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Anemia in Patients with Heart Failure: Current State of the Problem

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ABSTRACT The article reports the modern tactics of treating patients with chronic heart failure and concomitant anemia. The results of the most important randomized clinical trials that are the basis for developing approaches to the treatment of anemia in such cases are discussed. Attention is also paid to unresolved problems in the treatment of anemia in patients with heart failure. The data on the intravenous administration of iron preparations as the most effective approach to the treatment of anemia in patients with heart failure in the presence of iron deficiency are given. The main provisions of modern clinical guidelines on the management of patients with heart failure and anemia are considered.

Keywords: chronic heart failure, anemia, iron preparations

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CHF — chronic heart failure
CKD — chronic kidney disease
HF — heart failure
LVEF — left ventricle ejection fraction
RCT — randomized clinical trial

In patients with chronic heart failure (CHF), there is a varying degree of inadequate intake of oxygen and nutrients to the tissues. In addition, these patients have activated nervous and hormonal systems and enchanced inflammation, often combined with iron deficiency (approximately 50% of patients) and anemia (approximately 40% of patients) [1, 2]. The iron deficiency has been considered the cause of anemia in patients with CHF for many years. However, the results of relatively recent large-scale studies, which were aimed at eliminating either anemia or iron deficiency, showed a significant difference in the effects of such interventions. According to currently available data, therapy aimed at increasing the concentration of hemoglobin, apparently, has no advantages, while elimination of iron deficiency leads to significant clinical benefits, including patients with CHF in the absence of anemia.

Such data may be the basis for the question whether elimination of low hemoglobin levels can be considered the goal of therapy, or such a level simply indicates the severity of the disease or the presence of such comorbidities as renal failure or iron deficiency. So, it remained unclear whether the anemia itself affects the course of CHF. To clarify the role of anemia in CHF, it is advisable to refer to the literature data.

THE PROBLEM OF DIAGNOSING ANEMIA IN PATIENTS WITH CHRONIC HEART FAILURE

The strict definition of anemia is an absolute decrease in the number of erythrocytes in the body, which can be assessed using a complex and expensive analysis of blood volume with radioactive drugs. However, in clinical practice, such indirect indicators as hemoglobin level in blood and hematocrit index are used to diagnose anemia. It should be noted that both of these indicators depend on the degree of blood clotting. In patients with CHF and volume overload, so-called pseudoanemia often develops due to hemodilution [3].

In accordance with recommendations of the World Health Organization, anemia is diagnosed in men and women when hemoglobin levels are less than 13 and 12 g/dL, respectively. The validity of this definition of anemia has never been formally confirmed, but in the general population of individuals with normal renal function, the concentration of erythropoietin in the blood increases exponentially when hemoglobin is less than 13 and 12 g/dL in men and women, respectively [4]. According to various studies, there was a large variability in the prevalence of anemia in patients with CHF (from 17 to 70%), which may be associated with differences in the criteria for anemia, demographic characteristics of patients and

concomitant diseases, as well as differences in the type of studies on the severity of CHF [5-7].

ETIOLOGY AND PATHOPHYSIOLOGICAL LINKS OF ANEMIA IN CHF

The etiology of anemia in CHF is considered multifactorial. The highest risk of developing anemia is observed in patients with chronic kidney disease (CKD) or diabetes, as well as in elderly patients [6, 7]. CHF may cause anemia due to different mechanisms; however, anemia and CHF may have several common risk factors.

In patients with CHF, there is often an iron deficiency, which is observed in about 50% of patients [8-10]. The presence of chronic inflammation in CHF is considered as an important cause of "functional" iron deficiency and resistance to the action of erythropoietin [11]. In contrast, the inadequate level of erythropoietin is often noted in patients with concomitant chronic kidney disease (CKD), since erythropoietin is secreted in the kidney [12]. In addition, insufficient bone marrow sensitivity to erythropoietin due to internal defects in the bone marrow even more contributes to anemia [13]. The result is an excessive increase in the concentration of erythropoietin in the blood of patients with heart failure (HF) and intact production of erythropoietin. In such patients, an increased level of erythropoietin in the blood is accompanied by an increased risk of adverse outcome [14]. It should also be noted that the activation of the renin- angiotensin-aldosterone system leads to the retention of sodium and fluid, causing the development of the so-called pseudoanemia [3, 12].

The drug therapy used to treat CHF may also cause anemia. It is known that inhibitors of the angiotensin converting enzyme inhibit the activity of blood formation due to the effect on N-acetyl-serpentyl lysyl proline, which causes a higher risk of developing anemia. These effects were established during the course of *SOLVD (Studies of Left Ventricular Dysfunction)* in the enalapril group [15, 16]. In addition, there is evidence that carvedilol may reduce the concentration of hemoglobin due to the block of β_2-adrenoreceptors [17].

