Immunomodulating Therapy for Heart Failure

Gullestad L, Aass H, Fjeld JG, et al. Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. Circulation 2001;103:220–5.

Study Overview

Objective. To determine if intravenous immunoglobulin (IVIG) downregulates inflammatory responses and improves left ventricular function in patients with coronary heart failure (CHF).

Design. Double-blind, randomized controlled trial.

Setting and participants. Forty patients with chronic stable CHF for more than 6 months were recruited for the study. Patients were included if they were classified in New York Heart Association (NYHA) functional class II/III, had a left ventricular ejection fraction (LVEF) of less than 40%, did not change medications in the previous 3 months, and were receiving optimal medical treatment and considered unsuitable for surgical intervention. Exclusion criteria were evidence of myocardial infarction or unstable angina during the previous 6 months and significant concomitant comorbidities (eg, infections, pulmonary disorders, connective tissue disease).

Intervention. Subjects were randomized to receive either IVIG or placebo, administered daily for 5 days and thereafter as monthly infusions for a total of 5 months. IVIG doses or equal volumes of placebo were determined by the patient's weight.

Main outcome measures. Immunologic variables, including tumor necrosis factor–α (TNF-α), interleukin-10 (IL-10), soluble TNF receptors (sTNFRs) p55 and p75, IL-1 receptor antagonist (IL-1ra), and IL-1β; plasma levels of N-terminal pro–atrial natriuretic peptide (Nt-pro-ANP); LVEF and right ventricular ejection fraction, assessed by gated radionucleotide ventriculography; hemodynamic variables, assessed by right-side heart catheterization; exercise testing and measurements of oxygen consumption (V_{O_2}); clinical evaluation based on NYHA classification; and quality of life as assessed by the McMaster Overall Treatment Evaluation questionnaire. Measurements were performed at baseline and at the end of the study.

Main results. Subjects were divided evenly between study groups, with similar demographics between groups at baseline. More intervention patients were receiving β blockers (17 in the intervention group versus 13 in the placebo group), while more controls were receiving digitoxin (7 versus 9). Follow-up was completed for all patients. One treatment-group patient dropped out after 3 weeks because of paroxysmal atrial fibrillation.

Patients who received IVIG showed increased levels of IL-10, IL-1ra, and sTNFRs as well as decreases in IL-1β/IL-1ra and TNF-α/sTNFRs ratios compared with controls ($P = 0.001$ for TNF-α/sTNFRs ratio; $P < 0.001$ for the other measures). LVEF increased by 5 EF units after IVIG therapy ($P < 0.01$ versus baseline), while no change was noted in the placebo group. However, when the difference in changes between groups was measured, the P value was 0.076. The 4 intervention patients with the lowest LVEF showed no benefits from IVIG, and IVIG effects were independent of causes of heart failure (coronary artery disease and idiopathic dilated cardiomyopathy). A positive correlation was seen between LVEF changes and changes in IL-1ra, IL-10, and sTNFRs. Hemodynamic variables decreased slightly in the IVIG group but not in the placebo group after initiation of treatment. Peak V_{O_2} during exercise and peak workload also improved in the IVIG group. Of note, functional status as assessed by NYHA class and global estimate of changes in the quality-of-life questionnaire showed improvement in both groups. Plasma levels of Nt-pro-ANP, which correlate with CHF severity, decreased significantly after treatment with IVIG ($P < 0.001$ versus baseline).

Conclusion

IVIG decreases inflammatory responses that occur in CHF and modestly improves LVEF.

Commentary

The link between inflammation and heart disease has been the focus of much recent attention, but the exact significance of the association remains unclear [1]. This interesting study by Gullestad et al is the first randomized controlled trial to examine how immunoglobulins affect patients with CHF. Strengths of the study include its double-blinded design and low patient drop-out rate. However, some significant confounding variables may have been present that could explain certain outcome differences between study groups. For example, in the placebo group more patients were taking

digitoxin (45% versus 35%). The authors do not mention how many patients had atrial fibrillation, which is also associated with poor functional status and may explain the difference in digitoxin use between groups. Treatment effect was also not discussed in the article. Gullestad and colleagues' results showed an improvement in humoral and hemodynamic markers between baseline and 8 months. Humoral changes were significant, but hemodynamic changes were only modest. Moreover, these changes were statistically significant only when the IVIG and placebo groups were compared; clinically, patients did not show much symptom improvement according to the quality-of-life questionnaire. On average, subjects were in NYHA class 2.6 at the beginning of the study and in class 2.2 at the end. This change was not statistically significant, and the exact clinical significance of such a small change is unclear. Further, IVIG did not show any significant effects in patients with very low ejection fraction and long-term CHF.

Overall, this study demonstrated some improvement in biologic markers but failed to show significant improvements in clinical outcomes. These shortcomings probably resulted from the small study size, with only 40 enrolled patients. Gullestad and colleagues' work is hypothesis generating, and further studies should be conducted to determine the precise role of immunotherapy or immunomodulation in CHF, the type of CHF that would derive the most therapeutic benefit, and the disease stage at which this therapy should be administered. The question of whether this treatment could improve CHF survival as well as symptoms should also be explored.

Applications for Clinical Practice

Larger studies need to be conducted to confirm the findings in this study. Until then, immunoglobulin therapy cannot be recommended as therapy for CHF.

References

1. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ 2000;321:199–204.