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Commentary

Immunomodulation Therapy to Treat Patients with Chronic Heart Failure

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DESCRIPTION

A growing number of people are suffering from Heart Failure (HF), and almost half of them have HF with Intact Ejection Fraction (HFpEF). HFpEF is a diverse syndrome with a high rate of morbidity and death that is characterised by a preserved Left Ventricular Ejection Fraction (LVEF 50%) and diastolic dysfunction. Hypertension, type 2 diabetes, obesity, and renal failure are the underlying comorbidities of HFpEF that cause a systemic pro-inflammatory state and interfere with normal heart function. When compared to heart failure with reduced ejection fraction, patients with HFpEF had greater levels of inflammatory biomarkers, which indicate the occurrence of HFpEF. Randomized studies employing standard HF medications in HFpEF patients were unable to show a clear improvement on the hard goals (mortality and/or HF hospitalisation) [1]. Therefore, treatments for early HFpEF that focus on systemic inflammation and underlying comorbidities may offer improved chances. Here, we give a general summary of Immunomodulatory treatments for HFpEF as they stand today and in the future.

Heart failure (HF) causes inflammation. Pro-inflammatory cytokines, innate and adaptive immune cells responses, and other mechanisms have all been linked to HF. It is also clear that immune activation and dysregulated inflammation play a significant role in the gradual remodelling and dysfunction of the Left Ventricle (LV). Theoretically, improving poor LV remodelling and prognosis in HF requires therapeutic approaches that target immunological and inflammatory mechanisms. Various immunomodulation techniques have been tested in a number of, mostly modest, Randomised Controlled Trials (RCTs) in patients with HF, with varying degrees of success [2]. Numerous allogenic stem cell types can be used in cell-based therapies to differentiate indigenous cardiac stem cell populations or to transplant in order to produce new cardiomyocytes that can repair damaged myocardium after a MI. Cell-based therapy has, however, been severely constrained by the effectiveness of cell transport, engraftment, and differentiation of these populations within the infarcted myocardial. Despite these drawbacks, cell treatment has proven to be effective in improving heart function and preventing harmful cardiac remodelling after an AMI episode. According to current understanding, stem cell populations are concentrated in epicentres that secrete the bulk of substances, including cytokines, chemokines, exosomes, and miRNAs that are abundant in exosomes [3].

Normally, Soluble Guanylate Cyclase (sGC) is activated in cardiomyocytes and vascular smooth muscle cells as a result of NO production by cardiac microvascular endothelial cells. Cyclic Guanosine Monophosphate (cGMP), which is produced by sGC, controls Protein Kinase Guanylate (PKG). However, this route is frequently damaged in HFpEF, and decreased PKG activity causes cardiomyocytes hypertrophy, which can ultimately end in LVDD. Increased NO bioavailability caused by nitrate and nitrite contributes to vascular integrity and function. Nitrate isosorbide mononitrate decreased the activity of HFpEF patients in the NEAT-HFpEF trial, and no QoL improvement was seen. Inorganic nitrate was inhaled in the INDIE-HFpEF experiment, which once more failed to increase exercise capacity or quality of life. The anti-fibrotic, anti-proliferative, and anti-inflammatory properties of the sGCs riociguat have been established. Treatment of individuals with HFpEF and pulmonary hypertension increased stroke volume, decreased systolic blood pressure, and decreased right ventricular end-diastolic area but did not affect mean pulmonary artery pressure. Pro-inflammatory cytokines, such as TNF-, IL-1, and IL-6, can cause cardiomyopathy, pulmonary edoema, and progressive LV dysfunction and remodelling. TNF- primarily promotes LV remodelling by altering the Extracellular Matrix (ECM) [4].

Etanercept, an aldosteric antagonist for the TNF receptor, improved QoL, 6-min walk distance, and LVEF in HF patients. However, two multicenter trials employing various etanercept dosages (RECOVER and RENAISSANCE) were prematurely stopped since there was no improvement in patients' clinical outcomes. This might be connected to etanercept's abilities to stabilise TNF- and boost its *in vivo* bioactivity. Thus, worsening HF symptoms may be caused by elevated levels of physiologically active TNF- in the blood of HF patients. Infliximab, a chimeric

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antibody that neutralises TNF-, is useful for treating rheumatoid arthritis and Crohn's disease. Increased mortality and HHF were seen After Infliximab Treatment in HF Patients (ATTACH), probably as a result of complement fixation in the heart.

Immunomodulation significantly improves LV remodelling in HFrEF patients as measured by LVEF and LVEDD. With both anti-cytokine therapy and extensive immunomodulation, as well as across non-ischemic and ischaemic aetiologies of HFrEF, the LVEF was shown to improve. To clearly quantify differences in mortality risk, the TSA recommended using the scant information that is currently available. Future research is necessary to identify the appropriate group of HFrEF patients who would benefit from immunomodulation and the particular Immunomodulatory treatments that ought to be considered carefully [5].

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