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A REVIEW ON NOVEL MEDICATION ADVANCEMENT IN THE MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE), DIABETICS, DILATED CARDIOMYOPATHY

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Abstract:

Drug development is the process of bringing a new drug to market after a lead chemical has been identified through drug discovery. Before a medicine is available for clinical use, the drug development process can take up to 20 years and cost as much as $3 billion USD.As we see that recent drug developments in Systemic Lupus Erythematosus (SLE). IVRADINE is a unique agent that is distinct from beta-blockers as it reduces heart rate without affecting myocardial contractility or vascular tone. The main efficacy endpoint was major adverse cardiac events (MACE) at 30 days and 6 months, defined as a composite of cardiac death, myocardial infarction, and HF hospitalizations.

Keywords: *ANIFROLUMAB, TIRZETATIDE, IVABRADINE, VYMADA.*

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INTRODUCTION:

SLE or lupus; an autoimmune disease in which the immune system attacks healthy parts of the body such as joints, skin, blood vessels, and organs) in adults.

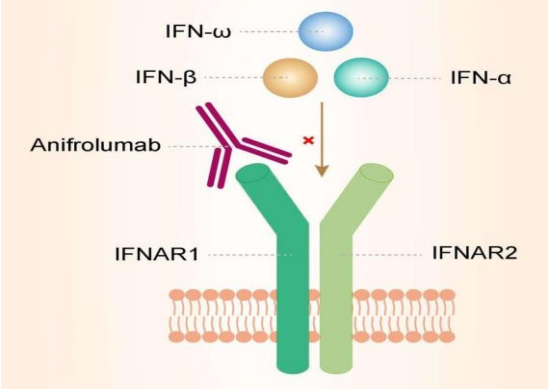
ANIFROLUMAB

INTRODUCTION OF ANIFROLUMAB:

Anifrolumab is a human monoclonal antibody to the type 1 interferon receptor which is used in the therapy of moderate-to-severe systemic lupus erythematous. Anifrolumab has been linked to a low incidence of transient serum enzyme elevations during therapy and ha not been linked to instances of clinically apparent liver injury.

MECHANISM OF ACTION:

Anifrolumab is a fully human monoclonal antibody that binds to subunit 1 of the type I interferon receptor, blocking the activity of all type I interferons including IFN-alpha, IFN- beta and IFN-omega. Type I interferons are cytokines involved in the inflammatory pathways.



PHARMACOLOGICAL ACTIONS:

- Anifrolumab is an immunoglobulin gamma 1 kappa (IgG1κ) monoclonal antibody that selectively binds to sub unit 1 of INFAR1.
- The binding of Anifrolumab to IFNAR1 inhibits the activity of the receptor, decreasing downstream signaling and gene transcription of inflammatory mediators.

PHARMACOKINETICS:

- Anifrolumab exhibited nonlinear PK due to target-mediated drug distribution.
- Body weight and baseline IFNGS status were significant covariates for Anifrolumab PK but had no clinically relevant impact on efficacy or safety requiring dose adjustments.
- Anifrolumab doses ≥ 300 mg provided sustained serum concentrations in a Q4W dosing regimen.

Uses:

Anifrolumab is used with other medications to treat moderate to severe systemic lupus erythematosus (SLE or lupus; an autoimmune disease in which the immune system attacks healthy parts of the body such as joints, skin, blood vessels, and organs) in adults.

ADVERSE DRUG REACTION

An adverse drug reaction (ADR) can be defined as 'an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product.

