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Anemia in Chronic Heart Failure: Unresolved Issues Treatment

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Abstract: 84 patients with chronic heart failure (CHF) NYHA II-IV FC with anemia were examined. Of these, 54 are men and 30 are women. All patients were diagnosed with anemia at a hemoglobin (Hb) level of less than 120 g/l in men and less than 110 g/l in women. The reason CHF was CHD (postinfarction cardiosclerosis) n=40, or CHD with type 2 diabetes mellitus (DM) n=10, with arterial hypertension (AH) n=14, or CHD +AH+DM n=10. Correction of the anemia syndrome in CHF with the use of MEB, effectively eliminates erythropoietin deficiency, anemia and cytokine aggression in patients with CHF with anemia.

Key words: heart failure, anemia syndrome, erythropoietin, iron deficiency.

INTRODUCTION

Despite the fact that anemia now occupies an important place in our understanding of the pathogenesis of heart failure, its structure remains a mystery, as it is the least studied. Anemia is widespread among patients with chronic heart failure (CHF) - from 7 to 50% and is of great clinical importance. Anemia in CHF is an independent predictor of mortality. The PRAISE study found that with a decrease in hematocrit by 1%, the risk of death in patients with NYHA III-IV functional class (FC) CHF increases the risk of death by 11%. Results of a meta-analysis of 20 clinical trials, they proved a reliable association of anemia with a high risk of death in HF, while these patients had the worst tolerance to NYHA class III-IV stress and a low left ventricular ejection fraction (LVEF). On the one hand, clinicians focused on the role of erythropoietin (EPO) and its dysfunction. The development of anemia in patients with CHF may be with low or elevated EPO. On the other hand, patients with CHF have iron deficiency (ID) in 37% of cases. Researchers They showed a significantly lower survival rate in CHF patients with ID compared with patients without ID. Patients without anemia had ID in 32% of cases. There is a growing awareness that HF, renal failure (PN), and anemia are often concomitant diseases that can mutually worsen in a vicious circle that has led to the concept of cardiorenal anemia syndrome (CRS) proposed by D.S. Silverberg. In 2011, clinicians supplemented this syndrome with the addition of iron deficiency - cardiorenal anemia iron deficiency syndrome. In patients with CHF NYHA IV F.K., the level of EPO in plasma increases by 6 times. Many researchers agree that the approximate activation of anti-inflammatory cytokines reflects the unfavorable development of LV remodeling and the non-stop progression of CHF. The established patterns of changes in the nature and degree of aggression of anti-inflammatory cytokines during the development of CHF make it possible to objectively assess the role of an insufficient erythropoietin response, which contributes to the development of anemia syndrome. Recently, there have been more and more reports about studies and their results on the possibility of identifying various drug programs using a particular first-line drug in the treatment of CHF. Thus, in the SOLVD study in patients with severe CHF (FC III-IV) and low LVEF, 6-week therapy with the ACE inhibitor enalapril at a dose of 20 mg/day did not lead to a significant decrease in TNF-α and prostaglandin E2 levels, while C-reactive protein B blood pressure decreased. According to 6-month therapy with α1, β1, β2-adrenoblocker carvedilol at a dose of 25 mg /

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day in patients with severe CHF (FC IV) with reduced LVEF, less than 30% increased LDL and low exercise tolerance inhibited TNF-α expression by 31%, and IL-6 by 25%. At the same time, in general, the level of anti-inflammatory cytokines remained elevated compared to the norm. However, these studies involved patients with CHF without anemia syndrome, or it was not taken into account. The treatment of anemia in CHF is still not precisely defined. Apparently, this is due to a vague understanding of its pathogenesis, uneven results of clinical trials using drugs that stimulate erythropoiesis (erythropoietins) and different designs of studies using iron preparations. The aim of the work was to study the erythropoietic efficacy, safety of methoxypolyethylene glycol epoetin beta (MEB), its effect on hemoglobin, ferritin, EPO, N terminal pro brain natriuretic peptide (NT proBNP), cytokines and regression of symptoms in patients with CHF.

