ANEMIA IN PATIENTS WITH END STAGE RENALE DISEASE

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Abstract: By definition, anemia refers to an absolute reduction of the total number of circulating red blood cells (RBCs). For practical purposes, anemia is considered when one or more of the following are decreased: hemoglobin, hematocrit, or red blood cell (RBC) count. This condition is a laboratory finding that signifies the presence of illness or disease; anemia should not be considered a diagnosis. Anemia usually is grouped into three etiologic categories: decreased RBC production, increased RBC destruction, and blood loss. Anemia of chronic illness and anemia of chronic kidney disease(CKD) both fall under the category of decreased RBC production. When the classification of anemia is based on the morphology of the RBCs, both anemia of chronic illness and chronic kidney disease usually fall under the classification of normochromic, normocytic anemia. In any individual, anemia may be the initial laboratory sign of an underlying medical problem.Consequently, a complete blood count, including the hemoglobin (Hb) concentration, is routinely part of global health assessment in most adults, whether or not they have chronic kidney disease (CKD). In patients with CKD but stable kidney function, the appearanceor progression of anemia may herald a new problem that is causing blood loss or is interfering with red cell production. Enda Stage Renal Disease(ESRD) is a pathological condition followed by physiological decrease of the kidney function or a gradual decrease of the glomerular filtration rate (GFR - Glomerular Filtration Rate). One of the most common consequence that appears in patients with ESRD, is renal anemia. Chronic Kidney Disease (CKD) is widespread all around the world, and the number of patients that are affected is continuing to grow. In the United States, is evaluated, that till the year 2010- 2 million people were affected with ESRD.The impact of anemia in patients with CKD is deep. Besides the known symptoms such as fatigue, dizziness, shortness of breath, chest discomfort anemia is associated with serious adverse outcomes, such as cardiovascular diseaseCVD)n , including left ventricular hypertrophy and congestive heart failure. Although the most severe form of ESRD is kidney failure and the need for renal replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplantation), many more patients are affected by less severe forms of the ESRD. Chronic kidney weakening presents gradual irreversible impairment of secretory, secretory endocrine, metabolic and homeostatic kidney functions as a result of various congenital or acquired kidney diseases. During CKF the production of the hormone- Eryth-ropoietin (EPO) is decreased which is a leading cause of renal anemia in these patients. The role of EPO (hormone which mainly secretes in kidney) is the stimulation of Erythropoese. So it is very clear that in TCKI when the secretory function of the kidney is weakened, the nefrone function is reduced then also the Erythropoietin concentration is ruduced too and in high positive correlation with the development of anemia. Anemia, as defined by CRF National Kidney Foundation, the values of hemoglobin (Hb) are <12 g / dl for women and <13.5 g / dl for men (1,2,3), on the other hand, best european guidelines for anemia management in patients with chronic kidney failure define anemia by age and gender. Anemia is defined as aHb concentration of <11.5 g / dl of the female gender, males ≤ 70 years Hb<13.5 g / dL in men and> 70 years Hb<12 g / dl. (4).**The aim of the paper**: The purpose of this study is to verify and document the positive therapeutic effects of Epoetin (stimulative preparations of erythropoese) in the renal anemia treatment in uremic patients treated with chronic repetitive hemodialysis. The Material and Methods: In the cohort-prospective study (,, cross-section ") were included a total N^0= 100, patients treated with hemodialysis from which: 45 were females whereas 55 were males, with an average age: 62.50 ± 8.00 years old, treated with dialysis for more than 12 years in the Clinic of Nephrology-Skopje. The anemia should be evaluated independently of CKD stage in order to identify any reversible process contributing to the anemia. The causes of acquired anemia are myriad and too many to include in a guideline such as this. The most commonly encountered reversible cause of chronic anemia or worsening anemia in CKD patients, other than anemia related directly to CKD, is irondeficiency anemia

