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TRENDS IN MOLECULAR MEDICINE

Inflammatory and anti-inflammatory cytokines in chronic heart failure: Potential therapeutic implications

PÅL AUKRUST[1,2], LARS GULLESTAD[3], THOR UELAND[1], JAN K. DAMÅS[1] & ARNE YNDESTAD[1]

[1]*Research Institute for Internal Medicine,* [2]*Section of Clinical Immunology and Infectious Diseases, and* [3]*Department of Cardiology, Rikshospitalet, University of Oslo, N-0027 Oslo, Norway*

Abstract
Persistent inflammation, involving increased levels of inflammatory cytokines, seems to play a pathogenic role in chronic heart failure (HF) by influencing heart contractility, inducing hypertrophy and promoting apoptosis, contributing to myocardial remodeling. While several stimuli may be operating such as heat shock proteins, microbial antigens and oxidative stress, it seems that the inflammatory response to these stimuli may represent a common final pathogenic pathway in HF regardless of the initial event. Traditional cardiovascular drugs appear to have little influence on the cytokine network, and immunomodulatory therapy has emerged as a possible new treatment modality in HF. Several animal studies and also some clinical studies have suggested that downregulation of inflammation may improve cardiac performance. However, the results from the placebo-controlled anti-tumor necrosis factor studies suggest no improvement or even adverse effects of such therapy. Although somewhat disappointing, these negative results do not necessarily argue against the 'cytokine hypothesis'. These studies just underscore the challenges in developing treatment modalities that can modulate the cytokine network in HF patients resulting in beneficial net effects. Further research will have to identify more precisely the most important actors in the immunopathogenesis of chronic HF in order to develop more specific immunomodulating agents for this disorder.

Key words: *Cytokines, heart failure, inflammation, therapy*

Introduction

Heart failure (HF) is a complex multi-step disorder in which a number of physiological systems participate (1). The involvement of neurohormones in the progression of HF has been firmly established leading to new treatment modalities such as angiotensin converting enzyme (ACE) inhibitors and β-blockers (2). However, despite state-of-the-art cardiovascular treatment, chronic HF is a progressive disease with high morbidity and mortality, suggesting that important pathogenic mechanisms remain unmodified by the present treatment modalities. Persistent inflammation may represent such unmodified mechanisms. Thus, since the initial observation by Levine et al. (3), numerous studies have demonstrated that HF patients have raised plasma/serum levels of inflammatory cytokines such as tumor necrosis factor (TNF)α, interleukin (IL)-1β, IL-6 as well as several chemokines, e.g. monocyte chemoattractant peptide (MCP)-1, IL-8 and macrophage inflammatory protein (MIP)-1α (4–8). Importantly, the rise in inflammatory mediators seems not to be accompanied by a corresponding increase in anti-inflammatory cytokines such as IL-10, resulting in an inflammatory net effect (4) (Figure 1). Increased expression of inflammatory cytokines in HF patients has also been demonstrated in circulating leukocytes at both protein and mRNA levels, with particularly high levels in the coronary circulation (9,10). Moreover, these inflammatory mediators are not only increased in the circulation, but enhanced expression has also been found within the failing myocardium (e.g. adhesion molecules, TNFα, IL-6-related cytokines and

Correspondence: Pål Aukrust, Section of Clinical Immunology and Infectious Diseases, Rikshospitalet, N-0027 Oslo, Norway. Fax: 47-23073630. E-mail: pal.aukrust@rikshospitalet.no

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Abbreviations

ACE	angiotensin converting enzyme
CTLA4	cytotoxic T lymphocyte-associated antigen 4
HF	heart failure
IDCM	idiopathic dilated cardiomyopathy
IL	interleukin
IVIG	intravenous immunoglobulin
L	ligand
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MIP	macrophage inflammatory protein
MCP	monocyte chemoattractant peptide
MMP	matrix metalloproteinases
NF	nuclear factor
OPG	osteoprotegerin
PBMC	peripheral blood mononuclear cells
RANK	receptor activator for NF-κB
RANKL	RANK ligand
TGF	transforming growth factor
TIMP	tissue inhibitors of MMPs
TLR	toll-like receptors
TNF	tumor necrosis factor

chemokine receptors), suggesting a potential central role for cytokine-related interactions in the pathogenesis of myocardial failure (11,12).

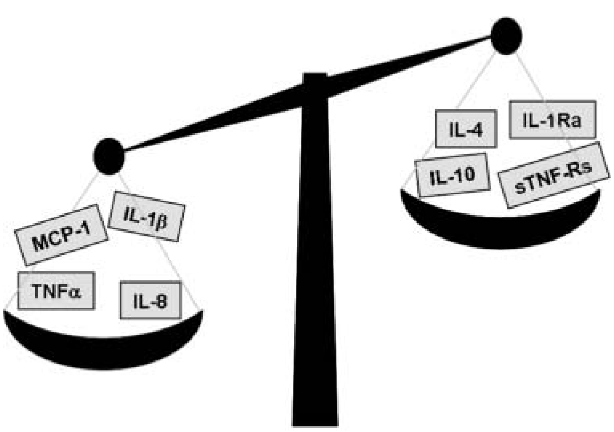

Figure 1. The cytokine network in patients with chronic HF showing an imbalance between inflammatory (left) and anti-inflammatory (right) mediators. This imbalance in the cytokine network could represent an important target for immunomodulating treatment modalities in chronic HF. IL=interleukin; TNF=tumor necrosis factor; sTNF-Rs=soluble TNF receptors; TGF=transforming growth factor; IL-1Ra=IL-1 receptor antagonist.

Key messages

- Persistent inflammation, involving increased levels of inflammatory cytokines, seems to play a pathogenic role in chronic heart failure by influencing heart contractility, inducing hypertrophy and promoting apoptosis, contributing to myocardial remodeling.
- Traditional cardiovascular drugs appear to have little influence on the cytokine network and immunomodulatory therapy has emerged as a possible new treatment modality in chronic heart failure.
- The negative results from the anti-TNF studies underscore the difficulties and the challenges in developing treatment modalities that can modulate the cytokine network in patients with chronic heart failure resulting in beneficial net effects.

Parameters of immune activation: Prognostic markers in chronic HF

Persistent immune activation in chronic HF has been found independently of the etiology of HF, possibly representing a final common pathogenic pathway in this disorder (4). Several studies have reported raised plasma levels of inflammatory cytokines and chemokines in direct relation to deterioration of functional class (i.e. New York Heart Association classification) and cardiac performance (e.g. left ventricular ejection fraction (LVEF)) (4–6). Moreover, it seems that these inflammatory mediators may give important prognostic information in patients with chronic HF. For example, in a sub-study to Studies on Left Ventricular Dysfunction, patients with plasma levels of TNFα <6.5 pg/mL had a better prognosis than those with higher TNFα levels (8). Furthermore, in a large population of HF patients (1200 patients, the cytokine database from the Vesnarinone trial) circulating levels of inflammatory cytokines (i.e. TNFα and IL-6) and cytokine receptors (i.e. soluble TNF receptors (TNFRs)) were found to be independent predictors of mortality in patients with advanced HF (13). These clinical data further support the notion that raised levels of cytokines in HF patients are not only epiphenomena, but may reflect important pathogenic mechanisms in these patients.

