



ANEMIA MANAGEMENT IN CKD (PREDIALYSIS) PATIENTS

A Lunchtime Symposium
during the XLII ERA-EDTA Congress

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Introduction

Professor George Aronoff from the University of Louisville, Kentucky opened this satellite session that took place during the XLII ERA-EDTA Congress in Istanbul on June 5, 2005, by explaining that iron deficiency is a very common problem and an important cause of anemia in patients with chronic kidney disease (CKD). It is of particular importance to clinicians and their patients to recognize that the use of erythropoietic-stimulating agents (ESAs) in the absence of adequate iron replacement is often unsuccessful in correcting the anemia of CKD.

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> Early Intervention: The Key to Success

Dr. Iain Macdougall, Consultant Nephrologist and Honorary Senior Lecturer in the Department of Renal Medicine, King's College, London, UK examined the need to begin anemia management in predialysis.

Data suggest that anemia is diagnosed in up to 90% of patients on dialysis and perhaps more importantly in up to two-thirds of patients who are starting dialysis.¹ Anemia is a common problem, which progresses as CKD develops. When renal function declines, (as documented by creatinine clearance, CrCl) the prevalence of anemia increases.² This has been confirmed more recently by data from the third National Health and Nutrition Examination Survey (NHANES III),³ showing that anemia becomes evident when the glomerular filtration rate (GFR) declines towards 60 mL/min GFR, i.e. with moderately severe renal dysfunction. This occurs earlier in diabetics than non-diabetics.

In CKD, anemia is caused by multiple factors, the most common being inappropriately low erythropoietin (EPO) production, iron deficiency and inflammation, which is becoming increasingly recognized. The anemia induced by inflammation

is known as the anemia of chronic disease, which is also seen in malignancy and chronic inflammatory conditions. Dr. Macdougall's presentation focused on iron deficiency.

Large surveys from Europe highlight the extent of the problem posed by iron deficiency in CKD patients. The European Survey of Anaemia Management I (ESAM I) and ESAM II^{4,5} largely concern dialysis patients. More recently, the PRE-dialysis Survey on Anaemia Management (PRESAM) shows data from 2000-2001, taken from patients who are just starting dialysis.⁶ These surveys all show that the prevalence of iron deficiency remains high. This is particularly apparent in the PRESAM where up to 61% of patients are iron-deficient. Most of these have functional iron deficiency and slightly less have absolute iron deficiency.

Dr. Macdougall presented data from a retrospective analysis from the Renal Unit at King's College Hospital⁷ involving 101 non-dialysis CKD patients. The inclusion criteria were: no previous EPO therapy, hemoglobin (Hb) concentration < 11 g/dL, and a serum ferritin (SF) < 150 µg/L. Patients received 200 mg intravenous (IV) iron sucrose weekly for three weeks. Hb response over 6 months was examined and the study focused on the proportion of patients who responded to IV iron alone. Response was defined as an increment in Hb of ≥ 1 g/dL after 4 months compared to baseline. Of the 101 non-dialysis patients who had been given a course of IV iron, 63 received EPO therapy. Twenty-seven (71.1%) of the 38 patients not receiving EPO did not respond to IV iron. The 11 responders (28.9%) had a significant and sustained increase in Hb (mean Hb rose from 9.9 g/dL to 12.6 g/dL) in response to IV iron. Median SF levels increased from a baseline of 111 µg/L to 216 µg/L following the course of IV iron and the maximum SF seen following three doses of iron was 712 µg/L.

From this study Dr. Macdougall concludes that SF levels should be checked in all CKD patients with anemia. Up to 30% of patients with a SF < 150 µg/L may respond to IV iron with a significant sustained rise in Hb. Given the current cost of EPO therapy, the potential savings in even this small proportion of CKD patients is of great importance.

