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RECENT ADVANCES IN MANAGEMENT OF ANEMIA IN HEART FAILURE

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Though treatment and outcomes have significantly improved over the past 15 years, morbidity and mortality of heart failure (HF) remains very high. In the setting of heart failure comorbidities such as iron deficiency is present in nearly 50% and anemia in 37%.[1,2] Prevalence of anemia in heart failure depending on the definitions used, varies from 15% to 56%.[3] In a retrospective study of outpatients with CHF, the prevalence of anemia, using the World Health Organization (WHO) definition (hemoglobin < 12 g/dL in women and < 13 g/dL in men), ranged from 9% to 19% in NYHA class I to II, to 79% in NYHA class IV.[4]

Anemia is defined as an absolute decrease in red blood cell mass, determined by extensive and costly analysis of radio labeled blood volume analysis. In routine practice derived parameters such as haemoglobin and hematocrit levels are used. Both are concentration dependent and in volume overloaded HF patients, hemodilution-induced "pseudo-anemia" is a common occurrence.[5,6] Anemia is multifactorial in origin as there is no single factor responsible for it. However, patients with concomitant diabetes mellitus, chronic kidney disease (CKD), older age, and with more advanced disease are at the highest risk of anemia.[7,8] Chronic inflammation in HF is supposed to be an important cause of functional iron deficiency and erythropoietin resistance. [9,10] Erythropoietin levels are excessively high in patients with HF but intrinsic bone marrow defects lead to bone marrow unresponsiveness to erythropoietin,which further increases susceptibility to anemia.[11,12] Patients with disproportionately high erythropoietin levels are associated with unfavorable outcome.[12] Medications prescribed in HF may contribute to anemia. In SOLVD (Studies of Left Ventricular Dysfunction) trial patients treated with enalapril had higher risk of anemia. This is because Angiotensin-converting enzyme inhibitors inhibit hematopoietic activity via N-acetyl-seryl-aspartyl-lysyl-proline.[13,14] There is evidence that carvedilol might decrease hemoglobin levels by blocking $ß_2$-adrenergic receptor.[15]

Anemia decreases oxygen carrying capacity and worsens symptoms of heart failure like dyspnea and fatigue;this further impairs effort tolerance and quality of life.[16] Increasing severity of anemia with increasing severity of HF symptoms has been well demonstrated in clinical trials.[17-19] In a large meta-analysis recruiting 153,180 patients with HF, the crude mortality risk of anemia was odds ratio of 1.96 (95% confidence interval: 1.74 to 2.21), and the adjusted hazard ratio was 1.46 (95% confidence interval: 1.26 to 1.69), with no difference between patients with reduced or preserved left ventricular ejection fraction (LVEF).[20] In many

patients of HF with anemia haemoglobin level increases with time. Resolution of anemia is hypothesized to be the effect of HF treatment per-se because of better control of fluid status and resolution of pseudo-anemia.[7]

Anemia has convincingly been shown to be a powerful predictor of re-hospitalization rates and survival in chronic heart failure.[21-26] Most studies have shown a linear relationship between hematocrit or haemoglobin and survival. SOLVD (Studies of Left Ventricular Dysfunction) trial reported 2.7% increase in the adjusted risk of death per 1% reduction in hematocrit and PRAISE (Prospective Randomized Amlodipine Survival Evaluation) trial described 3% increase in risk for each 1% decline in hematocrit.[22,23] In a study on significance of anemia among patients hospitalized with acute decompensated heart failure OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) documented that hemoglobin level independently predicted adverse events, even after adjustment for other covariates. For every 1 g/dl decrease in haemoglobin value, a 12% increase in the probability of death or re-hospitalization within 60 days of treatment was observed.[26] In patients of heart failure with preserved systolic function, anemia was found to be independently associated with adverse outcomes (adjusted hazard ratio: 1.6 to 1).[27]

Many treatment options offer to treat anemia, but none has been conclusively proven to improve morbidity and mortality. In patients with severe symptomatic anemia packed red blood cells transfusion is often considered. It has only temporary advantage but presents additional risks such as volume overload, hepatitis infection and ischemic events. Though data is limited on this subject in patients with HF, an observational studies on 596,456 persons showed that patients who received blood transfusions had worse clinical features and prognosis.[28] Another, though smaller study on 4,102 patients noted that transfusion seemed to be safe and even beneficial compared with propensity score-matched patients with HF who did not receive a blood transfusion.[29] As transfusion of blood presents risks of acute hemolytic reactions, infection, acute lung injury, allergic reactions, and the lack of evidence to suggest a liberal transfusion strategy in patients with heart disease, a restrictive transfusion strategy (trigger threshold of 7 to 8 g/dl) is recommended by the American College of Physicians.[30]

Awareness of high prevalence of iron deficiency around 70% in the anemic and 50% of the entire HF population and availability of new intravenous iron formulations provided opportunity to design trials to investigate effects of iron therapy. The earlier trials were conducted in patients with anemia but later it included patients with iron deficiency irrespective of anemia. IRONOUT (Oral Iron Repletion Effects On Oxygen Uptake in Heart Failure), a randomized placebo-controlled Phase II study, suggested that though oral iron offers practical advantages over intravenous but its use in HF is limited because of compliance due to gastrointestinal side effects and impaired iron uptake. This study on 225 HF patients received 150 mg of polysaccharide iron complex or placebo, twice daily for 16 weeks, resulting in a marginal increase of 11 µg/l of ferritin and 3% TSAT with oral iron. No significant effects on exercise capacity (measured according to maximal oxygen consumption [VO_2 max]) or N-terminal pro–B-type natriuretic peptide level were seen.[31]

