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The Current Evolutions in the Pharmacotherapeutic Management of Heart Failure

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Abstract

Periodontitis is an infectious disease resulting in inflammation the supporting within tissues of the teeth, progressive attachment loss and bone loss-carranza. Some of the etiology and risk factors are Microbial factors, local factors, systemic factors, genetic factors and behaviour factors. Periodontitis can occur at any age, most frequently observe in adults at the age of 30-35years. It involves the degeneration of periodontal ligaments, resorption of alveolar bone resulting in the disruption of the structure of the teeth. In global population nearly 10-15% of people are suffering with severe periodontitis according to WHO. In management of periodontal infection Antibacterial agents are most widely used. Widening of PDL space, generalised loss of alveolar bone are the radiographic feature. Treatment requires more aggressive surgical care. Because of abundant source, lack of toxicity and high tissue compatibility the Biodegradable polymers are extensively employed in periodontal drug delivery devices. In the last decades, the treatment has been optimized for the use of drug delivery systems to the periodontal pocket, with the advantage of delivering the drug in the specific site, sustaining and/or controlling the drug concentration. Recently, the use of new drug delivery systems has been receiving great interest. This review approaches the main delivery systems for the administration of drugs to the periodontal pocket, their usefulness as well as the advancement of these systems effectiveness in the periodontal therapy.

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Introduction

Heart failure is a clinical syndrome which is characterised as functional and structural dysfunction of the myocardial tissue which primarily leads to difficulties in ejecting blood or impairment of ventricular filling. It is complex clinical syndrome where the heart fails to face the metabolic requirements of the body. The very most prevalent aetiology of HF is reduced left ventricular myocardial function comparing to other dysfunctions of the pericardium, myocardium, endocardium and heart valves. The major pathophysiological aspects leading to heart failure include genetic mutations, ventricular remodelling, excessive neuro-humoral stimulation, abnormal myocyte calcium cycling, excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis, ischemia-related dysfunction and increased hemodynamic overload [1]. As morbidity and mortality rate are high in recent times across the globe heart failure considered as an alarming pandemic disorder. An epidemiological study revealed that nearly 26 million people around the world suffering from heart failure and leads to high economical cost [2]. The heart failure is categorized into groups based on ejection fraction and symptoms. A heart failure with ejection fraction less than 40% is termed as heart failure with reduced ejection fraction. A heart failure with ejection fraction greater than 50% is defined as heart failure with preserved ejection fraction. A heart failure with ejection fraction ranges from 40-50% is known as heart failure with mid-range ejection fraction [3]. This disease condition mainly deteriorate the metabolic functioning of the heart and puts the patient in death bed, hence it is mandatory to diagnose and treat the patients with effective treatment in order to prevent recurrent hospitalizations, enhance patient outcomes and to improve quality of life. The management of heart failure is a compound process involving in detection and prevention of disease worsening factors, potent pharmacological treatment to achieve good systolic and diastolic functioning of the heart and patient counselling [4]. As the morbidity and mortality are increasing day by day in mankind, many novel treatment approaches are emerging in the pharmaceutical market. This article, main focuses on the recent developments in heart failure pharmacological therapy and its impact in healthcare system.

Vericiguat:-A Promising Vasodilator

It is a new-fangled therapeutic agent emerged recently for the patients associated with reduced ejection fraction and chronic heart failure patients. It is most promising drug which is used in patients who are at high risk emergencies such as patient undertaking intravenous diuretic therapy, patients who are rehospitalized and patients whose life is getting worsen with heart failure [5-9]. On January 2021, Vericiguat has been legally endorsed by Food and Drug Administration (FDA) under a category of supplementary therapy for the patients associated

with reduced ejection fraction. This therapeutic agent is economically affordable by the patients as it budget factor is less than 100 cents [6-7].