Index Terms: esrd,anaemia,erythropoethin

1 INTRODUCTION

Etiology of renal anemia and the correlation with the kidney insufficiency depends on many different factors. In patients with TCKI treated with hemodialysis (HD), its recommended that as an treatment objective of anemia to be the value of Hb ≥ 11g / dl for female gender and ≥12 g / dl for male gender.Many studies have shown a high positive correlation between the Hb concentration and kidney function. The introduction of recombinant human erythropoietin (rHuEPO) into clinical practice in the 1980 s was a major breakthrough in the treatment of the anemia of patients with CKD. The development of rHuEPO was aimed at replacing the insufficient endogenous erythropoietin (EPO) production related to CKD progression. It remains unclear whether the main cause of anemia is a loss of kidney EPO production capacity or a derangement in oxygen sensing, as proposed more recently. In the early years, rHuEPO administration was regarded by the nephrology community as a beneficial therapy for long-term dialysis patients whose Hb values fell to extremely low levels, making them transfusion-dependent. The immediate benefit of rHuEPO in CKD patients with severe anemia and anemia-related signs and symptoms was clear. In addition, the reduction in the need for regular blood transfusions was another major benefit, resulting in less frequent transmission of blood-borne viral

diseases, such as hepatitis B and C, less allosensitization, predisposing to prolonged wait times or failure to receive a kidney transplant, transplant rejection, and less transfusional hemosiderosis.After introduction of rHuEPO into clinical practice its administration was limited to dialysis patients with the most severe forms of anemia. Progressively, its use was extended to the majority of dialysis patients with renal anemia, and subsequently also to anemic patients with CKD 4–5 in countries in which the high cost of rHuEPO did not limit the number of patients eligible for this treatment. Hb targets also increased progressively, often into the range of normal values. The idea that anemia should be corrected completely was based on pathophysiologic considerations and the demonstration by numerous observational studies of an inverse association between Hb concentrations up into the normal range and intermediate outcomes such as left ventricular hypertrophy,110 as well as hard patient outcomes such as cardiovascular events, hospital admission,114 and death. Of note, a recent study also showed that CKD 5D patients with naturally occurring Hb concentrations greater than 12 g/dl (120 g/l) were not at increased mortality risk. Anemia appears from the beginning of kidney weakening (when kidney function starts weakning by 30-50%), that's why

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Although patients with diabetes are monitored regularly for a variety of complications, such as polineuropathy, nephropathy and diabetic retinopathy, the Hb concentrations are often not routinely assessed. Interestingly, Hb reductions often occur prior to the beginning of diabethic nephropathy. This Hb reduction occurs for a variety of reasons. About 90% of the hormone erythropoietin is produced by the kidneys. Under normal physiological conditions, hypoxia in the kidneys leads to an increase in the production of erythropoietin, which then stimulates erythropoiesis (8) of the kidneys, in turn, having increased the oxygenation due to the formation of red blood cells and then reducement of the erythropoietin production. However, tubulointerstitial damage associated with diabetes occurs early in the course of diabetes, even before a reduction in GFR or the manifestation of albuminuria. Functional kidney tissue in patients with TCKI, are not able to produce sufficient amounts of erythropoietin in response to renal hypoxia. Several factors affect negatively in reducing the production of Hb such as metformin, fibrates, statins, thiazolidinediones, ACE inhibitors and finally, systemic inflammation (MIA syndrome) associated with the correction of the initial stages is of great importance, because the early correction of anemia not only corrects the blood statements, it also protects the body from its consequences: left ventricular hypertrophy, infections and other diseases of the blood vessels.. One of the major of studies, Health and Nutrition Survey of Third National Review (NHANES III -Third National Health and Nutrition Examination Survey (NHANES III)), has examined more than 15,000 people in the US general population in the period of the years1988-1994 and found an inverse relationship between GFR <60 ml / min /1.73 m2 and the prevalence of anemia. Using GFR and calculating the prevalence of anemia, defined as a concentration of Hb<12 g / dl in men and <11 g / dl in women, they found that anemia increases by 1% in patients with a GFR of 60 mL / min to 1.73 m2, by 9% in patients with the GFR degree of 30 mL / min/1.73 m2 and up to 33% for males and 67% for women when the rate of GFR falls of 15 ml/min/1.73 m2. (5, 6). Patients with stage four and five of TCKI and diabetes have higher prevalence of anemia compared with patients without diabetes and other underlying diseases (7). The microvascular disease in patient witj diabetes

which leads to in the production of inflammatory cytokine, mediators, such as interleukin, tissue necrosis factors. Other factors, though not specifically affecting in the worsening of anemia in patients with TCKI, are also: platelet dysfunction that leads to an increased risk of gastro-intestinal bleeding, short red blood cell lifespan (30-60%, whereas normally: 120 days) , hemolysis, accumulation of uremic toxins. In patients treated with HD as a cause of anemia, are also counted the chronic loss of blood resulting from frequent phlebothomy for frequent laboratory examinations, frequent punctions of arterio-venous fistulas and blood loss during dialyser rupture, malnutrition and iron deficiency, folate and vitamin B12, all influence in the manifestation of anemia and reduction of the Hb values and so in stimulating the production of erythropoietin and also erythropoesis. (10,11). The guidelines to treat or not to treat the anemia of CKDare also valid for CKD 4–5T patients. Outcomes of interest in RCTs of ESAs include mortality,cardiovascular and kidney endpoints, safety, quality of life(QoL), blood transfusions and cost. QoL outcomes areparticularly important for CKD 5D patients and for some may be more important than cardiovascular events ormortality, since they have relatively short life expectancy and the symptoms attributable to anemia (e.g., low energy, fatigue, decreased physical function, and low exercisecapacity) occur frequently and can be disabling.

