Increase in Anti-Inflammatory Cytokine Levels in Chronic Heart Failure: A Measure of Treatment Success or Failure?

To the Editor:

Gullestad and colleagues report on the effects of intravenous immunoglobulin given to patients with chronic heart failure (CHF). They demonstrated that intravenous immunoglobulin treatment is associated with an increase in soluble tumor necrosis factor-α receptors (sTNFRs) 1 and 2, interleukin-1 receptor antagonist (IL-1RA), and interleukin-10 (IL-10). There were no significant changes in inflammatory cytokine levels (tumor necrosis factor-α and IL-1β) after active treatment. The authors conclude that intravenous immunoglobulin therapy leads to a net anti-inflammatory effect in CHF, and they propose that this should be regarded in a favorable light.

A degree of caution should be exercised, however, when interpreting the significance of elevated levels of anti-inflammatory cytokines and their receptors in the context of CHF. It is well known, for example, that circulating sTNFR1 and 2 concentrations are raised in this condition, positively correlate with disease severity, and predict mortality. Furthermore, it is contentious that sTNFRs act only to reduce inflammation, because they can also stabilize and prolong the bioactivity of tumor necrosis factor. Similarly, sTNFRs, IL-10, and IL-1RA levels are increased in CHF patients and, again, relate to disease severity. Increased cytokine expression, whether inflammatory or anti-inflammatory, therefore seems to reflect a worse disease state.

With the exception of peak workload, there was no significant difference in any clinical or hemodynamic parameters between the active treatment and placebo groups in Gullestad et al’s study. In the absence of clear clinical improvement, treatment-related increases in anti-inflammatory cytokine levels in patients with CHF might even be seen as undesirable. Lending some support to this interpretation, β-blocker therapy, which is established as having important benefits in CHF in clinical, hemodynamic, and prognostic terms, has been shown to reduce circulating sTNFR2 and IL-10 levels. Given these contradictory findings, it becomes clear that a crude ratio of pro- and anti-inflammatory cytokine levels is not an entirely satisfactory measure of treatment benefit.

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3. Ferrari R, Bachetti T, Confortini R, et al. Tumor necrosis factor soluble receptors (sTNFRs) 1 and 2, interleukin-1 receptor antagonist (IL-1RA), and interleukin-10 (IL-10). There were no significant changes in inflammatory cytokine levels (tumor necrosis factor-α and IL-1β) after active treatment. The authors conclude that intravenous immunoglobulin therapy leads to a net anti-inflammatory effect in CHF, and they propose that this should be regarded in a favorable light.

Response

We appreciate the comments concerning our study of intravenous immunoglobulin (IVIG) and congestive heart failure (CHF). Bolger and Sharma argue that because levels of interleukin (IL)-10, soluble tumor necrosis factor receptors (sTNFRs) and IL-1 receptor antagonist are raised at baseline, a treatment-related increase in these mediators might not be beneficial in CHF. However, although raised levels of these mediators are positively correlated with disease severity in CHF, this does not necessarily mean that they are promoting myocardial failure. In fact, although sTNFRs seem to be stable and reliable plasma markers of TNF-α activity, therapeutic interventions that increase sTNFRs, particularly when there is no accompanying increase in TNF-α, may lead to impaired TNF-α activity with potential beneficial effects in inflammatory disorders. We are aware of the fact that sTNFRs may not only neutralize but also stabilize TNF-α. However, the latter effect seems to occur in situations with high TNF-α/sTNFRs ratios and not in plasma, where such ratios are low. Indeed, several studies suggest that the therapeutic administration of sTNFRs has anti-inflammatory effects. Likewise, although increased plasma IL-10 levels may reflect the severity of CHF, such an increase may be “inadequate” compared with the marked rise in TNF-α. Again, therapeutic interventions that increase IL-10 may have an anti-inflammatory net effect, with potential beneficial effects on cardiac performance, as suggested by some animal studies cited in the IVIG article. In the IVIG study, there was a significant improvement of left ventricular ejection fraction during IVIG that was positively correlated with the rise in anti-inflammatory mediators during such therapy, further supporting a potential positive effect of these mediators on cardiac performance.

Despite “state-of-the-art” cardiovascular treatment, CHF is a progressive disease with high mortality and morbidity, suggesting that important pathogenic mechanisms remain active and unmodified by the present treatment modalities. Although Bolger and Sharma are referring some suppressive effect of β-blockers on inflammatory and anti-inflammatory cytokines in a non-placebo-controlled study in patients with idiopathic cardiomyopathy, we have shown that β-blockers have no effect on cytokine levels compared with placebo in CHF patients. Although IVIG is not necessarily the “drug of choice,” the IVIG study suggests the potential for immunomodulating therapy in CHF patients in addition to “optimal” cardiovascular treatment regimens. However, further research in this area must more precisely identify the most important components in the immunopathogenesis of CHF to develop more specific immunomodulating agents in this disorder.

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