Managing anemia in dialysis patients: Old & New iron replacement strategies

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Outline of Presentation

- Prevalence of anemia & iron metabolism in CKD
- Current iron therapy (KDIGO)
- New iron replacement strategies
  - Intra-dialytic soluble ferric pyrophosphate (SFP)
  - Oral ferric citrate
  - HIF stabilizers (PHI)
Prevalence of Anemia

Anemia Begins at a GFR <60 mL/min

Hb <12.0 g/dl for men and women >50 yrs and Hb <11.0 g/dl for women <51 yrs

Why do CKD patients develop anemia?

Multifactorial etiologies ...

Uremic toxicity & inflammation both exacerbate anemia

Bowdry SK, Gatti E. Blood Purif 2011; 32: 210-219
Iron homeostasis & role for hepcidin

ID, hypoxia, ↑erythropoiesis

Liver stores 1000 mg Fe

BMP6, ↑TSAT, inflammation

duodenal absorption (1-2 mg/day)

enterocytes

Ferroportin

Plasma Transferrin

FE3+

losses (1-2 mg/day) mucosal exfoliation, menses

Erythroid precursors in Bone Marrow

Splenic macrophages

≈ 600 mg Fe

Circulating RBCs

≈ 2 g Fe

≈ 25 mg/day

Iron homeostasis is dysregulated in CKD

- Several factors lead to upregulation of hepcidin production

Hepcidin reduces iron bioavailability

- Blocks iron absorption in gut
- Blocks iron release from the cells of RES
Negative Iron Balance in CKD

- Blood losses associated with lab tests & hospitalization, hemodialysis (from dialyzer and access)
- GI losses due to anticoagulant or antiplatelet drugs.
- Reduced iron absorption due to medications (e.g., PPI, Pi binders).
- Reduced iron absorption due to increased hepcidin levels.
- Reduced iron intake due to poor appetite, diet, and malnutrition.

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>ND-CKD</th>
<th>Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Blood Loss</strong></td>
<td>0.83 ml/d</td>
<td>3.2 ml/d</td>
<td>5.0 ml/d</td>
</tr>
<tr>
<td><strong>Annual Blood Loss</strong></td>
<td>0.3 L/yr</td>
<td>1.2 L/yr</td>
<td>2–5 L/yr</td>
</tr>
<tr>
<td><strong>Annual Iron Loss</strong></td>
<td>0.1 g/yr</td>
<td>0.4 g/yr</td>
<td>1–2 to 4–5 g/yr</td>
</tr>
</tbody>
</table>

Available Treatments for Anemia in CKD

Absolute/Functional Iron Deficiency:
- EPO Deficiency (absolute or functional)
- Erythropoiesis Stimulating Agents
- Iron supplementation (PO, IV or Dialysate iron)
- RBC transfusion
Recent RCTs* suggest aggressive anemia treatment to normalize Hb using high doses of ESAs in CKD/ESRD patients more harmful than beneficial.

Trend in ESA & Iron therapies from DOPPS practice monitor (DPM) reported a decline in ESA dose & Hb levels, while an increase in IV iron use & serum ferritin levels.

Goal of anemia treatment no longer to achieve a particular Hb target, rather to achieve appropriate Hb levels using the lowest effective ESA or iron dose necessary for transfusion avoidance.
DOPPS IV (2010-2011) vs. KSN

- Intravenous iron use, by country
When to treat anemia with iron in CKD

2.1.2 For adult CKD patients with anemia NOT on iron or ESA therapy we suggest a trial of IV iron (or in CKD-ND patients alternatively a 1-3 month trial of oral iron therapy) if (2C):
- an increase in Hb concentration without starting ESA treatment is desired &
- TSAT is ≤30% and ferritin is ≤500 ng/mL

2.1.3: For adult CKD patients on ESA therapy who are NOT receiving iron supplementation, we suggest a trial of IV iron (or in ND-CKD patients alternatively a 1-3 month trial of oral iron therapy) if (2C):
- an increase in Hb concentration or a decrease in ESA dose is desired &
- TSAT is ≤30% and ferritin is ≤500 ng/ml

