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Updates on The Drug Treatment and Devices In Cardiac Failure Patients

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ABSTRACT

Cardiac failure simply means a condition in which the heart does not pump sufficient blood to fulfill requirements of body. Various drugs and devices are used for treatment of heart failure like: diuretics, beta blockers, ACE inhibitors, Cardioverter Defibrillators (ICDs) respectively. However there are new drugs and devices which have been approved and are now in use for treatment of heart failure including; angiotensin- receptor nephrilysin inhibitor (ARNIs) such as Sacubitril /valsartan; I_f channel blocker such as ivabradine; V-2 receptor antagonist such as tolvaptan; selective cardiac myosin activator such as omecamtiv macabre; cardiac contractility modulation device and baroreflex activation therapy devices respectively. Among these Sacubitril and ivabrdine have shown greater effect in reducing risk of cardiovascular death and hospitalization. Tolvaptan being an oral vasopressin V2-receptor antagonist resulted in relief in patients with heart failure through the clearance of free water. COSMIC-HF trial and ATOMIC-AHF trial proved that omecamtiv mecarbil acts by increasing contractility in heart failure patients as a result improving hearts pumping ability. New devices such as cardiac contractility modulation (CCM) device and baroreflex activation therapy (BAT) device had shown improvement in heart failure patients not responding to other treatement.

INTRODUCTION

Heart failure also commonly known as Cardiac failure/Congestive Heart Failure (CHF) in which heart does not pump enough blood. Common problems associated with heart failure are: breathing problems, swelling of the legs, excessive tiredness[1,2]. Common reasons of heart failure could be myocardial infraction (heart attack), high blood pressure (hypertension), excessive alcohol use, abnormal heart rhythm, atrial fibrillation, infection or heart damage. All these cause heart failure either by changing the structure of the heart or altering its normal functionality. Heart failure can affect either the right side or left side of the heart or both at the

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

same time thus leading to either acute (short term) or chronic (long term) condition[3-5].

There are almost four types of heart failure disease; left-sided heart failure, right-sided heart failure, diastolic heart failure and systolic heart failure and all these different types of heart failure have different approaches for treatment or medications[6,7]. There are new drugs and devices which have been approved: angiotensin-receptor nephrilysin inhibitor (ARNIs) such as Sacubitril/valsartan[8-10]; If channel blocker such as ivabradine[8,11,12]; V2 receptor antagonist such as tolvaptan[13-15]; selective cardiac myosin activator such as omecamtiv macarbil[16]; cardiac contractility modulation device[17] and baroreflex activation therapy devices[18] respectively.

NEW DRUGS FOR TREATMENT OF HEART FAILURE

1. SACUBITRIL-VALSARTAN

Sacubitril-Valsartan discovered and developed by Novartis, is an angiotensin receptor nephrilysin inhibitor indicated for treatment of patients with chronic heart failure. It has been associated with reduce risk of cardiovascular death and hospitalization.

Rationale for nephrilysin inhibition is based on the cardio renal effect of natriuretic peptides (NPs) and other nephrilysin substrates that oppose the effect of the activated renin-angiotensin-aldosterone system and the sympathetic nervous system[8].

MECHANISM OF ACTION

Sacubitril/valsartan contains two active components known as sacubitril and valsartan. This is the first angiotensin receptor nephrilysin inhibitor (ARNI) which reduces stress on the failing heart.

Sacubitril is a prodrug. Its active metabolite LBQ657 inhibits nephrilysin (neutral endopeptidase). This inhibition leads to decrease in metabolism of endogenous vasoactive peptides such as natriuretic peptides and therefore decreases vascular resistance, heart muscle fibrosis, cardiac hypertrophy and decreased sodium retention[8].

Valsartan through blocking the ATI receptor inhibits the actions of angiotensin II and also decreases the release of aldosterone[8].

The combination was also been found to be safe and more effective than enalapril. In

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

PARADIGM-HF trial, it was found that combination was superior to enalapril in decreasing the risk of the cardiovascular death or hospitalization for cardiac failure[8].

CONTRAINDICATIONS

The combination is contraindicated:

- To patients having either hypersensitivity to sacubitril or valsartan
- ACE inhibitor or ARB therapy related angioedema
- To patients with concomitant use of an ACE inhibitor.
- In diabetic patients along with the drug aliskiren[9]

WARNINGS AND PRECAUTIONS

- ✓ **Fetal Toxicity** - Sacubitril/valsartan may cause harm to fetus if administered to pregnant women especially during second and third trimester due to reduced fetal renal function.
- ✓ **Hypotension** – Patients under treatment with high dose of diuretics are at a higher risk.
- ✓ **Impaired Renal Function** – Decrease in renal function due to inhibition of renin-angiotensin-aldosterone system observed in patients prescribed sacubitril/valsartan[10].

