ANEMIA, HEART FAILURE AND TREATMENT WITH ERYTHROPOIESIS-STIMULATING AGENTS

Mariya Dimova, Elena Marinova, Liliya Stoyanova

Department of Propedeutics of Internal Diseases, Medical University of Varna
Clinic of Internal Medicine, St. Marina University Hospital, Varna,

ABSTRACT

Anemia is a common concomitant disease in patients with heart failure and is a cause for deteriorating prognosis and poor outcome of the disease. Anemia in the population of patients with heart failure is much more common than in the general population. It is estimated that it varies between 17 and 70% depending on whether the patients are hospitalized or not. The incidence of anemia among the hospitalized for acute heart failure patients in one Bulgarian study is 32.7%. The treatment of anemia with erythropoiesis-stimulating agents was initially promising, but the results that came out later showed disappointing data. Erythropoiesis-stimulating agents increase the thrombotic risk, the incidence of stroke, although an increase in the level of hemoglobin is found.

Keywords: anemia, heart failure, recombinant erythropoetin

Anemia is a common co-morbidity in patients with heart failure (HF) and is a cause of deterioration of the condition and the prognosis of patients (1,2,3). The incidence of anemia among the population of HF varies in the different studies from 17 to 70%. In any case, it is higher than the incidence in the non-HF population, which is estimated to be about 10% (4) according to the WHO definition. Although these values, hemoglobin <120 g/L for women and <130 g/L for men, have never been validated, erythropoietin rises exponentially below these levels (5).

We have obtained our information on the incidence of anemia among the Bulgarian population of patients with HF from the retrospective study of Angelov (6). A total of 324 consecutive patients at an average age of 67.6 ±11.2 years (118, 36.4% were women) hospitalized for acute HF were enrolled, 32.7% of whom had anemia. It was higher among women (40.7%) than
morbidly sъстояние сред българската populация пациенти със СН имаме от ретроспективното изследване на Ангелов (6). Обхванати са общо 324 последователи болни, хоспитализирани за остъра СН, на средна възраст 67,6±11,2 години (118, 36,4% са жени), като общо в цялата кохорта анемия се среща в 32,7%. По-висока е тя сред жените – 40,7%, отколкото сред мъжете – 28,2%, р=0,03. В друг, отново ретроспективен анализ на 444 болни с остъра СН, разглеждащ възрастовата разлика в честотата на анемията, се отчита по-висока честота при по-възрастните болни: при тези на възраст над 75 г. е 42%, а при тези под 75 г. е 27% (7). И още една интересна тенденция е отбелязана в същия анализ – покачване на честотата на анемията при болни на възраст над 80 г. за 5-годишен период – от 31% през 2006 г., на 40% през 2011 г., като подобна тенденция е налице и за други съпътстващи заболявания – захарен диабет, хронична обструктивна белодробна болест (ХОББ) и хронично бъбречно заболяване (ХБЗ). И въпреки тази висока и с тенденция за покачване честота на анемията сред хоспитализирани пациенти със сърдечно недостатъчност се оказва, че тя не е предиктор за рехоспитализация (8). От 314 хоспитализирани болни по повод остъра СН с анемия са 29,9%, хоспитализирани за една година са 21,3%. След прилагане на многофакторен регресионен анализ се установява, че предиктори за рехоспитализация са ХОББ, захарен диабет, лечение с бета-блокери, но не и анемия (8). Лечението на анемията при СН зависи много от етиологията с това състояние. Най-честата причина е железодефицитната анемия, но хроничното възпаление, което се наблюдава при пациентите със СН, е също често срещано. Немалка част от тези пациенти са и с ХБЗ. Лечението на анемията при пациенти със СН с рекомбинант еритропоетин беше задълбочено изследвано през последните няколко години. За съжаление, тези препрати не са показали първоначално очакванията благоприятен ефект, а дори се оказа, че могат да доведат до значими странични ефекти.

