ORIGINAL ARTICLE

Influence of the 6-month anemia therapy with erythropoietin on renal function and some hemodynamic parameters in predialysis patients

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KEY WORDS

anemia, chronic kidney disease (CKD), erythropoietin, renal function, systemic hemodynamics

ABSTRACT

OBJECTIVES The aim of this study was to evaluate the influence of a 6-month anemia therapy with recombinant human erythropoietin (rHuEpo) on glomerular filtration rate (GFR) and renal blood flow related to hemoglobin (Hb) concentration, changes in heart function and total peripheral resistance in patients with chronic kidney disease (CKD) treated conservatively.

PATIENTS AND METHODS We evaluated 13 patients (9 women and 4 men) aged 64.8 ±8.9 years with serum creatinine of 3.82 ±1.30 mg/dl and Hb concentration of 10.02 ±0.45 g/dl. rHuEpo was given in the mean dose of 2296 ±673 U/week *s.c.* to achieve Hb 12 g/dl. At baseline and after 6 months of rHuEpo therapy echocardiography and renoscintigraphy were performed.

RESULTS After 6 months' therapy Hb increased significantly, while blood pressure did not change significantly. Renal anemia correction led to a decrease in left ventricular end-diastolic dimension index, left ventricular end-diastolic volume index, stroke volume index and cardiac index. Total peripheral vascular resistance index increased significantly. At the same time a significantly reduced left ventricular mass index was observed. Correction of renal anemia and changes in systemic hemodynamics did not exert unfavorable effect on renal hemodynamic parameters. GFR index, blood flow rate index, renal vascular resistance index and filtration fraction remained unchanged. During rHuEpo therapy decline in renal function expressed as 1/serum creatinine did not differ compared with a 6-month period before initiating rHuEpo therapy.

CONCLUSIONS Therapy with rHuEpo in patients with stage 3 and 4 CKD with correct blood pressure control does not result in worsening of renal function despite changes in left ventricular function and increase of total peripheral resistance.

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INTRODUCTION Cardiac remodeling occurs in very early stages of chronic nephropathies, even with normal renal excretory function.[1] Changes in the heart muscle structure have been observed in a number of studies in patients with chronic kidney disease (CKD) already during conservative treatment, and the frequency of left ventricular hypertrophy (LVH) and left ventricular mass (LVM) increases with the stage of renal failure.[2,3] Of note, LVH is of unfavorable prognostic value as it is an independent and crucial risk factor of all clinical forms of ischemic disease, chronic heart failure and arrhythmias.[4] The results of previous studies showed that anemia can play an important role in LVH formation.[2,5-7] The cardiovascular system reacts to anemia with compensatory changes leading to optimal oxygen supply for tissues and organs.[8]

TABLE 1 Hemoglobin, creatinine, phosphorus, calcium and parathormone level changes before and after 6 months of recombinant human erythropoietin treatment

Parameter	Beginning of treatment Mean ± SD	After 6 months Mean ± SD	p
Hemoglobin [g/dl]	10.02 ±0.45	12.03 ±0.76	p <0.001
Creatinine [mg/dl]	3.82 ±1.3	3.97 ±1.51	NS
Parathormone [pg/ml]	171.5 ±109.2	178.4 ±122.6	NS
Calcium [mmol/l]	2.37 ±0.14	2.37 ±0.13	NS
Phosphate [mmol/l]	1.41 ±0.26	1.43 ±0.36	NS

Abbreviations: NS – non significant

TABLE 2 Changes in evaluated left ventricular structure parameters during 6 months of recombinant human erythropoietin treatment

Parameter	Beginning of treatment Mean ± SD	After 6 months Mean ± SD	p
LVIDsI (cm/m^2)	1.74 ±0.23	1.73 ±0.29	NS
LVIDdI (cm/m^2)	2.82 ±0.32	2.66 ±0.38	p <0.05
IVSd [cm]	1.45 ±0.43	1.42 ±0.47	NS
PWd [cm]	1.25 ±0.37	1.21 ±0.34	NS
LVMI [g/m^2]	166.4 ±90.9	147.8 ±87.6	p <0.05

