Where are we now in managing anaemia in patients with ND-CKD?
A Peptidomimetic Agonist of the EP2 Receptor

Iain C. Macdonald, M.D., Ph.D.
Erik K. Heren, M.D.
Richard B. Stein, M.D.

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

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KONSENSUSPAPIER
Eisen-Management bei Patienten mit chronischer Niereninsuffizienz


PRÄVALENZ UND URSACHEN DER RENALEN ANÄMIE

Transferinsättigung [TSAT] <20%), Vitamin- und Folsäuremangel, Blutverluste, Inflammation, Infektionen, Malignome oder Medikamente, die die Erythropoiese negativ beeinflussen können, von Bedeutung.

RISIKOFAKTOR EISENMANGEL
Iron management in predialysis (CKD stage 3–4)

Hb <11 g/dL

Iron diagnostics

Ferritin <100 ng/mL and TSAT <20%
orHYPO >10%orCHr <29 pg

CRP normal

Hb 10–11 g/dL

CRP elevated

Incompatibility
Lack of efficacy
Non-compliance

Hb <10 g/dL

Intravenous iron

Calculation of iron requirement using Ganzoni’s formula:
Total iron deficit (mg) = [target Hb – actual Hb (g/dL)] × body weight (kg) × 2.4 + 500 mg (depot iron)

Modified from Schaefer RM et al. NephroNews 8/2009
Disclosures

• Prof. Wanner has received consultancy fees and speaker’s honoraria from Vifor Pharma Ltd and a research grant from Amgen
Disclosures

• Dr Macdougall has received consultancy fees and speaker’s honoraria from Vifor Pharma Ltd and consultancy fees, speaker’s honoraria and research grants from Affymax, Amgen, Ortho Biotech, Roche and Shire Pharmaceuticals
Programme

Iron and anaemia management in ND-CKD: where are we going?

Co-chairs: Christoph Wanner (Würzburg, Germany) and Iain Macdougall (London, UK)

Introduction

Anaemia management in ND-CKD: where are we?
Bernard Canaud (Montpellier, France)

Iron metabolism: where is the science taking us?
Iain Macdougall (London, UK)

Optimizing anaemia management: which is the right path?
Simon Roger (Gosford, Australia)

Discussion
Iron and anaemia management in ND-CKD: where are we going?

XLVII ERA-EDTA Congress
Munich, Germany
26 June 2010
Anaemia management in non-dialysis CKD: where are we?

Bernard Canaud, MD, PhD
Nephrology, Dialysis and Intensive Care Unit, Lapeyronie University Hospital, Montpellier, France
Disclosures

- Professor Canaud has received speaker’s honoraria and/or research grants from Amgen, Baxter, Fresenius Medical Care and Roche
Anaemia is a frequent and severe comorbid complication that starts early in chronic kidney disease (CKD).

Anaemia is not correlated with circulating erythropoietin (EPO) but is aggravated by iron deficiency.

Optimal haemoglobin (Hb) and iron indices targets are still under debate in CKD.

Intravenous (i.v.) iron is effective and well-tolerated in patients with non-dialysis CKD.

Correction of anaemia and iron deficiency is a part of renal protective action and decreased morbidity in patients with CKD.

Early correction of anaemia is appropriate in patients with non-dialysis CKD.
Roadmap of presentation

- Anaemia is a frequent and severe comorbid complication that starts early in chronic kidney disease (CKD)
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- Early correction of anaemia is appropriate in patients with non-dialysis CKD
Natural history of CKD

**Clinical symptoms**
- Asthenia
- Nausea, vomiting, anorexia, weight loss, pruritus, insomnia, restless legs syndrome, cramps...

**Laboratory abnormalities**
- Oedema, dyspnoea...
- Urea, creat., uric acid
- HCO₃, K...
- Ca, PO₄, FGF23, 25(OH)D₃, PTH, CRP, lipids...
- Hb
- Iron

**GFR (mL/min/1.73 m²)**
- 120
- 90
- 60
- 30
- 15

**Stages of CKD**
- 1
- 2
- 3a
- 3b
- 4
- 5

Creat., creatinine; CRP, C-reactive protein; FGF, fibroblast growth factor; GFR, glomerular filtration rate; PTH, parathyroid hormone.
Prevalence of CKD in the US general population

NHANES III 1988–1994
NHANES 2-yr datasets from 1999-2004
n=62437

Creatinine clearance (mL/min)

- 0–14.9, 0.2%
- 15–29.9, 0.8%
- 30–59.9, 9.9%
- 60–90, 20.7%
- >90, 68.4%
Anaemia starts earlier in patients with diabetes

Males

GFR (mL/min/1.73 m²)

Females

GFR (mL/min/1.73 m²)

NHANES, National Health and Nutrition Examination Survey
DM, diabetes mellitus; MDRD, Modification of Diet in Renal Disease

Thomas MC et al. Diabetes Care 2003;26:1164–9
Prevalence of anaemia in CKD increases sharply after stage 4 (GFR <30 mL/min/1.73 m^2) in KEEP study

![Graph showing the prevalence of anaemia in CKD stages](image-url)

KW/DOQI, Kidney Disease Outcomes Quality Initiative; WHO, World Health Organization

Prevalence of 25(OH)D₃ deficiency, inflammation and anaemia is associated with CKD progression


NHANES III 1988–1994

NHANES, National Health and Nutritional Examination Survey
Anaemia amplifies CKD disease complications

- CKD
- ↓EPO
- ↓Iron
- Anaemia
- Functional symptom
- Comorbid factor
- Tissue damage
Roadmap of presentation

- Anaemia is a frequent and severe comorbid complication that starts early in chronic kidney disease (CKD).
- Anaemia is not correlated with circulating erythropoietin (EPO) but is aggravated by iron deficiency.
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- Intravenous (i.v.) iron is effective and well-tolerated in patients with non-dialysis CKD.
- Correction of anaemia and iron deficiency is a part of renal protective action and decreased morbidity in patients with CKD.
- Early correction of anaemia is appropriate in patients with non-dialysis CKD.
Hb concentrations are not linearly correlated to EPO levels in patients with CKD stages 1–3

