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A COMPREHENSIVE REVIEW OF THE NOVEL DRUG FOR RESISTANT HYPERTENSION: APROCITENTAN

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ABSTRACT

Context: Resistant hypertension (RH) is associated with increased cardiovascular risk and unmet treatment needs due to neglected pathophysiologic pathways in guideline-recommended therapies. Although spironolactone is regarded as the recommended fourth-line treatment, its safety profile restricts its wide range of use. The FDA has approved a novel dual endothelin (et) A and B receptor antagonist called aprocitentan. **Objective:** The purpose of this study is to provide an overview of the data that is currently available about the discovery, pharmacokinetics, pharmacodynamics, safety, and effectiveness of aprocitentan in the treatment of RH. **Methods:** To find pertinent studies on the usage of aprocitentan, we explored PubMed, clinicaltrials.gov, and worldwide Pharmaceutical Abstracts. A search of clinical trial registries was also conducted. **Conclusion:** Aprocitentan is a revolutionary medicine for managing RH that significantly lowers blood pressure compared to placebo. It broadens our understanding of the pathophysiology of RH and offers promising opportunities for future treatment strategies. On the other hand, information about its long-term safety profile and wider cardiovascular and renal protection is lacking.

KEYWORDS: Resistant Hypertension (RH), Aprocitentan, Endothelin Receptor Antagonist (ERA), Efficacy and Safety.

INTRODUCTION

Worldwide, hypertension is becoming a more significant public health issue. It has been

clearly connected to renal problems, cardiovascular diseases (CVD), and eventual mortality. A severe form of hypertension, resistant hypertension (RH) affects more than 10% of those receiving treatment; the estimate rises based on the population to reach 56% in kidney disease.

The American Heart Association (AHA) defines RH as a condition in which, even when three or more antihypertensive medications of various classes, including a diuretic, are used at their maximum tolerable doses, blood pressure (BP) stays over the goal range. Likewise, true resistant hypertension (tRH) is defined by the 2023 European Society of Hypertension (ESH) guideline as systolic blood pressure that remains ≥140 mmHg or diastolic blood pressure that remains ≥90 mmHg, even when lifestyle modifications and a three-drug combination are administered at optimal or maximally tolerated dosages. This combination needs to have a calcium channel blocker, a thiazide or thiazide-like diuretic, and a renin–angiotensin system (RAS) blocker (either an angiotensin receptor blocker or an angiotensin-converting enzyme inhibitor). RH is linked to an increased risk of hypertension-mediated damage to organs and cardiovascular events, including end-stage kidney disease, heart failure, stroke, ischemic heart disease, and all-cause mortality.

Currently approved antihypertensive medication classes primarily target the RAS (Aldosterone antagonist, angiotensin-converting enzyme inhibitors, angiotensin receptor Blockers and Direct renin inhibitor), calcium channel blockers (Dihydropyridine and non-dihydropyridine), sodium homeostasis and fluid retention (Different diuretic classes), adrenergic receptors (α- and β-blockers), central sympatholytic medications, and vasodilators. Interestingly, in the context of RH, the endothelin (ET) system—a crucial element in the pathophysiology of hypertension has been somehow disregarded.

Consequently, the Food and Drug Administration (FDA) approved aprocitentan, a novel, first-in-class dual ETA/ETB receptor antagonist, in March 2024, marking a new hope in the search for an innovative add-on therapy for uncontrolled hypertension, following years of pharmacologic research silence on this high-risk condition. In June 2024, the European Medicines Agency (EMA) authorized the use of aprocitentan in conjunction with a minimum of three antihypertensive drugs to treat RH in adult patients. Presenting the available data on aprocitentan development, pharmacokinetics, pharmacodynamics, clinical effectiveness, stability and tolerance, and its possible application in the treatment of RH is the goal of this article.

Classification

Endothelin receptor antagonist, antihypertensive.

Drug description on aprocitentan

Aprocitentan, an orally active dual ET receptor antagonist, inhibits ET-1 binding to both ETA/ETB receptors with a potency ratio of 1:16. It belongs to the class of sulfamides where a 5-(4-bro-mophenyl)-6-{2-[(5-bromopyrimidin-2-yl)oxy]ethoxy~pyrimidin-4-yl group replaces one of the amino groups of sulfonamide . TRYVIO (aprocitentan) is an ERA. It has a molecular formula of C16H14Br2N6O4S and a molecular weight of 546.2 g/mol. Aprocitentan is an active form of macitentan, an orphan medication used to treat pulmonary arterial hypertension that is generated by oxidative depropylation. The structural formula is:

