Erythropoietin in Cardiorenal Anemia Syndrome

Emir Fazlibegović[1], Mustafa Hadžiomerović[1], Slavica Ćorić[1], Emil Babić [1], Fadila Fazlibegović[2]

1. Clinical Hospital Mostar, Bijeli Brijeg bb, 88 000 Mostar, Bosnia and Herzegovina
2. Regional Medical Center "Dr. Safet Mujić" Mostar, Južni logor bb, 88 000 Mostar, Bosnia and Herzegovina

* Corresponding author

Abstract

Incidencies of heart and renal failure (HF, RF) together, are increasing in our country and all over the world, so a great attention has been dedicated to this problem recently. These diseases together have shown bad results because of the process of accelerated arteriosclerosis, structural changes of myocardium, oxidative stress, inflammation, increased activities of symphathetic nervous system (SNS), increased activities of a renin-angiotensin-aldosteron system (RAAS) (1). These factors are crucial in the development of patho-physiological process and consequential development of anemia, that together with heart and renal failure through interaction, cause serious disorder that we call the cardio-renal anemia syndrome (2). We examined effects of erythropoietin (Epoetinum beta) at 90 (60 men and 30 women) predialysed and dialysed patients with HF signs during a period of three years in individual dozes of 2000-6000 units subcutaneus (sc) weekly. Using computer S PLUS and SAS multiple variant analysis we have got correlations by Pearson. Epoetinum beta significantly develops anemia parameters: number of erythrocytes ($r=0,51779$; $p<0,0001$), hemoglobin ($r=0,38811$; $p<0,0002$), MCV ($r=0,59876$; $p<0,0001$) at patients with HF. Positive effects are seen at NYHA class ($r=0,59906$; $p<0,0001$), on quality of life before and after prescribing medicine. Parameters of renal functions are improving: more urea ($r=0,45557$; $p<0,0001$) than creatinine ($r=0,26397$; $p<0,00119$) and potassium values K^+) are not changed significantly ($r=0,02060$; $p<0,8471$). Epoetinum beta has been useful in treatment of predialysed and dialysed patients with HF and anemia by improving functional ability of myocardium and quality of life.

KEY WORDS: erythropoietin, Epoetinum beta, heart failure, renal failure, cardio-renal anemia syndrome

Introduction

Erythropoietin (EPO) is represented as a hormone that is synthesized in the peritubular interstice of renal and it is main regulator of erythropoiesis. It is connected with specific receptors at the surface of hematopoietic cells, proerythroblast and it affects maturing of erythrocytes and hemoglobin synthesis. Erythropoietin production is regulated by negative reversed power through oxygen concentration in the blood. As a response on hypoxia, kidneys produce a large quantity of Erythropoietin and in that way contribute to increasing of the number of erythrocytes, and by that improve supplying oxygen to the tissue. Erythropoietin repre-

