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Review

# The role of correction of anaemia in patients with congestive heart failure: A short review

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## Abstract

Many patients with Congestive Heart Failure (CHF) are anaemic. This anaemia is associated with more severe CHF and a higher incidence of mortality, hospitalisation and morbidity. The only way to prove that the anaemia is causing this worsening of CHF is to correct it. We review here some of the published papers about correction of anaemia. Many studies show a positive effect of Erythropoietin (EPO) or its derivatives when administered in combination with oral or IV iron, with improvements in left and right ventricular systolic and diastolic function, dilation and hypertrophy and renal function. In addition, a reduction in hospitalisations, diuretic dose, pulmonary artery pressure, plasma volume, heart rate, serum Brain Natriuretic Peptide levels, the inflammatory marker Interleukin 6, soluble Fas ligand — a mediator of apoptosis, and improvements in New York Heart Association class, exercise capacity, oxygen utilization, caloric intake, Quality of Life and the activity of Endothelial Progenitor Cells, have been observed. Iron deficiency may also play an important role in this anaemia, since improvements in CHF have also been reported following treatment with IV iron alone. However, until the ongoing large placebo-controlled studies of the EPO derivative darbepoetin or IV iron are completed, we will not know whether these treatments really influence CHF outcome.

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## 1. Introduction

Despite the fact that much progress has been made in the treatment of Congestive Heart Failure (CHF), mortality and morbidity remain high [1]. One reason for this could be that anaemia, which is very commonly seen in CHF, may contribute to the worsening of CHF.

## 2. What is the rationale for the use of Erythropoietin (EPO) or its derivatives along with oral or IV iron in CHF?

1) Anaemia, if defined as a haemoglobin (Hb) of less than 12 g/dl, is present in about 30% of non-hospitalised CHF patients and in about 50% of hospitalised patients [2–4].

- 2) The presence of anaemia is associated with increased mortality, hospitalisation and morbidity independent of all other risk factors including renal failure and diabetes [2–4].
- 3) The more severe the anaemia the more severe the mortality, hospitalisation and morbidity [2–4].
- 4) Worsening of anaemia during the follow up period is associated with more severe mortality, hospitalisation and morbidity, on the other hand, an improvement in Hb is associated with less mortality, hospitalisation and morbidity [5–7].
- 5) In several small studies, correction of anaemia with Erythropoietin (EPO) or derivatives such as darbepoetin, administered in combination with oral or IV iron has been shown to be associated with an improvement in hospitalisation and morbidity. These include uncontrolled studies [8–13], randomised or case controlled but not placebo-controlled studies [14,15], single blind placebo-controlled studies [16–18] and some small double-blind placebo-

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controlled studies [19,20]. Some of the improvements seen in these small studies include: reduced hospitalisation [8,9,11,14,17,19,20], improved New York Heart Association (NYHA) class [8–11,13,14,16,18–20] reduced diuretic dose [8,9], reduced heart rate [10], improved caloric intake [10], reduced Brain Natriuretic Peptide (BNP) levels [17–20], increased oxygen consumption during exercise [10,19], improved exercise capacity [16–19], improved renal function [8,19], improved Quality of Life (QoL) [16,17,22,23], improved sleep apnoea [13], and reduced plasma volume [16]. In addition, improved left ventricular systolic function [7–11,15,17–20], improved right ventricular systolic function and pressure [18], improved right and left ventricular diastolic function [15,18], reduced left ventricular hypertrophy [15,20] and dilation [18,20], improved right ventricular pressure [18], improved end-systolic wall stress [18], reduced pulmonary artery pressure [20], reduced soluble Fas/Fas ligand (a soluble apoptosis-signalling molecule) [17], reduced inflammatory factor Interleukin 6 (IL6) [17], and improved adhesive and proliferative properties of circulating Endothelial Progenitor Cells [12] have also been reported.

