Immunological Mediated Therapies for Heart Failure

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ABSTRACT: Experimental and clinical data suggest a causal relationship between immunological and inflammatory processes and heart failure. Inflammatory processes may be involved in the pathogenesis of heart failure and may play a role in the progression of ventricular dysfunction. In the last decade several immunological methods were developed that tried to address these questions and overcome the inflammatory and immunological insults. We hope that the present review will increase awareness of new treatment options and encourage researchers and physicians to investigate this novel approach to treat patients with heart failure.

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Despite state-of-the art cardiovascular treatments, heart failure is still a progressive disease with high mortality and morbidity. The overall effect of the traditional treatments in heart failure on certain pro-inflammatory cytokines is quite modest [1]. Since tumor necrosis factor-alpha was believed to play an active role in heart failure, there were great expectations from the targeting of this cytokine. Preliminary reports suggested that TNFα inhibition with a recombinant chimeric soluble TNF receptor type 2 (etanercept) may have beneficial effects on cardiac performance in the failing myocardium [2]. However, two double-blind placebo-controlled studies using TNFα inhibition – namely, RENAISSANCE and RECOVER (where etanercept was given vs. placebo to patients with heart failure) – were stopped because there was no evidence of benefit using this approach [3]. The reason for the lack of effect may be the "super-specificity" of the monoclonal antibodies against TNFα without affecting other cytokines that are involved in heart failure [4]. As a result, it is commonly held today that heart failure is a complex syndrome in which many cytokines are involved, and in order to influence the cascade of events a more general intervention or a different approach is required to manage this complicated syndrome.

INTRAVENOUS IMMUNOGLOBULIN THERAPY

Studies have shown that patients with heart failure are characterized by sustained immune activation. Patients with heart failure have increased circulating levels of the inflammatory cytokines TNFα, interleukin-1, as well as IL-6 and IL-18 [5,6], and within the failing myocardium there is enhanced expression of various inflammatory mediators such as adhesion molecules independent of the cause of the heart failure [5,7]. These inflammatory markers are not just markers of immune activation but they also induce myocardial dysfunction through regulation of apoptosis and impaired beta-adrenergic responsiveness [8,9].

Infusion of TNFα in concentrations comparable to circulating levels found in patients with heart failure promotes left ventricular dysfunction in rats. IVIG treatment is a well-known modality of treatment for several immune mediated disorders such as Kawasaki's syndrome, dermatomyositis, and multiple sclerosis [11]. One study (non-placebo controlled) even suggested a beneficial effect of IVIG in acute cardiomyopathy [12]. The rationale behind the beneficial effects of IVIG therapy could be related to neutralization of microbial antigens and autoantibodies, Fc-receptor blockade, and complement inactivation [13]. IVIG may affect levels of several cytokines and cytokine modulators, resulting in down regulation of inflammatory responses [14].

In a prospective double-blind placebo-controlled study 40 patients with heart failure and left ventricular ejection fraction less than 40% were randomized to therapy with IVIG or placebo for 26 weeks [15]. IL-1β level increased significantly in the placebo group but not in the IVIG-treated group, and IVIG also increased levels of IL-1 receptor antagonist with a marked rise in IL-10. IVIG induced an increase in soluble p55-TNF receptor and in p75-TNF receptor. According to the inflammatory profile in this group of patients with heart failure, IVIG has an anti-inflammatory effect, as reflected in enhanced levels of IL-10, IL-1ra, and soluble TNF receptors. Patients with heart failure who were treated with IVIG increased their ejection fraction by 5 units (unlike the placebo group who had no improvement at all). However, such an effect could not be demonstrated in patients with the lowest ejection fraction (< 15%). The effect of IVIG treatment was independent of the cause of heart failure (ischemic or idiopathic). After IVIG treatment there was an improvement in several hemodynamic parameters – namely, a decrease in pulmonary wedge and pulmonary artery pressures and an