KDIGO Clinical Practice Guideline for Anemia in CKD. Kidney Int Suppl 2012;2:283–287
OBJECTIVES & INDICATIONS
Iron supplementation is intended to:
• Assure adequate iron stores for erythropoiesis
• Correct iron deficiency
• Prevent iron deficiency from developing in patients receiving ESA

Iron treatment, particularly when administered IV, can enhance erythropoiesis and raise Hb levels in CKD patients even when TSAT and ferritin levels are not indicative of absolute iron deficiency, and even when BM studies reveal adequate iron stores.
# Hb & Iron Targets in Different Clinical Practice Guidelines

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>10-11</td>
<td>11-12</td>
<td>11-12</td>
<td>&gt;11 (&lt;13)</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>&gt;30 (30-50)</td>
<td>≥20 (&lt;50)</td>
<td>&gt;20 (30-40)</td>
<td>20</td>
<td>20</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>&gt;300 (300~500)</td>
<td>≥100 (&lt;800)</td>
<td>≥100 (200~500)</td>
<td>100 (&lt;500)</td>
<td>&gt;100</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Hypochromic RBC (%)</td>
<td>&lt;10 (&lt;2.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHr (pg/cell)</td>
<td>&gt;29 (-35)</td>
<td>&gt;29</td>
<td>&gt;29</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHr, reticulocyte hemoglobin content; DOQI, Disease Outcomes Quality Initiative; Hb, haemoglobin; K/DOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease Improving Global Outcomes; RBC, red blood cell; TSAT, transferrin saturation.

**KSN (2009) ND-CKD:** Ferritin <100 n/ml OR TSAT <20% and for HD: ferritin <200 ng/ml

*in EPO resistance: Ferritin < 300 ng/ml OR TSAT <30%

**JSDT:**
1. Anemic CKD not on ESA or iron, suggest iron therapy prior to ESA if serum ferritin <50 ng/ml
2. ESA (+), serum ferritin <100 n/ml OR TSAT <20% (keep serum ferritin ≤300 ng/ml)

Hung SC et al. Nephrolgy 2014; 19: 735-739
Evolution & Options for iron replacement

1981
Ferrous salts, iron polysaccharide, heme iron polypeptide

1999
Iron dextran

2000
Sodium ferric gluconate complex in sucrose

2009
Iron sucrose

2013
Ferumoxytol

2014
Ferric carboxymaltose

2015
Ferric citrates

Dialysate
Ferric pyrophosphate citrate

HIF-PHI

Oral iron

IV iron

Hepcidin modulators?

# Treatment Options: PO vs IV iron

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Potential benefits</th>
<th>Potential risks</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IV iron</strong></td>
<td>Improved Hb levels</td>
<td>Accumulation in tissue</td>
<td>More costly than oral iron (drug, travel and iv costs)</td>
</tr>
<tr>
<td></td>
<td>Delayed need for transfusion or ESA use</td>
<td>Transient increase in oxidative stress(?)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced ESA dosing</td>
<td>Risk of infection (?)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased fatigue and improved physical performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Improved QOL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PO iron</strong></td>
<td>Same as IV? Alternate day schedule of oral iron therapy? (hepcidin era)</td>
<td>Interference with concomitant medications</td>
<td>Pill burden</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited use in patients with chronic inflammatory bowel disease</td>
<td>Limited intestinal absorption GI AEs</td>
</tr>
</tbody>
</table>
Commonly available IV iron preparations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Stability</th>
<th>Maximum single dose</th>
<th>Total replacement dose in single infusion (1–1.5 g)</th>
<th>Minimum administration time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe-gluconate</td>
<td>Ferlixi^®</td>
<td>Low</td>
<td>125 mg</td>
<td>No <em>(repeated access needed)</em></td>
<td>30–60</td>
</tr>
<tr>
<td>Fe-sucrose</td>
<td>Venofer^®</td>
<td>Low-moderate</td>
<td>200 mg</td>
<td>No <em>(repeated access needed)</em></td>
<td>30</td>
</tr>
<tr>
<td>Fe-carboxymaltose</td>
<td>Ferinject^®</td>
<td>High</td>
<td>1000 mg</td>
<td>Yes</td>
<td>15</td>
</tr>
<tr>
<td>Fe-isomaltoside</td>
<td>Monofer^®</td>
<td>High</td>
<td>20 mg Fe/Kg</td>
<td>Yes</td>
<td>15</td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>Feraheine^®</td>
<td>High</td>
<td>510 mg</td>
<td>Yes/no</td>
<td>15</td>
</tr>
</tbody>
</table>

