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JOINT SESSION OF THE INTERNATIONAL SOCIETY FOR HEART RESEARCH EUROPE AND THE GERMAN CARDIAC SOCIETY: TNFα IN HEART FAILURE

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Tumour necrosis factor-α and the failing heart

Pathophysiology and therapeutic implications

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Abstract Immune activation plays a significant role in the development and progression of chronic heart failure (CHF). Indeed, pro-inflammatory cytokines, especially tumour necrosis factor-α (TNFα) are activated in this condition and exert direct detrimental actions on the myocardium. Physiological dampeners of TNFα production, such as interleukin-10, catecholamines, cortisol, and others fail in the course of the disease. However, the outcomes of two large-scale clinical trials with etanercept and infliximab, which directly antagonise TNFα have been rather disappointing. Nevertheless, TNFα antagonism remains a major target of CHF therapy, although counterbalancing this cytokine alone may not be sufficient.

Key words Heart failure – cytokines – tumour necrosis factor – therapy

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Introduction

Chronic heart failure (CHF) is rapidly becoming a major public health problem in developed countries with ageing populations (21). This condition represents a pathophysiologically complex terminal manifestation of a number of different cardiac diseases, which include coronary artery disease, valve disease, idiopathic cardiomyopathy, and several other causes. The prognosis of CHF is comparable to that of different malignant diseases (41). During the last three decades our understanding of CHF has developed from a rather simplistic model of mere pump failure to that of a multisystem disorder. Indeed, the haemodynamic hypothesis of the 1960s and 1970s has largely been abandoned, and it is becoming increas-

ingly apparent that CHF affects not only the cardiovascular system but also the musculoskeletal, renal, neuroendocrine and immune systems (31). Particularly the immune system has seen considerable interest in the last 13 years. Indeed, it is now commonly believed that CHF progresses due to activation of neurohormones and pro-inflammatory cytokines, and that it can be regarded as a state of chronic inflammation. There are several different components to this system which interact with each other in a complex manner. Inflammatory mediators play an important role in the development and progression of CHF, and several strategies to counterbalance different aspects of the inflammatory response have been proposed. The targets for these therapeutic efforts are still a matter of debate, but they include pro-inflammatory cytokines and their receptors, among which tumour necrosis factor-α (TNFα) and tumour necrosis factor receptors (TNFR) appear to be most important. Other targets involve endotoxin (lipopolysaccharide, LPS), the most important trigger for TNFα secretion from peripheral mononuclear cells, adhesion molecules, and different types of leukocytes. The aim of this review is to give an up-to-date overview of the pathophysiology of TNFα and its receptors as well as to discuss novel therapeutic possibilities in this rapidly expanding field of CHF understanding.

Tumour necrosis factor-α and its receptors

TNFα and downstream signalling

TNFα was first discovered in 1975 by Carswell and associates (17). They described a substance extracted from serum of bacillus Calmette-Guerin (BCG)-infected mice treated with LPS, which was able to mimic the tumour necrotic action of LPS itself. A decade later, a protein had been isolated from an LPS-treated macrophage cell line that was named cachectin, because it inhibited the activity of lipoprotein lipase and was presumed to play a role in the development of cachexia (11, 89). The subsequent cloning of the genes encoding these substances showed that they are identical (84). However, these early observations provided only a very narrow insight into the wide variety of TNFα actions.

TNFα is a member of a huge family of substances called cytokines. These substances form a vast array of low molecular weight, pharmacologically active proteins. Different cell types release cytokines for the purpose of altering either their own function or that of adjacent cells. Cytokines have been implicated in the development and progression of CHF, and the pro-inflammatory substances TNFα and interleukin (IL)-6 appear to be most important in this setting. These substances are redundant in that they share some of their major characteristics. TNFα is also acting in a pleiotropic sense in that it alters different types of cellular functions. It is released in response to a large number of inflammatory stimuli, such as LPS, viruses, fungal or parasitic antigens, and IL-1 (Fig. 1) (28). Indeed, these stimuli increase both transcription and translation of TNFα, which is then inserted into the cell membrane of the respective cell (14, 48). Proteolytic cleavage by TNFα converting enzyme (TACE) yields its soluble forms, whose biologically active form is a homotrimer (Fig. 1).

