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REVIEW ARTICLE

Emerging Drug Therapies for Heart Failure

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ABSTRACT

Heart failure is associated with high morbidity and mortality and is proving to be an economic burden in developing countries. A number of therapeutic agents are presently employed in heart failure; but they are not sufficient to control symptoms of heart failure. Moreover, the prevalence of chronic heart failure is progressively increasing and thus there is a continuing need to develop effective therapies for the management of this disease. The present review has discussed various potential therapeutic agents which may open new vistas for the management of heart failure.

Keywords: *Heart failure, Candisartan, Spironolactone, Conivaptan, Nesiritide, Omapatrilat*

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Heart failure is a condition in which cardiac muscle become weak and fail to pump blood efficiently to meet the metabolic requirement of body. It is characterized by inflammation, exercise intolerance, fatigability, dyspnea and fluid retention as a result of myocardial dysfunction [1]. Drugs like diuretics, vasodilators, inotropic agents, angiotensin converting enzyme (ACE) inhibitors and β adrenoceptor blockers have been employed to improve functional status of heart failure [2, 3]. In spite of effective drugs available to treat heart failure, it is still a progressive syndrome with high morbidity and mortality.

POTENTIAL DRUG THERAPY FOR HEART FAILURE

Various neurohormones and inflammatory mediators are identified as potential target sites and implicated in pathogenesis of heart failure. Thus the following agents have been proposed as potential drugs to be used in heart failure.

Angiotensin-II AT1 Receptor Blockers

Renin, angiotensin and aldosterone system (RAAS) have been implicated in pathophysiology of heart failure [4]. Angiotensin-II AT1 receptor blockers (ARB) are developed to block RAAS more completely and they do not produce dry cough and angioedema as compared to ACE inhibitors [5]. Candisartan (ARB) has been shown to improve diastolic dysfunction and reduce progression of cardiac remodeling in Dahl salt-sensitive (DS) rats [6]. Olmesartan, a novel AT1 receptor antagonist has been reported to produce cardioprotection by suppressing inflammatory cytokines [7]. ELITE I (Evaluation of Losartan In The Elderly) and ELITE II are the first long-term clinical trials to compare the safety and effectiveness of losartan (ARB) with captopril in heart failure with decreased left ventricular ejection fraction. These clinical trials have suggested losartan as an alternative agent in patients who are unable to tolerate ACE inhibitors [8, 9]. The clinical trial named RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) has compared efficacy of candisartan (ARB) with enalapril in patients of class III or IV (NYHA) heart failure. No significant difference has been noted in patients treated with candisartan and enalapril alone or in combination using six minutes walking test. Moreover, combination of candisartan and enalapril has markedly decreased end-diastolic volume, plasma aldosterone concentration and left ventricular remodeling [10]. Val-HeFT (Valsartan-Heart Failure Trial) trial has evaluated safety and efficacy of valsartan in heart failure with low left ventricular ejection fraction. Patients receiving β-blocker and ACE inhibitor , when treated with valsartan which have demonstrated increase in mortality suggesting that "triple therapy" has not been useful [11]. Moreover, valsartan alone is a safe and effective agent for heart failure as compared to combination of valsartan and ACE inhibitors [12].

CHARM (Candisartan in Heart failure Assessment of Reduction in Mortality and Morbidity) trials included three studies named as CHARM-Alternative, CHARM-Added and CHARM-Preserved trials. The CHARM-Alternative trial examined patients with 40% or less left ventricular ejection fraction who could not tolerate ACE inhibitors [13]. CHARM-Added trial included patients with 40% or less left ventricular ejection fraction who

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were given ACE inhibitor with or without β-blocker [14]. CHARM-Preserved trial included patients with 40% or more left ventricular ejection fraction [15]. The CHARM trials demonstrated that the ARB has reduced morbidity and mortality in heart failure. Further it was concluded that ARB was a good alternative for patients who could not tolerate ACE inhibitors [16]. But these trials have not yet confirmed the comparative efficacy of ARB in blacks as compared to white population since heart failure is more prevalent and progresses rapidly in blacks and studies are warranted for this view point.

Thus it may be suggested that ARBs are better alternative agents for heart failure patients who are unable to tolerate ACE inhibitors. The combination of ARBs with either ACE inhibitors or β-blockers may be beneficial; but triple therapy with combination of ARBs, ACE inhibitors and β blockers may be harmful due to excessive neurohormonal blockade.

