STUDIJA ML20474 PRIMJENE ERITROPOETINA BETA (NEORECORMON) u LIJEČENJU ANEMIJE PREDIJALIZNIH BOLESNIKA – HRVATSKO ISKUSTVO

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ML20474 STUDY: CROATIAN EXPERIENCE IN EFFICACY AND SAFETY OF ANEMIA CORRECTION IN PREDIALYSIS PATIENTS

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We performed observational multicenter study on CKD patients in stage 3-5, with renal anemia. Key inclusion criteria were: haemoglobin level > 6.0 g/dL, age >18 years and written inform consent. Exclusion criteria were dialysis and transplanted patients and haemoglobin level > 12.0 g/dL. Study was performed from 2006.-2012. and 368 patients were included. All patients received Erythropoietin beta (Neorecormon®; Roche, Basel, Switzerland) subcutaneously in dose of 4000-6000 IU every week during the correction phase of anemia treatment or once weekly 2000-4000IU during the maintenance treatment. Iron supplementation was administrated orally in >80% patients in order to achieve serum ferritin 200-500 µg/L. From 368 patients on beginning, 246 were followed and statistically analyzed (M:F=136/110). Mean duration study period was 13.6 (Std.dev.10.36) months (max 52 months). Patients were mainly men (55.3%), age >51 years (81.3%). The median of Hb level at baseline was 9.35 g/dL and after 12 months 10.4 g/dL respectively. After 12 months, most of patients had Hb range 10.0 g/dL to 11.0 g/dL. There were no statistically significant differences between Hb in groups of patients stratified according to the primary kidney disease and age, and between sex: mean level of Hb in M at the end of study was 10.27 g/dl and in F 10.58 g/dl (p=0.051). Baseline eGFR (Cocroft Gault) values were 16.31 (range form 4.1-62.6) vs. 16.71 (range from 4.9-43.8) mL/min after 12 months. The majority of patients had reported better exercise tolerance and sleep. 47.7% of patients have started after predialysis education with dialysis and in 2 patients preemptive transplantation was performed. The results of this multicenter observational study in Croatia suggest that the use of erythropoietin beta is effective and safe in correction of anemia in pre-dialysis CKD patients.

Key words: anemia, non-dialysis chronic kidney disease

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INTRODUCTION

Anemia is a common complication of patients with chronic kidney disease (CKD), which lowers their quality of life and causes cardiovascular diseases such as congestive heart failure and coronary heart disease, and accelerates the progression of kidney dysfunction[(1-2)]. Anemia is a decrease in the effective circulating volume of red blood cells and is measured by serum hemoglobin (Hb). The World Health Organization (WHO) defines anemia as Hb <13.0 g/dl in adult men and non-menstruating women and <12.0 g/dl in menstruating women[(3)]. The data from the US Renal Data System (USRDS) have shown that the prevalence of anemia is 4.3% in the general population, while patients with a glomerular filtration rate (GFR) <60ml/minute showed an average prevalence of 14.2%, with escalating prevalence of anemia with progression through stages of CKD: 6.2% in stages

1 and 2, 11.9% at stage 3, and from 47.8% to 95% in stages 4 and 5[4,5]. Symptoms generally occur when the Hb level is less than 10.0 g/dl and become more pronounced as Hb continues to decline[6-9]. The cause of anemia in CKD is often multifactorial, with the most common etiology being ineffective erythropoietin (EPO) production by the diseased kidneys, often complicated by iron deficiency[10]. There are other factors contributing to anemia in patients with CKD, such as acute and chronic inflammation and the accumulation of uremic toxins, but will not be the focus of this article. Recombinant human erythropoietin was introduced in the 1980s in the treatment of anemia associated with CKD. The majoritiy of the trials and evidence for use of ESAs in the CKD population was with patients on hemodialysis and have documented an improved QoL and functional status, as well as relief of symptoms associated with anemia[11-13]. Pre-dialyzed patients in Croatia can not afford the treatment with erythropoietin. Purpose of this Study was to evaluate efficacy and safety of erythropoietin administration subcutaneously once weekly for correcting anemia in the patients in Croatia with chronic kidney disease (CKD), not on dialysis.