Swiss cohort
1490 patients with CKD

Hb concentrations are not linearly correlated to EPO levels in patients with CKD stages 4–5

Swiss cohort
1490 patients with CKD

Prevalence of absolute iron deficiency increases with CKD progression

NHANES III 1988–1994
NHANES 2-yr datasets from 1999-2004
n=62437
Iron deficiency: Men: 57.8–58.8%; Women: 69.9–72.8%

Roadmap of presentation

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Toward universal recommendations: EBPG 2004–2007, ERBP 2009...
Hb target recommendations have changed over the past few years

**EBPG 2004**
- \( \geq 11.0 \text{ g/dL (Ht } > 33\%\) }\) with personal adaptation
- \( >12 \text{ g/dL} \) not recommended with diabetes or heart failure
- \( >14 \text{ g/dL} \) ‘undesirable’ in HD

**ERBP 2009**
- \( \leq 11.0 \text{ and } <13 \text{ g/dL (not intentionally } >13 \text{ g/dL)}\)

**NKF-K/DOQI 2001**
- 11–12 g/dL

**NKF-K/DOQI 2006**
- \( \leq 11.0 \text{ and } >13 \text{ g/dL} \) not recommended

**NKF-K/DOQI 2007**
- \( \leq 11.0 \text{ and } <13 \text{ g/dL} \)

**NKF-K/DOQI 2009**
- \( \leq 10.5 \text{ and } <12 \text{ g/dL} \)

EBPG, European Best Practice Guidelines; ERBP, European Renal Best Practice; HD, haemodialysis; Ht, haematocrit; NKF, National Kidney Federation
Normalization of Hb may be easily achieved in non-dialysis CKD management with ESA and iron

CREATE study
Randomized controlled trial (RCT), CKD3–5, 1/1 ESA conv/norm

Normalization of anaemia in CKD has a positive impact on quality of life (all components)

CREATE study  RCT, CKD3–5, 1/1 ESA conv/norm

But, normalization of anaemia in CKD has no significant impact on survival and CV events

CREATE study  RCT, CKD3–5, 1/1 ESA conv/norm
TREAT Study: Hb response to ESA

Mean Hb (g/dL) over time for Darbepoetin alfa (176 µg) and Placebo.

No. of patients

<table>
<thead>
<tr>
<th>Months after randomization</th>
<th>Darbepoetin alfa</th>
<th>Placebo</th>
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<tr>
<td>0</td>
<td>2004</td>
<td>2019</td>
</tr>
<tr>
<td>6</td>
<td>1768</td>
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<td>12</td>
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<tr>
<td>48</td>
<td>97</td>
<td>79</td>
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</table>

Complete correction of anaemia does not improve CV mortality in patients with CKD and diabetes

CV composite endpoint

Hazard ratio, 1.05 (95% CI, 0.94-1.17)
P=0.41

No. at risk

No. at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Months</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
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<td>Darbepoetin alfa</td>
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<td>1882</td>
<td>1717</td>
<td>1515</td>
<td>1180</td>
<td>817</td>
<td>551</td>
<td>318</td>
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<tr>
<td>Placebo</td>
<td>2026</td>
<td>1836</td>
<td>1687</td>
<td>1487</td>
<td>1178</td>
<td>834</td>
<td>529</td>
<td>319</td>
<td>122</td>
<td></td>
</tr>
</tbody>
</table>
Complete correction of anaemia does not delay ESRD in patients with CKD and diabetes

Anaemia is a frequent and severe comorbid complication that starts early in chronic kidney disease (CKD).

Anaemia is not correlated with circulating erythropoietin (EPO) but is aggravated by iron deficiency.

Optimal haemoglobin (Hb) and iron indices targets are still under debate in CKD.

Intravenous (i.v.) iron is effective and well-tolerated in patients with non-dialysis CKD.

Correction of anaemia and iron deficiency is a part of renal protective action and decreased morbidity in patients with CKD.

Early correction of anaemia is appropriate in patients with non-dialysis CKD.
Efficacy of i.v. ferric carboxymaltose vs oral iron in patients non-dialysis CKD and diabetes

Randomized, multicentre, open-label study

**Patients**

Non-dialysis CKD  
- n=245*  
- GFR ≤45 mL/min/1.73 m²  
- Hb ≤11 g/dL  
- Serum ferritin <300 μg/L  
- TSAT <25%

**Intravenous iron**

- Ferric carboxymaltose  
  - Maximum 1000 mg iron over 15 minutes with up to two additional 500 mg iron doses, as determined by iron indices  
  - n=144*

**Oral iron**

- Ferrous sulphate  
  - 325 mg (65 mg iron) t.i.d.  
  - 56 days  
  - n=101*

* Modified intent-to-treat population

Benjamin J. World Congress of Nephrology 2009, Abstract M574
Efficacy is greater with of i.v. ferric carboxymaltose vs oral iron

- Patients achieving Hb increase ≥1 g/dL at any time during the study (%); 56 days duration

\[ \text{Intravenous ferric carboxymaltose (n=144*)} \]
\[ \text{Oral iron (n=101*)} \]

\[ 60.4 \]
\[ 34.7 \]

\[ p<0.001 \]

* Modified intent-to-treat population
Efficacy and tolerability profile of i.v. ferric carboxymaltose vs oral iron

<table>
<thead>
<tr>
<th></th>
<th>Intravenous ferric carboxymaltose (n=147)*</th>
<th>Oral iron (n=103)*</th>
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</thead>
<tbody>
<tr>
<td>Hb increase &gt;1g/dL</td>
<td>60.4%</td>
<td>34.7%</td>
</tr>
<tr>
<td>Mean change to highest Hb</td>
<td>1.3 g/dL</td>
<td>0.8 g/dL</td>
</tr>
<tr>
<td>Mean increase in Hb by day 42</td>
<td>1.0 g/dL</td>
<td>0.5 g/dL</td>
</tr>
<tr>
<td>Incidence of adverse events</td>
<td>2.7%</td>
<td>26.2%</td>
</tr>
<tr>
<td>Serious adverse events or hypotensive episodes</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Safety population

