Case Presentation

41 yo Hispanic Male on chronic HD x 5 years via L AVF secondary to lupus nephritis

• Returned after vacation from Mexico (2 months)

• Found with anemia, pancytopenia
Case Presentation: Review of Systems

Complains of weakness, fatigue x 1 month

- No fever, chills
- Positive for weight loss
- No joint pains, rashes
- No chest pain, shortness of breath
- No abd pains, diarrhea, black stools
- Positive for ulcer over right ankle
Case Presentation

**PMH**
- SLE, diagnosed in 1993, on HCQ maintenance
- Lupus nephritis with ESRD, on HD x 5 years, MWF
- H pylori gastritis
- Foot ulcer

**PSH:** AVF placement

**FH:** None contributory

**SH:** Denies illicits, works as a night watchman
Medications

- ASA 81 mg po d
- Atenolol 12.5 mg po bid
- Phoslo 2 tab tid with meals
- Renagel 2 tab tid with meals
- HCQ 200 mg bid (not taking)
- Nephrocaps
Physical exam

• Vitals: BP 130/80s, HR 70-80s, RR 18, O2 sat 100% RA
• Gen: comfortable, NAD
• HEENT: PERRL, EOMI, mmm
• Neck: no elevated JVP
• CV: RRR, normal S1S2, no m/r/g
• Chest: CTABL
• Abd: soft nontender nondistended
• Ext: no LE edema, wwp, R medial aspect of ankle with ulcer, R AVF in situ
LABS

LFTs: AST/ALT: 31/47, ALP 147, T bil 0.5, Albumin 4.0

C3/C4: low
dsDNA : Positive
Tsat: 20%
Ferritin: 600
Course

- Fecal occult blood negative

- Patient sent to Rheumatology for SLE flare up, started on prednisone with taper

- Hb dropped further, received 1 unit PRBC, started on IV iron 100 mg X 10 doses and EPO
Outline

• Iron homeostasis
• Pathophysiology of ACD
• Burden of problem
• History of ESA
• Trials
• Side effects
• Newer Therapies for anemia in CKD
Fe Absorption

Mackenzie et al. Am J of Physiology - GI and LiverPhysiology November 2005
The Transferrin Cycle
Regulation of Systemic Fe balance

Intracellular and extracellular iron concentrations

Erythropoietic iron requirements

Inflammation

Hepcidin

Duodenal enterocytes

Splenic macrophages

Hepatocytes and Kupffer cells

Plasma iron

Ganz et al. Biochimica et Biophysica 2012
Molecular Mechanisms of Hepcidin Regulation

Ganz et al. Biochimica et Biophysica 2012
Mechanisms of Anemia in CKD

• Anemia first linked to CKD over 170 years ago by Richard Bright.

• Increasing prevalence with severity of CKD

• Anemia in CKD a/w reduced quality of life and increased cardiovascular disease, hospitalizations, cognitive impairment, and mortality.

Babitt and Lin. JASN 2012
Mechanisms of Anemia in CKD

- EPO deficiency is a predominant cause of anemia in CKD
- EPO levels inappropriately low relative to the degree of anemia VS patients with normal kidney function have 10–100 times higher EPO levels
- Circulating uremic-induced inhibitors of erythropoiesis
- Shortened red blood cell survival
- Increased iron losses due to chronic bleeding from uremia-associated platelet dysfunction, frequent phlebotomy, and blood trapping in the dialysis apparatus
- Hepcidin excess related impaired dietary iron absorption and reticuloendothelial cell iron blockade present in many CKD patients.