Both TNFα signalling itself and stimuli which yield TNFα production mostly involve intracellular signalling by the transcription factor nuclear factor κB (NF-κB, Fig. 1) (89). NF-κB was first described in 1986 as being necessary for immunoglobulin kappa light chain transcription in B cells, hence the name (78). A family of five subunits termed p50/p105, p52/p100, p65, c-Rel and RelB form either homo- or heterodimers to constitute the active form of NF-κB (57). In unstimulated cells, however, cytoplasmatic NF-κB is bound to its inhibitory protein IκB. Therefore, it is kept in an inactivated form in the cytoplasm with its nuclear localization signal being masked (10). Different stimuli lead to IκB degradation and therefore to NF-κB translocation into the nucleus, where it binds to promotor or enhancer regions of specific genes.

TNFα receptors

TNFα exerts its effects via specific cell membrane receptors (TNFR), which are expressed by almost all nucleated cells. Two distinct TNFRs have been described (14, 28). Signalling results from TNFα cross-linking these receptors (Fig. 1). TNFR-1 (p55) is more abundantly expressed and seems to be the main signalling receptor (14). Most deleterious and cytotoxic effects mediated by TNFα involve this receptor (12, 14). The other TNFα receptor, TNFR-2 (p75), appears to have a more protective role in the heart, although it may transduce cytotoxic effects as well (40). Considerable insight into the functions of the two receptors has been gained from animal "knock-out" studies. In essence, deletion of the TNFR-1 gene in mice causes pronounced immunodeficiency in mice with heightened susceptibility to *Listeria monocytogenes*, but also resistance to the lethal effects of LPS (46). "Knock-out" of the TNFR-2 gene in mice yields a minimal phenotype. However, an increased resistance to TNFα-induced death has been reported, and mice injected subcutaneously with TNFα show a dramatic decrease in tissue necrosis, indicating that this receptor may play a role in the necrotic effects of TNFα (12, 27). Since no significant homology between the intracellular domains of the two receptors exists, it has been speculated that each receptor is coupled to distinct signalling pathways (28).