TNFα = tumor necrosis factor-alpha

IL = interleukin
IVIG = intravenous immunoglobulin

increase in exercise capacity and peak workload – while no change was observed in the placebo group. The important finding of this study was the marked IVIG-induced change in the inflammatory system, with a net anti-inflammatory effect, that was correlated with an improvement in LVEF [15]. However, these effects were not sustained following discontinuation of IVIG treatment. Several explanations could account for the beneficial effects of IVIG in patients with heart failure: complement inactivation, impaired apoptosis, and inhibition of leukocyte adhesion to endothelial cells [16]. IVIG may also neutralize autoantibodies against β1-adrenoceptors and against anti-idiotypic antibodies. Another study found altered gene expression of several chemokines and their corresponding receptors in mononuclear cells of patients with heart failure, and these abnormalities were significantly inhibited during IVIG therapy [17]. That study found that in patients with heart failure there is a markedly raised gene expression of macrophage inflammatory protein-1α, MIP-1β and IL-8. IVIG modulated this gene expression (which was not found during placebo treatment). Down-regulation of MIP-1a gene expression was correlated with improvement in LVEF [17].

Heart failure is an immune inflammatory mediated syndrome

IMMUNE MODULATION THERAPY

Preclinical studies have shown that autologous blood exposed *ex vivo* to oxidative stress and administered intramuscularly decreased the production of inflammatory cytokines [18], increased anti-inflammatory cytokines and decreased apoptosis [19]. Clinical studies that were performed in patients with peripheral disease showed that such an approach, called immune modulation therapy, was safe and improved endothelial function and the claudication distance [20]. Another study examined this immune treatment in 75 patients with heart failure. All were in New York Heart Association functional class III to IV, had chronic heart failure, poor left ventricular function (less than 40%), and a 6 minute walk distance of < 300 m. All were treated with standard medical treatment that had not been changed in the preceding 3 months [21]. The treatment involved collection of 10 ml venous blood into 2 ml of 4% sodium citrate that was transferred to a sterile single-use container (VC7002, Vasogen Inc., Mississauga, Ontario, Canada) and inserted into the VC7001 Blood Treatment Unit (Vasogen Inc.). There the blood was exposed to controlled levels of oxidative stress at a temperature of 42.5 ± 1.0^{0}C for 3 minutes and to ultraviolet radiation. Approximately 10 ml of the treated blood was administered by slow intragluteal injection. This treatment vs. placebo (10 ml saline) was given on 2 consecutive days, followed by 6 monthly injections beginning 2 weeks later [21]. The immune modulation therapy was given to 38 patients and 37 received placebo. After 6 months the 6 minute walk distance for the IMT group improved by 18%, but the placebo group also improved, by 21%. Forty-one percent of the patients in the IMT group improved their functional NYHA class compared with 24% in the placebo group. However, Kaplan-Meier survival analyses showed that IMT significantly reduced the risk of death and of hospitalization [21]. No difference in ejection fraction, TNFα levels, or in IL-6, IL-10 and C-reactive protein were found between the two study groups. The mechanistic understanding of this method suggests that *ex vivo* exposure of blood to oxidative stress produces accelerated "senescence" of immune cells that undergo apoptosis following the intramuscular injection. Interaction of apoptotic cells with the immune system macrophages results in a decrease in inflammatory cytokines and up-regulation of anti-inflammatory cytokines [22]. In a double-blind study IMT treatment was given to 1213 heart failure patients while 1213 heart failure patients received placebo. The study was named "A non-specific immunomodulation therapy in chronic heart failure" (ACCLAIM trial) and the mean time of follow-up was 10.2 months. The primary endpoint was death from any cause or first cardiovascular hospitalization. Secondary endpoints included clinical status and health-related quality of life. By the end of the study there was no change in the primary and secondary endpoints between the groups [23]. However, among the 689 patients with NYHA class II, 92 primary events were recorded in the IMT group as compared with 124 in the placebo group (P = 0.0003). In patients with no history of myocardial infarction 105 primary events occurred in the IMT group versus 138 in the placebo group (P = 0.02). Even though no difference was found between the two groups (those on IMT and those on placebo) in the primary endpoints of death or hospitalization, the quality of life improved in the IMT group compared with placebo, and IMT was demonstrated to be a safe and a reliable method of treatment (26,500 intramuscular injections in heart failure patients, most of whom were on antiplatelet or anticoagulant therapy, resulting in a very small rate of hemorrhage – 0.14% – and fewer than 1% of the injections were associated with pain or discomfort in the injection site). More than that, the subgroup analysis found a significant advantage for IMT in patients with NYHA class II – a reduction of risk to develop the primary endpoint by 39%, and a 26% risk reduction in heart failure patients without a history of myocardial infarc-