*Figure 3.* In vivo comparison of labile iron potential of IV iron preparations. Results of the determination of detectable labile iron in human serum as a percentage of total dose given (200 mg and 500 mg), using the Ferrozine®-method (adapted from Jahn et al., 2011 [32]).
## Benefits & risks of IV iron therapy

### Potential Benefits
- Avoiding or minimize
  - Blood transfusions
  - ESA therapy
  - Anemia-related symptoms

### Risk of Harms
- Anaphylactoid and other acute reactions
- Oxidative stress
- Unknown long-term risks
  - Mortality
  - CV events
  - Infections
  - Tissue depositions

Immediate effects on surrogate biomarkers … but LONG-TERM OUTCOMES UNCLEAR
The weighted average change in ESA dose was a reduction of 23% (range –7% to –55%) attributable to appropriate dosing of IV iron.

Conclusion: Significant reductions in ESA dosing may be achieved with optimal IV iron usage in the HD population, and suboptimal iron use may require higher ESA dosing to manage anemia.
FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia

Iain C. Macdougall¹, Andreas H. Bock², Fernando Carrera³, Kai-Uwe Eckardt⁴, Carlo Gaillard⁵, David Van Wyck⁶, Bernard Roubert⁷, Jacqueline G. Nolen⁷, Simon D. Roger⁸ on behalf of the FIND-CKD Study Investigators†

- 56-wk, open-label, multicentre, prospective & randomized study
- N= 626 ND-CKD, anaemia and iron deficiency not receiving ESAs
- Randomized (1:1:2) to IV FCM, targeting a higher ferritin (400–600 ng/ml), N=155, or IV FCM, targeting a lower ferritin (100–200 ng/ml), N=154 or oral iron, ferrous sulfate, 200mg elemental iron daily, N=317
- The primary end point was time to initiation of other anemia management (ESA, other iron therapy or blood transfusion) or Hb <10 g/dL x2 consecutive values during weeks 8–52
### Results

The primary end point occurred in 36 patients (23.5%), 49 patients (32.2%) and 98 patients (31.8%) in the high-ferritin FCM, low-ferritin FCM and oral iron groups, respectively [hazard ratio (HR): 0.65; 95% confidence interval (CI): 0.44–0.95; \(P = 0.026\) for high-ferritin FCM versus oral iron].

### Conclusions

ND-CKD patients with anemia and iron deficiency may benefit from IV iron treatment, targeting a higher ferritin level (400–600 \(\mu\)g/L).
Randomized Trial to Evaluate IV vs. Oral Iron in CKD stage 3/4 with IDA (REVOKE STUDY)

- Open label RCT of 24 months follow up
  - 1) oral FeSO4 (325mg tid x 8 weeks, n=69)
  - 2) IV sucrose (200mg q2 weeks x 5 doses, n=67)
- Primary outcome: difference in slope of mGFR over 2 yrs
- Trial terminated early due to no difference in mGFR+
- Higher risk of SAEs in IV iron group;
  - Serious CVE: 55 among 17 subjects vs. 36 among 19 subjects (RR 2.51; 1.56 - 4.04)
  - Hospitalizations for infections RR 2.12 (1.24 – 3.64)

Thus, among moderate to advanced ND-CKD, compared to oral iron, **IV iron sucrose therapy** is associated with an increased risk of SAEs, including those from CV causes and infectious diseases. **Oral iron may be preferred initial mode therapy** for IDA in stage 3-4 CKD.
Intravenous Versus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-analysis

Conclusions: Results agree with current recommendations for IV iron replacement for patients with CKD 5D and support increased use of IV iron for patients with CKD 3 to 5.