ADVERSE DRUG REACTIONS

- Angioedema
- Decrease in blood pressure
- Hyperkalemia
- Impaired renal function[10]

2. IVABRADINE

Ivabradine is indicated to patients having sinus rhythm with symptomatic, stable chronic cardiac failure and a left ventricular ejection fraction (LVEF) of 35% or less.

MECHANISM OF ACTION

Ivabradine selectively decreases the heart rate by inhibiting the cardiac pacemaker current (If)[13, 14]. As per the placebo-controlled trial published in 2010 (SHIFT trial), ivabradine was found to reduce the cardiovascular death and hospitalization in cardiac failure by as much as 18 %[8,11].

PHARMACODYNAMICS PROFILE

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

Ivabradine decreases the heart rate in dose dependent manner. At both rest and exercising, the reduction of heart rate is approximately 10 bpm at recommended doses. The heart rate decreases with increase in dose of ivabradine up to 15-20 mg twice daily. At very high dose, there is no further therapeutic benefit[8]. Magnitude of the heart rate reduction depends on baseline heart rate; i.e., at baseline higher the heart rate, there will be greater reduction in heart rate and vice versa[12, 15].

CONTRAINDICATIONS

Ivabradine is contraindicated to:

- Patients with acute decomposed heart failure[12, 15]
- Patients with low blood pressure[12, 15]
- Patients with resting heart rate less than 60 bpm or pacemaker dependent[12, 15]
- Patients with severe hepatic impairment[12, 15]
- Patients taking cytochrome P4503A4 (CYP3A4) inhibitors[12, 15]

ADVERSE DRUG REACTIONS

The most common adverse events associated with ivabradine include bradycardia, atrial fibrillation, hypotension, syncope, angioedema, visual impairment and pruritus[8,12, 15].

WARNING AND PRECAUTIONS

Fetal Toxicity – Ivabradine administered to pregnant women may result in fetal toxicity. Pregnant women should be closely monitored for destabilization of HF especially during the first trimester. There is also risk for preterm birth in pregnant women with chronic HF[8,12, 15].

Atrial Fibrillation –There is increase risk of atrial fibrillation with Ivabradine. As per the SHIFT study, atrial fibrillation was among 5% patients treated with ivabradine as compared to 3% in placebo group[12, 15, 16].

Bradycardia and Conduction Disturbances –There is also increased risk of bradycardia, sinus

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

arrest and heart block with Ivabradine[12, 15].

3. TOLVAPTAN

Tolvaptan an oral V2 receptor antagonist is the first FDA approved treatment of euvolemic and hypervolemic hyponatremia in patients with heart failure, cirrhosis and the syndrome of inappropriate antidiuretic hormone secretion[17, 19]. In acute heart failure patients, congestion is the major reason for hospitalization. As Tolvaptan results in the clearance of free water from body, it helps in relieving congestion in heart failure patients[19].

MECHANISM OF ACTION

Cardiac failure, SIADH and liver cirrhosis may accompany symptomatic hyponatremia. ADH causes stimulation of vasopressin-2(V2) receptors present in collecting ducts of kidney. As a result, there is increase in synthesis and transport of aquaporin channels, decrease in plasma osmolality, urine volume is reduced but urinary Na+ excretion continues[18, 19]. This ameliorates some of the congestion symptoms in patients with AHF.

ADVERSE DRUG EFFECTS

Polyuria, dry mouth and feeling thirsty have been observed in almost 5% of patients treated with Tolvaptan. In heart failure patients, dehydration is reported in some cases[17, 18]. Tolvaptan may also lead to serious adverse effects like; cardiogenic shock and pulmonary embolism[17]. It has been contraindicated in pregnant women and breastfeeding mothers as tolvaptan's teratogenic effect was reported in animal model[17].

4. OMECAMTIV MERCABIL

Omecamtiv Mercabil is a cardiac myosin activator that results in cardiac contraction that's not connected with cytosolic calcium accumulation[8].

Background

In physiological perspectives, binding of myosin-ATP to actin filament is quite weak until hydrolysis from ATP to ADP and IP (inorganic phosphate) takes place. The remaining myosin-ADP complex causes cardiac contraction[20, 21]. Therefore hydrolysis of ATP to ADP and IP on myosin is the rate-limiting step[20, 22, 23].