The cardiovascular pathophysiology states that, in general there are dual forms of guanylate cyclase includes a receptor for nitric oxide which is known as soluble guanylate cyclase and a receptor for natriuretic peptides. These neurohormones elevates the level of phosphokinase G (PKG) which is responsible for myocardial diastolic function, by converting guanosine triphosphate to cyclic guanosine monophosphate (cGMP) by the help of catalyst soluble guanylate cyclase. This process is being corrupted in patients associated with cardiac dysfunctions, due the presence of oxygen species produced by the endothelium which mainly declines the nitric oxide levels and alters the function of sGC resulting in reduced (PKG) levels and thereby the myocardial tissues fails to do their function resulting stiffened cardiac tissue due to the collagen formation [8-9]. This agent impels soluble guanylate-cyclase (sGC) leads the formation of cGMP which is responsible for promoting vasodilation and makes to achieve a proper systolic and diastolic functioning of the myocardium [10-12].

The vericiguat mainly at a dose of 5 mg or higher gives a positive cardiac response such as decreased vascular resistance and increased cardiac output by increasing 4-10 beats per minute [13]. A case-controlled study revealed that the resistance of this vasodilator is higher than other in prolonged administration [14]. Patients with administered with vericiguat may experience postural dizziness and Headache due to vasodilation. In addition, the patient may experience abdominal discomfort, Diarrhea and nausea due to smooth muscle relaxation [15]. Some patients have observed with anemia, orthostatic hypotension and syncope as side effects. But no patients reported with serious adverse events (SAE). Vericiguat is highly contraindicated in patients who are taking long acting nitrates. Physician should be conscious in prescribing vericiguat for anemic patients as it decreases the hemoglobin levels. Routine monitoring should be done on clinical parameters such as hemoglobin, blood pressure, heart rate for patients taking vericiguat.

VICTORIA (Vericiguat Global study in subjects with Heart Failure with Reduced Ejection Fraction)a multi-center, randomized, parallel, placebo-controlled, double-blind, event-driven, pivotal phase III trial was done to determine the efficacy and safety of vericiguat in participants with heart failure with reduced ejection fraction. This trail was carried out on 5050 patients. In this study the patients were given 2.5 to 10 mg once in a day who is suffering heart failure with ejection fraction of 45% categorized under NYHA classes II-IV. The results states that vericiguat cannot cure heart failure completely but it avoids Re-Hospitalization [16-17].

Omecamtiv mecarbil: A potent inotropic agent

There collapse in Diastolic and Systolic function in evident if once there is a Progress in Heart failure18. This drug belongs to the Cardiac myosin activator class which facilitates a stronger cardiac contraction to prolong the Systolic duration by acting on Myosin-ATP complex. Initially, ATP will show some confirmatory changes by binding with Myosin and produces a complex [19-20]. This myosin-ATP complex usually undergo Hydrolysis and produces ADP complex and Pi (Rate limiting step) to make the bond between actin and myosin stronger, as the bond between myosin-ATP and Actin will we weaker. This whole cycle is known as Actin-Myosin ATPase cycle19. Omecamtiv mecarbil drug mainly works by activating the Myosin and making the Actin-Myosin ATPase cycle faster by speeding up the hydrolysis of ATP to ADP and release of Pi. This produces a force-increasing state by tightly bounding the myosin heads with actin compared to the usual physiology without disturbing the calcium channel or change in calcium uptake [21-22]. This tight bound between Actin-Myosin increases the contraction of cardiac muscle and prolongs total Systolic duration. Omecamtiv mecarbil shown various benefits in up-to-date experimental canine studies like increasing Systolic ejection time without disturbing the function of Calcium channel, Myocardial oxygen consumption and LV dP/dtmax; improving systolic wall thickening, Stroke volume and cardiac output; and reducing Left ventricular end diastolic pressure, mean left atrial pressure, peripheral vascular resistance and reduced heart rate [23].

Galactic-HF trial in 2021 did a study on Omecamtiv mecarbil which is previously discovered to be effective in prolonging Systolic duration in which it got evident that Omecamtiv mecarbil also increase Aortic blood flow per contraction, systolic ejection tine and mainly the dilation of ventricular systole. Omecamtiv mecarbilis a Myotrope as it activates the Myosin and making the Actin-Myosin ATPase cycle faster by speeding up the hydrolysis of ATP to ADP and release of Pi; without disturbing the function of Calcium channel. Hence, it is evident that Omecamtiv mecarbil can reduce Re-hospitalisation rather than curing the Heart failure completely [24-25].