LVEF = left ventricular ejection fraction
MIP = macrophage inflammatory protein

IMT = immune modulation therapy
NYHA = New York Heart Association

tion. Both these groups comprised younger patients with less severe disease – increased ejection fraction, higher hemoglobin concentrations, higher systolic blood pressure, and reduced C-reactive protein concentrations. The ACCLAIM trial has demonstrated that there is a role for non-specific immunomodulation as a potential treatment for many heart failure patients – mainly patients without a history of myocardial infarction and those with NYHA class II. It seems that the early intervention is superior to late intervention, and that younger patients benefit more if they have a higher ejection fraction, higher hemoglobin concentration, lower C-reactive protein level and shorter duration of disease [23].

IMMUNOADSORPTION THERAPY WITH IgG SUBSTITUTION

Immunoadsorption and subsequent IgG substitution represent an additional therapeutic approach to treat dilated cardiomyopathy and heart failure. Disturbances in humoral and cellular immunity have been described in myocarditis and dilated cardiomyopathy patients [24]. According to an experimental model of myocarditis induced by myosin, myocardial damage is mediated by T lymphocytes [25].

The role of T lymphocytes in heart failure and in dilated cardiomyopathy is still unclear. A number of antibodies against cardiac cell proteins have been identified in patients with heart failure or dilated cardiomyopathy, such as antibodies against mitochondrial proteins, contractile proteins, cardiac β1 receptors, and muscarinic receptors [26-28]. These antibodies can play a role in the pathogenesis of dilated cardiomyopathy by initiating the disease process or by contributing to the progression of myocardial contractile malfunction. Their removal may improve myocardial function. Cardiac antibodies can be extracted by immunoadsorption [29], after which intravenous immunoglobulins are given to prevent infections and the development of an immune deficiency state.

Previous pilot studies have shown that immunoadsorption with subsequent IgG substitution in patients with dilated cardiomyopathy and heart failure elicited an immediate improvement in cardiac index with a decrease in systemic vascular resistance. Immunoadsorption with IgG substitution continued for 3 months, parallel with hemodynamic improvement [39]. In a prospective double-blind placebo-controlled study, 25 patients with dilated cardiomyopathy were enrolled and separated into two groups: 12 patients were treated with immunoadsorption and IgG at monthly intervals for 3 months and 13 patients served as the control group. All patients had elevated levels of anti-β1-receptor antibodies. Patients in the control group received the regular management. In the treated group immunoadsorption was administered for 3 months. After every session the patients received polyclonal IgG to restore IgG plasma levels. All patients tolerated immunoadsorption and subsequent IgG substitution without any major complications. In the treated group levels of β-receptor autoantibodies decreased significantly, while LVEF increased significantly with a reduction in left ventricular end-systolic and end-diastolic diameters, and after 3 months of treatment there was also an improvement in NYHA functional class in the treated group. None of these beneficial effects were observed in the control group [31]. Histologically, the number of CD3 and CD4-positive cells decreased significantly within 3 months. The number of cells with leukocyte common antigens also decreased significantly with a decline in HLA class II antigen expression. Treatment with immunoadsorption/IgG may be an additional effective approach to treat patients with dilated cardiomyopathy and heart failure. This study also proved that various histological changes in dilated cardiomyopathy are reversible and that the reduction in autoantibodies may have contributed to the histological alterations. This therapeutic approach significantly ameliorates the inflammatory process in myocardial tissue and stabilizes myocardial function in patients with dilated cardiomyopathy and heart failure.