- Nasopharyngitis,
- Upper Respiratory Tract Infection,
- Urinary Tract Infection,
- Bronchitis And Infusion-Related Reaction

RECENT DRUG DEVELOPMENTS IN TYPE 2 DIABETES MELLITUS

INTRODUCTION OF TIRZEPATIDE:

Tirzepatide is an injectable dual glucagon-like peptide 1 (GLP-1) receptor and glucose- dependent insulinotropic polypeptide (GIP) receptor agonist (6). GIP is considered the dominant insulinotropic hormone when compared with GLP-1 and has demonstrated a stronger role in postprandial insulin secretion

MECHANISM OF ACTION:

- Glucagon-like peptide-1 (GLP-1) receptors (GLP-1R) are expressed throughout the body, including pancreatic beta-cells and the gastrointestinal tract.
- They have been implicated in the pathophysiology of type II diabetes mellitus as GLP-1R signaling is involved in glucose control by enhancing glucose-stimulated insulin secretion, delaying gastric transit, decreasing plasma glucagon levels, and reducing body weight by activating anorexigenic pathways in the brain.
- Both glucose-dependent insulin tropic polypeptide (GIP) and GLP-1 are peptide hormones involved in glucose homeostasis: they promote glucose-stimulated insulin secretion from the pancreatic beta-cells.
- However, GIP is the main incretin hormone that exerts insulin tropic effects in response to food intake.
- The exact mechanism of action of

Tirzepatide has not been fully elucidated; however, dual agonist at GIP and GLP-1R may contribute to the glycemic and weight control effects of the drug.

- Studies demonstrated that co-administration of GIP and a GLP-1R agonist more significantly increased insulin response and suppressed glucagon secretion compared to separate administration of either hormone alone.
- Tirzepatide binds to GIP and GLP-1R with high affinity.
- In vitro, Tirzepatide has a comparable GIP receptor binding affinity to native GIP and five times lower GLP-1R affinity than that of native GLP-1
- Tirzepatide potently activates the GLP-1R signaling pathway to stimulate glucose-dependent insulin secretion through activity at the GIP receptor (GIPR) or the GLP- 1R.
- However, the role of GIPR agonist in the drug's mechanism of action requires further investigation, as the evidence of GIPR agonist on glycemic and weight control in preclinical and clinical studies are conflicting.

PHARMACOLOGICAL ACTIONS:

In particular, Tirzepatide activation of GLP-1 receptors improves glucose-mediated insulin secretion and decreases secretion of glucagon. Tirzepatide activation of GIP receptors augments insulin sensitivity and secretion and thereby helps reinforce the mechanisms regulating blood glucose levels.

PHARMACOKINETICS:

- Pharmacokinetics appear dose proportional, Cmax reached within 24-48 h post-dose.
- Average accumulation following four weekly doses: 1.58.
- Tirzepatide delays gastric emptying; e greatest after 1 dose and undergoes tachyphylaxis with repeated once-weekly dosing.

PHARMACODYNAMICS:

- Tirzepatide is a synthetic peptide with glucose-lowering effects.
- Tirzepatide was also shown to delay gastric emptying, lower fasting and postprandial glucose concentration, decrease food intake, and reduce body weight in patients with type 2 diabetes.
- Tirzepatide can increase insulin sensitivity.
- As the peptide is conjugated to a C20 fatty diacid moiety through a hydrophilic linker at the lysine residue at position 20, the drug is highly bound to albumin in the plasma, which prolongs its half-life.

USES:

- Tirzepatide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- In Europe, it may be used as monotherapy or in combination with other drugs used to treat diabetes.
- This drug has not been studied in patients with a history of pancreatitis.

ADVERSE DRUG REACTION:

- Difficulty in breathing or swallowing.
- Heartbeat.
- Gaseous stomach pain.
- Heartburn.
- Recurrent fever.

RECENT DRUG DEVELOPMENTS IN DILATED CARDIOMYOPATHY

INTRODUCTION OF IVABRADINE:

Heart failure (HF) is a condition that results when the heart is unable to provide sufficient blood flow to meet the body's metabolic demands. The current American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines define HF as a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood.

HF is a major public health concern associated with a high prevalence and poor clinical outcomes. In the U.S., approximately 5 million people are affected, and more than 500,000 new cases are diagnosed each year. HF is the leading cause of hospitalization among adults older than 65 years of age.

More than 1 million patients are hospitalized each year with a primary diagnosis of HF, accounting for a total Medicare expenditure exceeding $17 billion.[4] Despite dramatic improvement in outcomes with medical treatment, admission rates after HF hospitalization remain high, with more than 50% of patients rehospitalized within six months of discharge.