What causes enhanced inflammation in HF?

While numerous studies have shown that HF is characterized by chronic inflammation, the cause for this immune activation is at present unknown, but several non-mutually exclusive mechanisms have been suggested (Figure 2). Autoimmunity and various microbes are known to play a pathogenic role in subgroups of idiopathic dilated cardiomyopathy (IDCM), and such mechanisms could clearly promote a persistent inflammation in HF (14). However, raised cytokine levels appear not to be restricted to IDCM, but are also found in ischemic cardiomyopathy (4). Infection with certain microbes (e.g. *Chlamydia pneumoniae* and cytomegalovirus) has recently been suggested to be involved in atherogenesis, and microbial antigens may also induce myocardial damage through molecular mimicry (15,16). Accordingly, persistent stimulation by microbial antigens might well lead to cytokine activation in HF patients. Moreover, endotoxins have been suggested to trigger immune activation in patients with HF during edematous episodes, possibly secondary to leakage from the gastrointestinal tract (17). Based on the 'infectious hypothesis', anti-microbial therapy could potentially be of interest in the management of chronic HF. However, except for the therapy of acute and chronic concomitant clinically apparent infections, the potentially beneficial effects of anti-microbial therapy in HF as well as in atherosclerosis are at present far from clear (18,19). Nonetheless, the 'cytokine hypothesis' does not depend on the infectious hypothesis and several other factors may lead to enhanced levels of inflammatory cytokines in these patients. First, mechanical overload and shear stress may induce cytokine expression (e.g. MCP-1 and IL-8) in several cell types (20,21). Second, hypoxia and ischemia are potent inducers of inflammatory cytokines such as TNFα, MCP-1 and IL-8, involving activation of the transcription factor nuclear factor (NF)-κB (22). Third, oxidized low-density lipoprotein (LDL) cholesterol may increase cytokine expression in endothelial cells and monocytes, and such mechanisms may be of particular importance in ischemic cardiomyopathy (23). Finally, recent studies have suggested that a group of pattern-recognition receptors named toll-like receptors (TLR) may be involved in myocardial inflammation, not only in response to microbes, but also in response to molecules released from injured and stressed cells, such as heat shock proteins and reactive oxygen species (24). TLR-stimulation can further lead to activation of transcription factors such as NF-κB with subsequent activation of inflammatory cytokines, potentially leading to immunological and inflammatory responses within the myocardium. In fact, experimental studies have demonstrated that TLRs may be important in the regulation of both adaptive and maladaptive responses to myocardial injury (25).

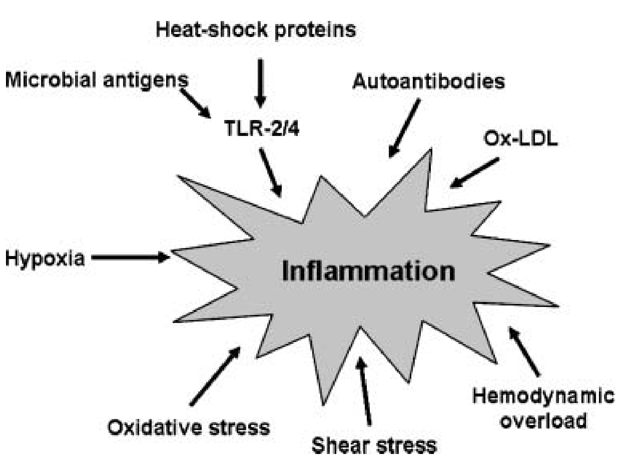

Figure 2. Induction of inflammation in chronic heart failure (HF). While several stimuli may be operating such as autoantibodies, heat shock protein, microbial antigen, bacterial lipopolysaccharide (LPS), shear and oxidative stress, hypoxia, hemodynamic overload and oxidized (Ox)-LDL, it seems that the inflammatory response to these stimuli may represent a common final pathogenic pathway in HF regardless of the initial event. TLR=toll-like receptor.

Pathophysiological consequences of immune activation in HF

In addition to identifying cytokines that are dysregulated during HF, it is important to investigate potentially pathogenic effects of these mediators, and a growing body of evidence indicates that the elevated level of inflammatory cytokines during HF is not merely a parameter for chronic inflammation in seriously ill patients. A series of experimental studies has revealed that the biological effects of cytokines may explain several aspects of the syndrome of chronic HF (26,27) (Figure 3). Thus, TNFα and IL-1β have negative inotropic effects on the myocardium by, for example, uncoupling β-adrenergic signaling (28,29). Moreover, cardiac-specific overexpression of TNFα has been found to promote a phenotype mimicking several features of clinical HF such as cardiac hypertrophy, ventricular dilation and fibrosis, as well as several biochemical and cellular defects (30). Also, infusion of TNFα in concentrations comparable to those found in circulation during HF seems to induce left ventricular dysfunction in rats (31). Moreover, recent data indicate that a complex TNFα-mediated regulation of matrix metalloproteinases (MMP) and tissue inhibitors of MMPs (TIMP) may contribute significantly to myocardial remodeling by modulating the balance between extracellular matrix synthesis

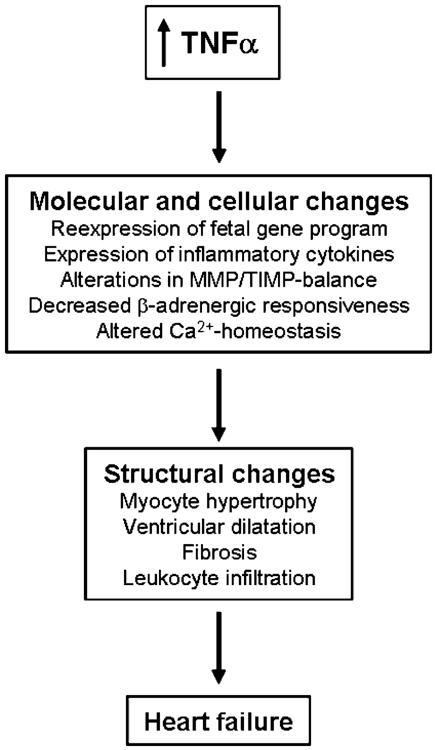

Figure 3. Potential pathogenic consequences of increased tumor necrosis factor (TNF)α activity within the failing myocardium. MMP=matrix metalloproteinases; TIMP=tissue inhibitors of MMPs.

and degradation (32,33). Furthermore, IL-6-related cytokines, such as leukemia inhibitory factor and cardiotrophin-1, signaling through their common receptor subunit gp130, have been found to be potent inducers of cardiomyocyte hypertrophy (34,35). A critical role for gp130-mediated signaling in cardiomyocyte homeostasis and survival was also supported by studies in ventricular restricted gp130 knock-out mice. Possibly due to profound myocyte apoptosis, these mice rapidly develop dilated cardiomyopathy when subjected to aortic pressure overload (36). Hence the gp130-signaling pathway seems to be critical in both adaptive and maladaptive responses within the myocardium.

