New and Emerging Pharmacologic Strategies in the Management of Chronic Heart Failure

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Summary: Chronic heart failure (CHF) is a complex syndrome involving activation of multiple cellular, metabolic, and neurohormonal pathways following the initial myocardial insult. Recently, there have been considerable advances in the pharmacologic management of CHF. The current approach to treatment recognizes the need to target neurohormonal activation, and the use of angiotensin-converting enzyme (ACE) inhibitors and beta blockers should now be regarded as part of standard therapy in many patients with CHF. However, because of the complexity of the disease, blockade of additional pathways is likely to be required to maximize the therapeutic benefit of intervention. To this end, there are several agents under active late-phase clinical evaluation. The most advanced of these new strategies (beyond renin-angiotensin-aldosterone blockade) is inhibition of the endothelin system. There is a substantial body of evidence that this system is intimately involved in CHF disease progression. Early-phase clinical data are very encouraging and support the potential utility of long-term endothelin inhibition. Other novel approaches involve the use of cytokine antagonists (e.g., agents that block tumor necrosis factor-α activity) and the augmentation of natriuretic peptides. If all these potential agents prove to be of benefit in CHF, the question of which agent or combination of agents to use in which patients will arise. There is therefore a need to develop scientific approaches in order to be able to identify more accurately patients who will obtain benefit from specific classes or combinations of drugs.

Key words: chronic heart failure, endothelin-1, natriuretic peptide, tumor necrosis factor-α

Introduction

There have been considerable advances in the pharmacologic management of chronic heart failure (CHF) over the last 20 years. Both angiotensin-converting enzyme (ACE) inhibitors and beta-adrenoceptor blockers have been shown to reduce mortality and improve symptom status in patients with systolic CHF.

In patients with mild-to-moderate CHF, ACE inhibitors reduce absolute annual mortality by around 1.5%, beta blockers by 3.6%, and the two agents combined by 4.9%. Nevertheless, data from large-scale studies of beta blockers in CHF, including the US Carvedilol Heart Failure Trials Program, the Metoprolol Randomized Intervention Trial (MERIT-HF), and the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), would suggest that mortality remains high in such patients (7.2–8.8% annual death rate in the latter two studies) despite optimal use of current agents. Furthermore, CHF is a debilitating condition with high morbidity, frequent hospitalization, and poor quality of life. Therefore, the need for new pharmacologic agents in addition to the above therapies continues to be a priority.

Novel therapies have emerged from our improved understanding of the pathophysiology of CHF. The benefits of blocking activated neurohormonal vasoconstrictor systems in CHF are now well recognized. This has been supported by the success of treatment strategies involving blockade of the renin-angiotensin-aldosterone system (RAAS) (specifically with ACE inhibitors) and the sympathetic nervous system (SNS) (specifically with beta blockers). More recently, further understanding of other key systems involved in pathophysiologic responses to myocardial injury (Fig. 1) have led to promising new avenues for pharmacologic intervention that may be of therapeutic benefit in this condition.

This review focuses on new pharmacologic approaches to the perturbation of a number of these pathways of disease progression. Because of the large number of candidate drugs under investigation, this paper concentrates only on agents that are currently in clinical development for the specific indication of CHF.
Novel Approaches to Renin-Angiotensin-Aldosterone System Blockade

The RAAS has been well characterized as an important mediator of disease progression in CHF. Angiotensin II is a potent vasoconstrictor (and activator of other vasoconstrictor systems), mitogen, and growth factor, as well as being arrhythmogenic within the myocardium. Aldosterone is independently an important fibrogenic growth factor, mediating pathologic extracellular matrix deposition within the myocardium and thus contributing to the ongoing remodeling process that characterizes the disease.

Angiotensin-converting enzyme inhibitors have been shown to reduce mortality, hospitalization for CHF, development of symptomatic CHF in patients with asymptomatic left ventricular dysfunction, and to improve quality of life. However, a concern with ACE inhibitors is that they may provide less than full long-term suppression of the RAAS, as observed by a return toward normal plasma levels of downstream peptides, that is, angiotensin II and aldosterone, with chronic therapy. Therefore, agents that may more profoundly block the RAAS or interrupt the pathway at other points may be of greater or additional benefit in CHF therapy.

