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Pharmacological Study for Investigation of Hypertension Activity of Baxdrostat: A Review

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***Abstract*—** Baxdrostat is an aldosterone synthesis inhibitor was given as the sole hypertensive drugs for 10-12 weeks to patients with hypertension of verity degrees severity. Intial systolic blood pressure from 130-240mmHg. Two patients has accelerated hypertension, eight had cardiomegaly with recent exertional dyspnea and baxdrostat 2mg , 1mg, 0.5mg given to the patients controlled both the supine and standing blood pressure and markedly attenuated the initial hypertension response to severe exercise. No deaths occurred during the trial, no serious adverse events were attributed by investigators or baxdrostat and there were no instances of adrenocortical insufficiency. Baxdrostat related increase in the potassium level to 6.0mmol per liter or greater occurred in 2 patients , but these increases did not recure after withdrawal and reinitiation of the drug. A significant hypotensive action developed with in 1 week after sudden interruption of therapy. The drug appeared to exert its maximum hypotensive effect at 0.5mg dosage. The main objective of this study was to determine the impact of drug baxdrostat use and addition on individual families, peers society and understanding the complex interaction of factors influencing drug use trajectories. And outline the accepted indications for baxdrostat use with focusing of MOA and adverse profile of baxdrostat.

Keywords— Key Words: Baxdrostat, hypertension, blood pressure, plasma level, pharmacokinetics, MOA, anti hypertensive, heart attack, heart failure, phase-I, phase-II, symptoms, risk factors, chest pain, kidney failure, bioavailability etc.

I. INTRODUCTION

Hypertension the condition called high blood pressure in which the force of the blood against the artery walls is too high. According to MAYOCLINIC.COM it defined as blood pressure above 140/90 and severe in case above 180/120. WHO defined it as Blood pressure is the force exerted by circulating blood against the walls of the body's arteries, BP written as 2 numbers The first (systolic) number represents the pressure in blood vessels when the heart contracts or beats. The second (diastolic) number represents the pressure in the vessels when the heart rests between beats, it diagnosed when it is measured on two different days, the systolic blood pressure readings on both days is ⩾140 mmHg and/or the diastolic blood pressure readings on both days is ⩾ 90 mmHg. According to MEDICAL NEWS TODAY Hypertension is a primary risk factor for cardiovascular disease, including stroke, heart attack, heart failure, and aneurysm. Managing blood pressure is vital for preserving health and reducing the risk of these dangerous conditions. And CENTERS FOR DISEASE CONTROL AND PREVENTION said that guidelines to diagnose high blood pressure may differ from health care professional to health care professional, example Some health care professionals diagnose patients with high blood pressure if their blood pressure is consistently 140/90 mm Hg or higher, Other health care professionals diagnose patients with high blood pressure if their blood pressure is consistently 130/80 mm Hg or higher.

How to understand high blood pressure readings:

Two numbers create a blood pressure reading. Systolic pressure (top number) indicates the pressure in your arteries when your heart beats and pumps out blood. Diastolic pressure (bottom number) is the reading of the pressure in your arteries between beats of your heart.

Five categories define blood pressure readings for adults:

Healthy: A healthy blood pressure reading is less than 120/80 millimeters of mercury (mm Hg).Elevated: The systolic number is between 120 and 129 mm Hg, and the diastolic number is less than 80 mm Hg. Doctors usually don't treat elevated blood pressure with medication. Instead, your doctor may encourage lifestyle changes to help lower your numbers. Stage 1 hypertension: The systolic number is between 130 and 139 mm Hg, or the diastolic number is between 80 and 89 mm Hg. Stage 2 hypertension: The systolic number is 140 mm Hg or higher, or the diastolic number is 90 mm Hg or higher. Hypertensive crisis: The systolic number is over 180 mm Hg, or the diastolic number is over 120 mm Hg. Blood pressure in this range requires urgent medical attention. If any symptoms like chest pain, headache, shortness of breath, or visual changes occur when blood pressure is this high, medical care in the emergency room is needed.

A blood pressure reading is taken with a pressure cuff. For an accurate reading, it's important you have a cuff that fits. An ill-fitting cuff may deliver inaccurate readings.

What are the risk factors for hypertension?

Modifiable risk factors include unhealthy diets (excessive salt consumption, a diet high in saturated fat and trans fats, low intake of fruits and vegetables), physical inactivity, consumption of tobacco and alcohol, and being overweight or obese. Non-modifiable risk factors include a family history of hypertension, age over 65 years and co-existing diseases such as diabetes or kidney disease.