Benjamin J. World Congress of Nephrology 2009, Abstract M574
Overview of results: Benjamin et al., 2009

- I.V. ferric carboxymaltose showed significantly greater efficacy compared with oral iron in patients with non-dialysis CKD with anaemia and low iron indices
  - A significantly greater proportion of patients achieved an Hb increase >1 g/dL (60.4% vs 34.7%, p<0.001)

- There was a markedly lower incidence of adverse events with i.v. ferric carboxymaltose vs oral iron (2.7% vs 26.2%)
  - No serious adverse events or hypotensive episodes occurred
Single-dose i.v. iron in non-dialysis CKD

Single-arm, single-centre study

Patients
- Non-dialysis CKD
- Hb <11g/dL
- Serum ferritin <300 μg/L
- No ESA or stable ESA dose ≥3 months prior to study entry

Intravenous iron
- Ferric carboxymaltose
- 800 mg iron over 15 minutes
- n=30

1 month post-treatment indices measured

5 ESA
25 no ESA

Single-dose i.v. iron is effective in patients with non-dialysis CKD

Patients meeting Hb targets (%)

- Hb >10.5 g/dL: 35.7%
- Hb >11 g/dL: 21.4%

Patients meeting iron indices targets (%)

- Ferritin ≥200 μg/L: 17.9%
- TSAT ≥20%: 28.6%

Pre-treatment (n=30)

1 month post-treatment (n=30)

Overview of results: Tagboto et al., 2009

- One month after a single 15-minute infusion of 800 mg iron as ferric carboxymaltose (25/30 patients did not receive ESA):
  - Hb levels increased in 80% of patients, did not change in 3% and fell slightly in 17%
  - The mean Hb level increased by 0.73 g/dL (0.53 g/dL after 2 weeks)
  - Only two patients reported minor side-effects (metallic taste in the mouth and discomfort at the infusion site)
- Authors’ conclusion: “Intravenous ferric carboxymaltose administration in predialysis patients rapidly improves Hb levels in the majority of patients after 2 weeks with a further small increase at 1 month”
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- Correction of anaemia and iron deficiency is a part of renal protective action and decreased morbidity in patients with CKD
- Early correction of anaemia is appropriate in patients with non-dialysis CKD
Anaemia correction with epoetin beta does not precipitate CKD progression

CREATE study  RCT, CKD3–5, 1/1 ESA conv/norm

Impact of i.v. FCM on renal function
Categorized by change in mL/min/1.73 m² at week 24

- 35% of FCM patients experienced >5 mL/min/1.73 m² change vs 25% for placebo

Change in eGFR from baseline (mL/min/1.73 m²)

Ponikowski P et al. HFA Congress 2010; Abstract 114 & LBT Oral Presentation
Anaemia increases the risk of hospitalization in paediatric patients with CKD

n=2779 paediatric patients with CKD
Prospective database registry

Anaemia increases consumption of health care resources (physician visits) in patients with CKD

Yearly physician visits

NHANES III 1988–1994

NHANES, National Health and Nutritional Examination Survey

Anaemia increases consumption of health care resources (hospitalization) in patients with CKD

Yearly hospitalization

**NHANES III 1988–1994**

NHANES, National Health and Nutritional Examination Survey

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Early correction of anaemia is appropriate in patients with non-dialysis CKD
Management of patients with non-dialysis CKD usually consists of nephroprotection

Diet, proteins, $\text{Na}^+$, $\text{HCO}_3^-$, exercise, stop smoking...

Anti-hypertensive agents: ACE-I, A2R-A, BB, diuretics...

Lipid-lowering agents, antiplatelet agents, antioxidants...

ACE-I, angiotensin converting enzyme inhibitor; A2RA, angiotensin 2 receptor antagonist; BB, beta-blocker
Today, optimal care of patients with non-dialysis CKD should correct anaemia and iron deficiency.

![Graph showing GFR and Hb levels across CKD stages.]

- **GFR (mL/min/1.73 m²)**
  - Stage 1: 120
  - Stage 2: 90
  - Stage 3: 60
  - Stage 4: 30
  - Stage 5: 15

- **Hb (g/dL)**
  - Stage 1: 14
  - Stage 2: 12
  - Stage 3: 10
  - Stage 4: 8
  - Stage 5: 6

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I.v. iron + ESA...
Iron metabolism: where is the science taking us?

Dr Iain C. Macdougall, MD
King’s College Hospital, London
UK
Disclosures

- Dr Macdougall has received consultancy fees and speaker’s honoraria from Vifor Pharma Ltd and consultancy fees, speaker’s honoraria and research grants from Affymax, Amgen, Ortho Biotech, and Roche
Questions regarding iron metabolism in chronic kidney disease (CKD)

- Why are patients with CKD prone to developing iron deficiency?
- How can we best detect iron deficiency?
- How can we best treat iron deficiency?
Why are patients with CKD prone to developing iron deficiency?

**Reduced intake**
- Poor appetite
- Poor gastrointestinal (GI) absorption
- Concurrent medication (e.g., omeprazole)
- Food interactions

**Increased losses**
- Occult GI losses
- Peptic ulceration
- Blood sampling
- Dialyser losses
- Concurrent medication (e.g., aspirin)
- Heparin on dialysis

**Increased iron needs during ESA therapy**

**ESA**, erythropoiesis-stimulating agent
Why are patients with CKD prone to developing iron deficiency? 

*Where is the science taking us?*
Questions regarding iron metabolism in CKD

- Why are patients with CKD prone to developing iron deficiency?
- How can we best detect iron deficiency?
- How can we best treat iron deficiency?
Iron metabolism

CHr, reticulocyte haemoglobin; RBC, red blood cell; TfR, transferrin receptor; TIBC, total iron-binding capacity; TSAT, transferrin saturation; ZPP, zinc protoporphyrin
Monitoring iron status

How best to detect iron deficiency?
Where is the science taking us?
Measure levels of hepcidin?
Questions regarding iron metabolism in CKD

- Why are patients with CKD prone to developing iron deficiency?

