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APROCITENTAN IN PATIENTS WITH RESISTANT HYPERTENSION

EXECUTIVE SUMMARY

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.[1] Although numerous safe and effective pharmacologic therapies are available to treat elevated blood pressure, different therapeutic approaches are warranted to improve the management and prognosis of patients with resistant hypertension. Aprocitentan is a dual endothelin receptor antagonist that could potentially reduce blood pressure and provide broader cardiovascular protection to patients with resistant hypertension in addition to the standard background treatment. Aprocitentan acts on both endothelin receptors involved in mediating the vasoconstricting, hypertrophic, proinflammatory, and profibrotic effects in hypertension. Early studies showed that addition of aprocitentan to the current treatment is effective in treating resistant hypertension and well tolerated.

Keywords: aprocitentan, ACT-132577, resistant hypertension, blood pressure

INTRODUCTION

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.[2] If the threshold of systolic blood pressure more than 140 mmHg was considered, 828 million adults had high systolic blood pressure worldwide.[2] The prevalence of resistant hypertension varies globally, but is estimated to be between 10-20% of patients with hypertension.[3] 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.[3]

A meta-analysis of data from 3.2 million patients in 2018 showed a high prevalence of resistant hypertension and was highest in chronic kidney disease patients.[4] The prevalence of resistant hypertension was 10.3% (95% CI; 7.6% to 13.2%).[4] 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.[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]

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.

THE TECHNOLOGY

Aprocitentan (ACT-132577) is a dual Endothelin (ET-1) receptor antagonist that prevents the binding of ET-1 to both ETA/ETB receptors in development for the treatment of resistant hypertension.[7] Endothelin-1 is a potent vasoconstrictor peptide that also causes neurohormonal and sympathetic activation, increased aldosterone synthesis and secretion, vascular hypertrophy and remodeling, fibrosis, and endothelial dysfunction.[8] This active metabolite of macitentan has a long half-life up to 44 hours and highly bound to plasma proteins and is eliminated in both urine and faeces.[9] Most studies recommend on dosing of 12.5mg once-daily orally.[10, 11]

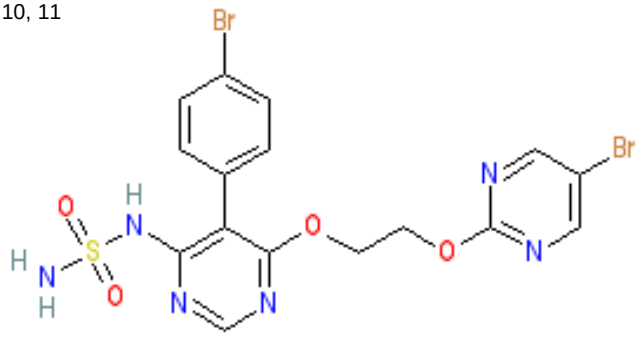

Figure 1: Chemical structure of aprocitentan

PATIENT GROUP AND INDICATION

Aprocitentan is indicated to help lowering the blood pressure in the patients with resistant hypertension in addition to the standard background therapy of hypertension. This is the active metabolites of macitentan with a longer half-life of 44 hours. It prevents the binding of ET-1 to both ETA/ETB receptors that involved in the vasoconstricting, hypertrophic, proinflammatory, and profibrotic effects of hypertension.

CURRENT PRACTICE

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.[1]

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.[1]

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.[1] This includes renal denervation therapy (RDN) and carotid sinus stimulation.[1]

EFFICACY AND SAFETY

Based on the systematic search up to 31st March 2023, there were 21 articles retrieved from the scientific databases (Medline, PubMed), the general search engines [Google Scholar] and from the references of retrieved articles. Out of these 21 articles, 7 articles were reviewed on effectiveness and safety of aprocitentan and 14 articles were excluded.

Aprocitentan has been tested in a multicentre, blinded, randomised, **P**a**R**all**E**l-group, Phase 3 study with apro**CI**tentan in **S**ubjects with Res**I**stant Hypertensi**ON** (PRECISION).[11] Trial was conducted from 2018 to 2022 involving 1965 individuals at 193 sites in 22 countries and 730 were randomly assigned. [11] The design of the study included the first part of 4-week double-blind, second part of placebo-controlled treatment phase; a 32-week single-blind, active-treatment phase; and the third part of 12-week double-blind, placebo-controlled

withdrawal phase.[11] At randomisation, 516 (71%) of 730 patients received the highest dose of standardised background therapy (amlodipine 10 mg) and 423 (58%) of 730 patients continued their β blocker treatment.[11] The primary and secondary endpoints were changes in unattended office systolic blood pressure from baseline to week four and from withdrawal baseline to week 40, respectively. Secondary endpoints included 24-h ambulatory blood pressure changes.[11]