Babitt and Lin. JASN 2012
Schematic representation of the mechanisms underlying anemia of CKD
Bone Marrow

ERYSRHROPOIETIN

IRON

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

Impair BFU-E & CFU-E
Inhibit Iron Availability
Shorten RBC Lifespan

Uremic Toxins
Elevated PTH

Inflammatory Cytokines, Hepcidin
Iron Deficiency Blood Loss

Day 0 → Day 12 → Day 18 → Day 20 → Day 22 → Day 25

Red Blood Cell Development in Uremia: Time to Mature
Estimated annual loss of iron in each chronic hemodialysis patient

Average annual iron losses due to:

- Repeated laboratory tests ~ 0.5 g
- Accidental losses during HD and other bleeding events ~ 1.0 g
- Blood retention in hemodialyzer and tubing ~ 1.0 g
- Normal iron losses ~ 0.5 g

Total annual iron loss ~ 3.0 g
Erythropoietin

• Molecular weight- 30.4 kd, 165 amino acid hemopoietic growth factor

• Produced in the peritubular fibroblasts in the kidneys and in the intercalated cells in hypoxic states

• In the presence of epo, erythroid progenitor cells in the bone marrow proliferate and differentiate, and, in its absence, these progenitor cells undergo apoptosis
• Eugene Goldwasser purified and characterized the properties of EPO

• Purified 8 mg of human urinary EPO from 2500 L of urine from patients with aplastic anemia in 1977

• 1983: peptide fragments were purified which finally led to cloning of human EPO gene and production of recombinant protein.
Erythropoietin Receptor

Nephrol Dial Transplant (2005)
Early Studies

CORRECTION OF THE ANEMIA OF END-STAGE RENAL DISEASE WITH RECOMBINANT HUMAN ERYTHROPOIETIN

Results of a Combined Phase I and II Clinical Trial*

J. W. Eschbach, M.D., Joan C. Egrie, Ph.D., Michael R. Downing, Ph.D.,
Jeffrey K. Browne, Ph.D., and John W. Adamson, M.D.

Abstract  We administered recombinant human erythropoietin to 25 anemic patients with end-stage renal disease who were undergoing hemodialysis. The recombinant human erythropoietin was given intravenously three times weekly after dialysis, and transfusion requirements, hematocrit, ferrokinetics, and reticulocyte responses were monitored.

Over a range of doses between 15 and 500 units per kilogram of body weight, dose-dependent increases in effective erythropoiesis were noted. At 500 units per kilogram, changes in the hematocrit of as much as 10 percentage points were seen within three weeks, and increases in ferrokinetics of three to four times basal values, as measured by erythron transferrin uptake, were observed. Of 18 patients receiving effective doses of recombinant human erythropoietin, 12 who had required transfusions no longer needed them, and in 11 the hematocrit increased to 35 percent or more. Along with the rise in hematocrit, four patients had an increase in blood pressure, and a majority had increases in serum creatinine and potassium levels. No organ dysfunction or other toxic effects were observed, and no antibodies to the recombinant hormone were formed.

These results demonstrate that recombinant human erythropoietin is effective, can eliminate the need for transfusions with their risks of immunologic sensitization, infection, and iron overload, and can restore the hematocrit to normal in many patients with the anemia of end-stage renal disease. (N Engl J Med 1987; 316: 73-8.)
Recombinant Human EPO

- Short half life after IV dose - 6-8 hrs

- Half life of subcut EPO much longer - 24 hrs
The New England Journal of Medicine

SUBCUTANEOUS COMPARED WITH INTRAVENOUS EPOETIN IN PATIENTS RECEIVING HEMODIALYSIS

JAMES S. KAUFMAN, M.D., DOMENIC J. REDA, M.S., CAROL L. FYE, R.PH., M.S., DAVID S. GOLDFARB, M.D., WILLIAM G. HENDERSON, PH.D., JACK G. KLEINMAN, M.D., AND CARLOS A. VAAMONDE, M.D., for the Department of Veterans Affairs Cooperative Study Group on Erythropoietin in Hemodialysis Patients*
• Methods:
  • RCT conducted in 24 VA hospitals dialysis centers compared 101 pts via subcut vs 107 pts by IV
  • Dosed to maintain Hct 30-33% for 26 weeks