За периода между 2000 и 2010 г. са проведени 13 малки или рандомизирани, плацебо-контролирани проучвания, които целят да установят ефекта на лекарства, стимулиращи еритропоезата върху стойността на хемоглобина. Освен чистото цифрово изражение на тази стойност, оценяване е и клиничната стойност на лечението, като при по-голямата част от тези проучвания се отчита и по-добряване на симптомите на пациентите със СН. among men (28.2%), p = 0.03. Another retrospective analysis of 444 acute HF patients showed age difference in the incidence of anemia - a higher rate in older patients: 42% were 75 years or older and 27% -below 75 years (7). Another interesting trend was established in the same analysis - an increase in the incidence of anemia in patients aged 80 years and over for a 5-year period - from 31% in 2006 to 40% in 2011. The same trend was noticed for other concomitant diseases - diabetes mellitus, chronic obstructive pulmonary disease (COPD) and chronic kidney disease. Despite this high and increasing incidence of anemia among hospitalized patients with HF, it appears that it is not a predictor of rehospitalization for HF (8). Of the 314 hospitalized patients for acute HF anemic were 29.9%, and re-hospitalized for a one-year period were 21.3%. With multifactorial regression analysis applied, the predictors of rehospitalization turned out to be COPD, diabetes mellitus, treatment with beta blockers, but not anemia (8).

The treatment of anemia in patients with HF with recombinant erythropoietin has been extensively studied over the last few years. Unfortunately, these agents did not show the initially expected beneficial effect, and even led to some significant side effects. Between 2000 and 2010, 13 small or randomized, placebo-controlled trials studying the effect of erythropoiesis-stimulating drugs on the level of hemoglobin were performed. In addition to that, clinical improvement in the symptoms of HF was also assessed. A meta-analysis based on 11 randomized clinical trials (9) studying the effect of erythropoietin in HF patients and anemia included a total of 794 patients followed-up for periods between 2 and 12 months. Part of these patients were treated with erythropoietin and part of them with placebo. Two of the studies were placebo-controlled, and five - double blind. In five of the studies, epoetin was the erythropoiesis-stimulating agent and in six - darbepoetin. The results showed an improvement in functional capacity with an increase of 96.8 s in physical exercise duration (p<0.04) as well as an increase in the distance in the 6-minute walking test by 69.3 m (p<0.009) compared to controls. Significant changes were also observed in oxygen consumption, in the NYHA functional class, which decreased on average by -0.73, (p<0.001), left ventricular ejection fraction, BNP value (~227 pg/mL, p<0.001), as well
Anemia, Heart Failure and Treatment with Erythropoiesis-Stimulating Agents

Metaanalysis, which is based on 11 randomized clinical trials (9) and compares the effectiveness of treatment vs. erythropoiesis in patients with anemia and CHF, a total of 794 patients, were included between 2 and 12 months with erythropoiesis or placebo. Two of the outcomes were statistically significant: a decrease in the incidence of myocardial infarction, stroke and thromboembolic events. It should be noted, however, that in the STAMINA-HeFT (Study of Anemia in Heart Failure Trial) (10), treatment with darbepoetin did not result in an improvement in functional capacity. In the largest study, comprising n=319 patients, in this group of small-scale studies.

In the 1990s, the studies with erythropoietin agents aimed to identify additional beneficial effects of this treatment above just normalizing hemoglobin levels. The study that showed increased risk of death, non-fatal myocardial infarction, thrombosis in chronic dialysis patients with epoetin-α treatment was Normal Hematocrit Cardiac Trial (NHCT) (11). A total of 1223 patients with HF or ischemic heart disease were randomized. Half of them received epoetin to achieve and maintain hematocrit levels of 42% and the other half received epoetin to achieve hematocrit of 30% with an average treatment duration of 14 months. The primary endpoint of treatment was the time to myocardial infarction or death. After 29 months of follow-up, 183 deaths and 19 non-fatal myocardial infarctions were observed in the normal hematocrit (42%) group and 150 deaths and 14 non-fatal myocardial infarctions, respectively, in the lower hematocrit group (30%). The study was terminated earlier for safety reasons. The investigators concluded that for patients with HF or ischemic heart disease (IHD) and end-stage renal failure on dialysis, it is not recommended to raise the hematocrit level to 42% when treated with epoetin.

Later, two other studies - CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment) (12) and CHOIR (13) also raised the concern about cardiovascular safety with treatment with erythropoietin. CREATE is a three-year clinical trial that randomized 603 patients with eGFR 15-30 mL/min/1.73 m² and mild anemia - hemoglobin value of 110-125 g/L. HF hospitalizations were reduced by 44% (p = 0.005), but mortality for all causes was with borderline significance (p=0.047). The side effects of erythropoietin therapy were rare, with no loss of hypertension control, without increasing the incidence of myocardial infarction, stroke and thromboembolic events. It should be noted, however, that in the CREATE (Study of Anemia in Heart Failure Trial) (10), treatment with darbepoetin did not result in an improvement in functional capacity, and this is the largest study, comprising n=319 patients, in this group of small-scale studies.

