Iron Isomaltoside… the new iron on the block!

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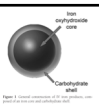
Introduction

- Iron deficiency very common in CKD patients
  - ↓ iron intake (↓ appetite, dietary restrictions)
  - Bleeding (GI, platelet dysfunction, loss with dialysis circuit)
  - Inflammation
    - ↑ hepcidin (decrease iron absorption and handling)
- Especially problematic for patients on ESA

Rottembourg et al. Nephrol Ther 2015; 11: 531-42.

Iron Isomaltoside 1000 (Monoferric®)



- Available in Canada since October 2018
- Studied in GI, gynecology, oncology and nephrology
- Colloid with strong bound iron in spheroidal in iron-carbohydrate particles, contains 3-5 glucose units.
  - More complex carbohydrate shell => higher stability and release much lower level of free iron
- PK/PD
  - Serum ferritin peaks 7-9 days; returns to baseline after about 3 weeks
  - Half-life for iron to be cleared from plasma: 1 to 4 days
    - Mostly taken up by RES, particularly the liver and spleen where the iron is slowly released

Hemodial Int 2017; 21: S83-92.

Iron Isomaltoside 1000 (Monoferric®)

- Contraindicated if hypersensitivity reaction to other IV iron preparations, multiple allergies
- Requires monitoring for at least 30 minutes post-administration for hypotension and hypersensitivity reaction
- Administration
  - **IV bolus:** up to 500 mg once weekly at a rate of 250 mg/min; may be administered undiluted or diluted in 20mL 0.9%NaCl
  - **IV drip:** up to 20 mg/kg body weight/week; dose up to 1 g must be given over at least 20 minutes, dose 1 to 1.5 g should be given over at least 30 minutes (dose above 1.5g are not recommended).
    - Should be diluted to min. 1 mg iron/mL of 0.9% NaCl (max 500 mL).
  - May be administered during HD directly into venous port of dialyzer (same procedure as IV bolus)

Iron Isomaltoside 1000 (Monoferric®)

- In studies with CKD-ND and CKD-D , dose of iron calculated based on body weight and Hgb (Ganzoni formula):
  Iron need (mg) = Body weight (kg) x (Target Hgb(**g/dL**)-Actual Hgb (**g/dL**)) x 2.4 x depot iron (10-15 mg/kg body weight)
- Transient hypopophatemia
  - PO4 < 0.65 mmol/L in 5-20% pts (1-2% in CKD), nadir in 1st week
  - Likely because acute increase of FGF-23
  - No Sx has been reported

Iron Isomaltoside 1000 (Monoferric®) in CKD-ND and D

Study	Design	Participants	Intervention	Outcomes	Results
Wikstrom et al. J Neph 2011	Multicenter prospective study F/U: 8 weeks	Adults, CKD-ND or CKD-D, not on IV iron or agreeable to switch with Hgb < 110 g/L, ferritin < 800 ug/L, life expectancy > 12 months (N= 182, 21 CKD-ND, 161 CKD-D, 150 on ESA)	II administered by 4 IV bolus with 100-200 mg of iron, or high single full iron depletion dose	1° =>Safety on II 2°=> effect on iron deficiency anemia parameter	- ADR reported in 62% of patients, all mild to moderate intensity. - ADR seen in 60% of pts receiving bolus dose and 68% of pts receiving infusion - 2 severe ADRs (sepsis and unstable angina, no allergic reaction). - 2 deaths unrelated to II - Mean ↑ in Hgb was 7.9 +/-10.1 g/L in dialysis pts and 8.5 +/-8.8 g/L in CKD-

Iron Isomaltoside 1000 (Monoferric®) in CKD-ND

Study	Design	Participants	Intervention	Outcomes
Kalra et al. NDT 2016 CKD-02	Multicentre Randomized2:1 Open-label, non-inferiority trial F/U: 8 weeks	Adults, eGFR 15-59 mL/min, Hgb < 110 g/L, either or both TSAT < 20%/ ferritin< 200 ug/L, no ESA x 8 weeks	II((IV infusion (N=116) or bolus (N=112)) vs. PO iron sulfate (PIS) 100 mg po BID (N=117)	1° => Change in Hgb at 4 weeks 2°=> Change in Hgb week 2 to 8, change in serum iron, ferritin, TSAT, TIBC, change in QOL from baseline to week 4 and 8

Iron Isomaltoside 1000 (Monoferric®) in CKD-ND

- II non-inferior to PIS to↑ Hgb (6.0 g/L vs. 3.7 g/L)
- ↑ Hgb baseline to 8 weeks larger between II vs. PIS (no difference between bolus vs. infusion); difference in Hgb between group started at 3 weeks
- TSAT/ferritin also ↑ in III vs. PIS group
- ADR reported 41.7% with III vs. 45.3% with PIS
- For II, 33.6% of infusion group had a reaction vs. 50% in bolus group => pyrexia, gastroenteritris, rhinitis, resp infx
- 2 episodes of hypersensitivity and 3 deaths with II (deaths believed not related to II)
- More pts withdrawing of study on PIS vs. II (4.3% vs. 0.9%)

