ROLE OF ERYTHROPOIESIS STIMULATING AGENTS (ESAs) IN RENAL ANEMIA

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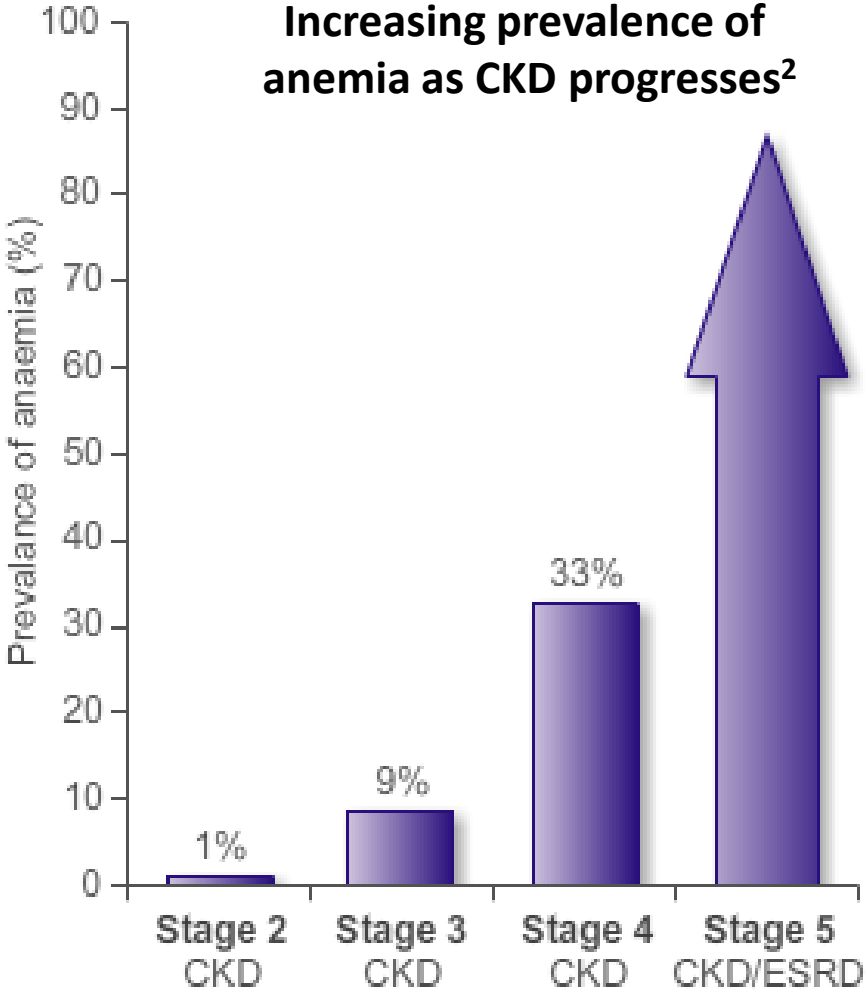
ROLE OF ESAs IN RENAL ANEMIA

- Historical background
- Mechanisms of ESAs
- Role of ESAs in renal anemia
- Types of ESAs
- Clinical Trials
- Newer agents in renal anemia

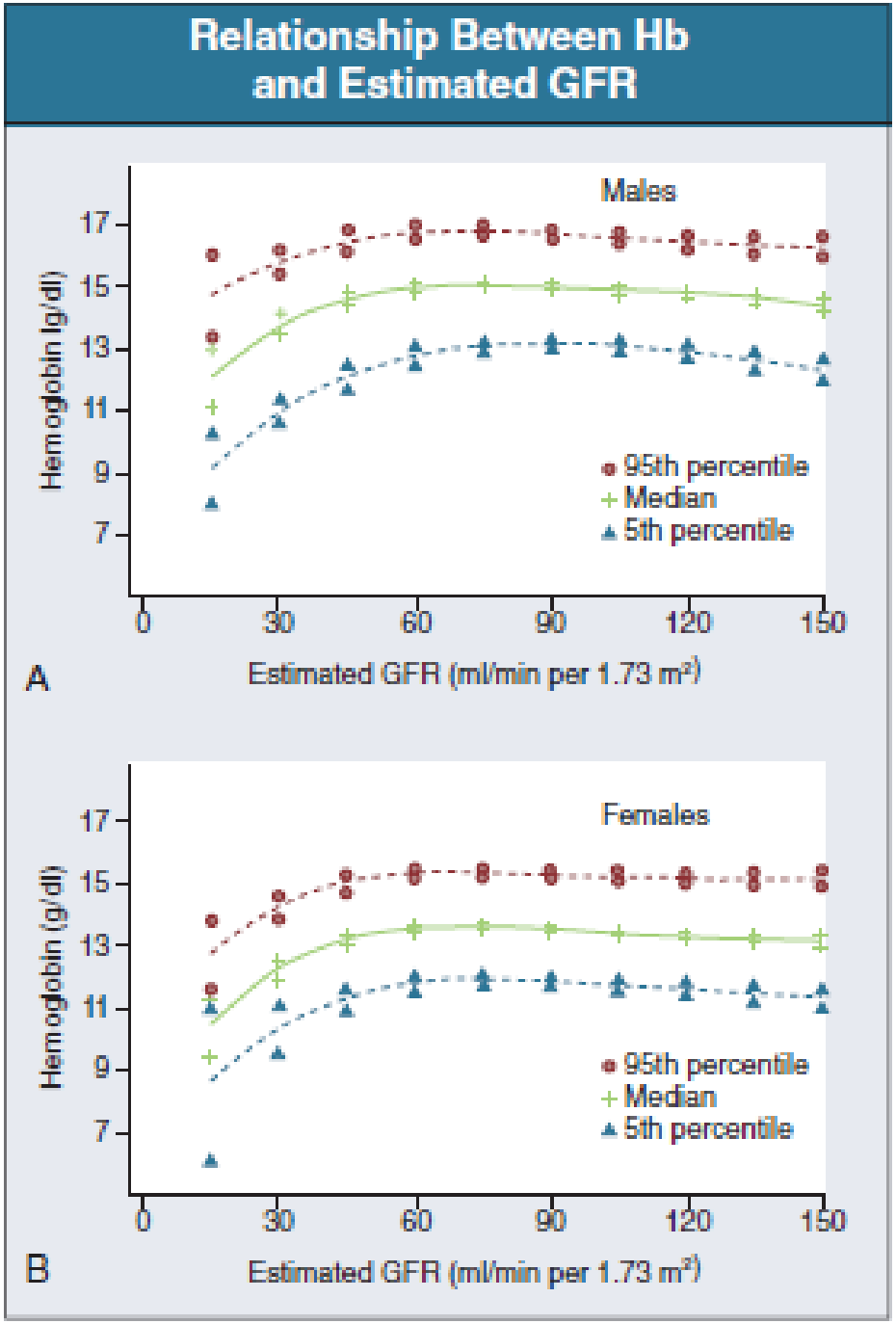
Prevalence of Anemia in CKD

- Anemia often develops in the early stages of CKD, but the likelihood increases as the disease progresses[1]
- A large proportion of patients with advanced CKD (stages 3b-4) are affected by anemia[2]