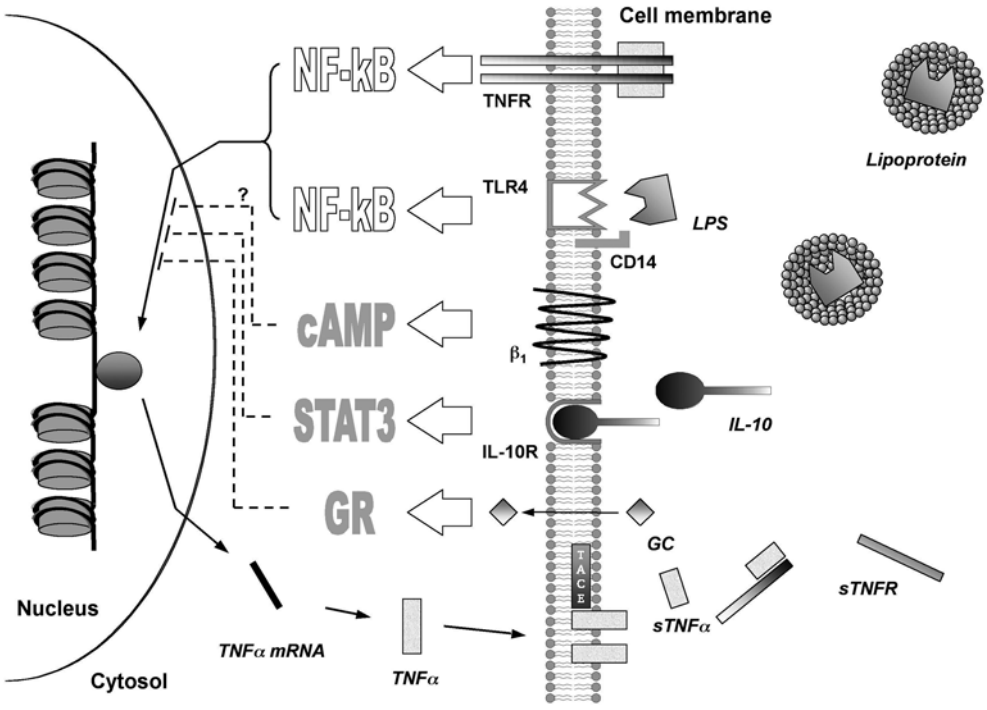

Fig. 1 TNFα signalling and physiological antagonism. Cross-linking of TNF receptors by trimeric TNFα and LPS-binding to the TLR4/CD14 receptor complex activate NF-κB, which acts as a transcription factor for TNFα and other pro-inflammatory cytokines. After translation, TNFα is inserted into the cell membrane. Proteolytic cleavage by TACE yields its soluble form. IL-10 signalling via IL-10R leads to STAT3 activation and eventually NF-κB inhibition, but also TNFR shedding from the cell surface. Soluble TNFR readily bind soluble TNFα. Catecholamines induce cAMP expression within the cell, which finally – via an unknown mechanism – inhibits TNFα secretion. Glucocorticoids (GC) enter the cell through the cell membrane and bind to their receptor (GR), which acts as a transcription factor. GR negatively regulates NF-κB dependent genes. Micelle formation via cholesterol-rich lipoproteins is a possible mechanism to block LPS activity in the plasma.
cAMP cyclic adenosine monophosphate, *CD* cluster of differentiation, *GC* glucocorticoid, *GR* glucocorticoid receptor, *IL* interleukin, *LPS* lipopolysaccharide, *NF* nuclear factor, *R* receptor, *s* soluble, *STAT* signal transducers and activators of transcription, *TACE* TNFα converting enzyme, *TLR* Toll-like receptor, *TNFα* tumour necrosis factor-α

Nevertheless, both types of receptors have been identified in non-failing and failing human myocardium (52).

Tumour necrosis factor-α and the failing heart

Early observations

The first description of TNFα in CHF comes from Levine and associates, who in 1990 showed that mean serum levels of TNFα were higher in CHF patients than in healthy subjects (115 ± 25 vs. 9 ± 3 U/ml, $p < 0.001$) (51). They also demonstrated that those patients with high levels of TNFα were more often suffering from cardiac cachexia (51), which is in keeping with very early evidence of TNFα action (11). Indeed, several workers have confirmed that elevated levels of TNFα are present in CHF (71, 82) and that elevated levels relate to poor prognosis (25, 82). Interestingly, the reproducibility of plasma levels of soluble TNFRs is higher than that of TNFα itself. This may help explain why soluble TNFRs better than TNFα predict short-term (29) and long-term (71) prognosis in CHF patients.

The role of the soluble TNFRs in CHF remains uncertain. Some data have accumulated to suggest that they act in stabilising the TNFα molecule, which potentiates its detrimental long-term actions. However, higher concentrations of TNFRs appear to inhibit TNFα activity (79), and there is ground to believe that high plasma levels of soluble TNFRs primarily indicate a history of raised TNFα levels.