> Intravenous Iron Administration: Advantages of Push Injections

With regard to the delivery of IV iron, there are concerns about whether it is safe to give iron as a push rather than an infusion. Dr. Macdougall advocates the use of a 200 mg IV iron push over 2 minutes, rather than a 2-4 hour IV infusion. In a prospective study conducted by Dr. Macdougall and colleagues, 2,297 injections in CKD patients using the two-minute push of 200mg were assessed.⁸ The endpoint of this study was to examine the safety of this mode of administration. The patients were all non-hemodialysis patients – no hemodialysis patients

**Up to 61%
of predialysis
patients are
iron-deficient**

**Up to 30%
of patients
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may respond
to IV iron**

**A 200 mg
IV iron sucrose
push can be given
over 2 minutes**

**Anemia is a
common problem
& progresses
as CKD develops**

Few side effects were reported

were included because they routinely receive IV iron – some were on peritoneal dialysis, some were transplant patients and others were patients attending Nephrology or Low-Clearance clinics with a GFR < 30 mL/min. There were slightly more females than males.

SAFETY

In 412 injections, patients noted a metallic taste, which was transient and passed usually within a minute. Of the 2,297 injections 97.5% proceeded uneventfully without reactions or side effects. In only 57 (2.5%) of injections was an adverse event reported. Seven of these were acute reactions, which is similar to that reported with iron infusions. Other reactions included some pain during injection and slight bruising. Three patients reported gastrointestinal symptoms, four reported tiredness and three had a feeling of light-headedness, although it is important to note that the patients were anemic. None of the seven acute reactions were severe, all resolved within 30 minutes and none required hospitalization.

COST

With regard to cost savings of the two-minute push compared with a two-hour infusion dissolved in 100 mL of saline, the two-minute push requires no expenditure on saline or administration tubing. The total cost saving during the study period was over US \$5,000. Time savings were also reported, the infusion requiring two hours to deliver and 15 minutes to prepare the iron, dissolve it in saline and dispose of equipment, whereas the two-minute push can be prepared in three minutes. Thus, a total of five minutes is required compared with 135 minutes for IV iron infusion. This corresponds to a time saving of 6.9 months over the period of study.

Cost Savings

	2-hour infusion (dissolved in 100 mL of 0.9% NaCl)	2-minute push (undiluted)
0.9% NaCl x 100 mL	2,297 x \$0.95 = \$2,182.15	Nil
Administration tubing	2,297 x \$1.23 = \$2,825.31	Nil
TOTAL	\$5,007.46 (= cost savings during the study)	---

Time Savings

2-hour infusion	2-minute push
Preparation of iron for infusion Securing IV access Programming infusion pump Disposal of all equipment post-injection = 15 minutes Iron administration = 120 minutes	Preparation of iron for injection Securing of IV access Disposal of equipment post-injection = 3 minutes Iron administration = 2 minutes
TOTAL = 135 Minutes	Total = 5 minutes
TOTAL SAVING = 130 minutes per administration	
TOTAL SAVING for 2,297 injections	= 130 minutes per administration = 2,297 x 130 minutes = 298,610 minutes = 4,976.8 hours = 207.4 days = 6.9 months

> **Anemia in Predialysis:
A Clinically Relevant Issue**

It is important to treat anemia in the predialysis period

Anemia in CKD patients results in left ventricular hypertrophy (LVH), which impacts on cardiovascular morbidity and mortality. It is also known that anemia develops early in patients who are not on dialysis, usually when GFR < 40 mL/min. Thus, there is strong rationale to treat anemia not only in dialysis patients, but also in the predialysis period.

Professor Nikolay N Khasabov, from the Russian State Postgraduate Medical Academy, Moscow, Russia presented data from an international, randomized, prospective, multicenter, open-label study. The aim of the study was to evaluate the efficacy and safety of IV iron sucrose (Venofer®) in anemic patients (n = 60) with CKD not on renal replacement therapy.

