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BAXDROSTAT IN PATIENTS WITH RESISTANT HYPERTENSION

Keywords: baxdrostat, CIN-107, resistant hypertension, blood pressure

SUMMARY OF TECHNOLOGY

Baxdrostat (CIN-107) is a highly selective, oral small molecule inhibitor of aldosterone synthase, the enzyme responsible for the synthesis of aldosterone in the adrenal gland, in the development for treatment-resistant hypertension.[1] Baxdrostat selectively targets aldosterone synthase, which is encoded by the CYP11B2 gene while having a much lower affinity for the blocking activity of 11ß-hydroxylase, the enzyme responsible for cortisol synthesis, which is encoded by the CYP11B1 gene.[2] It was prescribed as oral administration with once-daily dosing.[2]

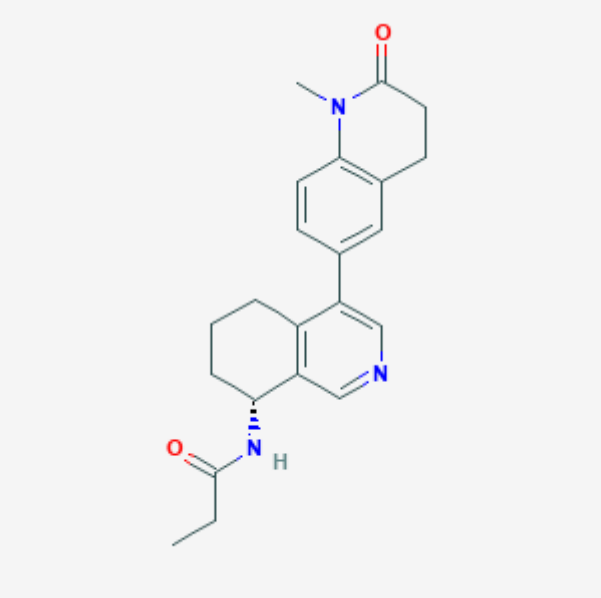

Figure 1: Chemical structure of baxdrostat[3]

Baxdrostat is a drug originally developed by Roche (RO68316191) and subsequently licensed to CinCor Pharma Inc company (CIN-107). In the first half of 2023, CinCor planned to launch another two phase 2 clinical trials designed to definitively confirm the efficacy and safety of baxdrostat in the treatment of resistant hypertension which is the

26-week FigHtn-CKD (NCT05432167) phase 2 clinical trial investigating baxdrostat in the patients with resistant hypertension and chronic kidney.[1] Another trial is the 12-weeks Spark-PA (NCT04605549) phase 2 clinical trial, which is testing baxdrostat for lowering blood pressure in patients with primary aldosteronism.[1]

INNOVATIVENESS

Novel, completely new	/
Incremental improvement of the existing technology	
New indication of an existing technology	

DISEASE BURDEN

Resistant hypertension is defined as uncontrolled hypertension (>140/90 mmHg) with good medication adherence while on three, or four anti-hypertensive agents (including a diuretic) in adequate doses.[4] Before diagnosing a patient with resistant hypertension, it is important that the practitioner is certain that the patient adheres to the medication (by definition at least 80%), blood pressure is properly measured, that they don't have 'office resistant hypertension', an appropriate combination and dosage of drugs is prescribed consisting three drugs including a renin-angiotensin-system (RAS) blocker, a calcium channel blocker and a diuretic and that the patient is not taking anything that could interfere with their hypertension medication (e.g. Non-steroidal anti-inflammatory drugs (NSAIDs), sympathomimetic, liquorice, oral contraceptives, corticosteroids).[4]

In Malaysia, a cross-sectional study conducted in Klang Valley primary care clinics involving a total of 594 elderly patients aged more than 60 years showed that the prevalence of resistant hypertension was 66.3% (n=394).[5] In another study conducted in the year of 2020, it was found that the overall prevalence of resistant hypertension was 8.8% (n=107/1217) in the primary care clinic with randomly selected sample of patients with hypertension.[6] In the multivariate logistic regression analysis, presence of chronic kidney disease was more likely to be associated with resistant hypertension (odds ratio 2.89, 95% CI; 1.56 to 5.35).[6]

