

Management of anemia in chronic kidney disease patients

How much ESA is too much?

Judith G. Marin, B.Pharm, M.Sc, PharmD
 Clinical Pharmacy Specialist
 FHA Renal Program
 CSHP- Spring 2007



Learning Objectives

1. To review assessment of anemia in general population and chronic kidney disease patients.
2. To summarize the recommendations from recently published clinical guidelines.
3. To provide an overview of the recent clinical trials published on anemia management in CKD patients and their impact on pharmacy practice.

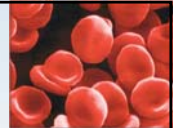


COI Declaration

I wish to declare that I do not at present have real or potential conflict of interests to disclose.



Definition of anemia



- WHO definition
 - Hb < 130 g/L for ♂ and postmenopausal ♀
 - Hb < 120 g/L for other ♀
 - 2 billions people worldwide (30% of population)
 - In Canada, 4% ♂ and 8% ♀
 - Symptom of underlying disease

http://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf



Causes of anemia

- Genetic (Thalassemia, Fanconi, G-6-PD deficiency, etc.)
- Nutritional (Iron, vitamin B12, Folate deficiencies, malnutrition)
- Hemorrhage
- Immunologic
- Physical effects (trauma, burn)
- Drugs and Chemicals
- Chronic disease (CKD, hepatic dysfunction, chronic infection, neoplasia, etc.)**
- Infection (viral, bacterial, protozoal)
- TTP and HUS

http://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf



Anemia in CKD

- 2nd most prevalent anemia (after iron deficiency anemia)

Markers	Anemia of CD	Iron-deficiency anemia
MCV	↓	↓
Transferrin	↓ or ↔	↑
Transferrin saturation	↓	↓
Ferritin	↑ or ↔	↓
Iron	↓	↓

Weiss G et al. NEJM 2005; 352:1011-23.



Chronic kidney disease

Stage of CKD	eGFR (ml/min/1.73m ²)	Complications
Stage 1	≥ 90	
Stage 2	60-89	<ul style="list-style-type: none"> ▪ ↑ BP ▪ ↑ iPTH
Stage 3	30-59	<ul style="list-style-type: none"> ▪ Ca²⁺/PO₄ disturbances ▪ Dyslipidemia ▪ LVH ▪ Anemia
Stage 4	15-29	<ul style="list-style-type: none"> ▪ Malnutrition ▪ Metabolic acidosis ▪ ↑ K⁺
Stage 5	< 15 or dialysis	<ul style="list-style-type: none"> ▪ Azotemia ▪ Volume overload

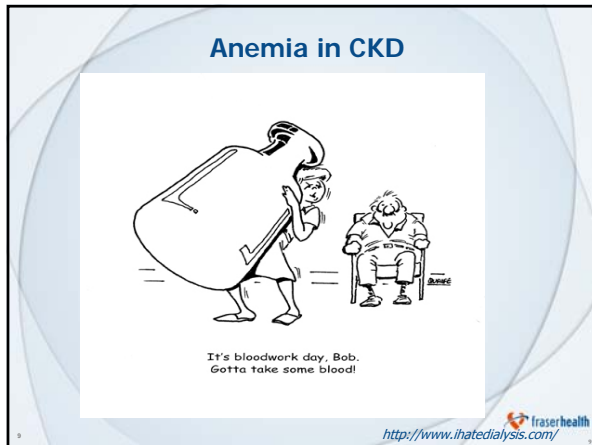
<http://www.health.gov.bc.ca/gpac/pdf/ckd.pdf>

Anemia in CKD

Stage of CKD	eGFR (ml/min/1.73m ²)	Anemia prevalence
Stage 3	30-59	5.2%
Stage 4	15-29	44.1%
Stage 5	< 15 or dialysis	100%

- Prevalence higher in african americans and diabetic patients

NHANES. J Am Soc Nephrol 2002; 13: 504-10.



