OPTIMAL TARGET HEMOGLOBIN LEVEL IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND ANEMIA TREATED WITH ERYTHROPOIESIS-STIMULATING AGENTS: CONTROVERSIAL ISSUES

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Anemia is a classical complication associated with chronic kidney disease (CKD). Frequency and intensity of anemia grows along with renal impairment progression [1–4]. In a number of recent studies with various populations of CKD patients the connection between anemia and increased risk of death, cardiovascular complications (CVC) and CKD progression has been established [3-6]. So in the recent cohort retrospective USA study with 5 885 CKD and estimated level of hemoglobin (Hb) patients, the degree of unfavorable anemia effects on the fatal outcomes from any reason, frequency of hospitalizations due to cardiovascular complications and due to end-stage kidney disease (individually for each end point) has been analyzed by method of cox-regression model [7]. In comparison to the patients without anemia, a higher death rate (hazards ratio – 5,27; 95% confidence interval – 4,37–6,35), a higher frequency of hospitalizations due to cardiovascular complications (hazards ratio – 2,18; confidence interval – 1,76–2,70) and of CKD end-stage cases (hazards ratio 5,46; confidence interval 3,38–8,82) have been registered among the patients with the most severe anemia, moreover, hazards ratio reflected changes in hemoglobin level and glomerular filtration rate. Association of anemia with the studied end points became more close along with anemia getting more severe. On the basis of the research results it was concluded that hemoglobin reduction is not just a marker of CKD progressive but also is independent and direct predictor of unfavorable prognosis and complications associated with CKD.

However, despite on the obvious relevance of the renal anemia correction problem its decision raises a number of questions. First of all concerns of the optimal target hemoglobin level in the each clinical setting. And, to a lesser extent, it concerns of the individual erythropoiesis-stimulating agents (ESA)

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Abstract

Controversies in strategy of achievement and maintenance of target hemoglobin level in conditions of chronic kidney disease and approaches to optimization of erythropoiesis-stimulating agents use are discussed in the article.

Keywords

chronic kidney disease, anemia, target hemoglobin level

efficiency which used to reach the optimal target level because of almost all used today ESAs can effectively increase hemoglobin concentration in patients with CKD and anemia.

The ambiguous results of the recent cohort and scale retrospective studies of ESAs' effect in the patients with CKD of dialysis and pre-dialysis stages have become the subject of the unceasing discussion carried on in the medical press about target hemoglobin level. Analysis of these results has allowed tracing the history of the problem development and coming to certain conclusions.

The earlier studies [8–11] proved the positive effect of hemoglobin level normalization and erythropoietin therapy on general and cardiovascular survival

of the patients undergoing renal replacement therapy (RRT). The results of multicenter study meta-analysis of the program hemodialysis patients conducted in 5 European countries allowed getting the data which confirm the link of the high hemoglobin level with reduction of the relative death risk and/or hospitalization [11]. Hemoglobin level normalization in this period seemed to be an indispensable condition of anemia treatment for both hemodialysis and pre-dialysis CKD patients. But as experience of anemia treatment with epoetin drugs was accumulated, this initial view was questioned as a subset of patients with CKD when the seemingly optimal level of hemoglobin there is a tendency to raise blood pressure, measured by an increased need for antihypertensive drugs or marked change in the rheological properties of blood with development of thrombosis [12–17]. Thus, an optimal target hemoglobin level in patients with renal anemia both in dialysis and pre-dialysis stages remained undefined.