The origin of elevated plasma levels of TNFα in CHF is still a matter of debate. Several hypotheses have been suggested to explain this phenomenon (8, 52). The production of pro-inflammatory cytokines has mostly been attributed to secretion by mononuclear cells, although the myocardium is also capable of TNFα release (35, 44). Indeed, cardiac myocytes and resident cardiac macrophages may produce a nearly evenly distributed amount of this cytokine (44). Myocardial injury (56) and underperfusion of peripheral tissues (85) appear to trigger TNFα secretion to some degree. However, we believe that increased bowel wall oedema causes LPS translocation from the gut into the circulation, which eventually yields

TNFα production and that of other pro-inflammatory cytokines (6). Mononuclear cells seem to be the most important source in this setting, but other tissues may also be involved (52), because LPS is capable of inducing myocardial TNFα production as well (35, 44, 58). Aker et al. have recently demonstrated, however, that serum but not myocardial TNFα is increased in rabbits with pacing-induced heart failure compared to sham-operated animals (2). These observations are in keeping with recent data from our group indicating significantly enhanced levels of NF-κB activity in peripheral blood leukocytes from CHF patients when compared to either healthy subjects or patients with coronary artery disease (without CHF) (42).

Indeed, LPS is one of the strongest inducers of TNFα release from mononuclear cells (Fig. 1). Very small, i.e. pathophysiologically relevant amounts of this substance induce TNFα secretion *in vitro* (33). Soluble CD14, a marker of endotoxin-cell interaction and shedding from the cell membrane, was found to be increased in patients with CHF (controls: 2714 ± 121 ng/ml; CHF patients: 3401 ± 134 ng/ml, p = 0.0048), especially in those with cachexia (6). Subsequently, elevated levels of LPS have been demonstrated in CHF patients with peripheral oedema, and diuretic therapy yields reduction of these levels (64).

Myocardial effects of tumour necrosis factor-α

TNFα has been implicated in several untoward myocardial and non-myocardial effects in the course of CHF. Indeed, a close relationship has been observed for TNFα and the development of left ventricular dysfunction, left ventricular remodelling, increased cardiac myocyte apoptosis, the development of anorexia and cachexia, reduced skeletal muscle blood flow, increased endothelial dysfunction, severity of insulin resistance, activation of the inducible isoform of nitric oxide synthase (iNOS), and β-receptor uncoupling from adenylate cyclase (8, 58).

The original observation of TNFα mediating detrimental cardiovascular effects was provided in 1986 by Tracey and associates (83). They observed that TNFα administered to rats caused hypotension, metabolic acidosis, hemoconcentration, and death within minutes to hours. Two animal models using transgenic mice that chronically overexpressed myocardial TNFα have recently shown that decreased myocardial contractility and reduced ejection fraction are directly attributable to TNFα action (16, 50). Indeed, mice in these studies died of congestive heart failure. Mice in one of these studies showed ventricular hypertrophy and dilatation, interstitial myocardial infiltrates and fibrosis, attenuation of β_1-adrenergic responsiveness, and expression of atrial natriuretic factor in the ventricle at the time of death (50). Moreover, Dorge et al. recently demonstrated in another animal model that TNFα is the mediator responsible for the profound contractile dysfunction following microembolisation of coronary vessels (26). Using a dog model they showed that infusion of TNFα without microembolisation decreased posterior systolic wall thickening from 27.3 ± 6.9% at baseline to 10.1 ± 4.9% after 8 hours ($p < 0.05$), whereas microembolisation in the presence of TNFα antibodies failed to show such effect (26).

Recent insights from animal models into TNFα action suggest that this cytokine also induces cardiac myocyte apoptosis (49). Nitric oxide (NO), a potent vasodilating substance, which is also involved in microbial killing, seems to play an important role in this setting (88). However, NO is a mixed blessing in CHF. Whilst low amounts of NO, being produced by the constitutive isoform of nitric oxide synthase (cNOS), are beneficial in the context of CHF, high amounts, as produced upon induction of iNOS, act in a detrimental sense (79). Lack of NO, on the other hand, causes endothelial dysfunction, another important feature contributing to limited exercise capacity in CHF (7). Apoptotic effects of TNFα seem highly dependent on the presence of iNOS expression, because iNOS "knock-out" mice display a significant attenuation of cardiomyocyte apoptosis (81). Surprisingly, transgenic mice overexpressing iNOS under the cardiospecific alpha-myosin heavy chain promoter, are viable and appear normal (39), and some evidence points to the fact that overexpression of iNOS confers negative effects only in the presence of increased oxidative stress, i.e. increased peroxynitrite production (96). TNFα also down-regulates cNOS activity thus promoting the development of endothelial dysfunction (98). Agnoletti et al. recently described that serum from CHF patients incubated with human umbilical vein endothelial cells significantly down-regulated cNOS expression and induced apoptosis in these cells (1).