According to the Global Burden of Disease 2019 study, the number of adults worldwide affected by high systolic blood pressure increased from 2.18 billion in 1990 (95%UI;2.11 to 2.26 billion) to 4.06 billion (95% UI;3.96 to 4.15) in 2019.[7] If the threshold of systolic blood pressure more than 140 mmHg was considered, 828 million adults had high systolic blood pressure worldwide.[7] The prevalence of resistant hypertension varies globally, but is estimated to be between 10-20% of patients with hypertension.[8] The prevalence of

resistant hypertension is expected to rise in the coming years due to the aging population, increasing rates of obesity and the prevalence of other cardiovascular risk factors.[8]

In a meta-analysis of data from 3.2 million patients in 2018, it showed a high prevalence of resistant hypertension and was highest in chronic kidney disease patients.[9] The prevalence of resistant hypertension was 10.3% (95% CI; 7.6% to 13.2%).[9] The prevalence of resistant hypertension was 22.9% (95% CI 19.1% to 27.0%), 56.0% (95% CI 52.7% to 59.3%) and 12.3% (95% CI 1.7% to 30.5%) in chronic kidney disease, renal transplant and elderly patients, respectively.[9]

Resistant hypertension is indeed a significant global disease burden that may cause increased morbidity, economic burden, higher mortality and co-morbidities highlighting the need for effective management and prevention strategies.

CURRENT OPTIONS FOR PATIENTS

According to the Malaysian Clinical Practice Guidelines on the Management of Hypertension, there are two treatment options for resistant primary hypertension which is non-pharmacological and pharmacological management.[4]

Healthy lifestyle choices are one non-pharmacological method of managing hypertension. In order to reduce blood pressure, it is recommended to reduce salt intake, do regular physical activity, limit alcohol intake to less than 2 drinks per day for those who drink, increase dietary potassium and lose weight.[4]

In pharmacological management, it was advised to add the fourth drug spironolactone to the combination of Renin-Angiotensin-System (RAS) blocker, calcium channel blocker (CCB) and diuretic. Besides that, device based therapy could be considered in patients with true resistant and refractory hypertension.[4] This includes renal denervation therapy (RDN) and carotid sinus stimulation.[4]

POTENTIAL IMPACT OF TECHNOLOGY

a. Clinical Impact

Based on the systematic search up to 8th February 2023, there were 3 articles retrieved from the scientific databases (Medline, PubMed), and general search engines [Google Scholar].

Baxdrostat has been tested in a multicenter, randomised, double-blind, placebo-controlled, dose-ranging phase II trial among 248 adult patients with treatment-resistant hypertension (BrigHTN).[10] All subject must adhere to a stable regimen of at least three

hypotensive drugs (including diuretic) and with blood pressure above 130/80 mm Hg.[10] Participants were given placebo or baxdrostat daily in three different doses (0.5 mg, 1.0 mg, or 2.0 mg) for 12 weeks and with the existing treatment regimen.[10] The primary and secondary endpoints were changes in systolic and diastolic blood pressure from baseline to the end of the 12-week treatment period.[10] At week 12, baxdrostat was associated with dose- dependent changes in the least-squares mean (±SE) systolic blood pressure of −20.3±2.1 mm Hg, −17.5±2.0 mm Hg, and −12.1±1.9 mm Hg at the 2-mg, 1-mg, and 0.5-mg doses, respectively.[10] In the placebo group, the decrease was 9.4 mm Hg compared in the 2-mg baxdrostat group (difference between the 2-mg group and the placebo group, −11.0 mm Hg; 95% confidence interval [CI], −16.4 to −5.5; p<0.001) and in the 1-mg baxdrostat group (difference between the 1-mg group and the placebo group, −8.1 mm Hg; 95% CI, −13.5 to −2.8; p = 0.003), but these decreases were not significantly greater with the 0.5-mg dose.[10] Baxdrostat reduced diastolic blood pressure by 14.3±1.31 mm Hg at the 2-mg dose.[10] The difference in the change in diastolic blood pressure between the baxdrostat 2-mg group and the placebo group was −5.2 mm Hg (95% CI, −8.7 to −1.6).[10] Thus, this trial showed significant reductions in systolic and diastolic blood pressure in patients with resistant hypertension.