PATIENTS AND METHODS

Study Design and Patients

This retrospective observational study was conducted in pre-dialyzed Croatian nephrology centers for follow-up of patient records. Records of CKD pre-dialyzed patients who were included in the ML20474 STUDY database between May 2006 and February 2012 were analyzed if they had at least one Hb value per month over a period of at least two months. Key inclusion criteria were: haemoglobin level > 6.0 g/dL, age >18 years and written inform consent. Exclusion criteria were dialysis and transplanted patients and haemoglobin level >12.0 g/dL, patients with cancer, chronic infectious disease (such as hepatitis B, C or HIV infection). On beginning 368 patients were included. All patients received Erythropoietin beta (Neorecormon®; Roche, Basel, Switzerland) subcutaneously in dose of 4000-6000 IU every week during the correction phase of anemia treatment (Hb value above 9.0-10.0 g/dL) or once weekly 2000-4000 IU during the maintenance treatment. Oral iron supplementation was administrated in patients in order to achieve serum ferritin 200-500 mg/L. Other medical treatment and diagnostic monitoring were left to the Centers' discretion following their routine practice.

The main objective of the study was the description of the therapeutic anemia management in pre-dialyzed patients in Croatia. Secondary objectives included a description of the used treatment strategies in comparison to national and international guidelines compared to target Hb levels.

Data collection

Anonymized data on sex, height, weight, underlying disease causing chronic kidney disease, glomerular filtration rate, co-morbidities (diabetes, hypertension), laboratory tests for anemia (complete blood count, Hb, serum ferritin, serum iron, transferrin saturation), C-reactive protein, serum albumin, serum creatinine, urea, potassium, treatments of anemia (transfusions, ESA, iron) and significant events such as hospitalizations and death were extracted from the database for 246 CKD pre-dialysis patients.

Statistical Analysis

No formal statistical hypothesis was tested. The statistical analysis was essentially descriptive (percentages, mean and standard deviation [SD], median range). Groups were compared using Student's t-test for quantitative variables and Chi-2 test for qualitative variables. All tests were considered statistically significant if $p < 0.05$. Statistical analysis was performed using STATISTICA 10, 2011 software (Stat Soft Inc., USA).

RESULTS

Primary purpose of this Study was to evaluate efficacy and safety of erythropoietin administration subcutaneously once weekly for correcting anemia in the patients in Croatia with chronic kidney disease (CKD), not on dialysis. This study in a cohort of 246 CKD pre-dialyzed patients (M:F=136/110) showed that 55.3% (M=136) of evaluable patients were male. The median age was 65.5, ranging from 19-91 years. The majority of patients (51.6%, 127 of 246) were in the age group of 51-75 years. Patients older than 75 years accounted for a significant proportion (29.7%, 73 of 246). Mean duration study period was 13.6 (SD 10.36) months (max 52 months).

The most common causes of primary renal disease were hypertensive renal disease (hypertensive nephrosclerosis in 31.3%, 77 pt) and diabetic nephropathy (27.6%, 68 pt), whereas chronic pyelonephritis and glomerulonephritis have been causes of primary renal disease in 48 (19, 5%) and 28 (11.4%) patients. Other causes of CKD accounted for 8.5%. It lacked data on underlying disease in 1.6% (4 patients). The largest number of patients (54.1%) had 3 or more concurrent diseases, while 45.9% had 2 or more accompanying diseases such as hypertension, diabetes and atrial fibrillation.

The median of Hb level at baseline was 9.35 g/dL (SD 10.76) and after 12 months 10.4 g/dL respectively. After 12 months, most of patients had Hb range above 10.0 g/dL. There were no statistically significant differences between Hb in groups of patients stratified according to the primary kidney disease and age, and between sex: mean level of Hb in M at the end of study was 10.27 g/dl and in F 10.58 g/dl (p=0.051).

The majority of patients prior to study entry did not treat anemia. Only 18.3% of patients received an oral iron therapy (100 mg). During the study 80% of patients were treated with oral iron (ferrous sulfate tablets 200 mg) with ESA supplemented and this was the most frequently used anemia treatment option.

Average iron value was 8.94 umol/L, (range 2-24.9), and the average ferritin value (only the part of the patient that is determined by ferritin) was 285.7 mg/L. Most patients were within 3/4 CKD stage (81.5%). The levels of hemoglobin (Hb) less than 9.0 g/dL had 35% of patients at baseline, while at the end of the study only 10.6%. At the end of the study 89.4% of patients achieved a level of hemoglobin (Hb) above 9.0 g/dL.