sents protein of molecular weight of 30400 daltons and made of 165 amino acids divided into three connected chains (3). In 1983 Amgen Laboratories and Fu-Kuen Lin cloned a gene for Erythropoietin, and 10 years later, in 1993, recombinant human Erythropoietin (Rh-EPO) was synthesized and has been used in human medicine. Erythropoietin has non-erythropoietic effects that could be seen in a protective role at vascular diseases, lowering the zone of ischemia (for example at heart failure and cerebral vascular failure) protection of apoptosis through its antioxidant characteristics, and proangiogenic potential with positive remodeling of myocardium. Continuing researches of new medicines that will have better clinical results, Amgen researchers have developed a new type of Erythropoietin called Darboepoetin Alfa (ARANESP) which has a higher potential and its activities lasts longer compared with Rh-EPO and it is prescribed in intravenous (iv) or subcutaneous (sc) dozes of 0,45 micrograms/kg weekly (3). Cardio-renal anemia syndrome was introduced in clinical practice by Silverberg with associates after he published the results of his study 2002 (2). He applied Erythropoietin in treatment of anemic patients with heart and renal failure with intravenous Ferum (Fe^{2+}) and managed to improve hemoglobin from 10,2 ±1 to 12,1±1,2 during 7,2±5,5 months and improving of EFLV, improving NYHA class and decrease of need for diuretics and hospitalizations. Anemia is often found in patients with chronic renal failure. By definition of WHO, anemia is characterized by decrease of hemoglobin (Hb)<12gr/dcl (or 7,5 mmol/L) at women, and <13gr/dl (or 8,1 mmol/L) for men and women in postmenopausal phase. Anemia is seen at 80% patients whose creatinine clearance is <25ml/min. Every decrease of hemoglobin for 1gr/dcl in chronic renal failure(CRF) causes dilatation of a left ventricle (LV) and creation or relapse of chronic heart failure (CHF). In the same time mortality is increased. Chronic anemia with increase of volume cause dilatation of heart cavity causing spreading of sarcomere and stronger myocardium contraction because of better folding of myofilament (Starling's law). Because of increase of the volume LV walls become thicker and eccentric LV hypertrophy appears. Anemia, hypertension and diabetes mellitus are main independent predictors of hypertrophy LV in CRF (4). The main patho-physiological mechanisms of anemia creation are decreased secretions of Erythropoietin in peritubular renal areas, negative effect of uremia toxins, appearance of hyperparatyreosis, increased blood loss through hemodialysis, appearance of hyperspleenism as a blood depot and places of fast wreck of erythrocytes, and toxic effects of

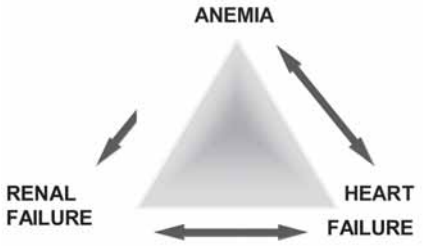

FIGURE 1. Cardio-renal anemia syndrome (2)

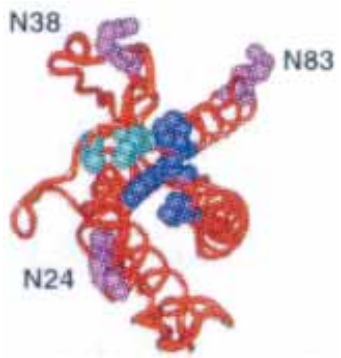

FIGURE 2. Molecular view of Erythropoietin (3)

aluminum that are applied in therapy at CRF patients (4, 5). On the other hand CHF development at anemic patients is followed by other patho-physiological mechanisms that are connected with tachycardia with increased heart volume and decrease of minute heart volume, venoconstriction, artery dilatation, dilatation and hypertrophic remodeling of LV. Apart from these mechanisms anemia creation in CHF is also influenced by medicines that are used frequently: aspirin, that additionally removes Ferum; ACE inhibitors that in CRF change renal production of erythropoietin; beta-blockers that slow transmission of prorenin into renin; anticoagulants and anti-aggregates that are frequently applied in CHF therapy and contribute anemia development by micro-bleedings into urinary and gastro tract (6, 7). In cardio-renal anemia syndrome due to signs of chronic inflammation with malnutrition, increased secretion of cytokinin, of substances similar to tumor necrotized factor alpha and tumor necrotized factor

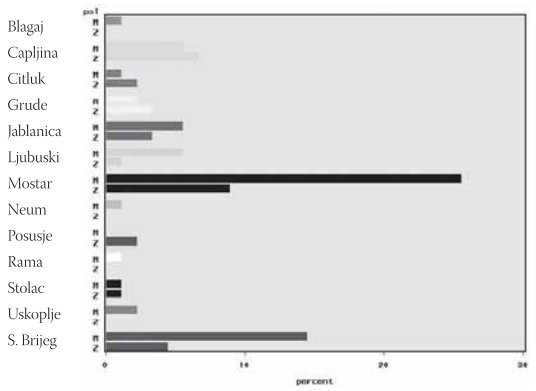

FIGURE 3. Distribution of patients (m-male; z-female)