2 MATHERIAL ND METHODS USED

In the cohort-prospective study (,, cross-section ") were included a total of N0 = 100 patients that were treated with hemodialysis, from which: 45 (45%) were females and 55 (55%) were males, with an average age: 62.50 ± 8.00 years, treated with dialysis for more than 18 years in Clinic of Nephrology and Hemodialysis in Medical Faculty in Skopje. From the total 120 patients, in a 100 of them (83%) was manifested anemia which showed a sensibility towards Erythropoetin. Whereas 20 (17%) patients had normal values of hemoglobin, erythrocytes, haematocrit and MCV. All anemic patients were treated with epoetin with a dose of 2000-4000 international units intravenously administrated at the end of haemodialysissaences. Before starting the Epo therapy administration, all patients were subjected to laboratory examination of :Er, Hg, Htc, Iron in serum, blood ferritine, Le, thromobcytes, urea, creatinine, uric acid, total proteins, albumin and Blood for analysis was taken at the morning 08h at room temperature (19-240C), prior to the haemodialysis seanses of arteriovenous fistula. After the correction of anemia over the fifth or six week and achieving the Hb target of 115 g / l we began to reduce the maintenance dose of 20-30 units in Kg / body weight applied intravenously, individually depending on each patients.

Table no. 1: Distribution of patients examined by sex and presence of anemia

Anemia	Number	%
The examined group	**100**	**83**
Males	**52**	**45**
Females	**48**	**55**

From the examined group = 100 patients, in 100 of them (83%) was verified the presence of anemia whereas in 20 of them (17%) was not noted signs of anemia.Significant comparison for p <0.001. Anemia was registered in 52 female patients and 48 male patients..

3 STATITICAL PROCESSING OF EXAMINED MATERIAL

From the statistical basic methods were used the arithmetic average value and the standard deviation X ± SD. Hemogram's comparative statistics were analyzed with a test called STUDENTOV test, Mann-Whitney-U test and,, Anonova Two-Factor" with the statistic value for p less than 5%, respectively <0.0005 and p <0.0001 . Results are presented in tabular and graphic form in standard statistical program (Statistic for Windows, version 6.0 A, Stat. softincTulsa, OK USA).

4 THE OBTAINED RESULTS

The obtained results presented in tabular and graphic methods represent the average values from the three consistent measurements with a difference of 3 months in identical conditions. For the examination was used 5 + (5) ml of venous blood taken from the arteriovenous fistula punction (FAV) while the patient was in a lying position.

Table No. 2: Average values of the Hemogramit (Hemoglobin, Erythrocytes and Hematocrit) of examined patients by sex before the application of erythropoetin

Gender	Hb	Er	Htc
Males	**86.20 ± 5.40**	**2.80 ± 0.64**	**0.28 ± 0.05**
Females	**80.5 ± 4.70**	**2.60 ± 0.59**	**0.24 ± 0.05**

Table No. 3. Hemogram's average values (Hb, Er, and Htc) in patients examined by gender, after the aplication of EPO therapy with a duration of 8 weeks (or 56 days)

100	1st WEEK			4th WEEK			8th WEEK		
	Hb	Er	Htc↓	Hb	Er	Htc	Hb	Er	Htc
Males	85.60↓	2.50 ↓	0.27 ↓	103.50	3.50	0.33	113.0	4.20↑	0.36
Females	82.50↓	2.40 ↓	0.26↓	97.80	3.30	0.30	107.4	4.10↑	0.34