Iron Isomaltoside 1000 (Monoferric®) in CKD-ND

Study	Design	Participants	Intervention	Outcomes	Results
Jensen et al. Clin Neph 2019 NIMO study	Prospective study F/U minimum 12 months after 1st dose (mean 15 months)	Adults, CKD 1-5 ND 20% Stage 2-3, 38% Stage 4 and 42% Stage 5, 38% on ESA, 4% on PO iron	II according to label and local clinical practice (N=108)	1° => Probability of needing retreatment with IV iron	- 65% received one II dose over 15 months, all the others received 2 doses, 89% receive 500 mg dose - ↑ Hgb (7-14 g/L), TSAT, ferritin - 1 episode of skin discoloration reported (? extravasation)

Iron Isomaltoside 1000 (Monoferric®) in CKD-ND and CKD-D

Study	Design	Participants	Intervention	Outcomes	Results
Biggar et al. Clin Nephrol 2016	Prospective survey, no intervention F/U: 9 months	Adults CKD Stage 3 to 5 and dialysis (N=698) 150 CKD-ND, 464 HD patients, 66 hemofiltration, 14 PD.	II as per local practice	1° => Effectiveness, safety and tolerability	- Mean dose of 2,574 +/- 2,401 mg over 9 months - No. of patients on ESA and mean ESA dose decreased during study period. - ↑ in Hgb↑ in TSAT/ferritin - As assessed by physician, the general safety of II was estimated to be good or very good in 99.4%. - No ADRs reported in study

Iron Isomaltoside 1000 (Monoferric®) in CKD-D

Study	Design	Participants	Intervention	Outcomes	Results
Bhandari et al. NDT 2015 CKD-03	Multicenter randomized (2:1) open-label study F/U: 8 weeks	Adults, CKD on HD for > 90 days, Hgb 95 to 125 g/L, ferritin < 800 ng/mL, TSAT <35% and receiving ESA with stable dosing (N=351)	II administered 500 mg IV bolus, 100mg/ 200mg dose x2 infusion; vs. iron sucrose(IS) 100/200mg x2.	1° => % pts maintain Hgb 95 to 125 g/L 2°=> TSAT, serum ferritin, retic count, safety outcomes, change QOL	- Both treatment had similar efficacy with > 82% Hgb within target range, no difference between II mode of administration - Higher ferritin and retic count at week 1 with II - No change in QOL - 47.8% ADRs with II vs. 41.2% ADRs with IS, serious ADRs was 0.4% (hypersensitivity reaction) and 1.8% (bacteremia and dyspnea) respectively.

Iron Isomaltoside 1000 (Monoferric®) in CKD-D

Study	Design	Participants	Intervention	Outcomes	Results
Mikhail et al. BMC Neph 2019 DINO study	Prospective study F/U: 12 months	Adults, HD for > 90 days, Hgb 95 to 125 g/L, ferritin < 800 ng/mL, TSAT <35% and receiving ESA with stable dosing (N= 198)	II administered as per clinical practice (average 5 x 100 mg Q3months) compared to historic data with iron sucrose (IS) in 3 months interval, within 9 months of starting II	1° => non-inferiority in Hgb maintenance	- Non-inferiority of II compared to IS to maintain Hgb (mean change 3 +/- 12 g/L) - 9 ADRs(2%) were reported with II, 2 being serious ADRs (burning sensation in face/ pruritus/ back pain/vomiting and the other upper abdominal pain/chills/pyrexia/ nausea), all pts had total recovery, but they discontinued the drug; ? Metallic taste (was more frequent with iron sucrose)

Cost comparison

Iron preparation	Dosage	BC Cost
PO Ferrous fumarate	300mg/d x 100 days	$11.98 (100 capsules)
IV iron dextran	300 mg	$95.98
IV iron sucrose	300 mg	$121.50
IV iron Isomaltoside	1 g	$486 ($145.80 for 300 mg)

- Other factors to consider:
  - ↓ utilization/cost of ambulatory visits
  - ↓ cost to patient (work, travel), convenience
  - ↓risk of cumulative infusion reactions, extravasation, IV line needed

Iron Isomaltoside 1000… take home message

- Some efficacy and safety data in CKD-ND andHD patients
  - Up to 15 months data
- Dosing regimen used in studies is not what we use in practice
  - What dose should we use?
  - How should we adapt our anemia management protocols?
- Some "real-life" data from prospective trial
  - ? ADRs profile in that setting

Iron Isomaltoside 1000

Anything new for PO iron

- Iron salts
  - Ferrous gluconate, sulfate, fumarate
- Heme iron
  - Proferrin® and OptiFer α ®
- Polysaccharide iron complex
  - FeraMAX ®, Niferex®
- Alberta's College of Physicians "Tool for Practice"
  - **Iron-ing Out the Wrinkles in Anemia Management**
    - **"Newer iron formulations appear inferior to older ferrous salt formulations. Ferrous salts improve hemoglobin up to 20g/L more with one in five more attaining IDA resolution at 3-months. Evidence that newer formulations have less adverse effects is inconsistent and likely cannot be supported."**

Introduction

- Human body contains 3 to 4 g of iron for men and 2.2 to 3.5 g of iron for women
  - 60% of iron used for Hgb
  - Erythropoiesis requires 25-30 mg of iron/day, mostly provided by iron from hemoglobin being recycled.
  - Iron storage
    - 30% liver and RES => ferritin
    - 10% myoglobin
    - 1% enzymes rich in iron
  - 0.2% circulating in blood, linked to transferrine
  - WHO recommend 10 mg/d iron (1-2 mg being absorbed by the GI system) to compensate for daily lost

Rottembourg et al. Nephrol Ther 2015; 11: 531-42.