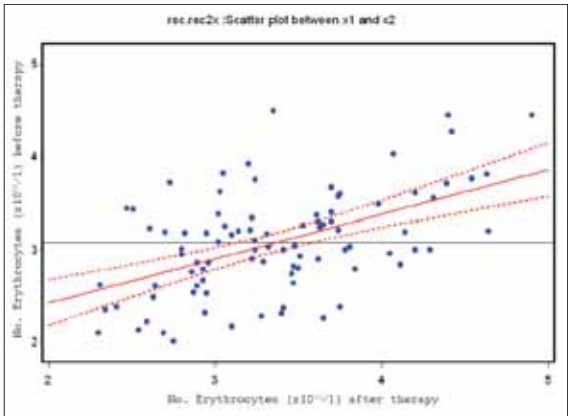

FIGURE 4. The effect of Epoetinum beta on the number of Erythrocytes r=0,51779, p< 0,0001;

alpha (TNF-α) that significantly inhibit hematopoiesis, cause anemia and play important role at CHF (4, 6, 8)

Materials and Methods

Effects of recombined Erythropoietin (rh-EPO) Epoetinum beta that has been given to pre-dialyzed and dialyzed patients have been examined. Dosage of Erythropoietin (rh-EPO) Epoetinum beta was from 2000 to 6000 I.U. sc 1-3 times a week depending of values of hemoglobin (Hb) (5). Patients are observed during three years (2002-2005). In this study 90 patients were included: 60 men and 30 women from 12 municipalities of Hercegovina that belong to Clinical Hospital Mostar. Most of the patients were from Mostar (32), Široki Brijeg (17), Čapljina (11), Jablanica (8), Ljubuški (6), Grude (5), Čitluk (3), Uskoplje (2), Stolac (2), Posušje (2), Rama (1) and Neum(1). All the patients had signs of chronic renal failure (CRF) from I-IV, signs of chronic heart failure (CHF) I-IV NYHA classification and anemia signs by WHO criteria. In analysis of Erythropoietin effects (rh-EPO) Epoetinum beta, anemia parameters have been observed, renal and heart failure before and after therapy during three years. From anemia parameters number of erythrocytes/L has been observed, hemoglobin gr/L, MCV; from renal function parameters we observed: urea/s, creatinine/s, glucose (GUK) and potassium/s (K^+); from parameters of heart failure we followed functional class by NYHA classification. Statistical elaboration was done by using the S PLUS computer program for multi-variant data analysis and results are shown by table and graphics with correlation coefficient by Pearson and classical statistic method, arithmetic middle with minimal and maximal values and standard deviation (SD) (8, 9, 10).

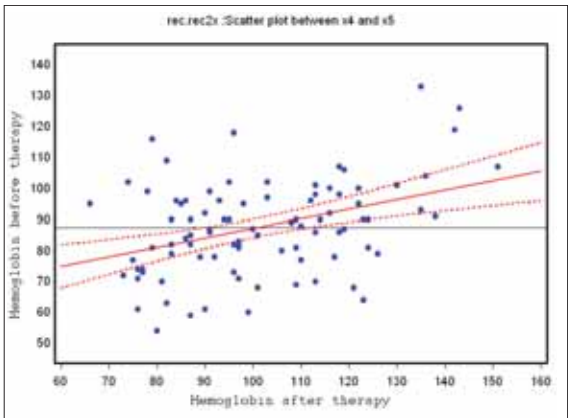

FIGURE 5. The effect of Epoetinum beta on values Hemoglobin r=0,38811, p< 0,0002;

Results

From 90 patients (predialysed and those on hemodialysis) aged 16-80, arithmetic average of 56 years of age, standard deviation (SD) 15 years, had chronic renal and heart failure with emphasized anemia. The average number of erythrocytes was 3,07 x 10^{12}/L at the beginning of the treatment with SD 0,55 and with range of 2,01-4,5 x 10^{12}L. Control measurement after observed period on an average was 3,36 x10^{12}/L with SD from 0,60 and range of 2,3-4,9 x 10^{12}/L. An average hemoglobin value (Hb) before start of the treatment was 87,41 gr/L with SD 15,07 gr/L and range from 54-133 gr/L; and after observatory period of three years an average value of hemoglobin (Hb) was 101,36 gr/L with SD 19,16 gr/L and range of 66-151 gr/L. An average value of MCV before the treatment was 88,67 ok/L with SD 6,04 and range of 66,4-100 and after the period of monitor-