Aldosterone Receptor Antagonists

The use of aldosterone antagonists is emerging as an attractive treatment for patients with severe heart failure [17-20]. In RALES study (Randomized ALdactone Evaluation Study), the effect of spironolactone has been analyzed in patients with severe heart failure (class III-IV). Spironolactone has been noted to inhibit fibrosis by decreasing procollagen (type III). Further spironolactone has reduced hospitalizations and increased survival rate (30%). This study has revealed that gynecomastia and hyperkalemia occur during spironolactone treatment [21, 22]. In EPHESUS study (Eplerenone Neurohormonal Efficacy and Survival study) eplerenone, another aldosterone receptor antagonist has reduced mortality, sudden death and duration of hospitalizations due to heart failure. The incidence of gynecomastia and hyperkalemia is low as compared to spironolactone study [23]. Moreover, spiranolactone and eplerenone are life saving agents in patients with advanced heart failure [24].

Arginine Vasopressin (AVP) Receptor Antagonists

Arginine vasopressin (AVP) is a peptide hormone that modulates a number of processes implicated in pathogenesis of heart failure [25]. AVP regulates vascular tone, cardiovascular contractility and is involved in cardiac remodeling through V1a receptor [26-29] where as it regulates free water re-absorption by acting on V2 receptor [30]. Increase in AVP concentration may be used as a potential marker of heart failure [31].

AVP acts on V2 receptors and stimulates biosynthesis of aquoporin-2 (AQ2), a water channel protein which is involved in free water re-absorption [30]. Selective nonpeptide V2 receptor antagonists are currently evaluated for acute and chronic heart failure. In contrast to a loop diuretic like furosemide, V2 receptor antagonist has been shown to stimulate free water excretion with little or no sodium loss [32]. Administration of OPC-31260, a V2 receptor antagonist, has been shown to induce diuresis, decrease urinary osmolality, increase plasma osmolality and mechanistically attenuate upregulation of AQ2 water channels [33]. OPC-31260 has produced diuresis without producing marked sodium or potassium loss [32]. Tolvaptan (OPC-41061), a synthetic analogue of OPC-31260 has been reported to block V2 receptors more selectivity [34]. Tolvaptan produced dose-dependent increase in urine volume and decrease in urine osmolality in patients of volume-overloaded heart failure. Moreover, it significantly reduced body weight, oedema, dyspnea and jugular venous pressure and normalized serum sodium concentration in patients with hyponatremia [35]. The clinical trial named ACTIVE in CHF study (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure) has suggested that tolvaptan administration relieved systemic congestion in patients of heart failure [36, 37]. Moreover, tolvaptan enhanced water excretion without changes in renal haemodynamics or sodium and potassium excretion in patients of heart failure [38]. VPA-985 and SIR-121463 are highly selective V2 receptor antagonists currently under development for treatment of heart failure [39, 40].

The AVP mediated activation of V1a receptors is associated with an increase in systemic vascular resistance, venous pressure, pulmonary capillary wedge pressure (PCWP) and left ventricular filling pressure [41]. Conivaptan (YM-087), a dual V1a/V2 receptor antagonist has been shown to inhibit pressor response and stimulate aquaresis in rats and dogs [42, 43]. In patients with severe symptomatic heart failure, conivaptan significantly reduced both PCWP and right atrial pressure. Further, it produced dose-dependent increase in urine out put [44].

In summary, AVP antagonists may be useful in the treatment of patients with volume-overloaded heart failure. AVP antagonists appear to produce effective and sustained reduction in congestion without worsening renal function, potassium depletion or hypotension [45]. ADVANCE (A Dose evaluation of a Vasopressin ANtagonist in CHF patients undergoing Exercise) is a double blind placebo controlled randomized trial investigating the effects of conivaptan in heart failure. EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome study with Tolvaptan) is another ongoing multi-centre trial designed to evaluate the long-term efficacy and safety of oral tolvaptan in subjects hospitalized with decompensated heart failure [46].

Natriuretic Peptides

The family of natriuretic peptides consists of 3 isoforms including atrial natriuretic peptide (ANP or A-type), brain natriuretic peptide (BNP or B-type) and C-type natriuretic peptide (CNP) [47]. ANP and BNP are circulating peptides produced principally by right atrium and ventricles, respectively where as CNP is produced by endothelial cells [48]. BNP is a specific biomarker of ventricular dysfunction and it is documented to produce natriuresis, diuresis, vasodilation, reduction in rennin and aldosterone secretion and decreas sympathetic activation [49-52].