Abbreviations: IVSd – intraventricular septal diameter, LVIDdI – diastolic left ventricular internal diameter, LVIDsI – end-systolic left ventricular internal diameter, LVMI – left ventricular mass index, NS – non significant, PWd – posterior wall in diastole

Early diagnosis and treatment of anemia with recombinant human erythropoietin (rHuEpo) in patients with CKD during conservative treatment can limit or reduce LVH when hypertension control is appropriate,[9,10] and further progression of cardiac function disturbances.[11] However, it is estimated that less than 35% of patients are treated with rHuEpo during conservative treatment.[12] This is due to high costs of therapy compared with the needs of this large patient population.[13] Moreover, there is a concern that anemia compensation worsens renal function.

At the present the influence of rHuEpo treatment on kidney hemodynamics and CKD development is still disputable. The aim of the study was to evaluate the effect of anemia treatment with rHuEpo on kidney filtration function and renal perfusion, structure and function of the left ventricle and total peripheral resistance, and to assess the relationship between systemic and kidney hemodynamics in patients with CKD treated conservatively.

PATIENTS AND METHODS

The study was performed in patients with CKD treated conservatively in the Nephrology Outpatient Clinic in the years 2001–2002. The group consisted of 13 patients (9 women and 4 men), at the age of 47–73 (average, 64.8 ±8.94) years qualified for anemia treatment with rHuEpo. The cause of CKD was chronic glomerulonephritis in 5 patients, polycystic kidney disease in 2 patients, ischemic nephropathy in 2 patients, diabetic nephropathy in one patient, chronic tubulointerstitial nephritis in one patient; in 2 patients etiology of CKD was unknown. Inclusion criteria were blood hemoglobin (Hb) level <11 g/dl, with balanced iron metabolism, expressed as transferrin saturation level (TSAT) >20% and the serum creatinine level of 2–6 mg/dl.

Exclusion criteria were: anemia of other causes than CKD, blood pressure >160/90 mmHg despite antihypertensive medication, ischemic heart disease (data from a history suggestive of coronary insufficiency and previous myocardial infarction independently of the time of occurrence), cardiac valve diseases, atrial fibrillation, heart failure New York Heart Association class III and IV, past stroke, cancer, infection with hepatitis B virus or hepatitis C virus, proteinuria >3.5 g/day, poorly controlled diabetes (glycated hemoglobin >7%, fasting glucose >110 mg/dl), secondary hyperparathyroidism (parathyroid hormone [PTH] >300 pg/ml) and the reproductive period in women. Only patients who were not treated with angiotensin-converting enzyme inhibitors were included into the study to abolish a potentially beneficial influence of this class of drugs on left ventricular remodeling and the course of CKD.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a mercurial sphygmomanometer, then mean blood pressure was calculated: mean arterial pressure [MAP] = DBP + (SBP-DBP)/3. Serum creatinine levels at the start of erythropoietin treatment were in the range of 2.01 mg/dl–5.94 mg/dl (average, 3.82 ±1.30), and blood Hb level in the range of 8.9 g/dl–10.5 g/dl (average, 10.02 ±0.45)

The study protocol was approved by the Bioethical Committee at the Collegium Medicum in Bydgoszcz (KB/57/2000). Each patient signed an informed consent form after receiving detailed information on the study.

According to recommendations, patients obtained rHuEpo subcutaneously once a week. The target Hb level was 12 g/dl. The mean rHuEpo dose in the analyzed group was 2296 ±673 UI/week subcutaneously. During the whole period of treatment all patients obtained oral iron sulphate preparations in tablets 2 times a day to achieve TSAT level >20%. In case of ineffectiveness of this therapy also intravenous iron preparations in the form of iron saccharate was administered in a dose of 100 mg once a week.

