

## OVERVIEW OF ANEMIA TREATMENT IN NON-DIALYSIS CHRONIC KIDNEY DISEASE

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Erythropoiesis-stimulating agents (ESAs) administered either subcutaneously (sc.) or intravenously (iv.), along with iv. or oral iron therapy, are currently the cornerstones for treating anemia in patients with chronic kidney disease (CKD). Multiple factors are involved in the pathogenesis of anemia in CKD: iron deficiency, inadequate production of erythropoietin (Epo), hepcidin and hypoxia-inducible factors (HIFs). Patients with CKD are prone to iron deficiency (absolute and functional). In this study, we compared the efficacy and safety profile of oral and intravenous iron with erythropoietin beta (subcutaneously in a dose of 4000-6000 IU every week) for the treatment of iron deficiency anemia in 43 non dialysis patients (ND-CKD) with the confirmed diagnosis of iron deficiency anemia (A) at Merkur University Hospital. Exclusion criteria were patients on dialysis or transplantation, with heart failure, secondary hyperparathyroidism, malignancy, thromboembolism, gastrointestinal bleeding, hsCRP >5 mg/L, patients taking medicines that suppress Epo production, and uncontrolled resistant hypertension. Patients were divided into groups on intravenous iron in doses of 1000 mg every month and oral daily intake of iron (ferrous fumarate 350 mg). Iron supplementation was administered in order to achieve serum ferritin 200-500 mg/L. Hemoglobin (Hb) was checked at the beginning and after 12 months in both groups. Paired sample t-test was applied for comparison of results. The mean level of iron at the beginning in M/F was  $9.7/7.9 \pm 0.28/0.31$  and after 12 months  $10.7/8.94 \pm 0.27/0.43$   $\mu\text{mol/L}$ . In the treatment groups, the mean Hb level was  $9.19 \pm 0.84$  g/dL (A) and  $9.72 \pm 0.95$  g/dL (B). The mean increase in Hb was  $10.65 \pm 0.97$  g/dL (A) and  $10.42 \pm 1.22$  g/dL (B) at 12 months ( $p < 0.001$ , if we compare Hb levels before and after 12 months of iron therapy). There were no statistically significant differences in Hb increase between groups A and B. Parenteral or oral iron in combination with Epo is effective treatment of anemia in ND-CKD patients if other factors are considered. In patients with recognized other causes of resistance to ESAs, new drugs such as hepcidin antagonists, HIF and ferroportin stabilizers will delay CKD progression. This alternative therapeutic approach in the future may avoid the overshoots and fluctuations in Hb levels seen with currently injectable ESAs and provide a steady and controlled rise in Hb concentration.

**Key words:** anemia, chronic kidney disease, predialysis

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### INTRODUCTION

Anemia is a very common complication in chronic kidney disease (CKD) patients, resulting in fatigue, reduced quality of life, shortness of breath and decreased exercise capacity (1-3). Multiple factors are involved in the pathogenesis of anemia in CKD: iron deficiency, inadequate production of erythropoietin

(Epo), hepcidin and hypoxia-inducible factors (HIFs) (2). Inflammation and oxidative stress are present in patients with CKD and produce a state of functional iron deficiency (2). Reduced oxygen delivery activates hypoxia-inducible factors (HIFs) leading to increased transcription of genes, in turn leading to Epo synthesis. Epo binds to the Epo receptor expressed on erythroid progenitor cells, inhibiting apoptosis and enhanc-

