Anemia and heart failure: Is there still a role for erythropoiesis-stimulating agents?

Anemi ve kalp yetersizliği: Eritropoiezi uyaran ajanların hâlâ bir rolü var mı?

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After early reports of erythropoiesis-stimulating agents (ESAs) having success correcting anemia in heart failure (HF), the Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) study, a large phase III trial, demonstrated that darbepoetin alfa was not able to improve clinical outcomes in patients with HF who had reduced ejection fraction and mild to moderate anemia, and indeed, it led to an excess of thromboembolic events. [1] In view of those results, recent guidelines do not recommend ESAs for the treatment of anemia in HF patients. [2]

Concerns regarding the safety of ESA therapy had been already raised for patients with chronic kidney disease (CKD). [3,4] In fact, in 2011, the US Food and Drug Administration issued a boxed warning for the label of ESAs for patients with CKD recommending initiation of ESA treatment when hemoglobin level was less than 10 g/dL (previously, 10-12 g/dL). Individualized dosing and using the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions were also recommended. [5] This has been addressed extensively in earlier review articles. [6-8]

At present, it remains unclear whether it is the dose of ESA administered, the level of hemoglobin achieved, or a hyporesponsiveness to therapy that explain these adverse outcomes.

It is well known that anemia is common in HF and is associated with an increased mortality risk. [9] The pathogenesis of anemia in HF is multifactorial, and includes renal dysfunction, chronic inflammation, iron deficiency, and erythropoietin (EPO) deficiency. [9,10] Patients with HF actually have markedly elevated plasma EPO level, which is related to the severity of HF and which is a prognostic marker for impaired survival, independent of hemoglobin levels. [11-13] Impaired renal perfusion, fluid retention, and general hypoxia are all factors that can contribute to increase in serum EPO. [14,15] Moreover, the presence of EPO resistance in the bone marrow, due to a state of inflammation, or of iron, vitamin B12, or folate deficiency, may explain why, although increased in absolute terms, plasma EPO levels are still relatively low and inadequate to stimulate hematopoiesis in the bone marrow. [10,16] Based on these data, it was postulated that ESAs could be a useful tool in the treatment of anemia in HF patients. A better understanding of the etiology of anemia, the optimal hemoglobin target, and of the comorbidities in which use of ESAs should be avoided, would likely permit one to identify the potential beneficial effect of ESAs that still might have a rationale in the treatment of HF. It might also be interesting to investigate the effect of ESA therapy in patients with HF with preserved ejection fraction, as it has pathophysiological and clinical expression that is substantially different from HF with reduced ejection fraction. This may imply different impact on treatments. [17]

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REFERENCES


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