The above considerations support a potential beneficial therapeutic role of angiotensin II receptor antagonists in CHF. These agents potently and selectively block the AT1 receptor subtype of angiotensin II, which appears to mediate the majority of the adverse effects associated with the peptide, as described above. The role of the AT2 receptor (which is left unblocked by these agents in the setting of increased circulating levels of angiotensin II) is controversial. In general, AT2 receptor agonism appears to mediate vasodilatation and antiproliferative effects, although the specific role of these receptors in patients with CHF has not been well elucidated.

Trials are underway to compare angiotensin II receptor antagonists with ACE inhibitors, as well as to study both groups of agents as combined therapy to maximize RAAS blockade (Table I). The preliminary results of the Evaluation of Losartan in The Elderly (ELITE)-II trial (which compared the angiotensin II receptor antagonist, losartan, with the ACE inhibitor, captopril) would suggest that both drug classes have a similar effect on survival, although ACE inhibitors were superior when combined with beta blockade.

An important observation in a recent pilot trial of an angiotensin II receptor antagonist and an ACE inhibitor—the Randomized Evaluation on Strategies for Left Ventricular Dysfunction (RESOLVD) study—was that combined therapy did not fully suppress production of aldosterone long term. The importance of blockade of aldosterone is underscored by the mortality benefit observed in a recent study using low doses of the aldosterone antagonist, spironolactone—the Randomized Aldactone Evaluation Study (RALES). This agent also affects estrogen and androgen receptors, contributing to a significant side-effect profile. A new generation of so-called “selective” aldosterone receptor antagonists (SARAs) has been developed; these agents have little or no pharmacologic activity beyond the aldosterone receptor. The first of the SARAs, eplerenone, is currently being evaluated in patients with symptomatic heart failure due to systolic left ventricular dysfunction following myocardial infarction.

Endothelin Blockade

Of the many potential therapeutic targets for inhibition of disease progression in CHF, other than the RAAS, blockade of the endothelin system is by far the most advanced in its clinical development.

![Fig. 1](image-url) Mechanisms of disease progression in congestive heart failure. SNS = sympathetic nervous system, RAAS = renin-angiotensin-aldosterone system, ET = endothelin, TNF-α = tumor necrosis factor-α, IL = interleukin, γ-IFN = γ-interferon, TGF-β = transforming growth factor-β, bFGF = basic fibroblast growth factor, IGF = insulin-like growth factor, NO = nitric oxide, MMP = matrix metalloproteinase, LV = left ventricular.
The endothelin family consists of three isopeptides (ET-1, ET-2, and ET-3). Endothelin-1 is derived predominantly from the vascular endothelium. It is a potent vasoconstrictor and has mitogenic and inotropic effects on the myocardium. It is also a potent stimulus for RAAS and SNS release. Endothelin-1 is formed from cleavage of larger peptides with the final step involving an endothelin-converting enzyme (ECE) which breaks down big (39-amino acid) endothelin to the active 21-amino acid peptide. Therefore, ECE inhibition and/or endothelin receptor blockade are two potential pharmacologic approaches to blockade of this system.

Endothelin-1 acts in an autocrine and paracrine manner through two endothelin receptor subtypes, which are described in Figure 2. The ETA receptors are located on the vascular smooth muscle cell (VSMC) and their activation mediates constriction, whereas activation of ETB receptors mediates both constriction on the VSMC and stimulates vasodilation, the latter predominantly via activation of endothelial cell nitric oxide. Given these physiologic actions, there has been some controversy as to whether blockade of the ETA receptor alone or both receptor subtypes may be of greatest therapeutic benefit (see below).

There is now considerable evidence to support the role of endothelin-1 in disease progression in CHF. Endothelin-1 is formed from cleavage of larger peptides with the final step involving an endothelin-converting enzyme (ECE) which breaks down big (39-amino acid) endothelin to the active 21-amino acid peptide. Therefore, ECE inhibition and/or endothelin receptor blockade are two potential pharmacologic approaches to blockade of this system.

