Anemia Management in Children with Chronic Kidney Disease

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Director, Dialysis and Transplantation
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Healthy RBC Production Requires EPO and Iron

Bone Marrow

Erythropoietin

Iron

Circulation

Stem Cell → BFU-E → CFU-E → Pro-erythroblast → Reticulocytes → RBCs

Time to Mature Cell Development, days

0 15 19 21 25

Evolution of Anemia of CKD

Healthy RBC Production Requires EPO and Iron

Prevalence of Anemia

Hemoglobin in anemia range for age & sex
Anemia (hgb in anemia range or ESA)

Clinical Manifestations of Anemia

- Fatigue
- Pallor
- Depression
- Impaired cognition
- Anorexia
- Blood transfusion
- Hospitalizations
- Mortality
KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease
Anemia Definition in Children

- using age- and sex-specific hemoglobin values to define anemia

Hb value is < the 5th percentile for age and sex or >2 SD below mean Hb values in children 0–24 months of age

2006 Pediatric KDOQI
## WHO Criteria for Anemia

<table>
<thead>
<tr>
<th>Hgb (g/dL)</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 11.0</td>
<td>0.5 – 5</td>
</tr>
<tr>
<td>&lt; 11.5</td>
<td>5 – 12</td>
</tr>
<tr>
<td>&lt; 12.0</td>
<td>12 – 15</td>
</tr>
<tr>
<td>&lt; 13.0 (males)</td>
<td>&gt; 15</td>
</tr>
<tr>
<td>&lt; 12.0 (females)</td>
<td>&gt; 15</td>
</tr>
</tbody>
</table>
CHRONIC KIDNEY DISEASE

- EPO defic.
- Iron defic.
- Blood Loss
- Inflammation
- Oxidative stress

ANEMIA

- Hemolysis
- Vitamin defic.
- Malnutrition
- HyperPTH
- Aluminum
- ACE/ARB

CHRONIC KIDNEY DISEASE
Evaluation of Anemia

- Complete blood count
- Erythrocyte indices
- Reticulocyte count
- Iron parameters
  - CRP
  - Stool occult blood
  - Vitamin B 12, folate, copper
  - PTH

- Serum ferritin
- Transferrin saturation
- Reticulocyte Hb content
- Hypochromic RBC
- Hemolysis
Molecular Structure of Erythropoietin
Regulation of EPO Gene Expression

- **INHIBITORY**
  - GATA-2
  - NF-κB
  - GATA
  - AGTCCCTGGGC
  - EPO Promoter

- **STIMULATORY**
  - HIF-1α or 2α
  - A/GCGTG
  - EPO Enhancer
Regulation of Hypoxia Inducible Factor (HIF) Activity

(i) Normal conditions (normoxia) -- HIF is degraded

(ii) Hypoxic conditions / inhibition of proxyl hydroxylase -- HIF is stabilized

EPO enhancer (see Fig 2)
Upregulation of EPO gene
↑ erythropoietin
Erythropoietin Producing Cells

Kidney under physiologic, non-stimulated conditions: small EPC pool size

Genetic mutations
Pharmacologic inactivation of HIF-PHDs
Hypoxia

HIF-2

Kidney with increased EPO production: expanded EPC pool size

Koury MJ and Haase VH., Nature Reviews Nephrol; 2015
Erythropoietin Receptor Activation and Intracellular Signal Transduction
Erythropoietin and CKD

Normal kidney

- EPCs
- Tubular epithelial cells
- Non-EPO-producing interstitial cells

Tubular epithelial cells

Myofibroblast transdifferentiation

Plasma EPO

Liver EPO

CKD

- Injured renal tubules
- Collagen
- Myofibroblasts

Koury MJ and Haase VH., Nature Reviews Nephrol; 2015
The Iron Economy

- **Average Human Male = 4 grams of Iron**
  - Majority (45%) in circulating RBCs as Hb
  - Storage:
    - Liver (25%)
    - RES macrophages (15%)
  - Sites of utilization:
    - Bone marrow (7.5%)
    - Muscle (7.5%)
  - Circulating iron:
    - Transferrin (0.075%)
IRON DEFICIENCY

Dietary restrictions
Anorexia

Malnutrition
Inflammation
Phosphate binders

Decrease in oral iron intake

Decrease in
intestinal
Iron absorption

Blood loss in HD
Blood sampling
GI bleeding

Stimulation of erythropoiesis by ESA

Chronic blood loss
Hepcidin as the Main Regulator of Systemic Iron Homeostasis

Iron loading, Inflammation, Erythropoietic signal

Liver, Reticuloendothelial macrophages, Bone marrow

Plasma Fe-Tf, Small intestine

Hepatocyte hepcidin production, Circulating hepcidin

(+), (-)