Increasing prevalence of anemia as CKD progresses[2]



1. *Hainsworth T. Nursing Times. 2006;102:23.*
2. *Mikhail , et al. Clinical Practice Guidelines – Anaemia of CKD: UK Renal Association. 2010:1-40.*

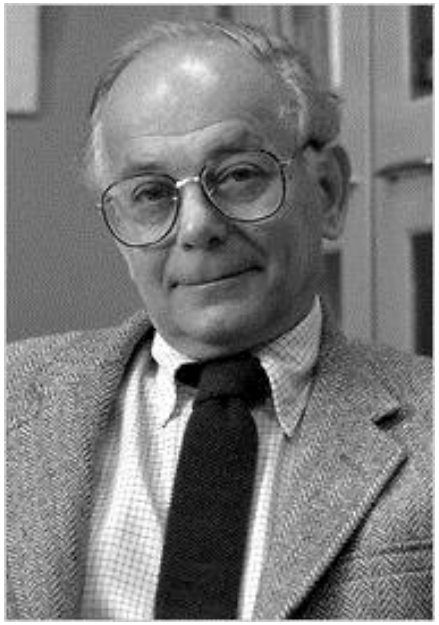

Relationship Between Hb and Estimated GFR
Males
Hemoglobin lg/dl)
17
15
13
11
9
7
0
30
60
90
120
150
95th percentile
Median
5th percentile
A
Estimated GFR (ml/min per 1.73 m²)
Females
Hemoglobin (g/dl)
17
15
13
11
9
7
0
30
60
90
120
150
95th percentile
Median
5th percentile
B
Estimated GFR (ml/min per 1.73 m²)

HISTORICAL BACKGROUND

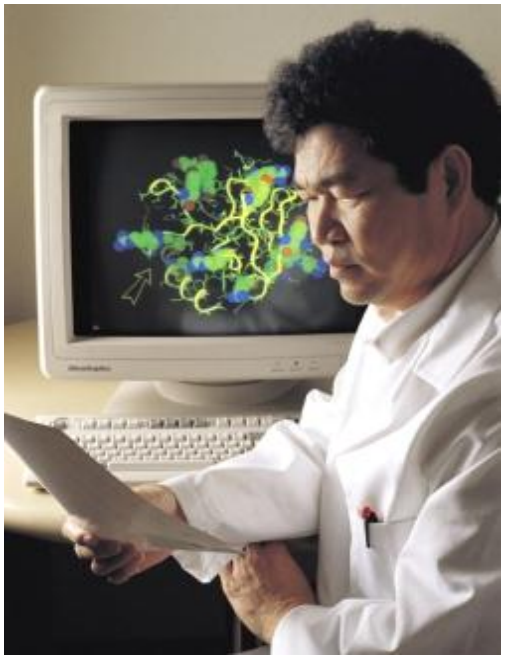
- 1974 - Allan Erslev demonstrated the presence of Erythropoietin in the kidney.
- 1977 - Eugene Goldwasser first isolated erythropoietin from urine.
- 1983 - Lin et al cloned and expressed the human Epo gene
- 1986 - Winearls et al reported the first use of rHu Epo in chronic hemodialysis patients
- 1989 - FDA approved of rHu Epo for treatment of renal anemia

Pioneers

Allan Erslev



Eugene Goldwasser



Fu Kuen Lin

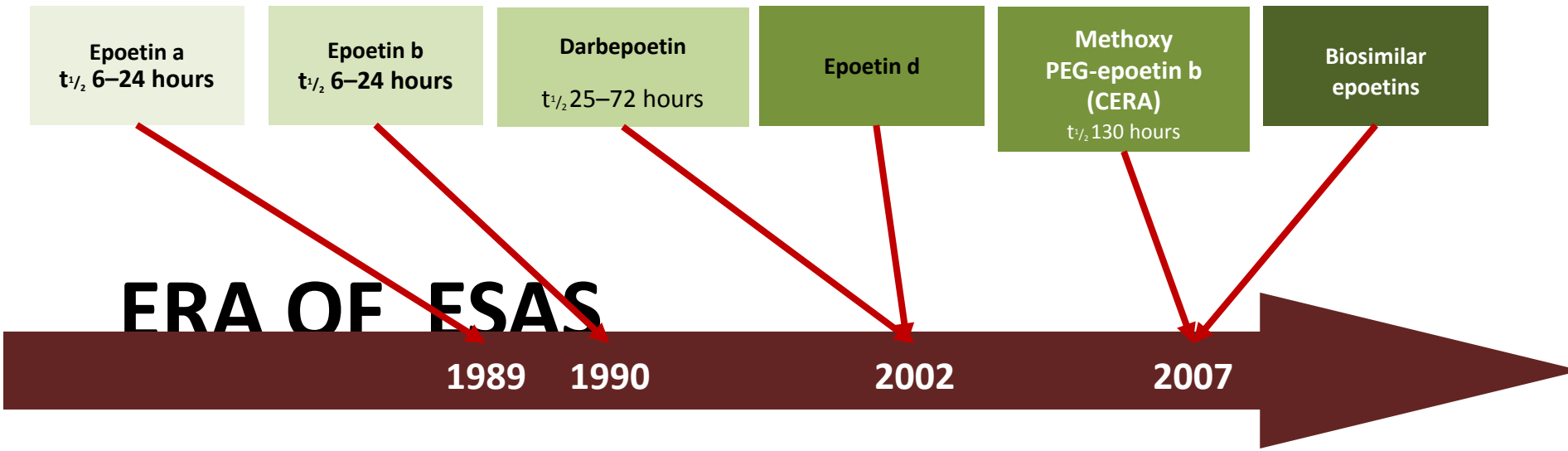
By 1991, in dialysis,

- There were no longer patients requiring regular transfusions for severe anemia (eg, hemoglobin concentration, <7 g/dL)
- Dialysis center–based transfusions had decreased by more than 65%.

ESA's **transformed** the management of CKD anemia

by allowing a **more sustained increase** in Hb…

HX575 and SB309



- Fishbane S. Curr Opin Nephrol Hypertens 2009;18:112–115

Macdougall IC & Ashenden M. Adv Chron Kid Dis 2009;16:117–130

Szu-Chun Hung a, Yao-Ping Lin b,c, Der-Cherng Tarng

;Journal of the Formosan Medical Association (2014) 113, 3e10

Table 1 Milestones in the use of erythropoiesis-stimulating agents in chronic kidney disease.