Risk ratio of % patients reaching an Hb response >1 g/dL with IV iron compared to oral iron was 1.61 (95% CI, 1.39-1.87) for CKD stages 3-5 and 2.14 [95% CI, 1.68-2.72] for CKD stage 5D.

Conclusions: Results agree with current recommendations for IV iron replacement for patients with CKD 5D and support increased use of IV iron for patients with CKD 3 to 5.
Evidence suggests increased infection risk in patients receiving bolus dosing, or high dose iron supplementation, compared with maintenance dosing, or low dose iron supplementation. Infectious risk appears to be augmented in patients dialyzing via a central venous catheter.

*Brookhart J Am Soc Nephrol 24: 1151-8, 2013*
IV iron: Infection risk in HD

- Review of observational studies evaluating infection risk association with a) ferritin, and b) iron usage showed:
  - Ferritin: 9 showed association (1.5- to 3.1-fold higher incidence of infection/infection-related mortality), 4 did not.
  - Iron usage: 12 showed association (14%–45% higher risk of infection-related mortality), 10 did not.

- Bolus dosing was reported to show higher risk than maintenance dosing for patients with a catheter and history of infection (In contrast, maintenance dosing or low dosing was not associated with increased risk).

**Association between hemoglobin variability, serum ferritin levels, and adverse events/mortality in maintenance hemodialysis patients**

Takahiro Kuragano¹, Osamu Matsumura², Akihiko Matsuda³, Taiga Hara⁴, Hideyasu Kiyomoto⁵, Toshiaki Murata⁶, Kenichiro Kitamura⁷, Shouichi Fujimoto⁸, Hiroki Hase⁹, Nobuhiko Joki⁹, Atushi Fukatsu¹⁰, Toru Inoue¹¹, Ikuhiro Itakura¹² and Takeshi Nakanishi¹

<table>
<thead>
<tr>
<th>Event</th>
<th>Iron administration</th>
<th>Hazard ratio (95% CI)</th>
<th><strong>P-value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non</td>
<td>1</td>
<td>0.056</td>
</tr>
<tr>
<td>Cardio-cerebral vascular disease</td>
<td>PO</td>
<td>3.7 (0.97–14.14)</td>
<td>0.117</td>
</tr>
<tr>
<td></td>
<td>IV (low)</td>
<td>0.85 (0.31–2.32)</td>
<td>0.751</td>
</tr>
<tr>
<td></td>
<td>IV (high)</td>
<td>6.02 (1.1–32.86)</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>PO+IV</td>
<td>1.56 (0.2–12.27)</td>
<td>0.671</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>PO</td>
<td>2.36 (0.81–6.87)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>IV (low)</td>
<td>1.78 (1.04–3.05)</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>IV (high)</td>
<td>5.22 (2.25–12.14)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>PO+IV</td>
<td>2.66 (0.93–7.59)</td>
<td>0.067</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>PO</td>
<td>2.05 (0.78–5.44)</td>
<td>0.147</td>
</tr>
<tr>
<td></td>
<td>IV (low)</td>
<td>1.11 (0.67–1.83)</td>
<td>0.693</td>
</tr>
<tr>
<td></td>
<td>IV (high)</td>
<td>2.77 (1.22–6.27)</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>PO+IV</td>
<td>2.47 (0.91–6.74)</td>
<td>0.077</td>
</tr>
<tr>
<td>Death</td>
<td>PO</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>IV (low)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>IV (high)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>PO+IV</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>All events</td>
<td>PO</td>
<td>2.79 (1.41–5.53)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>IV (low)</td>
<td>1.95 (1.25–3.02)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>IV (high)</td>
<td>4.37 (2.15–8.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PO+IV</td>
<td>5.24 (2.39–11.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Prospective, observational, multicenter study
- Serum ferritin & Hb levels q3M for 2 years
- N=1086 HD patients
- Risks of CCVD, infection, and hospitalization were significantly higher among patients who were treated with high weekly doses of intravenous iron compared with no intravenous iron