ing the population of circulating red blood cells (2). The cellular oxygen sensing is by a family of prolyl hydroxylases (PHDs) and their role is regulating HIFs. PHDs inhibitors serve as HIF stabilizers, and are currently investigated in clinical trials for the treatment of anemia in CKD (2). Anemia is mainly due to iron deficiency and inadequate renal production of erythropoietin (4). Other factors include elevated hepcidin levels in chronic inflammation state (as in CKD patients) removing non-transferrin bound iron from the circulation by iron trapping in macrophages (5). Hepcidin is produced by the liver in response to a number of factors including body iron status and inflammatory cytokines, and binds to ferroportin on the basolateral surface of gut enterocytes, and inhibiting absorption of iron from the gut lumen (5). Iron deficiency is one of the leading risk factors for disability and death and is the most prevalent nutritional disorder worldwide (6). Iron deficiency is a very important clinical concern in CKD patients (7). This problem gives rise to iron deficiency anemia and various impaired cellular functions (8). Oral supplementation, in particular with ferrous salts, is associated with a high rate of gastrointestinal side effects and is poorly absorbed (9). This problem is avoided with intravenous (iv.) iron. Iron deficiency is one of the most important causes of erythropoietin hyporesponsiveness. Erythropoiesis stimulating agents (ESAs) are today the main treatment for CKD patients with anemia (1). ESAs are effective in correcting and maintaining hemoglobin (Hb) levels and decreasing the need for blood transfusions. Partial correction treatment of anemia with ESAs is expensive, and full correction of Hb is not recommended (10). Before 1989 and the introduction of ESAs for anemia of CKD, repeated transfusions given to patients caused iron overload (2). After the introduction of ESAs, supplemental iron optimizes hemoglobin response and allows reduction of the ESA dose. Because of economic reasons and concerns about ESA safety, more questions were open (10). Prospective randomized controlled trials in patients with CKD not on dialysis (stages 3 to 5; CHOIR, CREATE and TREAT studies) did not demonstrate the expected beneficial effects of correcting anemia, but suggested an increased risk of death and cardiovascular (CV) events when targeting higher Hb levels ( $\geq 13$  g/dL) (11,12). Additional analyses suggest that the risk of death or CV events appears to be highest in CKD patients who fail to respond to ESAs, as indicated by lower achieved Hb levels and higher average ESA dose requirements and have led to changes in prescribing information and practice guidelines (10-12).

Iron supplementation is more efficacious *via* intravenous (more adherence) compared to oral administration and the use of intravenous iron has escalated in recent years (2). The safety of iron compounds is ques-

tionable due to their potential to induce iron overload, oxidative stress, hypersensitivity reactions, and permissive environment for infectious processes (2). In this prospective observational study, we compared the efficacy and safety profile of oral and intravenous iron with erythropoietin for the treatment of iron deficiency anemia in 43 non dialysis patients (ND-CKD) with the confirmed diagnosis of iron deficiency anemia (A) at Merkur University Hospital. We compared the benefits and risks of oral and parenteral iron, in order to provide strategies for its optimal use due to the risk for adverse effects.

## PATIENTS AND METHODS

### Patients

The study protocol included nonpregnant female and male patients with ND-CKD and anemia. Patients were aged 18-85 years, mean age 68.5 years and baseline proteinuria 0.64 g/24 h.

Exclusion criteria were patients on hemodialysis, peritoneal dialysis or patients with kidney transplantation, heart failure patients, history of secondary hyperparathyroidism, history of gastrointestinal bleeding, sign of inflammation (measured with C-reactive protein (CRP) or hsCRP  $>5$  mg/L), patients taking drugs such as cyclophosphamide, mycophenolate mofetil, angiotensin-converting inhibitors or angiotensin receptor blockers (medicines that suppress Epo production), patients with malignancy (such as myeloma), history of thromboembolism and uncontrolled resistant hypertension (confirmed diastolic blood pressure  $>90$  mm Hg or systolic blood pressure  $>140$  mm Hg without office blood pressure measurements to exclude white coat hypertension, common in patients with CKD). The largest number of patients ( $n=40$ ; 93%) had two or more accompanying diseases such as hypertension, metabolic syndrome or controlled diabetes type 2, hypothyroidism and atherosclerosis. Patients took 4-8 medications daily: antihypertensive drugs (3 or more, such as calcium channel blockers, beta blockers such as nebivolol or bisoprolol, moksonidine, urapidil, diuretics such as HCTZ or indapamide), drugs for diabetes and gastric protection (proton pump inhibitors 20 mg), hypothyroidism therapy (levothyroxine doses 25-50 mg) and antilipemic drugs. Laboratory values were measured by standardized methods and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) was used for estimating GFR categories of CKD. Home blood pressure measurement normal showed blood pressure value, controlled resistant hypertension ( $<140/90$  mm Hg), while office blood pressure measurements showed stage I hypertension in 70% of patients (140/90-159/99 mm Hg).