Duration of treatment with rHuEpo was 6 months. Retrospective analysis of the 6-month period prior to the treatment with rHuEpo was simultaneously performed. During the therapy patients used a low-protein diet in the range of 0.8–0.9 g/kg of body mass. The clinical state of patients was assessed according to the established protocol and the laboratory tests were performed to determine blood cell counts, creatinine, calcium, phosphate, iron and serum PTH levels. Moreover, iron metabolism was monitored by measurement of blood iron levels, total iron binding capacity and calculation of TSAT.

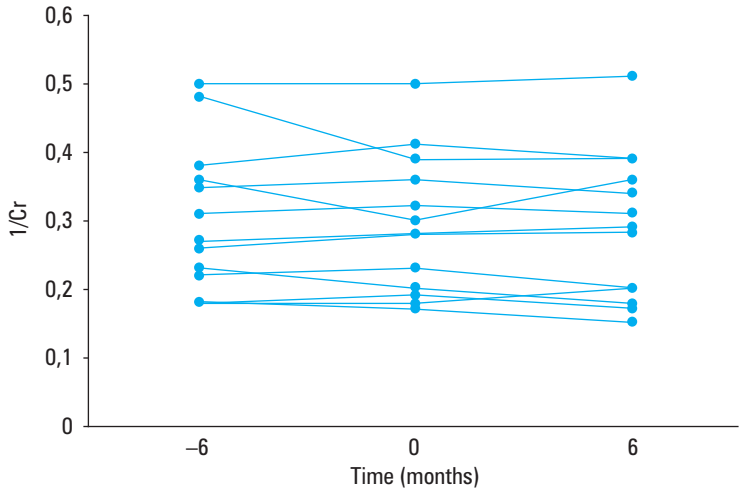

FIGURE 1 Each patients renal function evaluation with inverse of the serum creatinine level (1/Cr) 6 months before recombinant human erythropoietin treatment, immediately before the beginning of treatment and after 6 months of rHuEpo treatment

Progression of CKD was analyzed by comparison of inclination curves of the 1/plasma creatinine level coefficient in the period of 6 months prior to and 6 months after treatment with rHuEpo. Echocardiography and dynamic kidney scintigraphy were performed prior to and 6 months of treatment with rHuEpo.

Measurements were performed from the M-mode presentation in longitudinal parasternal view according to recommendations of the American Society of Echocardiography. The interventricular septal diameter (IVSd) and posterior wall in diastole (PWd) were measured. Diastolic left ventricular internal diameter (LVIDd) and systolic left ventricular internal diameter (LVIDs) were calculated on 1 m^2 of the body area (LVIDdI, LVIDsI).

Additionally, end-diastolic volume of the left ventricle (EDV) and end-systolic volume of the left ventricle (ESV) were calculated with area-length method from apical 4-chamber view. HR was assessed from registration of electrocardiograms.

These data allowed the calculation of left ventricular stroke volume (SV): SV = EDV-ESV (ml), cardiac output (CO): CO = HR x SV (ml/min) and left ventricular ejection fraction (EF): EF = [(EDV – ESV)/EDV] × 100 (%). The volumes of EDV, SV and CO were presented per 1 m^2 of the body area (EDVI, SVI and CI, respectively). Total peripheral resistance (TPR) was calculated according to the formula: TPR (dyne × s × cm^{-5}) = MAP (mmHg)/CO (l/min) × 80. The total peripheral resistance index presented in dyne × s × cm^{-5}/m^2 was calculated according to the formula: TPRI (dyne × s × cm^{-5}/m^2) = MAP (mmHg)/CI (l/min/m^2) × 80.