However, in 3 multicenter double-blind placebo-controlled studies [21–23] which used the long-acting EPO derivative darbepoetin, outside of an improvement in Quality of Life score and renal function in one of them [22] and improvement in Patient Global Assessment in another [23] there was no statistical improvement in any other parameters including NYHA class and exercise tolerance. In the STAMINA–HeFT study which included over 300 patients [21] the analysis of time to death by any cause or first heart failure hospitalisation at one year showed a trend towards lower risk for the composite end point (hazard ratio 0.68  $p$  0.10) in the darbepoetin treated group versus placebo. A post hoc analysis showed that there was a statistically significant haemoglobin-associated increase in exercise duration in the darbepoetin group and in the placebo group. In the darbepoetin treated group NYHA class was significantly correlated with the change in Hb.

In view of the fears of adverse cardiovascular effects of Hb levels above 12 g/dl when EPO was used in cancer studies [24,25], and haemodialysis and chronic kidney disease (CKD) studies [26–30], it is important to note that none of the 3 multicenter darbepoetin studies mentioned above [21–23] reported any significant differences in adverse effects with darbepoetin compared to placebo, even though the mean Hb levels achieved were over 13 g/dl. These results were enough to stimulate the initiation of a multicenter placebo-controlled double-blind study of darbepoetin in 3400 CHF patients, the RED-HF study, which is currently ongoing.

### 3. The non-haematopoietic biological effects of Erythropoietin

The usefulness of EPO in CHF has been demonstrated in animal studies of CHF due to myocardial infarction and

other causes. Irrespective of improvements in Hb, EPO has been shown to improve endothelial dysfunction, increase neovascularization, reduce apoptosis of the cardiomyocytes, reduce oxidative stress and inflammation, reduce fibrosis, improve wound healing, prevent hypoxic damage, and prevent functional impairment of the heart [31]. At least some of these effects are due to the increase in number and activity of Endothelial Progenitor Cells (EPCs) from the bone marrow [12,31].

### 4. What is the rationale for the use of IV iron alone in heart failure?

Iron deficiency can be of two types, pure or functional. In pure iron deficiency there is a reduction in both % Transferrin Saturation (%TSat) and serum ferritin (this is associated with reduced total body iron stores). In functional iron deficiency, %TSat is reduced but the serum ferritin is normal or elevated and body stores are normal or elevated. In functional iron deficiency, there is a defect in release of iron from iron stores, and iron is therefore not available for transfer from storage sites in the macrophages to the blood and then to the bone marrow. As shown in two recent studies, CHF patients have been shown to respond to treatment of functional iron deficiency with IV iron, improvements in Hb, Left Ventricular Ejection Fraction (LVEF), NYHA class, Quality of Life, exercise capacity and renal function, and reduced heart rate, BNP, CRP and hospitalisation rates have been reported [32,33].

In another recent CHF study of IV iron in patients with functional iron deficiency with or without anaemia, although Hb levels did not improve significantly in response to IV iron administration, there was still an improvement in NYHA class, patient Global Assessment and oxygen consumption [34]. This suggests that the effect of iron on the heart may be related not only to improved oxygenation from the increased Hb, but also directly to its' effects on the mitochondria and other cellular elements that require iron, unassociated with the correction of the anaemia. Since pure or functional iron deficiency may be commonly seen in CHF patients with anaemia [35,36], this relatively inexpensive form of therapy may have an important role to play in the correction of the anaemia and/or iron deficiency in CHF.

### 5. What are the common causes of anaemia in CHF

Anaemia in CHF is likely due to a combination of several factors [2–4,37] including:

- a) chronic kidney failure in which Erythropoietin (EPO) production in the kidney is inappropriately low for the level of anaemia.
- b) elevated cytokines such as Tumor Necrosis Factor alpha (TNF $\alpha$ ) and IL6 which can cause four haematological abnormalities: reduced EPO production in the kidney, reduced activity of EPO in the bone marrow, hepcidin-induced failure of iron absorption from the gut, and

hepcidin-induced trapping of iron in iron stores in the macrophages.

