Disclosures

• Advisory Board/Consultant
  • Akebia/Otsuka (vadadustat)
  • Vifor (IV iron)
  • AstraZeneca (roxudastat)

• Speakers Bureau
  • Akebia (ferric citrate)
  • AstraZeneca (anemia disease state)
Outline

• Risks and benefits of ESA therapy
• Risks and benefits of iron therapy
• Biosimilar ESAs
• New oral irons
• NOT HIF-PHIs
### What are the Harms of ESA Therapy?

<table>
<thead>
<tr>
<th>Study</th>
<th>Normal Hematocrit Study</th>
<th>CHOIR</th>
<th>TREAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1265</td>
<td>1432</td>
<td>4038</td>
</tr>
<tr>
<td>ESA</td>
<td>Epoetin alfa</td>
<td>Epoetin alfa</td>
<td>Darbepoetin alfa</td>
</tr>
<tr>
<td>Population</td>
<td>HD patients with coexisting HF or CAD, Hct 30±3% on epoetin alfa</td>
<td>ND-CKD patients with Hgb &lt;11 g/dL not previously administered ESA</td>
<td>ND-CKD patient with type 2 DM, Hgb &lt;11 g/dL</td>
</tr>
<tr>
<td>Hgb Target (g/dL)</td>
<td>14.0 vs. 10.0</td>
<td>13.5 vs. 11.3</td>
<td>13.0 vs. ≥9.0</td>
</tr>
<tr>
<td>Median Achieved Hgb level (g/dL)</td>
<td>12.6 vs. 10.3</td>
<td>13.0 vs 11.4</td>
<td>12.5 vs. 10.6</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>All-cause mortality or non-fatal MI</td>
<td>All-cause mortality, MI, hospitalization for HF, or stroke</td>
<td>All-cause mortality, MI, myocardial ischemia, HF and stroke</td>
</tr>
<tr>
<td>Hazard Ratio or Relative Risk (95% CI)</td>
<td>1.28 (1.06-1.56)</td>
<td>1.34 (1.03-1.74)</td>
<td>1.05 (0.94-1.17)</td>
</tr>
<tr>
<td>Adverse Outcome for Higher Hgb Group</td>
<td>All-cause mortality</td>
<td>All-cause mortality</td>
<td>Stroke</td>
</tr>
<tr>
<td>Hazard Ratio or Relative Risk (95% CI)</td>
<td>1.27 (1.04-1.54)</td>
<td>1.48 (0.97-2.27)</td>
<td>1.92 (1.38-2.68)</td>
</tr>
<tr>
<td>QOL</td>
<td>Better in high Hgb group (controversial)</td>
<td>No difference</td>
<td>No difference except less fatigue in high Hgb group</td>
</tr>
<tr>
<td>Comment</td>
<td>Increased VA thrombosis in high Hgb group</td>
<td></td>
<td>Increased cancer deaths in high Hgb group among patients with prior history of cancer</td>
</tr>
</tbody>
</table>

[https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103234s5363s5366lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103234s5363s5366lbl.pdf)
Balancing Risk vs. Benefit of ESA Therapy

- **Lower target Hgb**
  - Transfusions
  - ?Decreased QOL

- **Higher target Hgb**
  - MACE
  - Solid Tumor Growth
  - Vasc Access Thrombosis
Balancing Risk vs. Benefit of ESA Therapy

MACE = Major adverse cardiovascular events

Hgb Distribution

Lower target Hgb
More transfusions

Higher target Hgb
More MACE

MACE = Major adverse cardiovascular events
Balancing Risk vs. Benefit of ESA Therapy

• Since the institution of the PPS (bundled payment) for dialysis and the FDA ESA label change in 2011
  • Average ESA doses have decreased around 40%
  • Mean Hgb levels have decreased from 11.5 to 10.8 g/dL (DOPPS)
  • Observed rates of stroke, VTE and heart failure have decreased\(^1\)
  • Transfusion rates have increased from around 2.7% to 3.0% (DOPPS)
  • The increase in transfusions is primarily among patients receiving multiple transfusions who are less likely to be transplant candidates\(^2\)

• Is this an acceptable trade-off?
• What about quality of life?