Patients were divided into group A (n=20) receiving intravenous iron sucrose (10 patients, 5F/5M, infusion of 10 mL/200 mg elemental iron, diluted in 250 mL sodium chloride 0.9%, during 60 minutes administered on day 1, day 10, day 20, day 30, day 45 to give a cumulative dose of 1000 mg within a 45-day period) or ferric carboxymaltose (10 patients, 7F/3M) in doses of 1000 mg once /30-45 min infusion every 45 days. Clinical follow-up after the infusion for at least 30 minutes was mandatory. In group B (n=23, 10M/13F), oral daily intake of iron (ferrous fumarate 350 mg) was administered. Erythropoietin beta subcutaneously in doses of 4000-6000 IU every week during the correction phase of anemia treatment was given. Iron supplementation was administered in order to achieve serum ferritin and transferrin saturation (TSAT) in accordance with ERBP and KDIGO guidelines (11,12). In all patients, TSAT was >10% at the beginning. Hemoglobin (Hb) was checked at the beginning and every 45 days (to monitor Hb fluctuations) and after 12 months in both groups. All patients took vitamin B12 (500 mg) im. once a month and folate acid (oral, 5 mg/day) to prevent deficiency due to poor dietary intake.

Table 1.  
Characteristics of cohort results

	Hb (g/dL)	Fe (µmol/L)	TSAT (%)	Ferritin (ng/ml)	eGFR (mL/min/1.73m <sup>2</sup> )
Month 1	9.45±0.88	8.8±0.29	21±10.5	151±111	19.36
Month 12	10.53±1.09	9.82±0.35	27±11.2	285±208	23.14

Hb = hemoglobin value (g/dL), Fe = iron (µmol/L), TSAT = transferrin saturation (%), eGFR = glomerular filtration rate (CKD-EPI formula, mL/min/1.73m<sup>2</sup>). Values are expressed as mean ± standard deviation (SD). Other data are presented as number.

There were no differences between the groups in body mass index, race, social status and education. The study was conducted in accordance with the amended Declaration of Helsinki. The study was approved by the hospital Ethics Committee and all participants gave their informed written consent.

### Statistical analysis

Data were processed by use of the SPSS software. Statistical data analysis was performed using descriptive statistics. Continuous variables were presented as mean with standard deviation. Categorical variables were presented as percentage. Paired sample t-test was applied for comparison of results. The level of statistical significance was set at p<0.001.

## RESULTS

This study carried out in a cohort of 43 ND-CKD patients showed that 58.1% of patients were female