Nesiritide (Natrecor) is a recombinant form of human BNP. In PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with DobutaminE or Na-

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Trecor) clinical trial, infusion of nesiritide reduced PCWP and peripheral vascular resistance in patients with decompensated heart failure [53]. Intravenous administration of nesiritide has been shown to have beneficial natriuretic, diuretic and vasodilatory effects [54-57]. Nesiritide mimics the actions of endogenous BNP and produces venous and arterial vasodilation and it has been shown to improve cardiac haemodynamics more rapidly in patients with decompensated heart failure [58]. In VMAC (Vasodilation in the Management of Acute Congestive heart failure) trial, nesiritide reduced dyspnea and PCWP in patients with severe decompensated heart failure [59]. Anaritide (ANP) obtained by recombinant DNA technology is being currently investigated for heart failure. The major problems with natriuretic peptides are their peptidic nature, short half-life and intravenous administration [60].

Neutral Endopeptidase (NEP) Inhibitors

Natriuretic peptides are degraded in body by neutral endopeptidase (NEP) found in heart, kidney, brain and lungs [60, 61]. Hence agents that inhibit NEP and thus block the metabolism of endogenously generated natriuretic peptides have been developed and are known as neutral endopeptidase inhibitors. Candoxatril and ecadotril are highly specific inhibitors of NEP. Both these agents are prodrugs which are metabolized into their active congeners namely candoxatrilat and S-thiorphan respectively [62]. These agents prevent the degradation of natriuretic peptides and increase their biological activity [60]. Candoxatrilat, an active metabolite of candoxatril produced diuresis and natriuresis in patients with heart failure [63]. Further, it produced vasoconstriction rather than vasodilation in some subjects [64] which is still controversial. Candoxatril has been shown to have natriuretic and antialdosterone actions in canine model of heart failure [65]. Ecadotril (sinorphan) decreased plasma renin activity and PCWP [66] and it has been noted to produce severe pancytopenia and death in patients of heart failure [67]. Hence the development of NEP inhibitors has been discouraged.

Dual ACE/NEP Inhibition – Vasopeptidase Inhibitors

The combined effect of NEP and ACE inhibition produced vasodilation, diuresis and enhancement of myocardial function [60]. Omapatrilat, sampatrilat, fasidotrilat, MDL 100240, Z13752A, BMS 189921 and mixanpril are vasopeptidase inhibitors developed for the treatment of heart failure [62]. The inhibition of vasopeptidase with omapatrilat improved cardiac geometry and survival rate [68]. Omapatrilat is superior to ACE inhibitors in increasing glomerular filtration rate and sodium excretion and decreasing PCWP [69, 70]. Augmentation of bradykinin with omapatrilat has produced severe angioedema compared with enalapril in OCTAVE clinical trial [71]. The OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial of omapatrilat has demonstrated improvement in ventricular function in NYHA class II to IV heart failure [72].

Endothelin-1 Receptor Antagonists

Endothelin-1 (ET-1) is a potent vasoconstrictor peptide produced by vascular endothelium from big ET-1 via specific cleavage by endothelium converting enzyme (ECE) [73]. Plasma concentration of endothelin-1 is elevated in patients with moderate to severe chronic heart failure [74]. ET-1 produces its actions by acting on endothelin ETA and ETB receptors [75]. ETA receptor predominates in vascular smooth muscle cells and mediates vasoconstriction in both large and small blood vessels where as ETB receptors on endothelial cells mediate vasodilation through the production of nitric oxide and prostacyclin [76]. FR 139317, a selective ETA receptor antagonist has decreased cardiac pressures and increased cardiac output, glomerular filtration rate and renal blood flow. On the other hand RES-701-1, a selective ETB receptor antagonist has increased cardiac pressures and decreased cardiac output as well as renal blood flows [77]. Thus, blockade of ETB receptors may not be useful in heart failure [78].