Physiological antagonism of tumour necrosis factor-α production

In the context of this review, several substances merit consideration, which have been recognised to physiologically counterbalance an increased production of TNFα. These mechanisms fail in the course of an overwhelming inflammatory response. CHF thus shares some pathophysiological aspects with the sepsis syndrome. Some of these mechanisms are even promising candidates for therapeutic interventions. Since TNFα and IL-1 can mimic sepsis in animal models, several clinical trials were initiated to neutralise these pro-inflammatory mediators (47). However, a lot of experimental and clinical data contradicting this approach to sepsis treatment were ignored, and it seems that the models of this syndrome

were oversimplified. Similarly, our understanding of interactions between pro- and anti-inflammatory mediators in CHF is far from lucid. There is serious ground to apprehend that specific agents counteracting TNFα action in CHF will not show beneficial effects until we get our pathophysiological understanding clearer than it currently is.

Interleukin 10

IL-10 is a potent inhibitor of pro-inflammatory cytokines and chemokines (60). Indeed, it down-regulates the production of TNFα, IL-1, and IL-6 via activation of different transcription factors from the *signal transducers and activators of transcription* family (STAT), especially STAT1 and STAT3 (Fig. 1). IL-10 also induces the production of specific cytokine inhibitors, such as IL-1 receptor antagonist (IL-1RA) and TNFRs (18, 38). Moreover, IL-10 deactivates many of the inflammatory activities of antigen-presenting cells, such as monocytes and macrophages (13, 65), and it down-regulates class II major histocompatibility complex antigens on the surface of these cells (60).

The role of IL-10 in CHF is not entirely clear. Circulating IL-10 levels appear to be decreased in CHF patients (controls: 5.3 + 1.5/-1.1, CHF patients: 1.8 + 0.6/-0.4 pg/ml, $p = 0.03$) (6). We have recently demonstrated that IL-10 can reduce LPS-stimulated TNFα production from isolated peripheral blood mononuclear cells of CHF patients *in vitro* (mean reduction at 1 ng/ml LPS in CHF patients: 43%, controls: 55%) (15). The percentage reduction did not differ between the groups (p = NS). Similar to pro-inflammatory cytokines, IL-10 mRNA has been detected in the failing and non-failing myocardium (22, 32). Intravenous administration of immunoglobulin (IgG) to 40 stable CHF patients during a small double-blind, placebo-controlled trial increased the plasma levels of IL-10 (from 3.1 ± 0.2 at baseline to 5.1 ± 0.5 pg/ml after 6 months, $p < 0.001$), soluble TNFR-1 (from 1.5 ± 0.1 to 1.7 ± 0.1 ng/ml, $p < 0.01$) and TNFR-2 (from 1.6 ± 0.1 to 2.7 ± 0.3 ng/ml, $p < 0.001$) (37). Significant improvements in left ventricular ejection fraction were observed after treatment (from 26 ± 2% to 31 ± 3%, $P < 0.01$). Therefore, IL-10 administration has therapeutic appeal, especially in patients with cardiac cachexia, because these patients show the highest plasma levels of TNFα (89).