Five studies employing intravenous iron, recruited patients based on Ferritin and TSAT level.[32-35] Overall results were encouraging in spite of differences in treatment strategies and follow-up. The overall results of the trials showed that treatment with intravenous iron improved New York Heart Association functional class, exercise capacity and quality of life in a short period of time. In FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) and CONFIRM-HF (Ferric Carboxymaltose Evaluation on Performance in Patients With Iron Deficiency in Combination With Chronic Heart Failure), though significant overall increases in Hb levels were observed, the treatment effect was similar in anemic and nonanemic patients.[34,35] EFFECT-HF (Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure), a randomized controlled trial of intravenous ferric carboxymaltose in 172 iron-deficient patients with HF documented increase in VO_2 max besides an increase in Hb level of 0.74 ± 0.17 g/dl after 24 weeks.[36] Recent guidelines of American College of Cardiology Foundation/American Heart Association and European Society of Cardiology recognize anemia as an important comorbidity in patients with HF.[37,38] The focus should be to determine the underlying etiology with special attention to iron deficiency and its treatment with intravenous ferric carboxymaltose.

Parenteral administered exogenous erythropoietin is approved for the treatment of anemia as a result of CKD or chemotherapy-induced anemia.[38] RED-HF (Reduction of Events by Darbepoetin Alfa in Heart Failure) trial studied 2,278 patients and is the largest study to date. Patients with symptomatic chronic HF (LVEF $\leqslant$ 40%) and anemia (Hb level 9.0 to 12.0 g/dl) were randomized to receive darbepoetinalfa (with a target of 13 to 14.5 g/dl) or placebo. Co-treatment with oral or intravenous iron was allowed in both groups. Though median Hb levels increased in the intervention group, yet no effect was observed on the primary composite endpoint of death or hospitalization for worsening HF or any of the other endpoints. As against that, rates of ischemic stroke (41 [4.5%] vs. 32 [2.8%]; $p = 0.03$) and embolic/thrombotic events (153 [13.5%] vs. 114 [10.0%]; $p = 0.009$) increased in those treated with darbepoetinalfa.[39,40] This raised further safety concerns because increased rates of ischemic stroke and thrombotic events with ESAs were also observed in patients with CKD and chemotherapy-induced anemia.[41,42] As many patients with HF already have a disproportionately high erythropoietin level associated with bone marrow

resistance to erythropoietin, administering even more erythropoietin to these patients may prove to be counter productive.[13,14]

Newer therapies are being investigated in this field. It is being appreciated that first stages of erythropoiesis are dependent on erythropoietin (EPO) but during erythroblasts stage, iron availability is essential as it is incorporated in haemoglobin. Most new therapies target either EPO or iron. Hepcidin is recognized as the master iron regulatorthat can be antagonized by decreasing its production, neutralizing it or by preventing hepcidin–ferroportin interaction. Agents neutralizing hepcidin are the most promising to date. A phase I study showed that a fully humanized monoclonal antibody against hepcidin (LY2787106) was well tolerated and resulted in increases in serum iron levels and TSAT in patients with cancer and anemia.[43]Another hepcidin-binding agent, the Spiegelmerlexaptepid (NOX-H94), was shown to increase serum iron levels in healthy persons subjected to inflammation by injection of lipopolysaccharides.[44]

Drugs directly targeting erythropoiesis include erythropoietin receptor–targeting drugs (receptor antibodies, fusion proteins, gene therapy, and mimetic peptides) and activin receptor ligand traps. Activin traps are recombinant fusion proteins consisting of the immunoglobulin G1 Fc domain linked to the extracellular domain ofactivin receptor IIA. These bind a number of transforming growth factor-ß superfamily ligands, including activin A and activin B, and thereby inhibit their signaling. Sotatercept, the most studied activin trap, was initially studied as an osteoporosis agent. Surprisingly, an increase in Hb level, red blood cell number, and hematocrit were observed.[45] However, increased expression of angiotensin II has also been proposed as one of the possible mechanisms of increased erythropoiesis by stimulating erythroid differentiation directly through the AT_1 receptor or via induction of erythropoietin production by the kidney.[46] Increased angiotensin II levels are clearly not desirable in an HF population and thus far, no studies in HF have been conducted.

Hypoxia-inducible factor (HIF) stabilizers are the most promising group of drugs. HIF is the master regulator of the cellular response to hypoxia. It is rapidly degraded in the presence of oxygen, but in low oxygen conditions, it induces transcription of >60 genes (including erythropoietin and vascular endothelial growth factor). HIF stabilizers can be administered orally and induce physiological erythropoietin levels.[47] Several Phase I and II studies in patients with CKD have shown promising results with increasing levels of Hb and decreasing levels of hepcidin after therapy.[48] One of the compounds with the most data available is FG-4592, or roxadustat. Roxadustat was recently shown to be effective in increasing Hb levels and to be superior compared with epoetinalfa in correcting anemia in patients with CKD in 2 different phase II trials.[49] However, caution is warranted and further studies are needed to address safety and efficacy.

To conclude, anemia in patients with HF is present in approximately one-third of patients with HF, and these patients have a worse prognosis and poor quality of life. The problem may be far more worse in our scenario. Anemia has multifactorial causes and may be due to nutritional deficiencies, renal disease, and volume overload. Although it is recommended that underlying disorders should be addressed, there is no evidence for the clinical benefit of increasing Hb levels as such. Intravenous iron treatment in HF appears promising for iron-deficiency and anemia. , The benefit is partly independent of Hb levels, and data on hard clinical endpoints are not yet available. As per to date, ESA therapy has shown neutral results on rates of death and HF rehospitalization and causes more ischemic strokes, which outweigh their marginal effect on symptom improvement.

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