Review

Cytokines as new treatment targets in chronic heart failure

Jan Kristian Damås*†, Lars Gullestad‡ and Pål Aukrust†§

*Department of Cardiology, Rikshospitalet, Oslo
†Research Institute for Internal Medicine, Rikshospitalet, Oslo
‡Department of Medicine, Bærum Hospital, Sandvika, Norway
§Section of Clinical Immunology and Infectious Diseases, Medical Department, Rikshospitalet, Oslo

Correspondence: Jan Kristian Damås, j.k.damas@klinmed.uio.no

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Abstract

Inflammatory cytokines may negatively influence contractility and contribute to the remodelling process in the failing myocardium. Traditional cardiovascular drugs appear to have little influence on the overall cytokine network in chronic heart failure (CHF). Increased interest in anticytokine therapy has therefore evolved. Several small studies have used tumour necrosis factor (TNF)-α as a target, resulting in improved functional capacity and myocardial performance. Intravenous immunoglobulin (IVIG) represents another therapeutic approach in which the impact on myocardial performance appears to be correlated with anti-inflammatory effects. These studies demonstrate potential for immunomodulation as a therapy in addition to conventional cardiovascular treatment in CHF, but the most effective drugs in this regard have yet to be identified.

Keywords chronic heart failure, cytokines, immunomodulating therapy, intravenous immunoglobulin

The accepted paradigms and treatment strategies for heart failure have changed during the past 50 years. Traditionally, patients with CHF were treated with diuretics, vasodilators and inotropic drugs, resulting in improvement in functional status and symptoms, but with no decrease in long-term mortality [1,2]. However, the initial haemodynamic dysfunction of CHF has downstream effects on cardiovascular reflexes, and systemic organ perfusion and function. The arterial under-filling is sensed by baroreceptors that activate powerful neurohormones, which act as effectors of vasoconstriction and of avid sodium and water retention. Recognition of neurohormones as important substances in the pathogenesis of CHF has resulted in several new treatment modalities, including angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists and β-blockers, which yield marked improvements in morbidity and mortality of CHF patients [3–7].

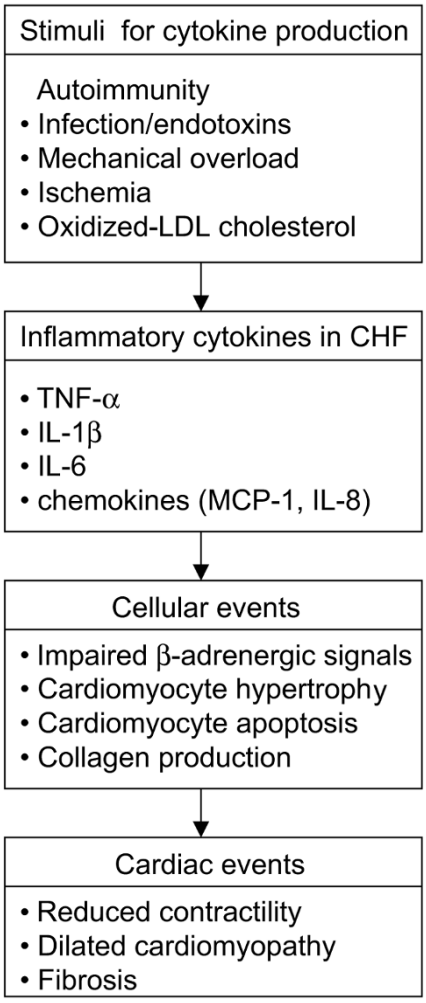
Despite 'state of the art' cardiovascular treatment, CHF is still a progressive disease with high morbidity and mortality, suggesting that important pathogenic mechanisms remain active and unmodified by the present treatment modalities. Persistent immune activation and inflammation may represent such 'unmodified mechanisms'. Attention has focused on mediators that are classically associated with innate immunity, including inflammatory cytokines [8].