Chemokines, a family of *chemo*tactic cyto*kines* causing directed migration of leukocytes into inflamed tissue, may both indirectly (e.g. recruitment and activation of infiltrating leukocytes) and directly (e.g. modulation of apoptosis, fibrosis and angiogenesis) promote myocardial failure (37). Thus, interstitial monocyte infiltration in the myocardium with development of a number of pathological changes characterizing HF, including cardiac hypertrophy, ventricular dilation and depressed contractile function, is found in transgenic mice with myocardial over-expression of MCP-1 (38). Moreover, gene therapy targeted against MCP-1 has been shown to attenuate LV function and HF after experimental MI (39). Finally, the observation of high embryonic mortality and developmental defects, including cardiac ventricular septum defects in the CXC-chemokine receptor (CXCR) 4 knock-out mice indicates a crucial and direct role of chemokines in the development and the function of the myocardium (40).

'New' inflammatory mediators in chronic HF

Much attention regarding the immunopathogenesis of HF has been drawn to central inflammatory mediators like TNFα, IL-1β and IL-6 (27). However, much less is known about the levels and potential pathogenic importance of other members of the cytokine network. An important task for future research in this area will therefore be to identify 'new' inflammatory and anti-inflammatory mediators in HF, possibly representing new targets for therapy.

Activin A: Potential role in myocardial remodeling

Based on their role in regulation of growth, differentiation and survival, several members of the transforming growth factor (TGF)-β superfamily such as activin A could potentially have biological effects of relevance to the development of HF (41). Moreover, growing evidence implicates that activin A may play a role in inflammation, and elevated levels of this cytokine have previously been associated with some inflammatory disorders (42). Recently, we demonstrated raised serum levels of activin A also in chronic HF with increasing levels according to disease severity as assessed by clinical, hemodynamic and neurohormonal parameters (43). Moreover, several lines of evidence suggest that this cytokine might also play a pathogenic role in myocardial remodeling. First, we showed that activin A could upregulate MCP-1 production in cardiomyocytes, indicating a role for activin A in inflammation within the failing myocardium. Second, probably connected to its role in wound repair (44), we found that activin A increased the cardiomyocyte expression of TGF-β_1, MMP-2 and TIMP-1, genes that previously have been related to fibrosis and remodeling of extracellular matrix. Third, activin A upregulated the gene expression of both atrial natriuretic peptide and brain natriuretic peptide in cardiomyocytes, encompassing the so-called fetal gene expression pattern associated with myocardial hypertrophy. However, while these findings support a role for activin A in myocardial remodeling, further studies are needed to identify the role of this cytokine more precisely in the progression of HF.

TNF superfamily ligands: Role in myocardial dysfunction

While the pathophysiological role of TNFα in HF has been extensively examined and several studies have reported raised TNFα levels in this disorder, recent reports suggest that also other ligands in the TNF superfamily could play a pathogenic role in chronic HF. Thus, some studies have found increased Fas/Fas ligand (FasL) levels in HF patients (45,46), and we have recently reported enhanced expression of several other ligands in the TNF superfamily in peripheral blood mononuclear cells (PBMC) from HF patients (e.g. CD40L, TNF Receptor Apoptosis Inducing Ligand and CD27L) (47). Based on the knowledge from other disorders and from experimental studies, these mediators could possibly contribute to inflammation, apoptosis and matrix degrading within the failing myocardium. Moreover, the osteoprotegerin (OPG)/receptor activator for NF-κB (RANK)/RANK ligand (RANKL) axis, being members of the TNF/TNF receptor superfamily, has been identified as a candidate mediator for paracrine signaling in bone metabolism (48), and we have recently demonstrated enhanced systemic and myocardial expression of these mediators in both experimental and clinical HF (49). As for serum levels of OPG and RANKL, increased levels were significantly correlated with functional, hemodynamic and neurohormonal parameters for disease severity. More importantly, RANKL was found to markedly induce MMP activity in human fibroblasts, possibly contributing to matrix degrading and remodeling within the failing myocardium. In addition to its role in bone homeostasis, the OPG/RANK/RANKL axis seems to be involved in immune responses (50). In particular, RANKL has been recognized as an important regulator of dendritic cell function. Thus, RANKL treatment prolongs dendritic cell survival and increases the release of inflammatory cytokines such as IL-15 and IL-1β (50). We have demonstrated enhanced RANKL expression in T cells from HF patients and it is tempting to hypothesize that interactions between T cells expressing RANKL and dendritic cells, for example in the failing myocardium, may represent a link between adaptive and innate immune responses, leading to both persistent and increased inflammation in HF patients. This demonstration of enhanced OPG/RANK/RANKL expression in HF suggests a role for known mediators of bone homeostasis in the pathogenesis of HF possibly representing new targets for therapeutic intervention in this disorder.

Immunomodulatory effects of traditional cardiovascular therapy

Based on the data outlined above, it is conceivable to hypothesize that treatment targeting immune activation and inflammation may have beneficial effects and represent a new therapeutic paradigm for treatment of patients with HF. Based on experimental studies, traditional cardiovascular drugs could also potentially attenuate this persistent inflammation. Thus several *in vitro* studies and studies in animal models have demonstrated that neurohormones such as angiotensin II and noradrenalin can induce the expression of inflammatory cytokines and that cardiovascular drugs such as ACE-inhibitors and β-blockers may have anti-inflammatory effects (51–53). However, few clinical studies have examined how conventional HF medication influences the immune activation in HF. High-dose ACE-inhibition with enalapril has been shown to cause a marked decrease in IL-6 bioactivity, associated with a reduction in left ventricular septum thickness (54). Thus, it is possible that the anti-hypertrophic effect of ACE inhibition on the myocardium may at least partly be mediated by a reduction in IL-6 levels. However, except for this effect on IL-6, ACE inhibitors seem to have only minor influence on inflammation in HF patients (54). Selective angiotensin II receptor blockers may theoretically in some aspects be superior to ACE-inhibitors, but we have recently shown that these receptor blockers do not differ from ACE-inhibitors in their ability to downregulate inflammation in HF (55,56). Reduced IL-6 levels may be of importance for the beneficial effect of amlodipine on mortality in patients with IDCM, but this agent had no effect on TNFα levels in these patients (57). Various lymphocyte subsets and monocytes express β-adrenergic receptors, and several *in vitro* studies have shown that β-adrenergic stimulation may modulate cytokine production in these cells, possibly secondary to enhanced intracellular levels of cyclic adenosine monophosphate (58). However, long term treatment with the β_1-selective blocker metoprolol had no significant effect on cytokine levels comparing placebo in patients with HF (59). On the other hand, a recent pilot study showed downregulatory effects of carvedilol on IL-6 levels in plasma, possibly implicating that more complete blockade of the β-receptors (i.e. non-selective), or combined α- and β-blockade may alter the cytokine network (60). Nevertheless, despite 'state of the art'-treatment, patients with HF still have elevated levels of inflammatory cytokines. Moreover, some of the observed effects on the immune system may be secondary to improved LV and not a direct effect of these drugs. Thus, while conventional HF therapy could have some anti-inflammatory effects, there is a need for more specific immunomodulatory treatment modalities in this disorder.