**Table 2. Results during the Maintenance Phase of Subcutaneous and Intravenous Epoetin Therapy.**

<table>
<thead>
<tr>
<th>Variable</th>
<th><strong>Subcutaneous-Therapy Group (N=107)</strong></th>
<th><strong>Intravenous-Therapy Group (N=101)</strong></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly maintenance dose of epoetin</td>
<td>95.1 ± 75.0</td>
<td>140.3 ± 88.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average (U/kg/wk)</td>
<td>7397 ± 6139</td>
<td>10,068 ± 6334</td>
<td>0.002</td>
</tr>
<tr>
<td>Average (U/wk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average hematocrit (%)</td>
<td>31.3 ± 2.9</td>
<td>31.1 ± 2.5</td>
<td>0.60</td>
</tr>
<tr>
<td>Average hemoglobin (g/dl)</td>
<td>10.4 ± 1.0</td>
<td>10.3 ± 0.9</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD.
Darbopoetin

- Created to have longer half life by adding more sialic acid residue (22 compared to 14)
  
- Half life 25.3 hrs compared to 6.5 hr when given IV
  
- Subcut dosing half life around 48-72hrs
  
- 2 RCTs in 2002- US and Europe showed no difference in using aranesp weekly compared to EPO TIW.

*American Journal of Kidney Diseases, Vol 40, No 1 (July), 2002
CERA- Continuous Erythropoietin Receptor Activator

- Next strategy to improve half life was to insert a polyethylene glycol (peg) polymer chain into the EPO molecule

- Methoxypolyethylene glycol EPOetin beta or trade name MIRCERA. (Not available in US due to patent protection issues)- Europe 2007

- Half life 130 hrs both IV and Subcut

*Advances in Chronic Kidney Disease, Vol 16, No 2 (March), 2009*
Maintenance treatment of renal anaemia in haemodialysis patients with methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa administered monthly: a randomized comparative trial

Fernando Carrera¹, Charmaine E. Lok², Angel de Francisco³, Francesco Locatelli⁴, Johannes F.E. Mann⁵, Bernard Canaud⁶, Peter G. Kerr⁷, Iain C. Macdougall⁸, Anatole Besarab⁹, Giuseppe Villa¹⁰, Isabelle Kazes¹¹, Bruno Van Vlem¹², Shivinder Jolly¹³, Ulrich Beyer¹⁴, Frank C. Dougherty¹⁴ and on behalf of the PATRONUS Investigators
PATRONUS

• **Design:** Multinational RCT comparing Aranesp vs CERA for monthly administration

• **Patients:**
  • 490 HD patients stable on weekly aranesp
  • Randomized to alternate week aranesp vs monthly CERA for 26 wks followed by monthly aranesp and CERA for further 26wks

• **Primary endpoint** – maintenance of Hb > 10.5

• **Secondary end point**- dose change over time
Fig. 2. Treatment protocol. R = randomization.
# Methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa

## Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Methoxy polyethylene glycol-epoetin beta</th>
<th>Darbepoetin alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>(n = 245)</em></td>
<td><em>(n = 245)</em></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>148 (60%)</td>
<td>156 (64%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.2 (13.6)</td>
<td>65.5 (13.9)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>233 (95%)</td>
<td>225 (92%)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (2%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Oriental</td>
<td>5 (2%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.3 (15.1)</td>
<td>73.8 (16.9)</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>12.09 (0.56)</td>
<td>12.07 (0.5)</td>
</tr>
<tr>
<td>Ferritin (μg/L)</td>
<td>427 (276–614)</td>
<td>446 (282–663)</td>
</tr>
<tr>
<td>TSAT</td>
<td>26.5% (19.5–33.0)</td>
<td>26.6% (21.0–32.8)</td>
</tr>
<tr>
<td>Iron supplementation</td>
<td>208 (85%)</td>
<td>209 (85%)</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.54 (0.29)</td>
<td>1.52 (0.27)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>38.9 (4.4)</td>
<td>39.2 (4.3)</td>
</tr>
<tr>
<td>Time since first dialysis (years)</td>
<td>4.20 (5.92)</td>
<td>4.15 (5.55)</td>
</tr>
<tr>
<td>Aetiology of kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension/large vessel disease</td>
<td>71 (29)</td>
<td>84 (34)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>74 (30)</td>
<td>72 (29)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>31 (13)</td>
<td>37 (15)</td>
</tr>
<tr>
<td>Interstitial nephritis/pyelonephritis</td>
<td>27 (11)</td>
<td>30 (12)</td>
</tr>
<tr>
<td>Polycystic kidney disease (adult type, dominant)</td>
<td>25 (10)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Previous median weekly darbepoetin alfa dose (μg)</td>
<td>30.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Darbepoetin alfa dose per week before randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 μg</td>
<td>155 (63%)</td>
<td>164 (67%)</td>
</tr>
<tr>
<td>40–80 μg</td>
<td>80 (33%)</td>
<td>65 (27%)</td>
</tr>
<tr>
<td>&gt;80 μg</td>
<td>10 (4%)</td>
<td>16 (7%)</td>
</tr>
</tbody>
</table>
Results