The least square mean difference changes in unattended automated office systolic blood pressure compared to placebo after the first four weeks of treatment were -3.8 ± 1.3 mm Hg (97.5% CI; 6.8 to 0.8, = 0.0042) for aprocitentan 12.5mg and 3.7 ± 1.3 mm Hg (6.7 to 0.8, p = 0.0046) for aprocitentan 25mg.[11] The office diastolic blood pressure decreased as well-compared to placebo (−3.9mm Hg, 95% CI: −5.6 to −2.3 for aprocitentan 12.5mg; −4.5mm Hg, 95% CI: −6.1 to −2.9 for aprocitentan 25mg). Blood pressure was maintained during part 2, while in part 3, after 4 weeks of withdrawal, a significant increase was detected in the placebo arm compared to aprocitentan in terms of both systolic (+5.8mmHg, 95%CI; 3.7 to 7.9, p < 0.0001) and diastolic blood pressure (+5.2mm Hg, 95% CI: 3.8 to 6.6, p< 0.0001).[11] In short, patients with resistant hypertension receiving standardised antihypertensive treatment including a diuretic, showed that the addition of aprocitentan lowered both standardised automated office and 24 hours ambulatory blood pressure compared with placebo after four weeks of initial treatment.[11]

In the randomised, double blind, multicenter phase 2 trial of aprocitentan, there were 490 eligible hypertension patients randomised to 5,10,25 and 50 mg treatment with aprocitentan in eight weeks of treatment compared to placebo to determine the efficacy and safety of aprocitentan in the treatment of hypertension.[12] Decreased in sitting systolic or diastolic automated office blood pressure, from baseline to week eight were 10.3/6.3, 15.0/9.9, 18.5/12.0 and 15.1/10.0 mmHg for aprocitentan 5, 10, 25, and 50 mg, respectively versus 7.7/4.9 mmHg for placebo and 12.8/8.4 mmHg for lisinopril.[12] No changes in heart rate or body weight were observed for any dose of aprocitentan. Modelling the dose-response in this study suggested that the use of aprocitentan at doses between 10 and 25 mg for further investigation as a potential treatment for hypertension.[12]

Another double-blind, randomised placebo-controlled, crossover study enrolled 28 subjects to evaluate the impact of aprocitentan on body weight, body fluid, and electrolyte homeostasis in healthy subjects on a high salt diet.[13] Three doses of aprocitentan (10, 25, or 50 mg/day for 9 days) were compared with placebo. Increases in body weight were observed with aprocitentan (placebo-corrected mean weight gains [90% confidence interval]) of 0.43 [0.05–0.80], 0.77 [0.03–1.51], and 0.83 [0.33–1.32] kg at 10 mg, 25 mg,

and 50 mg, respectively.[13] Decreases in haemoglobin and uric acid were observed.[13] Plasma volume increased at most by 5.5% without dose-response relationship.[13] Urinary sodium excretion decreased at 10 mg and 25 mg but not at 50 mg.[13] Therefore, aprocitentan induces a moderate weight increases in healthy subjects on high sodium diet at doses between 10mg and 50 mg, without obvious sodium retention.[12]

The phase 3 PRECISION trial showed that the fluid retention was the most common adverse event reported with aprocitentan within the first 4 weeks of treatment especially in patients with chronic kidney disease stage 3-4 and led to the discontinuation of seven patients receiving aprocitentan 25 mg.[11] The incidence was dose related, suggesting that 12.5 mg might represent a preferred dose for initiation of therapy.[11] This event was clinically manageable with the addition or up-titration of diuretic therapy.[11] In this population with multiple comorbidities, half of the incident cases of hospitalisation for heart failure were reported for patients with pre-existing heart failure, highlighting the potential importance of adequate diuretic therapy before initiating aprocitentan in these patients.[11] Overall, aprocitentan was well tolerated and the safety profile was comparable with placebo.