Quality of Life/Patient-Centered Care in Anemia Management

• Although most RCTs have failed to demonstrate any improvement in QOL by raising target Hgb from 9-11 to 13-14 g/dL with ESAs, these are population studies and there may be individuals who benefit from higher Hgb levels

• TREAT showed a decrease in fatigue and CREATE showed SF-36 improvement in all domains at higher target Hgb levels

• KDIGO acknowledges that some patients may feel better at target Hgb levels >11.5 g/dL and recommends that target Hgb levels be individualized for such patients if they are willing to accept the risks
Proposed Mechanisms for CV Events at Higher Target Hgb Levels and ESA doses: Which is Responsible?

• Since randomization of the RCTs was by target Hgb level, only the target Hgb level can be considered cause and effect.

• Higher ESA doses are highly associated with adverse events in secondary analyses:
  • Patients who achieved higher target Hgb levels at low ESA doses had fewer adverse events than patients who required high ESA doses to achieve lower target Hgb levels.
  • This is highly confounded by comorbidities that may lead to ESA resistance and poorer outcomes.
Proposed Mechanisms for CV Events at Higher Target Hgb Levels and ESA doses: Other Contributing Factors

• Increased blood viscosity due to higher Hgb level
• Improved platelet function at higher Hgb levels (more margination)
• Thrombocytosis due to ESA-induced functional iron deficiency
• Hypertension
  • Increased RBC volume
  • Decreased peripheral vasodilation at higher Hgb levels
  • Effect of ESAs on vascular smooth muscle (increased endothelin, angiotensin, impaired endothelium dependent relaxation and altered calcium homeostasis)
Pharmacologic Blood Levels of EPO Have Off-target Effects

- Peak serum EPO level is 600 mU/mL following IV injection of 30 units/kg EPO; EPO level is 4-24 mU/mL in patients with normal Hgb levels
- At high blood levels EPO may have paracrine effects on non-erythroid receptors in heart, brain, CNS and vasculature which are cytoprotective but also trophic
- Repetitive stimulation and resetting of cardiac growth signals could disorder cardiac modeling, increase vulnerability to stress, or impair the ability of higher Hgb to diminish left ventricular hypertrophy

ESAs Pros and Cons

• Pros
  • Reproduces deficient native hormone
  • Effective in most patients
  • Well tolerated in most patients
  • 30 years experience
  • IV administration invisible to HD patients

• Cons
  • SC administration in non-HD patients
  • Long-term cardiovascular events
  • ESA resistance
  • Do not address iron mobilization disorders
What About Iron?

• NDD-CKD
  • Iron deficiency is highly prevalent in patients with NDD-CKD and PD
  • KDIGO recommends 1-3 month trial of oral iron OR IV iron
  • Metaanalyses have demonstrated increased efficacy of IV over oral iron in raising Hb but no differences in morbidity or mortality
  • Oral iron associated with GI side effects; IV iron associated with hypotension and allergic reactions

• Hemodialysis
  • The vast majority (80%) of HD patients require regular doses of IV iron due to ongoing iron losses and ESA-accelerated erythropoiesis
  • Due to the inflammatory state of ESRD, many of these patients cannot adequately mobilize the administered iron and have serum ferritin levels which average 800 ng/mL
Ferroportin and Hepcidin: Key Factors in Iron Regulation

Iron-exporting cells

(duodenal enterocytes, macrophages, hepatocytes)

Fpn=ferroportin.
Ferroportin and Hepcidin: Key Factors in Iron Regulation

Adults With CKD Exhibit Significantly Increased Serum Hepcidin Levels\textsuperscript{1,2}

Factors Contributing to the Increased Hepcidin Expression Observed in CKD\textsuperscript{3,4}

- Chronic inflammation
- Infections
- IV iron therapy
- Reduced renal clearance of hepcidin

Means of Overcoming the Hepcidin Blockade Associated With CKD\textsuperscript{1,2}