Any condition that leads to an alteration in left ventricular (LV) structure or function can predispose a patient to the development of HF. Coronary artery disease (CAD) is the predominant cause of HF. Approximately 50% of HF patients

have a normal or preserved ejection fraction (EF) of 50% or greater. HF patients are broadly categorized into HF with a reduced EF (HFrEF; formerly systolic HF) or HF with a preserved EF (HFpEF; formerly diastolic HF). HFrEF is characterized by decreased myocardial contractility and inadequate emptying of the ventricle, whereas HFpEF is characterized by abnormal ventricular relaxation and impaired ventricular filling.

The cardinal clinical symptoms of HF include dyspnea, fatigue, and signs of volume overload, such as peripheral oedema and pulmonary rales.
The New York Heart Association (NYHA) functional classification scheme is the most commonly used system for assessing the severity of functional limitations in patients with HF.

Although it is difficult to predict prognosis in an individual, the development of symptomatic HF carries a poor prognosis. Patients who experience symptoms during moderate activity (NYHA class II) have an annual mortality rate of 5% to 10%, whereas patients with symptoms at rest (NYHA class IV) have an annual mortality rate of 30% to 70%.

MECHANISM OF ACTION:
Ivabradine is a heart-rate-lowering agent that acts by selectively and specifically inhibiting the cardiac pacemaker current (*I*f), a mixed sodium-potassium inward current that controls the spontaneous diastolic depolarization in the sinoatrial (SA) node and hence regulates the heart rate. The molecular channel belongs to the HCN family.

Inhibition of this channel disrupts I_f ion current flow, thereby prolonging diastolic depolarization, slowing firing in the SA node, and ultimately reducing the heart rate. The cardiac effects of ivabradine are specific to the SA node, and the drug has no effect on blood pressure, intracardiac conduction, myocardial contractility, or ventricular repolarization.
Ivabradine also inhibits the retinal current (I_h), which has properties similar to that of cardiac I_f. I_h participates in the temporal resolution of the visual system by curtailing retinal responses to bright light stimuli. Under triggering circumstances, such as rapid changes in luminosity, partial inhibition of I_h may underlie the luminous phenomena (phosphenes) experienced by patients.

PHARMACOLOGICAL ACTIONS:
Ivabradine is a heart-rate-lowering agent that acts by selectively and specifically inhibiting the cardiac pacemaker current (If), a mixed sodium-potassium inward current that controls the spontaneous diastolic depolarization in the sinoatrial (SA) node and hence regulates the heart rate.

PHARMACOKINETICS:
Ivabradine exhibits linear pharmacokinetics over an oral dosing range of 0.5 mg to 24 mg. After oral administration, the drug is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations (C_{max}) are reached in approximately one hour under fasting conditions. The absolute oral bioavailability of ivabradine is approximately 40% because of the first-pass effect in the liver and intestines. Food delays the absorption of ivabradine by approximately one hour and increases plasma exposure by 20% to 40%.

- Ivabradine is approximately 70% plasma protein-bound, and the volume of distribution at steady state is approximately 100 L
- Ivabradine is metabolized predominantly in the liver and intestines by the cytochrome P450 (CYP) 3A4 enzyme.
- Therefore, potent inhibitors or inducers of CYP3A4 may have a significant effect on plasma concentrations of ivabradine.
- The major active metabolite is *N*-desmethyl ivabradine (S-18982), which circulates at concentrations of approximately 40% and is also metabolized by CYP3A4.
- Ivabradine has a distribution half-life of two hours and an effective half-life of approximately six hours.
- The total clearance of ivabradine is 24 L/h, and the renal clearance is approximately 4.2 L/h. approximately 4% of an oral dose is excreted unchanged in urine
- The excretion of metabolites occurs to similar extents via faeces and urine.