Hepcidin is a protein released from the liver by IL6. It inhibits the protein ferroportin which is found in the gut and in macrophages and is responsible for the release of iron from these two types of cells into the blood. Therefore, if the ferroportin is inhibited, iron is not reabsorbed from the gut and not released from its' storage in the macrophages. This causes low serum iron and decreased delivery of iron to the bone marrow, resulting in iron deficiency anaemia.

- c) use of Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers both of which can cause reduced activity of EPO in the bone marrow, since angiotensin is a stimulator of erythropoiesis. ACE inhibitors also increase the levels of erythropoietic inhibitors in the blood, further inhibiting erythropoiesis.
- d) diabetes in which the EPO-producing cells in the kidney may be damaged early by glycosylation.
- e) haemodilution.
- f) gastrointestinal problems such as bleeding due to aspirin administration, malignant tumours, polyps or oesophagitis, or reduced iron absorption resulting from atrophic gastritis.

## 6. The cardiovascular and neoplastic consequences of high doses of EPO and its' derivatives in the anaemia related to cancer

In the treatment of anaemia in cancer patients, the use of very high doses of EPO may explain the increase in adverse effects reported. A recent meta-analysis of EPO therapy in cancer-associated anaemia in patients receiving chemotherapy showed an increased risk of venous thromboembolism (relative risk 1.57) and increased mortality risk (Hazard Ratio 1.10) [24]. In those patients treated for anaemia which was due to the cancer itself but without associated chemotherapy the mortality risk was even greater 1.29 [24]. The dose of EPO used to treat anaemia of cancer is 4–8 times the dose used in CHF and CKD. In cancer patients, the usual starting dose of EPO is 40,000 IU increasing to 60,000 IU/week [25] whereas in CHF and CKD patients the usual dose is 4000–10,000 IU/week of EPO or equivalent dose of darbepoetin. Part of the reason for the relative resistance to EPO and its' derivatives in cancer patients may be that the associated functional iron deficiency has not been treated.

## 7. The value of adding IV iron to EPO and its' derivatives for treating the anaemia of cancer, renal failure or heart failure

There is growing realization in chemotherapy-induced anaemia in cancer patients, that there is a role for IV iron in patients treated with EPO and its' derivatives [25]. In haemodialysis patients, administration of IV iron allows lower doses of EPO to be used to achieve the target Hb and increases the Hb more than treatment with EPO alone [38,39]. This

improvement occurs not only in patients with pure iron deficiency but also in patients with functional iron deficiency [38,39]. Similarly, in the anaemia of cancer, for those patients receiving EPO, IV iron may also be effective in both pure and functional iron deficiency [40–42] even where there are normal iron stores in the bone marrow [40]. Unfortunately, IV iron is rarely used for chemotherapy-induced anaemia of cancer patients, and consequently despite the high doses of EPO used, only about half of anaemic cancer patients respond to EPO at all. If IV iron is given, almost all such patients respond and most reach the target Hb of 12 g/dl [40–42]. Oral iron is far less effective than IV iron in EPO-treated patients [41,42]. The increased mortality associated with the high doses of EPO administered in cancer patients could also be due to increased rates of tumour progression, which has been reported in 8 studies in which these high doses of EPO were used [25].

Just as %TSat and serum ferritin appear to be poor predictors of who will respond to IV iron and who will not in EPO-treated renal failure patients [38,39], they are also poor predictors of Hb response in EPO-treated cancer patients [40]. IV iron alone, even without EPO, has been shown to increase Hb substantially in predialysis CKD patients [43,44] and in CHF patients, as discussed previously. It is possible that many anaemic cancer patients would respond to IV iron even without EPO, however, there are currently no studies of the efficacy or safety of IV iron alone in the anaemia associated with cancer.

## 8. What are the current US Food and Drug Administration (FDA) guidelines about anaemia treatment in chronic kidney disease and cancer?

