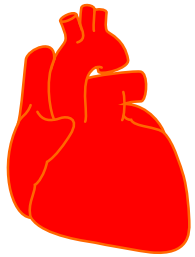
- Monitor for side effects
  - Hearing, vision, growth, bones

- Adjust dose based on body iron levels

# Deferasirox (Exjade, Jadenu)

- Dispersible tablet (Exjade) approved in 2005
- Film coated tablet (Jadenu) approved in 2015
- Granule form (Jadenu Sprinkle) approved 2017
- Taken by mouth, once daily

# How Well Does Deferasirox Work?

| Ferritin | Liver Iron | Heart Iron |
| --- | --- | --- |
|  |  |  |

Higher Doses

Very effective at reducing liver iron; may be less effective at removing heart iron (improves with higher doses)

# Deferasirox Side Effects

- Nausea, vomiting, diarrhea, abdominal pain (Exjade)
- Liver inflammation
- Kidney dysfunction
- Skin rash
- Hearing, vision

- Monitoring for side effects
  - Blood tests, urine tests

# Deferiprone (Ferriprox)

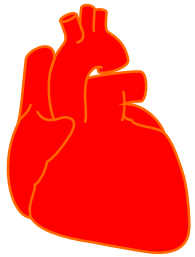
- Approved for use in 2011
- Second line agent
- Tablets or liquid solution
- Taken by mouth 3x per day
- Smaller, gets into cells better

# How Well Does Deferiprone Work?

Ferritin

Liver Iron


Heart Iron



Higher Doses

Very effective at reducing cardiac iron
May be less effective at removing liver iron (improves with higher doses)
Effective at removing iron from endocrine organs

# Deferiprone Side Effects

- Low white blood cell count
  - Increased risk of infection
- Joint pains
- Abdominal pain, nausea
  - Take with food
- Elevated liver enzymes

- Monitoring for side effects
  - Frequent blood tests – especially first year
  - HOLD drug if fever and check blood count

# Transfusion-Dependent Thalassemia
# When to Start Chelation

- Age 2 years and older
- After 10 to 20 transfusions
- Ferritin > 1,000 ng/mL
- Liver iron concentration > 5 mg/g dw

# Choosing a Chelator
# Factors to Consider

- Age of patient
- Iron levels in different organs (liver, heart, endocrine)
- Patient/family preference
- How easy it is to take
- Other medical problems, medications

Dose – depends on how much iron is present and the ongoing transfusion requirements

# Adjust Doses Based on Iron Levels

| Liver Iron mg/g dw | Cardiac T2* ms | Ferritin ng/mL | Significance |
|---|---|---|---|
| > 15 | < 10 | > 2500 | Too high |
| 7 - 15 | 10 - 20 | 1500 - 2499 | Too high/ caution |
| 2 - <7 | > 20 | 500 - 1499 | Goal Levels |
| < 2 | | < 500 | Monitor for toxicity |

# High/Rising Iron Levels

- Improve adherence
- Increase dose of chelator
- With deferasirox, consider splitting dose into twice daily
- Add a second chelator
  - Sequential or given together (combination chelation)

# Low Iron Levels

- Avoid holding chelation completely if still receiving transfusions
  - Free iron causes damage
  - Contrary to labeling ➔insurance issues
- Reduce iron chelation dose
- Deferiprone appears safe at low iron burden

# Chelation Therapy for Non-Transfusion Dependent Thalassemia (NTDT)

- Iron loading results from increased absorption of iron from the diet and from intermittent transfusions
- In the absence of transfusions, iron overload develops more slowly
  - Beta thalassemia – 10+ years
  - Hemoglobin H – 15+ years
- Ferritin underestimates iron loading
- Need to *monitor liver iron concentration* (MRI)
- Less heart iron loading

# Chelation for NTDT

When to start:

- Age ≥ 10 years
- Ferritin ≥ 800 ng/mL
- Liver iron concentration ≥ 5 mg/g dw

When to stop:

- Ferritin ≤ 300 ng/mL
- Liver iron

# Chelation Therapy for NTDT

- Most studies on iron chelation have been for transfusion dependent thalassemia
- Deferasirox labeled for use in NTDT
- All 3 iron chelators have been used individually with success
- Doses are lower than for TDT

| Chelator | TDT (mg/kg/day) | NTDT (mg/kg/day) |
|---|---|---|
| Deferasirox DT | 20 - 40 | 5 - 20 |
| Deferiprone | 75 - 99 | 25 - 75 |

# Future Strategies for Managing Iron Overload

- Reduce transfusion requirements
  - Ex. Luspatercept (BELIEVE trial)