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and 150 smyrtni slyachya i 14 nefatalni mikardni infarkta sotsvetno v grupata s po-niska stoynost na xematokritata (30%). Proouchvaniето е прекратено prеждевременно ot sobzhevanie za sigurnost. Izvodyt e, che pri pacientsi c klinichno izviena CN ili IBH na krohoniakliza ne se preporyvcha dostignane na niva na xematokrit do 42% s epoeeti.

Sled NHCT sa izneseeni i rezultatite na oche dve proouchvania - CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment) (12) i CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) (13), koto potvrdhavat opasenitata otnosno sverdleno-syдовata bezposonost pri izpolzvane na eritropoeti.

CREATE e klinichno izitvane, provodeno za periodot tri godini, koto sa randoimizirani 603 pacientsi c eGFR 15-30 ml/min/1.73 m² c s lekostennata anemija ssto stoynost na hemoglobinata na 110-125 g/L i koto sa razdeleni na dve rameni - v pryvoto, pacientit pronuvat epoetin-beta oche pri randoimizacija do dostignane na hemoglobinovite niva 130-150 g/L, a v vavorto - pronuvat epoetin, ako hemoglobinwit im pri vkluchwane e pod 105 g/L. Resultatite po otishhenie na pryvitchite kraini tseli, koto sa kompozitni pokazateli od osem sverdleno-sydivo iniwenta, ne pokaza razliki v dve grupi za prorsledwaeni period. Vtorichnite kraini tseli - levokamerona hipertrofia i prorgesia na bbrchenoto zabolvane, syyo sa bez razlika mezhdu dve grupi, dokato kachestvoto na zivot i funkcionaliin kapiacitet - signifikantno podobrenie v pryvata, s po-visoki扯e zelveni stoynosti na hemoglobinata gruba. Ne se usuvayva razlika po otishhenie na stranichnite efekti, no epizodite na povishena krivno naliyane i glavebolite sa biili po-chesti v pryvata grupa. Izvodite sa, che ranyoto i plino korigirane na anemichniy sindrom pri pacienti sa neprednala bbrchenata nedostatchnost ne vodi do namashvanie na sverdleno-sydivote sbityia.

CHOIR e proouchvane s podoben dizajn i vkluchva 1432 pacienti s ХБЗ, randoimizirani poravno na epoetiin-a do dostignane na hemoglobin 135 g/L ili 113 g/L. Proouchvaneeto e prodyljeno 16 meseca i e прекратено po-ранo od pirovonoahlano predvidenia srok poradi sobzhevanie za lipsa na pozitionelni i polzne rezultati. Obryonito, rezultatitite govorat za увеличение na kompozitnata kaiena tseli - syvrett, mikadren infarkt, hospitalizacija za sverdleno недостатчност i mouchen insult, c 34% (p<0.03) v grupata, poddyrrhana na po-visoki hemoglobunovite niva.
В метаанализа на Phrommintikul (14) се прави взаимовръзка на събраниите до момента данни за смъртността и достигнатите стойности на хемоглобин при лечение с еритропоетин при пациенти с анемия и ХБЗ. Девет са включените проучвания и резултатите показват увеличение на релативния риск от смърт по всички причини със 17% (p=0.03), тромбо зона на артерио-венозния достъп с 34% (p=0.0001) и по-лош контрол на кръвното налягане с 27% (p=0.004). Потвърждават се същите притеснения относно сърдечно-съдовата безопасност вследствие на покачването на хемоглобина. TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy) (15) е следващото (най-мащабно в тази насока) проучване, което сравнява 4038 пациенти със захранен диабет и ХБЗ, разделиeni на две групи – едната на дарбопоетин, а другата на плацебо лечение. Нивата на хемоглобини са 125 г/л срещу 106 г/л (p=0.0001); пациентите са разделeni на две групи – първата, n=2012 е рандомизирана на лечение с дарбопоетин до достигане на хемоглобинови нива около 130 г/л, а втората, n=2026 пациенти, получават дарбопоетин единствено при спадане на хемоглобина под 90 г/л. Проследяването е било за среден период от 29,1 месеца. Разликата с предходните проучвания е, че те сравняват ефекта от лечението с еритропоетин до постигане на по-високи или по-ниски нива на хемоглобин, а TREAT е плацебо-контролирано и се сравнява ефектът от лечение с еритропоетин спрямо плацебо. Първичните крайни цели са две – композитен сбор от смърт или сърдечно-съдово събитие (нефатален миокарден инфаркт, застойна сърдечна недостатъчност, инсул или хоспитализация за ишемична болест на сърцето) и смърт или достигане до краен стадий на бъбречно заболяване. Дарбопоетин показва неутрален ефект и в двете първични крайни цели, но рисъкът от мозъчен инсулт е двойно увеличен: 5% е той в рамото с активно лечение и 2,6% в рамото на плацебо с (HR, 1,92; 95% CI, 1,38-2,68; p<0,001).