**IV high: >50mg/wk; IV low: <50mg/wk**

Kidney Int 2014; 86, 845–854
Data from the DOPPS validate an association between high IV iron doses & mortality

DOPPS analyzed associations between IV iron dose and outcomes in >32,000 patients on HD over 9yrs

Increased risk of all-cause mortality among patients given higher doses of IV iron > 300 mg/mo

For monthly iron dose normalized to bwt, there was an increased risk of CV-related mortality at > 6 mg/kg/mo vs. 1-2 mg/kg/mo

Hospitalization risk was elevated at IV iron dose \( \geq 300 \) mg/mo vs. 100–199 mg/mo (HR = 1.12 [1.07–1.18])

Kidney Int 87: 162-8, 2015
Conclusions: **Higher-dose IV iron does not seem to be associated with higher risk of mortality, infection, CV events, or hospitalizations in adult patients on dialysis.** Strength of this finding is limited by small numbers of participants and events in the RCT and statistical heterogeneity in observational studies.
Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

IV iron RCT in Maintenance Hemodialysis
Proactive IV Iron Therapy in HD Patients (PIVOTAL) trial

PROACTIVE
- 2141 adults with ESKD
- Median monthly ESA dose: 29%
- Composite Primary Outcome: Death, MI, Stroke, Heart Failure
- Total RCC units transfused: 967

REACTIVE
- 1048 adults with ESKD
- Median monthly ESA dose: 32%
- Composite Primary Outcome: Death, MI, Stroke, Heart Failure
- Total RCC units transfused: 1122

From @NephJC
CONCLUSIONS
With median f/u of 2.1 yrs in HD patients, a **high-dose** IV iron regimen [median 264 mg (200 to 336)] administered **proactively** was superior to a low-dose regimen [145 mg (100 to 190)] administered reactively and resulted in lower doses of ESA being administered.

### Table 1: Select primary and secondary end points in the PIVOTAL trial

<table>
<thead>
<tr>
<th>End point</th>
<th>Proactive iron group</th>
<th>Reactive iron group</th>
<th>Estimated treatment effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death and nonfatal MI, stroke or HF hospitalization</td>
<td>29.3%</td>
<td>32.3%</td>
<td>0.85 (0.73–1.00)</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths and recurrent events of nonfatal MI, stroke or HF hospitalization per 100 patient-years</td>
<td>19.4</td>
<td>24.6</td>
<td>0.77 (0.66–0.92)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>22.5%</td>
<td>25.7%</td>
<td>0.84 (0.71–1.00)</td>
</tr>
<tr>
<td>Fatal or non-fatal MI</td>
<td>7.1%</td>
<td>9.7%</td>
<td>0.69 (0.52–0.93)</td>
</tr>
<tr>
<td>Hospitalizations for HF</td>
<td>4.75</td>
<td>6.7%</td>
<td>0.66 (0.46–0.94)</td>
</tr>
<tr>
<td>Transfused patients</td>
<td>18.1%</td>
<td>21.6%</td>
<td>0.79 (0.65–0.95)</td>
</tr>
<tr>
<td>Hospitalizations for infection</td>
<td>29.6%</td>
<td>29.3%</td>
<td>0.99 (0.82–1.16)</td>
</tr>
</tbody>
</table>

Cl, confidence interval; HF, heart failure; MI, myocardial infarction. *Rate ratio.
• **Iron deficiency** is **highly prevalent** in CKD and **IV iron** is **of proven benefit** for treatment of anemia in **HD** patients.

• However, a **number of concerns** regarding IV iron use, notably oxidative stress, CV toxicity, and infections exists.

• Previous observational & RCT showed **conflicting results** that give **uncertainty** to the relative benefit/risk of iron use in HD patients.

• Recent very large RCT, **PIVOTAL trial**, reported benefits of high-dose IV iron use and supports **more liberal use of iron** in HD patients.