- How can we best detect iron deficiency?

- How can we best treat iron deficiency?
Iron therapy

- **Oral**
- **Intravenous (i.v.)**
Oral iron

- Simple
- Cheap
  (a few pence/cents per week)
GI side-effects

- Healthy, pregnant patients (100 mg Fe/day)\(^1\): dyspepsia 10%, constipation 5%, diarrhoea 3%

- CKD stage 3–4 (325 mg FeSO\(_4\) t.i.d.)\(^2\): constipation 35%, nausea 13%, vomiting 8%, diarrhoea 6%

Oral iron and oxidative stress

Iron supplements

Colonic mucosa

Iron supplements

Fe^{2+}

Fenton reaction

OH\cdot

H_2O_2

OH^{-}

OH\cdot

OH^{-}

OH\cdot

OH\cdot

OH^{-}

Colonic mucosa

Gasche C et al. UNI-MED Verlag, 2008
Iron therapy

- Oral
- Intravenous
Absorption of iron is poor in CKD

Haemoglobin (Hb) response to i.v., oral and no Fe supplementation

* p<0.05 vs i.v.; † p<0.005 vs i.v.

Intravenous iron compounds

<table>
<thead>
<tr>
<th></th>
<th>High MW Iron Dextran</th>
<th>Low MW Iron Dextran</th>
<th>Iron Gluconate</th>
<th>Iron Sucrose</th>
<th>Ferric Carboxy-maltose&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td><strong>Trade names</strong>&lt;sup&gt;b&lt;/sup&gt; (US, Europe)</td>
<td>Dexferrum</td>
<td>Infed, Cosmofer Pharmacosmos</td>
<td>Ferrlecit</td>
<td>Venofer</td>
<td>Injectafer, Ferinject</td>
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<td><strong>Manufacturer</strong></td>
<td>Luitpold Pharmaceuticals</td>
<td>Sanofi-Aventis</td>
<td>Vifor Int.</td>
<td>Vifor Int.</td>
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<td><strong>Chemical properties</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
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<td></td>
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<tr>
<td>MW [kD]</td>
<td>265</td>
<td>165</td>
<td>&lt; 50</td>
<td>30–100</td>
<td>&gt; 100</td>
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<tr>
<td>Complex stability</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Acute toxicity</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
</tr>
</tbody>
</table>

MW, molecular weight.


<sup>b</sup> Prescribing information of marketed products.

<sup>c</sup> According to Crichton RR et al, Bremen: UNI-MED; 2005.
Benefits of i.v. iron in patients with CKD

- Intravenous iron can improve anaemia in patients with CKD, even in the absence of ESA therapy.
- Intravenous iron can significantly enhance the response to ESA therapy, even in iron-replete patients.

Tolerability of i.v. iron?

**Short-term**

- Anaphylactic reactions (iron dextran only; dextran antibodies)
- ‘Free iron’ reactions (all i.v. iron preparations)

**Long-term**

- Increased susceptibility to infection
- Increased oxidative stress
- Iron overload
Questions regarding iron metabolism in CKD

How best to treat iron deficiency?

Where is the science taking us?
Hepcidin as a target for CKD anaemia management
Hepcidin

- What is it?
- What does it do?
- How can we measure it?
- Implications for the nephrologist
What is hepcidin?

- Hepatic antimicrobial peptide
- Found incidentally by a French medical student
- **HAMP** gene
  - Pre-hormone: 84 amino acids
  - Active peptide: 25 amino acids
- Excreted by the kidney
Hepcidin

- What is it?
- What does it do?
- How can we measure it?
- Implications for the nephrologist
Hepcidin is the iron-regulatory hormone


Park et al.: JBC 276: 7806-7810, 2001
Hunter et al.: JBC 277:37597-603, 2002
Hepcidin regulates iron flow into plasma
Iron transport

- **Fe$^{3+}$**
  - Dcytb
- Transferrin
- Fe$^{2+}$
- Haemoglobin/haptoglobin
- TFR 1
- TFR 2
- Cubilin
- DMT1
- CD 163
- Endosome
  - DMT1
- Ferritin: storage, detoxification
- Ferroportin
- Fe$^{2+}$
- Caeruloplasmin
- Hephaestin
- Transferrin

Other iron utilization pathways
- Fe-S cluster biogenesis
- Heme synthesis
- Mitochondria

Dcytb, duodenal cytochrome B; DMT1, divalent metal transporter 1
Low hepcidin

Iron uptake

- ferritin

Low hepcidin

Iron release into plasma

High hepcidin

Iron uptake

- ferritin

- Iron-exporting cells (duodenal enterocytes, macrophages, hepatocytes)

- Fpn

- hepcidin

Fpn, ferroportin
Regulation of hepcidin by inflammation
Hepcidin

- What is it?
- What does it do?
- How can we measure it?
- Implications for the nephrologist
Measurement of hepcidin

- Radioimmunoassay (RIA)
- Enzyme-linked immunosorbent assay (ELISA)
- Ligand-binding assay
- Mass spectrometry (MS)
  - Surface-enhanced laser desorption (SELDI)/matrix-assisted laser desorption ionization (MALDI)
  - Liquid chromatography tandem MS

Blood hepcidin assays used to measure levels in CKD patients

Mean values (ng/mL)

RIAs:
- RIA 1: Ashby et al. 2009
- RIA 2: Busbridge et al. 2009

ELISAs:

 MALDI-TOF:
- Peters et al. 2009

SELDI-TOFs:
- SELDI-TOF 1: Tomosugi et al. 2006
- SELDI-TOF 2: Kato et al. 2008
- SELDI-TOF 3: Valenti et al. 2009

HD, haemodialysis; TOF, time of flight

Hepcidin

- What is it?
- What does it do?
- How can we measure it?