След излизането на резултатите от горното проучване е направен нов метаанализ – Post-TREAT meta-analysis (16), който включва девет проучвания и е с акцент върху пациентите със СН на лечение с еритропоетин-стимулиращи агенти (ESA). Резултатите показват неутрален ефект на ESA по отношение на смъртност (95% CI: 0.89-1.21, p=0.68), влошаване на СН (95% CI: 0.82-1.10, p=0.46) спрямо плацебо лечението. Следващото, изцяло насочено към пациенти със СН толово двойно сляпо, плацебо-контролирано, рандомизирано клинично изпитване, с общо 2278 на HF patients treated with erythropoietin-stimulating agents (ESA). The results show a neutral effect of ESA on mortality (95% CI: 0.89-1.21, p=0.68) or worsening of HF (95% CI: 0.82-1.10, p=0.46) vs. placebo. The next big trial is RED-HF - double-blind, placebo-controlled, randomized, clinical trial comprising 2278 patients with HF with reduced ejection fraction (EF), NYHA class II-IV and hemoglobin levels 90-120 g/L (17). All patients were treated according to the current recommendations for the treatment of patients with HF. Patients with iron deficiency, defined as transferrin saturation <15%, were not included in the study or were included after iron deficiency had been corrected. Exclusion criteria were history of bleeding, creatinine> 3 mg/dL, blood pressure more than 160/100mmHg. Patients were evenly split to receive either darbepoetin alfa to reach hemoglobin up to 130g/L or placebo. Patients in the actively treated group were given darbepoetin at a starting dose of 0.75 μg/kg every two weeks until a hemoglobin of 130 g/L was achieved in two consecutive measurements; then the darbepoetine was administered once a month to maintain this value without exceeding hemoglobin levels of 145g/L. Iron status was checked every three months and if transferrin saturation dropped below 20%, oral or intravenous iron was administered. The mean age of the patients was 72 years, 41% were women, 65% were in NYHA class III or IV and mean EF was 31%, mean glomerular filtration rate was 45.7mL/m² the mean hemoglobin value for both groups was 112g/L. One month after randomization and throughout the whole period of follow-up, the hemoglobin level achieved with darbepoetin was about 15 g/L higher (between 124 and 134 g/L) compared to the placebo group (107-122 g/L), p<0.001. Patients were monitored for 28 months, and darbepoetin did not change the primary endpoint of the study, which was all-cause mortality and hospitalization for HF - HR 1.01; 95% CI, 0.90-1.13; P = 0.87. The lack of difference in the results between the two groups was also taken into account in the subgroup analysis. There was no significant difference in the secondary endpoints either - fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hypertension and HF. In fact, stroke was more common in the darbepoetin group, although the difference was not significant. Overall, thromboembolic events were significantly more in active treatment group compared to the placebo group - 13.5% versus 10% (p = 0.01). The incidence of neoplastic diseases was the same in both groups. Despite this lack of difference in clinical status, darbepoetin patients reported an improvement in the quality of life as assessed by the Kansas City Car-
Mariya Dimova, Elena Marinova, Liliya Stoyanova