G.F. Strippoli with co-authors [18] performed a systematic analysis of 15 randomized controlled studies. The consequences of maintaining "low" (Hb ≤11 g/dl, Ht ≤33%) or "high" (Hb ≥14 g/dl, Ht ≥ 40%) hemoglobin level in pre-dialysis CKD and undergoing RRT patients were considered. A. Besarab with co-authors [16] in the largest open prospective study evaluated the risks and benefits of maintaining the normal level of hematokrit (Ht) among the hemodialysis patients with heart diseases. 1233 hemodialysis patients with associated chronic cardiac insufficiency or coronary heart disease (stenocardia, catheterization of coronary vessels or myocardial infarction) were involved in the study. (The patients with IV functional class (according to NYHA classification) chronic cardiac insufficiency were excluded as well as those having severe hypertension with diastolic blood pressure equal to or over 100 mm Hg). All the participants had the basis Ht level from 27 to 33% and had been taking a fixed moderate dose of epoetin alfa during the preceding 4 months. 618 (group 1) out of all the patients were randomized to normal Ht level (42%) for the achievement and maintained of which required increasing of the initial epoetin dose of 3 times . 615 (group 2) patients remained at the basis low Ht level (30%). After 29 months (observation period varied from 4 days to 30 months, the median of 14 months) the risk of reaching the primary endpoint (death or non-fatal cardiac infarction) was 7% higher among the patients with high (normal) Ht level, than among the patients from the control group (183 death cases and 19 non-fatal cardiac infarctions vs 150 death cases and 14 non-fatal cardiac infarctions; hazards ratio 1,3, 95% confidence interval 0,9-1,9). Causes of death

in 2 groups were similar, in most patients these were cardiovascular complications (sudden cardiac arrest, fatal acute myocardial infarction, arrhythmia, cerebrovascular events, etc.). Thrombosis of vascular access occurred more often in the group of patients with high Ht level (39% vs 29%, p = 0,001). At the same time, the quality of life evaluated by the scale of physical activity was higher among the patients with normal Ht level (p=0,03). But this advantage of the high Ht level was considered as less significant in comparison to the cardiovascular complication risk. The study was completed ahead of schedule (previously planned 3 years). Taking into account all the rest 14 studies, the results of which were processed with methods of G.F. Strippoli s meta-analysis authors made a conclusion that if hemoglobin level is maintained equal to or under 11 g/dl, risk of death among the patients with CKD and cardiovascular pathology is considerably lower than among the patients with hemoglobin level close to 14 g/dl. It should be noted that G.F. Strippoli with co-authors [18] analyzed a mixed groups of patients with CKD as the presence and absence of severe cardiovascular disease

In the study of H. Furland, T. Linde, J. Ahlmen and others [19] which included 416 pre-dialysis CKD and dialysis patients without severe concomitant cardiovascular pathology and/or coronary heart disease there were no difference in general mortality rate and rate of death due to cardiovascular complications between the group in which hemoglobin level was maintained in "normal" level (11–12 g/dl) and the group in which the hemoglobin level was maintained in "optimized" level (13,5–16 g/dl) in the course of the study period (12–19 months). At the same time no indisputable data confirming advantages of the policy of maintaining an increased hemoglobin level in comparison to a lower level (11–12 g/dl) were obtained.

Furland with co-authors' [19] study results pointed out that Strippoli with co-authors' [18] conclusions are not applicable to patients without cardiovascular pathology. In the randomized controlled study which was conducted by J. Rossert and co-authors [20] and published afterwards, authors compared two groups of patients – one with high hemoglobin level (13,0–15,0 g/dl) and another with lower one (11,0–12,0 g/dl), and thus evaluated effects of anemia correction by subcutaneous use of epoetin alfa on CKD progression. Decrease of glomerular filtration rate (GFR) was slower (though not statistically significant) in the group of patients with high (normal) hemoglobin level than in the group of patients with low hemoglobin level (0,058 versus 0,08 ml/min/1,73 m²/month). Despite the short duration of the trial (on average, 7.4 and 8.3 months respectively) on the basis of these data

it was concluded that normalization of hemoglobin level in CKD patients as a whole is safe, improves life quality and may slow the decline in GFR. At the same time the frequency of cardiovascular complications in patients with normal (high) level of Hb was no less than in the patients with low levels of it (25% and 18%).