- Implications for the nephrologist
Hepcidin – implications for the nephrologist

- Hepcidin is the reason patients with CKD (particularly those undergoing HD) do not absorb oral iron from the GI tract.
- It is the pivotal mediator of functional iron deficiency in inflammatory states.
- It may be a key factor in the pathogenesis of erythropoietin resistance in infectious and inflammatory states.
- Once assays are optimized, measurement of hepcidin may replace measurement of ferritin, iron, TIBC and hypochromic red cells.
Hepcidin – implications for the nephrologist

- Hepcidin may be a potential target for future anaemia therapies

Antihepcidin antibody treatment modulates iron metabolism and is effective in a mouse model of inflammation-induced anemia

Barbra J. Sasu,¹ Keegan S. Cooke,¹ Tara L. Arvedson,¹ Cherylene Plewa,² Aaron R. Ellison,² Jackie Sheng,² Aaron Winters,² Todd Juan,² Hongyan Li,³ C. Glenn Begley,¹ and Graham Molineux¹

Departments of ¹Hematology/Oncology, ²Protein Sciences, and ³Pharmacokinetics and Drug Metabolism, Amgen Inc, Thousand Oaks, CA

Iron maldistribution has been implicated in multiple diseases, including the anemia of inflammation (AI), atherosclerosis, diabetes, and neurodegenerative disorders. Iron metabolism is controlled by hepcidin, a 25-amino acid peptide. Hepcidin is induced by inflammation, causes iron to be sequestered, and thus, potentially contributes to AI. Human hepcidin (hHepc) overexpression in mice caused an iron-deficient phenotype, including stunted growth, hair loss, and iron-deficient erythropoiesis. It also caused resistance to supraphysiologic levels of erythropoiesis-stimulating agent, supporting the hypothesis that hepcidin may influence response to treatment in AI. To explore the role of hepcidin in inflammatory anemia, a mouse AI model was developed with heat-killed Brucella abortus treatment. Suppression of hepcidin mRNA was a successful anemia treatment in this model. High-affinity antibodies specific for hHepc were generated, and hHepc knock-in mice were produced to enable antibody testing. Antibody treatment neutralized hHepc in vitro and in vivo and facilitated anemia treatment in hHepc knock-in mice with AI. These data indicate that antihepcidin antibodies may be an effective treatment for patients with inflammatory anemia. The ability to manipulate iron metabolism in vivo may also allow investigation of the role of iron in a number of other pathologic conditions. (Blood. 2010;115(17):3616-3624)
MAb against hepcidin was effective in a mouse model of inflammation-induced anaemia

- Suppression of hepcidin mRNA improved anaemia in a mouse model of inflammation
- High-affinity Ab treatment neutralized hHepc and increased haemoglobin levels in hHepc knock-out mice
- Anti-hepcidin Abs may be an effective treatment for inflammatory anaemia
- Manipulation of iron metabolism *in vivo* may allow investigation of the role of iron in other conditions

Ab, antibody; hHepc, human hepcidin; MAb, monoclonal antibody

MAb against hepcidin was effective in combination therapy for anaemia of inflammation

Ab 2.7 restored response to ESA treatment in hHepc knock-in anaemia of inflammation mice

Administration time of *Brucella abortus*, anti-hepcidin (or control) Ab, and ESA or saline control
Conclusions

- Patients with CKD are at an increased risk of developing iron deficiency
- Several diagnostic markers are available to monitor iron status – all have limitations
- Intravenous iron is beneficial in patients with non-dialysis CKD, even in the absence of ESA therapy
  - Newer formulations may overcome the limitations of older i.v. preparations
- Hepcidin is a key regulator of iron availability
  - It is a potential future therapeutic target for managing anaemia in CKD
Optimizing anaemia management: which is the right path?

Dr Simon D. Roger, MD, FRACP
Gosford Hospital
Australia
Disclosures

• Dr Roger has served on advisory boards/speaker bureaux for Amgen, Hoffman-La Roche, Janssen-Cilag, Sandoz and Vifor Pharma Ltd

• In addition, he has undertaken clinical trials in anaemia/iron management for Takeda and the above companies
What is wrong with anaemia management in 2010?

- Is it the wrong target haemoglobin (Hb)?
- Is it the wrong target Hb for the wrong patient?
- Is it too much erythropoiesis-stimulating agent (ESA)?
- Is it underlying illness, compounded by high ESA dosages?
- Should iron be the starting point in anaemia management?
- Should there be a target Hb when considering iron repletion in patients with non-dialysis chronic kidney disease (ND-CKD)?
Is it the wrong target Hb for the wrong patient?

- Young vs elderly
Is it the wrong target Hb for the wrong patient?

- Young vs elderly
- ‘Better’ cardiac function vs heart failure
Is it the wrong target Hb for the wrong patient?

- Young vs elderly
- ‘Better’ cardiac function vs heart failure
- ‘Normals’ vs diabetics
Is it the wrong target Hb for the wrong patient?

- Young vs elderly
- ‘Better’ cardiac function vs heart failure
- ‘Normals’ vs diabetics
- ‘Normals’ vs chronic obstructive airway disease
Is it the wrong target Hb for the wrong patient?

- Young vs elderly
- ‘Better’ cardiac function vs heart failure
- ‘Normals’ vs diabetics
- ‘Normals’ vs chronic obstructive airway disease
- Patients with chronic inflammation vs others
- Males vs females
Is it the wrong target Hb for the wrong patient?

