Commentary

New therapies for heart failure: is thalidomide the answer?

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Summary

The syndrome of advanced heart failure is associated with considerable morbidity and mortality. Ideas about the reasons for the progressive nature of the heart failure syndrome have changed over the years, with the initial view that progression was principally due to pump failure (the ‘haemodynamic’ hypothesis), giving way to more modern views, which implicate neuro-endocrine activation (including catecholamine excess, renin-angiotensin system activation, etc.). More recently, an excess of inflammatory cytokines has been found in advanced heart failure and implicated in the progression of the disease. Amongst the cytokines found, TNF-α seems to be particularly important. The principle therapeutic action of thalidomide appears to be reduction due to pump failure (the ‘haemodynamic’ hypothesis), giving way to more modern views, which implicate neuro-endocrine activation (including catecholamine excess, renin-angiotensin system activation, etc.). More recently, an excess of inflammatory cytokines has been found in advanced heart failure and implicated in the progression of the disease. Amongst the cytokines found, TNF-α seems to be particularly important. The principle therapeutic action of thalidomide appears to be reduction of TNF-α levels. We therefore suggest that there may be a role for thalidomide, or its derivatives, in the management of advanced heart failure.

Introduction

Since Withering’s use of digoxin more than 200 years ago, a ‘magic bullet’ to treat heart failure (CHF) has been desperately sought. Among the reasons for this enthusiasm is CHF’s sobering morbidity, accounting for greater than 5% of hospital admissions in the UK, and greater than a million admissions per annum in the US.1,2 Similarly, the associated mortality of severe heart failure, although not perceived as such, is as severe as that of most cancers, with a mortality, in those moderately symptomatic at entry, of about 80% over 5 years.3 These figures outline the need for effective therapy. Though the past 20 years have been exciting times for heart failure research, current treatments are still woefully inadequate in reducing this high mortality. This means that novel and effective treatments are still desperately needed. In this article we explore the role of TNF-α in the pathogenesis of CHF, and that of thalidomide, acting as a TNF-α antagonist, as a potential novel adjunct for the for the management of heart failure.

Shifting paradigms in heart failure

The accepted pathophysiology and treatment of heart failure has evolved over the past 50 years. The haemodynamic model has given way to the neuro-hormonal hypothesis, which implicates the activation of sympathetic and renin-angiotensin-aldosterone system as the primary determinants of the heart failure syndrome.4 This shift was principally driven by the notable failure of cardiac inotropes to ameliorate heart failure, an important prediction made by proponents of the haemodynamic model, and by the remarkable efficacy of angiotensin-converting enzyme inhibitors (ACE-I), β-blockers and aldactone-antagonists as predicted by the neuro-hormonalists. This shift has been consolidated and extended by the inclusion of paracrine and cytokine elements such as endothelin, bradykinin, nitric oxide, TNF-α and IL-10 into the pathogenesis of heart failure (Table 1).

Among these more novel factors, TNF-α, a trimeric...
Table 1  Inflammatory mediators increased in heart failure

<table>
<thead>
<tr>
<th>Inflammatory mediator</th>
<th>Increased in Heart Failure</th>
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<tbody>
<tr>
<td>Tumour necrosis factor-alpha (TNF-α)</td>
<td>6</td>
</tr>
<tr>
<td>Soluble TNF receptors 1 &amp; 2</td>
<td>13,54</td>
</tr>
<tr>
<td>Elevated ratios of TNF-α/soluble TNF receptors</td>
<td>54</td>
</tr>
<tr>
<td>Interleukin-1</td>
<td>1,14-56</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>54,55</td>
</tr>
<tr>
<td>Enhanced interleukin-6 bioactivity</td>
<td>54</td>
</tr>
<tr>
<td>Soluble interleukin-6 receptor, glycoprotein (gp)</td>
<td>130</td>
</tr>
<tr>
<td>Interleukin-6/soluble gp130 ratio</td>
<td>54</td>
</tr>
<tr>
<td>Vascular cell adhesion molecule-1 (VCAM-1)</td>
<td>58</td>
</tr>
<tr>
<td>Intercellular cell adhesion molecule-1 (ICAM-1)</td>
<td>55</td>
</tr>
<tr>
<td>Endotoxin (oedematous heart failure)</td>
<td>13</td>
</tr>
<tr>
<td>Soluble CD14 (relates to endotoxin-cell interactions)</td>
<td>13</td>
</tr>
<tr>
<td>C-reactive protein (oedematous heart failure)</td>
<td>55,59</td>
</tr>
<tr>
<td>Uric acid</td>
<td>59</td>
</tr>
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</table>