Iron Export From Macrophages

**CKD**
Increased hepcidin results in reduced ferroportin-mediated iron export (hepcidin block)

**CKD + Oral Iron**
Iron absorption from oral iron may be inadequate to overcome the hepcidin block

**CKD + IV Iron**
IV iron results in high intracellular iron levels which may overcome the hepcidin block by increasing production of ferroportin

The Consequences of High Levels of Intracellular Iron Required to Overcome “Hepcidin Blockade”

• High serum ferritin levels
• Potential for iron overload and organ dysfunction
• Potential increased risk for infection
  • Impairment of host defenses
  • Stimulation of pathogen growth
• Potential oxidative effect of administered IV iron on vascular endothelium
  • Vascular injury
  • Accelerated atherosclerosis
Intravenous versus oral iron in CKD

Risks of IV iron
- Inflammation
- Oxidative stress
- Cytotoxicity
- Endothelial dysfunction
- Anaphylaxis
- Hemosiderosis
- Bacterial infections
- Cardiovascular events
- Mortality

Benefits of IV iron
- Better bioavailability
- Rapid efficacy
- No compliance issue
- Greater Hb increase
- Reduced ESA needs
- Reduced transfusion needs

Supplemental Iron Pros and Cons

• Pros
  • Addresses iron deficiency
  • IV iron easy to administer and usually well tolerated in HD patients
  • Replaces ongoing iron losses in HD patients

• Cons
  • Oral iron often poorly tolerated and ineffective
  • IV iron inconvenient in non-HD CKD patients
  • Acute reactions to IV iron
  • Long term safety issues
    • CV toxicity
    • Infection risk
    • Iron overload
PIVOTAL Trial (1)

• Phase IV study with a proactive, randomized, open-label, blinded endpoint (PROBE) design which investigated the incidence of all-cause mortality and non-fatal CV events in hemodialysis (HD) patients receiving one of two different IV iron regimens:
  • Reactive, low-dose IV iron arm (n=1,048): patients only received IV iron if ferritin<200µg/L or transferrin saturation (TSAT) <20%; proactive, high-dose IV iron arm (n=1,093): patients received IV iron 400mg/month (withheld if ferritin>700µg/L or TSAT>40%)
  • Primary endpoint: composite of non-fatal CV events - myocardial infarction [MI], stroke), hospitalization for heart failure (HF), or all-cause death
  • Median cumulative iron doses at 1 year in the two arms were statistically different: 3.8g vs. 1.8g (p<0.001)

PIVOTALAL Trial (2)

- Use of higher IV iron doses did not negatively impact mortality or incidence of CV events, nor increase risk of infection or hospitalization
- Improvements in ferritin and TSAT were statistically superior in the proactive, high-dose arm (p<0.001)
- Higher IV iron doses reduced median monthly ESA doses by 19.4% (p<0.01) and reduced the need for blood transfusions (HR: 0.79; p=0.014)
- No statistically significant differences in vascular access thrombosis, all-cause hospitalization, infection episodes, or hospitalization for infections between both treatment groups
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio (HR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, stroke or HF hospitalization</td>
<td>0.88</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.84</td>
<td>0.054</td>
</tr>
<tr>
<td>Fatal or non-fatal MI, fatal stroke, or HF hospitalization</td>
<td>0.85</td>
<td>0.114</td>
</tr>
<tr>
<td>Fatal or non-fatal MI</td>
<td>0.79</td>
<td>0.079</td>
</tr>
<tr>
<td>Fatal or non-fatal stroke</td>
<td>0.98</td>
<td>0.919</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.66</td>
<td>0.017</td>
</tr>
</tbody>
</table>
Biosimilar ESAs (1)

- A “biologic” drug is a substance made from living organism or its products for the prevention, diagnosis, or treatment of disease.
- A “biosimilar” drug is a copy or replica of a biologic drug with a target that is the same as the originator or reference agent.
- Biosimilar agents must meet strict criteria of quality and comparability with their respective reference biologics to be approved in highly regulated markets such as the EU and US.
Biosimilar ESAs (2)

- Biosimilars are not identical to their reference biologics because the nature of biologics is inherent variability; the reference biologics are variable and not identical to themselves
- Biosimilars are not generics and require a separate approval pathway from generics
- The approval pathway for biosimilars emphasizes structural and functional similarity and does not require extensive clinical studies of safety and efficacy
Unlike Producing Small Molecule Drugs, the Manufacturing Process for Biologics is Complex