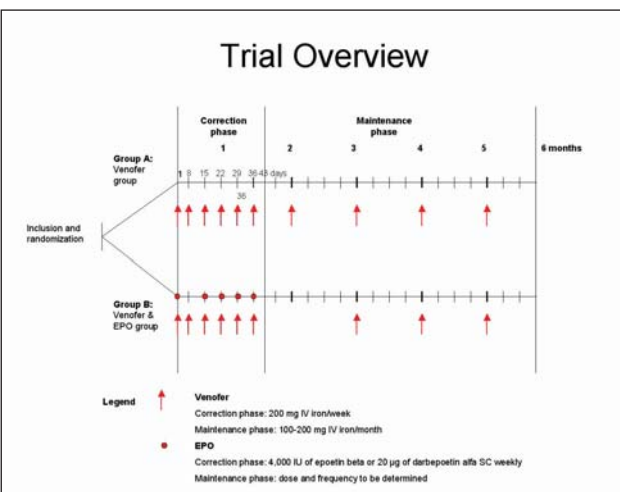
PATIENTS AND METHODS

The inclusion criteria were: patients with CKD (GFR < 60mL/min) not yet on dialysis; Hb level > 8 g/dL and < 11.5 g/dL, transferrin saturation (TSAT) < 20% or SF < 200 µg/L, male or female patients > 18 years of age. Exclusion criteria were: rapid progression of CKD (e.g. an increase in serum creatinine > 20% within 3 months); a need for dialysis therapy expected in the following 6 months; folate and/or vitamin B12 deficiency; history of IV iron or EPO treatment within the past 2 months; blood transfusion within the past 3 months; chronic heart failure NYHA class III-IV. Two treatment groups were formed randomly: group A (n = 31; iron sucrose alone); group B (n = 29, iron sucrose and epoetin). They received different treatment during the correction phase and the maintenance phase. The correction phase ran from

days zero to 33, where group A received a total of 5 infusions of 200 mg iron sucrose administered as 200 mg weekly between days one and 29 while group B received IV iron following the same protocol plus 4,000 IU epoetin beta or 20 µg of darbepoetin alpha weekly, delivered subcutaneously from days one to 36. The maintenance phase ran from days 33 to 169 where both groups received 100-200 mg IV iron sucrose month-

ly; in group A, EPO was added only if Hb fell below 9 g/dL while EPO treatment continued for group B as previously.

Trial Overview



Key Points

Targets:
Hb 11-12.5 g/dL
TSAT 30-50%
SF 300-500 µg/L

The targets for the maintenance phase were Hb of 11-12.5 g/dL, TSAT of 30-50% and SF 300-500 µg/L. Dose adjustments were made according to an algorithm: if SF > 500 µg/L or TSAT > 50%, IV iron was discontinued. If SF fell below 300 µg/L or TSAT < 30%, IV iron treatment was resumed. If Hb > 12.5 g/dL the EPO dose was reduced by 50%; if Hb < 9 g/dL, group A patients were administered EPO, and those already receiving EPO (group B) were given a 50% increase in EPO dose.

The primary efficacy endpoint was a change in Hb from baseline to day 43. Secondary efficacy endpoints were: a change in Hb from baseline to day 169; a change in TSAT and SF from baseline by day 43; the time course of Hb, SF and TSAT compared with baseline values over the study period in both groups; the proportion of group A patients requiring EPO; the proportion of group A patients maintaining Hb 11-12.5 g/dL, TSAT 30-50% and SF 300-500 µg/L; changes in serum creatinine and in GFR over the study period. The safety endpoint was the frequency of adverse events.

Algorithm

The doses of iron sucrose and EPO are adjusted as necessary according to the following algorithm:

Iron sucrose (Venofer®) Dose:

- If SF > 500 µg/L or TSAT > 50%, discontinue iron sucrose treatment
- If SF < 300 µg/L and TSAT < 30%, restart iron sucrose treatment

EPO Dose:

- If Hb > 12.5 g/dL, reduce EPO dose by 50%
- If Hb < 9 g/dL, restart EPO treatment for untreated patients (group A) or increase dosage by 50% for treated patients (group B)

RESULTS

In the correction phase Hb increased significantly between days zero and 43 (group A, $p = 0.001$; group B, $p < 0.001$). A significant increase in SF was reported in both groups ($p < 0.001$). At 43 days, patients in group A had a significantly higher level of SF than those in group B. This could be partly due to the development of functional iron deficiency. TSAT also rose significantly in both groups (group A, $p < 0.001$; group B, $p = 0.003$).