17-kDa protein, a potent cytokine and anti-tumour factor, seems to be particularly important in CHF (Tables 2 and 3). In 1990, while TNF-α was being used as an anti-tumour agent in renal carcinoma, a patient thus treated developed severe left ventricular failure consistent with CHF. This prompted further study of the role of TNF-α in established heart failure. These investigations found increased levels of serum TNF-α in severe CHF. 6,7 TNF-α levels correlated with functional class (exercise capacity) and severity of the haemodynamic compromise. 6,9 Furthermore, the SOLVD trial (Studies on Left Ventricular Dysfunction) found progressive increases in TNF-α levels in those who developed symptomatic heart failure. 8 Finally, just as seen in the adrenergic system in heart failure, an adaptive 30–40% downregulation of cardiac TNF receptors was also found, suggesting ongoing TNF-α receptor and second-messenger activation. 8,10

Investigations to identify the source of the TNF-α synthesis suggested that injured cardiomyocytes from failing hearts were a highly relevant and potent source of this cytokine as in, for example, viral myocarditis, cardiac allograft rejection and myocardial infarction. 10,11 Other possible sources of TNF-α in CHF are classical immunological cells such as macrophages. Bacterial lipopolysaccharides and Gram-positive cell wall components after engagement with their binding protein, interact with toll proteins such as CD14, and are capable of activating signalling pathways that result in the release of TNF-α from macrophages. 12 CD14 levels are increased in functional class (exercise capacity) and severity of heart failure: consistent with TNF-α production from LPS-stimulated macrophages. 13 Where the LPS originates is unknown, but according to one hypothesis, the bowel wall in CHF patients, when congested, is leaky and allows bacterial lipopolysaccharide translocation from bowel lumen to the blood, thus allowing LPS-macrophage interaction as the substrate for TNF-α in common CHF. 13 T cells are also capable of similarly stimulating macrophages, though data as to whether this occurs in heart failure are not, as yet, available. Finally excess mechanical stress to the heart, be it pressure or volume overload, results in a cellular stimulus that in turn leads to increased levels of TNF-α mRNA, protein product expression and TNF-α release. 14 These important data suggest that any significant insult to the heart, such as a remote myocardial infarct, may initiate TNF-α production, which, as we will see below, can result in further damage to cardiac and skeletal muscle as well as to the peripheral circulation, resulting in an exacerbation of the heart failure syndrome. Thus the stimuli to TNF-α production are relevant to explaining, at least in part, how cardiac dysfunction begets heart failure.

Table 2  General properties of TNF-α

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
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<tbody>
<tr>
<td>Embryogenesis regulator</td>
<td>Regulates haematopoiesis</td>
</tr>
<tr>
<td>Can trigger apoptosis</td>
<td>Can induce fibrosis</td>
</tr>
<tr>
<td>Initiates own transcription</td>
<td>Induces autocrine self amplification</td>
</tr>
<tr>
<td>Increased expression in obese human adipose tissue: thus promotes insulin resistance</td>
<td>Downregulates progesterone and testosterone release</td>
</tr>
<tr>
<td>Upregulates ACTH and GH release</td>
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From references 14, 23, and 60.