On the basis of these studies, in May 2006 a working group of NKF-KDOQI (National Kidney Foudation – Kidney Disease Improving Outcome Quality Initiative) published clinical practical guidelines for anemia treatment in conditions of CKD. According to these guidelines, target hemoglobin level for patients with CKD treated with ESA in general should be ≥ 11,0 g/dl (lower limit) but there is no ground to maintain it at the level over 13,0 g/dl (upper limit) [21]. By that time (end of 2006) the results of two large randomized studies [14, 15] had been published. Within the limits of these studies, effects of full anemia correction on general and cardiovascular mortality among the pre-dialysis CKD patients were published. The studies results had a significant impact upon further problem development. In CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with epoetin beta) study included 603 patients from Europe, Mexico and Asia predominantly with the IV stage of CKD accompanied with anemia, no advantage of normal target hemoglobin level (13,0–15,0 g/dl) versus the subnormal one (10,5–11,5 g/dl) was detected. In the course of the 3 year study the two groups did not differ much in the number of cardiovascular complications (158 vs 147), no differences either in general death rate or in hospitalization rate were registered. Both groups had almost the same mean value of GFR decrease within the 3 year period (3,4 vs 3,1 ml/min). However, the number of patients who reached hemodialysis within this period was more among those which had high hemoglobin level [14].

CHOIR study (Correction of Hemoglobin and Outcomes in Renal Insufficiency) involved 1432 patients with III and IV CKD stage, was interrupted ahead of schedule (before the planned 16 months) because of the risk of reaching the primary composite endpoint (death, myocardial infarction, hospitalization due to chronic cardiac insufficiency) turned out to be higher by 34% (p< 0,03) in the group of patients randomized to the hemoglobin level 13,5 g/dl than among the patients with the level 11,3 g/dl [15]. The CHOIR study patients population was characterized with a large number of diabetes mellitus patients, elderly patients suffering of arterial hypertension being a reason of kidney affection.

The mean dose of epoetin alfa used in this study was considerably higher (almost 3 times) than in the CREATE and other studies. The fact that the majority of the patients in the treated group, despite on high doses of epoetin, did not reach the target hemoglobin level of 13,5 g/dl, was explained with high co-morbidity, although not ruled out the role of the epoetin vasoactive properties, its ability to stimulate of norepinephrine-L-1 (3,4 dioxyphenil-2 aminoethanol) and provoke of hypertension independently of the hemoglobin level changes [22]. Among the anemia-evoking factors in conditions of diabetes mellitus, chronic inflammation and pro-inflammatory cytokines (interleukin-1, tumor necrosis factor-alfa, interferon-gamma) are taken into consideration. Their heightened level in serum is detected before renal insufficiency development [54].

These 2 studies, though very different in the kind of participants and the results of the secondary analyses, have shown that full correction of anemia don't reduce death rate or cardiovascular complications rate in patients with CKD compared with partial correction of anemia. They have as well shown that high ESA doses can be ineffective (not able to increase hemoglobin level up to the target one) and even dangerous for the patients with comorbid conditions. Obviously, different populations of patients need individual recommendations regarding the treatment [23]. Moreover it is still not completely clear of ESA therapy to affect whether inhibition of CKD progression.

The results of meta-analysis conducted by Phrommintikul A. and co-authors [24] included also CREATE and CHOIR, have confirmed the thesis that CKD patients with accompanied of high target hemoglobin level have significantly higher risk of death from various reasons and arteriovenous access thrombosis.

