Anemia and erythropoietin in cardiovascular disease
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Chapter 6

Should erythropoietin treatment in chronic heart failure be hemoglobin targeted?


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Erythropoietin (EPO) is traditionally known for its haematopoietic effect on the bone marrow, through salvaging erythroid precursors from apoptosis. Blunted EPO production can cause anaemia. In chronic heart failure (CHF) anaemia is prevalent and associated with a poor prognosis. Therefore, erythropoiesis stimulating agents (ESA’s) have been extensively investigated in a large number of experimental studies, and showed to possess cardioprotective effects as well. In addition, several studies have been performed to evaluate safety, feasibility, and clinical outcome of ESA treatment in patients with heart failure.

In the present issue of the European Journal of Heart Failure, Jin et al. present a meta-analysis on the effects of ESA on clinical outcome in patients with CHF. Seven clinical trials were included of which four evaluated darbepoietin alfa and three investigated other ESA’s. ESA treatment was associated with a mean increase in left ventricular ejection fraction of 7.55%. NYHA class improved by 1.2 and KCCQ scores improved by 4.61 points. The authors conclude that the treatment of anaemia with ESA in patients with symptomatic CHF can improve cardiac function, exercise capacity and quality of life.

The current study did not perform an analysis of hospitalization due to heart failure. In an earlier meta-analysis, the risk for hospitalization due to heart failure was proved to be decreased (risk ratio 0.59) in the ESA treated group. Similar to that study, Jin et al. were also unable to establish a significant protective effect of ESA treatment on overall mortality, although a strong trend was observed. The study by Jin et al. is particularly interesting because it strongly suggests that ESA treatment may also improve quality of life.

But how can these potentially beneficial effects of ESA on cardiac function and clinical outcome in heart failure patients be explained?

With the discovery of a functional EPO receptor in tissue other than bone marrow, it was hypothesised that EPO elicits extra-hematopoietic effects as well. This was supported when a functional EPO receptor was discovered in heart tissue. Exogenous stimulation of these receptors in animal models with human recombinant EPO proved to decrease infarct size and ameliorated left ventricular function. These results might be explained by the finding that stimulation of the EPO receptor in the heart increases neovascularisation through increase of vascular endothelial growth factor (VEGF) and endothelial progenitor cells (EPC) homing to the myocardium. In CHF patients myocardial cells grow (hypertrophy) without a concomitant growth of the number of capillaries; subsequently leading to a demand-supply mismatch of oxygen and nutrients. Therefore, especially in chronic heart failure, ESA’s might be an attractive approach to improve this demand-supply mismatch.
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In addition to delayed neovascularisation after ischemia, EPO exerts antiapoptotic effects as well. Following myocardial infarction, EPO prevents apoptosis of cardiomyocytes and this in turn might decrease permanent damage and loss of function. These findings led to the design of a randomized multicentre study to evaluate whether EPO can attenuate postmyocardial infarction loss of cardiac function.\(^8\)

Interestingly, the beneficial effects of ESA’s on myocardial function have been described with doses that did not influence haemoglobin and/or haematocrit.\(^9\) In addition, similar cardiac effects were demonstrated with carbamylated erythropoietin (CEPO), a non-erythropoietic derivative of erythropoietin.\(^10\) Therefore, the observed beneficial cardiac effects of ESA might not only originate from increased haemoglobin levels, but are rather due to the previously described non-haematopoietic effects of EPO. The definite mechanisms still remain elusive.

**Safety-issues**

The Trial to Reduce Cardiac Events With Aranesp® Therapy (TREAT), performed to evaluate cardiovascular events in chronic kidney disease, showed that treatment with darbepoietin alfa was associated with an increased risk of stroke and more hospitalisations.\(^9\) In a study in patients with stroke, ESA’s were associated with an increased incidence of stroke recurrence.\(^11\) Therefore, concerns are raised about the safety of ESA’s. It is unclear however whether the safety issues are similar in patients with heart failure.\(^12\) Jin et al. did not draw any conclusion about safety. They do however see a non-significant decrease in mortality in favour of the ESA treated group. Also, in the studies in patient with renal caused anaemia, the major aim was to improve clinical outcome with ESA’s through the increase of haemoglobin. In heart failure however, beneficial effects of ESA’s are probably caused by its non-haematopoietic effects.\(^13\) Therefore, new agents like CEPO are being developed that could elicit the beneficial protective effects of EPO, without its undesirable erythropoietic side effects.\(^14\)

Taken together, the study by Jin et al. confirmed that EPO has a large therapeutic potential in patients with heart failure and indicates there is a growing urge for larger studies to be performed. The ongoing Reduction of Events With Darbepoetin Alfa in Heart Failure (RED-HF) trial is a large multicentre, double-blind, randomized, placebo controlled trial, that will hopefully provide a definitive answer to the question whether erythropoietin in anaemic chronic heart failure will decrease mortality and morbidity.\(^15\) It should however be noted that in RED-HF erythropoietin is titrated to attain certain haemoglobin levels. So far about two thirds of the patients are recruited and the expected date of completion is in 2012. With the development of novel agents that have sim-
ilar cardioprotective effects, without increase of haemoglobin, the application of these agents might even be widened to non-anaemic heart failure patients as well.
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References


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