Biosimilar Evaluation–
Step-wise Totality of Evidence Approach

- Clinical
- Animal Studies
- Clinical Immunogenicity
- Clinical Knowledge (post-market experience)
- Human PK/PD
- Structural and Functional Characterization

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
Epoetin zeta (Hospira)

• Approved for use in the EU in 2008 under the brand name Retacrit®
• Same amino acid sequence as epoetin alfa
• Slightly less potent than Epogen® on molecular weight basis due to higher protein content of Epogen®
• Similar safety to reference agent
• Approved by FDA on May 15, 2018 as Retacrit® or epoetin alfa-epbx for IV or SC administration
# Intravenous Epoetin Alfa-epbx versus Epoetin Alfa for Treatment of Anemia in End-Stage Kidney Disease

Steven Fishbane, Bhupinder Singh, Seema Kumbhat, Wayne A. Wisemandle, and Nancy E. Martin

Table 2. Comparative efficacy of epoetin alfa-epbx and epoetin alfa, evaluated by coprimary efficacy end points of mean weekly hemoglobin level and mean weekly epoetin dose by body weight

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Epoetin alfa-epbx</th>
<th>Epoetin alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary analysis (ITT population)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean weekly hemoglobin level during last 4 wk of treatment, g/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least squares mean (SEM)</td>
<td>10.17 (0.05)</td>
<td>10.28 (0.05)</td>
</tr>
<tr>
<td>Difference (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.12 (-0.25 to 0.01)</td>
<td></td>
</tr>
<tr>
<td>Mean weekly epoetin dose by body weight during last 4 wk of treatment, U/kg per week&lt;sup&gt;b&lt;/sup&gt;</td>
<td>90.16 (3.87)</td>
<td>89.79 (3.88)</td>
</tr>
<tr>
<td>Least squares mean (SEM)</td>
<td>0.37 (-10.40 to 11.13)</td>
<td></td>
</tr>
<tr>
<td>Difference (95% CI)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity analysis (per protocol population)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean weekly hemoglobin level during last 4 wk of treatment, g/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least squares mean (SEM)</td>
<td>10.19 (0.06)</td>
<td>10.30 (0.06)</td>
</tr>
<tr>
<td>Difference (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.10 (-0.27 to 0.06)</td>
<td></td>
</tr>
<tr>
<td>Mean weekly epoetin dose by body weight during last 4 wk of treatment, U/kg per week</td>
<td>85.71 (4.73)</td>
<td>88.12 (4.88)</td>
</tr>
<tr>
<td>Least squares mean (SEM)</td>
<td>-2.41 (-15.77 to 10.95)</td>
<td></td>
</tr>
<tr>
<td>Difference (95% CI)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ITT, intent to treat; 95% CI, 95% confidence interval.

<sup>a</sup>The 95% CI for the least squares mean of the difference (epoetin alfa-epbx–epoetin alfa) in mean weekly hemoglobin had to reside within the equivalence margin of ±0.5 g/dl for equivalence to be concluded.

<sup>b</sup>One patient in each group did not have dose data reported at baseline. Therefore, primary analysis of mean weekly epoetin dose by body weight during last 4 wk of treatment in the ITT population is on the basis of data for 305 randomized patients in each treatment group.

<sup>c</sup>The 95% CI for the least squares mean of the difference (epoetin alfa-epbx–epoetin alfa) in mean weekly epoetin dose per kilogram of body weight had to reside within the equivalence margin of ±45 U/kg per week for equivalence to be concluded.
Mean (SD) weekly hemoglobin level (g/dl) and mean (SD) weekly epoetin dose by body weight (U/kg per week) were similar between epoetin alfa-epbx and epoetin alfa over the duration of the treatment period.