PHARMACODYNAMICS:
- Ivabradine causes a dose-dependent reduction in heart rate.
- The magnitude of this reduction depends on the baseline heart rate; i.e., a greater reduction in heart rate occurs in subjects with a higher heart rate at baseline.
- At recommended doses, the reduction in heart rate is approximately 10 bpm whether the patient is at rest or exercising.

- he heart rate decreases almost linearly with increasing doses of ivabradine up to 15 mg to 20 mg twice daily.
- At higher doses, this effect has a tendency to plateau.
- Ivabradine does not exert negative inotropic effects.
- It increases the uncorrected QT interval with heart-rate slowing but does not prolong the corrected QT (QTc) interval.

USES:

- Ivabradine is used to treat adults who have chronic heart failure to reduce their risk of hospitalization for worsening heart failure.
- It is also used to treat heart failure in children 6 months of age and older who have stable heart failure, with symptoms, caused by an enlarged heart (dilated cardiomyopathy).

ADVERSE DRUG REACTION:

- Blurred Vision.
- Fast or Irregular Heartbeat.
- Headache.
- Light-headedness, Dizziness, Or Fainting.
- Pounding In the Ears.
- Slow or Irregular Heartbeat.
- Unusual Tiredness.

INTRODUCTION OF VYMADA:

- Vymada 50mg Tablet contains two active substances, Sacubitril and Valsartan. It is a cardiovascular agent that belongs to angiotensin receptor-neprilysin inhibitors (ARNi). It is used to treat a type of long-term heart failure in adults. This combination is used with other medications to lower the risk of death and hospitalization in adults with certain types of heart failure.
- Do not take Vymada 50mg Tablet if you are allergic to Sacubitril, valsartan, or any of the other ingredients of this medicine. Do not take this medicine if you are having or ever had a reaction called angioedema (swelling of the face, lips, tongue, and throat, and difficulties in breathing). Do not take this medicine if you have diabetes or impaired kidney function and if you are being treated with a blood pressure-lowering medicine containing Aliskiren. Do not consume this tablet if you have severe liver disease or are pregnant and breastfeeding.
- Inform your doctor if you are taking any other heart medicines before starting this medicine. Tell your doctor if you have low blood pressure, severe kidney disease, dehydration, liver disease, hallucinations, or changes in your sleeping pattern. The most common side effects of Vymada 50mg Tablet are hypotension, increased potassium levels, cough, dizziness, and renal failure.

MECHANISM OF ACTION:

- The pathophysiology of heart failure involves a maladaptive response during which the renin-angiotensin-aldosterone system (RAAS) is activated. RAAS activation leads to vasoconstriction, hypertension, increased aldosterone levels, increased sympathetic tone, and eventually, cardiac remodeling, all of which are detrimental to the progression of the disease. ACEIs or ARBs play a major role in reducing morbidity and mortality due to heart failure by blocking these maladaptive elements.
- Simultaneously, the natriuretic peptide system is also activated, hence the elevated BNP and NT-pro BNP seen in heart failure exacerbations. This compensatory mechanism leads to vasodilation, natriuresis, and diuresis. Consequently, the natriuretic peptide system decreases blood pressure (BP), lowers the sympathetic tone, and reduces aldosterone levels. The natriuretic peptide system functions antagonistically to the RAAS and has favorable effects on the pathogenesis of heart failure. Natriuretic peptides are broken down by an enzyme called neprilysin
- Sacubitril/valsartan is a combination product. Sacubitril is a pro-drug that, upon activation, acts as a neprilysin inhibitor. It works by blocking the action of neprilysin, thus preventing the breakdown of natriuretic peptides, which leads to a prolonged duration of the favorable effects of these peptides.
- Valsartan is an angiotensin receptor blocker, and it works on blocking the RAAS system. However, because neprilysin breaks down angiotensin II, inhibiting neprilysin will accumulate angiotensin II. For this reason, a neprilysin inhibitor cannot be used alone; it must always be combined with an ARB to block the effect of the excess angiotensin II.
- Another important substance broken down by neprilysin is bradykinin; neprilysin inhibition will also cause a build-up of bradykinin. Therefore, sacubitril cannot be used with an ACEI due to an increased risk of angioedema if ACEI and ARNI are used together or dosed in a short timeframe. When switching between ACEI and sacubitril/valsartan, the patient must undergo a 36-hour washout period to lower the

risk of angioedema.