- ### Anemia in CKD
- **Causes**
 - EPO deficiency
 - Blood loss
 - Shorter RBC life span
 - Decreased bone marrow responsiveness to EPO
 - Vitamin deficiencies
 - Iron deficiency (poor iron absorption)
 - High uremia level
 - Intoxication impairing RBC development (Aluminium)
 - Hemolysis (copper, chloramines)
 - Chronic inflammation
- Nurko S. Clev Clinics J Med 2006; 73: 289-97.*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE
Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial
JW Eckhaub, JC Egrie, MR Downing, JC Browne, and JW Adamson

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, ferritin levels, 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 ferritin levels 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

- ### The initial EPO era
- Initial target Hct range between 30-33% (Hb 100-110 g/L)
 - Little emphasis on iron deficiency management

Observational studies on anemia in CKD

- Anemia in CKD associated with
 - ↓ QOL
 - ↓ energy and exercise capacity
 - ↓ neurocognitive function
 - ↑ mortality
 - ↑ LVH rate

Toto, *Kidney Int* 2006; 70: S17-20.

Observational studies on anemia in CKD

- Use of ESA to treat anemia in CKD
 - ↓ depression
 - ↓ fatigue
 - ↑ neurocognitive function
 - ↑ muscle strength and exercise capacity
 - ↓ progression of LVH
 - ↓ hospitalization
 - ↓ progression to ESRD
 - Better outcomes as dialysis patients

Toto, *Kidney Int* 2006; 70: S17-20.

Definition of CKD associated anemia

Authority	♀	♂
European Best Practice Guidelines 2004	< 115 g/L	< 135 g/L if younger than 70 y/o < 120 g/L if older than 70 y/o
CARI 2005	< 110 g/L if premenopausal < 130 g/L if postmenopausal	< 130 g/L
K/DOQI 2006	< 120 g/L if postmenopausal	< 135 g/L

Recommended target Hb

Authority	Recommended target Hb range
CSN 1999	110-120 g/L
European Best Practice Guidelines (ERA-EDTA) 2004	> 110 g/L Level should be reached within 4 months Hd patients ⇒ Hb > 140 g/L are not desirable Most patients with DM or severe CV ⇒ Hb > 120 g/L not recommended
CARI 2005	110-120 g/L Patients without significant CVD ⇒ 120-140 g/L
K/DOQI 2006	Hb > 110 g/L Insufficient evidence to recommend routinely Hb >130 g/L in ESA-treated patients

THE NEW ENGLAND JOURNAL OF MEDICINE

Targ Nephrology Analysis Transplantation

Editorial Comment

Understanding recent haemoglobin trials in CKD: methods and lesson learned from CREATE and CHOIR

Adeera Levin
Nephrology, Education and Research, Vancouver BC V6Z 1Y6, Canada


An Ongoing Study of Anemia Correction in Chronic Kidney Disease

TO THE EDITOR: Evidence-based medicine assimilates available data to direct decisions regarding the care of patients. Extrapolations from epidemiologic observations and laboratory or clinical markers of disease severity have supported new treatments that were subsequently found to be without value in randomized, controlled clinical trials.¹ In addition, therapies considered to be beneficial and safe owing to their effect on surrogate markers have been found to be ineffective or harmful in such trials.^{2,3} Even the results of randomized, controlled trials can be misleading, especially when the trials are not adequately powered.⁴ The use of erythropoietic agents to treat ane-

Clinical Question

In pre-dialysis patients, what is the appropriate Hb level to target to

- ↓ mortality
- ↓ hospitalization rate
- ↓ CV morbidity
- ↓ progression of CKD
- ↑ QOL
- Minimize ADRs?



Summary target Hb trials

Study	Targeted Hb N-Hb	Achieved Hb in N-Hb	Targeted Hb S-Hb	Achieved Hb S-Hb
Furuland et al. (n=72)	135-150 g/L	143±11 g/L (107 IU/kg/wk)	90-120 g/L	117±13 g/L (39 IU/kg/wk)
Roger et al. (n=152)	120-130 g/L	121±14 g/L (4,514 IU/wk)	90-100 g/L	108±13 g/L (2,730 IU/wk)
Levin et al. (n=152)	120-140 g/L	127±11 g/L (3,146 IU/wk)	90-105 g/L	114±12 g/L (3,552 IU/wk)
Rossert et al. (n=290)	130-150 g/L	144±12 g/L (4,514 IU/wk)	110-120 g/L	121±12 g/L (2,730 IU/wk)
CHOIR (n=1432)	135 g/L	126 g/L (11,215 IU/wk)	113 g/L	113 g/L (6,276 IU/wk)
CREATE (n=603)	130-150 g/L	126 g/L (5,000 IU/wk)	105-115 g/L	113 g/L (2,000 IU/wk)
ACCORD (n=170)	130-150 g/L	135 g/L	105-115 g/L	117 g/L