Obtained values from the group of 100 examined patients are shown in Table no. 4. The difference between genders was statistically insignificant for p <0.005 (tab. no 3). The optimal target was reached to in 20 of 40 female patients, whereas the desired response by the treatment with rHuEpo (110>Hb> 100g / l) was reached in 30 out of 50 examined females. In males the optimal target from the substitutional erythropoietin therapy was achieved (target ,, ,, Hgb-110g / l) in 24 out of 66 male examined patients, while desired values of 110> HGB> 100g / l was reached at N0 = 36/66. The whole group of examined male patients showed an optimal response to erythropoietin (Hb-110g/l) in N0 = 44/100 patients, while the desired hemoglobin value of 110 <Hb³100g/l was achieved in all examined patients. The inadequate effect from the Eriythropoetin therapy was dependent on patient's body weight, periods of not applying the erythropoietin in required dose because of unified drug aplication in all patients treated with recurrent haemodialysis (three times in a week a 2000 international unit without accounting the additional needs of the Epo), lack of the drug from the market, the frequent losses during the haemodialysissaences (different bleedings, bleedings from the arterio-venous fistula, femoral cathetra, grafts, extracorporal blood coagulation, menstrual disturbance of the female gender ...) disruption and discontinuity in the application of erythropoietin during hypertensive crisis, during intra/interdialysis, vitamin B12 deficiency, iron deficiency, etc. (11).The difference of the erythropoietin effect between genders in males is depended by the excessive stimulation of the bone marrow, and the frequent disturbance in the menstrual cycle and loss of blood from the female genitals. As expected the positive results of the Epo therapy began to express after the third week, respectively after the fourth week, whereas in 60% of patients the target Hb values were manifested after the sixth week. The values obtained are presented in the Table 1. In addition to Hb, Er, Htc we also analyzed serum iron values (Fes). The absence of iron in serum was treated individually depending on the needs through ampoules Venofer (ferric -hydroxyd-III) intravenously. At all the time during the study, we followed the adverse effects of the drug such as arterial hypertension, headaches, muscle pain. The drug was analyzed in patients who manifested clinical picture and symptoms of renal anemia and anemic syndrome (fatigue, apathy, dizziness, insomnia and also laboratory analysis documented for anemia: Hb<95g / l, Er<2.60, Htc<0.30 and the values of serum iron <7 micromoles / l ...) treated with intermittent HD at the in Clinic of Nephrology and Hemodialysis in Medical Faculty in Skopje.

5 DISCUSSION

Anemia is a condition in which the body has fewer red blood cells than normal. Red blood cells carry oxygen to tissues and organs throughout the body and enable them to use energy from food. With anemia, red blood cells carry less oxygen to tissues and organs—particularly the heart and brain—and those tissues and organs may not function as well as they should. Anemia commonly occurs in people with chronic kidney disease (CKD)—the permanent, partial loss of kidney function. Anemia might begin to develop in the early stages of CKD, when someone has 20 to 50 percent of normal kidney function. Anemia tends to worsen as CKD progresses. Most people who have total loss of kidney function, or kidney failure, have anemia.[1] A person has kidney failure when he or she needs a kidney transplant or dialysis in order to live. The two forms of dialysis include hemodialysis and peritoneal dialysis. Hemodialysis uses a machine to circulate a person's blood through a filter outside the body. Peritoneal dialysis uses the lining of the abdomen to filter blood inside the body. When kidneys are diseased or damaged, they do not make enough EPO. As a result, the bone marrow makes fewer red blood cells, causing anemia. When blood has fewer red blood cells, it deprives the body of the oxygen it needs.Other common causes of anemia in people with kidney disease include blood loss from hemodialysis and low levels of the following nutrients found in food:iron,vitamin B12,folic acid.These nutrients are necessary for red blood cells to make hemoglobin, the main oxygen-carrying protein in the red blood cells.If treatments for kidney-related anemia do not help, the health care provider will look for other causes of anemia, including other problems with bone marrow inflammatory problems-such as arthritis, lupus, or inflammatory bowel disease—in which the body's immune system attacks the body's own cells and organs chronic infections such as diabetic ulcers malnutrition