In CKD there is still uncertainty about what the ideal Hb levels should be for EPO treatment [26–30,45–47]. There are no FDA guidelines for anaemia in CHF. However, FDA guidelines are available for CKD [48]. Since most anaemic CHF patients also have some degree of CKD [2–4,37] these FDA guidelines probably apply to most anaemic CHF patients as well. The guideline recommendations are as follows [48]:

### 8.1. FDA guidelines for chronic kidney disease

- 1) The risks for death and serious cardiovascular events are greater when Erythropoietic Stimulating Agents (ESAs) are administered to achieve higher target haemoglobin levels (13.5 to 14 g/dl) versus lower haemoglobin levels (10 to 11.3 g/dl)
- 2) Dosing should be individualized to achieve and maintain haemoglobin levels within the range of 10 to 12 g/dl.
- 3) If a patient is hypo-responsive (haemoglobin levels do not increase or reach the recommended range despite appropriate dose titrations over 12 weeks):
  - Do not administer higher doses and use the lowest dose that will maintain a haemoglobin level to avoid the need for recurrent blood transfusions.

- Evaluate and treat other causes of anaemia, and continue monitoring haemoglobin levels.
- Follow instructions for dose adjustments.
- Discontinue ESAs if the patient remains transfusion dependent.

### 8.2. FDA guidelines for cancer

1. ESAs shortened the overall survival and/or time-to-tumour progression in patients with various cancers.
2. Risks of shortened survival and tumour progression have not been excluded when ESAs are dosed with the intent to achieve haemoglobin levels <12 g/dl.
3. Use the lowest dose of ESAs needed to avoid red blood cell transfusions. Do not exceed the upper safety limit for haemoglobin levels of 12 g/dl.
4. Reduce the ESA dose by 25% when haemoglobin reaches a level needed to avoid transfusion.
5. Withhold dosing with an ESA when haemoglobin level exceeds 12 g/dl.
6. Restart dosing at 25% below the previous dose when the haemoglobin approaches a level where transfusions may be required.
7. Use ESAs only for the treatment of anaemia due to concomitant myelosuppressive chemotherapy.
8. Discontinue treatment with an ESA following the completion of a course of chemotherapy.
9. Use of ESAs in cancer patients have not been demonstrated in controlled clinical trials to improve the symptoms of anaemia, quality of life, fatigue, or well-being.

### 9. Conclusion

Only the results of large multicenter placebo-controlled studies of EPO or its derivatives or IV iron alone or a combination of the two, will be able to answer the question about the recommended doses of these agents as well as the ideal target Hb level in CHF. Nevertheless, there is growing evidence that a target Hb of 12 g/dl is probably a safe target in CHF and may offer many benefits to anaemic CHF patients. The mean Hb level in hospitalised CHF patients is around 12 g/dl [2–4,49,50]; 25% of hospitalised patients may have Hb levels between 5 and 10.7 g/dl [49] so that between one-quarter to one half of hospitalised patients with CHF may be candidates for anaemia treatment. However, in the vast majority of these patients the anaemia is currently not recognized and therefore not investigated, treated or followed up [7]. Indeed some reviews of treatment of acute hospitalised CHF often do not even include anaemia correction as a management strategy [51]. Whether treatment of anaemia should start with EPO or its derivatives or IV iron alone or the two together is still uncertain. Certainly giving the two together will allow lower doses of EPO or its derivatives to be used, reduce the amount of IV iron needed, increase the chances of reaching the target Hb of 12 g/dl and reduce costs. Giving IV iron alone without EPO might be enough to

reach the target Hb level in a substantial number of CHF patients.

Despite the suggestive evidence to date that control of anaemia with EPO or its derivatives or IV iron may be useful in patients with CHF, until the ongoing large placebo-controlled studies of darbepoetin or IV iron, are completed we will not know for certain whether such treatments really do influence CHF outcome.

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