Cytokines as pathogenic mediators of chronic heart failure

Cytokines are peptides that mediate cell-to-cell interactions via specific cell-surface receptors. They regulate activation, differentiation, growth, death and acquisition of effector functions of various cell types [9]. As a result, they are increasingly recognized as important factors in the pathophysiology of CHF (Fig. 1).

ACE angiotensin-converting enzyme; CHF = chronic heart failure; CRP = C-reactive protein; IDCM = idiopathic dilated cardiomyopathy; IL = interleukin; IVIG = intravenous immunoglobulin; LVEF = left ventricular ejection fraction; MCP = monocyte chemoattractant protein; TNF = tumour necrosis factor.
RECOVER = the Research into Etanercept: Cytokine Antagonism in Ventricular function; RENAISSANCE = Randomized Etanercept North American Strategy to Study Antagonism of Cytokine; SOLVD = Studies on Left Ventricular Dysfunction; VEST = Vesnarinone Trial.

Figure 1



Overview of potential inflammatory mechanisms that are involved in the development of chronic heart failure (CHF). Various stimuli, including autoimmunity, chronic infections, mechanical overload, ischaemia and oxidized low-density lipoprotein (LDL)-cholesterol, may induce production of inflammatory cytokines in CHF. Inflammatory cytokines may further negatively influence contractility and contribute to the remodelling process in the failing myocardium (e.g. hypertrophy and apoptosis of cardiomyocytes), resulting in a cardiomyopathy-like phenotype with cardiac dilatation and fibrosis. IL=interleukin; MCP=monocyte chemoattractant protein; TNF=tumour necrosis factor.

Several studies have demonstrated that CHF patients are characterized by persistent immune activation *in vivo*. This is reflected in increased circulating levels of inflammatory cytokines (TNF-α, IL-1β and IL-6) and chemokines (monocyte chemoattractant protein [MCP]-1 and IL-8), as well as enhanced expression of various inflammatory mediators (TNF-α, IL-6 and adhesion molecules) within the failing myocardium, independent of the cause of CHF [10–20].

Although there is a lack of specificity of cytokine activation in patients with CHF, several lines of evidence suggest that these inflammatory mediators are not only markers of immune activation (an epiphenomenon in severely ill patients), but may also play a pathogenic role in CHF. The pathogenic role of inflammatory cytokines in CHF is supported by research conducted in mouse models. First, transgenic mice with cardiac-specific over-expression of TNF-α developed dilated cardiomyopathy [21]. Second, systemic administration of TNF-α, even at concentrations comparable to those found in the circulation of CHF patients, have been shown to induce a dilated-cardiomyopathy-like phenotype in animal models [22].

Inflammatory cytokines may modulate cardiovascular functions by a variety of mechanisms (Fig. 1). Cytokines such as TNF-α and IL-1β have been shown to depress myocardial contractility. This may be due to uncoupling of β-adrenergic signalling, increase in cardiac nitric oxide, or alterations in intracellular calcium homeostasis [23–26]. TNF-α, and members of the IL-6 family, may also induce structural changes in the failing myocardium such as cardiomyocyte hypertrophy and interstitial fibrosis [27,28]. Additionally, TNF-α and IL-1β may promote cardiomyocyte apoptosis as well as activate metalloproteinases and impair the expression of their inhibitors, possibly contributing to cardiac remodelling [29–31].

Stimuli for cytokine expression in chronic heart failure

Autoimmunity and various microbes are known to play pathogenic roles in subgroups of idiopathic dilated cardiomyopathy (IDCM) patients, and such mechanisms could clearly promote enhanced cytokine levels in CHF. However, raised cytokine levels appear not to be restricted to IDCM, but are also found in ischaemic cardiomyopathy. Infection with certain microbes (*Chlamydia pneumoniae*. and cytomegalovirus) has recently been suggested to be involved in the pathogenesis of atherosclerosis. Microbial antigens may also induce myocardial damage through molecular mimicry (Fig. 1) [32–34]. Moreover, endotoxins have been suggested to trigger immune activation in patients with CHF during oedematous episodes, possibly following leakage from the gastrointestinal tract [35]. Accordingly, persistent stimulation by microbial antigens might well lead to cytokine activation in CHF patients (Fig. 1). Elevation in cytokine levels seems to occur in CHF independently of chronic infection, however, and several other factors may lead to an enhanced inflammatory response in such patients.