Negative results of the anti-TNF studies

Preliminary reports suggested that TNFα inhibition with a recombinant soluble TNFR fusion protein (etanercept) may have beneficial effects on cardiac performance in HF patients (61). Given the potential central role of TNFα in the pathogenesis of HF, therapeutic modulation targeting this particular cytokine has received much attention. However, three clinical trials examining the effects of anti-TNF therapy in HF were recently discontinued because of lack of effect (RENAISSANCE, RECOVER) or higher rates of mortality and hospitalization (ATTACH) (62,63). The lack of positive effects of anti-TNF treatment in these studies may have several explanations. First, compared to previous pilot studies in HF patients (etanercept) and studies in other human disorders (infliximab) the dosage used in these new multicenter studies was rather high, and the correct dosage for anti-TNF therapy in HF patients needs to be established before any firm conclusion can be drawn. In particular, recent reports suggest a dose-dependent toxicity during anti-TNF therapy, further underscoring this issue. Second, a recent study in animal models showed that while etanercept decreased plasma cytokine levels, there was no decrease in IL-6 and MCP-1 within the myocardium (64). Third, the chimeric anti-TNF antibody (infliximab) used in the ATTACH trial, directly binds to the transmembrane form of TNF, resulting in damage to TNF-expressing cells by both antibody-dependent cellular toxicity, complement-dependent cytotoxic effector mechanisms and by induction of apoptosis (65). While such mechanisms may be beneficial in inflammatory disorders such as inflammatory bowel disease, it may result in deleterious effects in chronic HF, secondary to damage of TNF-expressing cardiomyocytes. Fourth, while too much of inflammatory cytokines such as TNF may be harmful, too little of these mediators may also have adverse effects on the myocardium reflecting the involvement of these cytokines in both maladaptive and adaptive responses (28,36,66). Fifth, using mice overexpressing TNFα, Li et al. recently demonstrated that intervention with an MMP-inhibitor had clear beneficial effects in young mice, but not in older mice with established HF (67). It is not inconceivable that some degree of irreversibility also may exist for other cytokine-mediated effects, and an important area for future research will be to establish when to initiate anti-cytokine treatment in HF. Finally, and most importantly, while several studies have focused on the possible pathogenic role of TNFα and targeted therapy against this molecule, further research in this area will have to identify more precisely the most important actors in the immunopathogenesis of chronic HF in order to develop more specific immunomodulating agents in this disorder. Thus, although the results of the placebo-controlled anti-TNF trials may seem disappointing, they do not mean the end of the cytokine era before it has even started. For example, although etanercept therapy resulted in increased mortality in patients with septic shock, few if anyone questioned the pathogenic role of inflammation in this disorder.

Other potential immunomodulators in HF: Clinical trials

In addition to anti-TNF therapy, several other potential immunomodulators have been investigated in HF patients (Table I).

Pentoxifylline

Pentoxifylline, a xanthine-derived agent known to inhibit the production of TNFα was the first immunomodulatory agent that showed beneficial effects in chronic HF patients in clinical trials (68). These results were confirmed in HF patients with IDCM receiving treatment with ACE inhibitors and β-blockers, showing a pentoxifylline-induced improvement in symptoms and left ventricular

Table I. Immunomodulation in heart failure: Potential immunomodulatory treatment modalities

Pentoxifylline
Thalidomide
Soluble TNF receptors
Intravenous immunoglobulin
Immunoadsorption
Statins
Chemokine antagonists
Interleukin-10
Interleukin-1 receptor antagonist
Peroxisome proliferator-activated receptor agonists
Mast cell-stabilizing agent, i.e. tranilast
Inhibitors of T cell activation (e.g. CTLA4Ig fusion protein)
Autologous stem cell transplantation

function (69). Although these findings were accompanied by decreased plasma levels of brain natriuretic peptide, TNFα and Fas, this does not prove any causal relationship. In fact, pentoxifylline is a non-specific inhibitor of phosphodiesterases with potential effects on the myocardium not necessarily related to immunomodulatory properties of this medication.

Thalidomide

The sedative and anti-nausea drug thalidomide has been shown to have both anti-inflammatory and anti-oncogenic properties, and diseases such as erythema nodosum, rheumatoid arthritis and cancers are currently being treated with thalidomide. Interestingly, thalidomide was recently shown to improve the LVEF in HF patients (70). However, few patients were studied in this open pilot trial. Moreover, thalidomide has also been shown to enhance $CD8^+$ T cell activity (71) and to increase plasma levels of IL-12 (72), and together with its anti-angiogenic properties (73), such effects might limit its use in HF.

Statins

Treatment with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) have led to a remarkable improvement in the prognosis of coronary artery disease (74,75). In addition to reducing LDL cholesterol, recent data suggest that statins also can act as immunomodulatory and anti-inflammatory agents, possibly related to the beneficial effects of these medications (76–78). Interestingly, *in vitro* experiments and studies in animal models have shown that statins may prevent the development of cardiac hypertrophy in a cholesterol-independent manner involving immunomodulatory as well as anti-oxidative and MMP-inhibiting effects of these medications (79–81). In fact, the combination of cholesterol-lowering, immunomodulatory and anti-oxidative properties suggest that statins should be an interesting therapeutic approach in HF. However, the loss of the protection that lipoproteins may provide through binding and detoxifying endotoxins entering the circulation via the gut may be potentially harmful in HF patients (82). Moreover, although statins exert anti-inflammatory properties, some important inflammatory cytokines have been shown to be unmodified or even up-regulated by these medications in some studies (83,84). These uncertainties indicate the need for a definitive outcome trial to assess the efficacy and safety of statins in HF.

Immunoadsorption

Cardiac autoantibodies against cardiac cell proteins such as mitochondrial proteins, contractile proteins, cardiac β_1-adrenergic receptors and muscarinergic receptors may play a pathogenic role in IDCM, and notably, their removal by immunoadsorption has been shown to improve cardiac function in this disorder (85,86). Interestingly, such therapy in combination with subsequent intravenous immunoglobulin (IVIG) therapy was recently shown to decrease the numbers of activated leukocytes within the failing myocardium (87). While IVIG has potent modulatory effects on the cytokine network (see below), no such effects have been demonstrated for immunoadsorption and although similarities exist, it is possible that these immunomodulatory treatment modalities may have different mechanisms of action with potential additive or even synergistic effects as a consequence.