(F=25). The majority of patients were in the >50 age group (62%). Primary endpoint was to evaluate the efficacy and safety of small doses of ESA and iron therapy in ND-CKD patients. There were no statistically significant differences in Hb values between the groups of patients stratified according to primary kidney disease (hypertensive nephropathy in 40%, diabetic kidney disease in 25%, glomerulonephritis in 11% and chronic pyelonephritis in 24% of patients), age and sex. The mean level of iron at the beginning was 8.8±0.29 µmol/L (male/female 9.7/7.9±0.28/0.31 µmol/L) and after 12 months 9.82±0.35 µmol/L (M/F 10.7/8.94± 0.27/0.43 µmol/L). Before starting the study, the mean TSAT was 2±10.5% and after 12 months 27±11.2%. The mean ferritin level at the beginning was 151±111 and at the end of the study 285±208 ng/mL. In the treatment groups, the mean Hb level at the beginning was 9.45±0.88 (9.19±0.84 g/dL in group A and 9.72±0.95 g/dL in group B). After 12 months, the mean Hb was 10.53±1.09 (10.65±0.97 g/dL in group A and 10.42±1.22 g/dL in group B). There was minor variability in Hb levels in controls and our study found Hb fluctuations 0.6 g/dL-1.15 g/dL above the starting Hb values in both groups of patients. Iron doses and ESA were stable at the mean TSAT (>20%) and ferritin (>200 ng/mL) levels in the majority of patients (82%). Doses were decreased if TSAT was increased >30% or ferritin levels were >500 ng/mL (18%). If we compare results before and after 12 months of therapy, there was a difference (p<0.001). If we compare the groups on parenteral or peroral iron therapy, there was no difference in efficacy. The majority of patients reported better exercise tolerance (96%) and sleep (65%). During the study, none of the patients had hypertensive urgency or emergency. None of the patients had acute reactions or skin adverse effects to ferric carboxymaltose or iron sucrose. If we compare the groups according to safety, there were no differences between parenteral iron therapy with ferric carboxymaltose and iron sucrose. Secondary endpoint of this study was evaluation of anemia therapy for improvement of kidney function. Most patients were within CKD stage 3b or 4 (90%). Baseline eGFR CKD-EPI values were 19.36 mL/min/1.73m<sup>2</sup> (19.31 in group A and 19.42 in group B (range 16.8-45.6)) vs. 23.14 mL/min/1.73m<sup>2</sup> (23.17 in group A and 23.11 in group B (range 17.3-46.8 mL/min/1.73m<sup>2</sup>) after 12 months and proven to improve renal function compared to baseline, but statistically significant differences between groups A and B were not found. During the study, two patients started dialysis treatment.

Clinical follow-up after 6 months revealed the following: two male patients started dialysis after predialysis education; two female patients and one male patient had urinary tract infections; one female patient had pneumonia infection (no hospitalization); one patient

had transient ischemic attack (no hospitalization); four patients had atrial fibrillation; two patients had uncontrolled resistant hypertension (no hospitalization); and worsening of kidney function due to contrast nephropathy (one hospitalization).

## DISCUSSION

According to the last guidelines, when transferrin saturation is lower than 30% and ferritin lower than 500 ng/mL, iron therapy should be started to avoid or to reduce the doses of ESAs needed to treat anemia in CKD patients (2,11). The risks associated with ESAs, including an increased risk of death and CV events, highlight the need for additional therapies that might minimize or avoid these risks when compared to currently available ESAs. Therefore, the unmet medical need for the treatment of anemia in non-dialysis dependent CKD (NDD-CKD) patients remains high, especially from a CV safety perspective. Supplementation of iron is recommended for all non-dialysis and dialysis CKD patients with iron-deficiency anemia and those who receive erythropoiesis-stimulating agents (11).

All iron products should be prescribed, administered orally or injected (at hospital) and the most stable intravenous iron complexes (low molecular weight iron dextran, ferric carboxymaltose, and iron isomaltoside 1000 mg) can be given in higher single doses and more rapidly than preparations such as iron sucrose. Test doses are no more mandatory for conventional low molecular weight (LMW) iron dextrans. In the ND-CKD population, the erythropoietic response is also significantly higher using intravenous *versus* oral iron, and tolerability is good (12). Intravenous iron supplementation might avoid or at least delay the need for erythropoiesis-stimulating agents and the need for dialysis (12). Pre-dialyzed patients today in Croatia can afford the treatment with ESA. The guidelines provided by KDIGO for ESA treatment in ND-CKD and CKD patients on dialysis recommended Hb target from 9.5 to 11.5 g/dL and should not exceed 12 g/dL, and European guidelines recommend Hb target levels of 10 to 12 g/dL (11,12). Today, we have the ability to achieve iron stores replenishment correctly in dialysis dependent and non-dialysis dependent CKD patients without compromising safety (13). But the risks of the increased iron use to treat CKD anemia, iron overload/toxicity through excess iron deposition and induction of oxidative stress, increased risk of infections, or mortality are open questions with this therapy (14,15).