Fig. 3. Median haemoglobin values over time with interquartile range (intent-to-treat population).

- Methoxy polyethylene glycol-epoetin beta
  - Baseline: 245
  - 4 weeks: 238
  - 8 weeks: 239
  - 12 weeks: 231
  - 16 weeks: 218
  - 20 weeks: 216
  - 24 weeks: 211
  - 28 weeks: 214
  - 32 weeks: 215
  - 36 weeks: 212
  - 40 weeks: 215
  - 44 weeks: 214
  - 48 weeks: 216
  - 52 weeks: 213

- Darbepoetin alfa
  - Baseline: 245
  - 4 weeks: 237
  - 8 weeks: 239
  - 12 weeks: 234
  - 16 weeks: 232
  - 20 weeks: 234
  - 24 weeks: 218
  - 28 weeks: 219
  - 32 weeks: 220
  - 36 weeks: 218
  - 40 weeks: 217
  - 44 weeks: 218
  - 48 weeks: 218
  - 52 weeks: 222

Horizontal lines denote an Hb range of 11–13 g/dL.
• 157/245 patients treated with CERA and 99/245 patients with Darbepoetin alfa met the response definition (64.1% and 40.4%; p<0.0001)

• Doses increased by only 6.8% with CERA vs 58.8% with darbepoetin alfa during once-monthly treatment

• No difference in adverse effects between the 2 groups
<table>
<thead>
<tr>
<th>Agent</th>
<th>Active Compound</th>
<th>Manufacturing Process</th>
<th>Year Licensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin alfa/beta (Epogen, Eprex, Erypo, NeoRecomron)</td>
<td>Recombinant human EPO</td>
<td>Recombinant DNA technology; EPO cDNA/gene–transfected CHO cells</td>
<td>1989 (Epogen, in US); 1990 (Eprex/Erypo/NeoRecomron, in Europe)</td>
</tr>
<tr>
<td>Epoetin delta (Dynepo)</td>
<td>Recombinant human EPO</td>
<td>Recombinant DNA technology; EPO cDNA/gene–transfected human cells</td>
<td>2006 (outside of US); product withdrawn by Shire in 2009</td>
</tr>
<tr>
<td>“Biosimilar” epoetins (Binocrit, Hexal, Retacrit, Silapo, Eporatio)</td>
<td>Recombinant human EPO</td>
<td>Recombinant DNA technology; EPO cDNA/gene–transfected CHO cells</td>
<td>2009 onward</td>
</tr>
<tr>
<td>Nonapproved or locally approved “copy” epoetins</td>
<td>Recombinant human EPO</td>
<td>Recombinant DNA technology; EPO cDNA/gene–transfected human cells</td>
<td>Available in many countries outside of US and Europe, e.g., India, China, Thailand, Argentina, Brazil</td>
</tr>
<tr>
<td>Darbepoetin alfa (Aranesp)</td>
<td>Hyperglycosylated recombinant human EPO analogue</td>
<td>Recombinant DNA technology; mutated EPO cDNA–transfected CHO cells</td>
<td>2001 (both US and Europe)</td>
</tr>
<tr>
<td>C.E.R.A. (Mircera)</td>
<td>Pegylated recombinant human EPO analogue</td>
<td></td>
<td>2009 (outside of US only)</td>
</tr>
</tbody>
</table>