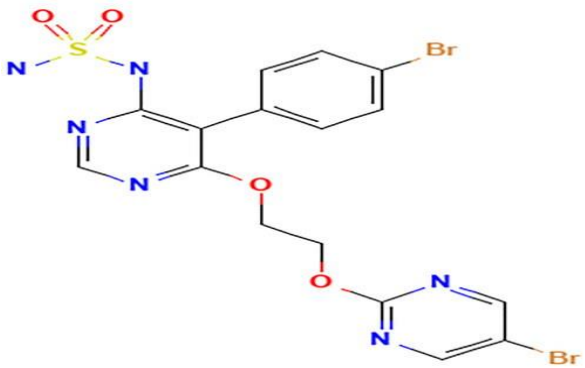

Figure 1: Structure of aprocitentan.

What makes aprocitentan better than other antihypertensives?

Aprocitentan lowers blood pressure in a dose-dependent manner and has been demonstrated to work in concert with renin-angiotensin system (RAS) blockers. Therefore, when existing medications are insufficient to control high blood pressure, it represents a viable new therapy approach.

Before aprocitentan, there were two unsuccessful initiatives to create and approve medications that target the ET route for the treatment of essential hypertension and RH, including bosentan and darusentan. These drugs showed a decreasing effect on blood pressure without triggering any reflex neurohormonal activation.

When compared to placebo, bosentan, a combination ETA and ETB receptor antagonist, significantly improved blood pressure control in individuals with mild to moderate hypertension, according to the first clinical research in humans to examine ET antagonism,

which was carried out in 1998. However, bosentan is linked to a number of negative side effects, such as anemia, peripheral edema, and hepatic transaminitis. Likewise, as an adjuvant treatment for RH, darusentan, a selective ETA receptor antagonist, demonstrated encouraging outcomes as an adjuvant treatment for RH; however, these results were not confirmed in a follow-up investigation. This unfavorable result led to the termination of additional studies on the long-term use of darusentan in resistant hypertension.

Mechanism of action

In the human cardiovascular system, the most common endothelin isoform is endothelin-1 (ET-1). Vascular smooth muscle cells, cardiomyocytes, fibroblasts, macrophages, neurons, and epithelial cells in the kidneys and lungs are among the many additional cells that contain it. Vascular endothelial cells create it constitutively to preserve vascular tone. One By causing vasoconstriction or vasodilation, ET-1 acts on two receptors, ETA and ETB, found on vascular smooth muscle cells and endothelial cells. These receptors help control blood pressure. ET-1 is a powerful vasoconstrictor that mainly acts by interacting with the ETA receptor.

In pathological situations, it also interacts with ETB2 to further cause vasoconstriction. One Numerous diseases, such as essential hypertension, pulmonary arterial disease, chronic kidney disease, dibetes mellitus and others, have been linked to the overexpression of both ET-1 and ET receptors.

Aprocitentan is an ERA that inhibits the binding of endothelin (ET)-1 to ETA and ET B receptors. ET-1, via its receptors (ETA and ETB), mediates a variety of deleterious effects such as vasoconstriction, fibrosis, cell proliferation, and inflammation. In hypertension, ET-1 can cause endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation, and increased aldosterone synthesis.

Pharmacokinetics

Absorption

The absolute oral bioavailability of aprocitentan is unknown.6 The mean Cmax and AUC0-tau following a single oral dose of 25mg are approximately 1.3 mcg/mL and 23 mcg.h/mL, respectively, with a Tmax between 4-5 hours**.**

Half-life

The effective half-life of aprocitentan is approximately 41 hours.

Distribution

The apparent volume of distribution of aprocitentan is approximately 20 L.

Protein binding

Aprocitentan is >99% bound to plasma proteins, primarily albumin. Protein binding is not affected byrenal or hepatic impairment. The aprocitentan blood-to-plasma ratio is 0.63.

Metabolism

Aprocitentan is primarily metabolized by UGT1A1- and UGT2B7-mediated N-glucosidation and non-enzymatic hydrolysis.

Elimination

The aprocitentan effective half-life is approximately 41 hours, and the apparent clearance is approximately 0.3 L/h.

Excretion

After a single dose of radiolabeled aprocitentan, approximately 52% of the dose was eliminated via urine (0.2% unchanged) and 25% via feces (6.8% unchanged).

Effect of food

No clinically significant differences in aprocitentan pharmacokinetics were observed following administration of a high-fat, high-calorie meal (Approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively) in healthy subjects.

Pharmacodynamics

Aprocitentan exposure-response relationships and the time course of pharmacodynamic response are not fully characterized.