NKF-KDOQI working group has introduced changes into its recommendations of 2006 regarding target level of hemoglobin in patients with CKD on the basis of the new data. To substantiate the new revision of the recommendations, the group has carried out an extended meta-analysis of all results by that time completed randomized controlled studies in the area of anemia treatment. Unlike Phromminticul A. and his co-authors [24], NKF-KDOQI working group considered separately dialysis and pre-dialysis patients. The analysis has shown that among the pre-dialysis CKD patients, there was no significant difference in general mortality rate (8 studies – 3038 intent-to-treat patients) between the group with a higher hemoglobin level and group with a lower one, while cardiovascular complications risk (6 studies – 2850 intent-to-treat patients) was higher among the patients randomized to a higher target hemoglobin level (hazards ratio 1.21; 95% confidence interval 1,02–1,5). Among the

dialysis patients there was no significant difference in general mortality rate (4 studies – 2391 intent-to-treat patients) or cardiovascular complications rate (3 studies – 1975 intent-to-treat patients) between the group with a higher hemoglobin level and group with a lower one. According to the revised recommendations of NKF-KDOQI working group (September, 2007), target hemoglobin level should make up 11-12 g/dl and not exceed 13,0 g/dl for the patients undergoing ESA therapy, "since the possibility of harm from high- hemoglobin level exceeds the potential benefit of improving the quality of life and reducing the blood transfusion" [21].

Coordination meeting convened in October, 2007, within of KDIGO (Kidney Disease Improving Global Outcome) to elaborate a common position with respect to NKF-KDOQI publication of 2007, recognized that taking into consideration the latest data contained in the above mentioned publication, hemoglobin level exceeding 13,0 g/dl can be unsafe for the people used ESA therapy and that hemoglobin level ranging from 9,5 to 11,5 g/dl is associated with better outcomes than the level over 13,0 g/dl. Nevertheless, it was agreed that the new data are insufficient to justify an immediate revision of the recommendations for treatment of patients with CKD and anemia.

ERBP working group for anemia research (European Renal Best Practice) considered sufficient grounds to support the NKF-KDOQI recommendations 2007 to keep relatively low target hemoglobin level as a more secure hemoglobin level At the same time, according to the group, the probability of harm from achieving a high target hemoglobin level while there, but it is mainly in certain populations of patients - those with diabetes mellitus, clinically significant cardiovascular diseases. [51].

Secondary CHOIR analysis was involved a large amount of such patients has shown that among the patients whose hemoglobin level did not reach the target one of 13,5 g/dl but who had a higher hemoglobin level in comparison to the control group, unfavorable outcomes like death or thrombosis were more often. Besides, the patients who needed high-dose ESA, marked by a 6% greater risk of end point studies, regardless of the hemoglobin level [21].

ERBP group underlined the importance of understanding whether the adverse events related to treatment with ESA only attempt to achieve higher hemoglobin level in patients with comorbidity, or they are caused by a reduced response of the patients for treatment of ESA. TREAT (The Trial to Reduce Cardiovascular Events with darbepoetin alfa) study which was finished in November, 2009, played an important role in support of the ERBP group opinion about target hemoglobin level [47]. Within this multicenter placebo-controlled study, cardiovascular outcomes (death, non-fatal myocardial infarction, cardiac insufficiency, stroke or hospitalization due to myocardial ischemia) and renal outcomes (terminal stage of kidney disease and death) were evaluated in the 4038 patients with type II diabetes associated with pre-dialysis CKD and anemia (12 of patients were kept under observation in our clinic). Two groups of the patients were compared: a group randomized to full correction of anemia with darbepoetin alfa (target hemoglobin level – 13,0 g/dl) and placebo group (with "saving" 9,0 g/dl hemoglobin level). At the end of the observation period (on average 29,1 months) the patients in the first group reached the primary cardiovascular composite endpoint as often as the patients in the second group (hazards ratio 1,05; 95% confidence interval 0,94–1,17, p=0,41); there was no difference between the two groups in the frequency of another primary end point, i.e. death or terminal stage of renal disease (hazards ratio 1,06; 95% confidence interval, p=0,29), either. But analysis of certain elements of the end points revealed an increased risk of fatal and non-fatal cerebral stroke among the patients who had in their anamnesis a carried stroke, which were treated with darbepoetin alfa and were randomized to the target hemoglobin level equal to 13,0 g/dl (101 cases vs 53 in the placebo group, hazards ratio 1,92; p<0,001). In this group a higher frequency of death from malignant tumors (if there were tumors in the anamnesis), from venous and arterial thromboembolia was registered. However, heart revasculization operation in the darbepoetin group was needed less often than in the placebo group. Full anemia correction provided only moderately more favorable effect on the patients' life quality in comparison to the placebo group patients. But it should note that half of the patients of control group were treated with intravenous injections of iron and hemotransfusions while their hemoglobin level was observed. Thus, it is questionable if this group satisfies the criteria for placebo group.