THE CLINICAL CONSEQUENCES OF ANEMIA IN PATIENTS WITH HEART FAILURE

In healthy individuals, oxygen delivery to tissues due to reduced hemoglobin concentration to as low as 5 g/dL may be compensated by increasing both heart rate and stroke volume. These mechanisms are impaired in patients with CHF [18]. Consequently, the development of anemia in patients with CHF may lead to a decrease in oxygen delivery to the tissues and, consequently, worsening of clinical manifestations of the disease such as dyspnea and increased fatigue, and further deterioration in exercise tolerance and quality of life [19].

The results of a large meta-analysis, including 153,180 patients with CHF showed an increased risk of death in the presence of anemia (standardized risk ratio 1.46 with a 95% confidence interval from 1.26 to 1.69) in the absence of differences in the effect on the prognosis between patients with a reduced or saved left ventricle ejection fraction (LVEF) [5]. The results of two observational studies have shown that anemia resolved in more than 40% of outpatients with CHF [6, 7]. Moreover, the prognosis in such patients did not differ from that in patients without anemia, while the persistence of anemia was accompanied by a decrease in survival. It should be noted that the frequency of use of iron preparations and agents that stimulate erythropoiesis was relatively low, 21% and 8%, respectively, and a decrease in the severity of anemia or its elimination was explained mainly by the effect of treatment for CHF, in particular, by reducing fluid overload, which eliminated pseudoanemia [6]. Patients with CHF often have a combination of anemia, CKD and/or iron deficiency, which is accompanied by progression of both CKD and CHF and an unfavorable prognosis [20]. However, it remains unclear whether anemia itself leads to worsening of CHF and the prognosis or it only reflects the presence of more severe CHF [1].

MODERN APPROACHES TO THERAPY

TRANSFUSION THERAPY

In the presence of severe anemia, which has clinical manifestations, transfusion of erythrocyte mass is often considered [1]. However, there are only limited data on the effectiveness of such tactics in patients with CHF. Transfusion therapy has only a temporary effect and is accompanied by an additional increase in risk in patients with CHF due to volume overload or the development of complications due to ischemia. The results of 2 large observational studies, including patients with CHF, indicated that blood transfusions were accompanied by worsening of the clinical manifestations of the disease and prognosis, despite the fact that during some small studies, the safety of blood transfusions was noted and even its advantage compared with patients with similar characteristics where blood wasn't transfused [21, 22]. Considering the risk of acute hemolytic reactions, infections, acute lung damage, allergic reactions and the lack of advantages of more extensive indications for blood transfusion, a more strict approach to determining indications for blood transfusions is currently recommended (for example, at a threshold hemoglobin level of 7-8 g/dL [23]).

THE USE OF AGENTS THAT AFFECT ERYTHROPOIESIS

Exogenous administration of erythropoietin is approved for use in the treatment of patients with chronic anemia, which is caused by CKD or the use of chemotherapy. The efficacy of treating anemia in patients with CHF using erythropoiesis stimulating drugs was studied during a randomized clinical trial (RCT) of *RED-HF (Reduction of Events by Darbepoetin Alfa in Heart Failure)*, which included 2,278 patients [24]. In this study, patients with clinical manifestations of CHF, where LVEF was 40% or less, as well as with the presence of anemia (hemoglobin 9-12 g/dL), were assigned to the darbepoetin alpha group (to increase the hemoglobin concentration up to 13-14.5 g/dL) or the placebo group. And in both groups, concomitant therapy with iron preparations was allowed (both orally and intravenously). The median hemoglobin concentration in the intervention group increased, but in the absence of any influence on the main combined indicator of total mortality or hospitalization rates for CHF, as well as other adverse outcomes. At the same time, there was a statistically significant increase in the incidence of ischemic stroke by 1.7% (p=0.03) and embolic or thrombotic complications by 3.5% (p=0.009) in the darbepoetin alpha group compared to the placebo group [24 , 25].

IRON THERAPY

Iron preparations were initially used as concomitant therapy in studies evaluating therapy that stimulates erythropoiesis [24]. The late awareness of a high prevalence of iron deficiency (approximately in 70% of patients with anemia and in general in approximately 50% of patients with CHF), as well as the establishment of negative clinical consequences of iron deficiency and the availability of new iron preparations for intravenous administration, became the basis for developing studies to assess the efficacy of iron preparations in the absence of erythropoiesis stimulating agents. Initially, such studies included patients with anemia, but then began to include patients with iron deficiency, regardless of the presence or absence of anemia. Despite the fact that the intake of iron preparations has practical advantages compared to intravenous administration, CHF has limitations due to the lack of compliance with the prescribed therapy and side effects associated with the effect on the gastrointestinal tract and impaired iron absorption that was noted during the study phase II *IRON-OUT (Oral Iron Repletion Effects On Oxygen Uptake in Heart Failure)* [26].

