NEW HORIZONS IN THE MANAGEMENT OF HEART FAILURE

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ABSTRACT

INTRODUCTION

Heart failure (HF) is a global problem with an estimated prevalence of 38 million people worldwide; a number that is increasing with the ageing of the population.

The heart failure is associated with high health expenditure, mostly because of cost of hospitalisations. The five year survival for individuals with heart failure is about 50%, and in advanced heart failure, the one year survival is as low as 22%, regardless of therapy.

The modern history of therapy for heart failure with reduced ejection fraction began with the introduction of vasodilatation with hydralazine plus isosorbide dinitrate. Research about heart failure is now quite active worldwide and many areas are being explored e.g. gene therapy, modification of function of micro RNAs by antagomirs, stem cell therapy besides development of new pharmacological therapeutic agents.

KEYWORDS

Heart failure, ejection fraction, angiotensin converting enzyme, stem cells and gene therapy.

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INTRODUCTION: In developed countries, around 2% of adults have heart failure and in those over the age of 65, this is the most common diagnosis; resulting in more than one million hospitalisations annually. There is dearth of data regarding incidence and prevalence of HF not only from India, but the whole of developing world. The present estimates about the incidence and prevalence in developing world are mostly extrapolated from the data collected in western nations. Based on government data, prevalence of heart failure in India ranges anywhere between 1.3 to 4.6 million, with an annual incidence of 491,600 to 1.8 million cases. The total cost involved has been estimated to amount to 2% of total budget of National Health Service in United Kingdom, and more than $35 billion in United States. Nearly, one out of every four patients hospitalised in US with congestive heart failure is readmitted within 30 days. Additionally, more than 50% of the patients seek readmission within 6 months after treatment. Thus, despite some progress, prognosis of heart failure is worse than that of most cancers. Although the outcomes for ambulatory HF patients with a reduced ejection fraction (EF) have improved with the discovery of multiple evidence based drug and device therapies, hospitalised heart failure (HHF) patients continue to experience unacceptably high post-discharge mortality and readmission rates, that have not changed in the last 2 decades.[1,2,3,4,5]

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Review of Literature: Treatment of heart failure: 28 years of evidence based management: The clinical trials in the last decade of 20th century established that angiotensin-converting–enzyme (ACE) inhibition with enalapril reduced overall mortality by 16 to 40% and that enalapril's benefit in reducing the rate of hospitalisations for heart failure extended even to asymptomatic patients with reduced ejection fraction. The closely related class of drugs, the angiotensin-receptor blocker (ARBs) interfere with the action of angiotensin II at its type 1 receptor, resulting in vasodilatation. However, as effects of ARBs on mortality has been inconsistent, these drugs are recommended primarily for patients who have unacceptable side effects while receiving ACE inhibitors.[6]

The use of beta-blocker therapy, now a cornerstone of heart-failure treatment, was once considered counterintuitive, because of concern that patients with reduced ejection fraction either would not benefit or would have unacceptable side effects. After this, in an important clinical trial, it was reported that addition of spironolactone, a mineralocorticoid-receptor antagonist (MRA), resulted in a 30% reduction in mortality among patients already receiving an ACE inhibitor and a loop diuretic.[6,7]

An older class of inotropic agents, the cardiac glycosides; however, proved a disappointment when the results of the clinical trials showed unequivocally that digoxin had no beneficial effect on mortality in heart failure, though it did reduce overall hospitalisations by about 28%. Therefore, despite their long history, cardiac

glycosides are no longer the first-line therapy for heart failure, though they may be used to mitigate symptoms and prevent hospitalisations for heart failure.[6,7]

Emerging Therapies in the Management of Heart Failure: Stem Cell Therapy: Acute management of myocardial infarction has reduced the early mortality, thus precipitating the unintended consequence of increased prevalence of chronic heart failure among survivors. Current therapies target impair contractility and hemodynamic decompensation without treating the parenchymal loss that underlies the development and progression of disease.[8]

To address this unmet need, the invention of stem cell therapy is an important development. In this technique, implantation of stem or progenitor cells into the failing or damaged heart are expected to cause regeneration of heart muscle and improve cardiac function. Thus, it is an interesting and challenging front in the war against heart failure. Stem cells are special cells which are able to differentiate into few (for multipotent adult stem cells) or any (for pluripotent embryonic stem cells) lineage-specific cell types while self-renewing extensively to generate more stem cells.[8]