Despite of the baxdrostat efficacy found in the BrigHTN trial, the HALO phase 2 trial that was conducted earlier seemed failed to reach the primary endpoint, set by a statistically significant difference with the placebo group in terms of reduction of systolic blood pressure.[11] HALO trial was a randomised, double-blind, placebo-controlled, multicentre clinical trial that enrolled 227 adult patients with resistant hypertension.[10] The systolic blood pressure decreased by 17.0 mm Hg, 16.1 mm Hg, and 20.0 mm Hg in baxdrostat group versus changes of −0.8 mm Hg, +0.1 mm Hg, and −3.8 mm Hg in the placebo subgroups (p=0.720, p=0.963, and p=0.100).[10] However, when data from Hispanic/Latino patients were excluded from the analysis, the result of systolic blood pressure showed significant result compared to the placebo.[10] Systolic blood pressure decreased by 16.2 mm Hg, 18.0 mm Hg, and 26.8 mm Hg — vs. decreases of 2.0 mm Hg, 3.8 mm Hg, and 12.6 mm Hg in the placebo subgroups (p=0.583, p=0.252, and p=0.001).[10] According to pharmacokinetic measures, Hispanic/Latino subjects were characterized by insufficient treatment adherence and the renin response in this patient population differed significantly from that in non-Hispanic/Latino.[10]

b. Cost.

There was no retrievable evidence on the exact cost and economic assessment of baxdrostat. The manufacturers have not announced the treatment's price yet.

Currently, baxdrostat is distributed for research purpose only at the price of USD 300 (MYR 1279.20; 1 USD=MYR 4.26) for 5mg.[12]

c. Societal/ethical

No societal or ethical issue identified

d. Safety

Baxdrostat phase 2 trial demonstrated that it caused sustained, dose-dependent decreases in serum aldosterone levels without causing a reduction in cortisol levels.[10] The most common adverse events were urinary tract infections, hyperkalaemia, headache, and fatigue, often mild and deemed to be unrelated to baxdrostat or placebo.[10] Moreover, none of the patients had to discontinue the trial because of hyperkalaemia.[10]

A phase 1 randomised, double blind trial was conducted to assess the pharmacokinetics, safety, and tolerability of a multiple ascending doses of baxdrostat in 54 healthy subjects following oral dosing once daily for 10 days with a normal or low salt diet.[2] There were five dosage of baxdrostat used in this study which was 2.5mg, 5.0 mg, 1.5mg, 2.5mg and 0.5mg.[2] Safety was assessed by adverse events, physical examinations, electrocardiograms, orthostatic vital signs, and clinical laboratory evaluations.[2] There were no deaths or serious adverse events, and all treatment-emergent adverse events in subjects receiving baxdrostat were mild in severity.[2] Plasma levels of baxdrostat increased proportionally with ascending doses, with peak concentrations observed within 4 h after dosing and a mean half-life of 26 to 31 hour.[2] A dose-dependent reduction of plasma aldosterone occurred with baxdrostat doses ≥1.5 mg, regardless of diet.[2] Decreases in plasma aldosterone were sustained, with levels reduced by approximately ~51 to 73% on day 10.[2] Baxdrostat had no significant impact on plasma cortisol levels and resulted in mild dose-dependent decreases in plasma sodium levels and increases in potassium levels.[2] In short, oral administration of baxdrostat was safe and well tolerated in all subjects and resulted in dose-proportional increases in plasma baxdrostat with a half-life that supports once-daily dosing.

CONCLUSIONS

In summary, early evidence of baxdrostat had shown a significant reduction in both systolic and diastolic blood pressure in patients with resistant hypertension with an acceptable safety profile. The decrease in blood pressure was associated with a decrease in plasma aldosterone levels and a compensatory increase in plasma renin activity, while there was no decrease in cortisol levels.

However, the clinical efficacy and safety of baxdrostat need to be confirmed in Phase 3 trials involving more patients treated for a longer term, in order to assess the influence of improved blood-pressure control on hypertension-mediated cardiovascular and renal damage.

EVIDENCE

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