Young, B. et al., Clin J Am Soc Nephrol, 2009
Hepcidin Regulates Cellular Iron Export Into Plasma

Low hepcidin

Iron uptake

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

ferritin

Fpn

Fe

Iron release into plasma

High hepcidin

Iron uptake

Fe

haptocidin

Fpn

Hepcidin in Pediatric and Adult CKD

Serum Hepcidin (ng/mL)

N = 20  N = 24  N = 48  N = 32  N = 26

Pediatric Controls  Adult Controls  PCKD2-4  ACKD2-4  PCKD5D

Median 25.3  Median 72.9  Median 127.3  Median 269.9  Median 652.4

HIF Coordinated Erythropoiesis

Koury MJ and Haase VH., Nature Reviews Nephrol; 2015
Mechanism of Renal Anemia

Koury MJ and Haase VH., Nature Reviews Nephrol; 2015
Treatment of Renal Anemia
Development of Erythropoietic Stimulating Agents (ESA)

- Human EPO purified – 1977
- Human EPO gene cloned – 1985
- Recombinant human EPO first produced – 1986
- Clinical trial completed – 1987
- Epoetin alfa approved by FDA and commercially available – 1989
Benefits of ESA Therapy

Reduction of RBC Transfusion

Baseline ≈ 0.5 transfusions per patient per 4 weeks

RBC transfusions virtually eliminated by Epoetin alfa by 2nd month of study
# Initial rHuEPO Dosing

<table>
<thead>
<tr>
<th></th>
<th>Hemodialysis dependent</th>
<th>Peritoneal Dialysis dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children &lt;5 years of age</strong></td>
<td>250-300 units/kg/week</td>
<td>100-150 units/kg/week</td>
</tr>
<tr>
<td><strong>Children &gt;5 years of age</strong></td>
<td>150-200 units/kg/week</td>
<td>50-100 units/kg/week</td>
</tr>
</tbody>
</table>

Yorgin P & Zaritsky J, IN: Pediatric Dialysis, 2012
Increased Sialic Acid Content of Darbepoetin alfa Results in a 3-times Longer Half-life

<table>
<thead>
<tr>
<th></th>
<th>EPO</th>
<th>Darbepoetin alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-linked carbohydrate chains</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Sialic acid</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Molecular Weight (Daltons)</td>
<td>~30,400</td>
<td>~37,100 daltons</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>~40%</td>
<td>~51%</td>
</tr>
</tbody>
</table>
Darbepoetin Alfa Registry Data

Schaefer F et al., Pediatr Nephrol, 2015
Darbepoetin Alfa Registry Data

Schaefer F et al., Pediatr Nephrol, 2015
Kaplan-Meier Plot of Time to Achieve Hemoglobin ≥10.0 g/dL in QW Group

Proportion of Subjects (%)

Study Week

0.45 µg/kg

Subjects:
- QW Group: 58 55 46 37 25 19 17 16 8 7 5 5 4 3 3 2 2 2 1 1
- LCL
- UCL

Warady BA, et al., (Submitted) 2016
Kaplan-Meier Plot of Time to Achieve Hemoglobin ≥ 10.0 g/dL in Q2W Group

Proportion of Subjects (%)

Study Week

Subjects: 56, 53, 44, 34, 24, 20, 16, 14, 12, 10, 7, 5, 5, 4, 4, 3, 3, 3, 2, 2, 2, 1, 1, 1

0.75 µg/kg

Warady BA, et al., (Submitted) 2016
Benefits of ESA Therapy

- Anemia correction
- Reduction in RBC transfusion
- Improvement in quality of life
- Partial regression of LVH and LV dilation
Adverse Effects of ESA Therapy

- Hypertension
- Seizures
- Edema
- Headache
- Flu-like syndrome
- Pure red blood cell aplasia due to Anti-EPO antibodies
- Pro-thrombotic
  - Cerebrovascular
  - DVT/PE
  - Hemodialysis Access
ESA Monitoring

- Administration of an ESA induces an increase in reticulocytes in 10 days and a clinically significant increase in Hb is detectable in 2-6 weeks.

- Do not increase the dose more frequently than once every 2-4 weeks. Decreases in dose can occur more frequently.

- If the hemoglobin rises rapidly (e.g., more than 1 gm/dL in any 2-week period), reduce the dose of ESA by 25% or more as needed to reduce rapid responses.