Table 3  Cardiovascular actions of TNF-α

<table>
<thead>
<tr>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>Triggers release of most inflammatory cytokines and arachidonic acid metabolites</td>
<td>Can create/organize immune granulomas/lymphocyte infiltrates</td>
</tr>
<tr>
<td>Increases iNOS enzyme</td>
<td>Increases amino acid transporters needed for L-arginine (NO precursor) uptake</td>
</tr>
<tr>
<td>Increases NO production</td>
<td>Increases NO production</td>
</tr>
<tr>
<td>Induces and enhances the production of reactive oxygen species</td>
<td>Induces free-radical-scavenging enzymes (mitochondrial superoxide dismutase and heat-shock proteins)</td>
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<tr>
<td>Decreases myocardial contractile response to isoprenaline</td>
<td>Decreases resting myocardial contraction (reduced ejection fraction)</td>
</tr>
<tr>
<td>Decreases L-type calcium current in myocytes</td>
<td>Anti- anabolic and pro-catabolic effects in peripheral skeletal muscle proteins</td>
</tr>
<tr>
<td>Relates to endothelial dysfunction in heart failure</td>
<td></td>
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Macrophages, Bacterial lipopolysaccharides and Gram-positive cell wall components after engagement with their binding protein, interact with toll proteins such as CD14, and are capable of activating signalling pathways that result in the release of TNF-α from macrophages. CD14 levels are increased in functional class (exercise capacity) and severity of heart failure: consistent with TNF-α production from LPS-stimulated macrophages. Where the LPS originates is unknown, but according to one hypothesis, the bowel wall in CHF patients, when congested, is leaky and allows bacterial lipopolysaccharide translocation from bowel lumen to the blood, thus allowing LPS-macrophage interaction as the substrate for TNF-α in common CHF. T cells are also capable of similarly stimulating macrophages, though data as to whether this occurs in heart failure are not, as yet, available. Finally excess mechanical stress to the heart, be it pressure or volume overload, results in a cellular stimulus that in turn leads to increased levels of TNF-α mRNA, protein product expression and TNF-α release. These important data suggest that any significant insult to the heart, such as a remote myocardial infarct, may initiate TNF-α production, which, as we will see below, can result in further damage to cardiac and skeletal muscle as well as to the peripheral circulation, resulting in an exacerbation of the heart failure syndrome. Thus the stimuli to TNF-α production are relevant to explaining, at least in part, how cardiac dysfunction begets heart failure. These studies suggested that TNF-α was central to the heart failure syndrome. However, an aetiopathological role (as opposed to TNF-α being an epiphenomena) for TNF-α had not yet been demonstrated. This changed when it was demonstrated that parenteral...
infusions of TNF-α induced and sustained CHF. The creation of transgenic mice expressing cardiac TNF-α and developing severe heart disease was further compelling proof for the ability of TNF-α to mediate heart failure. Interestingly, familial hibernian fever (FHF), one of the familial fever syndromes, has been found to be due to a missense mutations in the gene encoding type I tumour necrosis factor receptor, and is associated with high levels of TNF-α. Curiously, the incidence of heart failure appears to be low in FHF, for reasons which are not clear, but which may either include the need of TNF-α to synergize with other neuro-endocrine, cytokine and myocardial pathologies to produce the heart failure syndrome, or, more likely, given the circulatory abnormalities that are so central to the heart failure syndrome. Compelling proof for this statement comes from the finding of a close relationship between the severity of peripheral endothelial dysfunction in heart failure and TNF-α levels. This may relate to TNF-α inducing oxidative stress in endothelial cells, thus destroying local NO production and inducing apoptosis. Furthermore, TNF-α may also be directly involved in the skeletal muscle cell wasting and fibrosis that is such a prominent component of the advanced heart failure syndrome.

Complicating this apparently straightforward picture of TNF-α as a harmful molecule (the ‘conductor’ of a ‘harmful orchestra’) in heart failure is the finding that TNF-α has highly complex actions, some of which are contradictory. For example, TNF-α has been shown in different situations to be catabolic or anabolic, to induce iNOS (and thus NO), as well as to result in oxidative stress that consumes NO, to be involved in cachexia as well as obesity, to be involved in septic shock as well as, through the induction of heat-shock proteins and the free radical scavenger mitochondrial superoxide dismutase, protection from shock. Which of these different actions predominate probably depends on timing of release, dose and duration of action in the circulation. This (so-called) double-faceted action of TNF-α implies that it is extremely difficult to predict the net result of TNF-α activity, and whether it is are really harmful, helpful, or indeed neutral. Thus, to determine whether elevated levels of TNF-α really are dangerous in CHF, the result of blocking its action should be determined in the heart failure syndrome.

