Management of CKD anaemia: the past, the present, and the future

Iain C. Macdougall
Consultant Nephrologist & Professor of Clinical Nephrology
The past
Management of CKD anaemia prior to EPO

- Many dialysis patients had “top-up” transfusions every 2–4 weeks
- Effects transient
- Increased risk of infections, *esp. viral*
- Sensitisation to HLA antigens – transplantation problematic
- Iron overload
Mean baseline Hb = 6.3g/dl

Hb increment > 5g/dl

Correction of anaemia - benefits

- quality-of-life
- exercise capacity
- cardiac output
- angina
- LVH
- bleeding tendency
- brain / cognitive function
- depression
- sleep patterns

- sexual function
- endocrine function
- immune function
- muscle metabolism
- hospitalisations
- transfusions
- nutrition
Canadian EPO Study Group

- Double-blind
- Randomised
- Placebo-controlled

**Effect of EPO on:**
- Quality-of-life – KDQ
  – SIP
- Exercise capacity – 6-minute walk
- Naughton stress test

- **118 HD pts. – Hb < 9g/dl**
- **EPO produced**
  - ↑ global & physical score
  - ↑ distance on stress test
  - ↑ diastolic BP
  - ↑ vascular access clotting

\[11/78 \text{ vs. } 1/40 \text{ placebo}\]
Hb predicts survival in observational studies

*HD patients*

Hb predicts survival in observational studies

**ND-CKD patients**

![Graph showing survival of CKD patients by hemoglobin level.](image)

- Hemoglobin >= 130 g/L
- 120-129 g/L
- 110-119 g/L
- 100-109 g/L
- < 100 g/L

Log-Rank Test: p = 0.0001

And then the RCTs came along......
THE EFFECTS OF NORMAL AS COMPARED WITH LOW HEMATOCRIT VALUES IN PATIENTS WITH CARDIAC DISEASE WHO ARE RECEIVING HEMODIALYSIS AND EPOETIN

ANATOLE BESARAB, M.D., W. KLINE BOLTON, M.D., JEFFREY K. BROWNE, PH.D., JOAN C. EGRIE, PH.D., ALLEN R. NISSENSON, M.D., DOUGLAS M. OKAMOTO, PH.D., STEVE J. SCHWAB, M.D., AND DAVID A. GOODKIN, M.D.

ABSTRACT

Background In patients with end-stage renal disease, anemia develops as a result of erythropoietin deficiency, and recombinant human erythropoietin (epoetin) is prescribed to correct the anemia partially. We examined the risks and benefits of normalizing the hematocrit in patients with cardiac disease who were undergoing hemodialysis.

Methods We studied 1233 patients with clinical evidence of congestive heart failure or ischemic heart disease who were undergoing hemodialysis: 618 patients were assigned to receive increasing doses of epoetin to achieve and maintain a hematocrit of 42 percent, and 615 were assigned to receive doses of epoetin sufficient to maintain a hematocrit of 30 percent throughout the study. The median duration of treatment was 14 months. The primary end point was the length of time to death or a first nonfatal myocardial infarction.

Adaptation of this study, we found that 69 percent of the patients had hematocrits of 27 to 33 percent, 15 percent had values below 27 percent, and 16 percent had values above 33 percent (unpublished data). Yet the normal ranges for hematocrit values are 37 to 48 percent for women and 42 to 52 percent for men, prompting the question of whether increasing the doses of epoetin would benefit patients who are undergoing hemodialysis. Cerebral oxygen delivery among patients with ischemic cerebrovascular disease, for example, is maximal when the hematocrit is 40 to 45 percent.

Cardiac disease is the most common cause of death among patients who are regularly receiving dialysis. Among these patients, partial correction of anemia reduces exercise-induced cardiac ischemia and ameliorates the left ventricular hypertrophy that predisposes patients to death and cardiac-related mor-
US Normal Hematocrit Trial

US Normal Hematocrit Trial

- probability of death or first non-fatal MI


• Increased vascular access clotting
Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

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

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

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

Quality of life
General health and vitality index (SF-36)

CREATE study

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CHOIR Study

- 1,432 non-dialysis CKD patients
- 130 US centres
- Treated with epoetin alfa
- Composite end-point
  (mortality, stroke, heart attack, hospitalisation)


Hb 13.5 g/dl vs Hb 11.3 g/dl
CHOIR Study

- Composite endpoint events: Target Hb 13.5 g/dL (p<0.03)
- Deaths: Target Hb 11.3 g/dL

A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D., Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D., John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D., Ajay K. Singh, M.D., Scott D. Solomon, M.D., and Robert Toto, M.D., for the TREAT Investigators*

ABSTRACT

BACKGROUND

Anemia is associated with an increased risk of cardiovascular and renal events among patients with type 2 diabetes and chronic kidney disease. Although darbepoetin alfa can effectively increase hemoglobin levels, its effect on clinical outcomes in these patients has not been adequately tested.