• But, we still **lack** longer-term trials assessing clinical outcomes associated with **various** iron administration strategies and thus have many **unanswered questions**.
New Treatment options for iron replacement

• Dialysate iron replacement
  – Ferric pyrophosphate citrate

• Oral iron replacement
  – Ferric citrate

• Oral hypoxia inducible factor modulators
  – HIF-PHIs
Dialysate iron therapy: Infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis

AJAY GUPTA, NEETA B. AMIN, ANATOLE BESARAB, SUSAN E. VOGEL, GEORGE W. DIVINE, JERRY YEE, AND J. V. ANANDAN

Division of Nephrology, Department of Pharmacy Services, and Department of Biostatistics, Henry Ford Hospital, Detroit, Michigan, USA

Dialysate iron therapy: Infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis.

Background. Soluble iron salts are toxic for parenteral administration because free iron catalyzes free radical generation. Pyrophosphate strongly complexes iron and enhances iron transport between transferrin, ferritin, and tissues. Hemodialysis patients need iron to replenish ongoing losses. We evaluated the short-term safety and efficacy of infusing soluble ferric pyrophosphate by dialysate.

Methods. Maintenance hemodialysis patients receiving erythropoietin were stabilized on regular doses of intravenous (i.v.) iron dextran after oral iron supplements were discontinued. During the treatment phase, 10 patients received ferric pyrophosphate via hemodialysis as monthly dialysate iron concentrations were progressively increased from 2, 4, 8, to 12 μg/dl and were then sustained for two additional months at 12 μg/dl (dialysate iron group); 11 control patients were continued on i.v. iron dextran (i.v. iron group).

with prematurity and low birth weight during pregnancy, defects in cognitive and psychomotor development during childhood, and impaired work capacity in adulthood [3–8]. Oral iron supplementation programs have failed primarily because of noncompliance in addition to gastrointestinal adverse effects [9]. As an adjunct or alternative to the oral route, iron has been administered parenterally for more than 100 years [10]. Soluble iron compounds are considered too toxic for parenteral administration, as ionization of soluble iron salts liberates free iron, which catalyzes free radical formation and lipid peroxidation [11, 12]. The colloidal iron compounds used for parenteral administration such as iron dextran, saccharate, or gluconate are also associated with serious side-effects, including hypotension and anaphylactoid re-
Ferric Pyrophosphate Citrate (FPC)

- Iron-citrate-pyrophosphate complex
- Soluble, non-colloidal iron salt, not conjugated with a sugar moiety
- MW ~1313 Da, similar to vitamin B12
- Added to bicarbonate concentrate
- Crosses the dialyzer membrane during the HD and donates iron directly to transferrin, largely bypassing the RES
- Replaces the 5 ~ 7 mg of iron that is lost during HD treatment by trapping of blood in dialysis circuit, bleeding and blood draws
- Dialysate iron concentration of 2 μM (110 μg/L) maintains iron balance without overloading iron stores
- Indicated for iron replacement and Hb maintenance in adult CKD patients on HD (FDA approval in Jan 23, 2015)
Physiological Replenishment Iron Maintenance Equivalency (PRIME) study
- Prospective, randomized, placebo-controlled, double-blind trial
- Study duration: 9 mo  N= 108

Physiological Replenishment Iron Maintenance Equivalency (PRIME) study
- Prospective, randomized, placebo-controlled, double-blind trial (9m, N=108)

48% reduction in IV iron requirement

TRIFERIC does NOT increase iron stores
Safety & Efficacy of TRIFERIC: CRUISE 1 & CRUISE 2

Ferric pyrophosphate citrate (Triferic™) administration via the dialysate maintains hemoglobin and iron balance in chronic hemodialysis patients

Steven N. Fishbane¹,*, Ajay K. Singh²,*, Serge H. Cournoyer³, Kailash K. Jindal⁴, Paolo Fanti⁵, Carrie D. Guss⁶, Vivian H. Lin⁶, Raymond D. Pratt⁶ and Ajay Gupta⁶,⁷

Phase 3, placebo-controlled RCT (N= 599 iron-replete chronic HD patients, 48wk). Regular administration of FPC during HD by addition to the dialysate is well tolerated and effectively replaces ongoing dialytic and uremic iron losses, thereby maintaining iron balance and Hb concentration.
## Iron-based phosphate binders