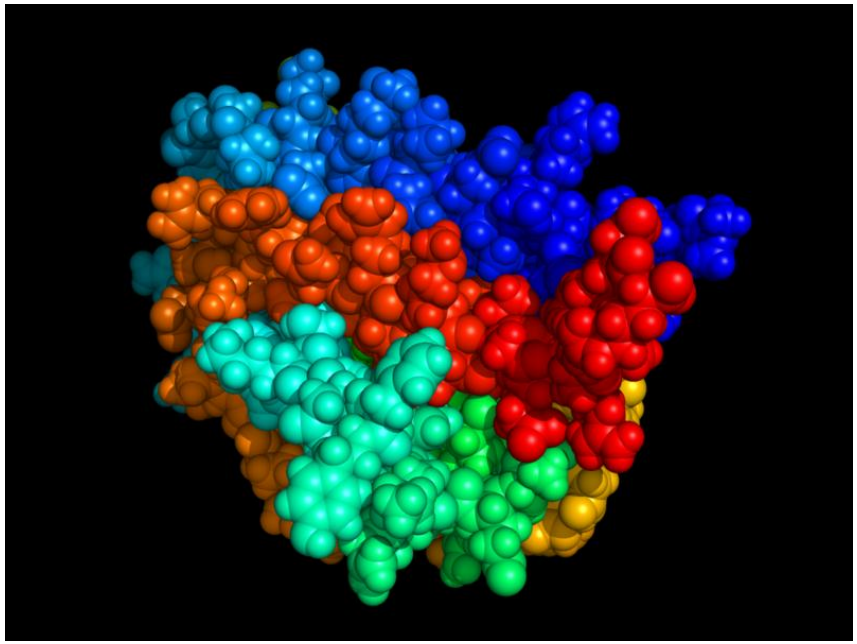
1836	Bright described anemia as a complication of renal failure[51]
1957	Jacobson et al established that the kidney produces EPO[52]
1977	Miyake et al purified human EPO from the urine of patients with aplastic anemia[7]
1983	Lin et al cloned and expressed the human EPO gene[8]
1986	Winearls et al reported the first use of rHuEPO for anemia in patients on chronic hemodialysis[14]
1987	Eschbach et al reported the correction of anemia of end-stage renal disease with rHuEPO. Results of a combined phase I and II clinical trial[1]
1989	FDA approval of the first rHuEPO for the treatment of renal anemia
1996	PRCA reported[9]
1998	Normal Hematocrit Trial[15]
2001	FDA approval of Aranesp (darbepoetin α)
2006	KDOQI guideline for anemia in CKD[53]
2006	CREATE and CHOIR studies[16,17]
2007	FDA approval of MIRCERA
2007	DRIVE study[34]
2009	TREAT study[18]
2011	FDA modifies dosing recommendations for ESAs
2012	KDIGO Clinical Practice Guideline for Anemia in CKD[21]
2012	CAPRIT study[22]
2013	EMERALD and PEARL studies[12,13]

ERYTHROPOIETIN

- It is a Gylcoprotein hormone, synthesized by the intrestitial fibroblasts of peritubular region of kidneys in adults and by liver in fetal and perinatal period.
- Molecular weight is 34kD.
- Gene is located on the long arm of chromosome 7 (7q11-q22).

- The primary structure of a mature erythropoietin(and hence rHuEPO) containing 165 amino acids

- The molecular mass of the polypeptide backbone and the glycosylated form of erythropoietin is estimated to be 18 kDa and 30 kDa respectively



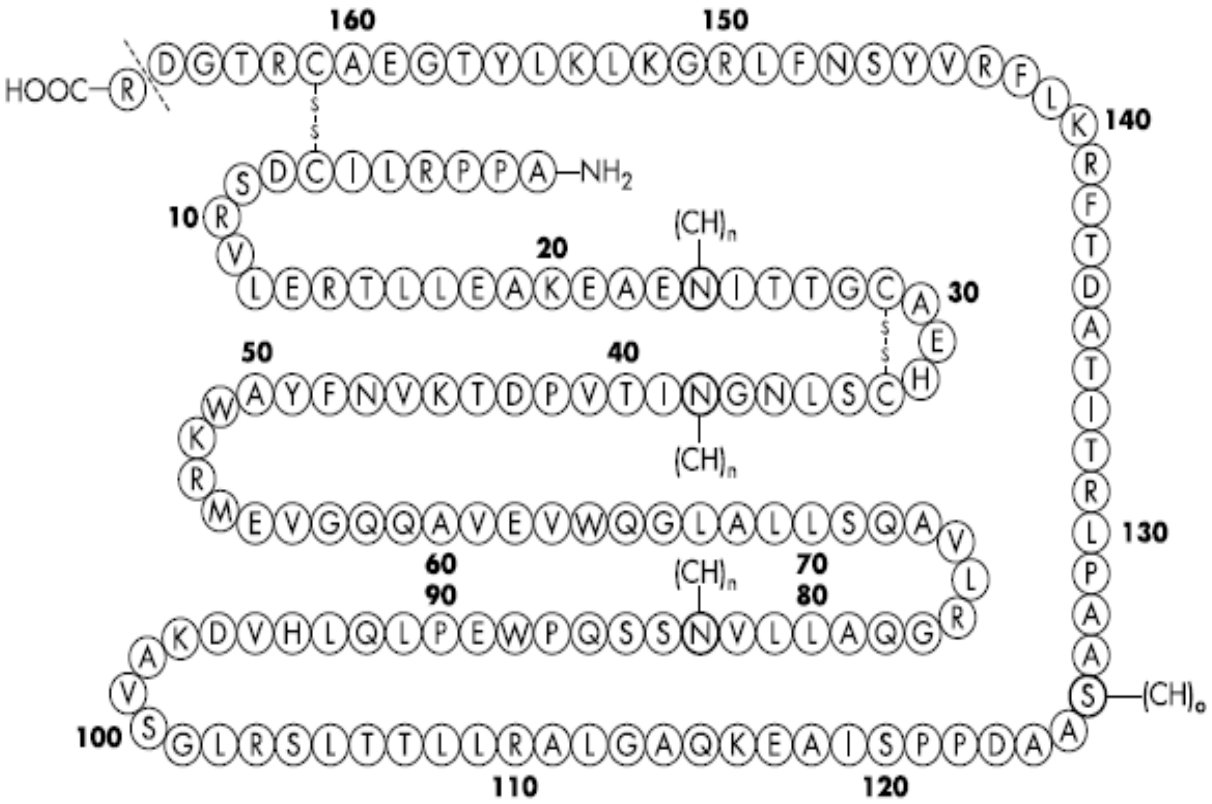


Figure 1 Primary structure of erythropoietin (hence RHuEPO). $(CH)_n$, *N*-linked glycosylation site at aspartyl residues 24, 38, 83; $(CH)_o$, *O*-linked glycosylation site at seryl residue 126. **NB**: The ARG-166 at the carboxyl terminal is removed before erythropoietin is released into the circulation.

