President's Page

Anaemia in Chronic Heart Failure: Is There a Rationale to Treat?

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Chronic heart failure (CHF) is an epidemic phenomenon in the western world, adversely affecting patient morbidity, mortality and quality of life. Although much has been achieved in CHF management, more than 1 million hospitalisations were reported in Europe in 2004 and the mortality of the syndrome remains high. For this reason, to improve prognosis, special attention has been paid recently to the treatment of various co-morbidities (i.e. anaemia, renal dysfunction, depression) that contribute to the clinical worsening of CHF. Anaemia is present in up to 25% of patients with chronic heart failure, and is strongly associated with dismal prognosis, increased risk of hospitalisation and reduced exercise tolerance. Anaemia in CHF has a multifactorial aetiology, including impaired secretion of erythropoietin (EPO) by the kidneys, haemodilution associated with fluid retention, intestinal malabsorption with subsequent iron deficient uptake, proteinuria with EPO and ferritin loss, and chronic use of anti-platelet or anti-coagulant drugs such as aspirin and coumadin.[1] Moreover, excessive activation of proinflammatory/pro-apoptotic mediators, such as TNF-alpha and interleukin-6, may cause EPO resistance and generate a condition called "anaemia of chronic illness". On the other hand, plasma levels of EPO are paradoxically increased in CHF and are a powerful predictor for poor prognosis, independently of haemoglobin concentration. However, the importance of this observation as well as the functional integrity of this increased intrinsic EPO remains unexplored.[2]

The triad of chronic heart failure, anaemia, and chronic renal dysfunction has recently been called the "cardiorenal anaemia syndrome".[3] Each component of this syndrome predisposes to further deterioration of the others, creating a vicious circle. Thus, low haemoglobin levels cause progression of both renal dysfunction and cardiac remodelling, and *vice versa*. A pathophysiological explanation of this process is the fact that anaemia causes tissue hypoxia, which leads to peripheral vasodilatation. This biological effect decreases peripheral vascular resistance and blood pressure and leads to an increase in sympathetic stimulation, heart rate, and stroke volume. The resulting renal vasoconstriction decreases renal blood flow and glomerular filtration rate, and therefore activates the renin-angiotensin-aldosterone system and vasopressin production. Subsequently, the plasma volume expands, the left ventricle dilates and develops hypertrophy, with subsequent cardiomyocyte loss through necrosis and apoptosis. As CHF develops, it is precipitated by the direct action of the up-regulated renin-angiotensin-aldosterone system, and also by pro-inflammatory cytokines, all of which beget a deterioration of CHF. Renal perfusion drops even more, and the vicious circle continues to cause cardiorenal damage.

In this context, a essential therapeutic target in order to interrupt the vicious circles of cardiorenal syndrome and protect the failing heart from progressive cardiac remodelling is to restore haemoglobin levels. This hypothesis has been successfully tested in recent clinical studies. In patients with beta-thalassaemia, it has been shown that the restoration of haemoglobin levels by frequent blood transfusions, as well as intense iron chelation and medical treatment, led to a dramatic improvement in 5-year survival (48%).[4] This prognosis is similar to that seen in the

general population of patients with heart failure, although it was known that most patients with thalassaemia and heart failure die within one year from the onset of symptoms.[5]

Other clinical observations in CHF have demonstrated significant improvement by the use of novel erythropoietic agents, such as the human recombinant EPO analogues. EPO administration, when combined with intravenous or oral iron, has beneficial effects on left ventricular systolic function and exercise capacity in anaemic CHF patients, resulting also in a significant reduction of re-hospitalisation rates.[6-8] More recently, in a single-blind, randomised trial (American Heart Association Scientific Sessions 2006 award),[9] our group showed that darbepoietin-alpha administration also modulates beneficially abnormal peripheral immune/pro-apoptotic responses in anaemic CHF patients, with a parallel improvement in their diastolic and systolic cardiac function and quality of life.

EPO has anti-apoptotic effects on a variety of cell types, including neurons, endothelial cells, smooth muscle cells, and cardiomyocytes. EPO exerts a significant anti-apoptotic effect on cardiac tissue after ischaemic injury. Moreover, EPO mobilises endothelial progenitor cells from the bone marrow and acts as an angiogenic factor. Both anti-apoptotic and angiogenic effects contribute to the cardiac protection of EPO during post-myocardial infarction cardiac dysfunction. These pleiotropic effects may explain the clinical benefits of EPO use in CHF beyond its erythropoietic role.[10]

The beneficial effects of EPO combined with oral or intravenous iron provide additional opportunities to improve quality of life and prognosis in anaemic CHF patients. New trials with a longer follow up of patients, as well as determination of the optimum dosing regimen and treatment time interval, are warranted, but already existing data are very encouraging in terms of therapeutic gains in this widespread comorbidity.

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