Steven Fishbane et al. CJASN 2018;13:1204-1214
Mean and median systolic and diastolic BPs after dialysis were unchanged over time and similar between epoetin alfa-epbx and epoetin alfa.
Table 4. Safety profiles of epoetin alfa-epbx and epoetin alfa: adverse events with ≥5% incidence and serious adverse events occurring in at least four patients in either treatment group

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Epoetin alfa-epbx, n=301</th>
<th>Epoetin alfa, n=304</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any adverse event, n (%)</strong></td>
<td>232 (77.1)</td>
<td>229 (75.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (10.0)</td>
<td>25 (8.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28 (9.3)</td>
<td>15 (4.9)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>27 (9.0)</td>
<td>24 (7.9)</td>
</tr>
<tr>
<td>Arteriovenous fistula-site complication</td>
<td>26 (8.6)</td>
<td>25 (8.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (7.6)</td>
<td>16 (5.3)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22 (7.3)</td>
<td>21 (6.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21 (7.0)</td>
<td>27 (8.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20 (6.6)</td>
<td>15 (4.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (6.3)</td>
<td>12 (3.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>16 (5.3)</td>
<td>22 (7.2)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>14 (4.7)</td>
<td>23 (7.6)</td>
</tr>
<tr>
<td>Back pain</td>
<td>13 (4.3)</td>
<td>16 (5.3)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>10 (3.3)</td>
<td>17 (5.6)</td>
</tr>
<tr>
<td>Noncardiac chest pain</td>
<td>7 (2.3)</td>
<td>17 (5.6)</td>
</tr>
<tr>
<td><strong>Any serious adverse event, n (%)</strong></td>
<td>75 (24.9)</td>
<td>82 (27.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (1.3)</td>
<td>8 (2.6)</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>4 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>4 (1.3)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3 (1.0)</td>
<td>8 (2.6)</td>
</tr>
<tr>
<td>Noncardiac chest pain</td>
<td>2 (0.7)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>2 (0.7)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1 (0.3)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>1 (0.3)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>0</td>
<td>6 (2.0)</td>
</tr>
</tbody>
</table>
What Happens After Biosimilar ESAs are Approved in the US?

• Smaller dialysis providers may adopt their use as a cost-sparing strategy since ESAs remain a relatively big budget item despite a 38% decrease in their use since 2007
• DaVita has a long term contract to use Amgen products and FMC has a long term contract to use Mircera®
• For non-dialysis CKD patients the drug plans will likely favor biosimilar ESAs due to their lower cost and make it more difficult to prescribe originator ESAs
• Patient co-pays will decrease if the drug costs less
• Costs for brand-name ESAs will decrease to preserve market share
• The biosimilar ESAs will not be interchangeable with brand name ESAs, so pharmacies and drug plans cannot substitute without the prescriber’s permission
Values for each month reflect prescription among ESA-treated patients.
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods").
Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").
Facility sample transitioned from DOPPS 6 to 7 in Feb-May 2018 (see "Study Sample and Methods").
Source: US-DOPPS Practice Monitor, October 2019; http://www.dopps.org/DPM
New More Bioavailable Oral Irons

• Ferric citrate
• Sucrosomial iron
• Ferric maltol
Effects of Ferric Citrate in Patients with Nondialysis-Dependent CKD and Iron Deficiency Anemia

Steven Fishbane,* Geoffrey A. Block,† Lisa Loram,‡ John Neylan,‡ Pablo E. Pergola,§ Katrin Uhlig,† and Glenn M. Chertow¶

Ferric citrate improves hemoglobin response.

Steven Fishbane et al. JASN 2017;28:1851-1858
Ferric citrate increases transferrin saturation and serum ferritin.

Steven Fishbane et al. JASN 2017;28:1851-1858
### Treatment Emergent AEs

(Reported in 5% or more in either group)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ferric Citrate (n=117), n (%)</th>
<th>Placebo (n=116), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-emergent AE</td>
<td>93 (79.5)</td>
<td>75 (64.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (20.5)</td>
<td>19 (16.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>22 (18.8)</td>
<td>15 (12.9)</td>
</tr>
<tr>
<td>Feces discolored</td>
<td>17 (14.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (11.1)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7 (6.0)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0)</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>8 (6.8)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (4.3)</td>
<td>6 (5.2)</td>
</tr>
</tbody>
</table>
Sucrosomial technology