Cardiac electrophysiology: At eight times the recommended dose, clinically significant QTc interval prolongation was not observed.

Dosage and Administration

Recommended dosage

- The recommended dosage of TRYVIO is 12.5 mg orally once daily.

- Swallow tablets whole. TRYVIO may be taken with or without food.

Toxicity

According to prescribing information, aprocitentan has been administered in single doses up to 600 mg, and as multiple doses of up to 100 mg daily, in healthy subjects (48- and 8-fold the recommended dose, respectively).6 Observed symptoms of overdosage included headache, nasal congestion, nausea, and upper respiratory tract infection. In the event of an overdose, standard supportive treatment should be employed as clinically indicated. As aprocitentan is highly protein-bound, dialysis is unlikely to be effective.

Safety measures for aprocitentan use in particular categories

Pregnancy

Aprocitentan is contraindicated during pregnancy due to a Boxed Warning on the label about embryo-foetal harm, which includes birth abnormalities and miscarriage. Animal research on macitentan, the parent compound of aprocitentan, which showed teratogenicity (abnormalities in the fusion of the mandibular arch and cardiovascular system) in models of rats and rabbits, is the basis for this warning.

Aprocitentan use may or may not have an influence on the risk of birth abnormalities, fetal death, or other unfavorable pregnancy outcomes, but the available data from published clinical trials is insufficient to draw a firm judgment. Currently, a Pregnancy Safety Study is being conducted to track the effects of aprocitentan exposure on the mother and fetus.

Aprocitentan is only accessible through the Risk Evaluation and Mitigation Strategy (REMS) program due to the possible risk of serious birth abnormalities. Before starting therapy, patients who are capable of becoming pregnant should get a negative pregnancy test. They should also take monthly pregnancy tests during and one month after treatment ends. Additionally, patients who can become pregnant are advised to use a reliable method of contraception prior to the start of, during, and for one month after discontinuation.

Lactation

Information about aprocitentan’s presence in human milk, its effects on breastfed infants, and its impact on milk production is lacking. Since Aprocitentan is more than 99% bound to plasma proteins, milk probably contains a little quantity of it. But because its t1/2 is 41 hours, it may build up in the baby. Since there is insufficient information about the use of

aprocitentan with breastfeeding, another medication might be better than aprocitentan, particularly when feeding a newborn or preterm infant.

Geriatric use

Whilst doses of 100mg once daily in the elderly population showed an increased rate of absorption (Tmax reached 1.5h earlier) and a slightly higher exposure to aprocitentan (Cmax: 1.31 (90% CI: 0.97, 1.78); AUCτ: 1.21 (90% CI: 0.92, 1.58)) compared to healthy adults, t1/2 was not affected. Hence, the authors concluded that no dose Adjustment is warranted in the elderly. In the Aprocitentan PRECISION research, 321 (44%) of the subjects were 65 years of age or older, and 72 (10%) were 75 years of age or older. Compared to younger patients, these patients experienced edema and fluid retention more frequently. For people above 65years, there is no need to modify the dosage.

Pediatric use

Aprocitentan effectiveness and safety in treating pediatric patients are unknown. Therefore, this is not meant for pediatric use.

Hepatic impairment

Since patients with mild to critical hepatic impairment (Child-Pugh classes B and C) may be more susceptible to negative hepatotoxicity results, Aprocitentan is not advised for these patients. For patients with minor hepatic impairment, there is no need to modify the dosage.

Renal impairment

Aprocitentan is not advised for dialysis patients or those with renal failure (eGFR <15 mL/min). It is uncertain how dialysis or renal failure (eGFR <15 mL/min) affect the pharmacokinetics of aprocitentan. Edema and fluid retention are more likely to occur in patients with renal impairment. No dose adjustment is required in patients with mild to severe renal impairment (eGFR ≥15 mL/min).

Overdosage

In healthy subjects, Aprocitentan has been given as a single dose of up to 600 mg and as several doses of up to 100 mg per day (48 and 8 times the suggested dosage of medication, respectively). Upper respiratory tract infections, headaches, nausea, and nasal congestion were noted side effects. Standard supporting measures should be implemented as needed in the instance of an overdose. Due to its strong protein binding, aprocitentan will probably fail

to be beneficial with dialysis.

Safety and Tolerance considerations

Fluid retention

ERAs, such as Aprocitentan, are known to cause peripheral edema and fluid retention. In the clinical trial, 9% of patients treated with Aprocitentan experienced edema or fluid retention, compared to 18% of patients getting aprocitentan 25 mg (double the prescribed dose) and 2% receiving a placebo. Some patients required additional diuretics as a result of this. Chronic renal disease and advanced age are indicators of risk for fluid retention and edema when using Aprocitentan. Aprocitentan has not been investigated in patients with NTproBNP ≥500 pg/mL, unstable cardiac function, or heart failure according to New York Heart Association stages III–IV. It is not advised to use Aprocitentan in these patients.