METHODS

In this study involving 4038 patients with diabetes, chronic kidney disease, and anemia, we randomly assigned 2012 patients to darbepoetin alfa to achieve a hemoglobin level of approximately 13 g per deciliter and 2026 patients to placebo, with
The TREAT Study

**Double-blind placebo controlled RCT: n = 4038**

**Anaemia**
- NIDDM
- ND-CKD

**Darbepoetin alfa 1x/4wks SC – treatment target Hb 13 g/dl**

**Placebo – treatment target Hb 9 g/dl**

**Up to 2 weeks Screening**

**Titration period**

**Follow-up 4 years**

**2 primary endpoints:**

- **Time to all-cause mortality or composite of MI, stroke, CCF, angina**
- **Time to all-cause mortality or chronic dialysis**
TREAT Study – Hb response

Figure 1. Mean Hemoglobin Levels through 48 Months among Patients Who Were Assigned to Receive Darbepoetin Alfa or Placebo.
I bars represent standard errors.
Red Cell Transfusions

TREAT study

![Graph showing percent of patients by months with Darbepoetin alfa and Placebo with HR: 0.56 (0.49-0.65) and P < 0.001]
TREAT Study – CV Endpoints
Safety Concerns in the TREAT Study


†, p<0.001 versus placebo
‡, p=0.02 versus placebo
§, p=0.04 versus placebo

*Amongst patients with a history of malignancy at baseline

†, p<0.001 versus placebo
‡, p=0.02 versus placebo
§, p=0.04 versus placebo

*Amongst patients with a history of malignancy at baseline
What have these studies told us?

Hb should not be “normalized” by ESA therapy

Hb correction with ESA therapy

- Reduced transfusions
- ? Improved QoL / ↑ exercise capacity
- Increased CVS events, stroke, VTE
- Increased cancer-related deaths
Is the CVS “harm” due to high EPO levels?


Three 40 U/kg SC doses/wk
Two 60 U/kg SC doses/wk
One 120 U/kg SC dose/wk
EPO has Non-erythropoietic Actions

High EPO levels

- ↑ VSMC $[Ca^{2+}]_i$
- ↑ RAS activation
- ↑ ET-1
- ↑ Thromboxane
- ↓ Prostacyclin
- ↑ ADMA
- ↓ NO

Hypertension

- VSMC proliferation
- EC proliferation
- Angiogenesis

Blood access stenosis
Proliferative retinopathy
Vascular remodeling
Tumor growth

- ↑ Platelet production
- ↑ Platelet activity
- ↑ E selectin
- ↑ P selectin
- ↑ vWF
- ↑ PAI-1

Thrombosis

IV iron
Better Hb response with IV iron compared to oral or no iron

*p<0.05, **p<0.005 vs IV iron

Reduction in Recombinant Human Erythropoietin Doses by the Use of Chronic Intravenous Iron Supplementation

Steven Fishbane, MD, Gill L. Frei, MD, and John Maesaka, MD

We have compared the efficacy of oral to intravenous iron for the chronic maintenance of iron stores in hemodialysis patients. Fifty-two hemodialysis patients with initial serum ferritin greater than 100 ng/mL and transferrin saturation greater than 15% were randomly assigned to one of two groups: those receiving oral iron therapy (n = 32) and those receiving intravenous iron dextran (100 mg twice weekly) (n = 20). At study completion (4 months), the mean hematocrit was significantly higher in the intravenous group than in the oral iron group.

Fig 1. Mean hematocrit at every month of follow-up in the two study groups. Squares indicate the intravenous group; diamonds indicate the oral group. *P < 0.05.

Fig 2. Mean rHuEPO dose at every month of follow-up in the two study groups. Squares indicate the intravenous group; diamonds indicate the oral group. *P < 0.05.
Concerns about IV iron

- Hypersensitivity reactions
- Oxidative stress
- Exacerbation of infections
- Iron overload
Iron management in chronic kidney disease: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference

Iain C. Macdougall¹, Andreas J. Bircher², Kai-Uwe Eckardt³, Gregorio T. Obrador⁴, Carol A. Pollock⁵,⁶, Peter Stenvinkel⁷, Dorine W. Swinkels⁸, Christoph Wanner⁹, Günter Weiss¹⁰, and Glenn M. Chertow¹¹; for Conference Participants¹²