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There is now considerable evidence to support the role of endothelin-1 in disease progression in CHF. Despite release of endothelin-1 predominantly in an abluminal direction, that is, away from the lumen and toward the VSMC, plasma levels of endothelin-1 are elevated in CHF and the magnitude of elevation correlates with disease severity. Plasma levels of endothelin-1 are a powerful predictor of subsequent mortality in patients with CHF. This acute observation has been subsequently confirmed in a 2-week placebo-controlled oral study with bosentan at a dose

**TABLE I Current clinical trials of angiotensin II receptor antagonists in congestive heart failure**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study drug</th>
<th>Patient population</th>
<th>Study design</th>
<th>Primary endpoint</th>
<th>Patient numbers</th>
<th>Study status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val-HeFT</td>
<td>Valsartan</td>
<td>Systolic HF (LVEF &lt; 35%); NYHA class II–IV symptoms</td>
<td>Valsartan vs. placebo additional to background therapy, e.g., ACE inhibitors</td>
<td>All-cause mortality</td>
<td>5,010 (final)</td>
<td>Recruitment closed, endpoints being accumulated</td>
</tr>
<tr>
<td>CHARM</td>
<td>Candesartan</td>
<td>Systolic and diastolic HF</td>
<td>Pooled analysis (of 3 studies below)</td>
<td>All-cause mortality</td>
<td>6,700</td>
<td>Recruitment ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(I) Diastolic HF</td>
<td>Candesartan vs. placebo (no background ACE inhibitors)</td>
<td>CV death/HF, hospitalization</td>
<td>2,500</td>
<td>Recruitment ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(II) Systolic HF</td>
<td>Candesartan vs. placebo (ACE inhibitor intolerant)</td>
<td>CV death/HF, hospitalization</td>
<td>1,700</td>
<td>Recruitment ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(III) Systolic HF</td>
<td>Candesartan vs. placebo (background ACE inhibitors)</td>
<td>CV death/HF, hospitalization</td>
<td>2,300</td>
<td>Recruitment closed, endpoints being accumulated</td>
</tr>
</tbody>
</table>

**Abbreviations:** HF = heart failure, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, ACE = angiotensin-converting enzyme, CV = cardiovascular, VAL-HeFT = Valsartan in Heart Failure Trial, CHARM = Candesartan in Heart Failure Assessment in Reduction of Mortality.

![Fig. 2 Endothelin subtypes, endothelin receptor subtypes in the peripheral vasculature. ET = endothelin, NO = nitric oxide, ECE = endothelin-converting enzyme, cGMP = cyclic guanosine monophosphate, cAMP = cyclic adenosine monophosphate, VSMC = vascular smooth muscle cell.](image-url)
of 2,000 mg/day. Of importance is the fact that this study was conducted in patients with CHF already optimally treated (at the time) with background ACE inhibitor therapy. In this study, bosentan reduced systemic and pulmonary artery pressures, increased cardiac output, and lowered systemic and pulmonary vascular resistance (PVR) (Fig. 3). The marked reduction in PVR with bosentan supports endothelin blockade as a potentially useful therapeutic strategy in both primary and secondary forms of pulmonary hypertension. A preferential effect on PVR may be occurring because endothelin is highly expressed within the pulmonary vasculature. In addition, there was no reflex increase in activation of the RAAS or SNS, supporting a facilitatory role for endothelin on those systems.

It is not clear, however, whether the hemodynamic effects observed with endothelin blockade necessarily translate into morbidity and mortality benefits with long-term therapy. Indeed, the history of drug development for CHF is associated with many promising agents which demonstrated short-term hemodynamic benefits that did not subsequently result in improved long-term outcomes, for example, milrinone, flosequinan, ibopamine, and xamoterol. Furthermore, these drugs are all characterized by a propensity to activate key neurohormonal systems pathologically involved in the CHF disease process further; in contrast, this is not observed with endothelin blockade.

The potential utility of endothelin blockade in CHF has been further supported by long-term mortality studies in rat models of the disease. Reductions in mortality (in comparison with placebo) have been noted in both the coronary ligation, left ventricular myocardial infarction model (with bosentan) and in spontaneously hypertensive stroke-prone rats fed a high-salt diet (with the mixed endothelin receptor antagonist, SB217242 [Enrasentan, SmithKline Beecham Pharmaceuticals, Philadelphia, Pa.]) (Willette et al.: The endothelin receptor antagonist SB217242 improves cardiac function and mortality in rat models of heart failure [HF]. Submitted for publication). These results may be due to the beneficial effects on ventricular remodeling that have been demonstrated with these agents (Willette et al.).