IVIG therapy in HF: Modulatory effects on the cytokine network

Therapy with IVIG has been evaluated in a wide range of immune-mediated disorders, such as Kawasaki syndrome, dermatomyositis, idiopathic thrombocytopenic purpura and multiple sclerosis (88,89). Beneficial effects of IVIG have also been suggested in acute and peripartum cardiomyopathy (90,91), and recently we demonstrated in a double-blind, placebo-controlled study that IVIG significantly enhanced LVEF by 5% in HF patients, independent of the etiology of HF (92). Several non-mutually exclusive modes of action may be of importance for the clinical effects of IVIG in inflammatory disorders such as neutralization of microbial antigens and superantigens, Fc-receptor blockade, impairment of leukocyte adhesion to endothelial cells and decreased apoptosis (93–95). All these factors may be involved in the pathogenesis of HF and may be potential targets for the beneficial effects of IVIG in HF patients. IVIG has also been found to attenuate complement inactivation (93), but this appears not to be the case in HF patients. In fact, we have recently shown that rather than inactivation, IVIG induced complement activation in these patients suggesting a role for complement inhibitors in addition to IVIG in HF (96). In our opinion, particular attention should be drawn towards the effect of IVIG on the cytokine network. Thus, we and others have demonstrated that IVIG may influence the levels of several cytokines and cytokine modulators, resulting in downregulation of inflammatory responses (93,97,98). Indeed, we showed that the improvement in LVEF in HF patients was correlated with a marked rise in the anti-inflammatory mediators IL-10, IL-1 receptor antagonist (IL-1Ra) and soluble TNFRs, accompanied by a slight decrease in TNFα and IL-1β, suggesting an anti-inflammatory net effect with potentially beneficial effect on the myocardium (92). Moreover, we have recently reported that IVIG therapy, but not placebo, may also downregulate chemokines and their corresponding receptors in PBMC from HF patients, possibly contributing to the beneficial effect of IVIG in HF (9). Thus, IVIG appears to have a balanced and dual effect on the cytokine network with a downregulation of certain inflammatory mediators (e.g. IL-8 and IL-1) combined with an upregulation of anti-inflammatory mediators (e.g. IL-10 and IL-1Ra).

New therapeutic targets in HF

In addition to therapy directed against TNFα several immunomodulatory treatment options with the potential to improve myocardial function have been investigated in animal models and *in vitro* systems as well as in some pilot studies in HF patients (Table I). Recently, the plasticity of uncommitted stem cells has opened up new perspectives in tissue regeneration, and such an approach has also been applied to restore cardiac function after myocardial infarction (MI) (99). Interestingly, members of the TGF-β superfamily seem to promote differentiation of embryonic stem cells into cardiomyocytes, and other cytokines including chemokines and members of the TNF superfamily could also be involved in this process (100). Thus, these cytokines could have a therapeutic potential as adjuvants in stem cell therapy.

We have recently demonstrated enhanced T cell activation in chronic HF, potentially contributing to both systemic and myocardial inflammation (10). Thus, intervention that inhibits this unwanted T cell activity could represent a new treatment modality in HF. Cytotoxic T lymphocyte–associated antigen 4 (CTLA4) has been suggested as an attractive target for modulation of T cell activity (101). CTLA4 is expressed on the surface of T cells hours or days after they become activated, and a genetically constructed CTLA4Ig fusion protein has been shown to block T cell activation by binding to CD80 and CD86 on antigen-presenting cells, thereby preventing these molecules from engaging CD28 on T cells. By blocking the engagement of CD28, CTLA4Ig prevents the delivery of the second co-stimulatory signal that is required for optimal T cell activation (101). Such an approach to inhibit T cell activation has demonstrated beneficial effects in many animal models of autoimmune disease and allograft rejection, and CTLA4Ig was recently shown to improve signs and symptoms of disease activity in patients with rheumatoid arthritis (102). Based on the potential pathogenic role of T cell activation in chronic HF such an approach for T cell inhibition could also be beneficial in HF patients.

In addition to therapy directed against TNFα, several immunomodulatory treatment options with the potential to improve myocardial function have been investigated in animal models and *in vitro* systems. Thus, gene therapy with an MCP-1 antagonist was recently found to attenuate the development of ventricular remodeling in a mouse model for post-MI HF (39). Also, IL-10 has been found to have protective effects on the development of viral myocarditis in mice (103), and IL-1 receptor antagonist may provide cardioprotection against ischemia-reperfusion injury in rat cardiomyocytes (104). Moreover, activators of peroxisome proliferator-activated receptors have been shown to impair endotoxin-stimulated TNFα expression in rat cardiomyocytes and to impair cardiac hypertrophy in pressure overload exposed mice, at least partly by inhibiting NF-κB activation leading to a decreased inflammatory response (105,106). Furthermore, treatment with tranilast, a mast cell-stabilizing agent, has been found to prevent the evolution from compensated hypertrophy to HF in mice, suggesting a role for these immunocompetent cells in the progression of HF (107). Interestingly, tranilast has also been shown to modulate other cell types with relevance to cardiac remodeling such as fibroblasts (108).

Conclusion

Several lines of evidence suggest a role for inflammatory cytokines in the pathogenesis of chronic HF. Although somewhat disappointing, the negative results from the placebo-controlled anti-TNF studies do not necessarily argue against this 'cytokine hypothesis'. These studies just underscore the difficulties and the challenges in developing treatment modalities that can modulate the cytokine network in HF patients resulting in anti-inflammatory and beneficial net effects (Figure 1). Further research in this area will have to identify more precisely the most important actors in the immunopathogenesis of chronic HF in order to develop more specific immunomodulating agents for this disorder.