**Current anti-TNF treatments in heart failure**

We suggest therefore that, even in the context of increased TNF-α in CHF patients and its fall in response to effective heart failure treatment, formal proof of a role for TNF-α in the heart failure syndrome...
can only be shown by directly reducing this cytokine and then either inducing remission or slowing the progression of CHF.\textsuperscript{13,25,26} Though it is clear that successful treatment per se of acute exacerbations of the heart failure syndrome reduces inflammatory mediators, data as to whether chronic conventional treatments influence TNF is very sketchy. The action of β-blockers is unknown, but by extension from work in sepsis, is unlikely to be great.\textsuperscript{27} Some studies suggest that ACE-Is reduce TNF levels \textit{in vitro} but not \textit{in vivo}.\textsuperscript{38,29} Worryingly, amiodarone treatment appears to increase TNF-α levels in ischaemic heart failure.\textsuperscript{27} Given these disappointing findings with conventional therapies, novel treatments have been looked for. To this end a recombinant soluble p75 TNF-α receptor protein has been synthesized (which contains two molecules of the extracellular portion of sTNF-R2 linked to the Fc portion of the IgG1 molecule), which has been shown to be safe and is capable of reducing the raised levels of TNF-α (through TNF-α sequestration) and concomitantly lessening the severity of heart failure in patients with NYHA Class III CHF.\textsuperscript{16} Patients in this study showed sufficiently increased exercise tolerance, ejection fraction and reported life scores to prompt the initiation of a much larger prospective trial (named \textsc{RENAISSANCE}, for Randomized \textsc{Etanercept} North American Strategy to Study \textsc{Antagonism} of \textsc{Cytokines}), which aims to reduce TNF-α levels by using the p75 TNF receptor fusion protein (\textsc{Etanercept}) to verify these results. However, one of the problems with using this approach to decrease TNF-α levels is that Etanercept needs to be infused, and that as Etanercept is fairly rapidly broken down \textit{in vivo} (over 7–14 days, though TNF levels remain depressed for > 14 days), infusions may need to be repeated frequently to achieve long-term TNF-α suppression. Furthermore, repeated infusions of TNF receptors may, paradoxically, increase TNF levels. An orally active and persistently effective anti-TNF-α agent is needed. Pentoxifylline, an anti-inflammatory agent that inhibits endotoxaemia and lipopolysaccharide (LPS)—induced release of TNF-α has been used in a small study of heart failure due to dilated cardiomyopathy, where it improved both exercise capacity and ejection fraction.\textsuperscript{31} The success of this early study has been criticized, in that the decrease in TNF-α levels in placebo and treatment groups was roughly the same.\textsuperscript{15} Nonetheless, these data are felt sufficiently encouraging to justify further larger-scale studies investigating whether pentoxifylline will reduce mortality.

Other approaches to TNF-mediated cardiac disease include inhibition of the TNF transcriptional factor NF-κB using pyrrolidine-dithiocarbamates, although the specificity of this drug is felt to be low, and its systemic side-effects are unknown.\textsuperscript{14} Alternatively, it has been suggested that as NF-κB is activated by oxidative stress, it might, at least theoretically, be decreased by vitamin E. However, it seems as though this approach is only theoretically helpful, as the results of the vitamin E post-myocardial-infarction trials, in which significant numbers of patients with heart failure were included, have not produced encouraging results.\textsuperscript{32} It has also been suggested that if LPS in heart failure arises from the bowel, that bowel ‘purging’ to minimize bacteria with translocating LPS may be helpful.\textsuperscript{13} Finally, there are drugs whose actions include depression of TNF-α levels, and thus which theoretically may be helpful, but whose other actions are so overwhelmingly dangerous as to render the overall action negative. Such drugs include the positive inotropic agent vesnarinone, which has been shown to decrease TNF-α levels, by increasing intracellular CAMP levels, and which is also a potassium channel antagonist. These latter actions may account for the increased mortality seen with vesnarinone in heart failure.\textsuperscript{33,34}

These data emphasize that for an anti-TNF-α drug to be useful in heart failure, it should not only be highly effective in reducing TNF-α levels, but also should have minimal or only positive other actions, should be orally active and cheap. As yet, no drug fits this description.

**Thalidomide as an anti-TNF-α drug and its role in heart failure**

Thalidomide’s use as a drug was initially terminated, after its use in the 1950s and 1960s in pregnant women was associated with severe birth defects.\textsuperscript{35} In addition to causing serious foetal deformities (phocomelia), thalidomide has been associated with other adverse reactions such as permanent peripheral neuropathy. Despite its poor reputation, thalidomide has recently been found to be extremely effective in treating a variety of conditions such as leprosy, cancers, HIV, cachexia and, most recently, myeloma.\textsuperscript{36–39}

It appears that there are numerous mechanisms to account for this efficacy in diverse disorders. In cancer treatment, for example, thalidomide may act as a potent angiogenic inhibitor.\textsuperscript{40} It does however seem that thalidomide’s best-recognized action has consistently been its powerful anti-TNF-α activity, although it does have a multiplicity of other actions (Table 4).\textsuperscript{41,42} This activity has been ascribed to a powerful specific transcriptional inhibitor effect, binding to critical cell proteins and interruption of a phorbol-ester-sensitive pathway by different groups.\textsuperscript{33,44} Whatever the mechanism, this anti-TNF-α effect appears to be robust and reproducible.\textsuperscript{35} Amino-substituted thalidomide analogues may have
Table 4  Actions of thalidomide