Anemia from the World Health Organization (WHO) is determined when the concentration of hemoglobin (Hb) is lower than 13.0 g / dL in adult men and women in post-menopausal period <12.0g / dL. Based on these criteria, nearly 90 percent of patients with a glomerular filtration rate (GFR) of less than 25-30 mL / min have anemia, levels of Hb<10g / dL. Since the adoption and disclosure of recombinant human erythropoietin (epoetin alfa, beta, zeta etc.), this and also other stimulating agents of the eritropoesis have become the gold standard of care for the treatment of anemia that occurs in a large number of patients with advanced chronic renal disease (CKD) and terminal chronic renal failure (ESRD). By the year 2006, 90% of patients treated with chronic hemodialysis in the United States were treated with an epoetine with an average Hb level of 12.0 g / dl. While two thirds of all patients had Hb levels between 11-13 g / dL. Anemia is also considered as a contributing factor in many of the symptoms associated with reduced kidney function. Other factors, though not specific to patients with diabetes, further aggravate anemia in patients with CKD. These include platelet dysfunction that leads to an increased risk of gastrointestinal bleeding, short erythrocyte lifespan (30-60% of the normal 120 days), hemolysis and accumulation of uremic toxins. Hypoxia caused by anemia stimulates the Renin-Angiotensin-Aldosterone System and contributes in kidney vasoconstriction. These factors further exacerbate proteinuria in TCKI by raising proteins in renal tubes. In a large number of patients with type 2 diabetes, it's shown that anemia is an independent risk factor associated with loss of renal function (12).Thoughts are that anemia significantly impacts in accelerating the progress of nephropathy and diabetic neuropathy (11), other general complications that are related to the reduction of renal function, reduction of thinking function, physical activity, increased libido, damaged lifestyle, and the need for transfusion . The correction of anemia showed that significantly affects the improvement of cardiac function or myocardial ischemia. Numerous studies have examined mortality reduction in predialytic patients and in those treated with HD and also with Erythropoietin (12,13,14,15). As a result of the possible severe consequences of anemia in patients with kidney failure, discovery, management and early treatment of anemia are necessary. In 2006 the NKF KDOQI objective, recommended that Hb concentrations should be brought ≥11-12g / dl. Finally, the trial was terminated prematurely by the Data and Safety Monitoring Board due to the inability to show a benefit (futility) and due to the suggestion of harm from higher Hb objective, which was not achieved (17, 18). A large number of authors have concluded that in predialytic patients, the anemia correction does not influence in the risk reduction of cardiovaskular diseases (17,18,19).In 2007 NKF / DOQI took consensus over the Hb values recommendations that the lower limit for the Hb treatment would remain 11 g / dl, while those receiving rHuEpo objective of Hb it would be ≤ 13 g/dl. (20,21,22,23). The cause of renal anemia, whether normocrome or normocite is not only the reduced concertation of erythropoietin but also: reduced erythro-poesis, short red blood cell lifespan , iron deficiency, the impact of uremic toxins, the beginning of bone marrow fibrosis and many other factors. Presenting symptoms of anemia start when the glomerular filtration rate is decreased under 40 ml / min, although at this stage the concentration of hemoglobin (Hb) and hematocrit values are normal (reference values of Hb = 7.76-10.6 mmol / l while for Htc = 0.37 to 0.54). With the progressive weakening of renal function and glomerular filtration rate <40 ml / min, starts the fall of the Hb concentration value, Htc and red blood cells (erythrocytes), which results in an increase and higher activity of erythropoietin which in this stage appears as a protectant and inhibitor of renal anemia presentation.For increasing the concentration of the erythropoietin in this phase when glomerular filtracioni is under 40 ml / min as the main incentive is exactly anemia and the high and increased activity of the renin-angiotensin system. In this phase the body is adapted and does not manifests signs of anemia. With the passing of time and the progressive weakening of kidney function we have weakened and decreased glomerular filtration and reduction of erythropoietin production which results in high anemia.Manymulticentric-clinical studies among patients with weakened kidneys and among the healthy population proved that mortality is significantly higher in patients with weakened kidneys as a result of cardiovascular disease (left ventricular hypertrophy, congestive heart weakening, myocardial infarction ...) and cerbrovaskulardeseases compared with a healthy population. Left ventricular hypertrophy appears as a result of renal anemia with increased volume of the heart, hypertension, increased sympathetic activity and cardiac rhythm being manifested with sinus tachycardia and paroxysmal.Cardio-cerebrovascular comlicaions in patients with weakened kidneys as a result of renal anemia start to appear especially with declining Hb concentration under the values of 0.5 g / dl and then the risk to left ventricular hypertrophy increases to 32-40%. In the past, renal anemia in patients with chronic renal insuficency (preterminal) is treated by transfusion of red blood cells or whole blood, but it jeopardized the immunization and so the transfer of virus B and C hepatitis, which inspired the experts to think of any drug in order to avoid this contemporary occurrence.Renal anemia treatment instructions are supported under the proposals that are based on the principles of evidence-based medicine (evidence-based-medicine). For optimal treatment of renal anemia most commonly used instructions are the instructions of two associations: the Europe-European-Best-Practice-Guedlines (EBPG) and America: National-Kidney-Foundation (NFK) K-doqi Guidelines. Between these two associations are many similarities, such as: ways of applying epoetinës is generally the same except (alpha epoetin) all other types are given in subcutaneous administration and this kind of application reduces the risk of hypertension caused by epoetina compared with administrating it intravenous way. Association-EBPG proposes that treatment with epoetin should be started when Hb> 11 g / dl and association-NFK / doqi proposes that target Hb values should range from 11-12g / dl. Modern studies suggest that the values of Hb in patients with chronic kidney failure (before the terminal phase) is not allowed to be over 14g / dl. In patients with chronic kidney weakening is presented the absence of a stimulating agent of the erythropoesis, the so-called Erythropoietin. Erythropoietin (EPO) is a glycoprotein hormone produced mainly in the kidneys and to a lesser extent in liver. Erythropoietin synthesis has been demonstrated in the brain, uterus, testis and spleen.This is the most important hematopoietic factor of the phylogenetic growth that belongs among cytokines - and somatotropin, interleukins 2-7, etj. The gene for Eritropoetin which is located on the seventh chromosome with the chain of 193 amino acid polypeptide.The]native form is composed of 62% protein and 38% sugar.