- For patients who do not respond adequately (e.g., hemoglobin has not increased by more than 1 gm/dL after 4 weeks of therapy), increase the dose by 25%.

- Monthly Hb monitoring is recommended once the Hb has stabilized.
Sufficient iron should be administered to generally maintain the following indices of iron status during ESA treatment:

- Serum ferritin > 100 ng/mL and
- TSAT > 20%

(for HD, PD and ND-CKD)
Hgb and Serum Ferritin

P < 0.005

% iron suppl.

Hemoglobin (g/dL)

Ferritin (ng/mL)

88 73 80 88 84 84 73 57

Borzych-Duzalka, et al., JASN, 2013
# Oral Iron Preparations

<table>
<thead>
<tr>
<th>Iron preparation (w/o added vitamins or folic acid)</th>
<th>Tablet size (mg)</th>
<th>Amount of Elemental Iron (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous gluconate</td>
<td>325</td>
<td>35</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>325</td>
<td>65</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>325</td>
<td>108</td>
</tr>
<tr>
<td>Iron polysaccharide</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>
The preferred route of iron administration is IV in patients with HD-CKD. *(STRONG RECOMMENDATION)*

The route of iron administration can be either IV or oral in patients with ND-CKD or on PD.
<table>
<thead>
<tr>
<th>Drug (Trade name)</th>
<th>Year Approved</th>
<th>Test Dose Necessary</th>
<th>Maximum Approved Single Dose</th>
<th>Iron Repletion Dose (adult)</th>
<th>Pediatric Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low molecular weight iron dextran (InFed)</td>
<td>1992</td>
<td>25 mg over 15-30 min</td>
<td>100 mg over 30 s</td>
<td>1 g</td>
<td>&lt;10 kg – 25 mg 10-20 kg – 50 mg &gt;25 kg – 100 mg for 8-10 HD sessions</td>
</tr>
<tr>
<td>High molecular weight iron dextran</td>
<td>1996</td>
<td>25 mg over 15-30 min</td>
<td>100 mg over 30 s</td>
<td>1 g</td>
<td>&lt;10 kg – 25 mg 10-20 kg – 50 mg &gt;25 kg – 100 mg for 8-10 HD sessions</td>
</tr>
<tr>
<td>Sodium ferric gluconate (Ferrlecit) Generic: Nulecit</td>
<td>1999 2011</td>
<td>No</td>
<td>125 mg iv push over 10 min</td>
<td>125 mg for 8 HD session</td>
<td>1.5 mg/kg for 8 HD sessions</td>
</tr>
<tr>
<td>Iron Sucrose (Venofer)</td>
<td>2000</td>
<td>No</td>
<td>200 mg iv push over 2-5 min</td>
<td>100 mg iv for 10 consecutive or 200 mg iv for 5 consecutive HD sessions</td>
<td>0.5 mg/kg ever other week (maintenance)</td>
</tr>
<tr>
<td>Ferumoxytol (Feraheme)</td>
<td>2009</td>
<td>No</td>
<td>510 mg iv push over &lt;1 min</td>
<td>510 mg x2 doses over 2 different visits</td>
<td>--</td>
</tr>
<tr>
<td>Ferric carboxymaltose (Injectafer, Ferinject)</td>
<td>2013</td>
<td>No</td>
<td>750 mg slow push or infusion over 15 min</td>
<td>750 mg x2 over 1 wk</td>
<td>--</td>
</tr>
</tbody>
</table>
# RE Blockade vs. Functional Iron Deficiency

<table>
<thead>
<tr>
<th></th>
<th>RE Blockade</th>
<th>Functional Iron Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSAT</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Serum iron level</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cause of normal/high serum ferritin</td>
<td>Acute phase response: stored iron cannot be accessed</td>
<td>Normal or increased iron stores</td>
</tr>
<tr>
<td>Iron delivery from RES</td>
<td>Blocked</td>
<td>Too slow for ESA-mediated erythropoiesis</td>
</tr>
<tr>
<td>Response to IV iron</td>
<td>No / incomplete improvement until inflammation subsides</td>
<td>↑ Hb; ↓ ESA requirement</td>
</tr>
</tbody>
</table>
FDA approves iron replacement drug for dialysis patients

Triferic

JANUARY 26, 2015  No Comments

The U.S. Food and Drug Administration approved Rockwell Medical Inc.’s Triferic as an iron replacement product to maintain hemoglobin in adult patients on hemodialysis.