Hepatotoxicity

ERAs, such as Aprocitentan, are known to cause hepatotoxicity and elevated aminotransferases. In the clinical trial, aprocitentan-treated patients, including those with positive rechallenge, seldom had spikes in alanine transaminase (ALT) or aspartate aminotransferase (AST) of more than five times the upper limit of normal (ULN). No occurrences of liver failure or patients who had ALT and/or AST >3 × ULN or total bilirubin >2 × ULN were reported in the clinical studies with Aprocitentan. Prior to starting treatment, monitor blood aminotransferase levels and total bilirubin; during treatment, repeat as needed and as clinically advised to lower the risk of potentially severe hepatotoxicity.

Patients with moderate to severe hepatic impairment or high aminotransferases (>3 × ULN) shouldn't initiate Aprocitentan.

Embryo-Fetal toxicity

According to information from research on animal reproduction using endothelin receptor antagonists (ERAs), Aprocitentan is contraindicated for usage in pregnant individuals and may harm the fetus if given during pregnancy. Before starting Aprocitentan medication, rule out pregnancy and make sure appropriate contraception techniques are being used. Patients who are capable of getting pregnant should be advised of the risks to the developing foetus. Before beginning aprocitentan treatment, during treatment, and for one month following the last dosage of Aprocitentan, patients should use appropriate contraceptive methods to prevent pregnancy. They should also check for pregnancy every month during treatment and one

month after stopping it. If pregnancy is found, stop taking Aprocitentan.

Hemoglobin decrease

The clinical experiment with Aprocitentan indicated decreases in levels of hemoglobin and hematocrit, which have happened after the administration of previous ERAs.

Typically, hemoglobin declines began early, stabilized, and were reversible after treatment was stopped. In comparison with 1% of placebo patients, 7% of patients had a hemoglobin drop of more than 2 g/dL from baseline. Compared to 0 participants receiving a placebo, 3% of patients treated with Aprocitentan showed a drop of less than 10.0 g/dL.

It is not advised to start Aprocitentan in people who have severe anemia. Before starting treatment and as often as clinically required during treatment, measure hemoglobin levels.

Decreased sperm counts

Similar to other ERAs, Aprocitentan may negatively impact spermatogenesis. Men should be advised about the potential consequences on fertility.

Adverse reactions

- Embryo-fetal toxicity
- Hepatotoxicity
- Fluid retention
- Hemoglobin decrease
- Decreased sperm counts

Other adverse effects

Other advers effects include liver problems like

- Nausea
- Vomiting,
- Yellowing of The Skin
- Whites of The Eyes,
- Pain In The Upper Right Stomach,
- Dark Urine, Tiredness,
- Fever,
- Loss of Appetite,

- Itching
- Extreme Tiredness.
- Unusual Weight Gain.
- Trouble Breathing.
- Swelling of the Hands, Legs, Ankles Or Feet.
- Rash.

Contraindications

Pregnancy

Use of Aprocitentan is contraindicated in pregnancy. To prevent pregnancy, patients who can become pregnant should use acceptable contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with Aprocitentan.

Hypersensitivity

Aprocitentan is contraindicated in patients who are hypersensitive to aprocitentan or any of its excipients.

Drug interaction studies

The clinical Trials and Model-informed approaches

Concurrent usage of aprocitentan with midazolam (a CYP3A4 substrate) or rosuvastatin (a substrate of the breast cancer resistance protein [BCRP]) did not result in any clinically relevant changes in their pharmacokinetics.

In vitro studies

Aprocitentan exposure may be reduced by administering it concurrently with UDP-glucuronosyltransferase (UGT) inducers.

All CYP2C family members and CYP3A4 are inhibited by Aprocitentan, however CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP2E1 are not. Aprocitentan did not induce CYP1A2 or CYP2C9, however it did induce CYP3A4.

UGT enzymes: UGT1A1 and UGT2B7 are both substrates and inhibitors of Aprocitentan.
Transporter systems: BCRP and P-glycoprotein (P-gp) both bind to Aprocitentan.

However, it is not expected that inhibitors of these transporters will affect aprocitentan's PK. The bile salt export pump (BSEP), sodium taurocholate co-transporting polypeptide (NTCP),

and BCRP are all inhibited by Aprocitentan; however, P-gp, OCT1, OCT2, human multi-drup and toxin compound extrusion (MATE)1, and MATE2K are not. Aprocitentan does not inhibit organic anion transporter (OAT)1, OAT3, OATP1B1, or OATP1B3 at therapeutic concentrations.