Both mechanical overload and shear stress may induce cytokine expression (MCP-1 and IL-8) in both endothelial and smooth muscle cells [36]. Moreover, hypoxia and ischaemia have been found to be potent inducers of inflammatory cytokines (TNF-α, MCP-1 and IL-8) within the myocardium. This may occur through production of reactive oxygen species, with secondary activation of the transcriptional factor nuclear factor-κB [37,38]. Finally, oxidized low-density lipoprotein cholesterol may increase cytokine expression

(IL-1β, TNF-α, IL-6 and IL-8) in endothelial cells and monocytes, and such mechanisms may be of particular importance in myocardial failure secondary to coronary artery disease [39]. The relative importance of the stimuli for cytokine production in various forms of CHF is uncertain, however.

Are parameters of immune activation prognostic markers in chronic heart failure?

The persistent immune activation in CHF has been reported to occur independently of the aetiology of heart failure [11,18], possibly representing a final common pathogenic pathway in this disorder. Several studies have reported raised plasma levels of inflammatory cytokines in direct relation to deterioration of functional class and cardiac performance (left ventricular ejection fraction [LVEF]) [11–13]. Even more importantly, it appears that these inflammatory mediators may provide important prognostic information in CHF patients. For example, in a substudy of the Studies on Left Ventricular Dysfunction (SOLVD) [13], patients with TNF-α plasma levels of less than 6.5 pg/ml had a better prognosis than did patients with higher levels. Moreover, in a recent report from a large population of CHF patients (the cytokine database from the Vesnarinone Trial [VEST]) [40,41], circulating levels of inflammatory cytokines (TNF-α and IL-6) and cytokine receptors (soluble TNF receptors) were found to be independent predictors of mortality in patients with advanced heart failure. These new clinical data further support the notion that raised levels of cytokines in CHF patients are not only epiphenomena, but also may reflect important pathogenic mechanisms in such patients.

Effect of cardiovascular therapy on cytokine levels in chronic heart failure patients

There are few data on how traditional cardiovascular medications influence the persistent immune activation that occurs in CHF. In the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial [42], the calcium channel blocker amlodipine was found to reduce IL-6 levels, which has also been suggested to be important to the beneficial effect of this agent on mortality in patients with IDCM. However, amlodipine had no effect on TNF-α levels. Furthermore, we recently showed that high-dose ACE inhibition with enalapril causes a marked decrease in IL-6 bioactivity, associated with reduction in left ventricular septum thickness [43]. Thus, it is possible that an important 'antihypertrophic' mechanism of ACE inhibitors on the myocardium may be a reduction in IL-6 levels, possibly combined with impaired IL-6 signal transduction. Except for a favourable effect on IL-6, all of the other immunological parameters were markedly elevated in CHF patients and remained unchanged during treatment with enalapril.

Interestingly, other investigators have reported that ACE inhibitors may prevent nuclear factor-κB activation and MCP-1 expression, and reduce macrophage infiltration in both experimental and clinical atherosclerosis [44,45]. Additionally, a combination of ACE inhibitors and angiotensin receptor antagonists was recently found to reduce cardiac infiltration of macrophages following acute myocardial infarction in rats [46]. Whether ACE inhibitors have such effects in CHF patients must be addressed in future studies.

Several studies have shown that β-adrenergic stimulation may modulate cytokine production in various lymphocyte subsets and monocytes [47]. In rats, adrenergic activation has been found to increase myocardial expression of inflammatory cytokines (TNF-α and IL-1), which was reduced by β-adrenergic blockade (metoprolol) [48]. This may not to be the case in CHF patients, however. A non-placebo-controlled study in patients with IDCM [49] reported some suppressive effects of β-blockers on plasma levels of both inflammatory (TNF-α) and anti-inflammatory (IL-10) cytokines. However, we have recently shown [50] that long-term treatment with the β_1-selective blocker metoprolol CR/XL had no significant effect on cytokine levels, as compared with placebo, in patients with CHF. It remains to be determined whether more complete blockade of the β-receptors (i.e. nonselective), or combined α- and β-blockade with carvedilol alters the cytokine network.