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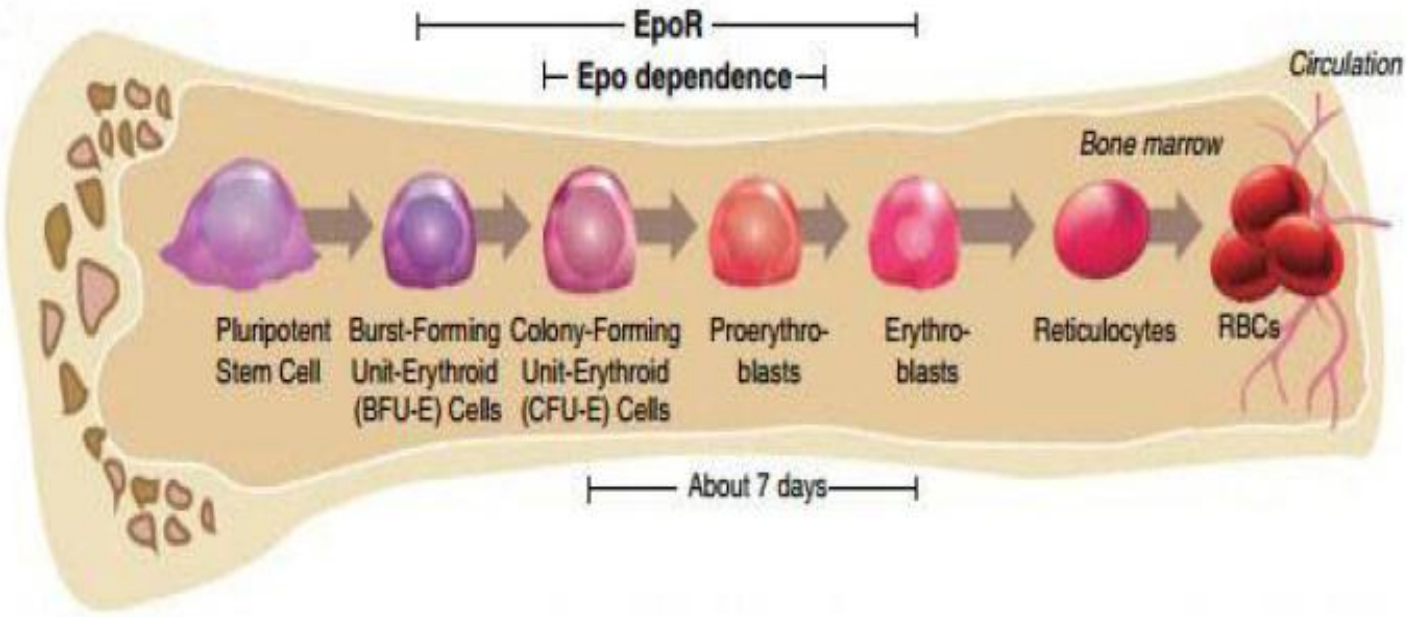


Figure 1: The process of erythropoiesis. Depend on Epo and EpoR, erythroid progenitors differentiation into mature red blood cells. Quote from *Ann Hematol*2014; 93(2):181-192. Elliott S1, Sinclair A, Collins H, Rice L, Jelkmann W. Progress in detecting cell-surface protein receptors: the erythropoietin receptor example

- Erythropoietin is essential for the proliferation, differentiation,and maturation of RBCs in bone marrow.
- Erythropoietin is critical for the survival of RBC progenitors in bone marrow
- Erythropoietin may also have immunomodulatory activity