The secondary analysis of TREAT results [26] confirmed the necessity to be cautious when correcting anemia in patients with diabetes and CKD. On the other hand, it should not ignore the fact that mean dose of darbepoetin alfa used in this study was around 175 mcg/month, that is 2 times more than a mean ESA dose given to hemodialysis patients in Europe. It follows that complications hazard could be to a greater extent more caused by high ESA dose than by hemoglobin concentration that was discussed while the secondary analysis of CHOIR study [26]. It is difficult to give an unambiguous interpretation of TREAT results because new secondary CHOIR analysis [27] on a het-

erogeneous model did not confirm that the risk grows due to a higher target hemoglobin level in patients with diabetes and those with cardiac insufficiency.

The results of secondary analyses of CHOIR studies, US Normal Hematocrit trial [28] showed as well that the patients who had the worst outcomes had been resistant to the treatment and so had been given higher doses of ESAs. According to ERBP group's opinion [25], ESA dose necessary for reaching target hemoglobin level (11,0–12,0 g/dl without intentional increase up to 13,0 g/dl) should be taken into consideration for evaluation of possible complications during treatment. Thus, if there is no need in ESAs or only small ESA doses are needed for maintaining target hemoglobin level, there are much fewer reasons to fear of adverse events, first, increased thrombogenic effects, than in cases when high ESA doses are needed to reach this hemoglobin level. At the same time, unexpected data obtained in TREAT study: more frequent of deaths from malignant tumors (in case there was a tumor in the anamnesis) was among the patients randomized to darbepoetin alfa and full anemia correction (1,9% from 2 012 patients in the treatment group and 1,2% from 2 026 patients in placebo group, p=0,08). These data, despite small sampling, is in accordance with the results of meta-analysis of randomized studies in the oncology area which give evidence of increase in tumor growth and death rate among the patients with certain types of cancer due to ESA use [52]. ESA can promote growth of tumors through increased angiogenesis in cancer tissue after connection of exogenous erythropoietin to erythropoietin receptors expressing on cancer cells surface. Besides, use of ESA in patients with cancer can increase the risk of venous thromboemboliae [21, 57, 58].

It is notably difficult to keep patients' hemoglobin level within a narrow range of target hemoglobin concentration values.

The effect of short-acting epoetin use in 281 patients being given hemodialysis treatment was subject to retrospective analysis: in the course of one year approximately three cycles were noted, which were characterized by increasing of the mean hemoglobin level up to 12,8 g/dl and its decrease to 10,3 g/dl, in most cases (84% episodes) due to the change of epoetin dose which was made on average 6 times a year [53].

Use of iron preparations, extension of intervals between introductions of erythropoiesis stimulators with a short elimination also contributed to the cyclic fluctuations in hemoglobin level. According to the our data and literature sources, patients with chronic cardiac insufficiency, systemic diseases and undercurrent infections are subject to significant fluctuations in hemoglobin level [29–34].