Based on the above considerations, several larger clinical endpoint studies with endothelin receptor antagonists have recently been undertaken. The results of a 6-month placebo-controlled clinical efficacy study of bosentan involving 370 patients with CHF with severe (New York Heart Association [NYHA] Class III–IV) symptoms have recently been reported. The study was terminated prematurely because of concerns regarding asymptomatic elevations in liver function parameters. Nevertheless, in patients who received the full 6 months of therapy, bosentan significantly improved the likelihood of clinical improvement and decreased the likelihood of CHF deterioration (p = 0.045). In addition, there was a reduction in the combined endpoint of death and worsening heart failure, shortened hospital stay, and reduced total days in hospital with bosentan. This study was conducted at a dose of 500 mg b.i.d., following up titration from lower doses. Patients who were uptitrated more slowly experienced fewer episodes of worsened CHF early in the study. For this reason, as well as the possibility that the liver function abnormalities may be dose related, a large morbidity study with bosentan in patients with Class III–IV CHF is now underway at a lower dose (125 mg b.i.d.).

The liver function abnormalities seen with bosentan may be related to its structure (it is a sulphonamide) and therefore may not necessarily be a class effect of endothelin receptor antagonists. Many other endothelin receptor antagonists, which thus far do not appear to possess this side-effect, are therefore being actively studied in this disease (Table II). Agents in the latter stages of clinical development include the mixed endothelin receptor antagonist Enrasentan (SmithKline Beecham), which is currently being evaluated in a large phase II trial program in both symptomatic (NYHA class II–III) patients with CHF and those with asymptomatic left ventricular dysfunction.

As mentioned earlier, a major issue regarding the use of endothelin receptor antagonists in CHF is whether mixed antagonists or ETA-selective agents confer the greatest benefit. While the ETB receptor appears to mediate vasodilation in the forearm of normal subjects and has natriuretic effects within the kidney, this may not necessarily be the case in the setting of disease states such as hypertension and CHF. Thus, the above question remains controversial and will only be resolved by comparative studies between the two types of endothelin receptor antagonists. Currently, a number of ET_A-selective agents are being studied in CHF, including SB247083 (SmithKline Beecham), TBC-11251 (Texas Biotechnology Corp., Houston, Tex.), and BMS187308 (Bristol-Myers Squibb Company, Princeton, N.J.), as well as the mixed antagonists previously mentioned.

Highly specific ECE inhibitor compounds have recently been developed. Data from our laboratory suggest a beneficial early effect on ventricular remodeling. Further studies with this group of agents are ongoing in preclinical models of CHF. Agents that block not only ECE but also ACE and neutral endopeptidase (NEP) may also be a potentially beneficial pharmacologic strategy in the setting of human CHF.
Cytokine Antagonists

Congestive heart failure is associated not only with activation of circulating neurohormonal factors but also with the activation of a number of key proinflammatory cytokines that may contribute to progression of this disease. The best characterized of these proinflammatory cytokines is tumor necrosis factor-α (TNF-α). Plasma levels of TNF-α have been found to be elevated in CHF.41, 42 Furthermore, increased plasma levels of the soluble receptors that clear TNF-α from the circulation have also been described, suggesting an overall upregulation of the system.43 Perhaps even more important, TNF-α gene expression is markedly activated within the myocardium.44 The exact cause of this activation is unclear, but it has recently been proposed to be related to chronic low-grade infection associated with altered gut permeability to microorganisms in the setting of CHF.45

There is now considerable evidence that TNF-α contributes to the CHF disease process. A 14-day infusion of TNF-α in rats via a mini-pump resulted in impaired ventricular function similar to that observed in dilated cardiomyopathy.46 Furthermore, a murine TNF-α overexpression model produced a phenotype in heterozygotes very similar to that of dilated cardiomyopathy, with dilation and fibrosis of the ventricle, atrial enlargement, and the clinical sequelae associated with symptomatic CHF (lethargy and weight loss).47