A statistically comparable proportion of patients in both groups maintained Hb > 11 g/dL at the end of the study (40.7% vs. 53.8%, in groups A and B, respectively). Group A patients were able to maintain Hb > 11 g/dL without requiring EPO. Changes in SF were seen in patients from both groups. In group A, mean SF reached the target range (300 µg/L) at day 36 and did not exceed the upper target limit of 500 µg/L. In group B, the mean SF of 300 µg/L was only exceeded on day 127. There was no significant statistical difference by the end of the study. Group A attained mean target TSAT (30%) at day 36 compared with day 114 for

group B. There was no significant statistical difference by the end of the study. There was no significant difference in GFR over the six-month period.

Only four of 31 patients from group A required EPO in addition to Venofer® during the maintenance phase – as indicated by the algorithm, i.e. when Hb < 9 g/dL. Thus, the vast majority of predialysis patients were successfully managed with IV iron alone. In group B, 6 patients were able to reduce the required EPO dose by 50% by day 82, and EPO was discontinued for 15 patients by day 99.

The incidence of adverse events was low (12 patients experienced 15 adverse events) and there was no drug-related death or serious adverse event. SF > 800 µg/L was not seen after the correction phase (where 5 x 200 mg of IV iron sucrose were administered over 4 weeks).

Professor Khasabov concludes that iron sucrose (Venofer®) without EPO is a safe and effective treatment for anemic non-dialysis CKD patients.

> Anemia in Patients with Diabetes

Norbert Lameire, Professor of Internal Medicine and Chief of Renal Division, University of Ghent, Belgium, reviewed the data concerning anemia in patients with diabetes. In the audience physicians indicated that between 10-30% of CKD patients in their units were diabetic. Indeed, the prevalence of anemia in diabetic patients is evaluated at > 25% and 30-40% of diabetic patients have SF < 100 µg/L. In addition, the projected burden of diabetes over the next 20-25 years is of concern and should draw the attention of healthcare authorities including the World Health Organization, the International Society of Nephrology and the EDTA. The absolute number of diabetics is expected to be 370 million worldwide and the increase is much more significant in developing countries.

Diabetes is mostly part of what is called the metabolic syndrome: this is a compilation of dyslipidemia, type 2 diabetes, hypertension and obesity, although the syndrome covers much more, and we are only seeing the tip of the iceberg. Epidemiological studies show that cardiovascular events and mortality are multiplied by three when more parameters of the metabolic syndrome are fulfilled.⁹ Metabolic syndrome is common and the rate is rising.¹⁰ The increase of type 2 diabetes is therefore of no surprise given this evolution.

The death rate from cardiovascular disease is higher in patients with diabetes than in those without diabetes or disturbed glucose tolerance. The death rate of diabetic patients is raised, even if they do not have clinical cardiovascular disease. If the patient already has cardiovascular disease, the death rate is importantly higher when a patient is also diabetic.⁹ A prospective study by Foley et al. shows that cardiovascular mortality and other signs of cardiovascular abnormality are much greater in diabetics than non-diabetics.¹¹

The majority of predialysis patients were managed with IV iron sucrose alone

30-40% of diabetic patients have SF < 100 µg/L

Only 4 patients required EPO in addition to IV iron sucrose

Anemia increases the risk of patients with diabetes developing ESRD

Diabetes is independently correlated with anemia

EPO response to anemia is blunted in diabetic patients

In non-diabetic patients anemia is a factor of mortality risk. A follow-up study by Medicare looked at a 5% sample collected between 1996 and 1997.¹² The relative risk of death before end-stage renal disease (ESRD) was high in anemic patients without CKD or diabetes. When these factors are combined the relative risk of death increases significantly and importantly, namely from 1.5 fold in patients with diabetes mellitus alone to 3.5 fold when anemia, diabetes and CKD are combined while the risk is two fold in patients with anemia and diabetes. Thus, anemia by itself in the non-diabetic is an important risk factor, and even more so in diabetic patients.

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study examined the risk factors that predict the impairment of kidney function (doubling of serum creatinine) or ESRD (dialysis or transplantation) in patients with type 2 diabetes in whom blood pressure was controlled.¹³ Anemia alone was associated with a more than 4-fold higher hazard ratio of developing ESRD once Hb < 11.2 g/dL, compared with patients without anemia.