In a large observational study from the USA [29] (152 846 hemodialysis patients treated with ESA) found that many patients reach the target hemoglobin level, but not its stability (Fig. 1): only 10,3% of the patients had a stable hemoglobin level over a period of 6 months, while target hemoglobin level maintained itself in the course of that period only in 6,5% of the patients. The rest of the patients had fluctuating hemoglobin level over that period; in 40% cases it crossed both minimal and maximal limits of the target hemoglobin level range.
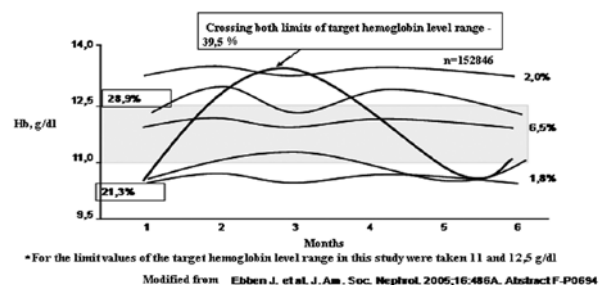
Fig.1. *In 40% patients hemoglobin concentration value in the course of 6 month therapy crosses both minimal and maximal limits of the target hemoglobin level range*

In this study the relation between hemoglobin concentration variability and unfavorable outcomes over 6 month period was evaluated [29]. The groups of patients were formed on the basis of mean monthly hemoglobin level (low level Hb < 11 g/dl; intermediate level Hb = 11,0–12,5 g/dl; high level Hb ≥ 12,5 g/dl) and on the basis of hemoglobin concentration fluctuations (constant value, low- and high-amplitude fluctuations). The groups were compared by morbidity and hospitalization rate.

Association between hemoglobin concentration variability and frequency of unfavorable outcomes was found. Among all considered groups, the patients with constantly low hemoglobin level had highest risk of morbidity and hospitalizations.

In another study conducted in the USA [30] (159 720 hemodialysis patients treated with ESA), the same algorithm was used: mean monthly hemoglobin concentration (low, intermediate, high) and the most considerable fluctuations of hemoglobin concentration over 6 month period (low-lower, low-high) were measured. The task of the study was to evaluate relation between hemoglobin parameters and death rate. It was established that the determining factor in death risk evaluation is general direction of hemoglobin level deviations from target values. Death risk growth was

associated with stably low hemoglobin level or with hemoglobin reduction over a period of time (under 11 g/dl in the course of over 3 months) and high variability of hemoglobin level. The lowest death rate was among the patients with CKD with stable hemoglobin level within the range from 11 to 12,5 g/dl.

Lately, a European study which included 5037 hemodialysis patients has been published [50]: in a multifactor model it was found that stably low hemoglobin level is an independent death rate predictor. There was established the importance of risk factors and other hemoglobin level changes such as, for example, high-amplitude fluctuations of hemoglobin level and stably high hemoglobin level , however, in adjusted model they did not prove it.

A more lengthy reduction of hemoglobin concentration down to under 11 g/dl before start of epoetin use as well as a more lengthy period of reaching target hemoglobin level (11–12 g/dl) make the risk of hospitalization and fatal outcome go up [35–37]. This fact should be taken into consideration when one chooses ESA prescription scheme.

Despite certain inconsistency, the results of these studies in total allow to make a conclusion that an important task when treating anemia in patients with CKD is to reduce fluctuations (variability) of target hemoglobin level within optimal range towards minimal as well as maximal limit.

One of the approaches to this problem solution can be use of long-acting epoetins, such as darbepoetin alfa and mircera for renal anemia treatment [37, 39–40].

Darbepoetin alfa molecule contains 2 more N-combined carbohydrate chains which impart to it a higher metabolic activity in vitro; darbepoetin alfa molecule's final half-life period is three times longer than that of epoetin alfa, this property allows using of darbepoetin alfa once in 1–2 weeks to the patients undergoing RRT well as to the pre-dialysis CKD patients.

Even more lengthy period of action has III generation drug with brand name Mircera (methoxy polyethylene glycol - epoetin beta) –a long-acting erythropoietin receptors activator, which differs from epoetin beta by having in its molecular structure a long polymer chain (polyethylene glycol) [57]. Molecular weight of Mircera (two times heavier than epoetin beta) determines the pharmacokinetic and receptor interaction characteristics of this drug. Mircera is the only drug which, being once a month provides stable and constant control of hemoglobin level independently of the previous other erythropoiesis stimulators scheme use.