MATERIALS AND METHODS OF RESEARCH

84 patients with CHF NYHA II-IV FC with anemia were examined. The average age of the patients was 59.7±1.6 years. Of these, 54 were men and 30 were women. LVEF for patients with FC II was 45% or less, for FC III 40% or less, for FC IV 30% or less. Levels of ferritin, transferrin, erythropoietin, NTproBNP, and pathological cytokines were determined in all patients before and after 6 months of treatment. All patients were divided into 2 randomized groups: group I included 44 CHF patients receiving basic CHF therapy, and Group II (main group) included 40 patients CHF with anemia, who received basic OIE medications. MAB was prescribed to patients without ID. G was considered at a ferritin level of less than 100 mcg/l and 299 mcg/l if transferrin saturation was less than 20%. All patients were randomized into 2 groups: the main group -40 and placebo - 44 patients. According to the study protocol, the exclusion criteria were severe or malignant hypertension, acute cerebral circulatory disorders less than 12 months old, and acute MI. 6 months old, acute coronary syndrome, chronic obstructive pulmonary disease, mental disorders. All patients included in the study protocol received the following drug therapy prior to the start of the treatment program: ACE inhibitors, prolonged nitrates, diuretics, digoxin, beta blockers. MEB was prescribed to patients once a month at a dose of 0.60 mcg / kg subcutaneously (50 units) for 6 months. If the hemoglobin level increased by less than 10 g / l during the month, the dose was increased approximately by 25% each month until the individual Hb target level is reached. If the rate of increase in Hb levels exceeds 20 g/l per month or the concentration of Hb increases and approaches 120 g /l, the dose was reduced by about 25%. If the Hb level continued to increase, treatment was interrupted until Hb began to decrease. The clinical efficacy, laboratory and functional parameters, and safety of OIE administration were evaluated against the background of the use of basic traditional CHF therapy. They took into account patients' well-being, baseline level and dynamics of exercise tolerance according to bicycle ergometry and a 6-minute walking test. The follow-up of patients during OIE treatment continued for 6 months. Initially and after 6 months of follow-up, clinical, functional and laboratory studies were performed, including bicycle ergometry, a 6-minute walking test, biochemical blood tests (lipid composition, blood aspartate and alanine aminotransferases, creatinine and blood glucose), echocardiographic assessment of intracardiac hemodynamics. Serum cytokines interleukin-1(IL-1), IL-6, and tumor necrosis factor alpha (TNF-α) were determined using commercial test systems using enzyme immunoassay using a standard technique on automatic analyzers. The level of NTproBNP in the blood was determined by immobilization of antibodies using the Biomedica reagen. The level of EPO and ferritin in the blood was determined on automatic analyzers by the enzyme immunoassay method. Each patient gave their written informed consent to participate in the study. Throughout the study, patients kept observation diaries, in which daily information about their well-being, exercise tolerance, self-measured blood pressure and heart rate was recorded. In the clinical evaluation, the criteria for a good erythropoietic effect of MEB were considered to be an increase in Hb levels, regression of HF symptoms, a decrease in daily diuretic requirements, as well as an increase in exercise tolerance by 30-40% or more, and satisfactory by 20-30%, unsatisfactory by less than 20% compared to the initial data. The tolerance of OIE was assessed according to the following gradations: excellent - absence of local and general effects during a 6-month follow-up; a good one is in the presence of transient side effects that did not require drug withdrawal.; unsatisfactory - in the presence of side effects that required drug withdrawal. The quality of life (QOL) of patients with CHF was assessed using a specialized

Minnesota questionnaire on QOL in CH (Minnesota Living With Heart Failure Questionnaire, MLWHFQ).