Data from the Kidney Early Evaluation Program (KEEP) study, a follow-up epidemiological study on the kidney early evaluation program in the USA were used to determine the prevalence of anemia by level of kidney function and diabetes status.¹⁴ Anemia was defined as Hb <12 g/dL in men and in women aged >50 years, and <11 g/dL in women ≤ 50 years. In every given category of the estimated GFR the anemia prevalence in diabetics was almost twice that in non-diabetics. Diabetes was independently correlated with anemia, more so in men than women, and may be linked to premature expression of anemia in persons with moderate reductions in kidney function.

Several studies show that there is a blunted EPO response to anemia in diabetic patients. There is now evidence that, while EPO production increases in non-renal anemia, this response is blunted in diabetic patients.¹⁵⁻¹⁶ Indeed, while one would expect endogenous EPO concentrations to rise when Hb falls, some diabetic patients – both type 1 and type 2 – show a EPO blunted response to anemia.¹⁷

There are several causes of decreased EPO production in CKD patients.^{15,18,19,20} However, diabetic glomerulopathy alone is insufficient to fully explain the etiology of the anemia. Tubulointerstitial injury may contribute to the anemia, and is more common in patients with type 2 diabetes, and may occur prior to the onset of overt proteinuria. There is an association between autonomic neuropathy and the impaired modulation of EPO production by the autonomic nervous system. There is also a relationship between hyporeninemic hypoaldosteronism – where patients have a high potassium level and a degree of acidosis, out of proportion with the GFR – and decreased EPO production. When treated with EPO, these patients may not only correct their anemia, but also correct their hyporeninemic hypoaldosteronism.

IRON STATUS IN DIABETES MELLITUS

NHANES III³ observed a high frequency of low SF (< 100 µg/L) in diabetic patients matched for CrCl clearance. The prevalence of low SF in men and in women was not negligible and it appeared that the assessment of iron status had been neglected in this population. While anemia starts at approximately a CrCl of 40-60 mL/min in CKD patients, in diabetics it occurs both sooner and with a higher prevalence.

Iron deficit and low TSAT are more common in diabetics than in non-diabetics.²¹ In an Australian study, Thomas *et al.*²² looked at diabetic patients with moderate chronic renal failure. Patients who had an appropriately increased EPO level were iron-depleted as documented by low TSAT and low SF. There was also iron depletion in the group that had an inappropriately low EPO level. When Hb concentrations in patients who had low TSAT (< 16%) were considered in relation with EPO concentrations, there was more iron depletion in the patients with appropriately increased EPO, although there was also some iron depletion in patients with a normal EPO concentration. In this way the EPO response does not explain entirely the early occurrence of anemia in diabetes. In a comparative study²³ of responders and non-responders to EPO in diabetic anemic patients with so-called EPO deficiency, a segment of users did not respond to even high doses of EPO. SF and TSAT were significantly lower in the non-responders than in the responders. Therefore, it is of the utmost importance to pay attention to the iron status.

The inhibitory effect of inflammatory cytokines on the EPO receptor is still unknown. The assessment of C-reactive protein (CRP) concentrations shows that systemic inflammation is present in patients having components of the metabolic syndrome. Macrophages produce interleukin-6 during inflammation, and it seems that interleukin-6 causes hepatocytes to produce hepcidin. Recent studies indicate that hepcidin blocks both iron release from the macrophage and intestinal iron absorption.²⁴ This might be the missing link between inflammation, anemia and high CRP. Not only is there an infiltration in the fat tissue of cytokine-producing macrophages, but the adipocyte itself becomes a very active proinflammatory cell and also produces inflammatory cytokines. Indeed, a study which looked at diabetic and non-diabetic patients with the same degree of glycemia control (as shown by Hb glycation), blood pressure control and proteinuria, reported that the major difference was that diabetics showed a higher levels of CRP and higher tumor necrosis factor-alpha (TNF-α) production.²⁵ The diabetic patient is an inflamed patient, particularly those with type 2 diabetes.

In the view of these data, Professor Lameire concluded that anemia work-up should be carried out in diabetic patients before Hb falls below 11 g/dL, even if they still have GFR of 70-80 mL/min. While it is important to administer EPO therapy in patients with renal anemia, IV iron supplementation should not be neglected.

EPO response does not explain entirely the early occurrence of anemia in diabetics

Hepcidin blocks both iron release from the macrophage and intestinal iron absorption

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