LVM was determined according to the formula proposed by Devereux et al.: LVM = 0.8 [1.04 (IVSd + LVIDd + PWd)^3 – LVIDd^3] + 0.6 (g). Then the LVM index was calculated using the equation: LVMI = LVM/BSA. LVMI >100 g/m^2 for women and LVMI >131 g/m^2 for men were established as the diagnostic criteria of LVH.[14]

Dynamic radionuclide renography was performed on the gamma single-head PRISM or dual-head AXIS cameras, and quantitative analysis of its result was performed with a programme from the ODYSSEY system (by the PICKER-PHILIPS Company) in the Department of Nuclear Medicine in the Oncology Centre at the Prof. Franciszek Łukaszczyk Hospital in Bydgoszcz. The evaluation of GFR was performed with technetium 99m diethylenetriaminepenta-acetic acid (^{99m}Tc – DTPA), and for effective renal plasma flow (ERPF) measurement technetium 99m ethyl cysteine (^{99m}Tc – EC) was used as a single intravenous injection.

Effective renal blood flow (ERBF) was calculated on the basis of the formula: ERBF (ml/min) = ERPF × 100/(100 – Ht), and filtration fraction (FF) (%) was the GFR/ERPF × 100 proportion. Renal vascular resistance (RVR) presented in dyne × s × cm^{-5} was calculated according to the formula: RVR = MAP (mmHg)/ERBF (ml/min) × 80 000. Renal hemodynamic indices (GFR, ERPF, ERBF and RVR) were calculated per 1 m^2 of the body area.

Statistical analysis Results of the study were presented as mean and standard deviation. Conformity of variables with the normal distribution was tested with the Shapiro-Wilk W test. If the distribution was similar to normal, Student's t test for dependent variables to compare means was used. When the distribution was non-normal, significance of the difference was tested with non-parametric Wilcoxon test. Associations between variables were evaluated with linear Pearson's correlation coefficient for variables with the normal distribution or Spearman's correlation coefficient for variables with non-normal distribution.

RESULTS

Therapy with rHuEpo caused a significant increase in Hb levels. However, creatinine, PTH, calcium and phosphate levels in plasma were not statistically significantly different prior to and after 6 months of treatment with rHuEpo (TABLE 1). Statistically significant changes in blood pressure were not observed; SBP before the therapy was 150.0 ±14.1 mmHg, and after 6 months of therapy 148.5 ±12.1 mmHg (non significant – NS), DBP 83.5 ±5.9 and 83.1 ±5.6 mmHg (NS), respectively, and MAP 105.6 ±7.7 and 104.9 ±5.7 mmHg (NS).

The mean inclination of curves reflecting a change in the reverse of plasma creatinine level in 6 months of treatment was not statistically significantly different compared with the 6-month period prior to the treatment (FIGURE 1).

There were no significant changes in systolic, diastolic and mean blood pressure values, compared with the period prior to the treatment with rHuEpo.

Echocardiography performed after 6 months of treatment with rHuEpo showed several changes, presented in TABLE 2. Statistically significant decreases were simultaneously observed, EDVI from 56.6 ±22.8 to 45.3 ±16.5 ml/m^2 ($p < 0.05$), SVI from 38.2 ±18.3 to 29.4 ±12.0 ml/m^2 ($p < 0.05$) and CI from 2482 ±923 to 1953 ±700 ml/min/m^2 ($p < 0.01$), while heart rate (HR), 68 ±10 vs. 67 ±9/min (NS)