- Reduce iron absorption
  - Enhance hepcidin

# Role of Hepcidin

Inflammation

Low Hepcidin

Hepcidin

Intestine

Blood

Iron

Iron

Macrophage

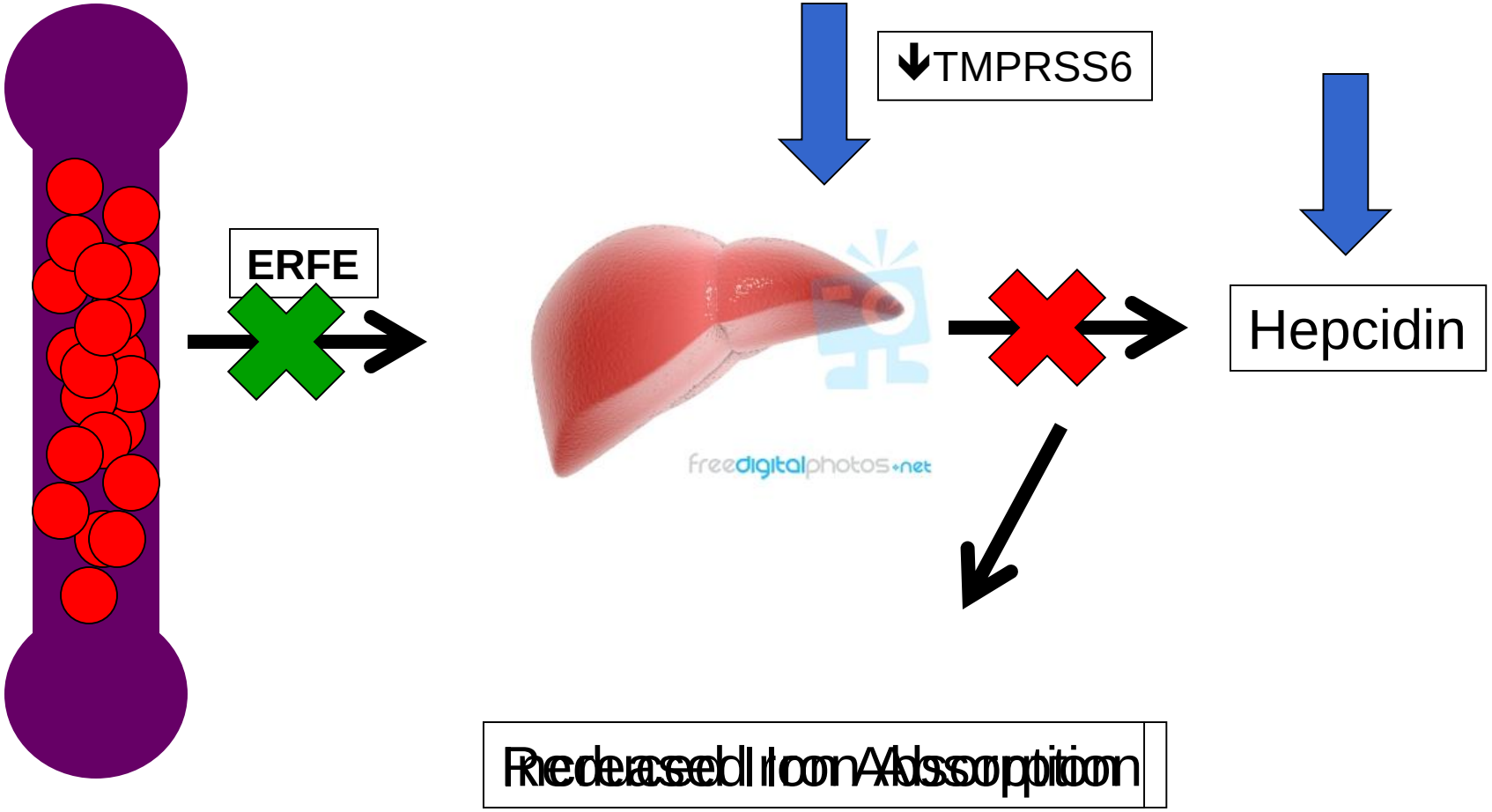
Iron

Iron

Iron

Iron

# Hepcidin is LOW in Thalassemia



# Take Home Points

- Iron overload results from transfusions and increased iron absorption
- Currently 3 different chelation medications are available – different organ-specific effectiveness and side effects
- Monitoring ferritin, liver and heart iron is important and helps adjust chelation
- Whatever chelation is used, it is most important to take the chelator medicine(s) – these drugs can’t work otherwise