- Young vs elderly
- ‘Better’ cardiac function vs heart failure
- ‘Normals’ vs diabetics
- ‘Normals’ vs chronic obstructive airway disease
- Patients with chronic inflammation vs others
- Males vs females

...patients in whom higher Hb concentrations are achieved may be healthier and therefore more responsive to ESAs...
What is the wrong target Hb?
…The recently published landmark study the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) has turned the world of anaemia management upside down…
The world...
Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

Tilman B. Drücke, M.D., Francesco Locatelli, M.D., Naomi Clyne, M.D., Kai-Uwe Eckardt, M.D., Ian C. Macdougall, M.D., Dimitrios Tsakiris, M.D., Hans-Ulrich Burger, Ph.D., and Armin Scherhag, M.D., for the CREATE Investigators

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

Ajay K. Singh, M.D., B.S., Lynda Szczech, M.D., Kezhen I. Tang, Ph.D., Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D., and Donal Reddan, M.B., B.S., for the CHOIR Investigators

The New England Journal of Medicine

THE EFFECTS OF NORMAL AS COMPARED WITH LOW HEMATOCRIT VALUES IN PATIENTS WITH CARDIAC DISEASE WHO ARE RECEIVING HEMODIALYSIS AND EPOETIN

Anatole Besarab, M.D., W. Kline Bolton, M.D., Jeffrey K. Browne, Ph.D., Joan C. Egrie, Ph.D., Allen R. Nissenson, M.D., Douglas M. Okamoto, Ph.D., Steve J. Schwab, M.D., and David A. Goodkin, M.D.
Is it too much ESA?

- ESA did not reduce the risk of cardiovascular composite endpoints.
- It increased the risk of fatal and non-fatal stroke and thromboembolism.
- An increase in cancer incidence was observed in patients with a prior history of malignancies.

...vs placebo

Is it underlying illness, compounded by high ESA dosages?

• Should ESAs be avoided?\textsuperscript{1,2}
• Is it a question of (median) dose?
  – CHOIR\textsuperscript{3} 10925 units/week epoetin alfa
  – TREAT\textsuperscript{4} 8800 units (equiv.)/week darbepoetin alfa\textsuperscript{*}
  – CREATE\textsuperscript{5} 5000 units/week epoetin beta

\textsuperscript{*}176 \mu g/month, converted at 200 units/\mu g

Is it underlying illness, compounded by high ESA dosages?

• Should ESAs be avoided?¹,²
• Is it a question of (median) dose?
  – CHOIR³ 10925 units/week epoetin alfa
  – TREAT⁴ 8800 units (equiv.)/week darbepoetin alfa*
  – CREATE⁵ 5000 units/week epoetin beta

…or is it the ESA?
• Methoxy polyethylene glycol-epoetin beta (Mircera)?
• Peginesatide (Hematide)?
• Hypoxia-inducible factor inhibitors?


*176 µg/month, converted at 200 units/µg
Is it underlying diabetes that skews the results?

- **TREAT¹**: all patients had diabetes
- **CHOIR²**: 50% of patients had diabetes
- **CREATE³**: 25% of patients had diabetes

What about blood transfusions?

- Is reduction in transfusions the aim of ESAs?
- Cancer patients?
- Patients on the transplant waiting list?
What about quality of life (QoL)? (I)

- Evaluated multiple patient-reported:
  - Outcomes
  - QoL indices
- Overall QoL effects were small and inconsistent:
  - Normal Haematocrit Study\(^1\):
    - Significant improvement on the physical-functioning scale of the short-form 36 (SF-36)
    - No significant effects on any of the other seven scales of the SF-36

What about QoL? (II)

– CHOIR\(^1\):
  • Did not show significant improvement on any scale of the SF-36 in the high vs low Hb group

– TREAT\(^2\):
  • Showed a significant effect on the Functional Assessment of Cancer Therapy–Fatigue instrument
  • No effect on QoL assessments based on the SF-36

CREATE: QoL (SF-36) 12 months

CREATE: QoL (SF-36) 24 months

What does the FDA think?

Perspective

Erythropoiesis-Stimulating Agents — Time for a Reevaluation
Ellis F. Unger, M.D., Aliza M. Thompson, M.D., Melanie J. Blank, M.D., and Robert Temple, M.D.
“Epoetin alfa was approved in 1989 by the Food and Drug Administration (FDA) for the treatment of anemia associated with chronic kidney disease ‘to elevate or maintain the red blood cell level…and to decrease the need for transfusions.’”

What is wrong with anaemia management in 2010?

- Is it the wrong target Hb?
- Is it the wrong target Hb for the wrong patient?
- Is it too much ESA?
- Is it underlying illness, compounded by high ESA dosages?
- **Should iron be the starting point in anaemia management?**
- Should there be a target Hb when considering iron repletion in patients with ND-CKD?
TREAT Study: Hb response to ESA

Mean (standard error) Hb levels through 48 months among patients who were assigned to receive darbepoetin alfa or placebo.

TREAT – interventions

• Iron repletion was frequent throughout the study:
  – 66.8% in the darbepoetin alfa group vs 68.6% in the placebo group received oral iron (P=0.25)
  – More patients in the placebo group received i.v. iron (20.4% vs 14.8% in the darbepoetin alfa group; P<0.001)

• Red-blood-cell transfusion was more frequent in the placebo group (24.5% vs 14.8% in the darbepoetin alfa group; P<0.001)
Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D., Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D., Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D.,* Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D., Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D., Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D., Philip A. Poole-Wilson, M.D.,* and Piotr Ponikowski, M.D., Ph.D., for the FAIR-HF Trial Investigators†

ABSTRACT

BACKGROUND
Iron deficiency may impair aerobic performance. This study aimed to determine whether treatment with intravenous iron (ferric carboxymaltose) would improve
• 459 patients
• Chronic heart failure NYHA II or III
• Left ventricular ejection fraction (LVEF) of 40–45%
• Iron deficiency: ferritin level
  – <100 μg/L or
  – between 100 and 299 μg/L if TSAT <20%
• Hb level of 9.5–13.5 g/dL
• 200 mg of intravenous (i.v.) iron (FCM)/week to achieve iron repletion or saline (placebo) and maintenance of 200 mg iron every 4 weeks