Because of their potency of differentiation, stem cells are often foreseen as the hope of novel cell replacement based therapies to regenerate tissues/organs damaged by injury or disease. Stem cells traditionally isolated from bone marrow, a readily used source, demonstrate excellent safety in clinical setting; yet patient to patient variability in outcome remains a recognised limitation necessitating further optimisation. By processing myocardial tissue excised during cardiac surgery or obtained by endovascular biopsy, it is now possible to derive resident stem cell population. This new method provides the prospect of anatomically matching the regenerative cell source with the target organ. Such an approach is; however, hampered by the invasive nature of heart tissue sampling and limited quantity of starting material. Orienting bone marrow stem cells for cardiac repair would eliminate the need for patient to undergo cardiac harvest, rendering this accessible and renewable compartment an alternative to heart tissue.[8,9,10]

Recently, hallmark traits of cardiac development were successfully triggered within bone marrow-derived mesenchymal stem cells, establishing the first human lineage–specified phenotype derived without heart tissue harvest. In a study involving administration of derived autologous cardiopoietic stem cells into the hibernating myocardium of the patients with heart failure, the consistent improvement in left ventricular ejection fraction was demonstrated compared with standard care, thus, providing a rationale for further clinical validation. CAP-1002 is one such promising allogeneic stem cell therapy for the treatment of heart disease. The cells are derived from the donor heart tissue introduced into patient's heart via infusion into a coronary artery using standard cardiac catheterisation techniques. The drug is in phase –1/11 clinical trial to evaluate its efficacy and safety in patients with advanced heart failure.

However, several important questions regarding stem cell therapy of heart failure remains to be answered. These include determination of optimal cell types, methods of processing of cells and the optimum, dose and timing of their administration. At present, mesenchymal stem cells and cardiac stem cells seems to be most promising for further research.

The Gene Therapy: The field of myocardial genetic manipulation is vast because of complex and multifaceted disease mechanisms. The gene therapy describes the transfer of genes to target cell or organ to treat or prevent disease. The goal is to correct the molecular defects using the affected cell's own genetic machinery. Successful delivery of gene to the target is paramount to therapeutic efficacy.

A number of gene delivery methods have been developed using both viral and non-viral based vectors. Non–viral methods include using naked DNA alone or complexed with liposomes. The viral vectors, which include retroviruses, adenoviruses and adeno-associated viruses, are more commonly used for cardiovascular applications because they transfer genes to cardiac myocytes much more efficiently than any of the non-viral methods. The gene carrying vector might be delivered by infusion into a coronary artery, by catheter directed subendocardial injection, by intracardiac injection, and by percutaneous method.

The ongoing or completed clinical trials for gene therapy in cardiac failure have included those testing the sarco/endoplasmic reticulum calcium ATPase 2a (SERCA2a), stromal derived factor (SDF-1) and adenylate cyclase-6.

The calcium cycling in the cardiomyocyte is crucial to both cardiac contraction and relaxation. The sarcoplasmic-endoplasmic reticulum ATPase (SERCA2a) pumps calcium ions from the cytoplasm back into the sarcoplasmic reticulum, shutting off contraction and initiating relaxation. Several components in the calcium cycling process can be disturbed and cause heart failure. Impairment of SERCA2a activity can result from reduced ATP generation, as occurs in ischemia and has been reported in both animal models and patients with heart failure. This impairment diminishes the calcium pumped back into the sarcoplasmic reticulum during diastole, interfering with both contraction and relaxation.[10] The calcium upregulation by percutaneous administration of gene therapy trial involving patients of advanced heart failure have shown promising results (CUPID).[20] A phase 2b trial is underway in 200 patients in 10 countries, the results of which will be known in next few months (NCT01643330).[11,12,13,14]

MicroRNAs (MiRNAs): These are short non-coding RNAs, which are present in all higher eukaryocytes. Their function is to silence miRNA by pairing with its messenger sites, thereby preventing protein translation and gene expression. Preclinical research into miRNAs has shown the important role of these molecules in the control of calcium cycling and in the development of ventricular hypertrophy and heart failure, several miRNAs are promoters and others are inhibitors of hypertrophy, thus, making miRNAs the

potentially important targets of therapy. For example, overexpression of miRNA133 blocked the adverse effects of β-adrenergic stimulation in transverse aortic constriction in mice, reducing cAMP formation and inhibiting apoptosis, suggesting that over expression of this miRNA might enhance the effects of β blockers in heart failure. The antagomir to miR208a (miRNA208a precursor) prevented cardiac remodelling and improved survival in a hypertensive rat model. miRNA25 is also unregulated in mice with heart failure secondary to transverse aortic constriction in which it interferes with cardiomyocyte calcium cycling by blocking the SERCA2a pump. miRNA25 is also increased in the hearts of patients with heart failure and their response to this antagomir would be interesting and potentially very important to study. If beneficial, it could herald a novel approach to the treatment of clinical heart failure.