- Represents a phospholipid containing carrier in which ferric pyrophosphate is protected by a phospholipid bilayer membrane mainly from sunflower lecithin plus sucrose esters matrix
Clinical Study in HD-CKD: vs IV Iron

• **Inclusion criteria:**
  • Anemic patients on chronic hemodialysis since at least three months
  • Hb <11g/dl, TSAT <20%, Ferritin < 100 mcg/l
• **Treatment regimen:**
  • 9 months subdivided into 3 periods (3 months for each period):
    • first period (iv1) during which it was administered intravenous iron at a dose of 62.5 mg/week at the end of the hemodialysis sessions
    • second period (os) where the same patients suspended intravenous iron and replaced with liposomal oral iron to dosage of 30 mg/day
    • third period (iv2) in which all patients resumed iron intravenous therapy at the same dose of period iv

Results: Hb & TSAT levels were maintained by sucrosomial iron
Potential Advantages of Sucrosomial Iron

- Higher absorption than conventional oral iron agents
- Appears to be as effective as intravenous iron.
- Non-interference with absorption of other nutrients
- Higher bioavailability than conventional oral iron agents
- Better tolerability than conventional iron agents
- No discoloring of stools
- Suitable for celiac disease patients
- Available without a prescription as Sideral®
Ferric maltol

• Reaches duodenum unaltered
• Higher percentage iron absorption than ferrous salts
• Favorable results in phase 3 studies of iron deficiency in UC
  • Rapid significant improvements in Hgb over 4-12 weeks
  • GI side effects similar to placebo
• Phase 3 study of IDA in NDD-CKD patients, NCT02968368
  • 24 US sites
  • 168 subjects
  • Primary outcome: change in Hgb from baseline at week 16 vs. placebo
  • Results not published
• Drug approved in US 7/25/19, brand name Accrufer®
Ferric maltol (2018 Renal Week abstract)

› Phase III, multicenter, double-blind, randomized controlled study evaluated the efficacy and safety of ferric maltol vs. placebo for the treatment of anemia in patients with Stage 3-4 CKD or IDA
  › Patients with eGFR ≥15 to <60mL/min/1.7m²; Hb ≥8.0 to <11.0g/dL and ferritin <250 µg/L + transferrin saturation (TSAT) <25% or ferritin <500µg/L + TSAT <15% were randomized 2:1 to oral ferric maltol 30mg or PBO for 16 weeks
  › Change in Hb concentration from baseline (BL) to Week 16 [LSM (SE)] in ITT population for ferric maltol vs. PBO was 0.5 (0.122) vs. -0.02 (0.165), with treatment difference 0.52 (0.210) (p=0.0149)
  › AEs observed with ferric maltol vs. PBO:
    › Gastrointestinal disorders 40.5% vs. 30.4%; metabolism and nutritional disorder: 18.9% vs. 23.2%; infections and infestations: 15.3% vs. 23.2%; renal and urinary disorders: 9.0% vs. 10.7%; blood and lymphatic system disorders: 4.5% vs. 16.1%
  › Ferric maltol showed statistically significant increases in Hb and all iron parameters from BL to Week 16 vs. PBO
    › Ferric maltol was well tolerated, with lower rate of discontinuation due to AEs vs. PBO
Summary and Conclusions

• Current anemia management (ESAs and iron) is reasonably effective in about 80-85% of ESRD patients to maintain Hgb levels >9 g/dL (DOPPS)
• ESAs and IV iron can be administered via the HD circuit without the patient having to worry about it
• There are concerns regarding the long-term effects of IV iron resulting in mean serum ferritin level of 800 ng/mL among HD patients in the US
• There are unmet needs for treatment of anemia in patients with CKD
  • Oral administration of meds in non-HD patients
  • ESA resistance
  • Decreasing IV iron requirements and increasing efficacy of oral iron by decreasing hepcidin activity
• Newer forms of oral iron offer greater bioavailability than conventional agents and may be safer than IV iron
• HIF-PH inhibitors offer promise as alternatives to ESAs with improved iron mobilization and lower EPO levels producing similar Hb response
Thank you.
Questions?