Individual molecules exist in the 4 glycosylation sites. These are 3 through a nitrogen atom and 1 through oxygen atom. Sugar components are not important for the in vitro activity of erythropoietin, erythropoietin as receptor binds with the protein part. Sugar component is important for the prolonged duration of erythropoietin action and reducing it's elimination. Erythropoietin biological activity in vivo is eliminated practically, if the molecule is not glycosylated.Sugar components play an important role in expanding its operation and reducing its elimination. The formation of red blood cells or erythropoesis is controlled by a system of humoral growth factors and cytokines. Erythropoietina acts directly on erythroid progenitor cells some of the precursors of red blood cells in the bone marrow, control their proliferation, maturation and differentiation. Eritropoetina is 85-90% of kidney origin, the rest being excreted by hepatocytes. Formation of erythropoietin in the kidneys, in particular, increases the state of hypoxia, where red blood cells are important to ensure a steady supply of oxygen. This link between hypoxia and the number of red blood cells and anemia was observed clinically from the late 19th century, when they noticed an increase in the number of red blood cells, when staying at higher altitudes. Erythropoietin is insulated quite late (in 1977) from the urine of patients with aplastic anemia. Above mentioned hypoxia leads to anemia with increased erythropoietin level in the blood which in turn stimulates erythropoiesis.The normal plasma concentration value of erythropoietin i.e./ml range from 0.01- 12:03. Due to hypoxia and anemia, the value can be increased by 100-1000 times. In patients with obstructed IRKT is prevented the enough erythropoietin formation, in order for it to develop anemia. In the market there are different forms of the erythropoietin isoforms (alpha, beta, delta darbepoetin, eqralys) that are recombinated (rHuEpo) which are heterogeneous and change the structure of the sugar chains but with the same biological properties. Recombinant erythropoietin alfa, beta and delta are called epoetins. Introduction of the rHuEpo therapy in the treatment of renal anemia in uremic predialytic patients and those treated with hemodialysis represents a major revolution in contemporary medicine. Before starting treatment with Simulatin Preparations of Erythropoesis-PSE (PSE-is the term of the new appointed by EDTA-European Association for dialysis-transplant and artificial organs who replaces termen of Epoetinës) in patients with chronic renal insuficcency-preterminal must be completed the following laboratory tests: concentration of hemoglobin (Hb) values of hematocrit (Htc), concentration of red blood cells (erythrocytes), index of erythrocyte (average volume cell-MCV and hemoglobin average cell-MCH)., conce-ntration of ferritin in the plasm (so that the depo quantity of iron would be valuated) transferinit serum values, the values of C-reactive-protein in the plasma to value the inflamation. In general, patients with Chronic Kidney weakening, the values of Hb should be brought>ll g / dl and Htc> 33% or these values should be reached in the period of 4 months (these values are individual and are depended largely by-race, age, ethnicity, genetic predisposition ...).In patients with cardiovascular disease os scale III according to NYHA-New York Heart Association Classification of Congestive Heart Failure, in patients with Diabetes Mellitus and with peripheral vascular disease is not preferred that the Hb values to be > 12 g / dl).PSE therapy should be apply to all patients with chronic kidney weakening, to which the values of Hb (assigned at least twice within the distance of 14 days) are <11 g / dl and Htc<33%. Erythropoietin application way in patients with chronic kidney weakening in the phase before terminal, is subcutaneous, whereas patients treated with reccurent hemodialysis the erythropoietin application is in intravenous way. Dosage of PSE (EPO erythropoietin) in patients with Chronic Kidney weakening in preterminal stage is individual and dependent on the values of Hb and Htc (3x 2,000 units per week during the correction of anemia to 2000 or 4000 unit International week during the maintenance phase). During maintenance of PSE therapy is preferred also the administration of the iron preparates (25-150 mg per week dose intravenously) . In these last years, in addition to PSE and iron preparations administration, is preferred also the body supplementation body with high doses of vitamins which significantly affect growth Hbvalues.There is verifiable evidence that treatment with Vit. E, Vit. C, Folic Acid and L-Carnitine decreases the possibility of the appearance of oxidative stress, resistance to therapy PSE which appears in rare cases. The most common cause of resistance to epoetineve are iron deficiency, inflammation, hyperpa-rathyroidism, aluminum-hydroxide intoxications, hemoglob-inopathies, chronic and frequent bleedings, multiply myeloma, malnutrition, hemolysis, absence of Vit. B-12, folic acid, side effects of immunosuppressive preparations, enzyme inhibitors and angiotensin-converter. Over the last decade with the discovery of erythropoietin and its application, numerous studies documented that correction of renal anemia by erythropoietin has shown higher effects. At the beginning of the presentation of these studies, this theory, from some experts and other studies were objections by insisting to prove that the use of erithropoietin in inital stages of renal failure-preterminl speeds the appearance of anemia and weakening the nefrone function.But many multicentric and contemporary studies proved and verified the opposite of the above theory. Some contemporary studies on the application of epoetin have proven that during the use of it, is presented a very serious complication-ablation of erythrocytes caused by antibodies against erythropoietin, but this occurence is not verified completely therefore still remains as contemptuous. The beneficial effects of the use of erythropoietin and correction of anemia in the early stages of renal failure menifests with these symptoms: reduction of the energical body needs, increasing physical activity, improvement of the health and mental status, increased social activity, slows the rapid development of kidney weakening, slows the development of early left ventricular hypertrophy, reduces risks of cardiovascular and cerebrovascular diseases. All studies on the role of erythropoietin and on its positive effects have proven that it is more than necessary the early beginning of treatment and correction of renal anemia in patients with preterminal renal insufficiency. Often the question is submitted that which are the adequate values of hemoglobin, hematocrit and red blood cells to initiate the correction of anemia in patients with preterminal renal insufficiency. A multicenter-international-study-CREATE (The Cardiovascular Risk Reduction Early Anaemia By epoetin ß treatmeneit.) in which the study wereincluded over 600 patients with preterminal kidney weakening with a creatinine clearance of 35ml / min and values Hb = 10.0- 15.0 g / dl.In the first group the treatment with Erythropoietin began when Hb values were 12.0-15.0 g / dl, while the treatment of the second group began when Hb values were 10.5 g / dl. After finishing the study, which lasted four years, experts found that patients with values of Hb<10.5 g / dl, although it was applied Erythropoietin dose similar to other group morbidity, symptoms of left ventricular hypertrophy, arterial hypertension, cardiovascular and cerbrovaskulardeseases were 40% more manifested than in the other group when the treatment with Erythropoietin began with the Hb values = 12.0-15.0 g / dl. Therefore the treatment of renal anemia