¹Department of Renal Medicine, King’s College Hospital, London, UK; ²Allergy Unit, Dermatology Clinic, University Hospital Basel, Basel, Switzerland; ³Department of Nephrology and Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; ⁴Universidad Panamericana School of Medicine, Mexico City, Mexico; ⁵University of Sydney, Sydney, Australia; ⁶Royal North Shore Hospital, Sydney, Australia; ⁷Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska University Hospital, Stockholm, Sweden; ⁸Department of Laboratory Medicine, Translational Metabolic Laboratory, Radboud University Medical Center, Nijmegen, the Netherlands; ⁹Renal Division, University Hospital of Würzburg, Würzburg, Germany; ¹⁰Department of Internal Medicine VI, Infectious Disease, Immunology, Rheumatology, Pneumology, Medical University of Innsbruck, Innsbruck, Austria; and ¹¹Division of Nephrology, Stanford University School of Medicine, Palo Alto, California, USA
Iron Management in CKD Conference

Steering Committee

Glenn Chertow, USA – Conference Co-Chair
Iain Macdougall, UK – Conference Co-Chair

Iron Overload Co-Chairs
Kai-Uwe Eckardt, Germany & Dorine Swinkels, Netherlands

Inflammation & Oxidative Stress Co-Chairs
Peter Stenvinkel, Sweden & Christoph Wanner, Germany

Iron & Infection Co-Chairs
Gregorio Obrador, Mexico & Günter Weiss, Austria

Hypersensitivity Reactions to IV Iron Co-Chairs
Andreas Bircher, Switzerland & Carol Pollock, Australia
The present
Use ESA therapy to correct anaemia when Hb <10 g/dl (or 11 g/dl if symptoms)

- Aim for target Hb in range 10–12 g/dl; individualize
- Use lowest doses of ESA as possible
- Use supplemental iron to prevent iron deficiency and reduce ESA dose requirements – IV in HD; oral or IV in ND-CKD
- Aim for ferritin > 100 ug/l and TSAT > 20%
- Upper limit of ferritin not clear; do not actively exceed 800 ug/l with IV iron
Questions needing answers

- How much IV iron should be given to HD patients?
- What ferritin/TSAT targets are optimal in HD?
UK multicentre prospective open-label 2-arm RCT of IV iron therapy in incident HD patients

- Lead investigator: Iain Macdougall
- Clinical Trial Manager: Claire White
- No of sites: 50
- No. of patients: 2080
- Commenced: November 2013
- Trial oversight: Glasgow Clinical Trials Unit
- Funder: Kidney Research UK

This investigator-led clinical trial is supported through an unrestricted grant from:

- Vifor Fresenius Medical Care Renal Pharma
- University of Glasgow
- NHS Greater Glasgow and Clyde
- The Renal Association founded 1950

Kidney Research UK

Registered Charity No: 252892 Registered Scottish Charity No. SC039245
**Study design**

**Proactive IV iron arm – IV iron 400mg/month**

(withhold if ferritin $>700$ ug/l; TSAT $>40\%$)

**Primary endpoint**

- Time to all-cause mortality or composite of MI, stroke, HF hosp

**Reactive – minimalistic IV iron arm**

(give IV iron if ferritin $<200$ ug/l; TSAT $<20\%$)

Total study period approximately 4 years *(event-driven)*

- 2 years recruitment; 2-4 years follow-up per patient

**Sample size:** 2080 patients
Primary endpoint

- Time to all-cause death or a composite of non-fatal cardiovascular events (MI, stroke, and HF hospitalisation)
  -- adjudicated by a blinded Endpoint Adjudication Committee

Secondary endpoints

- Incidence of all-cause death and a composite of myocardial infarction, stroke, and hospitalisation for heart failure as recurrent events.
- Time to (and incidence of) all-cause death
- Time to (and incidence of) composite cardiovascular event
- Time to (and incidence of) myocardial infarction
- Time to (and incidence of) stroke
- Time to (and incidence of) hospitalisation for heart failure
- ESA dose requirements
- Transfusion requirements
- EQ-5D QOL and KDQOL
- Vascular access thrombosis
- All-cause hospitalisation
- Infections; hospitalisation for infection
NETWORK OF SITES

England
Queen Elizabeth Hospital, Birmingham; Heartlands Hospital, Birmingham; Royal Free, London, King’s College Hospital, London; Guy’s & St Thomas’, London; St Helier, Surrey; St George’s, London; Royal Liverpool Hospital, University Hospital Aintree; Sheffield Teaching Hospital; Lister Hospital, Stevenage; Salford Royal Hospital, Manchester; Manchester Royal Hospital; Queen Alexandra Hospital, Portsmouth; Kent & Canterbury Hospital, Leicester General Hospital, Hull Royal Infirmary; Freeman Hospital, Newcastle; Churchill Hospital, Oxford; University Hospital of North Staffordshire, Stoke-on-Trent; Southmead Hospital, Bristol; Royal Cornwall Hospital; Nottingham City Hospital; Norfolk & Norwich Hospital; New Cross Hospital, Wolverhampton; Royal London Hospital; Wirral University Teaching Hospital; Royal Shrewsbury Hospital, Royal Devon & Exeter Hospital, Royal Preston Hospital, St James’ Hospital, Leeds; Hammersmith Hospital, London; Royal Sussex Hospital, Brighton; Bradford Teaching Hospital; Coventry University Hospital; Southend University Hospital; Gloucestershire Royal Hospital; Derriford Hospital, Plymouth; Royal Berkshire, Reading