What are common symptoms of hypertension?

Hypertension is called a "silent killer". Most people with hypertension are unaware of the problem because it may have no warning signs or symptoms. For this reason, it is essential that blood pressure is measured regularly. When symptoms do occur, they can include early morning headaches, nosebleeds, irregular heart rhythms, vision changes, and buzzing in the ears. Severe hypertension can cause fatigue, nausea, vomiting, confusion, anxiety, chest pain, and muscle tremors. The only way to detect hypertension is to have a health professional measure blood pressure. Having blood pressure measured is quick and painless. Although individuals can measure their own blood pressure using automated devices, an evaluation by a health professional is important for assessment of risk and associated conditions.

What are the complications of uncontrolled hypertension?

Among other complications, hypertension can cause serious damage to the heart. Excessive pressure can harden arteries, decreasing the flow of blood and oxygen to the heart. This elevated pressure and reduced blood flow can cause:

- Chest pain, also called angina.
- Heart attack, which occurs when the blood supply to the heart is blocked and heart muscle cells die from lack of oxygen. The longer the blood flow is blocked, the greater the damage to the heart.
- Heart failure, which occurs when the heart cannot pump enough blood and oxygen to other vital body organs.
- Irregular heart beat which can lead to a sudden death.

Hypertension can also burst or block arteries that supply blood and oxygen to the brain, causing a stroke. In addition, hypertension can cause kidney damage, leading to kidney failure.

How can the burden of hypertension be reduced?

Reducing hypertension prevents heart attack, stroke, and kidney damage, as well as other health problems.

Prevention

- Reducing salt intake (to less than 5g daily).
- Eating more fruit and vegetables.
- Being physically active on a regular basis.
- Avoiding use of tobacco.
- Reducing alcohol consumption.
- Limiting the intake of foods high in saturated fats.
- Eliminating/reducing trans fats in diet.

Management:

- Reducing and managing stress.
- Regularly checking blood pressure.
- Treating high blood pressure.
- Managing other medical conditions.

A new drug called Baxdrostat has been shown to significantly reduce high blood pressure (hypertension) in patients who may not respond to current treatments for the condition, according to results from a phase II trial led jointly by a Queen Mary University of London researcher and colleagues at CinCor Pharma, USA.(Nov 7, 2022;SOURCE :Queen Mary University of London)

Mechanism of action:

Baxdrostat selectively targets aldosterone synthase, which is encoded by the CYP11B2 gene. Importantly, it has low affinity for 11ß-hydroxylase, the enzyme responsible for cortisol synthesis, which is encoded by the CYP11B1 gene. In multiple preclinical in vivo studies, baxdrostat significantly lowered aldosterone levels without affecting cortisol levels, across a wide range of doses. Similar observations were made in multiple Phase 1 clinical trials in healthy volunteers.

Multiple Phase 1 clinical trials of baxdrostat have been conducted in healthy volunteers to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of baxdrostat. Baxdrostat was well tolerated in healthy volunteers across all Phase 1 clinical trials conducted to date, with no serious adverse events, or SAEs, or treatment-emergent adverse events, or TEAEs, leading to treatment withdrawal associated with baxdrostat. In addition, a Phase 1 clinical trial was conducted in subjects with varying degrees of renal function. In this trial, one SAE not related to baxdrostat was observed.

Based on the preclinical and clinical data available to date, we are developing baxdrostat in multiple diseases where aldosterone plays a significant role in disease pathophysiology, including hypertension and *primary aldosteronism. We are also exploring its utility in ameliorating complications of chronic kidney disease.*

Our Phase 2 trial (BrigHtn) in patients with treatment resistant hypertension was completed in 2022. BrigHtn topline results, published in August 2022, demonstrated that treatment with baxdrostat at 1 mg and 2 mg led to a

statistically significant lowering of SBP in patients with rHTN. Patients treated with baxdrostat at 2 mg demonstrated a 20.3 mmHg reduction in SBP and a placebo-corrected reduction of 11.0 mmHg (p value=0.0001). The 1 mg dose demonstrated a 17.5 mmHg reduction in SBP resulting in a significant placebo-adjusted SBP decline of 8.1 mmHg (p value=0.003).

Bioavailability:

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Pharmacokinetics of Baxdrostat:

Baxdrostat is a selective inhibitor of aldosterone synthesis designed for the treatment of disorders associated with elevated aldosterone. Baxdrostat had a favorable pharmacokinetic profile in humans. Plasma exposures increased in a dose proportional manner over the expected therapeutic dose range with a mean half life of 29 hours a result that supports once daily dosing. Side effects were mild and included headache, nasopharyngitis and diarrhea.

