Iron Repletion in ESRD

Mansi Mehta
October 2015
Case: Patient Medical History

65 year old AA M with history of ESRD secondary to diabetic nephropathy on HD for 7.5 years. Compliant with home medications and HD 3x/week following in outpatient HD unit

PMH: HTN, PVD and IDDM

PSH: AVF creation and LLE angioplasty s/p stent placement

Social: hx of tobacco use; no EtOH/illicit drug use

Meds: ASA 81mg, Amlodipine, Lantus SQ qhs, Sevelamer 800mg TID AC, cholecalciferol 2000U daily and EPO 4000U/week

ROS: significant for fatigue, weakness and DOE
Physical Exam

- VS: Afebrile, BP: 143/74 P: 75  O2: 98% on RA
- Gen: Elderly AA Male, chronically ill appearing
- HEENT: mild conjunctival pallor
- CVS: +s1s2, RRR, no murmurs appreciated
- Resp: CTA B/L
- Abd: soft, NT/ND
- Ext: trace pitting edema of LE, L brachial AVF with +thill
Labs and Treatment course

• Labs significant for **Fe deficiency Anemia**
  • Na: 137 K: 4.3 Cl: 104 CO2: 24 BUN: 56 Creat: 6.3 P: 5.4

  • **Hgb of 9.4, Fe: 54  TIBC: 333  Ferritin 445 and TSAT: 16%**

  • Started on Ferrlecit 125mg IV x 8 doses to be administered w/ each HD session (for a total course of 1g) and continued on EPO 4000U/week

  • 4 weeks later: Hbg is 9.6  and 8 weeks later Hbg is 9.4  (Fe studies not checked at this time)

  • 12 weeks later: **Hgb: 9.6, Fe: 83  TIBC: 245  Ferritin 635 and TSAT: 33%**

  • He is continued on EPO 4000U/weekly

  • Hgb is followed monthly and remains between 9.6-10.3
Data from the National Health and Nutrition Examination Survey (NHANES) showed that the distribution of Hbg levels starts to fall at an eGFR of less than 75ml/min in men and 45ml/min in women.

Incidence of anemia in CKD 5 is greater than 70%.

Primarily attributed to inadequate EPO production and Iron Deficiency.
Types of Fe Deficiency Anemia in ESRD

1. Absolute Fe Deficiency
2. Functional Fe Deficiency
3. Inflammatory or Reticulo-endothelial block
## Type 1: Absolute Fe Deficiency

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• “True” Fe deficiency anemia</td>
<td>• Decreased oral iron intake from prescribed dietary protein restriction</td>
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<tr>
<td>• Defined as low whole body stores as indicated by serum ferritin levels &lt;200ng/mL or a Tsat of &lt;20%</td>
<td>• Occult GI bleeding from uremia-associated platelet dysfunction</td>
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<tr>
<td>• Fe losses are estimated at 5-7mg per dialysis session and 1-3g/year in HD patients</td>
<td>• Frequent phlebotomy</td>
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<td>• Blood trapping in dialysis apparatus</td>
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<td></td>
<td>• Decreased duodenal absorption</td>
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<td></td>
<td>• Decreased RBC life span with increased rate of Fe turnover to maintain decreased RBC mass</td>
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<td></td>
<td>- Normal 120days; CKD patients 60-90days</td>
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<td></td>
<td>• ESA administration depletes circulating Fe pool by increasing erythropoeisis</td>
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</tbody>
</table>
Type 2: Functional Fe Deficiency

- Characterized as impaired Fe release from adequate body stores that is unable to meet the demand for erythropoeisis
- Fe studies are significant for a low serum transferrin saturation (<20%) and normal or high serum ferritin levels
- Hallmark of functional Fe deficiency is that it responds to Fe supplements with an increase in Hbg and/or decrease in ESA requirements despite normal or elevated serum Ferritin levels

Type 3: Inflammatory or Reticulo-endothelial blockade

• Also characterized by a Tsat <20% and elevated Ferritin levels though there is a lack of response in Hbg or ESA requirements to Fe supplementation

• Refractory anemia due to an underlying inflammatory state

• Hepcidin excess account for the impaired Fe absorption and reticuloendothelial cell Fe blockade which prevents the release of iron from macrophages to circulating transferrin
Novel Approaches for Treating Fe Deficiency Anemia
Ferric Pyrophosphate Citrate (FPC)

• Carbohydrate free, water soluble iron salt
• First used to deliver iron by dialysate in 1999
• Added to liquid bicarbonate to generate dialysate containing 2uM iron → FPC crosses the dialyzer membrane, enters the blood, donates its iron directly to transferrin and is rapidly cleared from circulation
• Approved by the FDA in January 2015 as the first iron product indicated to maintain Hgb in ESRD patients
• CRUISE and PRIME Studies
Study A: Continuous Replacement Using Iron Soluble Equivalents (CRUISE)

• **Hypothesis:** FPC administered via dialysate can sustain Fe delivery for erythropoiesis and is more effective than placebo in maintaining Hgb concentration in HD patients

• **Study Design:**
  • Prospective, randomized, single-blind, placebo-controlled, multicenter Phase 3 study conducted from March 2011 to July 2013
  • 599 chronic HD patients were randomized to receive FPC dialysate or placebo/standard dialysate for every dialysis session
  • Oral and IV iron products and changes in ESA dosage were prohibited
  • Completion defined as when: (a) Hgb became <9 or <12g/dL or >11.5 with an associated increase of >1.0g/dL over 4 weeks; (b) Ferritin was <100ug/L; (c) 48 weeks of treatment had elapsed

Source: A. Gupta et al kidney International ; July 2015
Primary Endpoint: mean change in Hgb

• FPC met the primary efficacy endpoint w/ a treatment difference of .4g/dL in the mean change in Hgb from baseline to end of treatment (P<.001)
Study A Results