Catecholamines

Epinephrine and norepinephrine have recently been shown to decrease pro-inflammatory cytokine secretion in LPS-stimulated *ex vivo* whole blood samples from healthy volunteers (36, 87). This has been confirmed in experimental human endotoxemia (86). Indeed, catecholamines seem to be natural dampeners of TNFα production in this setting and may withhold pro-inflammatory cytokine release to some extent via a cAMP-dependent pathway (Fig. 1). In one *ex vivo* model, epinephrine selectively upregulated monocytic TNFR-2 expression in LPS-treated whole blood (epinephrine + LPS: 110 ± 8, LPS alone: 54 ± 6 mean channel fluorescence in flow cytometry) (36). This effect was completely abrogated by propanolol, an unselective β-adrenergic receptor antagonist. Infusion of epinephrine (30 ng/kg body weight/min) in healthy humans exposed to intravenous LPS (single dose of 2 ng/kg body weight administered on each of 2 consecutive days) yields a significant attenuation of plasma TNFα levels, but also an increase in IL-10 release (86).

Plasma catecholamine levels are usually elevated in CHF patients (3). Using an *ex vivo* whole blood model, we have recently suggested that catecholamines decrease TNFα production in stable CHF patients (90). However, compared to healthy subjects, this effect is significantly attenuated (healthy subjects: suppression to 26 ± 5% by 10^{-6} mol/l norepinephrine as compared to baseline, CHF patients: 48 ± 10%, $p < 0.05$) (90). The β_1-selective antagonist bisoprolol seems to restore a "normal" pattern of TNFα production (90). Since beta-blocker treatment improves prognosis in CHF (20, 59, 66, 67), the role of these agents requires further clarification in terms of interaction with the immune system.

Cortisol

The anti-inflammatory action of glucocorticoids, for example cortisol, is mainly due to inhibition of NF-κB and other transcription factors (23). Glucocorticoids freely penetrate cell membranes to bind to the cytosolic glucocorticoid receptor, which itself serves as a transcription factor and negatively regulates certain genes (Fig. 1). Recently, two interesting studies have suggested that a major mechanism of glucocorticoid action may be the induction of IκB synthesis (9, 75). Moreover, IκB might even be able to remove NF-κB actively from its DNA binding site. Dexamethasone, a highly potent synthetic glucocorticoid, blocks TNFα and IL-1 dependent induction and translocation of NF-κB (Fig. 1) (76).

Elevated plasma levels of cortisol in CHF patients have been reported in CHF patients as early as 1960 (69). An elevated cortisol/dehydroepiandrosterone (i.e. catabolic/anabolic) ratio has been observed in CHF patients (controls: 1.45 ± 0.35, CHF patients: 1.71 ± 0.34, $p = 0.009$) (4). This ratio is closely related to TNFα levels in CHF patients ($r = 0.5$, $p < 0.001$). It is likely that these findings can explain the preferential effect of catabolism over anabolism in CHF (77). However, cortisol does not appear to reduce TNFα levels in this disease.

Cholesterol and lipoproteins

The endotoxin-lipoprotein hypothesis suggests that lipoproteins can inactivate LPS to a large extent thus attenuating the production of TNFα (70). Indeed, different lipoprotein classes have been shown to bind LPS in direct proportion to their cholesterol content (30). Formation of micelles seems to be the most plausible mechanism in this context (Fig. 1) (97). When we spiked whole blood samples with LPS at pathophysiologically occurring concentrations, the recovery was generally only around 10 – 30%, indicating that a huge amount of LPS is left bound in the plasma (34). Similarly, when we investigated the relationship between LPS-stimulated TNFα production and age in isolated peripheral blood mononuclear cells, we observed a strong relationship in CHF patients and control subjects, but this effect was lost when whole blood samples were used (91). This may hint at an LPS-binding substance in the plasma, and this substance may indeed be lipoprotein-bound cholesterol.

Therapeutic options for CHF

The introduction of ACE-inhibitors and β-blockers into the treatment of heart failure has significantly improved the prognosis of these patients. However, the overall prognosis remains fairly poor, and CHF patients usually die of CHF. Recent insights into the pathophysiology of this disease provide promising targets for future therapies. TNFα antagonism still remains a priority as a means to treat CHF, although preliminary results from the first large-scale clinical trial to counterbalance TNFα activity have been rather disappointing. Other drugs known to reduce TNFα production include amiodarone (54), the cardiac glycoside ouabain (53), the positive inotropic agent vesnarinone (55), thalidomide (73, 89), adenosine (28, 92), and several other substances (Table 1). Some workers have suggested that pentoxifylline may also be able to inhibit TNFα production in CHF, however, this is not the case (80). It may be found that TNFα antagonism alone is too simplistic a model to meet all pathophysiological changes of CHF.