Cosmic-HF trial in 2021 estimated the Omecamtiv mecarbil effect in Stable Heart failure with reduced ejection fraction (Systolic dysfunction) patients. This trial is done by randomizing participants into three groups, one receiving placebo for 20 weeks, another group (pharmacokinetic-titration group) with 25 mg BD titrated to 50 mg BD. By the end of the study, it is observed that when comparing Placebo group with pharmacokinetic-titration group there is reduction in NT-proBNP serum level and left ventricular end-systolic and end-diastolic diameter levels; Increase in stroke volume and systolic ejection time [26].

Sodium-Glucose Cotransporter 2 Inhibitors

Sodium Glucose Cotransporter 2 inhibitors (SGLT2-i) are collectively named as gliflozins, they exhibit a fascinating results as renal and cardio protective drug. These drugs mainly mask the activity of SGLT2 in the renal system. Some studies revealed that patients administering gliflozins are prone to glucosuria. In early stages, these drugs are approved only for the use of oral hypo-glycemic agents. Many clinical trials demonstrated that these drugs are not only reduce blood glucose level but also have many beneficiary effects in the health care system and these drugs have positive results in the field of cardiology and urology.

In general SGLT2 cotransporters are one among the group of symporters which involves in the solutes facilitated transportation. This process is catalysed by positive sodium gradient [27-28]. The sodium-glucose cotransporters in the body are two in number, one is SGLT1 which is located in skeletal muscle, heart, small intestine, Kidney (S3 segment of

The proximal tubule). And secondly SGLT2 which is located internal tissue, the first segments of the proximal tubules (S1 and S2) [26-31]. The renal physiology states that the SGLT1 (high-affinity, low-capacity Co transporter) reabsorbs 3–10% of glucose and SGLT2 (low-affinity, high-capacity Co transporter) reabsorbs 3–10% of glucose and sodium in the proximal convoluted tubule of the nephron. If any glucose or sodium remains they are taken back to the circulation by the transporters GLUT2 (for cells with SGLT2) and GLUT1 (for cells with SGLT1) present in the basolateral membrane. This unidirectional transported is facilitated by sodium-potassium pump located in the basolateral membrane.

These drugs work by inhibiting the reabsorption of sodium and make the sodium ion available in the distal tubule of the renal system. This inhibition greatly influences multiple physiological function. A Clinical study noted that these drugs lowers afterload and preload of the heart and gives a negative feedback for the sympathetic activity. These drugs also lowers the level of inflammatory markers such as TLR-4, IL-6, TNF, IFNγ, NF-κβ, and IL-6and TGF-β [32-35]. These drugs improve the functioning of mitochondria and decline the count of myofibroblast in myocardial tissue [36-37]. These drugs influences the interleukin-β-pathway in proximal tubular cells [38], thereby induces metabolic and hemodynamic effects. These effects reduces numerous negative effects includes oxidative stress, fibrosis, and inflammation in renal and cardiac system.

The patient administering these drugs experiences very less often and not significant adverse event use of SGLT2 inhibitors is associated with adverse events and it is very important to manage these adverse events. A clinical study revealed that the incidence of osmotic diuresis and volume contraction is seen higher in geriatric patients. Some patients taking these drugs may experience euglycemic diabetic ketoacidosis but the incidence and prevalence is very low. One in four patient may experience genital mycotic infections who in the treatment of SGLT2 inhibitors. The above mentioned adverse events should be managed and studies revealed that they are undoubtedly curable. In CANVAS trial, the patient experienced amputations and bone fractures in the usage of SGLT2 inhibitors. The clinical results of Emperor-reduced trials and DAPA-HF states the patient being treated with empagliflozin proved to reduce the incidence of morbidity and mortality and prevents Re-hospitalisation. In EMPEROR-reduced trial, the positive outcomes were not associated to the diabetes and its treatment. A recent, Placebo-Controlled trail revealed that empagliflozin gives a positive therapeutic outcome in the interest of Rehospitalisation in patient associated with HF and cardiac morbidity. Empagliflozin gives better renal outcomes and reduces the Glomerular Filtration Rate [39-41].