Abbreviations: EPO, erythropoietin; cDNA, complementary DNA; C.E.R.A., continuous erythropoietin receptor activator; CHO, Chinese hamster ovary; US, United States.
Side Effects of ESA

• Cardiovascular Safety

1. **HTN:**
   • Increase in blood viscosity secondary to anemia correction
   • Enhanced vascular reactivity and vasoconstrictor responses
   • CHOIR, TREAT AND CREATE RCTs: Higher Hb, inc ESA dose a/w HTN but no difference in strokes, MI
   • Close monitoring of BP while on ESA therapy

2. **Vascular Access Thrombosis:** Can contribute to vascular access stenosis or occlusion by promoting intimal hyperplasia and thrombosis.

*Robert Robles, Clin Drug Investig. Feb 2016*
Side Effects of ESA

1. **Stroke:**
   - KDOQI meta-analysis of available trials in the dialysis (CKD stage V) and non-dialysis pts
     - found a trend toward increased CV risk in 2850 patients not on dialysis assigned to higher Hb targets this was not confirmed in dialysis patients.
   - **TREAT study**
     - 4000 patients multicenter double blinded RCT – CKD 2-4 / type 2 DM
     - Primary end point- mortality and non- fatal cardiovascular events
     - Results- initial poor response to the 2 doses of aranesp had subsequent higher rates of cardiovascular events and death from any cause
     - **Increased risk of stroke in ESA arm**: Showing a 92 % higher odds ratio of fatal or non-fatal stroke in those patients assigned to darbepoetin alfa and an Hb value of 13 g/dl than those in the placebo group [101 patients (5.0 %) vs 53 patients (2.6 %), respectively; p < 0.001

*NEJM 363;12, September 16, 2010*
Pure Red Cell Aplasia

• Since 1998, following a change in EPREX formulation (the replacement of human serum albumin by polysorbate 80 because of the fear of BSE, a rapid increase in the number of PRCA cases

  • This stabilizer may stimulate formation of immunogenic epoetin-containing micelles which produces a higher immunogenicity
  
  • Leachates released by the uncoated rubber stoppers of the prefilled syringes may interact with polysorbate 80 and act as an immune reaction adjuvant.
  
  • the interruption of cold chain may have also played a role.
  
  • SQ epoetin alfa can increase immunogenicity

• The number of reported cases of PRCA has decreased since 2003 and no more cases were reported in 2007.

Nicolas Robles Clin Drug Investig Feb 2016
• Number of RCTs and meta-analyses have strengthened the theoretical concerns about ESA use in cancer patients in terms of increased mortality, enhanced tumor proliferation and higher risk of thromboembolic complication

• Particularly true for solid tumors and, regarding tumor growth, especially for patients with head and neck cancer receiving radiotherapy only.

Nicolas Robles Clin Drug Investig Feb 2016
### Meta-analyses of ESAs and Cancer risk