Table 1 Substances with TNFα inhibitory potential

Drug	Mechanism	TNFα production	Clinical trial in CHF	Outcome	Reference
Adenosine	possibly mediated by adenosine receptor A_2 and transduced through a G protein-adenylyl cyclase pathway	decreases TNFα in a dose-dependent manner in LPS-stimulated neonatal rat myocytes	missing	not applicable	[92]
Amiodarone	unknown	concentration-dependent decrease in LPS-stimulated human PBMC	missing	not applicable	[54]
Etanercept	TNFR-2 fusion protein (extracellular domain of TNFR-2 is fused to Fc region of human IgG_1), which binds and inactivates TNFα	data not yet available	RENAISSANCE RECOVER	trial halted prematurely due to missing clinical benefit	[5]
IC14	chimeric (mouse/human) monoclonal antibody, which blocks the monocytic LPS-receptor CD14	dose-dependent reduction of TNFα release from human whole blood	missing	not applicable	[34]
Infliximab	chimeric (mouse/human) IgG_1 monoclonal antibody, which binds and neutralises soluble and membrane-bound TNFα	decreased serum levels of TNFα immediately after infusion, but significantly elevated at all other time points	ATTACH	trial halted prematurely due to missing clinical benefit	[19]
Ouabain	inhibits TNFα transcription in LPS-stimulated human PBMC (possibly Na^+/K^+-ATPase dependent)	concentration-dependent in LPS-stimulated human PBMC; inhibits LPS-dependent increase of TNFα plasma level in mice	missing	reduces mortality in LPS-treated BALB/c mice significantly	[53]
Thalidomide	enhances TNFα mRNA degradation	selective decrease in human monocyte TNFα production	missing	not applicable	[61, 73]
Vesnarinone	inhibits TNFα transcription in LPS-stimulated human mononuclear phagocytes (possibly K^+-channel dependent)	concentration-dependent decrease in LPS-stimulated human mononuclear phagocytes and whole blood	missing	not applicable	[43, 55]

TNFα antagonism with etanercept and infliximab

Etanercept is a TNFR-2 fusion protein, which binds to TNFα and functionally inactivates this cytokine (Table 1). In rheumatoid arthritis, etanercept was associated with dose-related reductions in disease activity (62), and it was therefore approved by the Food and Drug Administration for use in this condition (28). In CHF, a pilot study in 18 patients with moderate heart failure showed promising results (24). These observations pared the way for designing a large-scale clinical trial. Both the American arm RENAISSANCE (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines) and the European arm RECOVER (Research into Etanercept: Cytokine Antagonism in Ventricular Dysfunction) recruited a total of 2048 CHF patients, most of them with mild to moderate disease (5). The combined analysis of the two trials was termed RENEWAL. After 24 weeks of subcutenous application of etanercept or placebo in a double-blind fashion, etanercept did not show significant advantages compared to placebo. Indeed, the number of patients classified "improved", "unchanged" or "worsened" was similar for patients on placebo or any dose of etanercept (5). Death or hospitalisation due to CHF were the primary endpoints of the study; however, these were not different between the two groups (risk ratio 1.10, 95% confidence intervall 0.91 to 1.33, $p = 0.33$) (5). The secondary endpoint (all-cause mortality) did also not differ between groups (RR 1.13, 95% CI 0.86 to 1.50, $p = 0.39$), and the survival curves overlapped throughout the first year of treatment (5).