Heart failure can be managed by immunological methods, such as IVIG treatment, immune modulation therapy, immunoadsorption therapy, and with thalidomide

THALIDOMIDE AND HEART FAILURE

Pro-inflammatory cytokines, particularly TNF, have been implicated in disease progression in heart failure. TNF levels are elevated in patients with advanced heart failure and have been reported to correlate with severity of symptoms and with mortality. At high levels, TNF mimics some aspects of heart failure, including left ventricular dysfunction, cardiomyopathy, fetal gene expression, and left ventricle remodeling.

Thalidomide selectively inhibits TNF production in monocytes by enhancing mRNA degradation. Thalidomide exhibits anti-inflammatory, anti-angiogenic, and immunosuppressive properties and is used in inflammatory and autoimmune disorders [32]. In an *in vitro* study lipopolysaccharide stimulated cardiac myocytes to excrete TNF in a dose-dependent manner, a phenomenon that could be inhibited by thalidomide and thalidomide analogues [33]. In a pilot non-placebo controlled clinical study that examined the effects of thalidomide on patients with heart failure, it was found to be safe in doses of up to 100 mg/day, but at higher doses patients reported

IgG = immunoglobulin G

drowsiness and peripheral neuropathy that reversed with down-titration. After 12 weeks of maintenance with thalidomide there was a significant improvement in the 6 minute walk with a trend to improved ejection fraction. No significant change was observed in any of the cytokines measured – IL-10 and soluble TNF receptors. In another pilot study nine patients with heart failure and LVEF lower than 40% who were on "optimal" therapy were given thalidomide 200 mg daily for 6 weeks. TNFα and LVEF were measured at baseline and after 6 weeks of treatment [34]. At baseline, plasma TNF levels were elevated and the ejection fraction was 26 ± 9%. After 6 weeks of treatment TNF levels decreased significantly and the ejection fraction increased to 34 ± 10% ($P < 0.05$). The LVEF rose significantly without a significant change in left ventricular end-diastolic and end-systolic dimensions. This improvement was seen in all patients regardless of the cause of heart failure. In most of the patients the heart rate decreased from 76 ± 18 beats per minute to 60 ± 12, and that change could explain the improvement in cardiac output that was observed in all patients with heart failure. A larger double-blind study followed 56 patients with heart failure and ejection fraction < 40% who were randomized to thalidomide or placebo for 12 weeks. The primary endpoint was LVEF, and secondary endpoints included left ventricular end-diastolic volume and clinical evaluation (NYHA), heart rate, blood pressure, quality of life, and plasma levels of N-terminal brain natriuretic peptide. After 12 weeks of treatment the ejection fraction increased by 7 EF units in the thalidomide group (vs. no change in the placebo group), with a significant decrease in LV volume, accompanied by a significant decrease in heart rate (no change in the placebo group). Plasma levels of NT-proBNP , blood pressure, NYHA classification, and quality of life remained unchanged in both treatment groups [35].

Interestingly, thalidomide markedly improved LVEF in patients with idiopathic dilated cardiomyopathy, and there was a more modest and non-significant increase in patients with heart failure secondary to coronary artery disease. However, the effect of thalidomide on left ventricular end-diastolic volume and heart rate were independent of the etiology. Still, our knowledge will have to be further examined in forthcoming studies.

SUMMARY

Since there have been no major advances in heart failure treatment in the last decade, we should consider other possible mechanisms and should try treating heart failure accordingly. Since the immunological and inflammatory systems play an important role in heart failure, the medical community should be open-minded to treatments that manipulate these systems and thereby affect the heart failure syndrome from a different angle.

In this review four options of medical treatment were described, all of which affect the immune system and alter the inflammatory balance. Each of them – IVIG treatment, immune modulation therapy, immunoadsorption therapy with immunoglobulin substitution, and thalidomide treatment – attempts to affect heart failure through the immune system. Some of these approaches have proved beneficial and effective, some less so, but the general impression is that through this approach we may generate some future breakthroughs that will enable us to treat heart failure more efficiently. The immunological/inflammatory pathways may be the answer for treating patients with different stages of heart failure.

EF = ejection fraction
NT proBNP = N-terminal brain natriuretic peptide

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