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

PHARMACOLOGY AND MECHANISM OF ACTION

Omecamtiv mecarbil mainly binds with cardiac myosin without having any significant action on the other types of myosin such as smooth and skeletal muscles[20, 21].

The site where omecamtiv mecarbil binds is the amino acid serine 148[24]. Binding of the drug to this modulates cardiac myosin activity. These conformational changes increase the rate of ATP hydrolysis. Therefore, there is increase in force of cardiac contraction[21, 25]. This is the mechanism of omecamtiv mecarbil's action[26]. Omecamtiv mecarbil prolongs total systole duration and as a result, a stronger cardiac contraction[20, 21, 25].

CLINICAL TRIALS WITH OMECAMTIV MECARBIL

COSMIC-HF trial – It was a randomized, parallel study conducted with a primary pharmacokinetic objective of dose titrating omecamtiv mecarbil so that the patients could receive appropriate dose[20].

ATOMIC-AHF trial – It was a double blind, randomized, placebo controlled study designed to research the safety, pharmacokinetics, pharmacodynamics and efficacy of omecamtiv mecarbil in ADHF patients[20].

GALACTIC-HF – It is a phase III, double-blind, randomized, placebo-controlled multicenter clinical trial designed to compare omecamtiv mecarbil with placebo when added to the standard treatment. This trial may complete in January 2021[20].

NEW DEVICES FOR HEAT FAILURE TREATMENT

Heart failure is one of the major cause for death around the world. Mortality rates are high despite the device therapy for treatment of heart failure. The main devices for treatment of HF include: cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD). There are new devices that can be used for treatment of heart failure discussed as follows that can decrease mortality[27].

1. CARDIAC CONTRACTILITY MODULATION DEVICE

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

This device is like a pacemaker that delivers modulates the contraction of heart. This device throughout the myocardial refractory period applies non-excitatory electrical signals (NES), adjusted to and synchronized with the electrical action in the heart[27, 28].

The duration of CCM therapy is 7 to 12 hours. The signal's voltage can be varied between a minimum of 4V and a maximum of 7.5V. The higher values are preferred but the strength of voltage depends on patient's tolerance[29].

MECHANISM OF ACTION

There are multiple mechanisms of actions by which this new device work on to increase the contraction of heart[30]. These include:

I. There is up-regulation of the L-type calcium channels and an increase in the calcium level inside cardiac cells[31-33]
II. There are long term changes in the expression of genes and phosphorylation pathways that will improve the regulation of calcium[31-33]

2. BAROREFLEX ACTIVATION THERAPY

The progression of heart failure involves the activation of sympathetic nerves and inhibition of parasympathetic nerves and this also leads to reduced ejection fraction[34-36]. This imbalance in the activity of autonomic nervous system results into cardiac remodeling, peripheral vasoconstriction, salt and water retention. Therefore the treatment that inhibits the activity of sympathetic nervous system and increases the activity of parasympathetic nervous system or preferably achieves both the aims reduces the symptoms and hospitalization in patients with HFrEF[37,38].

Baroreflex Activation Therapy (BAT) is a new device that works on principle of neuromodulation. This device is also similar to cardiac pacemaker and it does the neuromodulation through electrical stimulation technology[39-42]. BAT stimulates the carotid baroreceptor that results into decrease of sympathetic activity and increased parasympathetic outflow, leads to relieve of symptoms of cardiac failure[34].

BAROSTIM NEO

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

It is a baroreflex activation device which is an alternative to improve the signs and symptoms in patients with Heart Failure with reduced ejection fraction who cannot undergo Cardiac Resynchronization Therapy (CRT)[43]. It consists of subcutaneously implanted generator which is connected to an electrode placed on the carotid sinus. Its function is to stimulate the baroreceptors, thus creating a signal which will surpass the sympathetic activity and boost parasympathetic activity[44, 45].

CONCLUSION

Sacubitril-valsartan an angiotensin receptor nephrilysin inhibitor and Ivabradine an I_f channel blocker have shown to be the most effective new drugs for treatment of heart failure by reducing mortality and hospitalization of heart failure patients respectively. Other promising drugs that could also be of new hope are Omecamtiv mecarbil a myosin activator which is still on phase III and Tolvaptan a selective V_2 receptor antagonist which causes water retention in order to maintain blood pressure. But also new devices like optimizer smart system and barostim neo which work by cardio contractility modulation therapy and baroreflex activation therapy respectively are the new most effective heart failure devices.

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ISSN: 0971-1260
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