Summary target Hb trials

Study	Mortality rate		Hospitalization	
	Targeted Hb N-Hb	Targeted Hb in S-Hb	Targeted Hb N-Hb	Targeted Hb S-Hb
Furuland et al.	13.4%	13.5%	4.8 ± 9.4 d	3.8 ± 8.8 d
Roger et al.	N/A	N/A	N/A	N/A
Levin et al.	N/A	N/A	N/A	N/A
Rossert et al.	0.5%	3%	16%	13%
CHOIR	7.3%	5.0%	9.7 ± 11.4 d	9.0 ± 9.0 d
CREATE	10%	7%	61%	59%
ACCORD	N/A	N/A	N/A	N/A

* p=0.03

Summary target Hb trials

Study	CV morbidity
Furuland et al.	N/A
Roger et al.	<ul style="list-style-type: none"> No change SS in LVMI over 2 years (2.5± 20 g/m² in N-Hb arm vs 4.5 ± 20 g/m² in S-Hb arm)
Levin et al.	<ul style="list-style-type: none"> No change SS in LVMI over 2 years (0.4 ± 25.0 g/m² in N-Hb arm vs 5.2 ± 30.3 g/m² in S-Hb arm)
Rossert et al.	<ul style="list-style-type: none"> No difference in the rate of cardiovascular events (25% in N-Hb arm vs 18% in S-Hb arm (OR 1.49, 95%CI (0.92-2.44))
CHOIR	<ul style="list-style-type: none"> No difference in hospitalization for HF rate (9.0% in N-Hb arm vs 6.6% in S-Hb arm (HR 1.41, 95%CI (0.97-2.05)) No difference in MI rate (2.5% in N-Hb arm vs 2.8% in S-Hb arm (HR 0.91, 95%CI (0.48-1.73)) No difference in hospitalization for HF (9.0% in N-Hb arm vs 6.6% in S-Hb arm (HR 1.41, 95%CI (0.97-2.05)) No difference in stroke rate (1.7% in N-Hb arm vs 1.7% in S-Hb arm (HR 1.01, 95%CI (0.45-2.25)) Higher rate hospitalization for CV cause (32.6% in N-Hb arm vs 27.5% in S-Hb arm (HR 1.23, 95%CI (1.01-1.48))

Summary target Hb trials

Study	CV morbidity
CREATE	<ul style="list-style-type: none"> No difference in rate of 1st cardiovascular event (19.3% in N-Hb arm vs 15.6% in S-Hb arm (HR 0.78, 95%CI 0.53-1.14)) No difference in mortality rate from CV cause (4% in N-Hb arm vs 3% in S-Hb arm (HR 0.74, 95%CI 0.33-1.70)) No difference in rate of change of LVMI (-6.4 g/m² in N-Hb arm vs -7.8 g/m² in S-Hb arm)
ACCORD	<ul style="list-style-type: none"> No difference in LVMI at 15 months (112.3 ± 32.9 g/m² in N-Hb arm vs 116.5 ± 35.9 g/m²)

Summary target Hb trials

Study	Renal function progression		Need for RRT	
	Targeted Hb N-Hb	Targeted Hb in S-Hb	Targeted Hb N-Hb	Targeted Hb S-Hb
Furuland et al. (ml/min/1.73 m ² / 48 wks)	-3	-1	8.3%	0%
Roger et al. (ml/min/1.73 m ² / 2 yrs)	-8 ± 9	-6 ± 8	32%	19%
Levin et al. (ml/min/2 yrs)	-4.9 ± 7.5	-7.2 ± 8.4	14.1%	10.8%
Rossert et al. (ml/min/1.73 m ² / month)	-0.058 ± 0.898	-0.081 ± 1.167	4%	1.1%
CHOIR	N/A	N/A	21.7%	18.7%
CREATE (ml/min/3 years)	-6.8	-5.0	42.2%	36.8%
ACCORD (ml/min/15 months)	-5.5 (-11.5-0.3)	-3.4 (-11.4-2)	2.3%	3.7%