Mineralocorticoid Receptor Antagonist:

Myocardial fibrosis, ventricular hypertrophy, endothelial dysfunction are the major complications that occurs due to Sodium and water retention is the major pathophysiology that gets initiated due to a neurohormone called Aldosterone that get release after activation of RASS mechanism [42]. According to EPHESUS (Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), and RALES (Randomized Aldactone Evaluation Study) in patients with moderate to severe chronic HF in the absence of hyperkalaemia Or significant renal dysfunction, these guidelines recommended that the Optical therapy will be the low dose MRA. Hence, in addition to ACE inhibitors the class Mineralocorticoid receptor antagonist (MRA) has placed an important role in the Heart failure treatment in patients with condition of NYHA class III and I [43-46].

In 2011, EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) the Eplerenone reduced the risk of death by 37% compared to the Placebo group. In this study, the 2737 patients were randomized who had decreased Left Ventricular Ejection Fraction and NYHA II condition. Hyperkalaemia was the frequent AE that are reported by the patients in the study.

In 2015, a study titled TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) tested the effectiveness and outcome of spironolactone in patients with Heart failure with preserved ejection fraction. This showed a positive correlation in the final outcome of the study [47-52]. In this study, the 3445 patients were randomized who had Heart failure with preserved ejection fraction. One group receive Spironolactone treatment and other received Placebo. By the end of study, it was evident that Spironolactone reduces the Re-Hospitalization but there is no effect on cardiovascular associated deaths or aborted cardiac arrest [53-54]. The incidence of benefitary rate is seems to be higher in Americans followed by Russia [55]. Same like other studies in Spironolactone, Hyperkalaemia was the frequent AE reported in this study. Hence, the efficacy of Spironolactone in Heart failure with preserved ejection fraction can be assessed in future only with more efficient protocol.

Ivabradine: A heart beat regulator

According to Human physiology, a prolonged sequential stimulus results in flight and fight response i.e sympathetic nervous system activation leads to increase in heart rate, a negative symptom for the cardiac system. So in order achieve a rhythmic and normal heart rate in cardiac patients researchers have discovered a potent drug with fascinating results known as ivabradine to regulate to heart beat in patients experiencing palpitation and tachycardia. In the past days of healthcare system, beta blockers have been used to regulate the heart beat in cardiac patients but these drugs precipitate many adverse reaction. Unfortunately, the incidence and prevalence of beta blocker adverse reaction seems to be high [56-59]. This novel potent therapeutic agent works as artificial pacemaker in the SA (Sino-atrial) node which selectively inhibits the direct pathway without influencing intra cardiac conduction, ventricular repolarization and myocardial contractility or relaxation. It is proven to precipitate beneficial outcomes in the management of HF patients [60-65]. The mechanism of action of this drug is totally a dissimilar mechanism comparing to beta blocker and calcium channel blocker as these drugs are known to cause multiple adverse events such as vasoconstriction in the bronchi, constipation, hypotension and negative inotropism.

Conclusion

The risk for heart failure is higher across the world, the health metrics worsening the functioning the heart to be noted and to be controlled. Many novel therapies encouraged in order to

Reduce the morbidity and mortality of this alarming disease condition. Recent clinical instances proved that the combinational drugs have brought a greater impact in heart failure patients. Combinational drugs should be discovered in future in order to attain better heart failure outcome. Novel drug therapies should emerge to act against different aetiologies. The pathophysiology of the heart failure drugs to be discovered in order to deal with it. Many promising drug molecules are under preclinical studies and investigation. If those molecules comes to the market will greatly benefit to patients with severe cardiogenic shock. Though the positive results of the novel therapies, the management of heart failure with preserved ejection fraction is still great challenge to the drug developers as it is still in the Insilco analysis. These novel therapies are the only hope for the patients in order to increase their life span as it is more promising than the conventional therapies.

Conflicts of interest statement

The authors declare that they have no conflicts of interest.

Authorship statement

All listed authors comply with the Journal's authorship policy.

Ethics statement

Ethical approval was not required for this review.

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