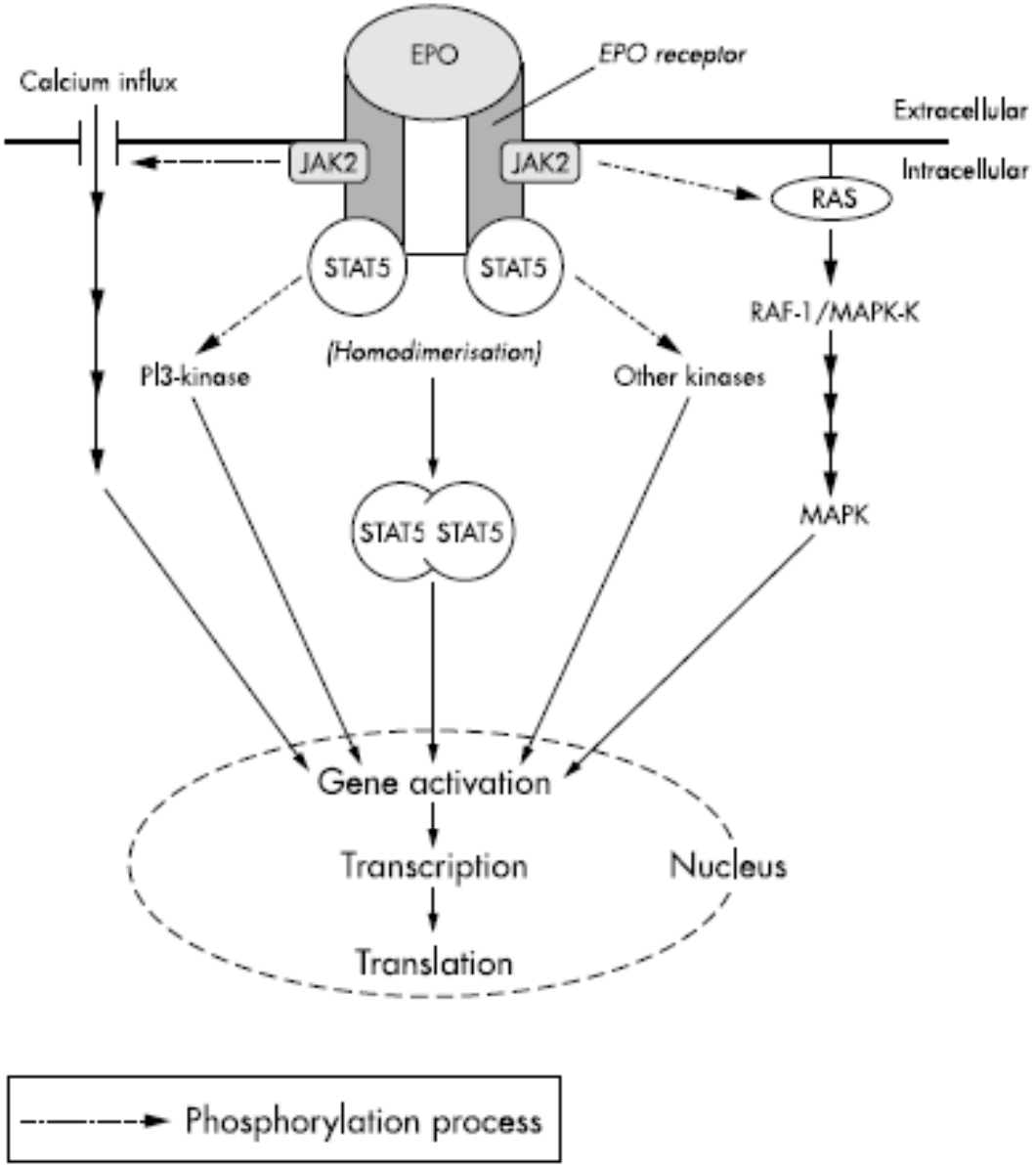
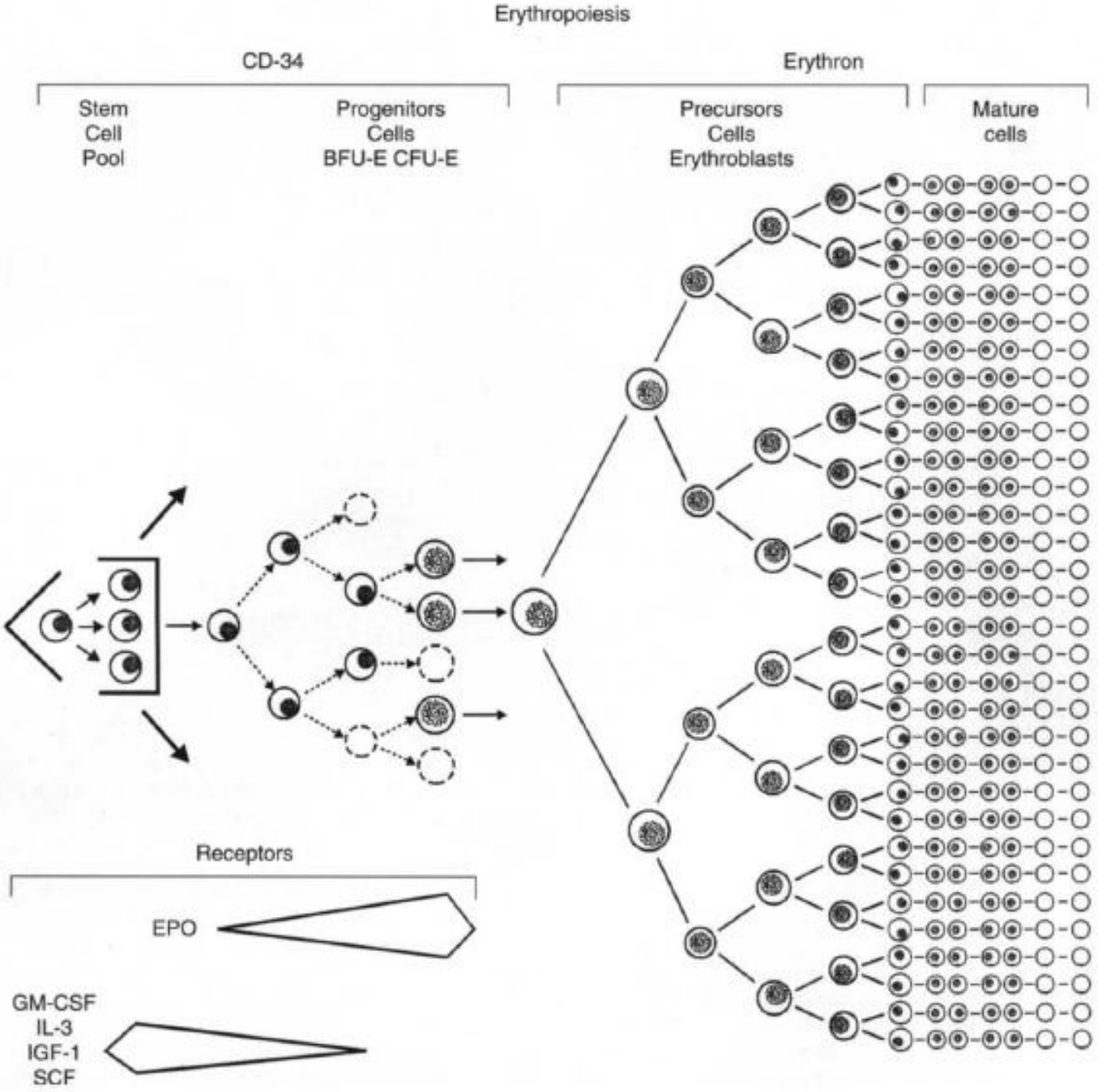


Figure 3 Simplistic view of the main signal transduction pathways activated by the erythropoietin (EPO) receptor.


Erythropoiesis
CD-34
Erythron
Stem Cell Pool
Progenitors Cells BFU-E CFU-E
Precursors Cells Erythroblasts
Mature cells
Receptors
EPO
GM-CSF
IL-3
IGF-1
SCF

Types of ESAs

Protein based ESA therapy

Epotein (alfa, beta, delta, omega)
Biosimilies (epoetin zeta)
Darbopoietin alfa—Glysocylated erythropoietin
CERA(methoxy polythylene glycol epoetin beta)
Synthetic Erythropoietin (SEP)
EPO fusion protein----- EPO-EPO
- GM-CSF-EPO
- Fc-EPO
- CTNO 528

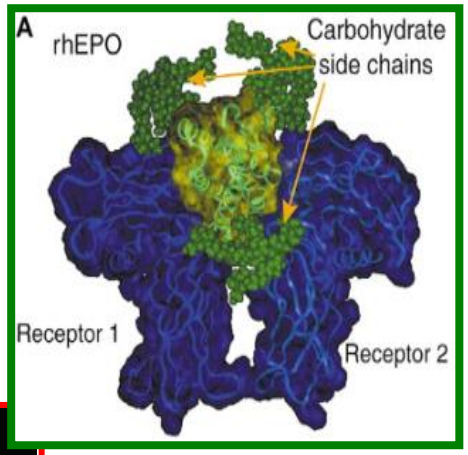
Small molecule ESAs

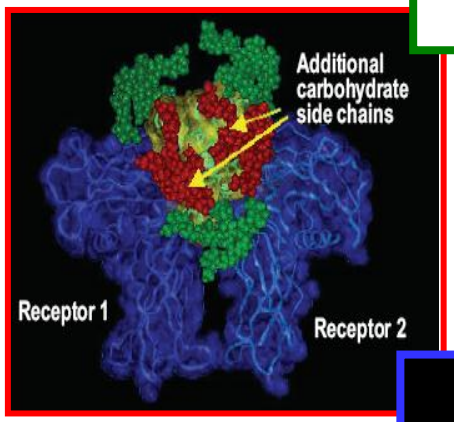
Peptide based (e.g. Hematide)
Non-peptide based.