- Inhibits TNF-α synthesis\(^{42,47}\)
- Upregulates Th2-type immunity\(^{42}\)
- Increases IL-2 levels\(^{47,49}\)
- Increases interleukins 4 and 5\(^{42}\)
- Inhibits interferon-γ\(^{42}\) (but see reference 47)
- Inhibits mitogen-stimulated peripheral mononuclear cells (PBMC)\(^{42,47}\)
- Inhibits IL-12 production\(^{42}\)
- May promote T-cell responses\(^{42}\)
- Can increase or decrease IL-12 levels\(^{47}\)
- Does not inhibit TNF-α production from anti-CD3-antibody-stimulated monocytes\(^{47}\)
- Upregulates CD40L function\(^{47}\)
- Inhibits angiogenic growth factor\(^{37}\)
- Inhibits basic fibroblast growth factor\(^{37}\)
- Anti-tumour action (myeloma)\(^{37}\)

an even greater TNF suppression action, with fewer other actions.\(^{46,47}\) In particular, the derivatives that do not inhibit phosphodiesterase 4, the so-called class I or Immunomodulatory Imide Drugs—ImiDs, may be particularly useful in heart failure, as they also inhibit LPS-induced monocyte inflammatory cytokines.\(^{47}\) The role of thalidomide in human heart failure has not been explored, although intriguingly, thalidomide has been found to blunt the development of the (TNF-α-related) circulatory abnormalities in animal models of portal hypertension.\(^{48}\)

We therefore contend that in the CHF population group, a population that is almost completely devoid of pregnant women, thalidomide could, acting through its anti-TNF-α mechanism, ameliorate heart failure.

This suggestion of course raises a number of issues. The first is that of long-term efficacy and safety. The source and mechanism of TNF-α in heart failure has not yet been proven, and if through non-classical pathways, may not be amenable to thalidomide.\(^{47}\) Furthermore, as CHF is a spectrum of disease with a multitude of underlying causes, thalidomide may be relevant to only some varieties. On the other hand, the cardiomyopathy of heart failure seems to end in a single common path and responds to therapies such as ACE-inhibitors in a relatively uniform way, suggesting that thalidomide may be useful. There will of course need to be further studies to address this and identify exactly whether TNF-α is critical in the maintenance or just the initiation of disease which will crucially dictate the time course and pattern of thalidomide use. Secondly, thalidomide has complex actions, most, though not all, of which will be expected to be advantageous in heart failure. These other actions are however subsidiary to its anti-TNF-α effect, and though some of these may theoretically be harmful, we suggest that as the anti-TNF-α action will predominate, that the overall action of thalidomide in heart failure will be beneficial. Clearly its anti-basic-fibroblast-growth-factor action may be useful. One action that may be thought to be worrying, though in reality is unlikely to be, is its anti-angiogenesis role.\(^{49}\) New vessel formation is not prominent in ischaemic heart disease, and previous drugs whose actions include that of inhibiting angiogenesis, including spironolactone, have been found, despite this, to be beneficial in advanced CHF.\(^{50,51}\) This slight concern might mean, however, that initial studies should be confined to those with non-ischaemic heart failure. Finally, though thalidomide has been used safely over long periods of time in leprosy and chronic mouth ulcers, chronic therapy can be associated with a (mainly sensory) peripheral neuropathy, the incidence of which can, over time, be around 10–20% clinically, with more having electrophysiological changes.\(^{52}\)

There may be genetic differences in those prone to neuropathy, though information about these are not yet sufficient to allow accurate prediction of this distressing side-effect.\(^{53}\) In those with advanced heart failure, with its attendant high mortality, patients may be prepared, with careful monitoring, to take the risk of this complication.

For these reasons, although the FDA has approved the use of thalidomide in a number of conditions, and other late-phase trials are in progress, it may prove important to use analogues of thalidomide that retain TNF-α suppressing qualities but that avoid unacceptable side-effect profiles. It may also be necessary to assess pharmacokinetic and in due course pharmacogenomic properties of these drugs and patients in the context of differing underlying aetiologies for the syndrome of CHF to optimize its use. If the thalidomide is capable of acting at the site of TNF-α production, studies with it, in conjunction with the RENAISSANCE trial, may identify anti-TNF-α medications as useful adjuncts in the treatment of heart failure.

Acknowledgements

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References


Heart failure and thalidomide