FCM, ferric carboxymaltose; NYHA, New York Heart Association; TSAT, transferrin saturation
**FAIR-HF: baseline demographics**

Baseline demographic and clinical characteristics of the study population in the intent-to-treat population, according to study group

<table>
<thead>
<tr>
<th>Laboratory measurements*</th>
<th>FCM</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>11.9 (1.3)</td>
<td>11.9 (1.4)</td>
</tr>
<tr>
<td>Mean corpuscular volume (µm$^3$)</td>
<td>92 (8.1)</td>
<td>92 (6.7)</td>
</tr>
<tr>
<td>Serum ferritin (µg/L)</td>
<td>53 (55)</td>
<td>60 (67)</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>17.7 (12.6)</td>
<td>16.7 (8.4)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>7.5 (5.3)</td>
<td>9.1 (5.5)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>141 (3)</td>
<td>141 (3)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.65 (0.61)</td>
<td>4.58 (0.52)</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>20.5 (12.3)</td>
<td>18.8 (8.1)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>23.1 (10.4)</td>
<td>22.4 (7.2)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2 (0.6)</td>
<td>1.2 (0.6)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (mL/min/1.73 m$^2$)</td>
<td>64 (21)</td>
<td>65 (25)</td>
</tr>
</tbody>
</table>

* Mean (SD)
FAIR-HF: improved symptoms and functional status

Patient Global Assessment Score

NYHA Functional Class

Odds ratio (95% CI)

Favours FCM

Favours Placebo

FAIR-HF: improved exercise capacity and QoL

Change (m)  6-minute walk test  Change in score  EQ-5D VAS

EQ-5D, European Quality of Life – 5 Dimensions; VAS, visual analogue scale

In the anaemic sub-population, a significant rise in Hb of almost 1 g/dL was observed over the 6-month treatment period.
Impact of i.v. FCM on renal function

Change in eGFR (mL/min/1.73m²)*

<table>
<thead>
<tr>
<th>Treatment effect (mL/min/1.73 m²)*</th>
<th>P=0.054</th>
<th>P=0.049</th>
<th>P=0.017</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8 ± 1.5</td>
<td>3.0 ± 1.5</td>
<td>4.0 ± 1.7</td>
<td></td>
</tr>
</tbody>
</table>

* Least square mean ± SE

Ponikowski P et al. HFA Congress 2010; Abstract 114 & LBT Oral Presentation
Treatment effect on renal function in predefined subgroups

<table>
<thead>
<tr>
<th>Endpoint (Week 24)</th>
<th>FCM</th>
<th>Placebo</th>
<th>Treatment effect mL/min/1.73m²</th>
<th>P_interaction value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
<td>8.19 ± 1.42</td>
<td>6.13 ± 2.00</td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73 m²</td>
<td>-0.24 ± 1.23</td>
<td>-5.31 ± 1.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb ≤12 g/dL</td>
<td>4.11 ± 1.42</td>
<td>1.10 ± 2.04</td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td>Hb &gt;12 g/dL</td>
<td>2.76 ± 1.22</td>
<td>-2.46 ± 1.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin ≤39 µg/L</td>
<td>4.35 ± 1.30</td>
<td>-1.58 ± 2.02</td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>Ferritin &gt;39 µg/L</td>
<td>2.32 ± 1.34</td>
<td>0.36 ± 1.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤69.7 years</td>
<td>3.22 ± 1.42</td>
<td>-2.64 ± 2.15</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Age &gt;69.7 years</td>
<td>3.61 ± 1.21</td>
<td>1.45 ± 1.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.29 ± 1.54</td>
<td>2.02 ± 2.40</td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Female</td>
<td>3.46 ± 1.09</td>
<td>-2.41 ± 1.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>1.31 ± 1.63</td>
<td>-1.80 ± 2.45</td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>3.88 ± 1.09</td>
<td>-0.20 ± 1.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF ≤33%</td>
<td>4.21 ± 1.41</td>
<td>2.45 ± 2.31</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>LVEF &gt;33%</td>
<td>2.44 ± 1.11</td>
<td>-3.40 ± 1.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ischaemic HF</td>
<td>5.40 ± 2.73</td>
<td>0.64 ± 3.89</td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>Ischaemic HF</td>
<td>2.97 ± 0.95</td>
<td>-0.86 ± 1.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non diabetic</td>
<td>3.30 ± 1.07</td>
<td>-1.63 ± 1.50</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Diabetic</td>
<td>3.77 ± 1.88</td>
<td>2.88 ± 3.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≤27.37 kg/m²</td>
<td>3.66 ± 1.25</td>
<td>-1.67 ± 1.90</td>
<td></td>
<td>0.55</td>
</tr>
<tr>
<td>BMI &gt;27.37 kg/m²</td>
<td>3.08 ± 1.39</td>
<td>0.12 ± 1.98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; HF, heart failure

Ponikowski P et al. HFA Congress 2010; Abstract 114 & LBT Oral Presentation
FAIR-HF: QoL subanalysis

- FCM improved HRQoL in patients
  - *with and without* **anaemia** (p-values for interaction: 0.93 [VAS] and 0.66 [KCCQ overall score])
  - *with and without* **chronic kidney disease** (42% had eGFR <60 mL/min/1.73 m²; p-values for interaction: 0.36 [VAS] and 0.24 [KCCQ overall score])

- “Intravenous FCM significantly improved QoL during 24 weeks of therapy. The positive effects were seen after 4 weeks of treatment and were independent of anaemia status and the presence of CKD.”