The results of the open randomized darbepoetin alfa and Mircera studies confirmed their safety and efficiency for subcutaneous and intravenous introduction once of 1-2 weeks and once of 2–4 weeks respectively [34]. In ARCTOS study [37], which included 324 patients with pre-dialysis CKD, efficiency of subcutaneous Mircera (C.E.R.A.) and darbepoetin alfa was compared: 162 patients used Mircera (once in 2 weeks) and 162 patients used darbepoetin alfa (once a week) in the course of 18 weeks of the correction period and 10 weeks of the maintenance therapy. Increase of hemoglobin level was registered in 97,5% of the patients used Mircera and in 96,3% of the patients used darbepoetin alfa. Hemoglobin level remained stable in both groups over the whole study period, and the patients tolerated the therapy well (Fig. 2).
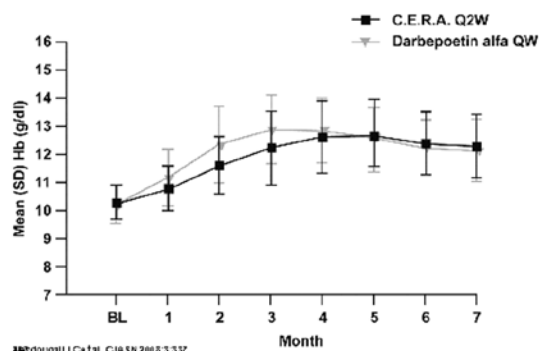

Fig. 2. *Results of ARCTOS study (Clin. J. Am. Soc. Nephrol. 2008; 3(2): 337–347)*

The ability of long-acting erythropoietin to restore and maintain stable hemoglobin levels in patients with various stages of CKD in combination with a decrease in the multiplicity of drug administration provides predictable control of hemoglobin level and simplifies the treatment of anemia for doctors and patients.

For economic calculations (Sauressing U., 2007) [51], the cost of anemia treatment by short-acting drugs (injections 3 times per week) in the dialysis Center in Germany amounted to an average of 17000€/100 patients, in Great Britain – 18379£/100 patients (excluding the cost of epoetin). In case of replacement of short-acting stimulant epoetin on long-acting erythropoiesis – Mircera (1 injection once a month) the cost of anemia treatment in the dialysis Center in Germany could be reduced by 58% , in Great Britain – 35%.

Currently, two drugs approved for clinical use and are available in our country.

In 2009 ERBP working group has summarized the results of the controlled studies of the recent years (TREAT, CHOIR, CREATE, US Normal Hematocrit Trial) and formulated its position with respect to anemia treatment and target hemoglobin level in patients with CKD [25]. The following conclusion can be made on the basis of these recommendations.

It is getting more and more evidents that the common "protocol" approach to renal anemia treatment does not provide improvement of ESA therapy results. Anemia management in patients with CKD requires individual approach taking into account the influence of the underlying disease of CKD, comorbidities, environmental factors and some other reasons individual for each patient. Choice of target hemoglobin level makes up an important part of therapy strategy.

ESA therapy of anemia should be started when 2 consecutive blood tests made with two-week interval have shown that hemoglobin level is under 11 g/dl (for patients of high risk, such as, for example, with II type diabetes mellitus and with cardiovascular complications in the anamnesis – when hemoglobin level is under 10 g/dl), but only in case no other reasons for anemia except CKD were detected within the diagnostic tests.

The newly obtained data allow recommending a narrow range of target hemoglobin concentration values: 11–12 g/dl and the values not exceeding 13 g/dl for the majority of patients with CKD and anemia.