<table>
<thead>
<tr>
<th>Author</th>
<th>Studies</th>
<th>Patients</th>
<th>Risk (95% CI)</th>
<th>SM</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bohlius, 2005 [43]</td>
<td>19</td>
<td>2805</td>
<td>0.84 (0.69–1.02)</td>
<td>HR</td>
<td>AD</td>
</tr>
<tr>
<td>Hedenus, 2005 [56]</td>
<td>4</td>
<td>1129</td>
<td>0.95 (0.78–1.16)</td>
<td>HR</td>
<td>IPD</td>
</tr>
<tr>
<td>Aapro, 2006 [54]</td>
<td>9</td>
<td>1413</td>
<td>0.97 (0.69–1.36)</td>
<td>RR</td>
<td>IPD</td>
</tr>
<tr>
<td>Bohlius, 2006 [45]</td>
<td>42</td>
<td>8167</td>
<td>1.08 (0.99–1.18)</td>
<td>HR</td>
<td>AD</td>
</tr>
<tr>
<td>Seidenfeld, 2006 (epoetin) [46]</td>
<td>35</td>
<td>6918</td>
<td>1.11 (1.00–1.23)</td>
<td>HR</td>
<td>AD</td>
</tr>
<tr>
<td>Seidenfeld, 2006 (darbepoetin) [46]</td>
<td>4</td>
<td>973</td>
<td>0.96 (0.78–1.18)</td>
<td>HR</td>
<td>AD</td>
</tr>
<tr>
<td>Ross, 2006 [48]</td>
<td>17</td>
<td>3048</td>
<td>1.14 (0.90–1.45)</td>
<td>OR</td>
<td>AD</td>
</tr>
<tr>
<td>Wilson, 2007 [44]</td>
<td>26</td>
<td>5308</td>
<td>1.03 (0.97–1.16)</td>
<td>OR</td>
<td>AD</td>
</tr>
<tr>
<td>Bennet, 2008 [49]</td>
<td>51</td>
<td>13,611</td>
<td>1.10 (1.01–1.20)*</td>
<td>HR</td>
<td>AD</td>
</tr>
<tr>
<td>Aapro, 2008 [51]</td>
<td>12</td>
<td>2297</td>
<td>1.13 (0.87–1.46)</td>
<td>HR</td>
<td>IPD</td>
</tr>
<tr>
<td>Ludwig, 2009 [53]</td>
<td>7</td>
<td>2122</td>
<td>1.11 (0.84–1.47)</td>
<td>HR</td>
<td>IPD</td>
</tr>
<tr>
<td>Bohlius, 2009 [38]</td>
<td>53</td>
<td>13,933</td>
<td>1.17 (1.06–1.30)*</td>
<td>HR</td>
<td>IPD</td>
</tr>
<tr>
<td>Tonelli, 2009 [47]</td>
<td>28</td>
<td>6525</td>
<td>1.15 (1.03–1.29)*</td>
<td>RR</td>
<td>AD</td>
</tr>
<tr>
<td>Glaspy, 2010 [39]</td>
<td>60</td>
<td>15,323</td>
<td>1.06 (0.97–1.15)</td>
<td>HR</td>
<td>AD</td>
</tr>
<tr>
<td>Tonia, 2012 [50]</td>
<td>37</td>
<td>11,226</td>
<td>1.17 (1.04–1.31)*</td>
<td>HR</td>
<td>AD</td>
</tr>
<tr>
<td>Li, 2014 [52]</td>
<td>8</td>
<td>2387</td>
<td>1.09 (0.87–1.38)</td>
<td>OR</td>
<td>AD</td>
</tr>
</tbody>
</table>

Box 1. New Strategies Under Development to Stimulate Erythropoiesis

### Not Directly Targeting the EPO Receptor
- HIF stabilizers
  - FG-4592 (Roxadustat)
  - AKB-6548
  - GSK1278863
  - BAY 85-3934 (Molidustat)
  - JTZ-951
  - DS-1093a
- Activin traps
  - Sotatercept (ACE-011)
  - Luspatercept (ACE-536)
  - LY2157299

### Targeting the EPO Receptor
- EPO mimic peptides
  - Centocor molecules: CNTO 528, CNTO 530, CNTO 531
  - AplaGen GmbH: AGEM400(HES)
  - Peginesatide
- EPO fusion proteins
  - EPO-EPO dimers
  - EPO-CPT
  - EPO-(CPT)_3
  - Albumin-EPO
  - EPO-hyFc (Genexine GX-E2)
- Antibody agonists to EPO receptor
  - Mouse monoclonal IgG
  - Ab12 molecule
  - Ab12.6 (Abbott Laboratories ABT-007) molecule
- EPO gene therapy (TARGT EPO)
- Dimerization of EPO receptor intracellular domain with a CID