The efficacy of intravenous iron administration has been studied in the course of performing several RCTs [27–30]. In all such studies, patients were included based on a certain level of ferritin and transferrin saturation. Despite the differences in treatment tactics and features of observation, in general, the results of such studies were similar: intravenous administration of iron preparations led to an improvement in the functional class according to the *NYHA* classification *(New York Heart Association)*, exercise tolerance and quality of life for a short period of observation. In the course of performing 2 largest RCTs, *FAIR-HF (Ferinject Assessment in Patienties with Iron Deficiency and Chronic Heart Failure)* and *CONFIRM-HF (Ferric Carhoxymaltose Evaluation on Performance in Patienties With Iron Deficiency in Combination With Chronic Heart Failure)*, a statistically significant increase of hemoglobin in blood was noted, but the therapeutic effect was similar in the presence of anemia and without it [29 , 30]. Results of RCT *EFFECT-HF (Effect of Ferric Carhoxymaltose on Exercise Capacity in Patienties With Iron Deficiency and Chronic Heart Failure)* assessing the efficacy of intravenous iron carboxymaltose compared to standard treatment in patients with CHF (n=172) and iron deficiency showed an increase in the maximum oxygen consumption in the intravenous iron carboxymaltose group compared to the control group without therapy [31].

Thus, despite the fact that anemia and iron deficiency are often combined, isolated iron deficiency has a high prevalence in patients with CHF, and the benefits of therapy with iron preparations, apparently, are associated not only with the effect on blood formation. The effect of intravenous iron administration on the risk of adverse clinical outcomes remains to be established. Given such data, according to experts [1], it is considered to monitor the level of iron in the blood of all patients with CHF, regardless of the hemoglobin concentration. In large RCTs, iron deficiency was usually diagnosed with a combination of certain saturation of transferrin and the level of ferritin in the blood (the concentration of ferritin was less than 100 mg/l or ferritin concentration in the ranged from 100 to 300 mg/l in combination with transferrin saturation less than 20%). It should be noted that the validity of such criteria has never been formally confirmed, and the level of ferritin in the blood is an unreliable indicator, since ferritin is an acute phase protein. At the same time, the results of the study have been presented recently, where the validity of transferrin saturation of less than 20% (using the bone marrow stain for iron as the “golden standard”) was confirmed as a reliable parameter [32]. So the level of ferritin in the blood has no diagnostic value [1]. This view is supported by evidence that low ferritin saturation, but not low ferritin levels, is associated with high risk of death. The results of meta-analysis also evidence the reasonability of such an idea, as they showed the lack of improvement in prognosis due to the use of iron preparations in patients with CHF with ferritin saturation of 20.1% or more, and improved prognosis in patients with CHF and a lower ferritin saturation level [33].

CURRENT GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH HEART FAILURE AND ANEMIA

In most clinical guidelines, in particular, the recommendations of the European Society of Cardiology and the recommendations of the American College of Cardiology and the American Association of Cardiologists, anemia in patients with CHF is considered as a clinically significant concomitant disease [34, 35]. In the treatment of anemia in such patients, the focus is on the possible elimination of the causes of anemia, despite the fact that in most cases it is not possible to find a specific cause of anemia. A special role in the treatment is given to the management of iron deficiency by intravenous administration of iron carboxymaltose. Experts of the European Society of Cardiology do not recommend the use of drugs stimulating erythropoiesis in patients with CHF [34].

CONCLUSION

Thus, anemia in patients with chronic heart failure remains a clinically significant concomitant phenomenon, despite the fact that the results of most clinical studies do not confirm the effectiveness of managing anemia itself in such cases. Anemia is diagnosed in about 30% of patients with chronic heart failure; and the prognosis and quality of life in patients with anemia and chronic heart failure are less favorable. The presence of anemia may indicate the presence of comorbidities or complications, such as nutritional deficiency, kidney disease or volume overload, although in the latter case anemia is referred to as pseudoanemia .

Despite the validity of finding a specific cause of anemia in patients with chronic heart failure, there is no evidence of the effectiveness of increasing hemoglobin levels with the help of drugs that stimulate erythropoiesis. The use of such therapy did not affect the risk of death or the frequency of repeated hospitalizations due to the worsening of chronic heart failure, but led to an increase in the incidence of ischemic stroke, which levels a slight positive effect of erythropoietin on the clinical manifestations of chronic heart failure. Intravenous iron administration for iron deficiency anemia in patients with chronic heart failure seems to be the most promising approach to treating anemia in such cases, but the effect of therapy cannot be explained only by an increase in hemoglobin level in the blood. In addition, there is still no data on the positive effect of intravenous administration of iron preparations in patients with chronic heart failure and anemia on the risk of adverse clinical outcomes.

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