Summary target Hb trials

Study	QOL Evaluation
Furuland et al.	<ul style="list-style-type: none"> QOL results only available for HD population
Roger et al.	<ul style="list-style-type: none"> No change according to SF-36 and KDQ total scores
Levin et al.	<ul style="list-style-type: none"> N/A
Rossert et al.	<ul style="list-style-type: none"> Based on SF-36, patients N-Hb arm had higher mean vitality score
CHOIR	<ul style="list-style-type: none"> Based on LASA, KDQ total score and SF-36, no improvement, except a better mental health in S-Hb arm (p=0.01)
CREATE	<ul style="list-style-type: none"> Based on SF-36, QOL better at 2 year in N-Hb group with regard to general health (p=0.008) and vitality (p=0.01)
ACCORD	<ul style="list-style-type: none"> Based on SF-36, better QOL in N-Hb arm (p=0.04)

Summary target Hb trials

Study	SBP		dBP	
	Targeted Hb N-Hb	Targeted Hb S-Hb	Targeted Hb N-Hb	Targeted Hb S-Hb
Furuland et al. 48 wks	147 ± 21	148 ± 24	90 ± 6*	83 ± 11
Roger et al. B	139 ± 19	137 ± 18	80 ± 11	81 ± 10
2 years	147 ± 21	148 ± 24	90 ± 6†	83 ± 11
Levin et al. B	137 ± 18	141 ± 19	76 ± 13	80 ± 11
2 years	134 ± 21	133 ± 23	77 ± 13‡	75.1 ± 11
Rossert et al. B	139 ± 17	141 ± 19	76 ± 10	78 ± 10
Last measure	134 ± 21	133 ± 23	78	77

* p=0.04; †p<0.001; ‡p=0.027



Summary target Hb trials

Study	SBP		dBP	
	Targeted Hb N-Hb	Targeted Hb S-Hb	Targeted Hb N-Hb	Targeted Hb S-Hb
CHOIR B	137 ± 20	136 ± 20	72 ± 12	71 ± 11
Last measure	134 ± 23	133 ± 22	72 ± 13*	70 ± 12
CREATE B	139 ± 17	139 ± 16	79 ± 10	80 ± 9
Last measure	136 ± 21	135 ± 19	79 ± 11	77 ± 12
ACCORD B	134	133	78	80
15 months	134	134	76	80

* p=0.02



Trials summary

- Most trials not powered to show difference in clinical outcomes like mortality, hospitalization
- High withdrawal/lost to follow-up rate
- Different targeted and achieved Hb level
- No standard for iron replacement therapy
- No standard definition for ADR
- Different study populations



Meta-analysis by Phrommintikul et al. *Lancet 2007; 369: 381-8.*

- Objective:** Association between targeting different Hb concentrations with ESA is associated with altered all-cause mortality and CV events in anemic CKD patients (pre-dialysis and dialysis)
 - Inclusion criteria**
 - Published in English
 - RCT in adult population
 - Studies assessing effect of targeting different Hb concentration with ESA (EPO α, EPO β, darbepoetin)
 - Exclusion criteria**
 - < 100 patients
 - Follow-up < 12 weeks
 - Baseline Hb < 80 g/L
- Outcomes assessed:** all-cause mortality, MI, change in BP, AV access thrombosis, effect on LV mass



Meta-analysis by Phrommintikul et al. *Lancet 2007; 369: 381-8.*

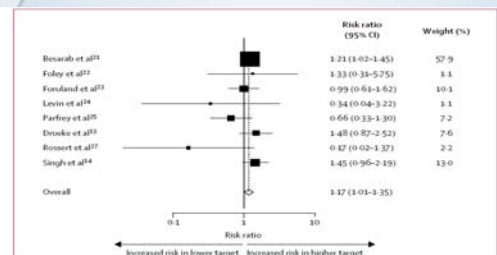


Figure 2: Risk of all-cause mortality in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

Sub-analysis in pre-dialysis patients: 1.33 (95% CI 0.98-1.81)



Meta-analysis by Phrommintikul et al. *Lancet 2007; 369: 381-8.*

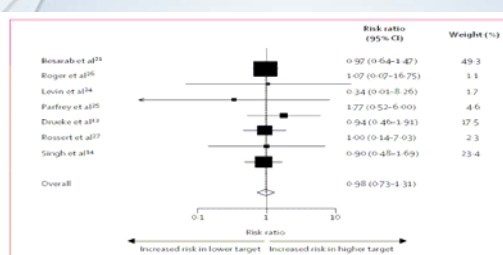


Figure 3: Risk of myocardial infarction in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

Sub-analysis in pre-dialysis patients: 0.90 (95% CI 0.58-1.41)