Triferic is delivered to hemodialysis patients via dialysate, replacing the ongoing iron losses that occur during their dialysis treatment, according to Rockwell. The drug is introduced into bicarbonate concentrate, on-site at the dialysis clinic, and subsequently mixed into dialysate. Once in dialysate, Triferic crosses the dialyzer membrane and enters the blood where it immediately binds to transferrin and is transported to the erythroid precursor cells to be incorporated into hemoglobin. In completed clinical trials to date, Triferic has demonstrated that it can effectively deliver sufficient iron to the bone marrow to maintain hemoglobin and not increase iron stores.
Intradialysate Soluble Ferric Pyrophosphate (Triferic)

- Water soluble, non-CHO, tightly complexed salt of Fe, electrostatically bonded to pyrophosphate
- Donates iron directly to apo-transferrin, bypassing RES
- Convenient
- Delivered in dialysis where iron is lost (5-7 mg)
- Slower delivery than IV iron
- Dialysate iron concentration of 2 μMol (110 μg/L) maintains iron balance without overloading iron stores

Courtesy of Dr. Ajay Gupta
And now the hemoglobin target
Mean Monthly Hgb Level and Mean Weekly EPO Dose in Adult PD Patients

Mean Hgb (All pts) - Mean Hgb (ESA pts) - Mean weekly EPO dose (Monthly average)

Treat Study

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Guideline 3.4.3

For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dL (90 g/L) by starting ESA therapy when the hemoglobin is between 9.0 – 10.0 g/dL (90 – 100 g/L). (2B)

Guideline 3.5.1

In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dL (115 g/L) in adult patients with CKD. (2C)
Pediatric Target Hemoglobin Recommendation

“Selection of the Hb target . . . in the individual pediatric patient should include consideration of potential benefits (including improvement in quality of life, school attendance/performance, and avoidance of transfusions) and potential harms (including the risk of life threatening adverse events)
Anemia - Mortality

Relative risk of death

- Hct <33% vs >33%
  - Relative risk: 1.52

- Hct 33-36% vs 27-30%
  - Relative risk: 1.81

- Hct 33-36% vs <27%
  - Relative risk: 1.8

*adjusted for age at initiation of dialysis, race, treatment modality, etiology of ESRD, iron usage, and rHuEPO usage

Warady BA, Ho M. Pediatr Nephrol, 2003
Kaplan-Meier Survival Curve by Hb Categories

- Hb < 10 g/dl
- Hb 11 – 12 g/dl
- Hb 10 & <11 g/dl
- Hb >12 g/dl

Days at risk

Cumulative Survival

p=0.0007

S. Amaral et al., J Am Soc Nephrol, 2006
Kaplan Meier Actuarial Survival Curves for Patients with Mean Hgb Greater or Less than 11 g/dL

N=1411

Observational time (years)
Guideline 3.7

In all pediatric CKD patients receiving ESA therapy, we suggest that the selected Hb concentration be in the range of 11.0 to 12.0 g/dL (110 to 120 gmL). (2D)
Regional Variation of Anemia Control

Mean weekly epoetin equivalent dose per country

Borzych-Duzalka, et al., 2013 JASN
GETTING FLUID UNDER CONTROL

Hospitalizations, impact on kidney patient health give it priority
<table>
<thead>
<tr>
<th>Characteristics Associated with Hgb Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb range (g/dL)</td>
</tr>
<tr>
<td>No. of observations</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>% pubertal male</td>
</tr>
<tr>
<td>Use of biocompatible PD fluids (%)</td>
</tr>
<tr>
<td>Estimated deviation from dry weight (%)</td>
</tr>
<tr>
<td>Ultrafiltration volume (L/m²/day)</td>
</tr>
<tr>
<td>Urine volume (L/m²/day)</td>
</tr>
<tr>
<td>ESA dose (*1000 IU/m²/week)</td>
</tr>
<tr>
<td>Serum ferritin</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
</tr>
<tr>
<td>Plasma PTH (pg/mL)</td>
</tr>
<tr>
<td>% hypertensive</td>
</tr>
<tr>
<td>% LVH</td>
</tr>
</tbody>
</table>
## Characteristics Associated with Hgb Distribution

<table>
<thead>
<tr>
<th>Hgb range (g/dL)</th>
<th>No. of observations</th>
<th>&lt; 8.5</th>
<th>8.5 – 9.99</th>
<th>10.0 – 11.49</th>
<th>11.5 – 12.99</th>
<th>13 – 14.49</th>
<th>&gt; 14.5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>250</td>
<td>698</td>
<td>1274</td>
<td>1073</td>
<td>363</td>
<td>89</td>
</tr>
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</table>