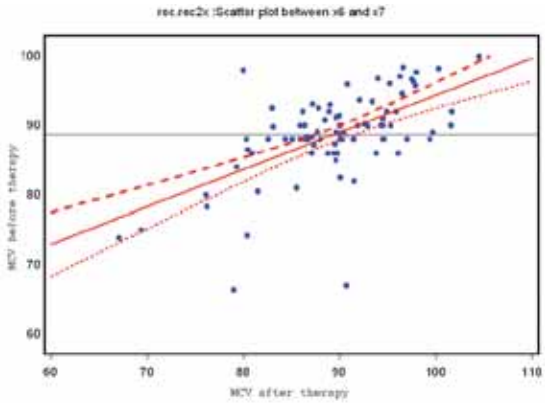

FIGURE 6. The effect of Epoetinum beta in MCV r= 0,59876, p<0,0001;

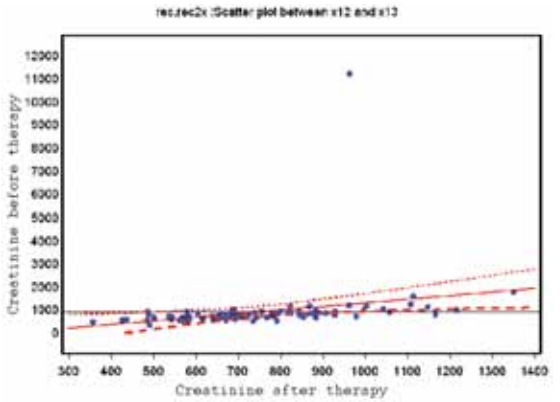

FIGURE 9. The effect of Epoetinum beta in Creatinine r=0,26397, p<0,00119;

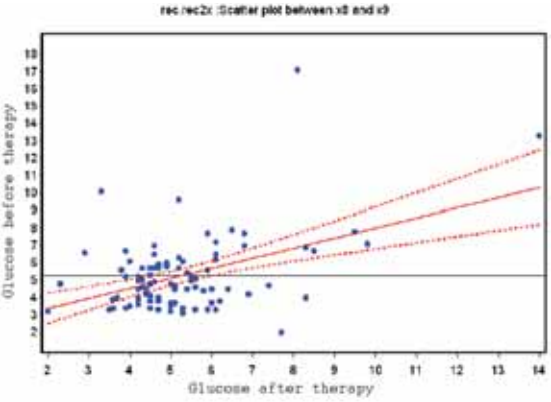

FIGURE 7. The effect of Epoetinum beta in Glucose/s r=0,45557, p<0,0001;

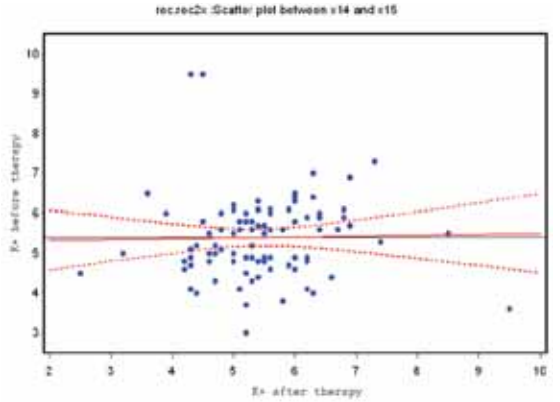

FIGURE 10. The eEffect of Epoetinum beta in K+ r=0,02060, p<0,8471;

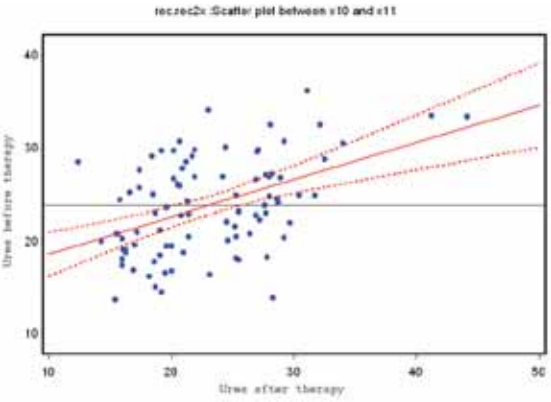

FIGURE 8. The effect of Epoetinum beta in urea r=0,45557, p<0,0001;