THE RESULTS AND THEIR DISCUSSION

All patients showed good tolerance to OIE. Systolic and diastolic blood pressure and heart rate actually returned to normal or remained normal during the follow-up. Under the influence of OIE, there was a significant ($p<0.05$) regression of pathological LV remodeling. Thus, there was a tendency to decrease the final diastolic size (CDR) by 26.4% in the OIE group. ($p<0.05$). The LV final systolic size (CSF) decreased by 8.9% ($p<0.02$). LVEF in the MEB group increased by 23.3% ($p<0.02$). LV myocardial mass (MM), reflecting compensatory cardiac hypertrophy, was reduced in the MEB group by 8.97% ($p<0.05$) compared with the first group. The isovolumic relaxation time (IVRT) in group I was reduced by 8.6%, but not significantly, indicating a pronounced diastolic function that could not be corrected due to anemia. The initially reduced exercise tolerance (according to the 6-minute walking test) in the MEB group compared with the first group turned out to be significantly increased by 30% ($p<0.001$). The positive hemodynamic effect was accompanied by a distinct positive clinical effect of a 32-35% decrease in the daily need for diuretics, as well as an improvement in QOL. At the same time, in group I, CDR decreased by 13.4%, DAC – by 3.5%, breast cancer – by 3.2%, exercise tolerance - by 23.6%. Hb level in group I It increased significantly to 104.5 g/l, and in the group receiving OIE therapy it significantly increased to 113.7 g/l. Dynamics of Hb, EPO, ferritin, NTproBNP, and anti-inflammatory cytokines IL-1, IL-6, and alpha-TNF in blood serum in patients of both groups during 6-month therapy. In group II, compared with group I, the Hb level rose to 113.7±25 g/l, by 21.9% ($p<0.05$), and the EPO level rose to 28.9±11.3 IU/ml ($p<0.01$) compared with group I, where erythropoietin deficiency was observed. Moreover, the increase in EPO was accompanied by an insufficient decrease in ferritin levels to 102.7±21.2 micrograms/l with transferrin saturation of more than 20%. In group II, an increase in EPO levels in blood serum caused suppression of cytokine activation, an increase in IL-1 by 0.97% ($p<0.02$) and IL-6 decreased by 48.4% ($p<0.05$), TNF-α - by 39.7% ($p<0.01$). The ongoing changes have affected the level of NTproBNP in the blood, which decreased by 47.4% ($p<0.02$). The positive results caused a decrease in Reactive protein, creatinine in blood serum, and increased glomerular filtration rate by 30.5%. Moreover, an analysis of the results of a decrease in cytokine aggression showed that OIE reduced the level of IL-6 to a greater extent - by 48.4%, while OIE had no significant effect on the level of IL-1. a significant increase in its level by 0.97% ($p<0.02$). In general, a decrease in the activation of anti-inflammatory cytokines was accompanied by a reverse development of clinical symptoms of HF, regression of LV remodeling, and therefore LV CDR decreased by 26.4% ($p<0.05$) in 6 months, by 13.4% in group I; LVEF increased by 23.3% (from 30 ±1.2 to 37.0±3.3) in group II, and in group I, its increase was noted by 16.6%; breast cancer decreased by 8.97% ($p<0.05$) compared to group I, where this indicator decreased by 3.2%. And initially very low exercise tolerance according to the results of the 6-minute walking test increased in group I by 23.6%, and in group II by 42.8% ($p<0.001$). These positive changes in intracardiac hemodynamics, humoral immune status, and increased Hb levels were accompanied by a clear improvement in QOL. The presented data indicate the important role of the anemia syndrome in the pathogenesis of CHF. Established changes in Hb, EPO, ferritin combined with an increase in NTproBNP and cytokine aggression cause low effectiveness of traditional drug therapy, or developing its refractoriness and unfavorable long-term prognosis. Indeed, the presence of anemic syndrome in patients with CHF is accompanied by an increase in the severity of CHF to FC IV and a clear decrease in LV pumping function EF is 30% or less, and is associated with depression of inotropic heart function and low exercise tolerance. The results of the study also confirm the important pathogenetic significance of anti-inflammatory cytokines (IL-1b, IL-6, TNF-α) in the development of erythropoietin refractory and in the development of LV remodeling. At the same time, increased expression of TNF-α, IL-1b, and IL-6 is associated with the severity of CHF, decreased cardiac contractility, and increased LVEF, which are unfavorable independent factors for the prognosis of CHF. This was accompanied by a marked decrease in exercise tolerance.

CONCLUSIONS

1. Therapy of patients with chronic heart failure with anemia with a combination of basic drugs with methoxypolyethylene glycol epoitin beta causes regression of left ventricular remodeling: LV CDR decreased by 26.4% in 6 months ($p<0.05$), LVEF increased by 23.3% (from 30.0±3.3 to 37.0±2.1) ($p<0.02$), LVEF decreased by 8.97% ($p<0.05$), compared with group I exercise tolerance according to the test results with 6-minute walking, it increased by 42.8% ($p<0.001$).

2. During a 6-month prospective follow-up against the background of basic traditional therapy for chronic heart failure with the additional inclusion of methoxylene ethylene glycol epoitin beta, the positive dynamics of general clinical indicators leads to a significant decrease in the frequency of exacerbations and severity of heart failure, a decrease in the daily need for diuretics by 32-35%, an increase in exercise tolerance by 30%, and an improvement in the quality of life.

3. Under the influence of methoxypolyethylene glycol epoitin beta, significant positive changes in hematological and humoral parameters related to the severity of CHF were recorded: The hemoglobin level increased by 21.9%, as a result of normalization or increase in serum erythropoietin levels by 14.29%, there was a decrease in serum TNF-α levels by 39.7%, IL-6 by 48.4%, which was accompanied by a decrease in NT pro BNP in the serum of patients with CHF II-IV FC by 47.4%.

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