References

1. Jessup M, Brozena S. Heart failure. N Engl J Med. 2003;348:2007–18.

2. Mann DL, Deswal A, Bozkurt B, Torre-Amione G. New therapeutics for chronic heart failure. Annu Rev Med. 2002;53:59–74.
3. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med. 1990;323:236–41.
4. Aukrust P, Ueland T, Lien E, Bendtzen K, Müller F, Andreassen AK, et al. Cytokine network in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1999;83:376–82.
5. Aukrust P, Ueland T, Müller F, Andreassen AK, Nordøy I, Aas H, et al. Elevated circulating levels of C-C chemokines in patients with congestive heart failure. Circulation. 1998;97:1136–43.
6. Damås JK, Gullestad L, Ueland T, Solum NO, Simonsen S, Frøland SS, et al. CXC-chemokines, a new group of cytokines in congestive heart failure–possible role of platelets and monocytes. Cardiovasc Res. 2000;45:428–36.
7. Testa M, Yeh M, Lee P, Fanelli R, Loperfido F, Berman JW, et al. Circulating levels of cytokines and their endogenous modulators in patients with mild to severe congestive heart failure due to coronary artery disease or hypertension. J Am Coll Cardiol. 1996;28:964–71.
8. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol. 1996;27:1201–6.
9. Damås JK, Gullestad L, Aass H, Simonsen S, Fjeld JG, Wikeby L, et al. Enhanced gene expression of chemokines and their corresponding receptors in mononuclear blood cells in chronic heart failure–modulatory effect of intravenous immunoglobulin. J Am Coll Cardiol. 2001;38:187–93.
10. Yndestad A, Holm AM, Müller F, Simonsen S, Frøland SS, Gullestad L, et al. Enhanced expression of inflammatory cytokines and activation markers in T-cells from patients with chronic heart failure. Cardiovasc Res. 2003;60:141–6.
11. Torre-Amione G, Kapadia S, Lee J, Durand JB, Bies RD, Young JB, et al. Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. Circulation. 1996;93:704–11.
12. Eiken HG, Øie E, Damås JK, Yndestad A, Bjerkeli V, Aass H, et al. Myocardial gene expression of leukaemia inhibitory factor, interleukin-6 and glycoprotein 130 in end-stage human heart failure. Eur J Clin Invest. 2001;31:389–97.
13. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). Circulation. 2001;103:2055–9.
14. Calabrese F, Thiene G. Myocarditis and inflammatory cardiomyopathy: microbiological and molecular biological aspects. Cardiovasc Res. 2003;60:11–25.
15. Becker AE, de Boer OJ, van Der Wal AC. The role of inflammation and infection in coronary artery disease. Annu Rev Med. 2001;52:289–97.
16. Penninger JM, Bachmaier K. Review of microbial infections and the immune response to cardiac antigens. J Infect Dis. 2000;181(Suppl 3):S498–504.
17. Niebauer J, Volk H-D, Kemp M, Dominguez M, Schumann RR, Rauchhaus M, et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. Lancet. 1999;353:1838–42.
18. Conraads VM, Jorens PG, De Clerck LS, Van Saene HK, Ieven MM, Bosmans JM, et al. Selective intestinal decontamination in advanced chronic heart failure: a pilot trial. Eur J Heart Fail. 2004;6:483–91.
19. Gelfand EV, Cannon CP. Antibiotics for secondary prevention of coronary artery disease: an ACES hypothesis but we need to PROVE IT. Am Heart J. 2004;147:202–9.
20. Shioi T, Matsumori A, Kihara Y, Inoko M, Ono K, Iwanaga Y, et al. Increased expression of interleukin-1 beta and monocyte chemotactic and activating factor/monocyte chemoattractant protein-1 in the hypertrophied and failing heart with pressure overload. Circ Res. 1997;81:664–71.
21. Okada M, Matsumori A, Ono K, Furukawa Y, Shioi T, Iwasaki A, et al. Cyclic stretch upregulates production of interleukin-8 and monocyte chemotactic and activating factor/monocyte chemoattractant protein-1 in human endothelial cells. Arterioscler Thromb Vasc Biol. 1998;18:894–901.
22. Singal PK, Khaper N, Palace V, Kumar D. The role of oxidative stress in the genesis of heart disease. Cardiovasc Res. 1998;40:426–32.
23. Janabi M, Yamashita S, Hirano K, Sakai N, Hiraoka H, Matsumoto K, et al. Oxidized LDL-induced NF-kappa B activation and subsequent expression of proinflammatory genes are defective in monocyte-derived macrophages from CD36-deficient patients. Arterioscler Thromb Vasc Biol. 2000;20:1953–60.
24. Knuefermann P, Vallejo J, Mann DL. The role of innate immune responses in the heart in health and disease. Trends Cardiovasc Med. 2004;14:1–7.
25. Shishido T, Nozaki N, Yamaguchi S, Shibata Y, Nitobe J, Miyamoto T, et al. Toll-Like Receptor-2 Modulates Ventricular Remodeling After Myocardial Infarction. Circulation. 2003;108:2905–10.
26. Blum A, Miller H. Pathophysiological role of cytokines in congestive heart failure. Annu Rev Med. 2001; 52:15–27.
27. Mann DL. Inflammatory Mediators and the Failing Heart: Past, Present, and the Foreseeable Future. Circ Res. 2002;91:988–98.
28. Meldrum DR. Tumor necrosis factor in the heart. Am J Physiol. 1998;274:R577–95.
29. Feldman AM, Combes A, Wagner D, Kadakomi T, Kubota T, Li YY, et al. The role of tumor necrosis factor in the pathophysiology of heart failure. J Am Coll Cardiol. 2000;35:537–44.
30. Kubota T, McTiernan CF, Frye CS, Slawson SE, Lemster BH, Koretsky AP, et al. Dilated Cardiomyopathy in Transgenic Mice With Cardiac-Specific Overexpression of Tumor Necrosis Factor-alpha. Circ Res. 1997;81: 627–35.
31. Bozkurt B, Kribbs SB, Clubb FJ, Jr., Michael LH, Didenko VV, Hornsby PJ, et al. Pathophysiologically relevant concentrations of tumor necrosis factor- alpha promote progressive left ventricular dysfunction and remodeling in rats. Circulation. 1998;97:1382–91.
32. Bradham WS, Bozkurt B, Gunasinghe H, Mann D, Spinale FG. Tumor necrosis factor-alpha and myocardial remodeling in progression of heart failure: a current perspective. Cardiovasc Res. 2002;53:822–30.
33. Sivasubramanian N, Coker ML, Kurrelmeyer KM, MacLellan WR, DeMayo FJ, Spinale FG, et al. Left ventricular remodeling in transgenic mice with cardiac restricted overexpression of tumor necrosis factor. Circulation. 2001;104:826–31.
34. Kodama H, Fukuda K, Pan J, Makino S, Baba A, Hori S, et al. Leukemia inhibitory factor, a potent cardiac