Another trial programme to counterbalance TNFα was the ATTACH trial (Anti-TNFα Therapy Against Chronic Heart failure). 150 CHF patients were enrolled to investigate if patients would benefit from intravenous treatment with infliximab, a chimeric (mouse/human) IgG_1 monoclonal antibody that binds and neutralises both soluble and membrane-bound TNFα (Table 1). Again, this study was designed in a multicentre, randomised, double-blind, placebo-controlled fashion (19). All patients enrolled in this study were in NYHA class III or IV with an LVEF ≤ 35%. It was also stopped prematurely. Of the 150 patients enrolled, 49 were randomised to placebo, 50 to 5 mg/kg body weight infliximab, and 51 to 10 mg/kg infliximab. However, the plasma levels of infliximab achieved in the patients were many times higher than expected and remained well above the levels associated with clinical benefit in rheumatoid arthritis (19). This may account for the increased risk of death in the group receiving the higher dose of infliximab (i.e. 10 mg/kg body weight) observed in this study (RR 2.84, 95% CI 1.01 to 7.97, $p < 0.05$). There was no adverse risk associated with 5 mg/kg body weight infliximab (RR 0.80, 95% CI 0.22 to 2.99) and in fact in patients receiving this dose LVEF improved ($p < 0.05$) (5).

Statins

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) block the rate-limiting step in cholesterol biosynthesis in the liver and other tissues. The advent of statins has therefore revolutionised the treatment of hypercholesterolemia. Five different substances are available, which are administered orally. They are normally well tolerated and generally considered safe. It has been reported that statins can improve the prognosis of coronary artery disease irrespective of serum cholesterol levels, thus giving rise to research efforts into the so-called pleiotropic effects of statins (94).

Indeed, some substances from this group have been shown to improve endothelial function by inducing cNOS gene transcription (88). Moreover, statins have been found to reduce C-reactive protein levels after myocardial infarction (72) and in hypercholesterolemia (63), and some have been shown to decrease the production of TNFα, IL-1 and IL-6 from macrophages (68). Since statins have also been reported to selectively inhibit the expression of the cell adhesion molecule leukocyte function antigen-1 (LFA-1), it is tempting to speculate that these drugs may also interfere with transendothelial cell migration (93).

The availability of clinical data of statin use in CHF is scarce. The Scandinavian Simvastatin Survival Study (4S) demonstrated fewer instances of new-onset CHF after simvastatin treatment (45, 74). The pleiotropic effects of simvastatin seem to play a crucial role in this setting, because changes in the lipoprotein profiles and baseline characteristics were similar in patients with or without future events. The clinical benefit associated with statin therapy was also independent of baseline cholesterol levels in the West of Scotland Coronary Prevention Study (WOSCOPS) (95). A subgroup analysis revealed that cholesterol-independent mechanisms may provide additional benefits. Prospective data are needed to examine the effects of statin treatment in CHF. The doses needed to achieve the desired effects may be much lower than those needed to treat hypercholesterolemia.

Conclusion

The role of TNFα and other pro-inflammatory cytokines is still not entirely understood. Two large-scale trials to counterbalance TNFα in CHF had to be stopped prematurely because of missing benefit. Both studies included only a very limited number of patients with severe CHF. This is unfortunate, because these patients can be expected to have significant inflammatory immune activation and the highest levels of TNFα. ATTACH initially aimed to recruite patients with severe CHF, but none of the 49

patients in the placebo group died during the first 28 weeks of follow-up (5, 19).

However, we still do not know enough about the origin of pro-inflammatory cytokine activation in CHF, although several hypotheses were suggested to explain the development of this aspect of CHF. Almost no data are available on the role of leukocytes. Indeed, our models may be oversimplified, and it may be an option to go back to understanding the pathophysiology and the role of naturally occurring inhibitors of TNFα action. The role of LPS in triggering inflammation needs further study. There is reason to apprehend that the disappointing results of recent trials will lead to a slow-down of drug development processes. We believe that the "cytokine story" is still very much alive in CHF and requires further clarification. Anti-inflammatory strategies need to be broad and focussed on patients with significant immune activation. New therapeutic developments will hopefully lead to an improvement of the still poor prognosis of CHF patients.

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