should begin early when hemoglobin values are 11.0 g / dl. In the begining of treatmentErythropoietin (Eritropoetin of Recombinant Human) should be applied from 2000-4000 international units once a week bearing in mind that the increase in Hb level are not to be exceed the values of 11.5-13.3 g / dl. It is known that patients with preterminal weakened kidneys lack iron which increases the negative effects of anemia in renal failure, so that to correct this phenomenon and the effect of eritopoetinës to be more powerful while using epoetin, it is necessary to be given also iron medications (Amp. Ferri (III) Oxidum Saccharatum) year.C, year.E, folic acid and L-Carnitine. In 2009 the ERBP Anaemia Working Group published its first position paper, which focused on the 2007 update on the haemoglobin (Hb) targets by the National Kidney Foundation: Dialysis Outcome Quality Initiative[3] and on emerging issues that were not covered by the complete set of KDOQI recommendations in 2006. In 2009, the Trial to Reduce Cardiovascular Events with Eritropoetin Therapy (TREAT) study was published. This large, randomized, placebo-controlled trial raised a number of safety issues about erythropoiesis-stimulating agent (ESA) use in the chronic kidney disease (CKD) population with type 2 diabetes when administered with the aim of normalizing Hb values. Promptly, the Anaemia Working Group of ERBP published a second position paper giving guidance on the interpretation of these new findings together with their possible implication on Hb targets and treatment strategy when using ESAs in CKD patients.