• 45.8% of FPC treated patients and 57.3% of placebo treated patients completed the study due to the defined change in Hgb or ESA dose change
  • increase in Hgb>12 in 55.4% of the FPC vs 38.4% in placebo group
  • decrease in Hgb to <9 30% of FPC group vs 43% of patients in placebo

• Conclusion: “Study demonstrates that regular administration of FPC during HD by addition during HD effectively replaces ongoing Fe losses, thereby maintaining iron balance and Hgb concentration’’

*Limitations:
  - high drop out/withdrawl rate
  - mean change in hbg of .4g/dL statistically significant? attributed to lab variation?
  - deviates from clinical practice – placebo group expected to not receive additional Fe supplementation for 48 weeks
Study B: Physiological Replenishment Iron Maintenance Equivalency (PRIME)

• **Hypothesis**: administration of FPC via dialysate during HD would reduce prescribed ESA use and maintain Hgb in the recommended range

• **Study Design**:
  • 9 month, randomized, placebo controlled, double blind, multicenter clinical study
  • 108 patients randomized to receive either FPC or placebo
  • Blinded central anemia management group performed ESA dose adjustments
  • IV Fe was administered according to approved indication when ferritin levels fell <200ug/l

*75% of randomized patients completed the study; 11 patients from each group discontinued prematurely

Source: S. Fishbane et al Nephrol Dial Transplant; June 2015
Study B Results

- Mean serum Fe level during a single dialysis treatment increased in FPC group from 63.5 ug/dl to 215ug/dl post-HD
- Mean TSAT before and after dialysis increased from 23.9% to 74.7% in FPC group but did not change significantly in placebo group (22.6-25%)
- FPC iron was cleared rapidly from circulation as indicated by maintenance of pre-dialysis serum levels at baseline levels
Approximately twice as many placebo-treated patients as FPC-treated patients received IV iron (20 vs 11)

Placebo treated patients received approximately twice as much IV Fe during the study (7304mg vs 3790mg)

Mean change from baseline in serum ferritin from end of treatment was significantly smaller in the FPC group

Serum ferritin levels did not increase in FPC group suggesting that FPC does not increase total body Fe stores
FPC treated patients required 35% less ESA than placebo treated patients to maintain Hgb in the target range

Conclusion: “FPC can effectively deliver iron and maintain Hgb levels without increasing Fe stores while reducing need for ESA”

Limitations:
• High drop out rate – 11 patients in each group
• Fe levels were not maintained per guidelines – patients receiving placebo were administered Fe only when their ferritin levels fell to <200 or Tsat <15% → requiring higher IV Fe and ESA doses for repletion
• Increase in EPO in FPC group during weeks 4-24 not addressed
Ferric Citrate

• Oral, insoluble, aluminum and calcium free, ferric iron-based phosphate binder
• After administration, dissociates into its ferric ion (Fe+3) and citrate components → ferric ion binds phosphate → ferric phosphate precipitate → excreted in stool
• Ferric iron is reduced to Ferrous form and absorbed by duodenal enterocytes
• Contains 210mg of ferric iron supplied as 1g of ferric citrate
Ferric Citrate Reduces IV Iron and ESA Use in ESRD

• Phase 3, randomized, open label trial conducted at 60 sites across US and Israel
• 441 subjects randomized – 292 to FC and 149 to sevelamer carbonate or calcium acetate and followed for 52 weeks
• Both FC and control were titrated on basis of centrally measured P levels to achieve prespecified targets
• ESA dosing and IV Fe was at discretion of local investigator
Results

• FC group exhibited increased ferritin and T sat levels compared with control group by week 12 and persisted throughout f/u period at week 52

• Increase in Ferritin w/ mean difference of 281 and TSAT of 9.55%

• FC group subjects required less cumulative elemental iron (12.9mg/week compared to 26.8mg/week in control group)

• Cumulative ESA use was lower in FC group compared with AC group (5303U/week vs 6954U/week) P=.04
Summary of other published trials with Ferric Citrate

<table>
<thead>
<tr>
<th>Author/journal year</th>
<th>Study phase</th>
<th>Subjects enrolled</th>
<th>Comparator</th>
<th>Duration</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yokoyama K</td>
<td>Dose-response</td>
<td>192</td>
<td>Placebo</td>
<td>28 days</td>
<td>PI decrease is dose dependent up to 6 g/day. PI decreased ~2.16 with 3 g/day. PI &lt; 5.5 in 30% with 3 g/day.</td>
</tr>
<tr>
<td>Dwyer JP</td>
<td>Dose-response</td>
<td>151</td>
<td>None</td>
<td>28 days</td>
<td>FC 6 g/day decrease PI ~1.9 ± 1.7 mg/dL and 8 g/day, ~2.1 ± 2.0 mg/dL.</td>
</tr>
<tr>
<td>Yokoyama K</td>
<td>III</td>
<td>230</td>
<td>Sevelamer HC 3-9 g/day</td>
<td>12 weeks</td>
<td>PI ~0.82 mmol/L with FC and ~0.78 with sevelamer (non-inferiority) with sig. increase in ferritin and transferrin sat.</td>
</tr>
<tr>
<td>Lee CT</td>
<td>III</td>
<td>166</td>
<td>Placebo</td>
<td>8 weeks</td>
<td>PI decrease with 4 and 6 g/day; increase in ferritin and transferrin sat: PI ~2.2 mg/dL compared to Placebo and similar to active control but higher mean iron parameters with less IV iron.</td>
</tr>
<tr>
<td>Lewis JB</td>
<td>III</td>
<td>441</td>
<td>Active control and Placebo</td>
<td>52 weeks</td>
<td></td>
</tr>
</tbody>
</table>