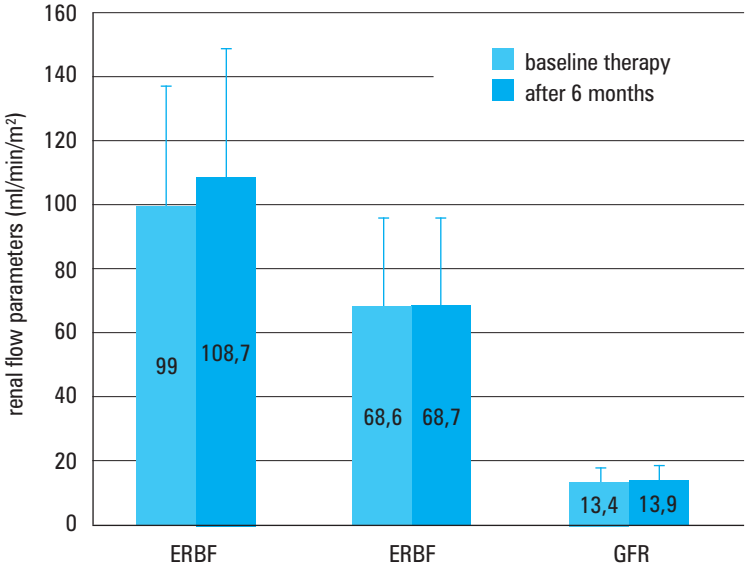

FIGURE 2 Mean values of renal hemodynamic parameter indices at the beginning of recombinant human erythropoietin treatment (light columns) an after 6 months (dark columns) Abbreviations: ERBF – effective renal blood flow, ERPF – effective renal plasma flow, GFR – glomerular filtration rate

and left ventricular EF, 66.9 ±9.2% vs. 65.0 ±6.5% (NS) remained unchanged. However, during the 6-month therapy a significant increase in the total peripheral resistance index (TPRI) from 3859 ±1532 to 4671 ±1247 dyn × s × cm^{-5}/m^2 ($p < 0.05$) was observed.

Such indices as glomerular filtration rate (GFR/m^2), effective renal plasma flow ($ERPF/m^2$), effective renal blood flow ($ERBF/m^2$) did not alter significantly in the treatment period (FIGURE 2). In this period filtration fraction (20.1 ±4.1 vs. 20.7 ±4.2%; NS) and renal venal resistance index (99 555 ±46 168 vs. 88 996 ±37 726 dyn × sec × cm^{-5}/m^2); NS) also remained unchanged.

DISCUSSION The results obtained in the current study confirm the role of anemia in the pathogenesis of abnormalities in the circulatory system. As anemia improved, some indices of left ventricular systolic function such as the stroke volume index and cardiac output index statistically significantly decreased. In this group of patients, the decrease in stroke volume without the accompanying reduction in heart rate was the main factor that affects the observed cardiac index decrease. Unaltered heart rate could result from administration of β-blockers in antihypertensive therapy before and during the treatment with rHuEpo. In the current patients a decrease in stroke volume and cardiac output was associated with a significant reduction in LVIDdI and EDVI. This phenomenon is unusually beneficial for heart function, as it may indirectly speak for a preload decrease. A significant increase in TPRI was simultaneously observed, which in turn might directly contribute to the afterload increase.

There are very few publications concerning simultaneous assessment of changes in circulatory hemodynamics and morphology of the left ventricle as a result of anemia treatment with rHuEpo. Previously only 2 such studies with 20 patients with CKD in the conservative treatment period were performed.[9,10] Results of these studies are concordant with the results presented here.

In the study by Portoles et al.[10] in 11 analyzed patients just after 3 months of treatment with rHuEpo and partially compensated anemia, a significant decrease in CI with a simultaneously significant TPR increase were observed. Hayashi et al. demonstrated a similar trend in hemodynamic changes in 9 patients[9] and reported a decrease in SV and CI after partial anemia compensation, which however did not reach the level of statistical significance. However, peripheral resistance was not calculated. In both those studies there were no alterations in heart rate of the treated patients. Moreover, in the current study a tendency to reduced end-diastolic diameter was presented, which may also indirectly suggest the preload decrease.

In the current study, despite the observed hemodynamic changes during treatment with rHuEpo, significant changes of blood pressure were not noted; only one female patient required treatment modification by increasing a dose. The lack of significant changes in blood pressure was probably caused by the use of small initial doses of rHuEpo and a slower increase in Hb levels.[15] Furthermore, rHuEpo administered subcutaneously does not cause an increase in the circulating endothelin level, which limits the probability of the elevation in blood pressure.[16] Good blood pressure control despite the occurrence of increased total peripheral resistance may be a result of efficient compensation mechanisms responsible for hemodynamic changes in the form of the cardiac output decrease.[17]