Weekly doses of NeoRecormon varied at the start and at the end of treatment: at baseline over 50% of patients required a week of dose administration of 4000-6000 IU sc. Theere were about 17% requiring a higher dose of 6000 IU sc. weekly. At the end of follow-up only 6.5% of patients required a dose higher than 6000 IU sc (2.5 x times less than at the beginning of the study). At the end of the study there was an increase in the number of patients with application of a lower doses of 4000 IU sc. weekly. Analysis of variance (ANOVA) showed that the values of Hb at baseline were statistically significantly lower than the value at the end of the Hb monitoring for all weekly dosage ($p<0,05$) (Figure 1).

Table 1.
Characteristic of parameters of the cohort

Descriptive Statistics					
Variables	Valid N	Mean	Minimum	Maximum	Std.Dev.
Hb beginning (month1)	243	93.50	61.0	123.0	10.757
Hb end (month 12)	239	104.23	59.0	134.0	12.037
Fe beginning	202	8.94	2.0	24.9	3.775
Creatinine (month 1)	243	383.33	107.0	1300.0	171.302
Creatinine (month 12)	113	377.99	141.0	820.0	171.164
GFR (month 1)	235	16,31	4,1	62,6	8,638
GFR (month 12)	112	16,71	4,9	43,8	9,042

Hb=hemoglobin value (g/L), Fe= iron (umol/L),
creatinine = serum value (IDMS standardization, umol/l)
GFR=glomerular filtration rate (CG/Cockroft-Gault, ml/min),
Values are expressed as mean standard deviation (SD). Other data are presented as number

Secondary endpoint of study was evaluation of impact of anemia on improvement of kidney function: Renal function after 6 months of treatment of anemia remains stable. Baseline eGFR (Cockroft-Gault) values were 16.31 (range from 4.1-62.6) vs. 16.71 (range from 4.9-43.8) mL/min after 12 months and statistically proven to improve renal function compared to baseline after 6 months ($p <0.05$) (Table 1). During the study 9 patients (3.7%) died and 2 (1F/1M) received a preemptive kidney transplant. We do not consider 9 deaths related to administration of NeoRecormon. After predialysis education 47.7% of patients have started with dialysis.

DISCUSSION

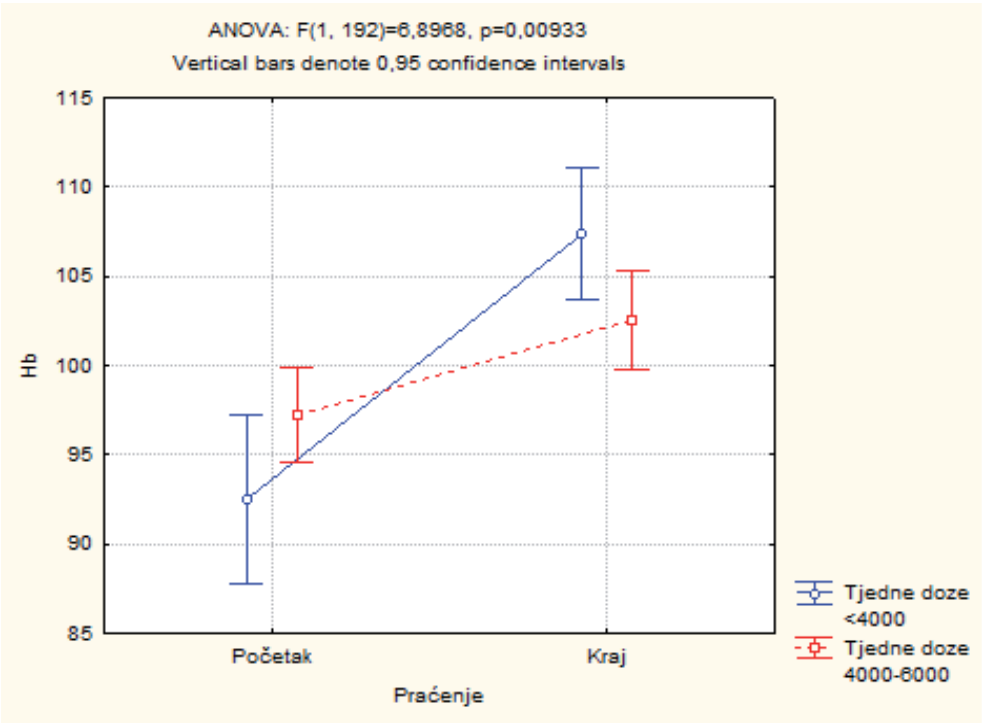
Chronic kidney disease (CKD) is a major global health problem and anemia is a frequent complication. Anemia may, if there is no proteinuria, be the first sign of kidney disease. In all patients with anemia and CKD diagnostic evaluation is required. Prior to diagnose a renal anemia, it is necessary to eliminate possible other causes. The cause of anemia is often multifactorial in patients with CKD. After controversy about the optimal (upper) limit of Hb levels based on three studies in patients with CKD not on dialysis, comparing ESA treatment with high Hb target levels (≥13 g/dL) vs. low Hb targets (~11 g/dL) or placebo (CHOIR, CREATE and TREAT study), European guidelines for ESA-treated dialysis and non-dialysis patients recommend Hb target levels in the range of 10–12 g/dL[6,12]. The guidelines provided by KDIGO recommended Hb target from 9.5 to 11.5 g/dL[8]. Hb levels should not exceed 12 g/dL, particularly in patients with severe cardiovascular disease or diabetes and concurrent peripheral vascular disease[8,12].