Meta-analysis by Phrommintikul et al. *Lancet 2007; 369: 381-8.*

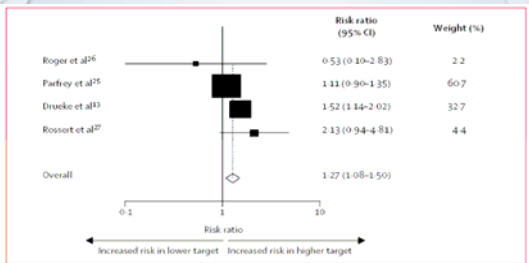


Figure 4: Risk of poorly controlled blood pressure in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

Coming up soon ... Results from TREAT

- Trial to reduced CV events with Aranesp therapy (TREAT)
 - Multicenter DB RCT
 - 4000 CKD (eGFR of 20-60 ml/min/1.73 m²) patients with type II DM
 - Darbepoietin α to maintain target Hb of 130 g/L or control arm where darbepoietin will be administered only if Hb < 90 g/L.
 - Primary endpoint: Time to mortality or non fatal CV events (MI, stroke or HF).
 - Results expected in 2008...

Coming up soon ... Results from STIMULATE study

- Anemia correction and HRQOL outcomes in elderly CKD patients
 - Multicenter SBRCT
 - 260 CKD (Stage 3-5 not on dialysis) patients older than 70 y/o
 - Darbepoietin α to maintain target Hb of 130 g/L or control arm where darbepoietin will be administered only if Hb < 90 g/L.
 - Primary endpoint: Patient-reported-vitality, as measured by SF-36
 - Results expected in 2008...

Coming up soon ... Results from NEPHRODIAB2 study

- Effect of 2 Hb levels on clinical outcomes
 - Open-label RCT
 - 200 CKD (eGFR of 25-60 ml/min/1.73 m²) patients with type II DM
 - ESA to maintain target Hb between 130-150 g/L or control arm where Hb level maintained between 110-130 g/L
 - Primary endpoint: Decline in renal function
 - Results expected in 2009...

Anemia in CKD

- Workup before starting ESA
 - CBC
 - Reticulocytes count
 - Iron study (serum iron, TIBC, Tsat, ferritin)
 - Stool for occult blood
 - Serum vitamin B12 and folate levels
 - Albumin level
 - iPTH level; Ca/Phosphorus level

Anemia in CKD



Anemia in CKD

- **FHA PD/CKD protocol**

- [\\My Documents\Fraser Health Renal program\FHA CKDPD anemia pathway.pdf](#)



37

A little talk about EPO!

- Hormone which is principal regulator of erythropoiesis
- Stimulates proliferation/maturation and inhibits apoptosis of erythroid progenitors
- Induces release of reticulocytes into bloodstream
- Primarily produced by cells of kidney peritubular capillary endothelium
- Production inversely proportional to O₂ availability and Hb concentration (if Hb < 105 g/L)



Priyadarshi. Seminars in dialysis 2006; 19: 273-8.

38

Pharmacotherapy

1. **Epoetin agents**

- Epoetin alpha (EPO α)
 - 1st recombinant human erythropoietin launched on the market
 - Shorter half-life
 - Administration 1-3 times/week (up to monthly)
 - 1 U SC : 1.3 U IV
- Darbeoetin alpha
 - Longer serum t_{1/2} and higher relative potency
 - Administration Q1-2 weeks (up to monthly)
 - Same dose IV vs SC
- Immunogenicity?



Deicher. Drugs 2004; 64: 499-509.

39

ADR with ESAs

1. **Hypertension**
 - 20-40% of patients with partial Hb correction
 - Mainly due to increase systemic vascular resistance
 - Mostly during the first 4 months of therapy
2. **Metabolic disturbances**
 - \uparrow sCr; \uparrow K⁺; \uparrow PO₄
 - \downarrow Dialyzer efficiency; and \uparrow appetite
3. **Myalgia and Flu-like illness**
 - Only report with IV EPO
 - Slow drug infusion
4. **Red eye syndrome**
 - Correction anemia for Hb > 100 g/L
 - Cosmetic effect



Zhu. Seminars in Dialysis 2006; 19: 279-84.

40

Possible ADR with ESAs

5. **Injection site pain**
 - Hypertonic citrate in formulation
6. **Thrombotic complications**
 - Vascular access thrombosis
 - Phrommintikul et al. MA, RR 1.34 (95%CI 1.16-1.54) for AV access thrombosis
7. **Exacerbation of diabetic retinopathy**
8. **Seizure**
 - Hypertensive encephalopathy



Zhu. Seminars in Dialysis 2006; 19: 279-84.