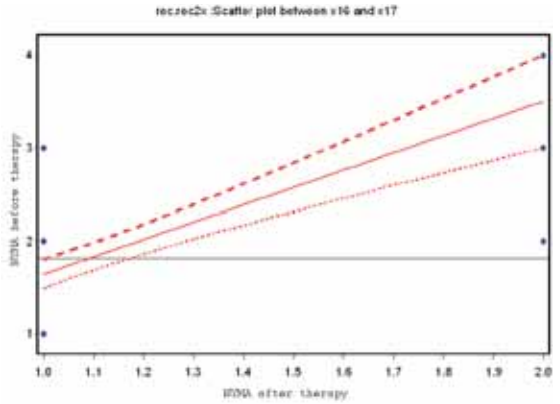

FIGURE 11. The effect of Epoetinum beta in NYHA classes r=0,59906,p<0,0001

ing an average value was 89,47; SD 6,75 with range of 67,1-104,5. An average value of urea/serum before the treatment was 23,76 mmol/L with SD 5,14 and range of 13,7-36,2, and after the treatment an average value of urea was 23,01 mmol/L with SD 5,85 and range of 12,4-44,1. An average creatinum/serum value before the treatment was 924,89 μmol/L with SD 112,08 μmol/L and range of 362-1.123 μmol/L and after the treatment

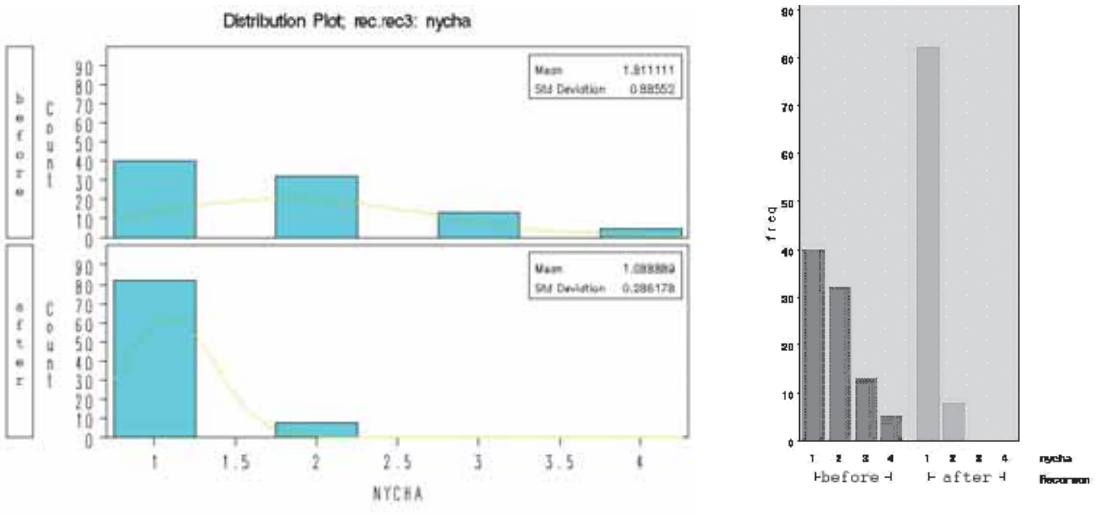

FIGURE 12. The effect of Epoetinum beta in changes of NYCHA classes

an average value of creatinum was 743,17 μmol/L, SD was 189,71 mol/L with range of 357-1.350 μmol/L. An average potassium (K+) value before the treatment was 5,39 mmol/L with SD 1,02 mmol/L and the range of 4,1-6,3mmol/ L ; an average K+ value after the treatment was 5,43 mmol/L, SD was 1,02 mmol/L with the range of 2,5-7,4 mmol/L. An average NYHA class before the treatment was II and with range of I-IV; and after the treatment an average NYHA class was I with the range of I-II. By using multi-variant data analysis and statistical program S PLUS we have got correlation coefficients by Pearson that for the effect of Epoetinum beta on the number of erythrocytes was r=0,51779; p<0,0001; We also stress that four of our patients in observed period had significant bleeding and one patient had developed inflammation; on MCV r=0,59876, p<0,0001; the functional ability of myocardium by NYHA classification r=0,59906, p<0,0001. The results were shown graphically.