Currently Available ESAs

- **Recombinant human erythropoietin (rHuEPO)**
  - Epoetin alfa
  - Epoetin beta
  - Epoetin delta
  - Epoetin theta (Europe)
- **Longer-acting ESAs**
  - Darbepoetin alfa (Aranesp)
  - Methoxy-PEGylated epoetin beta (Mircera)

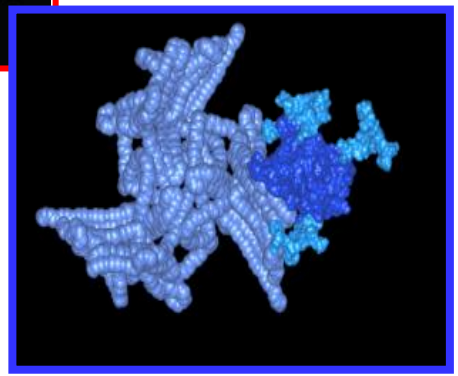
rHuEPO





Darbepoetin alfa

Mircera



Elliott S, et al. Nat Biotechnol. 2003;21(4):414-421.

ADMINISTRATION OF ESAs
IV or SC ?

Route of administration

- Both intravenous and subcutaneous administrations are commonly used to deliver rHuEPO to renal patients.
- Clinical studies have demonstrated that the subcutaneous route offers a few advantages over intravenous administration.
- subcutaneous administration is more convenient as it does not require any venous access.

- subcutaneous RHuEPO administration significantly prolongs the increase of serum erythropoietin, thus sustaining the stimulation of erythropoiesis.
- up to 30% reduction in total weekly RHuEPO dosage on haemodialysis patients could be achieved to maintain the same haemoglobin level when switching intravenous to subcutaneous administration.

- Intraperitoneal administration of RHuEPO could be an alternative for the subcutaneous route to renal patients receiving peritoneal dialysis.
- A larger dose of RHuEPO may be required to maintain the same haemoglobin level if RHuEPO has to be applied intraperitoneally.

- increasing concern of pure red cell aplasia associated with subcutaneous EPO-alpha administration to renal patients, the Department of Health in UK recommends EPO-alpha administration to intravenous.
- However, it remains uncertain whether similar measure will be applied to the other recombinant erythropoietins.

- Outside the uraemic setting, both intravenous and subcutaneous RHuEPO have been employed
- The subcutaneous route was used in the majority of the studies.
- However, there have been no studies to compare the efficacy of these routes.

ESA ADMINISTRATION

3.9.1: For CKD 5HD patients and those on hemofiltration or hemodiafiltration therapy, we suggest either intravenous or subcutaneous administration of ESA. (*2C*)

3.9.2: For CKD ND and CKD 5PD patients, we suggest subcutaneous administration of ESA. (*2C*)

Frequency of administration

3.10: We suggest determining the frequency of ESA administration based on CKD stage, treatment setting, efficacy considerations, patient tolerance and preference, and type of ESA. (*2C*)

ESA dosing

Generic name	Trade name	Half-life	Initial dosing	eg. Starting dose
Epoetin α	Eprex,Epogen Procrit	4-8 hrs	80-120 IU/kg in 3 divided doses	2000 IU x 3 /wk
Epoetin β	Neo Recormon	4-12 hrs	80-120 IU/kg in 3 divided doses	2000 IU x 3 /wk
Darbepoetin α	Aranesp	21-25 hrs	0.45 ug/kg 1 x wk	30 ug 1 x wk
Methoxy polyethylene Glycol Epoetin β	Mircera	130 hrs	0.6 ug/kg fortnightly	50 ug fortnightly

Before & After starting ESAs

- Ensure iron replete
- Measure Hb and BP 2-4 weekly at first and after a dose change
- Aim for increase in Hb of 1-2 g/dl / month until target achieved
- Increase dose monthly (25% increment) if slow Hb rise.
- Reduce dose by 25-50% if Hb rises >2 g/dl in a month

Blood pressure monitoring

- All patients on ESA therapy (initiation and maintenance) require blood pressure measurement prior to administration
- ESA should not be given if the diastolic blood pressure consistently exceeds 100mmHg or the systolic consistently exceeds 170mmHg

Guidelines for target indices in CKD associated anemia

	Hb target (g/dl)	Iron indices
KDOQI	11-12 (AVOID > 13)	Ferritin > 200 mg/l (HD) or >100 (non-HD) TSAT >20%
UK RENAL ASSOCIATION	11-12	Ferritin 200-500 ug/L (HD) or >100-500 ug/L (non-HD) TSAT >20% or HRBC <6 %
KDIGO	≥ 10-11.5	TSAT ›30% and ferritin ›500 ng/ml

Influential clinical trials

- NHCT
- CHOIR
- CREATE
- TREAT

Four randomized controlled trials of hemoglobin-raising in chronic kidney disease

	NHCT[52]	CHOIR[53]	CREATE[54]	TREAT[55]
Population	Patients with chronic heart failure and end-stage renal disease on dialysis	Chronic kidney disease	Chronic kidney disease	Chronic kidney disease with diabetes
Hemoglobin target	10 vs 14 g/dL	13.5 vs 11.3 g/dL	> 13 vs 11 g/dL	> 13 vs 9 g/dL
Target achieved?	No	No	Yes	No
Primary outcomes	Time to death or first myocardial infarction	Composite of death, myocardial infarction, hospitalization for chronic heart failure, stroke	Time to first cardiovascular event	Composite of death or a cardiovascular event and death or end-stage renal disease
Risks with higher hemoglobin level	Trend toward increased risk of primary outcome resulted in early study interruption	Increased risk of primary outcome	Trend toward risk increase that was nonsignificant: no benefits	No risk increase or reduction
Other results	Higher rate of thrombosis in high-target group		Improved quality of life	Higher rate of stroke

NHCT = Normal Hematocrit Study,[52] CHOIR = Correction of Hemoglobin and Outcomes in Renal Insufficiency trial,[53] CREATE = Cardiovascular Risk Reduction by Early Anemia Treatment trial,[54] TREAT = Trial to Reduce Cardiovascular Events With Aranesp Therapy[55]

Other Uses of ESAs

- Replacement therapy (low endogenous erythropoietin level) in anaemia associated with:

(A) Chronic renal failure.
(B) Malignancy.
(C) Prematurity.
(D) HIV infection.

- Supportive therapy (to maintain/accelerate erythropoiesis) in:

(A) Post-chemotherapy/post-radiotherapy.
(B) Post-transplantation.

- Augmentative therapy (increase haemoglobin above physiological level) in:

(A) Surgery.
(B) Situations where blood transfusion is refused/disallowed.
(C) Sport (potential abuse by athletes).

- To enhance autologous transfusion so as to maintain haemoglobin perioperatively.
- Other potential therapeutic applications:

(A) Anaemia associated with—autoimmune diseases, acute haemolysis, haemoglobinopathy.
(B) Acute renal failure.
(C) Critically ill patients.
(D) Neuroprotection.
(E) Congestive cardiac failure.