41

Iron deficiency in renal anemia

- **Definition**
 - Ferritin < 100 ng/ml
 - Iron transferrin saturation < 20%
- **Causes**
 - ESA
 - GI bleeding
 - Lab tests
 - Phosphate binder




Fishbane. Semin Nephrol 2006; 26:319-24.

42

Iron replacement therapy


- **Clinical situations**
 - Alternative to ESAs to obtain modest ↑ Hb
 - Prior to ESAs therapy, to boost iron store prophylactically
 - Treatment of absolute or function iron deficiency in patient receiving ESAs
 - Adjuvant therapy to enhance ESAs response
 - Decrease 33-75% ESA requirement
- **Administration route**
 - PO
 - IV
 - IM ⇒ only iron sorbitol; painful, skin discoloration, bleeding risk; absorption and bioavailability variable

Fishbane.Semin Nephrol 2006; 26:319-24. 

Iron replacement therapy

- **PO iron supplement**
 - No trial looking at PO iron vs placebo in CKD
 - GI intolerance (eg. dyspepsia, constipation)
 - Poor compliance and limited absorption from gut


Iron salts	Dosage	Elemental iron
Ferrous fumarate	300 mg	66 mg
Ferrous sulfate	300 mg	60 mg
Ferrous gluconate	300 mg	35 mg
Iron polysaccharide	150 mg	150 mg

Fishbane.Semin Nephrol 2006; 26:319-24. 

Iron replacement therapy

- **IV iron supplement**
 - 5 trials looking at IV vs po iron
 - Mixed results... but overall IV iron seems more effective
 - Concern about renal tubular toxicity and damage to blood vessels
 - Administration... bolus vs infusion?

Formulation	Usual dosage
Iron dextrose	100 mg
Iron sucrose	100 mg
Sodium ferric gluconate complex	125 mg

Fishbane.Semin Nephrol 2006; 26:319-24. 

Pharmacotherapy

2. Continuous erythropoietin receptor activator
 - CERA (to be launched by Roche in June 2007)
 - Longer elimination half-life
 - Administration Q3-4 weeks




Possibly on your shelves soon...

3. Synthetic erythropoiesis protein
4. Erythropoietin fusion protein
5. Erythropoietin-mimetic peptides
6. HIF- α stabiliser
7. Erythropoietin gene therapy

Lancet 2006; 368:947-53. 


Economic impact of normal Hg

- U.S Normal Hematocrit Study
 - Dose of EPO 3 times higher in Hb=140 g/L vs Hb=100g/L group
 - Cost-effectiveness study by Tonelli et al.
 - Incremental cost per QALY of 50,000-60,000\$ if Hb maintained between 110-120 g/L vs 95-105 g/L
 - Incremental cost per QALY of 800,000\$ if Hb maintained at target of 140 g/L vs 120-125 g/L



Individualizing target Hb level


- Age
- Gender
- Comorbidities
 - CVD
 - DM
 - COPD
- Occupation
- Starting Hb
- Vascular access
- Dialysis Modality
- Length of time with anemia/CKD



Macdougall, Blood Purif 2001; 19: 157-67.

Still unknown area

- **Lake of data to individualize therapy**
 - Optimal Hb range according to patient CKD stage
 - Optimal Hb range for CKD patients obtaining normal hemoglobin with low dose of ESA
 - Optimal Hb range according to age, sexe, level of activity, co-morbidities
 - Optimal time to start ESA treatment
 - Predictors of low Hb
 - Treatment of anemia in peritoneal patients
 - Treatment of anemia with daily and nocturnal dialysis patients



Questions?






Better health. Best in health care.

EPO resistance

- Failure to achieve Hb in presence of adequate iron store at EPO IV dose 450 UI/kg/week within 4-6 months OR maintain target Hb at this dosage
- **Causes**


▪ Infection/Inflammation	▪ Malnutrition
▪ Blood loss	▪ Carnitine deficiencies
▪ Osteitis fibrosa	▪ PRCA
▪ Aluminium toxicity	▪ Dialysis dose/frequency
▪ Hemoglobinopathies	▪ Drugs (eg. ACE inh.)
▪ Folates and vit. B12 deficiencies	
▪ MM	
▪ Hemolysis	



Nurko S. Clev Clinics J Med 2006; 73: 289-97.