patients, i.e. the RED-HF study (17). Results from this study were published in 2013, as the criteria for inclusion were reduced to an EF <40%, NYHA class II-IV and hemoglobin levels between 90 and 120 g/l. Since the patients were excluded those patients with iron deficiency, defined as ferritin levels <15%, were included in the study or were included after correction of the parameter. Exclusion criteria were further history of bleeding, creatinine >3 mg/dl, AH >160/100 mmHg. Patients were randomly assigned to receive either darbepoetin for hemoglobin up to 130 g/l, or placebo. Patients on active treatment received darbepoetin at a starting dose of 0.75 μg/kg every two weeks until reaching a hemoglobin level of 130 g/l, followed by monthly dosing to maintain this level, without exceeding levels of 145 g/l. The iron status parameters were evaluated every three months and in case of a decrease in ferritin levels below 20% iron was given orally or intravenously. The average age of the patients was 72 years, 41% were female, 65% were in NYHA class III or IV, and the average EF was 31%, the average glomerular filtration rate was 45.7 ml/min/m², the average hemoglobin level was 112 g/l for both groups. One month following randomization and during the whole follow-up the hemoglobin level achieved with darbepoetin was 15 g/l higher (between 124 and 134 g/l) compared to the placebo group, p<0.001. Patients were followed for 28 months and it was found that darbepoetin did not change the primary endpoint of the study, which was death from any cause and hospitalization in connection with heart failure – HR 1.01; 95% CI, 0.90–1.13; P=0.87.

The lack of difference between the two groups is also observed when analyzing the subgroups. No significant difference was found in the secondary endpoints treated with darbepoetin, which were fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hypertension and heart failure. In fact, cerebrovascular events were significantly more common in the actively treated group compared to the placebo group – 13.5% vs. 10% (p=0.01). Fatality of diomyopathy Questionnaire, although of borderline significance. It is important to note that all patients have been treated with iron supplements. The darbepoetin group received a larger dose of iron supplementation due to the higher requirements of erythropoiesis. There was no iron deficiency in either group.

As a whole, RED-HF, a large and important study, failed to demonstrate the benefit of treating patients with HF and anemia with erythropoietin. Although the increase in hemoglobin was associated with a slight improvement in quality of life, this was not entirely convincing, partly due to the increased incidence of thromboembolic events in the darbepoetin arm.

TREAT-like RED-HF patients with chronic kidney disease and diabetes mellitus (18) was a combination group between TREAT study patients (15) plus 816 patients from the RED-HF study (17) meeting the inclusion criteria of the TREAT study. Combination analysis of 4854 patients confirmed a nearly twice as high risk of stroke with HR 1.94, 95% CI 1.43-2.05, higher hemoglobin levels with darbepoetin, and neutral mortality, with HR 1.00, 95% CI 0.89-1.12 versus the placebo group. The incidence rate of stroke among these 816 TREAT-like RED-HF patients with diabetes mellitus, HF and chronic kidney disease was similar to that of the TREAT study - 5.4% vs. 2.4% (HR 2.07, 95% CI 0.98-4.38). Fig. 1 shows the incidence of cardiovascular events and mortality in the three stud-
Anemia, Heart Failure and Treatment with Erythropoiesis-Stimulating Agents

Address for correspondence:
Mariya Dimova
Faculty of Medicine
Medical University of Varna
55 Marin Drinov St
9002 Varna
e-mail: mdimovabg@yahoo.fr

These data show clearly that increasing hemoglobin to relatively high levels of erythropoietin has either a neutral or negative effect - deteriorating cardiovascular morbidity and mortality, an increase in thrombotic risk, and a risk of stroke (19). The US Food and Drug Administration (FDA) position from 2017 on the use of erythropoietin stimulating agents contains some serious concerns and warnings (20): "1. In controlled studies with erythropoietin, patients had a higher risk of death, serious side-effects of cardiovascular disease and stroke when hemoglobin is elevated to values higher than 110 g/L; 2. There is no defined level of hemoglobin, erythropoietin dose or dose strategy established in any study that does not increase this risk; 3. Use this dose of erythropoietin that is sufficient enough to reduce the need of hemotransfusions. The statement of the American Initiative on the Outcome of Kidney Disease and Quality of Life (KDOQI) (21) regarding the treatment of anemic syndrome is similar - discontinue treatment with erythropoietin at hemoglobin levels above 110 g / with CKD."

In summary, the FDA and KDIGO recommendations on the initiation of erythropoietin is to start this treatment in hemoglobin below 100 g/L in patients undergoing chronic dialysis and an individualized approach in patients with CKD who are not yet on dialysis treatment.

Taking into consideration the data from all small and short-term studies, large studies and meta-analyses of erythropoietin use in HF suggest that correcting anemia with erythropoietin does not improve the outcome of the disease and even increases the risk of thromboembolic events. The data do not support the use of erythropoiesis-stimulating agents to increase the level of hemoglobin in HF patients with reduced ejection fraction and mild to moderate anemia. This is the reason why the recommendations of the European Society of Cardiology (22) and the American Heart Association (23) for management of patients with HF place them in Class III, i. e. not recommended.
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