Discussion

The renal anemia at dialysed patients: Wizemann and associates (7) examined patients with CHD and concluded that Erythropoietin decrease ischemia caused by loading, and correction of the anemia decrease minute and heart volume and consuming of oxygen. That was confirmed by our patients too. Besarab and associates (7, 11) found normal hematocrits at 42% (618 patients) from which 183 ended terminally, 19 got nonfatal heart failure at study taken on 1233 patients with evident angina pectoris and CHF signs at dialysed patients with CRF during 29 months observation. At 30% of the patients (615) with low hematocrits 150 ended terminally, 14 got nonfatal heart failure. They have stressed that mortality decrease with increase of hematocrits in both groups of patients. In our population we did not find any fatal results during the observation period. The Australia study (11) found out that patients with high levels of hemoglobin show significantly low dilatation LV, and incidence of hypertrophy LV was lowered at hemodialysed patients with CRF who was given rh-EPO. Thoraco-cardial measurements at our patients didn't show any significant differences in the observation period. Canadian multi-centric study (7, 11) has shown that hemoglobin normalization at patients with cardiomyopathy causes decrease of concentric hypertrophy LV and its dilatation. Hayashi and associates (11) has examined effects of rh-EPO at predialysed patients and have shown that increase of hematocrites for more than 30% decrease in LV hypertrophy. At patients in the late CHF and CRF phase with hypertrophy or dilatation LV the effects of anemia correction are weaker, and that is also shown in our study. The rh-EPO treatment has good effect at preventing hypertrophy LV. Patients with advanced dilatation LV have weaker effect because of long term hypertrophy development and dilatation LV with structural abnormalities, and also weaker effects of rh-EPO. Al-Ahmad and associates (12) have shown that rise of mortality and morbidity because of heart diseases at patients with anemia, which is not the case in our study with our patients. Decrease of renal function and anemia as a risk factor increase mortality at patients with dysfunction LV. SOLVD study at 6635 patients has shown that based on the multi-variant analysis of parameters of LV dysfunction on decrease of renal function and loss of hematocrits are risk factors for all causes of mortality. Loss of hematocrits for 1% together with increase of risk of 1.027 times for all causes of mortality (5,10,11,12). McClellan and associates (13) examined 665 patients with CHF and found out that hematocrits and creatinine are independently combined

risk factors for mortality increase. Horwich and associates (14) examined anemia effect on mortality at 100 patients with CHF NYHA III-IV classification and found out that anemia of the medium degree (Hb<12,3 gr/dcl or 7,7 mmol/L) was observed with decrease of surviving and decline of the symptoms and functional status. Ezocowitz and associates (15) have found out that anemia is frequent in HF and combined with bad prognosis for the whole population of 12.065 patients with newly formed HF. Anemia is, at 17% of patients, independent prognostic marker for mortality. Silverberg and associates (1) have examined the role rh-EPO and usage of i.v Ferum (Fe^{2+}) at CHF patients with LVEF≤ 40% and with Hb from 10-11 gr/dcl (6,3-7,2 mmol/L). During 8,2 ± 6 months there was increase of hemoglobin 10,3-12,9 gr/dcl (6,4-8,1 mmol/L) and improving of NYHA class at 42% of patients (11% had a decrease of NYHA class in the controlled group) and EFLV has increased for 5,5% in the treated group (it was decreased for 5,4% in the controlled group). The number of hospitalizations decreased for 79% which is in accordance with our observations. Cristina Opasich with associates (16) has stressed the need for establishing individual mechanisms of anemia creation in CHF in order to make better and right therapy by ferum, folic acid, B12 vitamins and Erythropoietin.