hypertrophic cytokine, activates the JAK/STAT pathway in rat cardiomyocytes. Circ Res. 1997;81:656–63.
35. Wollert KC, Chien KR. Cardiotrophin-1 and the role of gp130-dependent signaling pathways in cardiac growth and development. J Mol Med. 1997;75:492–501.
36. Hirota H, Chen J, Betz UA, Rajewsky K, Gu Y, Ross J, Jr., et al. Loss of a gp130 cardiac muscle cell survival pathway is a critical event in the onset of heart failure during biomechanical stress. Cell. 1999;97:189–98.
37. Sasayama S, Okada M, Matsumori A. Chemokines and cardiovascular diseases. Cardiovasc Res. 2000;45:267–9.
38. Kolattukudy PE, Quach T, Bergese S, Breckenridge S, Hensley J, Altschuld R, et al. Myocarditis induced by targeted expression of the MCP-1 gene in murine cardiac muscle. Am J Pathol. 1998;152:101–11.
39. Hayashidani S, Tsutsui H, Shiomi T, Ikeuchi M, Matsusaka H, Suematsu N, et al. Anti-Monocyte Chemoattractant Protein-1 Gene Therapy Attenuates Left Ventricular Remodeling and Failure After Experimental Myocardial Infarction. Circulation. 2003;108:2134–40.
40. Tachibana K, Hirota S, Iizasa H, Yoshida H, Kawabata K, Kataoka Y, et al. The chemokine receptor CXCR4 is essential for vascularization of the gastrointestinal tract. Nature. 1998;393:591–4.
41. Chen YG, Lui HM, Lin SL, Lee JM, Ying SY. Regulation of cell proliferation, apoptosis, and carcinogenesis by activin. Exp Biol Med (Maywood). 2002;227:75–87.
42. Phillips DJ, Jones KL, Scheerlinck JY, Hedger MP, de Kretser DM. Evidence for activin A and follistatin involvement in the systemic inflammatory response. Mol Cell Endocrinol. 2001;180:155–62.
43. Yndestad A, Ueland T, Øie E, Florholmen G, Halvorsen B, Attramadal H, et al. Elevated levels of activin A in heart failure: potential role in myocardial remodeling. Circulation. 2004;109:1379–85.
44. Munz B, Smola H, Engelhardt F, Bleuel K, Brauchle M, Lein I, et al. Overexpression of activin A in the skin of transgenic mice reveals new activities of activin in epidermal morphogenesis, dermal fibrosis and wound repair. EMBO J. 1999;18:5205–15.
45. Yamaguchi S, Yamaoka M, Okuyama M, Nitoube J, Fukui A, Shirakabe M, et al. Elevated circulating levels and cardiac secretion of soluble Fas ligand in patients with congestive heart failure. Am J Cardiol. 1999;83: 1500–3, A8.
46. Nishigaki K, Minatoguchi S, Seishima M, Asano K, Noda T, Yasuda N, et al. Plasma Fas ligand, an inducer of apoptosis, and plasma soluble Fas, an inhibitor of apoptosis, in patients with chronic congestive heart failure. J Am Coll Cardiol. 1997;29:1214–20.
47. Yndestad A, Damås JK, Eiken HG, Holm T, Haug T, Simonsen S, et al. Increased gene expression of tumor necrosis factor superfamily ligands in peripheral blood mononuclear cells during chronic heart failure. Cardiovasc Res. 2002;54:175–82.
48. Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS, Luthy R, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell. 1997;89:309–19.
49. Ueland T, Yndestad A, Øie E, Florholmen G, Halvorsen B, Frøland SS, et al. Dysregulated Osteoprotegerin/RANK Ligand/RANK axis in Clinical and Experimental Heart failure. Circulation. In press, 2005.
50. Walsh MC, Choi Y. Biology of the TRANCE axis. Cytokine Growth Factor Rev. 2003;14:251–63.
51. Sano M, Fukuda K, Kodama H, Pan J, Saito M, Matsuzaki J, et al. Interleukin-6 family of cytokines mediate angiotensin II-induced cardiac hypertrophy in rodent cardiomyocytes. J Biol Chem. 2000;275:29717–23.
52. Prabhu SD, Chandrasekar B, Murray DR, Freeman GL. Beta-Adrenergic Blockade in Developing Heart Failure: Effects on Myocardial Inflammatory Cytokines, Nitric Oxide, and Remodeling. Circulation. 2000;101: 2103–9.
53. Wei GC, Sirois MG, Qu R, Liu P, Rouleau JL. Subacute and chronic effects of quinapril on cardiac cytokine expression, remodeling, and function after myocardial infarction in the rat. J Cardiovasc Pharmacol. 2002; 39:842–50.
54. Gullestad L, Aukrust P, Ueland T, Espevik T, Yee G, Vagelos R, et al. Effect of high- versus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure. J Am Coll Cardiol. 1999;34:2061–7.
55. Ueland T, Jemtland R, Godang K, Kjekshus J, Hognestad A, Omland T, et al. Prognostic value of osteoprotegerin in heart failure after acute myocardial infarction. J Am Coll Cardiol. 2004;44:1970–6.
56. Ueland T, Aukrust P, Yndestad A, Otterdal K, Frøland SS, Dickstein K, et al. Soluble CD40 ligand in acute and chronic heart failure. Eur Heart J. In press, 2005.
57. Mohler ER 3rd, Sorensen LC, Ghali JK, Schocken DD, Willis PW, Bowers JA, et al. Role of Cytokines in the Mechanism of Action of Amlodipine: The PRAISE Heart Failure Trial. J Am Coll Cardiol. 1997;30:35–41.
58. Werner C, Werdan K, Ponicke K, Brodde OE. Impaired beta-adrenergic control of immune function in patients with chronic heart failure: reversal by beta1-blocker treatment. Basic Res Cardiol. 2001;96:290–8.
59. Gullestad L, Ueland T, Brunsvig A, Kjekshus J, Simonsen S, Frøland SS, et al. Effect of metoprolol on cytokine levels in chronic heart failure–A substudy in the Metoprolol Controlled-Release Randomised Intervention Trial in Heart Failure (MERIT-HF). Am Heart J. 2001;141: 418–21.
60. Matsumura T, Tsushima K, Ohtaki E, Misu K, Tohbaru T, Asano R, et al. Effects of carvedilol on plasma levels of interleukin-6 and tumor necrosis factor-alpha in nine patients with dilated cardiomyopathy. J Cardiol. 2002; 39:253–7.
61. Bozkurt B, Torre-Amione G, Warren MS, Whitmore J, Soran OZ, Feldman AM, et al. Results of Targeted Anti-Tumor Necrosis Factor Therapy With Etanercept (ENBREL) in Patients With Advanced Heart Failure. Circulation. 2001;103:1044–7.
62. Mann DL, McMurray JJV, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted Anticytokine Therapy in Patients With Chronic Heart Failure: Results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation. 2004;109:1594–602.
63. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, Double-Blind, Placebo-Controlled, Pilot Trial of Infliximab, a Chimeric Monoclonal Antibody to Tumor Necrosis Factor-alpha, in Patients With Moderate-to-Severe Heart Failure: Results of the Anti-TNF Therapy Against Congestive Heart failure (ATTACH) Trial. Circulation. 2003;107:3133–40.
64. Kadokami T, McTiernan CF, Kubota T, Frye CS, Bounoutas GS, Robbins PD, et al. Effects of soluble TNF receptor treatment on lipopolysaccharide-induced