### Age (years)

<p>| | |</p>
<table>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>% pubertal male</td>
<td>10.1 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>11.2cdef</td>
</tr>
</tbody>
</table>

### Use of biocompatible PD fluids (%)

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<th></th>
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<tbody>
<tr>
<td></td>
<td>22.4cdef</td>
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</table>

### Estimated deviation from dry weight (%)

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<tr>
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<tbody>
<tr>
<td></td>
<td>0.75 (3.1)</td>
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</table>

### Ultrafiltration volume (L/m²/day)

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<tbody>
<tr>
<td></td>
<td>0.62 (0.54)cdef</td>
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</tbody>
</table>

### Urine volume (L/m²/day)

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<tbody>
<tr>
<td></td>
<td>0.14 (0.67)cdef</td>
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</tbody>
</table>

### ESA dose (*1000 IU/m²/week)

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<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>5.98 (4.27)bcddef</td>
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</tbody>
</table>

### Serum ferritin

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<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>250 (386)bcdef</td>
</tr>
</tbody>
</table>

### Serum albumin (g/L)

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<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>33.0 ± 3.9bcdef</td>
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</tbody>
</table>

### Plasma PTH (pg/mL)

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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>345 (569)cdef</td>
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</tbody>
</table>

### % hypertensive

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<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>49.6bcde</td>
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</tbody>
</table>

### % LVH

<p>| | |</p>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>62.5bcdef</td>
</tr>
</tbody>
</table>

Borzych-Duzalka, et al., JASN, 2013
Kaplan Meier Actuarial Survival Curves for Patients with Mean Administered ESA Equivalent Dose Greater or Less than 6000 IU/m² per week

Borzych-Duzalka, D. et al, JASN, 2013
New Treatment Approaches

- Hypoxia-Inducible Transcription Factor Stabilizers
- Mircera
- Biosimilars
- Other new ESAs
Pharmacologic Inhibition of HIF-PH to Selectively Activate HIF-Dependent Erythropoiesis

Lando O et al. Genes Dev. 2002

Normoxia

Proline Hydroxylation

Proteasomal Degradation

Complete Erythropoiesis

↓Hepcidin
↑Erythropoietin
↑Epo Receptor
↑DMT1
↑DcytB
↑Transferrin
↑Tf-R
↑Ceruloplasmin

HIF-1a
HIF-2a
HIF-3a

HIF-PH-1
HIF-PH-2
HIF-PH-3

HIF-PH Inhibitor

HIF-α

HIF-β

HIF-β

HIF-α

HIF-1a
HIF-2a
HIF-3a

HIF Stabilization

Transcription

Heterodimerization & Translocation
<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Stage of Clinical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>FG-4592 (Roxadustat)</td>
<td>Fibrogen&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Phase 2 studies completed (NDD CKD, HD, PD); phase 3 studies ongoing (NDD CKD, HD, PD)</td>
</tr>
<tr>
<td>AKB-6548</td>
<td>Akebia Therapeutics</td>
<td>Phase 2 studies completed (NDD CKD) or ongoing but not recruiting HD</td>
</tr>
<tr>
<td>GSK1278863</td>
<td>Glaxo Smith Kline</td>
<td>Phase 2a studies completed (NDD-CKD, HD); phase 2b studies ongoing, but not recruiting (NDD CKD)</td>
</tr>
<tr>
<td>BAY 85-3934 (Molidustat)</td>
<td>Bayer Pharmaceuticals</td>
<td>Phase 2b studies ongoing (NDD CKD, HD)</td>
</tr>
<tr>
<td>JTZ-951</td>
<td>Akros Pharmaceuticals</td>
<td>Phase 1 study completed (HD)</td>
</tr>
<tr>
<td>DS-1093a</td>
<td>Daiichi Sankyo</td>
<td>Phase 1 study ongoing (CKD 3b-4)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Collaboration with Astra Zeneca in the United States and China and with Astellas Pharma for Europe, Japan, the Middle East, and South Africa

Bonomini M, et al., AJKD, 2016
Summary

- Anemia management is a key aspect of clinical care provided to children with CKD
- ESAs and iron serve as the core elements of anemia related therapy
- Close patient monitoring is mandatory to optimize benefits, address factors which modify efficacy, and to minimize adverse outcomes
- Newer pharmacologic agents are being introduced and will need to be evaluated in pediatric CKD/ESRD patients to assess their safety and efficacy
END