In our study, there was no anaphylaxis or adverse events encountered during administration of ferric

carboxymaltose or iron sucrose. There was no sign of iron overdosing, heart failure or mortality, but we excluded patients with secondary hyperparathyroidism (a recognized cause of resistance to ESAs. High phosphorus levels have been shown to increase fibroblast growth factor 23 levels, which is associated with klotho suppression and low klotho levels cause deficiency in activated vitamin D, and vitamin D deficiency has been implicated in the development of anemia), patients with gastrointestinal bleeding (from medical records to prevent iron AE) or patients with any sign of inflammation (elevation of hsCRP), as well as patients with heart failure. In our study, iron deficiency was defined based on a combination of two commonly used markers, ferritin and transferrin saturation (TSAT) (16,17). Eisenga *et al.* have shown that of the traditionally used markers of iron status, reduced TSAT <10% is most strongly associated with the risk of adverse outcomes (cardiovascular mortality) in CKD patients irrespective of serum ferritin level (4).

A study by Lee *et al.* showed that TSAT was associated with less severe anemia in early CKD patients. Serum hepcidin was associated with more severe anemia in advanced CKD patients (18). Cardiovascular disease is a common complication in patients with CKD. One of the most important functions of the cardiovascular system is oxygen delivery, therefore cardiovascular disease is linked to insufficient tissue oxygenation; the cellular oxygen sensing by a family of prolyl hydroxylases (PHDs) and their role in regulating hypoxia-inducible factors (HIFs) in the future will give new data on PHD inhibition and impact on anemia in CKD (2).

Neutrophil gelatinase-associated lipocalin (NGAL), a biomarker of acute kidney injury, is known to be associated with iron metabolism. A new study showed that plasma NGAL (best cut-off value  $\leq 394$  ng/mL) was superior to serum ferritin (suggested cut-off value  $\leq 500$  ng/mL) in both sensitivity and specificity and was associated with iron status in anemic patients with predialysis CKD (19). Data in our study showed an additional effect of anemia treatment in slowing natural progression of CKD. In the majority of patients, Hb levels were within the acceptable target range according to the last European and Croatian guidelines and studies (12,16,17). In contrast to managing patients on hemodialysis in whom iron strategies are more focused on intravenous iron, ND-CKD patients may receive either oral or intravenous iron (20). The healthcare, social care, and economic costs of CKD patients are a growing problem. Any interventional program to decline progression to end stage renal disease (ESRD) is very important as indicated by the fact that patients with ESRD make up less than 1% of Medicare patients in USA but the cost of their care accounts for more than 5% of the Medicare total budget (21).

In ND-CKD patients, anemia can be successfully treated by small doses of ESA and by oral or intravenous iron (ferric carboxymaltose or iron sucrose) supplementation in order to reduce cardiovascular risk and kidney failure progression. In this study, we performed home blood pressure measurement to improve adherence to medication in ND-CKD patients and to exclude WCH (22). Our aim was to exclude Epo-induced hypertension and none of the patients had hypertensive urgency or emergency during the study.

Further investigations should be conducted to analyze the implications of new drugs to treat anemia in CKD patients.

### LIMITATIONS OF THE STUDY

The main limitation of this study was its observational nature. Another limitation was that we had no data on serum albumin levels to conclude about malnutrition.