For patients with CKD combined with a severe pathology (such as diabetes mellitus and cardiovascular complications) it would be justified to establish target hemoglobin level within the range of 10-12 g/dl (but not over 12 g/dl, especially for those who have risk of stroke). On the other hand, for patients with CKD without any combined severe pathology, it is common to establish target hemoglobin level within the range of 11–12 g/dl. This range can be accidentally exceeded due to hemoglobin variability, but not over 13 g/dl.

Patients with CKD who have in their anamnesis oncological diseases should be prescribed the possible lowest ESA doses, on the basis of careful analysis of "damage-benefit" relation. For patients with nonhematologic tumors (solid tumors) and anemia which treated with chemotherapy, ESA therapy is justified for the purpose of reducing frequency of hemotransfusions. In this case target hemoglobin level should not exceed 12 g/dl, keeping within the range between 9,0 and 11,0 g/dl. One should be very careful with hemotransfusions: if possible, hemotransfusions should be avoided before renal translanation [25, 57, 58].

At the beginning of ESA therapy patients with CKD and anemia should be given low ESA doses, after some time ESA dose should be titrated in order to prevent quick increase in hemoglobin concentration. At the first stage of the therapy hemoglobin concentration should increase at a rate of 1–2 g/dl/month, hemoglobin concentration increase by more than 2 g/dl per month is undesirable. If dose escalation does not lead to hemoglobin concentration increase, before doing further correction one should carefully evaluate the risk for the given patient and determine the most acceptable ESA dose for this patient, as well as exclude the possibility of interrelation between anemia severity degree and extrarenal causes.

Varying hemoglobin levels is expected, but the large fluctuations, as well as constantly low or constantly high values beyond the target level should strive to avoid.

In each particular case certain factors which are related to the therapy or to the patient should take into consideration in order to minimize ESA dose and to maintain stable hemoglobin level within the target range.

All CKD patients with anemia, which is planned to epoetin therapy, require the prior correction of iron deficiency, preferably by intravenous iron administration. Adequate intake of iron is an important element of supportive ESA treatment.

For the dialysis patients, important conditions of inflammation risk reduction and improvement of response to ESA therapy are as follows: high quality of dialysis water and biocompatibility of membranes, everyday dialysis and operative hemofiltration, hyperparathyroidism correction, malnutrition correction.

One should take into account impact of drugs, in particular of angiotensin-converting enzyme inhibitors, because angiotensin II takes part in erythropoiesis regulation and its inhibition leads to weakening of response to erythropoietin, thus, being in certain cases a reason for erythropoietin resistance [55].

Pharmacological characteristics of the various ESA, including frequency of administration, dose required to achieve the target level of hemoglobin may determine the choice of ESA. For not on dialysis patients subcutaneous administration and less frequent dosing regimen, ie, use of long-acting ESA is more conveniented, at the same time for patients receiving regular dialysis treatment, these parameters can not be preferred.

Benefits and risks of ESA therapy should be straightforwardly discussed with the patient as well as the purposes of therapy which can be different depending on the patient's way of life – active or passive.

In current medical literature is put up for discussion the question: do we need new studies on the ESA treatment and the target hemoglobin level in CKD patients? It appears clearly needed to better understand

the relationship between the hemoglobin concentration, the dose of ESA and the features of the underlying kidney disease.

Anemia is a modifiable risk factor and its correction on the safe level not only improves life quality of patients, but can also decelerate CKD progression, that is why renal anemia treatment remains one of the most relevant issues in nephrology.

For sure, the treatment of anemia in patients with CKD will be improving and becoming more individual by way of taking into consideration underlying kidney disease and comorbidity, as well as the factors influencing erythropoiesis in each patient (iron metabolism, infections and inflammation, dialysis parameters, protein-energy status, intake of drugs, etc.).

Individual approach to the selection of optimal target hemoglobin level will allow to go beyond of a narrow hemoglobin corridor of 11,0–12,0 g / dL is recommended for patients with CKD in general, to reduce its variability, and thus to optimize the strategy for the treatment of anemia in predialysis as well as in dialysis CKD patients.

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