In the analyzed group of patients, the increase in Hb level did not significantly influence the EF. In reports of other authors, EF changes after improved anemia were not observed.[9,10]

Anemia compensation – as a result of rHuEpo administration – causes not only the reverse of its unfavorable hemodynamic consequences, but also leads to structural changes, mainly of the left ventricle, decreasing cardiac muscle hypertrophy. In the patients LVMI significantly decreased. Available data confirm that even short-term treatment of anemia with rHuEpo may be beneficial to left ventricular remodeling in patients with CKD during conservative treatment.[9,10,18]

The approach to anemia treatment with rHuEpo has been cautious for many years for fear of CKD progression. Clinical[19] and experimental studies[20] indicated marked significance of hematocrit (Ht) in the direct regulation of renal hemodynamics. It was demonstrated that changes of renal vascular resistance in response to increasing Ht may lead to increased intraglomerular pressure, which favors acceleration of glomerular sclerotization and impairment of renal function. On the contrary, anemia decreases resistance of efferent glomerular arterioles, which is associated with a disproportionately higher increase in ERPF than in GFR, and with a decrease in FF value.[20]

In the current study, anemia improvement did not influence changes of ERPF and GFR. Moreover, FF, which increase could have indicated

to occurrence of the unfavorable phenomenon of glomerular hyperfiltration, did not change. However, renal vascular resistance was not noted with the increase in Hb level. Thus, ERBF in analyzed patients could be maintained at the same level due to an adaptive dilatation of efferent glomerular arterioles, as shown by Frenken et al.[21]

It should be noted that in the current study the increased total peripheral resistance index with a simultaneous decrease in the cardiac output index, obtained as a result of treatment with rHuEpo, was not unfavorable to ERPF and ERBF. Even a tendency towards an increase in ERBF was observed (FIGURE 2).

In patients with CKD autoregulation mechanisms are disturbed. In consequence, renal blood flow is dependent on heart function to a large measure. However, despite a decrease in cardiac output index, a reduction in renal vascular resistance index was simultaneously observed. This change was not statistically significant; however, the renal vascular resistance index was on average 10% lower than before the treatment. It cannot be excluded that it was a sufficient qualitative decrease in renal vessel resistance that maintained renal plasma flow at the same level.

Hence, the hematocrit increase obtained by treatment with rHuEpo simultaneous with good blood pressure control does not have an unfavorable influence on renal hemodynamics. In contrast, in experimental studies on rats with kidney insufficiency-related anemia caused by the excision of 5/6 of renal parenchymal volume, the efferent glomerular arteriole resistance increase, the transcapillary pressure gradient increase, and the renal plasma flow decrease and the GFR decrease in a single nephron were observed during rHuEpo administration.[22] The above hemodynamic changes could be a result of a systemic blood pressure increase and a rapid increase in blood viscosity in efferent glomerular arterioles resulting from the rapid compensation of Ht to a value of 50%, that led to an increase in proteinuria, glomerular sclerotization and acceleration of kidney insufficiency compared with untreated rats with anemia. Further experimental studies confirmed that hypertension appearing during treatment with rHuEpo is the main causative factor intensifying progression of kidney disease.[22]

Special attention should be paid to the results of one of the previously published trials by Onoyama et al.,[23] which is the most comparable with experimental studies discussed above. The authors reported, after the 4-week therapy with rHuEpo, a significant increase in FF (glomerular hyperfiltration). However, it should be stressed that in all analyzed patients, as the anemia improved, an increase in blood pressure from an average of 171/93 mmHg prior to the treatment with rHuEpo to 190/105 mmHg was observed.

Thus it might be surprising that the aim of the current study was to achieve the blood pressure <160/90 mmHg during treatment with rHuEpo, which is not optimal for patients with CKD. The cause was a will to maintain similar values of blood pressure in 2 compared follow-up periods and also to avoid the influence of possible antihypertensive treatment modifications on the obtained results. What is more, similar criteria were accepted also in other studies assessing the influence of treatment with rHuEpo on renal functions.[18,24,25] The mean blood pressure value after 6 months of treatment with rHuEpo was 149/83 mmHg and it can be expected that at lower target blood pressure values, recommended changes in renal blood flow for conservatively treated CKD patients would be more beneficial.