**Table 1. Main characteristic of iron-based intestinal phosphate binders**

<table>
<thead>
<tr>
<th>Name</th>
<th>Composition</th>
<th>Recommended daily dose</th>
<th>Mean daily number of pills</th>
<th>Main side effects</th>
<th>Pros/Cons</th>
<th>Pharmaceutical company</th>
</tr>
</thead>
<tbody>
<tr>
<td>VELPHORO PA21</td>
<td>Sucroferric oxyhydroxide</td>
<td>1500 mg</td>
<td>Three pills per day</td>
<td>Discolored feces diarrhea, nausea</td>
<td>Iron not absorbed</td>
<td>Vifor (Fresenius)</td>
</tr>
<tr>
<td>ZERENEX JTT-751</td>
<td>Ferric citrate coordination complex</td>
<td>6000 mg</td>
<td>Six pills per day</td>
<td>Discolored feces diarrhea, nausea</td>
<td>Iron absorbed risk Al absorpt higher ferritin</td>
<td>Keryx Bio-pharmaceuticals</td>
</tr>
<tr>
<td>ALPHAREN Fermagate SBR-759 PT20</td>
<td>Iron-magnesium hydroxycarbonate Polymeric iron (III) Ferric oxide adipate</td>
<td>3000 mg</td>
<td>Three pills per day</td>
<td>Discolored feces gastrointestinal</td>
<td>Elevation in serum Mg levels</td>
<td>Shire Novartis Phosphate therapeutics</td>
</tr>
</tbody>
</table>
Ferric citrate (JTT-751, KRX-0502) - Auryxia, Fexeric, Nephoxil -

- Ferric citrate, ferric ammonium citrate, ferric chloride all lower serum Pi
- However, in terms of safety, Ferric Citrate shows balance of safety & efficacy


The ferric iron component of AURYXIA binds with dietary phosphate in the GI tract and precipitates as ferric phosphate.

This compound is insoluble, and is excreted in the stool.

Additionally, AURYXIA has been shown to increase serum iron parameters through systemic absorption, which is managed by the body’s GI regulatory mechanisms.
Ferric Citrate Controls Phosphorus and Delivers Iron in Patients on Dialysis

Safety Assessment Period

- Ferric Citrate
  - n = 292

Washout (2 weeks)

Active Control
  - Sevelamer and/or calcium
  - n = 149

Efficacy Assessment Period

- Ferric Citrate
  - n = 96
- Placebo
  - n = 96

Open Label Ext

Secondary endpoints:
- Mean change in serum ferritin
- Mean change in TSAT
- Cumulative iron use
- Cumulative ESA use
- Mean change in Hb

Primary efficacy:
- Mean change in serum phosphorus

Up to 2 y
Figure 3. Iron parameters by study time point during the 52-week active control period. (A) Serum ferritin and (B) serum TSAT, with missing values imputed using the last follow-up observation carried forward. Box plots display 5th, 25th, 50th, 75th, and 95th percentiles. AC, active control; FC, ferric citrate.
Subjects on FC needed less iv iron compared with subjects on AC over 52 weeks (median [interquartile range] dose=12.9 [1.0–28.9] vs. 26.8 [13.4–47.6] mg/wk; P<0.001), and the % of subjects NOT requiring iv iron was higher with FC (P<0.001). Cumulative ESA over 52 weeks was lower with FC than AC dose=5303 [2023–9695] vs. 6954 [2664–12,375] units/wk; P=0.04.
Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients

Anatole Besarab¹, Robert Provenzano², Joachim Hertel³, Raja Zabaneh⁴, Stephen J. Klaus¹, Tyson Lee¹, Robert Leong¹, Stefan Hemmerich¹, Kin-Hung Peony Yu¹ and Thomas B. Neff¹

Data are for the EE population. BIW and TIW placebo groups and all roxadustat treatment groups were combined. P-values are from intergroup two-sample t-tests comparing roxadustat change from BL with placebo change from BL. EOT was Day 29 (BIW) or Day 26 (TIW).