Figure 2. Regulation of *EPO* (erythropoietin) gene expression, showing transcriptional factors that suppress the *EPO* promoter or activate the *EPO* enhancer. Abbreviations: -ve, negative; +ve, positive; HIF, hypoxia inducible factor; NF-κB, nuclear factor κB.
Hypoxia Inducible Factor

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

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

*Figure 3. Regulation of hypoxia inducible factor (HIF) activity. Abbreviations: EPO, erythropoietin; VHL, von Hippel Lindau protein.*

Kalantar-Zadeh Adv in CKDisease, Vol 16, 2009
Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study

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• **Study design:** phase 2, randomized (3:1), open-label, active-comparator, safety and efficacy study.

• **Setting & participants:** Patients with stable ERSD treated with HD previously Hb levels maintained with epoetin

• **Intervention:**
  - **Part 1:** 6-week dose-ranging study in 54 individuals of thrice-weekly oral roxadustat doses versus continuation of IV epoetin alfa.
  - **Part 2:** 19-week treatment in 90 individuals in 6 cohorts with various starting doses and adjustment rules (1.0-2.0 mg/kg or tiered weight based) in individuals with a range of epoetin alfa responsiveness. Intravenous iron was prohibited.

• **Outcomes:** primary end point Hb level response, defined as end-of-Rx Hb level change of 0.5 g/dl or greater from baseline (part 1) and as mean Hb level > 11.0 g/dl during the last 4 treatment weeks (part 2).

• **Conclusions:** in this phase 2 study of anemia therapy in patients with ESRD on maintenance HD, roxadustat was well tolerated and effectively maintained Hb levels
<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Stage of Clinical Development</th>
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<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>
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<td>AKB-6548</td>
<td>Akebia Therapeutics</td>
<td>Phase 2 studies completed (NDD CKD) or ongoing but not recruiting (HD)</td>
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<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>
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<td>BAY 85-3934 (Molidustat)</td>
<td>Bayer Pharmaceuticals</td>
<td>Phase 2b studies ongoing (NDD CKD, HD)</td>
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<td>JTZ-951</td>
<td>Akros Pharmaceuticals</td>
<td>Phase 1 study completed (HD)</td>
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<td>DS-1093a</td>
<td>Daiichi Sankyo</td>
<td>Phase 1 study ongoing (CKD 3b-4)</td>
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<sup>a</sup> Fibrogen<sup>a</sup> has an additional indication for anemia in dialysis patients.
Activin Trap

- Activins: Dimers of inhibin b-type chains belonging to TGFβ Superfamily.

- Trigger growth and differentiation by binding to type I and type II STK receptors (transmembrane proteins)

- Activin, BMPs and other members of TGFβ family contribute to regulation of erythropoiesis either by directly affecting erythroid progenitor or precursor cells or by altering the behavior of bone marrow accessory cells via signaling pathway involving the SMAD proteins.

Sotatercept

• Sotatercept is a dimeric fusion protein in which the extracellular domain of the activin receptor type IIA (ACTRIIA) is linked to the Fc portion of the human IgG1 Ab

• Sotatercept traps circulating activin and other members of TGFβ Superfamily that signal through ACTRIIA.

• Double-blind phase 1 trial of healthy postmenopausal women, treatment with Sotatercept a/w enhanced bone formation and decreased bone resorption. Increase in Hb unanticipated

• Proposed Mechanisms:
  • Binding of ACTRIIA ligands, resulting in modulation of their function regarding erythroid development.
  • By neutralizing TGFβ family members, Sotatercept can modulate the SMAD signaling pathway in stromal cells, leading to changes in the transcription of SMAD target genes that encode proteins affecting erythroid development

Sotatercept

- Sotatercept currently being evaluated in patients with CKD 5D in a phase 2a, randomized, double-blind, placebo controlled, Single-dose (0.1 mg/kg subcutaneously) study, followed by a double-blind, placebo-controlled, multiple-dose, dose-escalation study.

Others

• GATA-2 inhibition
• EPO gene therapy
Thank You