Finally, several studies have suggested that statins may exert direct cardiovascular effects, such as attenuating inflammatory responses and promoting plaque stability, that are clearly independent of their cholesterol-lowering effects. Statins reduce C-reactive protein (CRP) levels and may be effective in preventing coronary events in patients with relatively low lipid levels but with elevated CRP [51]. Standard aspirin treatment also appears to reduce IL-6 and CRP levels in patients with stable angina [52]. Reduction in cytokine and CRP levels by statins and aspirin may well explain part of their therapeutic action. However, their effects in reducing systemic and myocardial inflammation in CHF patients require further assessment.

The cytokine network as new targets for therapy in myocardial failure?

Although traditional cardiovascular treatment may have some immunomodulatory effects, the persistent immune activation in CHF patients appears generally to be unmodified by these medications. Several forms of anticytokine and immunomudulatory therapy, in addition to conventional cardiovascular treatment regimens, have recently emerged as possible new and promising treatment modalities in these patients (Table 1) [53–61].

Etanercept

Given the central role of TNF-α in the pathogenesis of CHF, therapeutic modulation targeting this cytokine has received much attention. Preliminary reports suggest that TNF-α inhibition with recombinant chimeric soluble TNF receptor type 2 (etanercept) may have beneficial effects on cardiac performance in CHF patients [53,54]. However, anticytokine therapy with soluble TNF receptors may have some limitations. Recent studies in animal models showed that, although

Table 1

Immunomodulation in heart failure: potential treatment modalities

Agent	References
Soluble tumour necrosis factor receptors (etanercept)	[53,54]
Pentoxifylline	[55,56]
Thalidomide	[57]
Intravenous immunoglobulin	[58]
Interleukin-10	[59]
Interleukin-1 receptor antagonist	[60]
Chemokine modulators	[61]

such therapy decreased plasma cytokine levels, there was no decrease in IL-6 and MCP-1 levels within the myocardium. Notably, the Randomized Etanercept North American Strategy to Study Antagonism of Cytokine (RENAISSANCE) and the Research into Etanercept: Cytokine Antagonism in Ventricular function (RECOVER) outcome studies of etanercept were recently stopped because of lack of evidence of beneficial effects [62,63]. The studies had randomized over 1500 patients and were due to be completed at the end of 2001, but interim analysis revealed no likelihood of a difference between etanercept and placebo developing if the studies had run to completion.

Pentoxifylline

Pentoxifylline is a xanthine-derived agent that has been shown to inhibit various inflammatory cytokines such as TNF-α, IL-1β and interferon-γ. Recently, addition of pentoxifylline to treatment with digoxin, ACE inhibitors and carvedilol in patients with IDCM was shown to be associated with a significant improvement in symptoms and LVEF [55,56]. That was in a single-centre, prospective, double-blind, randomized, placebo-controlled study. Thirty-nine patients with IDCM and LVEF below 40% were randomly assigned to pentoxifylline (400 mg three times daily; $n = 20$) or placebo ($n = 19$).

Although the published studies with etanercept and pentoxifylline are small, the improvement in LVEF appears to be greater with pentoxifylline. Furthermore, other advantages of pentoxifylline over etanercept are its easier form of administration, lower cost and that it might inhibit the production of TNF-α rather than neutralize its effects. Although large-scale trials are needed to evaluate the safety of pentoxifylline in patients with CHF, this drug has been used in patients with peripheral vascular disease for more than 25 years with a very low incidence of side effects.

Intravenous immunoglobulin

Therapy with IVIG has been evaluated in a wide range of immune-mediated disorders, such as Kawasaki syndrome, dermatomyositis and multiple sclerosis [64,65]. Beneficial effects of IVIG have also been suggested in acute and peripartum cardiomyopathy [66,67].