ESAs additional benefits

- Enhanced quality of life scores
- Improved exercise capacity
- Improved cardiac function status
- Regression of LVH and improved LV architecture
- Improved immune responses
- Improved cognitive function

ESA resistance or hyporesponsiveness

- True ESA resistance is defined as;

➢ Failure to reach target Hb or

➢ The need to administer above a threshold ESA dose (eg.≥ 300 IU/kg/wk of epo α or β) or

1.5 ug/kg/wk of darbepoetin α to maintain target Hb

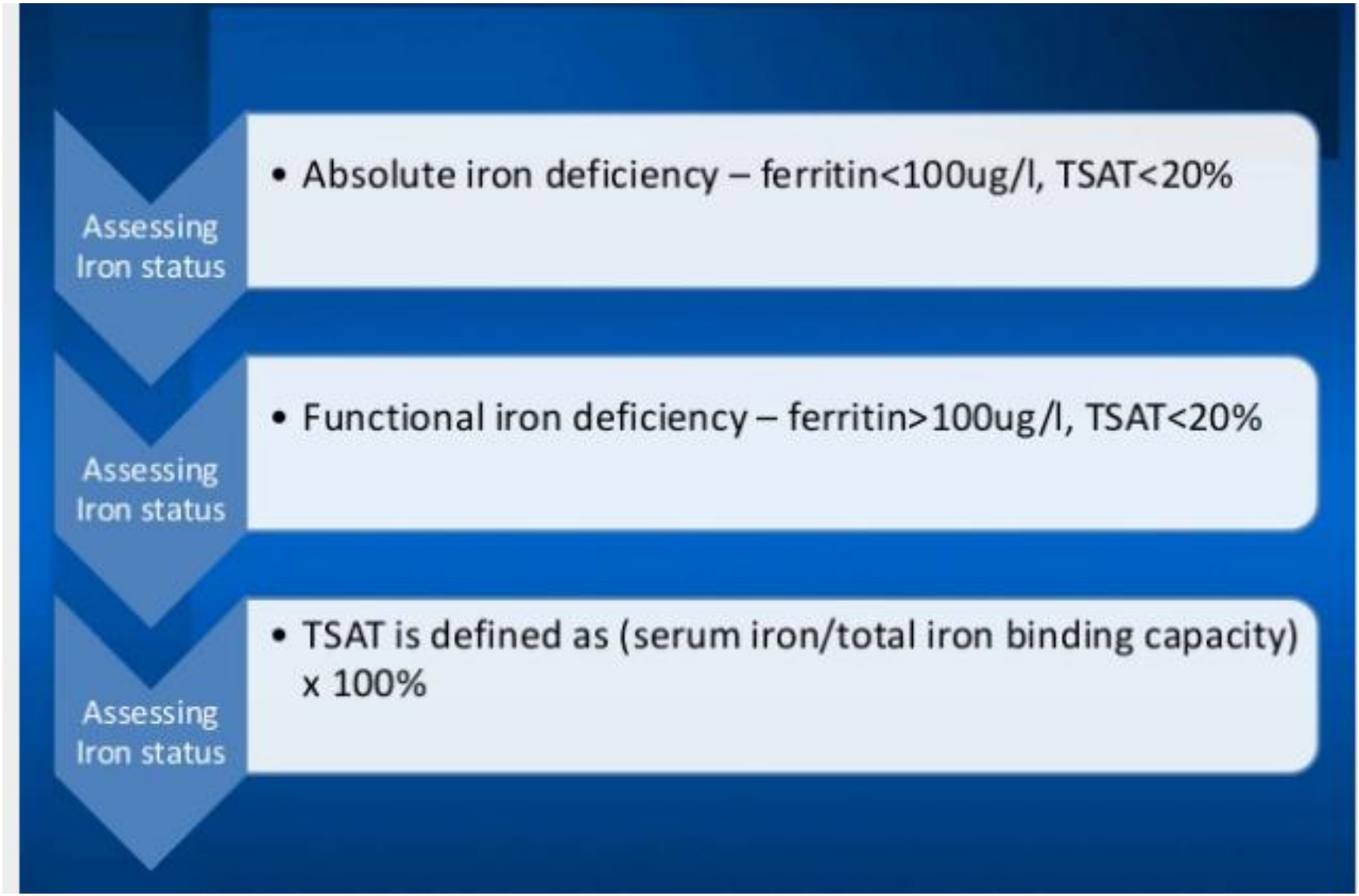
Factors influencing on the response to ESAs

Therapeutic

- Non-compliance.
- Suboptimal treatment: "faulty" delivery, incorrect dosage of RHuEPO, under-dialysis.

Pathological

- Iron deficiency.
- B12/folate deficiency.
- Infection.
- Inflammation.
- Blood loss: haemorrhage, haemolysis (intravascular/extravascular).
- Metabolic disorder—for example, secondary hyperparathyroidism.
- Extensive bone marrow involvement: malignant cells, fibrosis, aluminium toxicity.
- Erythropoietin antibody ± pure red cell aplasia.


Assessing Iron status
• Absolute iron deficiency – ferritin<100ug/l, TSAT<20%
Assessing Iron status
• Functional iron deficiency – ferritin>100ug/l, TSAT<20%
Assessing Iron status
• TSAT is defined as (serum iron/total iron binding capacity) x 100%

RBC parameters

- Haemoglobin level.
- Packed cell volume.
- Reticulocyte: absolute count, relative percentage, mean haemoglobin.
- Percentage of hypochromic RBCs.

Cytokines

- Serum erythropoietin level.
- Tumour necrosis factor-α.

Iron status

- Serum ferritin level.
- Transferrin saturation.
- Soluble transferrin receptor.

Pure red cell aplasia

- A very rare complication of RHuEPO treatment.
- Associated with patients chronic renal failure requiring dialysis.
- Persistent or worsening anaemia despite maximised RHuEPO therapy.
- Median age of presentation: 61 years.
- Male to female ratio: 2 to 1.
- Median duration of RHuEPO treatment to time of diagnosis: seven months.
- Aetiology: unknown.
- Associated with neutralising antierythropoietin antibody directed against the polypeptide backbone (rather than the glycosylated moiety).