Wales
Morriston Hospital, Swansea; University Hospital, Cardiff

Scotland
Western Infirmary, Glasgow; Victoria Hospital, Kirkcaldy; Ninewells Hospital, Dundee; Royal Edinburgh Hospital

N. Ireland
Belfast City Hospital, Antrim Area Hospital; Daisy Hill Hospital, Newry; Altnagelvin Hospital, Derry
HIF stabilizers
– prolyl hydroxylase inhibitors
Regulation of erythropoietin

Hypoxia-Inducible Factor (HIF)
The physiology of hypoxia mediated through hypoxia inducible factor (HIF)

**NORMAL OXYGEN**

**LOW OXYGEN** (e.g. High Altitude)

HIF-α Degradation

Gene Transcription

HIF-PH Enzymes

**HIF-PH^1** Enzymes

HIF-α Degradation Rapidly

EPO Within or Near Physiological Range

Iron Transport to the Bone Marrow and Hemoglobin (Hb) Synthesis

Iron Absorption

Hepcidin Levels

Red Blood Cell Production

Slide courtesy of Dr. Lynda Szczech, Fibrogen Inc.
HIF stabilisers

- HIF is degraded by a prolyl hydroxylase enzyme
- Orally-active inhibitors of PH have been synthesised
- These drugs cause HIF levels to increase
- More HIF leads to more EPO
# HIF PHIs in development

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A new strategy

Erythropoiesis range

Time (days)

EPO conc. (mU/mL)

Three 40 U/kg SC doses/wk
Two 60 U/kg SC doses/wk
One 120 U/kg SC dose/wk


Patient’s own EPO level

Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients

Anatole Besarab, Robert Provenzano, Joachim Hertel, Raja Zabaneh, Stephen J. Klaus, Tyson Lee, Robert Leong, Stefan Hemmerich, Kin-Hung Peony Yu and Thomas B. Neff

**FIGURE 3**: Mean change from BL in Hb (ΔHb) in TIW cohorts (EE population). Mean (SD) BL Hb was 10.1 (0.7) g/dL for roxadustat TIW subjects and 10.1 (0.6) g/dL for placebo subjects. Last-observation-carried-forward (LOCF) method was used to impute missing values. *P < 0.01 intergroup two-sample t-tests comparing roxadustat change from BL with placebo change from BL. End of treatment (EOT) for TIW was Day 26.

**Fig. 2.** Observed mean hemoglobin (Hb) concentration over the trial period during administration of vadadustat or placebo (modified intent to treat population). Data are expressed as the mean ± SEM Hb value at each time point. *p < 0.05 for comparisons with baseline. † p < 0.05 for comparisons with placebo.
HIF target genes

- **Cell Survival**
  - ADM
  - EPO
  - IGFBP1-3
  - TGFα

- **Transcriptional regulation**
  - ETS1
  - DEC1-2

- **Erythropoiesis**
  - Epo

- **Iron metabolism**
  - Ceruloplasmin
  - TRF
  - TRFR

- **Proliferation**
  - CyclinD1
  - IGF2
  - IGFBP1-3

- **Angiogenesis**
  - VEGF
  - VEGFR1
  - LEP
  - EGF

- **Mitochondrial function**
  - PDK
  - COX4-1
  - LON

- **Vascular tone**
  - ADM
  - iNOS
  - ET1
  - BNP

- **Cell motility**
  - CXCR4
  - c-Met

- **Glucose metabolism**
  - GLUT1
  - HK
  - LDH1
  - PGK
  - ENO1

- **pH regulation**
  - CA9
  - MCT4
  - NHE1

- **Apoptosis**
  - BNIP3
  - NIX

- **Extracellular matrix metabolism**
  - PAI1
  - MMP2
  - FN
  - UPAR

**Adapted from Schofield & Ratcliffe, Nat Rev Mol Cell Biol 2004**
Conclusions

- We have to accept that ESA therapy is not as safe as we thought 25 years ago.

- Nevertheless, it keeps patients off blood transfusions and improves anaemic symptoms / quality-of-life.

- IV iron can augment Hb response and reduce ESA doses.

- However, there are potential concerns about IV iron’s safety.

- There are several ‘new kids on the block’, esp. HIF stabilizers.