Nonclinical toxicology

Carcinogenesis

In mice and rats that produced approximately equivalent exposures to aprocitentan, two-year carcinogenicity experiments using macitentan (of which aprocitentan is a significant metabolite) did not find any malignant risk at dosages up to 100 mg/kg/day and 250 mg/kg/day. Based on AUC, the clinical aprocitentan exposure at the MRHD was 30-fold and 11-fold, respectively.

Mutagenesis

In a conventional battery of in vitro and in vivo tests, which included an in vivo bone marrow micronucleus test in rats, a chromosome aberration test in human lymphocytes, and a bacterial reverse mutation assay, Aprocitentan did not cause mutagenicity or genotoxicity.

Impairment of fertility

In a research on male rats' fertility, aprocitentan dosages up to 250 mg/kg/day for 15 weeks had no effect on spermatogenesis or fertility at 52 times the clinical exposure at the MRHD based on AUC. Male rats and dogs treated with aprocitentan at high doses of 250 mg/kg/day and 25 mg/kg/day, respectively, experienced testicular tubular degeneration/atrophy in repeated dose toxicity studies. This amounts to roughly 41 and 52 times the clinical exposure at the MRHD, based on AUC, respectively. At 50 mg/kg/day and 5 mg/kg/day, respectively, which correspond to roughly 14 and 10 times the clinical exposure at the MRHD based on AUC, testicular damage did not appear noticeable in male rats or dogs.

Female rats given aprocitentan just before mating showed negligible pre-implantation loss at doses of ≥50 mg/kg/day, which is approximately 23 times the clinical exposure at the MRHD based on AUC. At 10 mg/kg/day, which is five times the clinical exposure at the MRHD based on AUC, no effect on fertility was seen.

Indications

Aprocitentan is an endothelin receptor antagonist indicated for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adult patients who are not adequately controlled on other drugs. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions**.**

Aprocitentan focuses a pathophysiologic route that is still uncontested by first-line treatments available today. The idea that aprocitentan could broaden our antihypertensive resources in RH is supported by the encouraging safety and effectiveness findings from seminal clinical trials. Although aprocitentan has a risk of fluid retention, this risk seems to be lower than that of first-generation selective ETA blockers. Additionally, it does not have the same risk of hyperkaliemia as spironolactone. Because hyperkaliemia represents a major prescribing constraint in daily practice, aprocitentan is therefore a compelling potential substitute for fourth-line therapy, especially in patients with proteinuric severe CKD (stages 3 and 4).

Furthermore, current guidelines for the treatment of hypertension emphasize the risks of cardiovascular and target-organ damage in addition to lowering blood pressure. These risks are explained by other antihypertensive therapies like betablockers (BB), angiotensin conversing enzyme (ACE-I), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and mineralocorticoid receptor antagonists (MRA). The capacity of aprocitentan to further lower blood pressure, which is regarded as a surrogate marker, has been the primary focus of study on the drug thus far, accounting for other possible cardiovascular consequences.

Future studies examining how aprocitentan affects cardiovascular outcomes are necessary. Based on exploratory results, the PRECISION trial revealed an anti-proteinuric effect that is more pronounced in patients with CKD stages 3–4. Because it may increase its function in treatment guidelines, this result necessitates particular attention to aprocitentan’s therapeutic potential. Due to a non-medical decision, one phase 3 research (NCT04162366) that sought to examine the safety and effectiveness of aprocitentan in patients with chronic kidney disease and resistant hypertension (INSPIRE-CKD) was canceled before enrollment was finished. Given that prior research has shown that kidney impairment has no effect on the PK profile, additional efforts to explore the role of aprocitentan in CKD and end-stage renal illness are essential, particularly given the dearth of agents that are safe and effective for hypertensive patients with advanced CKD.

CONCLUSION

Aprocitentan is an ensuring novel therapy for RH that lowers blood pressure by inhibiting ET-1 binding to ETA and ETB receptors. Its unique pharmacological profile lowers the risk of drug-drug interactions by avoiding CYP450 and BCRP-mediated elimination. There are promising opportunities for its application in the treatment of RH because of the notable drops in blood pressure seen in clinical trials. Anaemia and fluid retention are the most often reported side effects, and they should be carefully taken into account in clinical practice.

Regarding its long-term safety information and effects on cardiovascular and renal protection, there is not enough proof. Its clinical usefulness needs to be thoroughly investigated.

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