Further observations did not confirm the unfavorable influence of anemia treatment with rHuEpo on kidney hemodynamics, with maintained stable blood pressure values.[26] It seems that hypertension and the grade of CKD at the start of treatment with rHuEpo play an important role in progression of the disease.[27]

Results obtained in the present study are concordant with multiple clinical observations, in which treatment of anemia with rHuEpo did not influence CKD progression assessed on the basis of the picture of plasma creatinine level reverse.[9,10,15,28-32] However, in the majority of these studies a small number of patients was analyzed, follow-up periods were short, and the necessity to use a properly chosen rHuEpo-naïve control group was not taken into account. It was also stressed that treatment of anemia not only does not accelerate, but simply inhibits CKD progression providing there is properly obtained good blood pressure control.[24,25,31,33] Interestingly, in the study by Wanic-Kossowska et al. is that in CKD patients in predialysis period, treated with darbepoietin α, the inhibition of CKD progression was not reported despite anemia compensation and good blood pressure control.[34,35]

It is also an important issue of clinical importance to establish a target level of anemia compensation. Until now the prevalent opinion has been that Ht >35% during treatment with rHuEpo may have unfavorable influence on intraglomerular pressure.[36] Thus, the studies in which normalization of Hb level[9,37] did not affect renal functions are of interest.

Obtaining a definitive answer to the question whether treatment with rHuEpo may influence the speed of natural CKD progress is possible only on the basis of prospective studies on a large group of patients. The recently published CREATE trial, performed in 603 patients with stage 3 and 4 CKD, has provided some important data.[38] Results of complete anemia compensation (Hb 13.0–15.0 g/dl) with values lower than the reference range (Hb 10.5–11.5 g/dl) were compared. Initial glomerular filtration, and the GFR decrease were not significantly different between the analyzed groups; however, in the group of higher Hb level the necessity to begin therapy with dialysis and worse blood pressure control were

more frequently observed. Risk of cardiovascular events and LVMI changes did not differ between the analyzed groups. However, in the group with complete compensated anemia the improvement in quality of life indices was observed.[38] In the CHOIR trial with 1432 patients with CKD, increased risk of cardiovascular incidents in patients with higher Hb level (target 13.5 g/dl) compared with patients with Hb 11.3 g/dl was presented. Moreover, significant differences in life quality indices between the analyzed groups were not observed. However, in this study the difference in the frequency of beginning the renal replacement therapy between the analyzed groups of patients was not reported. It should be stressed that significantly higher rHuEpo doses were used (5000 and 11000 UI/week on average) to obtain the target Hb level.[38,39]

The review of available data presented in the current paper and the results of the discussed study indicate that treatment of anemia with rHuEpo in patients with CKD treated conservatively is beneficial for the diameter, structure and function of the left ventricle. However the question concerning the target Hb level in non-dialyzed patients remains open, even though there are signs showing that complete anemia compensation does not reduce cardiovascular risk.[38-40]

Despite a number of publications, there is no definitive answer to the question of whether treatment of anemia with rHuEpo inhibits the progression of CKD. However, given the results of this study it can be assumed that among multiple therapeutic interventions in CKD, anemia compensation with rHuEpo will find its appropriate place.

rHuEpo used for 6 months in stage 3 and 4 CKD patients does not impair excretory kidney functions, if blood pressure is simultaneously well controlled.

Treatment of anemia with rHuEpo in patients with CKD causes a decrease in volume and mass of the left ventricle with a simultaneous increase in total peripheral resistance.

Despite changes in the left ventriclar functions and total peripheral resistance during the therapy with rHuEpo significant changes in the renal blood flow are not observed.

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