Chelation Overview

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Disclosures

- DSMB Apopharma

Overview

- Why is iron overload an issue
- Overview of chelators
- How we use chelators

Why is Iron Overload “bad”

- Iron as a part of RBCs is not harmful.
- When RBCs die, they release iron.
- This iron is usually bound up by proteins and recycled, BUT there is a limit to how much iron our bodies can handle.
- Extra iron not bound up by proteins is called “free iron”, or NTBI. This “free iron” is toxic to our tissues.
- Our body then resorts to storing it in places where it is toxic (liver cells, heart cells, pancreas, etc.)

What causes Iron Overload

- Normally our body only absorbs what it needs through signals to our intestines (1-2 mg/day)
- Transfusion dependent patients take in 1 mg Fe for every ml blood transfused (15-30 mg/day)
- Thalassemia patients have abnormal gut signaling (5 mg/day)

Goals of Chelation

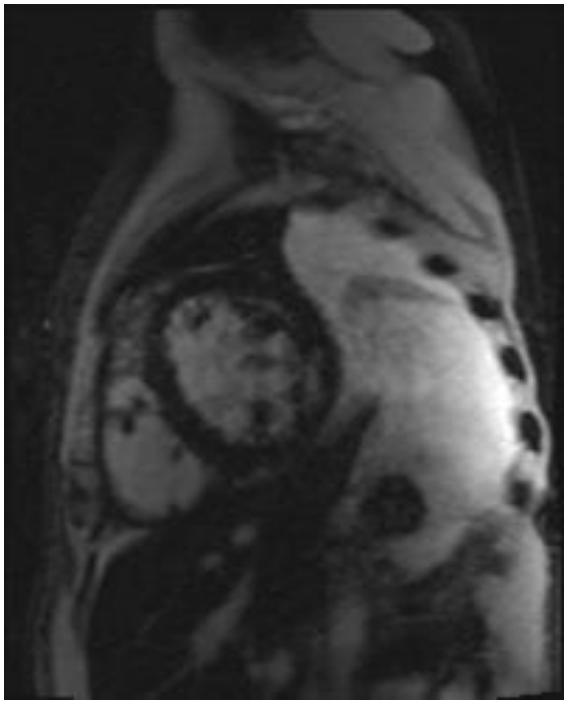
- Keep a “safe level” of Fe
  - Prevent iron build up
  - Remove the built up iron in order to reverse organ injury
  - Bind up “free iron” to make it less toxic to tissues

Monitoring Iron Levels

- Ferritin: Trending. Pitfalls

- Liver Iron
  - Liver biopsy
  - MRI
  - SQUID

- Heart Iron
  - MRI



The “ultimate” Chelator

- Easy to take (by mouth, once a day)
- Removes iron from all organs at the same rate
- 24 hour coverage
- Few to no side effects

Current Chelator Options

- Deferoxamine (Desferal)

- Deferasirox (Exjade and Jadenu)

- Deferiprone (Ferriprox)

Deferoxamine (Desferal)

- Available since the 1970's
- Given as an infusion either SubQ or IV for 8-12 hours, 5-7 nights/week
- Side effects
  - Local skin reactions
  - Allergic reactions
  - Ears: high frequency hearing loss
  - Eyes: night blindness, color vision changes
  - Bones/Growth: < 2-3 yo

Deferoxamine (Desferal)

- Advantages:
  - Very good at removing liver iron, good at removing heart iron
  - Not dependent on oral absorption

- Disadvantages:
  - Very short half-life: Does not provide 24 hour coverage
  - IV/SQ

Deferasirox (Exjade, Jadenu)

- Exjade: 2005
- Jadenu: 2015 (coated tablet) 2017 (sprinkles)
- Taken by mouth once a day

- Side effects:
  - GI: nausea, vomiting, diarrhea (Exjade), abdominal pain (both)
  - Liver inflammation
  - Kidney dysfunction (Fanconi's Syndrome)
  - Rash
  - Hearing Vision

Deferasirox (Exjade, Jadenu)

- Advantages:
  - Very good at removing liver iron, good at removing heart iron
  - Oral
  - Long half-life: Provides 24 hour coverage

- Disadvantages:
  - Dependent on oral absorption
  - Fanconi’s syndrome requires discontinuation

Deferiprone (Ferriprox)

- Available in U.S since 2011
- FDA: second line agent
- Tablets or liquid taken 3 times/day

- Side effects:
  - Low WBC, neutropenia, Agranulocytosis
  - Joint symptoms
  - Nausea (take with food)
  - Liver enzyme elevation

Deferiprone (Ferriprox)

- Advantages:
  - Very good at removing heart iron, good at removing liver iron
  - Oral

- Disadvantages:
  - Dependent on oral absorption
  - half-life requires 3 x/day dosing
  - Risk of Agranulocytosis requires frequent CBC's and discontinuation if it occurs

Starting Chelation: When

- ≥ 2 yo
- > 10-20 transfusions
- ? Ferritin > 1000
- Liver Iron > 5 mg/g dry weight

Starting Chelation: Which one

- Age of patient/how long on transfusions
- How easy is it to take
- Matching Chelator to Goal of chelation
- Other medical issues
- Patient/Family preference “the best chelator is the one that is actually taken”

Starting Chelation: How much

- All chelators require an escalation process

- Goal dose depends on how severe the iron overload is and ongoing transfusion requirements

Adjusting Chelation

Iron overload is	Liver Iron mg/G dry wt	Cardiac T2* msec	Ferritin ng/ml
Very high	>10	<10	> 2500
High	5-10	10-20	1000-2500
At goal	2-5	>20	< 1000
Low, closely monitor	< 2		< 500

Adjusting Chelation: Iron levels are High or Rising

- Address compliance
- Increase dose of chelator
- If on Deferasirox, consider splitting the dose
- Add a second chelator
- Special challenge: when liver iron decreases to goal but cardiac is still too high

Adjusting Chelation: Low Iron levels

- Contrary to drug labeling and insurance policies, do not interrupt chelation
  - “free Iron” (NTBI)
  - Get out of the habit

- Solution: reduce the dose

Chelation in NTDT

- Iron loading from the gut, slower
- Ferritin often underestimates the level of Iron overload. Use Liver MRI
- Deferasirox is labeled for use in NTDT
- All 3 chelators can be used at LOWER doses

Resources

- http://www.thalassemia.org/boduw/wp-content/uploads/2018/05/Monitoring-Deferasirox-Therapy.pdf
- http://www.thalassemia.org/boduw/wp-content/uploads/2018/05/Guidelines-for-Managing-Transfusion-Therapy-for-Thalassemia.pdf
- http://www.thalassemia.org/boduw/wp-content/uploads/2018/05/Monitoring-of-Iron-Overload-in-Transfusion-Dependent-Thalassemia-TDT-1.pdf

Future

- Deferiprone trial in younger patients
- Dr. Quarmyne’s talk at 2:30