EDITORIALS

Is Anemia a Marker of Advanced Disease or a Therapeutic Target in Heart Failure?

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"After all, in spite of opinion, prejudice or error, time will fix the real value upon this discovery."
Sir William Withering, Birmingham, 1785

Heart failure is a health-care problem of increasing magnitude and the principal cause of hospital admissions in the developed world. Despite recent therapeutic advances, short-term mortality remains very high.[1] The introduction of beta-adrenergic blocking agents associated with angiotensin converting enzyme (ACE) inhibitors led to a substantial improvement in prognosis.[2] The benefit derived from beta blockade encouraged the search for new drugs that would inhibit renin-angiotensin and sympathetic system activation more fully and also permit modeling of other factors activated in heart failure such as inflammation and endothelial dysfunction. However, in the last 4 years research into the benefits of new drugs has produced neutral results. New ACE inhibitors, endothelin and tumor necrosis factor (TNF) alpha inhibitors and angiotensin receptor antagonists[3] have failed to live up to expectations. This suggests we are unlikely to obtain additional benefits from trying to increase the blockade of circulating neurohormones. In fact, many authors have hastened to suggest that this line of research has been exhausted and that we need to look for other therapeutic options.

The persistence of substantial ventricular remodeling in spite of optimal treatment has been associated with worse prognosis in heart failure.[4] In recent years, research has focused on possible interventions that might block the signals that activate the mechanisms that mediate progressive ventricular remodeling.[5] In spite of our efforts, we still have a long way to go before this becomes a reality that enables us to generate new drugs.

The lack of new treatments has directed research towards a more profound analysis of the factors that affect the prognosis of heart failure and anemia is one of these. In fact, anemia is frequent in patients with heart failure, above all in advanced phases of the illness.

PREVALENCE

The prevalence of anemia in heart failure varies greatly and can range from 5% to 55% according to series.[6,7] Such a wide range is due to the different diagnostic criteria used and differences in the populations studied. The presence of anemia tends to be greater in epidemiologic studies with older patients, patients in worse New York Heart Association (NYHA) functional classes and greater comorbidity; in pharmacologic studies, with patients who tend to be younger and to have been selected, the prevalence of anemia decreases notably. One factor that greatly increases prevalence of anemia is chronic renal insufficiency, which in heart failure is usually multifactorial and to which ventricular dysfunction contributes *per se* and in its etiology, especially arterial hypertension and associated diabetes mellitus. Lupón et al[8] found 30% prevalence in a population with a mean age of 64 years, predominantly male, with few cases of associated renal insufficiency, in a tertiary level hospital and their data fall within the range described. In older patients, with greater incidences of women and of associated renal insufficiency, the prevalence may be much greater.

PROGNOSTIC IMPLICATIONS

In recent years, numerous studies have linked a decrease in hemoglobin with an increase in mortality.[9-11] The fact that correction of anemia can open the door to new treatments is still controversial. We must remember that anemia in heart failure can be secondary to a wide range of causes. At the onset of the illness it is highly unlikely that anemia will have an impor-

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tant prognostic implication and in some cases it may even be secondary to blood loss in patients receiving aspirin. In fact, in series with relatively young patients referred for heart transplantation, the presence of anemia was not a determining factor in global mortality.[6]

As heart failure progresses, much comorbidity that can favor the appearance of anemia is associated with it. One retrospective study found that in 98% of patients anemia was not due to heart failure alone but to other causes, the most frequent of which was associated chronic renal insufficiency, followed by iron,[12] folic acid or vitamin B_{12} deficiency. What does appear certain is that in advanced heart failure numerous mechanisms can cause anemia: for example, cytokine activation that favors cachexia, chronic malnutrition, hemodilution, worsening renal insufficiency that reduces cardiac output, decreased bone marrow perfusion that diminishes its regenerative response and, finally, the heart failure treatment itself.[13] In reality, all these mechanisms can be found simultaneously in terminal heart failure and interact, making it difficult to establish the ultimate cause of anemia and determine its real prognostic implications.

ANEMIA AS A THERAPEUTIC TARGET

Various studies have shown that, because it reduces the capacity to transport oxygen, anemia can contribute to a worsening of symptoms, induce hypoxia and even favor neurohormonal activation. Moreover, in patients with heart failure, mild or moderate degrees of anemia may well have greater repercussion on the symptoms than in healthy patients. Some studies report a significant correlation between low levels of hemoglobin and exercise capacity[14] that disappears when hemoglobin levels are >13 g/dL. This would indicate that exercise tolerance depends largely on hemoglobin levels, especially when these are low.

Undoubtedly, correction of anemia can improve symptoms as it corrects oxygen supply to the tissues, especially in patients with heart failure secondary to ischemic heart disease in whom ischemia can aggravate dyspnea. Pilot studies suggest that recombinant erythropoietin (rHuEPO) treatment improves functional class, ventricular function and quality of life in these patients and reduces the need for oral or intravenous diuretics. In some studies, albeit with limited numbers of patients, erythropoietin treatment has also been associated with reduced mortality.[15,16]

However, despite the aforementioned clinical repercussions, anemia may still only be a marker of severity that appears as heart failure progresses or comorbidity increases. This is supported by the fact that low hemoglobin levels are more frequent in patients in NYHA functional classes III and IV. Although correction of anemia can improve symptoms, evidence that this implies a reduction in mortality is unclear, bearing in mind that the proposed rHuEPO treatment can increase the risk of thrombosis and arterial hypertension.[17] Current follow-ups of rHuEPO studies are relatively short (<1 year) and benefits of this treatment should be analyzed in the longer term as this may be controversial in patients with ventricular dysfunction secondary to ischemic heart disease. Consequently, in spite of initially hopeful results, before following up this new line of treatment we should wait until current studies have been completed. As has happened before with heart failure, it may be that the improvement in symptoms is not associated with a reduction in global mortality.

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