EVALUATION FOR PURE RED CELL APLASIA (PRCA)

3.17.1: Investigate for possible antibody-mediated PRCA when a patient receiving ESA therapy for more than 8 weeks develops the following (*Not Graded*):

- Sudden rapid decrease in Hb concentration at the rate of 0.5 to 1.0 g/dl (5 to 10 g/l) per week *OR* requirement of transfusions at the rate of approximately 1 to 2 per week, *AND*
- Normal platelet and white cell counts, *AND*
- Absolute reticulocyte count less than 10,000/μl

3.17.2: We recommend that ESA therapy be stopped in patients who develop antibody-mediated PRCA. (*1A*)

3.17.3: We recommend peginesatide be used to treat patients with antibody-mediated PRCA. (*1B*)

Newer agents

- HIF stabilizers
- Hepcidin modulation
- EPO gene therapy
- EPO fusion proteins
- GATA inhibitors
- Hemopoietic cell phosphatase inhibitors

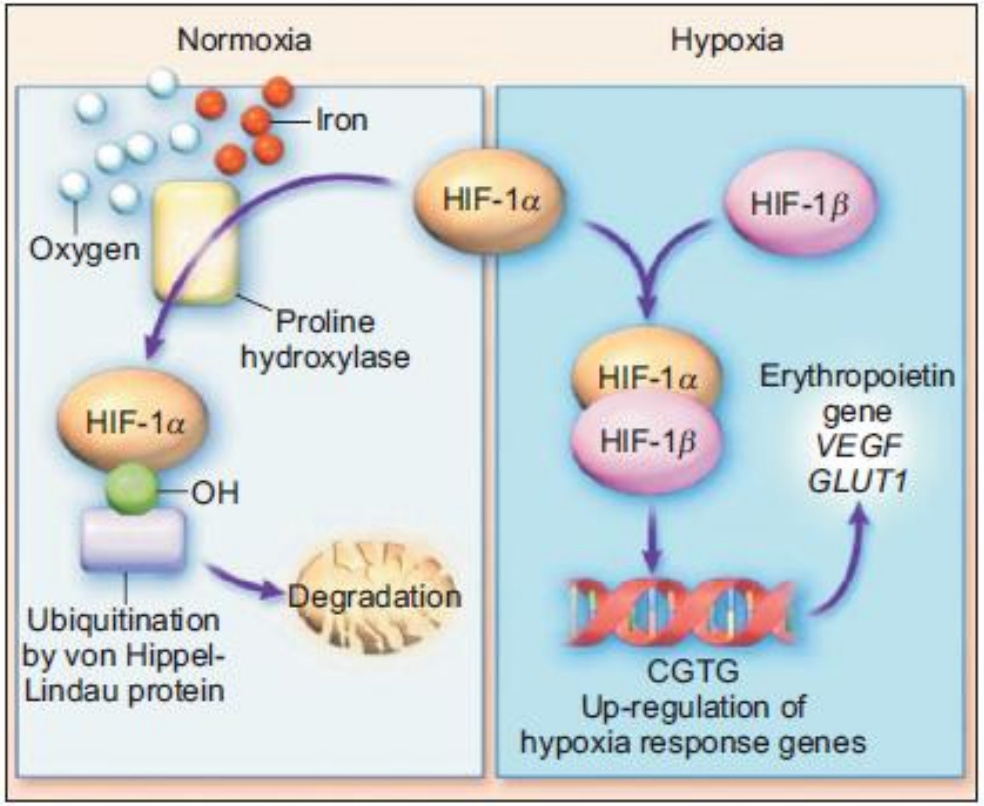


Figure 5. In the presence of oxygen, prolin hydroxylase oxidates hypoxia inducible transcription factors (HIF)-1α, which is then degraded (ubiquination) via the Hippel-Lindau-protein, thus inhibiting conglomeration of the HIF-1α/HIF-1β-complex, which would otherwise up-regulate the hypoxia-response genes.
Adapted from the article of Prchal (N Engl J Med 348:1282-1283, 2003) [53] with original copyright holder's permission.

HIF stabilizers

- The HIF-prolyl-hydroxylase inhibitors
  - GSK1278863 [daprodustat],
  - BAY 85-3934 [molidustat],
  - FG 4592 [roxadustat])
- exert their effects via the molecular oxygen sensing mechanisms and influence several systems.

Characteristics of HIF-PH Inhibitors Under Development

Generic Name	Investigational Name	Generic Name	Sponsor	Half Life (hr)	Dosing Frequency	Investigational Status
Roxadustat	FG-4592	Roxadustat	FibroGen, Astellas & AstraZeneca	12-13	3x weekly	Phase 3
Vadadustat	AKB-6548	Vadadustat	Akebia	4.5	Daily	Phase 3
Daprodustat	GSK-1278863	Daprodustat	Glaxo-SmithKline	4	Daily	Phase 2 (US) Phase 3 (Japan)
Molidustat	BAY 85-3934	Molidustat	Bayer	NA	Daily	Phase 2

Adjuncts to ESA therapy

- Ascorbic acid
- L- carnitine
- androgens

Ascorbic acid

- Increase iron release from ferritin and the RE system
- Enhances iron utilization during Hb synthesis
- Needs to be given IV as orally ineffective
- Secondary oxalosis is a safety concern
- Insufficient evidence for routine use

L- carnitine

- Required for long chain fatty acid transport into mitochondria
- Membrane stabilizing effect- increade RBC survival and increas formation of bone marrow erythroid clones
- IV administration may increase Hb and reduce ESA requirement
- Inadequate and unconvincing body of evidence

Androgens

- Patchy evidence to support nandrolone use
- Side effects including acne, virilization and abnormal LFTs

KDIGO: Use of ESAs

- Address all correctable causes of anemia before initiation of ESA therapy (not graded)

- Balance the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm (1B)
  - Stroke
  - Vascular access loss
  - Hypertension

- Use ESAs with great caution in patients with active malignancy when cure is the anticipated outcome (1B)

KDIGO: Initiation of ESA Therapy in Adult Hemodialysis Patients

- To avoid having the Hgb level fall below 9.0 g/dL, start ESA therapy when the Hgb level is 9-10 g/dL (2B)

- Individualization of therapy is reasonable as some patients may have improvement in QOL at higher Hgb levels and their ESA therapy may be started at Hgb levels above 10 g/dL (not graded)

KDIGO: Maintenance ESA Therapy in Adult Hemodialysis Patients

- In general, ESAs should not be use to maintain Hgb levels of >11.5 g/dL (2C)

- Individualization of therapy will be necessary as some patients may have improvements in QOL at Hgb levels >11.5 g/dL (not graded)

- ESAs should not be used to intentionally increase the Hgb level to >13 g/dL (1A)

KDIGO: ESA Dosing in Adult Hemodialysis Patients

- Determine the initial ESA dose based on patient's Hgb level, body weight and clinical status (1D)

- ESA dose adjustments should be made based on (1B):
  - Hg level
  - Rate of change of Hgb level
  - Current ESA dose
  - Clinical circumstances

- Decrease ESA dose in preference to withholding dose (2C)

- Re-evaluate ESA dose if patient has an ESA-related event or has an illness that may cause ESA hyporesponsiveness (not graded)

TAKE HOME MESSAGES

- ESAs are crucial in management of CKD anemia
- First take necessary measures before starting ESA therapy
- Monitoring is necessary to assess response and adjustment to maintain stable target Hb level
- To find out the possible causes once ESA hyporesponsiveness occurs
- Seek for expert opinions

THANK YOU