Conclusion

Erythropoietin significantly improves anemia parameters (erythrocytes, hemoglobin, MCV) at patients with HF. Positive effects were seen at renal function by decreasing urea more than creatinine. Epoetinum beta in our study does not show any significant effect of potasssium (K^+) values. The positive effects were seen on the LV function and improving the quality of life, especially at patients on hemodialisys. The functional ability of myocardium is improved for one to two classes of NYHA classification. Further studies of non-hematopoetic effects of Epoetinum beta, its effect on decrease of ischemia level, size of heart or brain failure, effect at endothelium remodeling and proangiogenic effects can be interesting for further studies and researches.

References

(1) Dahlstrom U. Frequent non-cardiac comorbidities in patients with chronic heart failure Eur. J. Heart Fail. 2005; 7 (3): 309-316.

(2) Silverberg D.S., Wexler D., Laina A. The importance of anemia and its correction in the management of severe congestive heart failure. Eur. J. Heart Fail. 2002;4: 681-686.

(3) ARANESP nephrology product monograph, Amgen, Lucerne, 2001.

(4) Kaira P. The importance of anemia correction in chronic heart failure. Cardiol News 2004; 8(1): 6-9

(5) Van der Meer P., Adriaan A., Voors Adriaan A, Lipsic E, Wiek H., van Gilst, W.H, van Veldhuisen D.J. Erythropoietin in cardiovascular disease. Eur. Heart J. 2004; 25: 285-291.

(6) Hayashi T.,Suzuki A.,Shoji T. et al. Cardiovascular effect of normalizing the hematocrits' level during Erythropoietin therapy in predialysis patients with chronic renal failure. J. Am. Ren. Dis. 2000; 35:250-256.

(7) Van der Meer P., Lipsic E., Boer R.A. et al. A functional erythropoietin receptor in a rat heart is linked to anti-apoptotic effects. J. Am. Coll. Card. 2003; 41: 330 A

(8) Ćorić S., Kažinić Z., Rončević D., Tomić M., Fazlibegović E., Hadžiomerović M.: The place of Erythropoietin in the therapy HF of dialysis patients in KB Mostar, II Congress of Nephrology B&H with international participation,Tuzla,06.-09.04.2005.

(9) Ćorić S., Fazlibegović E., Hadžiomerović M., Kažinić Z., Fazlibegović F.: The place of Erythropoietin in the therapy of patients in dialysis with heart failure, XV meeting of Association of Cardiologists and Angiologists B&H with International Participation, Brčko, 20.11.2004.

(10) Fazlibegović E., Ćorić, S., Hadžiomerović M., Kažinić Z., Fazlibegović F.: The place Erythropoietin in the care Heart Failure the patients with anemia in Clinical Hospital Mostar, XV meeting of Association of Cardiologists and Angiologists of B&H with International participation, Brčko, 20.11.2004

(11) Van der Meer P.,Voors A.A., Lipsic E., Smilde T.D.J.,Van Gilst W.H.,VanVeldhuisen P.J. Prognostic value of plasmaerythropoietin on mortality in patients with chronic heart failure. J. Am. Coll. Card. 2004;44:63-67

(12) Al-Ahmad A.,.Rand W.M., Manjunath G. et al. Reduced renal function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J. Am. Coll. Card. 2003;38: 955-962.

(13) McClellan W.M.,Flanders W.D.,Langston R.D., Jurkovitz C.,Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J. Am. Soc. Nephro. 2002; 13:1928-1936.

(14) Horwich T.B., Fonarow G.C., Hamilton M.A. et al. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J. Am. Coll Card. 2002; 39:1780-1786.

(15) Ezekowitz J.A., McAlister F.A., Armstrong P.W.Anemia is common in heart failure and is associated with poor outcomes; insights from a cohort of 12065 patients with new-onset heart failure. Circulation 2003; 107:223-225.

(16) Opasich C., Cazzola M., Scelsi L.et al. Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anemia in patients with chronic heart failure. Eur. Heart. J. 2005, 26; 2232-2237.