MiRNAs within the myocardium might also be altered with therapy of heart failure.[15,16]

Some Other Novel Therapeutic Agents on the Horizon: Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering neurohormonal overactivation that contributes to vasoconstriction, sodium retention and maladaptive remodelling. The combined inhibition of rennin-angiotensin system and neprilysin had effects that were superior to those of either approach alone in experimental studies, but in clinical trials, the combined inhibition of ACE and neprilysin was associated with serious angioedema. LCZ696, a combination of neprilysin inhibitor sacubitril (AHU377) and ARB, valsartan was designed to minimise the risk of serious angioedema. The inhibitor blocks the action of neprilysin, resulting in higher levels of peptides such as natriuretic peptides, which have vasodilator properties, facilitate sodium excretion, and most likely have effects on remodelling. In a study involving patients with chronic heart failure and a reduced ejection fraction, the LCZ696 was more effective in reducing the risk of death from cardiovascular causes or hospitalisation for heart failure than was ACE inhibition with enalapril alone. As compared with enalapril, LCZ696 also reduced the risk of hospitalisation for heart failure by 21% ($P<0.001$) and decreased the symptoms and physical limitations of heart failure ($P=0.001$). The superiority of LCZ696 over enalapril was not accompanied by important safety concerns. The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema, but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril. The trial was stopped early, according to prespecified rules, after a median followup of 27 months (seven months before it was due to finish), because the boundary for an overwhelming benefit with new drug had been crossed.[17]

Omecamtiv Mecarbil: A small molecule omecamtiv mecarbil, previously codenamed CK-1827452 is a cardiac specific myosin activator. It specifically targets and activates myocardial ATPase and improves energy utilisation. This enhances the effective myosin cross bridge formation and duration, while the velocity of contraction remains the same.

It also increases rate of phosphate release from myosin, thereby accelerating the rate determining step of cross bridge cycle, which is the transition of actin-myosin complex from the weakly bound to the strongly bound state, thus increasing the left ventricular systolic ejection time, sarcomere shortening and stroke volume, while the systolic pressure remains the same. Because this drug increases stroke volume by prolonging the duration, but not the velocity of myocyte contraction, it does not seem to increase the heart's requirement of oxygen or to increase intracellular calcium as phosphodiesterase-3 inhibitors, such as milrinone, do. In a phase 2 clinical trials on patients with reduced ejection fraction, this drug increased the duration of systolic ejection period and the stroke volume, while reducing both the left ventricular end systolic and end diastolic volumes. Clinical trials of the treatment of chronic heart failure with omecamtiv mecarbil are ongoing.[18]

MYK-461: It is an oral, selective, small molecule allosteric modulator of cardiac myosin. The studies are underway to assess the MYK-461's therapeutic mechanism by demonstrating reduction in cardiac muscle contractility via echocardiography as evidence of target engagement. Thus, MYK-461 has been designed to correct one of the most common molecular mechanisms causing HCM, and the clinical program will evaluate patients whose disease is caused by this specific mechanism, as identified by genetic screening. There is hope that by targeting the underlying molecular defect causing hypercontractility, the new molecule will be able to restore normal heart muscle contraction and relaxation, and reduce or potentially even prevent the downstream consequences of disease. HCM is the most common heritable heart disease, affecting one in 500 people, and complications of HCM include progressive heart failure and sudden cardiac death in young adults and adolescents.[19]

TRV027: It is an investigational peptide drug in phase 2b trial for the treatment of acute heart failure, with an innovative biased ligand mechanism that simultaneously vasodilates while increasing cardiac performance. It is an intravenous preparation acting at the Angiotensin II type I receptor, which is the same target inhibited by the oral ARBs, that are successfully used as chronic daily therapy to slow the progression of heart failure, but only TRV027 has a profile suggesting potential use in treating acute heart failure.[20]

Apelin is a peptide that in humans is encoded by the APLN gene and was first identified in 1998. It is widely expressed in various organs and is the endogenous ligand for the angiotensin-like 1 receptor. The apelin receptor is expressed early during the embryonic formation of the heart, where it regulates the migration of cell progenitors fated to differentiate in the contractile cells, the cardiomyocytes. Its

expression is also detected in the cardiomyocytes of the adult where apelin behaves as one of the most potent stimulator of cardiac contractility. Apelin is a powerful inotrope, peripheral vasodilator and may be involved in fluid homeostasis. Apelin infusion has been shown to increase the cardiac output in humans and is likely to represent a combination of positive inotropism and reduced peripheral vascular resistance. Researchers at the University of Alberta have been successful in developing a synthetic form of the peptide which is far more stable and potent than the naturally occurring peptide making drug therapies possible.[21]

CONCLUSION: Thus to conclude, the increased efforts to enhance the understanding of the pathophysiology of heart failure and to develop new approaches for prevention or improvement of care of the patient with this condition is important.

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