Croatian Society of Nephrology, Dialysis and Transplantation (HDNDT) has already published its own guidelines based on the recommendations and the positive experience of European and international professional societies, as well as on own experience.

To the best of our knowledge, this is the first multicentar report of beneficial treatment in CKD pre-dialyzed patient in Croatia. However, our data show additional effect of anemia treatment in slowing natural progression of CKD. As expected, most patients of our study were treated with an ESA and/or iron to control anemia. In the majority of patients Hb levels were in the novel Hb target range of 10–11 g/dL and was within the acceptable today target range according to European guidelines.

Further research documenting the frequency and investigating the mechanisms of those effects reported in CKD pre-dialysed patients with long lasting is necessary, as treatment of anamia in pre-dialysed patients may constitute an effective treatment option to reduce cardiovascular risk and kidney failure progression and prepare patients for preemptive kidney transplantation.

Figure 1.
Levels of Hemoglobin and EPO doses during the study



Hb = hemoglobin value (g/L)
EPO = Erythropoietin beta doses therapy
(<4000 IU sc, 4000-6000 IUsc) on begining and the end of study

CONCLUSIONS

Anemia is independent risk factor for kidney disease progression and recognition of the appropriate treatment is essential for providing renoprotection.

The results of this multicenter observational study in Croatia suggest that the use of erythropoietin beta is effective and safe in correction of anemia in pre-dialysis CKD patients.

Conflict of Interest: None to declare.

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SAŽETAK

STUDIJA ML20474 PRIMJENE ERITROPOETINA BETA (NEORECORMON) U LIJEČENJU ANEMIJE PREDIJALIZNIH BOLESNIKA – HRVATSKO ISKUSTVO

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Prikazano je prospektivno, neintervencijsko, opservacijsko praćenje učinkovitosti i podnošljivosti eritropoetina beta (NeoRecormon®) u liječenju anemije u bolesnika s kroničnom bubrežnom bolesti (KBB) koji još nisu podvrgnuti nadomjestnom bubrežnom liječenju u Hrvatskoj. U studiji ML20474 uključeno je ukupno 368 bolesnika u 3 do 5. stadiju KBB s anemijom u kojih je bilo indicirana primjena lijekova koji stimuliraju eritropoezu (LSE). Svi su bolesnici primili eritropoetin beta (Neorecormon) supkutano u dozi od 4000 do 6000 IU jednom tjedno u razdoblju do korekcije anemije ili porasta Hb za 10 g/L a potom jednom tjedno u reduciranoj dozi od 50% u odnosu na početnu. Bolesnici su praćeni u razdoblju od 3 do maksimalno 52 mjeseca, prosječno 13.6 (Std.dev.10,36) mjeseci. Većina bolesnika bili su muškarci (55,3%), dob preko 51 godina (81,3%). Medijan vrijednosti razine hemoglobina iznosio je 93.5 g/L na početku studije a nakon 12 mjeseci 104,23 g/L. Nije bilo statistički značajne razlike u razini Hb ovisno o uzroku osnovne bubrežne bolesti i dobi bolesnika. Na kraju praćenja većina je bolesnika navela bolje podnošenje napora, bolje spavanje i manju razdražljivost. Nuspojave primjene terapije eritropoetinom beta nismo uočili. Rezultati pokazuju da je primjena učinkovita i sigurna u liječenju anemije u bolesnika s KBB koji nisu započeli liječenje nadomještanjem bubrežne funkcije.

Ključne riječi: anemija, kronična bolest bubrega