Change from BL in mean serum iron, TIBC, ferritin, TSAT & serum hepcidin levels
Roxadustat (FG-4592): Correction of Anemia in Incident Dialysis Patients


Anatole Besarab,* Elena Chernyavskaya,† Igor Motylev,‡ Evgeny Shutow,§ Lalathaksha M. Kumbar,‖ Konstantin Gurevich,¶ Daniel Tak Mao Chan,** Robert Leong,* Lona Poole,* Ming Zhong,* Khalil G. Saikali,* Marietta Franco,* Stefan Hemmerich,* Kin-Hung Peony Yu,* and Thomas B. Neff*

N=60, incident HD or PD with Hb <10.0 g/dL + roxadustat x 12weeks

Evaluate effect of therapy on hepcidin level

Table 3. Hepcidin levels and changes from baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>HD, No Iron (n=22)</th>
<th>HD and PD, Oral Iron (n=21)</th>
<th>HD, IV Iron (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OV (ng/ml)</td>
<td>84.1±13.7</td>
<td>107.4±27.1</td>
<td>85.6±24.4</td>
</tr>
<tr>
<td>4 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OV (ng/ml)</td>
<td>16.4±3.2</td>
<td>51.1±14.3</td>
<td>50.9±15.6</td>
</tr>
<tr>
<td>Δ (ng/ml)</td>
<td>-67.7±12.0</td>
<td>-56.3±19.2</td>
<td>-34.7±12.6</td>
</tr>
<tr>
<td>P value*</td>
<td>&lt;0.0001</td>
<td>0.0082</td>
<td>0.0252</td>
</tr>
<tr>
<td>12 wk (end of treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OV (ng/ml)</td>
<td>20.7±6.9</td>
<td>59.2±14.2</td>
<td>73.0±25.9</td>
</tr>
<tr>
<td>Δ (ng/ml)</td>
<td>-63.4±13.3</td>
<td>-48.2±18.2</td>
<td>-12.6±31.6</td>
</tr>
<tr>
<td>P value*</td>
<td>&lt;0.0001</td>
<td>0.0156</td>
<td>NS</td>
</tr>
<tr>
<td>End of study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OV (ng/ml)</td>
<td>46.0±6.6</td>
<td>136.9±27.7</td>
<td>183.4±45.2</td>
</tr>
<tr>
<td>Δ (ng/ml)</td>
<td>-38.2±13.7</td>
<td>29.6±21.7</td>
<td>97.8±26.5</td>
</tr>
<tr>
<td>P value*</td>
<td>0.0112</td>
<td>NS</td>
<td>0.0061</td>
</tr>
</tbody>
</table>

The lesser hepcidin reduction in the IV iron cohort at end of treatment, as well as the large post-treatment increase (by end of study), is likely attributable to competing feedback loops by higher circulating iron levels.
Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHI)

- Coordinately regulates transcription of EPO gene, mobilization of iron and overcomes suppression of anti-erythropoietic cytokine effects
  - Improves iron absorption, transport, and bioavailability for heme synthesis, including reducing the expression of hepcidin to relieve block on iron bioavailability
  - Increases endogenous EPO and enhances sensitivity to EPO
  - Overcomes suppression of EPO production by TNFalpha & IL-6
- Stimulate erythropoiesis at MUCH lower peak EPO levels
- Corrects anemia in Dialysis and NDD-CKD
- Concerns: several hundred genes are HIF dependent
Summary (2)

• **Ferric pyrophosphate citrate**, iron that is delivered by dialysate, has been shown to be highly effective in maintaining TSAT and reducing IV iron and ESA dose.

• The **iron-based phosphate binder (ferric citrate)** has been shown to be highly effective in increasing serum ferritin, TSAT, and Hb values and significantly reduce IV iron & ESA requirements.

• **HIF stabilizers** suppress hepcidin and effectively promote iron bioavailability
Conclusions

• There continue to be new developments in the field of nephrology & in the understanding of iron deficiency anemia.

• Several new treatment options are emerging that can potentially help optimize management of IDA in CKD.
Thank you!