In a single and multiple-dose tolerability, safety, pharmacokinetics, and pharmacodynamics study of aprocitentan, 5 mg were prescribed for single doses participants and 25, 100, 300, and 600 mg once daily in multiple doses subjects.[9] This study aimed to explore the pharmacokinetics, tolerability, safety following different doses of aprocitentan in 70 healthy subjects.[9] Single-and multiple-dose administration of aprocitentan was well tolerated up to 600 and 100 mg once a day, respectively.[9] Adverse events in this study were mostly mild and the most frequently reported was headache.[9] Plasma concentration–time profiles of aprocitentan were similar after single- and multiple-dose administration, and support a once a day dosing regimen based on a half-life of 44 hours.[9] After multiple doses, pharmacokinetics was dose proportional.[9] Accumulation at steady state, reached by Day 8, was 3-fold.[9] Only minor differences in exposure between healthy females and males, healthy elderly and adult subjects, and fed and fasted conditions were observed.[9] Plasma ET-1 concentrations, reflecting ETB receptor antagonism, significantly increased with doses ≥25 mg.[9] Time-matched analysis of electrocardiogram (ECG) parameters did not suggest drug-induced ECG effects.[9] Exposure–response analysis indicated no QTc prolongations at plasma levels up to 10 µg/mL.[9]

The, safety and tolerability of aprocitentan were then investigated as monotherapy in patients with essential hypertension in the multicenter phase 2 dose finding study. The overall incidence of adverse events observed in the aprocitentan groups (ranging from 22.0% to 40.2%) was similar to that seen in the placebo group (36.6%).[12]

An open-label, phase 1 trial was conducted to assess the pharmacokinetics, safety, and tolerability of a single oral dose of 25 mg aprocitentan in subjects with moderate hepatic impairment compared to healthy subjects.[14] The pharmacokinetics of aprocitentan were similar between subjects with moderate hepatic impairment and healthy subjects, with maximum plasma concentrations reached at 4.0 hours.[14] There was no difference in plasma concentrations, indicated by the geometric means ratio (90% CI) of 1.03 (0.86 to 1.24).[14] There was a lower apparent clearance, a similar apparent volume of distribution, a longer terminal half-life (56.4 hours vs 48.3 hours in healthy subjects), and an increase in area under the curve from zero to infinity of 23% in moderate hepatically impaired subjects compared to healthy subjects.[14] There were no differences observed in plasma protein binding (range 98.7 to 99.0%).[14] Aprocitentan was well tolerated, and headache was the only adverse event reported by one subject.[14] In conclusion, there were no clinically relevant differences in pharmacokinetics between subjects with moderate hepatic impairment and healthy subjects.

The safety data in the open-label, single-center, phase 1 study include eight subjects with severe renal function impairment and eight healthy subjects showed that the pharmacokinetics of aprocitentan were similar in severe renal function impairment and healthy subjects with maximum plasma concentrations reached at 7.6 hours and 5.0 hours, respectively.[10] Subjects were given 50mg of aprocitentan on day 1 in the morning with fasted condition. Maximum plasma concentrations did not differ as indicated by a geometric means ratio (GMR) (90% CI; 1.04 (0.85 to 1.28).[10] Due to a slightly lower observed clearance in severe renal function impairment subjects, half-life was longer (53.2 hours compared to 47.4 h in healthy subjects), while exposure expressed as area under the curve was 34% higher (GMR 90% CI 1.13 to 1.58).[10] There were no differences in plasma protein binding (> 99% bound).[10] Aprocitentan was well tolerated in subjects with severe renal function impairment with no notable difference compared to healthy subjects.[10] Therefore, aprocitentan can be administered without dose adjustment in subjects with any degree of renal impairment.

ESTIMATED COST

There was no retrievable evidence on the exact cost and economic assessment of aprocitentan. The manufacturers have not announced the treatment's price yet. The price of the drug of the same group, Macitentan (Opsumit) oral tablet 10 mg is about USD 6 369 (MYR 27,131.94; 1 USD=MYR 4.26) for a supply of 15 tablets, depending on the manufacturer.

Currently, aprocitentan is distributed for research purpose only at the price of USD 300 (MYR 1279.20; 1 USD=MYR 4.26) for 5mg.[15]

POTENTIAL IMPACT

Aprocitentan is a potential novel therapy in treating resistant hypertension. Early clinical trials have showed that addition of aprocitentan to the standard therapy is able to clinically meaningfully lowering the systolic and diastolic blood pressure with an acceptable safety profile.

However, future studies with a long-term follow-up evaluating the effects of aprocitentan on cardiovascular outcomes and target-organ damage are warranted. A full economic evaluation will be needed to determine the cost-effectiveness and affordability in incorporating aprocitentan into the current treatment strategies.

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