Comin-Colet J. XLVII ERA-EDTA 2010; Abstract 451242.
FIND-CKD STUDY
Intravenous iron in the ND-CKD population:

Hypothesis

That the use of i.v. iron in patients with ND-CKD with iron-deficiency anaemia will provide effective Hb correction to postpone the use of ESA therapy

Rationale for FIND-CKD Study

• Guidelines for the management of iron deficiency in CKD

• Available studies examining the management of iron deficiency in pre-dialysis CKD
Iron in patients with CKD and anaemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Iron agents</th>
<th>N</th>
<th>Follow-up</th>
<th>% on ESA</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverberg DS et al.</td>
<td>Intravenous iron sucrose (previously failed on oral iron)</td>
<td>33</td>
<td>6 months</td>
<td>0</td>
<td>22/33 patients treated with i.v. iron had an Hb response 0.4–3.6 g/dL</td>
</tr>
<tr>
<td>Mircescu G et al.</td>
<td>Intravenous iron sucrose</td>
<td>60</td>
<td>12 months</td>
<td>0</td>
<td>55% of patients reached Hb &gt;11 g/dL after 12 months’ i.v. iron</td>
</tr>
<tr>
<td>Nephrol Dial Transplant 2006;21:120–4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silverberg DS et al.</td>
<td>Intravenous iron sucrose</td>
<td>90</td>
<td>12 months</td>
<td>50%</td>
<td>Intravenous iron augmented low-dose ESA in patients with ND-CKD</td>
</tr>
<tr>
<td>Clin Nephrol 2001;55:212–9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tagboto S et al.</td>
<td>Intravenous FCM</td>
<td>30</td>
<td>1 month</td>
<td>20%</td>
<td>Hb levels increased in 80% of patients</td>
</tr>
<tr>
<td>J Ren Care 2009;35:18–23</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
### Iron in patients with CKD and anaemia

#### Randomized controlled trials (RCTs)

<table>
<thead>
<tr>
<th>Study</th>
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<th>N</th>
<th>Follow-up</th>
<th>% on ESAs</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Wyck DB et al. <em>Kidney Int</em> 2005;68:2846–56</td>
<td>Intravenous iron sucrose vs oral ferrous sulphate</td>
<td>95 vs 93</td>
<td>8 weeks</td>
<td>38–41%</td>
<td>Intravenous iron superior to oral iron; no difference in AEs</td>
</tr>
<tr>
<td>Charytan C et al. <em>Nephron Clin Pract</em> 2005;100:c55–62</td>
<td>Intravenous iron sucrose vs oral ferrous sulphate</td>
<td>48 vs 48</td>
<td>6 weeks</td>
<td>100%</td>
<td>Intravenous iron superior to oral iron; no difference in AEs</td>
</tr>
<tr>
<td>Agarwal R et al. <em>Am J Nephrol</em> 2006;26:445–54</td>
<td>Intravenous sodium ferric gluconate vs oral ferrous sulphate</td>
<td>36 vs 39</td>
<td>6 weeks</td>
<td>0</td>
<td>Faster repletion of iron stores with i.v. iron; ↑ QoL</td>
</tr>
<tr>
<td>Aggarwal HK et al. <em>J Assoc Physic India</em> 2003;51:170–4</td>
<td>Intravenous iron dextran vs oral ferrous sulphate</td>
<td>20 vs 20</td>
<td>3 months</td>
<td>100%</td>
<td>Intravenous iron superior to oral iron; no difference in AEs</td>
</tr>
<tr>
<td>Stoves J et al. <em>Nephrol Dial Transplant</em> 2001;16:967–74</td>
<td>Intravenous iron sucrose vs oral ferrous sulphate</td>
<td>22 vs 23</td>
<td>6 months</td>
<td>100%</td>
<td>No difference between i.v. iron and oral iron</td>
</tr>
<tr>
<td>Spinowitz BS et al. <em>J Am Soc Nephrol</em> 2009;19:1599–605</td>
<td>Intravenous ferumoxytol vs oral iron</td>
<td>228 vs 76</td>
<td>5 weeks</td>
<td>36–43%</td>
<td>Intravenous iron superior to oral iron; fewer AEs</td>
</tr>
<tr>
<td>Qunibi W et al. <em>ERA-EDTA Congress</em> 2008;Abs MO018</td>
<td>Intravenous FCM vs oral ferrous sulphate</td>
<td>147 vs 103</td>
<td>8 weeks</td>
<td>23–25%</td>
<td>Intravenous iron superior to oral iron; fewer AEs</td>
</tr>
</tbody>
</table>

AE, adverse event
FIND-CKD: defining the role of iron in CKD

- **Screening (up to 4 weeks)**
  - Patients with ND-CKD
  - ESA-naïve
  - Hb 9–10.5 g/dL
  - Ferritin <100 µg/L

- **Visits**:
  - Every 2 weeks (weeks 0–8), then every 4 weeks (weeks 8–52)
  - Dosing every 4 weeks

- **End of study – week 56**
  - (or 4 weeks after last dose of study drug)

- **FCM: high dose**
  - Ferritin target 400–600 µg/L
  - 254 patients

- **FCM: low dose**
  - Ferritin target 100–200 µg/L
  - 254 patients

- **Oral ferrous sulphate (200 mg iron/day)**
  - 508 patients

- **No ESA/anaemia management (weeks 0–8)**

- **Anaemia management per standard practice**

- **Rescreening permitted**

www.clinicaltrial.gov; NCT00994318
FIND-CKD: study objectives

• Primary objectives:
  – Evaluate the long-term efficacy of FCM or oral iron to delay and/or reduce ESA use and/or other anaemia management options in patients with ND-CKD and iron-deficiency anaemia

• Secondary objectives:
  – Evaluate the ESA requirements, long-term safety and tolerability of iron therapy
  – Assess the health resource and economic burden of the treatment of anaemia in patients with ND-CKD

What is wrong with anaemia management in 2010?

- Is it the wrong target Hb?
- Is it the wrong target Hb for the wrong patient?
- Is it too much ESA?
- Is it underlying illness, compounded by high ESA dosages?
- Should iron be the starting point in anaemia management?
- Should there be a target Hb when considering iron repletion in patients with ND-CKD?
Iron and anaemia management in ND-CKD: where are we going?

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