Pure red cell aplasia


- Severe, isolated anemia of sudden onset with
 - Complete absence of RBC precursors
 - Reticulocyte count < 10 x 10⁹/L
- Induction of Antibody against EPO molecule
- Antibody cross-reactivity between recombinant erythropoietic products
- No case confirmed with IV ESA
- Could be linked to stabilizer solution; uncoated rubber stoppers



Boven K. Nephrol Dial Transplant 2005; 20 : iii33-40.

Lab values interpretation

- **Hemoglobin (Hb)**
 - Concentration of hemoglobin in whole blood
 - Mean Hb 140 g/L in premenopausal ♀
 - Mean Hb 155 g/L in postmenopausal ♀ and ♂
 - Value post-dialysis 10-30 g/L superior
- **Hematocrit (Hct)**
 - % of whole blood comprised of RBC
 - Mean Hct of 41% in premenopausal ♀
 - Mean Hct of 47% in postmenopausal ♀ and ♂
 - Higher variability than Hb value
- Value with high intra- and interpatient variability



http://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf

Retrospectives studies

- Mostly data from HD population
- Hb level between 110-120 g/L
 - ↓ mortality
 - ↓ hospitalization
- Collins et al.
 - CKD Medicare database
 - Anemia has ↑RR of mortality than DM
 - Anemia independently increased mortality to other known risk factors

55

Nurko S. *Clev Clinics J Med* 2006; 73: 289-97. 

Sub-analysis

- RENAAL study
 - Hb < 112 g/L ⇒ 60 % event rate of doubling sCr or ESRD
 - Hb > 138 g/L ⇒ 20 % event rate of doubling sCr or ESRD
- SOLVD
 - Every 1% ↓ in Hct increase RR for mortality by 7.4%
- ARIC
 - Strong correlation between anemic state and stroke in CKD patients

56

Nurko S. *Clev Clinics J Med* 2006; 73: 289-97. 

Retrospectives and Observational studies... Limitations!

- Acute illness
 - Can take months before resolution and Hb back into normal range
 - Anemia marker of disease severity
- Association between rHuEPO dose and all-cause mortality rate
- Anemia as causative factor or marker of disease severity???
- Does not imply that correcting anemia will improve outcome!

57

Nurko S. *Clev Clinics J Med* 2006; 73: 289-97. 

Prospectives studies

- Renal failure progression
 - Hypoxia associated with kidney tissue damage
 - Chronic reduction in nephron number associated with increased O₂ consumption and increased production of ROS
 - EPO may protect vs kidney cells apoptosis
 - Kuriyama et al. *Nephron* 1997
 - RCT, untreated anemic patients vs treated anemic patients (Hct 33-35%) and untreated nonanemic group
 - Epo 6000 UI IV weekly x 36 weeks
 - Renal survival (doubling of sCr) higher in treated anemic group vs untreated anemic group (p=0.0003)
 - Renal survival better in nondiabetic patients (p=0.0029)
 - Gouva et al. *Kidney Int* 2004
 - RCT, early EPO treatment (target Hb 116 -130 g/L) vs deferred EPO treatment (if Hb < 90 g/L) in nondiabetic patients
 - EPO α, 50 UI/kg sc weekly x 17 months
 - Less initiation of renal replacement therapy or death in early EPO group (RH 0.43 95%CI 0.22-0.85)
 - Similar benefit in patients with high vs low baseline creatinine

58



Prospectives studies

- US Normal Hematocrit study
 - 1233 HD patients with cardiac disease (CHF or IHD)
 - Epo to obtain Hct 42 ± 3% vs 30 ± 3%
 - Stopped prematurely because of safety concerns
 - Time to death or non-fatal MI ↑(1.3; 95% CI 0.9-1.9) in higher Hct group
 - ↑ rate of vascular access thrombosis in normal Hct group
- Canadian Normalization of Hemoglobin trial
 - 146 HD patients with asymptomatic cardiomyopathy
 - Epo to obtain Hb 95-105 g/L vs 130-140 g/L
 - No regression of LVH
 - Improve QOL

59

Nurko S. *Clev Clinics J Med* 2006; 73: 289-97. 

Anemia in CKD

- Less than 35% of CKD patients non-dialysis dependant are receiving ESA
- 75% of patients initiating dialysis have an Hb level < 110 g/L

60