### CONCLUSIONS

Parenteral or oral iron in combination with Epo is effective treatment of anemia in ND-CKD patients if other factors are considered. Oral or intravenous iron supplements are an important adjunct in the treatment of anemia in patients with CKD. In the future, we will have new drugs such as hepcidin antagonists, HIF and ferroportin stabilizers in order to delay CKD progression. This alternative therapeutic approach in the future may avoid the overshoots and fluctuations in Hb levels seen with currently injectable ESAs in ESRD and provide a steady and controlled rise in Hb concentration.

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## SAŽETAK

### LIJEČENJE ANEMIJE KRONIČNE BUBREŽNE BOLESTI U PREDIJALIZNOJ FAZI

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Kamen temeljac liječenja anemije kronične bubrežne bolesti (KBB) danas čini primjena eritropoietina uz liječenje preparatima željeza. Anemija KBB je multifaktorska, a najčešće uključuje poremećaj željeza (apsolutni ili funkcionalni manjak), nedostatnu proizvodnju eritropoietina, a u posljednjih nekoliko godina sve više se navode i povišeni hepcidin i čimbenici indukcije hipoksije (*hypoxia-inducible factor, HIF*). U budućnosti najviše obećava primjena stabilizatora HIF-a koji stimuliraju eritropoezu endogenim putem, reguliraju metabolizam željeza te interakciju s hepcidinom, no još uvijek su u fazi istraživanja i nedostupni. Bolesnici s KBB imaju značajne dodatne čimbenike koji mogu doprinijeti rezistenciji u liječenju anemije kronične bubrežne bolesti. Cilj studije bio je utvrditi učinkovitost i sigurnost primjene liječenja željezom uz niske doze eritropoetinske terapije u predijaliznoj fazi ako su isključeni čimbenici koji mogu doprinijeti rezistenciji u liječenju anemije KBB-a. U neintervencijskoj, prospektivnoj opservacijskoj studiji ispitan je utjecaj primjene eritropoietina beta (supkutano, jednom tjedno u dozi 4000-6000 IU) u kombinaciji s peroralnom ili parenteralnom primjenom željeza u 43 bolesnika u fazi predijalize, a koji nisu liječeni ranije dijalizom ili transplantacijom, bez sekundarnog hiperparatiroidizma ili srčanog popuštanja, anamneze tromboembolizma i zloćudne bolesti, neregulirane rezistentne hipertenzije, gastrointestinalnog krvarenja, koji nisu liječeni lijekovima poput ciklofosfamida, mikofenolatmofetila, blokatorima renin angiotenzin sustava. Bolesnici su podijeljeni u dvije skupine prema načinu primjene željeza (parenteralno, 2 oblika u dozi 1000 mg tijekom 45 dana ili peroralno, željezo fumarat 350 mg svaki dan) kako bi se postigla razina feritina od 200-500 mg/L i TSAT >20%. Srednja razina vrijednosti željeza na početku iznosila je u M/F 9,7/7,9±0,28/0,31, dok je na kraju studije bila 10,7/8,94±0,27/0,43 μmol/L. Razina hemoglobina (Hb) je na početku iznosila 9,19±0,84 g/dL (skupina A) i 9,72±0,95 g/dL (skupina B). Na kraju praćenja došlo je u obje skupine do porasta razine Hb u odnosu na početne vrijednosti: 10,65±0,97 g/dL (skupina A) i 10,42±1,22 g/dL (skupina B) (p<0,001), no između skupina A i B nije utvrđena statistički značajna razlika. Rezultati studije pokazuju da je liječenje anemije KBB postojećim dostupnim lijekovima učinkovito u slučaju isključenja čimbenika koji mogu doprinijeti rezistenciji na liječenje. Kako najveći broj bolesnika s KBB ima postojeće čimbenike koji doprinose rezistenciji liječenja anemije KBB-a, u budućnosti najviše obećava primjena stabilizatora HIF-a.

**Ključne riječi:** anemija, kronična bubrežna bolest, predijaliza