Tumor necrosis factor-α may impair ventricular function via a number of potential mechanisms. Activation of the cytokine is associated with an increase in inducible nitric oxide synthase (iNOS) within the myocardium,48 and this may directly and indirectly impair ventricular function. It also has pro-oxidant and apoptotic properties and is a potent stimulator of endothelin production.49

The above observations support the development of agents that block TNF-α activity. Pentoxifylline has been used for many years in peripheral vascular disease although there are limited clinical data to support its use. More recently, it has been found to be a potent inhibitor of TNF-α in vitro, at the level of gene transcription. Clinical trials with this agent in CHF have noted dramatic improvements in left ventricular function, supporting the use of this therapeutic strategy.50 More recently, agents have been developed to specifically target blockade of TNF-α activity. A chimeric TNF receptor fusion protein, etanercept, has been genetically engineered to bind TNF-α within the circulation and thus potentially to limit its activity within the myocardium. This strategy has been found to be of benefit in animals studies, and recent 3-month clinical data would suggest a benefit in patients with CHF (Fig. 4).51

The advantage of this agent is that it does not appear to have many contraindications and limitations to its use, in contrast to many other agents currently used (e.g., beta blockers) and proposed for use in CHF. The major adverse effect thus far reported with etanercept appears to be an impaired immune response to severe systemic infection.

![Fig. 4 Three-month study of etanercept on clinical composite in patients with congestive heart failure. □ = Better, ■ = unchanged, ■ = worse.](image-url)
Augmentation of Natriuretic Peptides

Natriuretic peptides are a family of hormones that are activated in CHF as a result of ventricular and atrial wall stretch. The peptides are potent vasodilatory and natriuretic factors, and thus further augmentation of their physiologic effects may be of therapeutic benefit in CHF.52

Two major therapeutic strategies have been employed in augmenting natriuretic peptides. The first is to provide these peptides exogenously, particularly in the setting of salt and water overload. Intravenous infusion of a human b-type natriuretic peptide (nesiritide) has been shown to improve cardiac hemodynamic parameters acutely in patients with decompensated CHF.53 It is not clear, however, whether these effects are greater than those that could be achieved by intravenous use of a loop diuretic.

An alternative approach has been to block the breakdown of natriuretic peptides via inhibition of the catalytic enzyme, NEP; however, such agents have been found to be of little benefit in the absence of concomitant RAAS blockade.54 Natriuretic peptides play a counter-regulatory role in the setting of RAAS activation, as in CHF.55 In turn, RAAS activation limits natriuresis and diuresis produced by natriuretic peptides. These observations have led to the development of so-called dual metalloprotease or vasopetidase inhibitors, blocking both ACE and NEP. The first of these agents, omapatrilat, has recently been found to be of hemodynamic and clinical benefit in patients with CHF in comparison with an ACE inhibitor,56 leading to plans for a large phase III clinical trial. If these preliminary data can be confirmed, the potential exists for these agents to replace ACE inhibitors as standard background therapy for patients with symptomatic systolic CHF.

Conclusion

Chronic heart failure is a complex syndrome involving activation of multiple cellular, metabolic, and neurohumoral pathways following the initial myocardial insult. It is apparent that perturbation of multiple pathways is required to maximize the therapeutic benefit of intervention in the condition. New drug strategies in addition to ACE inhibition and beta blockade are currently under active late-phase clinical evaluation to test hypotheses regarding the pathogenic role of these pathways in CHF as well as the therapeutic potential of long-term intervention. The most advanced of these new strategies (beyond RAAS blockade) is inhibition of the endothelin system. There is a substantial body of evidence that this system is intimately involved in CHF disease progression, and early-phase clinical data support the potential utility of long-term endothelin inhibition.

An important issue for future management of patients with CHF is the number of different classes of pharmacologic agents that may be of proven benefit in the condition. It is unlikely that any one patient would be able to tolerate all such agents, especially multiple drugs with vasodilator actions. Therefore, scientific approaches need to be developed to select patients who would benefit most from specific drug classes. These approaches may, in the future, include selection of an agent according to the neurohormonal and cytokine profile of the individual patient or pharmacogenetic profiling to target therapy according to presence or absence of relevant genetic polymorphisms.

References