Recently, we demonstrated that IVIG significantly improves LVEF by 5% in CHF patients, independent of the aetiology of heart failure [58]. That was a double-blind, placebo-controlled study, with 40 CHF patients (both ischaemic and IDCM with LVEF below 40%). IVIG also improved some haemodynamic variables (pulmonary capillary wedge pressure) and exercise capacity. IVIG, but not placebo, was accompanied by a marked but gradual decline in plasma levels of amino-terminal pro-atrial natriuretic peptide. In contrast, a recent study conducted by McNamara *et al.* [68] found no significant impact of IVIG, as compared with placebo, on recent-onset IDCM. Although this may be due to the marked improvement in the study group as a whole (with or without IVIG), it is noteworthy that the dosage schedule differs between the 'IDCM' and the 'CHF' study.

Although both studies described above gave induction therapy, maintenance therapy (monthly infusions for a total of 5 months) was only given in the 'CHF' study [58]. Notably, in the 'CHF' study there was as a gradual decline in amino-terminal pro-atrial natriuretic peptide throughout, which became pronounced at the end of study. Moreover, a recent follow-up study (Gullestad L, Aukrust P, unpublished data) showed that most of the CHF patients in the IVIG group had a decrease in LVEF 1 year after termination of the study. Those data suggest that maintenance therapy is needed for an extended period of time, as in other chronic inflammatory disorders.

Several modes of action may be of importance for the clinical effects of IVIG in inflammatory disorders, such as neutralization of microbial antigens, Fc-receptor blockade and impairment of apoptosis [64,69]. In our opinion, however, particular attention should be drawn toward the effect of IVIG on the cytokine network. In the IVIG study the improvement in LVEF was associated with a marked rise in the anti-inflammatory mediators IL-10, IL-1 receptor antagonist and soluble TNF receptor, which was accompanied by a slight decrease in TNF-α and IL-1β [58]. This suggests an anti-inflammatory net effect with potential beneficial results on the myocardium. Taken together with the imbalance between pro- and anti-inflammatory cytokines in CHF patients [11], upregulation or administration of anti-inflammatory cytokines such as IL-10 might be a useful strategy for intervention in CHF patients. Interestingly, administration of IL-10 has recently been shown to have therapeutic effects on murine viral myocarditis [59].

Finally, we also reported that IVIG therapy, but not placebo, may downregulate chemokines and their receptors on peripheral blood mononuclear cells in CHF patients, possibly contributing to the beneficial effect of IVIG in CHF [61]. Accordingly, direct blockade of the chemokine network may represent another interesting approach for future intervention in CHF patients.

Recently, the technique of immunoadsorption has been used in several studies to treat patients with IDCM [70]. Immunoadsorption has been found to improve functional capacity, and left ventricular structure and function in IDCM patients [70]. The mechanisms that underlie these effects may involve removal of circulating antibodies to β_1-adrenoreceptors, reduction in oxidative stress and mitigation of myocardial inflammation [70–72]. IVIG replacement therapy is often given to these patients and, as discussed above, may *per se* lead to improvement in clinical status in patients with IDCM [58,70].

Conclusion

Although not necessarily the 'drugs of choice', recent studies of various anticytokine (etanercept) and immunomodulating agents (IVIG and pentoxifylline) in CHF patients clearly suggest a potential for such therapies in these patients, in addition to 'optimal' cardiovascular treatment regimens. However, the results in these small studies will have to be confirmed in larger, placebo-controlled mortality studies. Several studies have focused on the possible pathogenic role of TNF-α, and targeted therapy against this molecule is ongoing. In order to develop more specific immunomodulating agents in the immunopathogenesis of CHF, further research will need to identify precisely the important players. Regardless of these shortcomings, we believe that cytokines might lead to quite new treatment modalities in CHF, resulting in reduced morbidity and mortality in such patients.

Competing interests

None declared.

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