myocardial cytokine expression. Am J Physiol Heart Circ Physiol. 2001;280:H2281–91.
65. Lugering A, Schmidt M, Lugering N, Pauels HG, Domschke W, Kucharzik T. Infliximab induces apoptosis in monocytes from patients with chronic active Crohn's disease by using a caspase-dependent pathway. Gastroenterology. 2001;121:1145–57.
66. Kunisada K, Tone E, Fujio Y, Matsui H, Yamauchi-Takihara K, Kishimoto T. Activation of gp130 transduces hypertrophic signals via STAT3 in cardiac myocytes. Circulation. 1998;98:346–52.
67. Li YY, Kadokami T, Wang P, McTiernan CF, Feldman AM. MMP inhibition modulates TNF-alpha transgenic mouse phenotype early in the development of heart failure. Am J Physiol Heart Circ Physiol. 2002;282:H983–9.
68. Sliwa K, Skudicky D, Candy G, Wisenbaugh T, Sareli P. Randomised investigation of effects of pentoxifylline on left-ventricular performance in idiopathic dilated cardiomyopathy. Lancet. 1998;351:1091–3.
69. Skudicky D, Bergemann A, Sliwa K, Candy G, Sareli P. Beneficial effects of pentoxifylline in patients with idiopathic dilated cardiomyopathy treated with angiotensin-converting enzyme inhibitors and carvedilol: results of a randomized study. Circulation. 2001;103:1083–8.
70. Gullestad L, Semb AG, Holt E, Skardal R, Ueland T, Yndestad A, et al. Effect of thalidomide in patients with chronic heart failure. Am Heart J. 2002;144:847–50.
71. Haslett PA, Corral LG, Albert M, Kaplan G. Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. J Exp Med. 1998; 187:1885–92.
72. Haslett PA, Klausner JD, Makonkawkeyoon S, Moreira A, Metatratip P, Boyle B, et al. Thalidomide stimulates T cell responses and interleukin 12 production in HIV-infected patients. AIDS Res Hum Retroviruses. 1999;15:1169–79.
73. Adlard JW. Thalidomide in the treatment of cancer. Anticancer Drugs. 2000;11:787–91.
74. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–9.
75. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med. 1998;339:1349–57.
76. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. Nat Med. 2000;6:1399–402.
77. Waehre T, Damas JK, Gullestad L, Holm AM, Pedersen TR, Arnesen KE, et al. Hydroxymethylglutaryl coenzyme a reductase inhibitors down-regulate chemokines and chemokine receptors in patients with coronary artery disease. J Am Coll Cardiol. 2003;41:1460–7.
78. Waehre T, Yndestad A, Smith C, Haug T, Tunheim SH, Gullestad L, et al. Increased expression of interleukin-1 in coronary artery disease with downregulatory effects of HMG-CoA reductase inhibitors. Circulation. 2004;109:1966–72.
79. Laufs U, Kilter H, Konkol C, Wassmann S, Bohm M, Nickenig G. Impact of HMG CoA reductase inhibition on small GTPases in the heart. Cardiovasc Res. 2002;53:911–20.
80. Hayashidani S, Tsutsui H, Shiomi T, Suematsu N, Kinugawa S, Ide T, et al. Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, attenuates left ventricular remodeling and failure after experimental myocardial infarction. Circulation. 2002;105:868–73.
81. Takemoto M, Node K, Nakagami H, Liao Y, Grimm M, Takemoto Y, et al. Statins as antioxidant therapy for preventing cardiac myocyte hypertrophy. J Clin Invest. 2001;108:1429–37.
82. Krum H, McMurray JJ. Statins and chronic heart failure: do we need a large-scale outcome trial? J Am Coll Cardiol. 2002;39:1567–73.
83. Holm T, Andreassen AK, Ueland T, Kjekshus J, Froland SS, Kjekshus E, et al. Effect of pravastatin on plasma markers of inflammation and peripheral endothelial function in male heart transplant recipients. Am J Cardiol. 2001;87:815–8, A9.
84. Kiener PA, Davis PM, Murray JL, Youssef S, Rankin BM, Kowala M. Stimulation of inflammatory responses in vitro and in vivo by lipophilic HMG-CoA reductase inhibitors. Int Immunopharmacol. 2001;1:105–18.
85. Felix SB, Staudt A, Friedrich GB. Improvement of cardiac function after immunoadsorption in patients with dilated cardiomyopathy. Autoimmunity. 2001;34:211–5.
86. Felix SB, Staudt A, Landsberger M, Grosse Y, Stangl V, Spielhagen T, et al. Removal of cardiodepressant antibodies in dilated cardiomyopathy by immunoadsorption. J Am Coll Cardiol. 2002;39:646–52.
87. Staudt A, Schaper F, Stangl V, Plagemann A, Bohm M, Merkel K, et al. Immunohistological changes in dilated cardiomyopathy induced by immunoadsorption therapy and subsequent immunoglobulin substitution. Circulation. 2001;103:2681–6.
88. Ballow M. Mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory diseases. J Allergy Clin Immunol. 1997;100:151–7.
89. Mobini N, Sarela A, Ahmed AR. Intravenous immunoglobulins in the therapy of autoimmune and systemic inflammatory disorders. Ann Allergy Asthma Immunol. 1995;74:119–28. Quiz 128–33.
90. McNamara DM, Rosenblum WD, Janosko KM, Trost MK, Villaneuva FS, Demetris AJ, et al. Intravenous immune globulin in the therapy of myocarditis and acute cardiomyopathy. Circulation. 1997;95:2476–8.
91. Bozkurt B, Villaneuva FS, Holubkov R, Tokarczyk T, Alvarez RJ, Jr., MacGowan GA, et al. Intravenous immune globulin in the therapy of peripartum cardiomyopathy. J Am Coll Cardiol. 1999;34:177–80.
92. Gullestad L, Aass H, Fjeld JG, Wikeby L, Andreassen AK, Ihlen H, et al. Immunomodulating Therapy With Intravenous Immunoglobulin in Patients With Chronic Heart Failure. Circulation. 2001;103:220–5.
93. Wolf HM, Eibl MM. Immunomodulatory effect of immunoglobulins. Clin Exp Rheumatol. 1996;14 Suppl 15: S17–25.
94. Vassilev TL, Kazatchkine MD, Van Huyen JP, Mekrache M, Bonnin E, Mani JC, et al. Inhibition of cell adhesion by antibodies to Arg-Gly-Asp (RGD) in normal immunoglobulin for therapeutic use (intravenous immunoglobulin, IVIg). Blood. 1999;93:3624–31.
95. Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science. 1998;282:490–3.
96. Aukrust P, Gullestad L, Lappegård KT, Ueland T, Aass H, Wikeby L, et al. Complement activation in patients with congestive heart failure: effect of high-dose intravenous immunoglobulin treatment. Circulation. 2001;104: 1494–500.
97. Andersson UG, Bjork L, Skansen-Saphir U, Andersson JP. Down-regulation of cytokine production and interleukin-2

receptor expression by pooled human IgG. Immunology. 1993;79:211–6.

98. Aukrust P, Frøland SS, Liabakk NB, Müller F, Nordøy I, Haug C, et al. Release of cytokines, soluble cytokine receptors, and interleukin-1 receptor antagonist after intravenous immunoglobulin administration in vivo. Blood. 1994;84:2136–43.
99. Lee MS, Makkar RR. Stem-cell transplantation in myocardial infarction: a status report. Ann Intern Med. 2004;140:729–37.
100. Tiedemann H, Asashima M, Grunz H, Knochel W. Pluripotent cells (stem cells) and their determination and differentiation in early vertebrate embryogenesis. Dev Growth Differ. 2001;43:469–502.
101. Green JM. The B7/CD28/CTLA4 T-Cell Activation Pathway . Implications for Inflammatory Lung Disease. Am J Respir Cell Mol Biol. 2000;22:261–4.
102. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, et al. Treatment of Rheumatoid Arthritis by Selective Inhibition of T-Cell Activation with Fusion Protein CTLA4Ig. N Engl J Med. 2003;349:1907–15.
103. Nishio R, Matsumori A, Shioi T, Ishida H, Sasayama S. Treatment of experimental viral myocarditis with interleukin-10. Circulation. 1999;100:1102–8.
104. Suzuki K, Murtuza B, Smolenski RT, Sammut IA, Suzuki N, Kaneda Y, et al. Overexpression of Interleukin-1 Receptor Antagonist Provides Cardioprotection Against Ischemia-Reperfusion Injury Associated With Reduction in Apoptosis. Circulation. 2001;104 (Suppl 1):1308–13.
105. Takano H, Nagai T, Asakawa M, Toyozaki T, Oka T, Komuro I, et al. Peroxisome proliferator-activated receptor activators inhibit lipopolysaccharide-induced tumor necrosis factor-alpha expression in neonatal rat cardiac myocytes. Circ Res. 2000;87:596–602.
106. Asakawa M, Takano H, Nagai T, Uozumi H, Hasegawa H, Kubota N, et al. Peroxisome Proliferator-Activated Receptor gamma Plays a Critical Role in Inhibition of Cardiac Hypertrophy In Vitro and In Vivo. Circulation. 2002;105:1240–6.
107. Hara M, Ono K, Hwang MW, Iwasaki A, Okada M, Nakatani K, et al. Evidence for a role of mast cells in the evolution to congestive heart failure. J Exp Med. 2002;195:375–81.
108. Hocher B, Godes M, Olivier J, Weil J, Eschenhagen T, Slowinski T, et al. Inhibition of left ventricular fibrosis by tranilast in rats with renovascular hypertension. J Hypertens. 2002;20:745–51.