6 CONCLUSION

Results of our study showed that the application of Epoetinm represents an extremely safe and effective way for the correction and treatment of renal anemia and also preventing left ventricular hypertrophy in a timely manner, thus also having the reduction of the incidence of cardiovascular diseases and cerebrovascular desease. Besides the therapy and substitution of lack of iron with iron preparations, uremic patients treated with HD because of oxidative stress and as a prevention against the resistance (although rare) on erythropoietin have a need for antioxidants therapy with: Ascorbit (Vit. C) , vit. B6, Tocopherol (Vit. E),Folic Acid, L-Carnitine. As a conclusion we can ascertain and suggest that the inhibition and prevalence of presentation of above mentioned consequences of renal anemia, oblige us to start its treatmend at an early stage of manifestation of the first symptoms.

A health care provider may advise people with kidney disease who have anemia caused by iron, vitamin B12, or folic acid deficiencies to include sources of these nutrients in their diets. Some of these foods are high in sodium or phosphorus, which people with CKD should limit in their diet. Before making any dietary changes, people with CKD should talk with their health care provider or with a dietitian who specializes in helping people with kidney disease. A dietitian can help a person plan healthy meals.

REFERENCES

1. National Kidney Foundation: Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. Am J Kidney Dis5 (Suppl. 3):S1 –S108, 2006

2. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis39 (Suppl. 1):S1 –S266, 2002

3. U.S. Department of Health and Human Services: Healthy People 2010. 2nd ed. Washington, D.C., U.S. Government Printing Office,2000

4. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. Nephrol Dial Transplant 19 (Suppl. 2):ii1 –ii47, 2004

5. Astor BC, Muntner P,et.al.Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). Arch Intern Med 162:1401 –1408, 2002

6. Coresh J, Astor BC, Greene T,et.al. Prevalence of chronic kidney disease and decreased kidney function in the adult U.S. population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis41 :1–12,2003

7 LiVecchi M, Fuiano G, Francesco M, et al.: Prevalence and severity of anemia in patients with type 2 diabetic nephropathy and different degrees of chronic renal insufficiency. NepronClinPract 105:c62 –c67, 2007

8. Mohanram A, et.al. Anemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. Kidney Int 66:1131 –1138, 2004

9 Daugirdas JT, Blake PG, Ing TS, Eds.: Handbook of Dialysis. 4th ed. New York, Lippincott Williams & Wilkins, 2006

10. Al-Khoury S, Afzali B, et al.: Diabetes, kidney disease and anaemia: time to tackle a troublesome triad? Int J ClinPract 61:281 –289, 2007

11. Silverberg DS, Wexler D, et al.: The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. Nephrol Dialysis Transplant 18:141 –146,2006.

12. Mohanram A, Zhang Z,et al.: Anemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. Kidney Int 66:1131 –1138, 2004

12. Painter P, Moore G, et.al. Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. Am J Kidney Dis39 : 257–265,2002

13. Silverberg DS, et.al. The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. Nephrol Dialysis Transplant 18:141 –146,2003

14. Valderrabano F, Jofre R, Lopez-Gomez JM: Quality of life in end-stage renal disease patients. Am J Kidney Dis 38:443 –464, 2001

15. National Kidney Foundation: Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target [article online]. Available from Accessed 15 October 2007

16.Singh AK, et.al. Choir Investigators: Correction of anemia with epoetinalfa in chronic kidney disease. N Engl J Med355 : 2085–2098,2006
17. Aranesp package insert. Thousand Oaks, Calif., Amgen, 2007
18. Levin A: Understanding recent haemoglobin trials in CKD: methods and lessons learned for CREATE and CHOIR. Nephrol Dial Transplant22 : 309–312,2007
19. Mix T, Brenner R, et. al.: Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT): evolving the management of cardiovascular risk in patients with chronic kidney disease.Am Heart J149 : 408–413,2005
20. Procrit package insert. Raritan, N.J., Ortho Biotech, 2007
21. Drueke TB, Locatelli F, et al. CREATE Investigators: Normalization of hemoglobin levels in patients with chronic kidney disease and anemia. N Engl J Med355:2071 –2084, 2006
22. Aranesp package insert. Thousand Oaks, Calif., Amgen, 2007
23. Pisioni RL, Bragg-Gresham JL, et al. Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 44:94 –111, 2004

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