PHARMACOLOGICAL ACTIONS:

Mechanism of action: Sacubitril-valsartan exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1).

PHARMACOKINETICS:

ABSORPTION:

- Following oral administration, sacubitril/valsartan is broken down into sacubitril and valsartan. Sacubitril is metabolized to LBQ657.
- The absolute oral bioavailability of sacubitril is estimated to be ≥ 60%.
- The peak plasma concentrations (Cmax) of sacubitril, LBQ657, and valsartan are obtained at 0.5 hours, 2 hours, and 1.5 hours, respectively.
- Sacubitril and valsartan do not accumulate significantly at a steady-state (achieved in 3 days), but LBQ657 is accumulated by 1.6-fold.
- Food has no clinically significant effect on the absorption parameters of sacubitril or valsartan.
- Consequently, it can be administered with or without food.

DISTRIBUTION:

- The mean apparent volumes of distribution of valsartan and sacubitril are 75 and 103 L, respectively.
- Sacubitril, LBQ657, and valsartan have high plasma protein binding (94% to 97%). LBQ657 crosses the blood-brain barrier to a small extent (0.28%).

METABOLISM:

- Sacubitril is converted to LBQ657 by esterase.
- Valsartan is minimally metabolized (20%), and a hydroxyl metabolite is present in plasma at low concentrations (< 10%).

ELIMINATION:

- After oral administration, 52% to 68% of sacubitril (as LBQ657) and approximately 13% of valsartan are excreted in the urine.
- 37% to 48% of sacubitril (as LBQ657) and 86% of valsartan are excreted in feces.
- Sacubitril, LBQ657, and valsartan have a mean elimination half-life (t1/2) of about 1.4 hours,
- 11.5 hours, and 9.9 hours.

PHARMADYNAMICS:

- The pharmacodynamic effects were evaluated after single and multiple dose administrations in healthy subjects and in patients with heart failure, and are consistent with simultaneous neprilysin inhibition and RAAS blockade.
- In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of sacubitril-valsartan resulted in an initial increase in natriuresis, increased urine cGMP, and decreased plasma levels of mid-regional pro- atrial natriuretic peptide (MR-proANP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) compared to valsartan.
- In a 21-day study in HFrEF patients, sacubitril-valsartan significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1 compared to baseline.
- The AT1-receptor was also blocked as evidenced by increased plasma renin activity and plasma renin concentrations.
- In the PARADIGM-HF study, sacubitril-valsartan decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril.
- In PARAGON-HF, sacubitril-valsartan decreased NT-proBNP, troponin and soluble ST2 (sST2) and increased urine cGMP compared to valsartan. BNP is not a suitable biomarker of heart failure in patients because BNP is a neprilysin substrate. NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.
- In a thorough QTc clinical study in healthy male subjects, single doses of sacubitril-valsartan 400 mg and 1200 mg had no effect on cardiac repolarization.
- Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β (Aβ) from the brain and cerebrospinal fluid (CSF).
- Administration of 400 mg once daily for two weeks to healthy subjects was associated with an increase in CSF Aβ1-38 compared to placebo; there were no changes in concentrations of CSF Aβ1-40 and 1-42.

SAFETY DATA

USES:

Vymada 50mg Tab is a combination medicine used

to treat high blood pressure (hypertension) in order to reduce the workload of the heart. This medicine helps prevent heart attacks and strokes and is usually used when only one medicine is not able to control the blood pressure effectively.

ADVERSE DRUG REACTION;

- Dizziness
- Increased potassium level in blood
- Fatigue
- Hypotension (low blood pressure)
- Angioedema (swelling of deeper layers of skin)
- Anemia (low number of red blood cells)
- Loss of consciousness/Syncope

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