Infusion of bosentan, a nonselective ETA/ETB receptor antagonist has been shown to improve systemic and pulmonary haemodynamics in patients with heart failure [79]. REACH-1 (Research on Endothelin Antagonists in Chronic Heart failure) trial has investigated long term effects of bosentan which has been shown to improve ventricular function in failing heart [80]. This trial has not been continued because increase in liver transaminases was noted with bosentan in patients with heart failure. The ENABLE (ENdothelin Antagonism with Bosentan and Lowering of Events) trial of bosentan did not demonstrate any improvement in mortality or hospitalizations due to heart failure [81]. Further, RITZ-4 (Randomized Intravenous TeZosentan study) trial investigated tezosentan, a non-selective ETA/ETB receptor antagonist and reported it not to improve the functional status of patients with heart failure. Moreover, RITZ-4 study reported that tezosentan produced proischemic effect in patients with decompensated heart failure and acute coronary syndrome [82]. Thus, nonselective ETA/ETB receptor antagonists are ineffective in heart failure and thereby selective ETA receptor antagonists are clinically evaluated because activation of ETB receptors produces nitric oxide mediated vasodilation. Darusentan, a selective ETA receptor antagonist did not improved symptoms of heart failure and it increased mortality [83]. Although earlier pre-clinical studies with endothelin receptor antagonists gave promising result, the recent clinical trials with these agents have demonstrated no ameliorative effect in patients with heart failure and as these negative results remain speculative, further studies are needed.

Dual Neutral Endopeptidase (NEP) and Endothelin Converting Enzyme (ECE) Inhibitors

Phosphoramidon, an ECE inhibitor produced vasodilation in patients with heart failure [84]. GGS 34043,

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GGS 34226 and GGS 26303 are dual inhibitor of ECE/NEP in development stages as future therapy for heart failure. They decreased preload, afterload and LV hypertrophy and increased cardiac output [85-87]. SLV 306 is an another dual inhibitor which has been reported to be useful in patients with heart failure due to its property of reducing right and left cardiac filling pressures [88].

Triple Enzyme Inhibitors of ECE/NEP/ACE

The triple enzyme (ECE/NEP/ACE) inhibitors are currently developed for heart failure. GGS 26670, a benz fused macrocyclic lactams has the property to inhibit ECE/NEP/ACE [89]. The triple enzyme inhibition improved LV function and reduced LV collagen accumulation better than either ACE alone or ECE-NEP inhibition [90].

Dual Dopamine D2 (DA2)-α2 Adrenoceptor Agonist

The active moiety of nolomirole (CHF-1025) is CHF-1024 which has been shown to have selective DA2-α2 receptor agonistic property. Treatment with nolomirole stimulates DA2-α2 receptors and inhibits catecholamine release from sympathetic nerve endings [91] and also inhibits the release of TNF-α from cardiac tissue to improve ventricular function [92]. Nolomirole significantly reduces hypertrophy and attenuates signs and symptoms of monocrotaline-induced heart failure [93].

Dopamine β-Hydroxylase Inhibitor

Dopamine β-hydroxylase (DBH) catalyses the conversion of dopamine (DA) to norepinephrine (NE) in sympathetic nerves. Nepicastat is a DBH inhibitor which has been reported to reduce norepinephrine synthesis. Nepicastat at low doses maintain normal plasma concentrations of norepinephrine in dogs with chronic heart failure. Further, it attenuates ventricular remodeling and prevents systolic dysfunction [94]. Moreover, inhibition of DBH may augment the levels of DA that act via dopamine receptors leading to renal vasodilation.

Adenosine A1 Receptor Antagonists

BG 9719, a selective A1 receptor antagonist increased GFR, urine flow and sodium excretion in a dose-dependent manner [95]. Development of BG 9719 was discontinued due to its poor solubility as well as the lack of a suitable oral formulation. BG 9928, another A1 receptor antagonist has the properties of improved potency, solubility and stability than BG 9719. Blockade of A1 receptor with BG 9928 protects renal function and exerts additive natriuretic effects without excessive potassium loss [96]. The clinical trial of BG 9928 in heart failure is currently underway [97].

Positive Inotropic Agents

Levosimendan, a new inotropic and vasodilator agent is being developed as an emerging therapy for heart failure [98]. The inotropic effect is mediated by calcium concentration dependent conformational changes in troponin-C during systole leading to sensitization of the contractile apparatus to calcium ions. The vasodilatory effect is mediated by opening ATP-sensitive potassium channels. Levosimendan produced positive inotropism and vasodilation and reduced plasma concentrations of endothelin-1 in patients with severe heart failure [99]. In patients with class IV heart failure, levosimenden reduced dyspnea and fatigue [100, 101]. In RUSSLAN (Randomized stUdy and Safety and effectivenesS of Levosimendan in patients with left ventricular failure after an Acute myocardial iNfarct) trial, levosimendan has significantly reduced the risk of death due to heart failure [102]. Further, in LIDO (Levosimendan Infusion versus DObutamine) trial, levosimendan has reduced PCWP and mortality; but arterial hypotension with levosimendan has been reported [103]. SURVIVE and REVIVES are the ongoing clinical trials to study the safety and efficacy of levosimendan in decompensated heart failure. Pimobendan has calcium sensitizing effects with PDE-III inhibition and it has been reported to improve hemodynamics and exercise tolerance in patients of heart failure [104].