Anti hypertensive effects:

The selective aldosterone synthase inhibitor baxdrostat significantly lowers blood pressure in patient with resistant hypertension. Resistance hypertension is defined by blood pressure (BP) targets not achieved despite the use of at least 3 anti hypertensive drugs of different classes, including a diuretic diagnosed in more than 10% of hypertensive patients, it represents a high risk phenotype, leading to an increased risk of cardiovascular disease and all cause mortality. A BP that cannot be controlled with the use of at least 5 hypertensive agents of different classes including a long acting thiazide like diuretic such as chlorthalidone and spironolactone is defined refractory hypertension substantial evidence indicates that aldosterone excess is very common in patient with resistant hypertension and primary aldosteronism is present in 20% of patients with confirmed resistant hypertension ; intriguingly a positive relationship (more pronounced in men) between weight gain and aldosterone levels has also been demostated. Despite its side effects the mineralocorticoid receptor antagonists spironolactone remains the preffered 4th line add-on therapy in patient with resist hypertension. The adverse effects of spironolactone (which include reduced testosterone synthesis, hyperkalemia gynecomastia, breast tenderness, menstrual irregularities and postmenopausal bleeding) are essentially due to the off-target blockade of several steroid hormone receptors. To counteract these obstacles a different approach has been applied that is directly targeting the synthesis of aldosterone instead of blocking its receptor. However osilodrostat the first inhibitor of the enzyme aldosterone synthesis was associated with off-target inhibition of cortisol synthesis, an effect explained by the >90% sequence similarity between 11β-hydrolase(the final enzyme required for cortisol synthesis, encoded by the gene (γP11β1) and aldosterone synthase (encoded by the gene γp11β2)

Results:

Blood pressure:

Many of the patients on baxdrostat administration reduced their systolic blood pressure levels enough to be classified with either stage I hypertension a range from 130mmhg and diastolic blood pressure of 80mmhg or less.

Heart rate:

60-90 beats per minute.

Muscular exercise:

Ten minutes of brisk or moderate walking three times a day. thirty minutes a day of biking or stationary cycling or three 10 minute blocks of cycling., hiking., desk trade miling or pedal pushing, weight training.

Baxdrostat plasma level:

Plasma levels of baxdrostat increased proportionally with ascending doses, with peak concentrations observed within 4 hours after dosing a mean half-life of 26 to 31Hrs

Side effects:

Common spironolactone side effects include vomiting, diarrhea, increased hair growth and fatigue. Dangeresly low pressure. Abnormal low sodium levels. Unusually high potassium levels.

Review of baxdrostat trials:

This is broadly divided into trials, which compared baxdrostat to other antihypertensive and baxdrostat used in observational trials or vs placebo.

Baxdrostat vs placebo trials:

Aldosterone synthase controls the synthesis of aldosterone and has been a pharmacologic target for the treatment of hypertension for several decades. Selective inhibition of aldosterone synthesis is essential but difficult to achieve because cortisol synthesis is catalyzed by another enzyme that shares 93% sequence similarity with aldosterone synthase. I preclinical and phase I studies, baxdrostat had 100:1 selectivity for enzyme inhibition and baxdrostat at several dose levels reduced plasma aldosterone levels but not cortisol levels. In this multicenter, placebo controlled trial we randomly assigned patients who had treatment resistant hypertension with BP of 130/80mmhg or higher and who were receiving stable doses of at least three antihypertensive agents, including a diuretic, to receive baxdrostat (0.5mg, 1mg or 2 mg) once daily for point was the change in systolic blood pressure from baseline to week 12 in each baxdrostat group as compared with the placebo groups.

CONCLUSION

The main goal of this study was to examine some of factors that might influence the magnitude the study of the hypertensive actions of baxdrostat. In previous studies they have limited information regarding, because it was a newly designed drug. Baxdrostat demonstrated a compelling safety profile and was well tolerated ,and it demonstrated dose-proportional increases in plasma concentration with a half-life that supports once-daily dosing. The dose-dependent decrease in plasma aldosterone and lack of effect on cortisol demonstrate the selective blockade of aldosterone synthase. Baxdrostat produced a transient increase in sodium excretion and mild diuretic effect. We believe these results support our continued study in ongoing phase 2 clinical trials evaluating the efficacy and safety of baxdrostat for treatment resistant or uncontrolled hypertension and primary aldosteronism.

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