In heart failure, an imbalance between left ventricular performance and myocardial oxygen consumption (MVO2), a phenomenon known as mechanoenergetic uncoupling, leads to decrease in cardiac contractile efficiency. Xanthine oxidase inhibitors (XOIs) are the first to be shown to reduce mechanoenergetic uncoupling in the failing heart. Oxypurinol, the active metabolite of allopurinol and a potent XOI, has been shown to improve cardiac performances in heart failure [105, 106]. Oxypurinol has positive inotropic effects and it ameliorates endothelial dysfunction in humans with heart failure [107]. The OPT-CHF (OxyPurinol Therapy for Congestive Heart Failure) is an ongoing study to investigate safety and efficacy of oxypurinol in heart failure.

Partial Fatty Acid Oxidation (pFOX) and Carnitine Palmitoyl Transferase-1 (CPT-1) Inhibitors

Ranolazine, a pFOX inhibitor, suppresses oxidation of fatty acids and improves mechanical efficiency and ventricular function in dogs with chronic heart failure [108]. Increase in glucose oxidation can also be obtained by etoxomir, an inhibitor of CPT-1. Etoxomir reverses fetal gene expression, preserves cardiac function and prevents ventricular dilation [109]. Etoxomir improved ventricular function and reduced PCWP in patients with heart failure [110]. Oxfenicine is another inhibitor of carnitine palmitoyl transferase-I and it prevented ventricular remodeling in heart failure [111].

Matrix Metalloproteinase (MMP) Inhibitors

It has been shown that enhanced expression of MMP triggers signaling cascade of cardiac remodeling and inhibition of MMP may be a potential therapeutic strategy for heart failure [112, 113]. Batimastat, ilomastat, marimastat and prinomastat are inhibitors of MMP being developed for heart failure. Evidence suggests that inhibition of cardiac MMP could prevent ventricular dysfunction and delay heart failure progression [114].

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Recently it has been shown that PG-53072, a selective MMP inhibitor has attenuated progression of left ventricular dysfunction and remodeling in dogs with chronic heart failure [115].

CelacadeTM - A New Emerging Therapy

CelacadeTM is an immune modulator which prevents chronic inflammation and apoptotic cell death by activating physiological immune system's IL-10 mediated anti-inflammatory process. A double-blind trial showed CelacadeTM to improve quality of life in patients of NYHA class III or IV heart failure [116]. In another phase II clinical trial CelacadeTM has been shown to reduce the risk of death and hospitalization due to chronic heart failure [117]. Further, Vasogen's ACCLAIM (Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy) trial has been going on in different cardiac centers of United States.

Gene Therapy

In heart failure, SERCA2a mRNA levels are decreased [118] and gene transfer of SERCA2a has been reported to increase cardiac contractility [119]. Further in heart failure, expression of Na^{+}-Ca^{2+} exchanger (NCX) is increased which results in high influx of Ca^{2+} into myocytes which prolongs action potential duration and produces early and delayed after depolarization-induced arrhythmias in failing myocardium [120]. Thus NCX inhibition may be a novel target to manage arrhythmias in heart failure. In heart failure, there is high expression of β-adrenergic receptor kinase-1 (βARK1) that desensitizes adrenergic receptors. Inhibition of overexpression of βARK1 may offer a new therapeutic option.

CONCLUSION

New therapeutic developments such as AT1 receptor blockers, aldosterone receptor antagonists, AVP receptor antagonists, natriuretic peptides, vasopeptidase inhibitors, dopamine D2-α2 adrenoceptor agonist, DBH inhibitor, adenosine A1 receptor antagonists, xanthine oxidase inhibitors, pFOX inhibitors, CPT-1 inhibitors, MMP inhibitors and immune modulation therapy like Celacade^{TM} may be potential candidates in future for heart failure. Further advances in understanding of pathophysiology of heart failure will probably help to develop novel therapeutic agents for patients with poor prognosis of heart failure.

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