Review: A Novel Drug Firibastat Is First-In-Class Brain Aminopeptidase A Inhibitor Treatment On Hypertension

Ajay Bhojane[1], Dipak Ghodekar[2], Vikas Kandekar[3], Narendra Gowekar[4]
[1, 2, 3, 4] Dept of Pharmaceutical Quality Assurance
[1, 2, 3, 4] Siddhant Collage of Pharmacy (Sudumbare) Pune, Maharashtra, India

Abstract- *Firibastat is the new first-in-class centrally acting Aminopeptidase A inhibitor prodrug. Pharmacologically, firibastat prevents the conversion of angiotensin-II to angiotensin-III, one of the main effector peptides of the brain Renin–angiotensin system that exerts central stimulatory regulation over blood pressure. Preclinical studies in various hypertensive animal models demonstrated the safety and clinical efficacy of firibastat in improving blood pressure control. These conclusions were also shown in human phase I-II clinical trials, highlighting that firibastat may constitute a potential alternative therapy in the management of high-risk patients with difficult to treat or resistant high blood pressure. The safety and efficacy of firibastat should be further solidified in patients with hypertension through the design of metacentric, randomized, large-sized, and highly powered phase III clinical trials. No severe adverse effects related to firibastattreatment have been reported yet. Results from studies show that firibastat is generally well tolerated and safe to use in high blood pressure patient. The aim of this review is to investigate, collect & reform the current knowledge in suitable form about firibastat drug.*

Keywords- Hypertension, Aminopeptidase, stimulation, Quantum Genomics

I. INTRODUCTION

Firibastat is the new first-in-class centrally acting Antihypertensive drug develop by Quantum Genomics. The firibastat (originally named QGC001) product is the first BAPAI candidate-drug selected by Quantum Genomics. The firibastat product is a prodrug that delivers in the brain the EC33 product, a selective and specific inhibitor of Aminopeptidase A, thus preventing the conversion of angiotensin-II to angiotensin-III, one of the main effector peptides of the brain Renin–angiotensin system that exerts central stimulatory regulation over blood pressure. The main purpose of firibastat is to target the brain Renin–angiotensin system in contrast to other antihypertensive treatment options that target the system Renin–angiotensin–aldosterone system. It has been found that over activity in the brain Renin–angiotensin system can be related to the development and maintenance of hypertension. Therefore, the brain Renin–angiotensin system is a possible therapeutic treatment target when it comes to hypertension. All members of the systemic RAAS are present in the brain Renin–angiotensin system, which include the precursor angiotensinogen, enzymes, peptides, and angiotensin receptors.

II. DESCRIPTION

Firibastat (QGC001), an orally active brain penetrating prodrug of EC33, is a first-in-class brain **aminopeptidase A (APA)** inhibitor ($\mathbf{K_i}$=200 nM). Firibastat selectively and specifically inhibits conversion of brain angiotensin-II into angiotensin-III and decreases blood pressure in hypertensive rats.

Name – Firibastat (QGC001)
IUPAC Name - (S)-3-amino-4-(((S)-2-amino-4-sulfobutyl)disulfaneyl)butane-1-sulfonic acid
Formula -C8H20N2O6S4
Molecular weight- 368.51
Storage- powder form drug store in -20°C &4°CFor 3 year and 2 years respectively. In solvent form drug store in -80°C&-20°C for 6 months & 1 months respectively.
Solubility-Soluble in DMSO, water

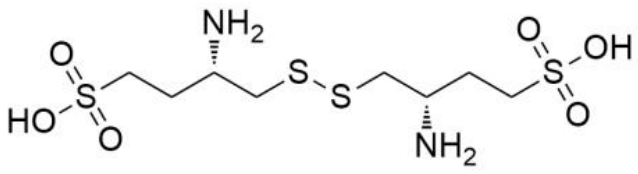

Fig1. Chemical Structure

III. MECHANISM OF ACTION

Firibastat is an aminopeptidase A (APA) inhibitor. APA plays an important rolein the brain RAS where it

hydrolyses the N-terminal aspartate residue from Ang-II to angiotensin-III (Ang-III). APA is a membrane-bound zinc metalloprotease. Another membrane bound zinc metalloprotease is aminopeptidase N (APN). APN cleaves the N-terminal of Ang-III to generate angiotensin IV (Ang-IV). Figure 2 shows a simplified schematic overview of the brain RAS.

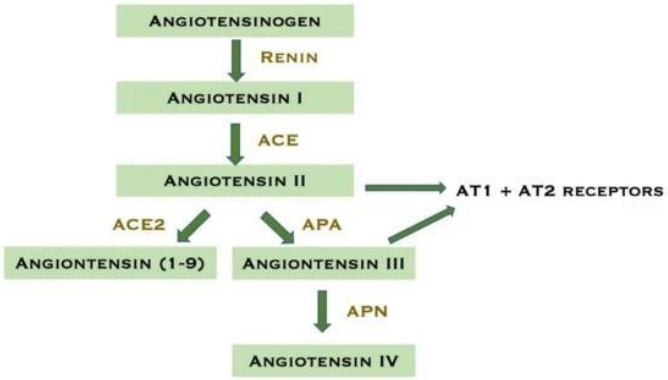

Fig 2. Schematic diagram of the brain renin–angiotensin system.

Ang-II and Ang-III exhibit a similar affinity for angiotensin type 1 receptor (AT1) and angiotensin type 2 receptor (AT2). Binding to these receptors increases BP through three mechanisms: increased release of arginine-vasopressin (AVP),sympathetic nerve activation and inhibition of the barore flex. In a study by Mark et al., it was found that by inhibiting APA activity and the formation of Ang-III with firibastat, a dose-dependent decrease in BP occurred in rats. EC33 ((3S)-3-amino-4-sulfanyl-butane-1-sulfonic acid) is an APA inhibitor. When EC33 binds to APA it inhibits the conversion of Ang-II to Ang-III. EC33 is unable to cross the gastrointestinal, liver and blood–brain barrier (BBB), when taken orally. For this reason, a prodrug of EC33 has been manufactured. This prodrug consists of twoEC33 molecules connected by a disulfide bridge. The prodrug is called RB150 (4,4-dithiobis(3S)-3-aminobutyl sulfonic acid), which was later named firibastat. The thiol group inRB150 is engaged in the disulfide bridge and is unable to interact with the zinc atom inactive site of APA. By binding two EC33 molecules together to form RB150, it is possible to cross the gastrointestinal, liver and BBB. Once the RB150 has crossed the BBB, it is cleaved by brain reductases into two active EC33 molecules. These two EC33 molecules are now able to bind to APA's active site and inhibit the conversion of Ang-II to Ang-III, and thus Ang-III systemic effects. Figure 3 shows how firibastat affects the brain RAS and thereby decreases the BP.

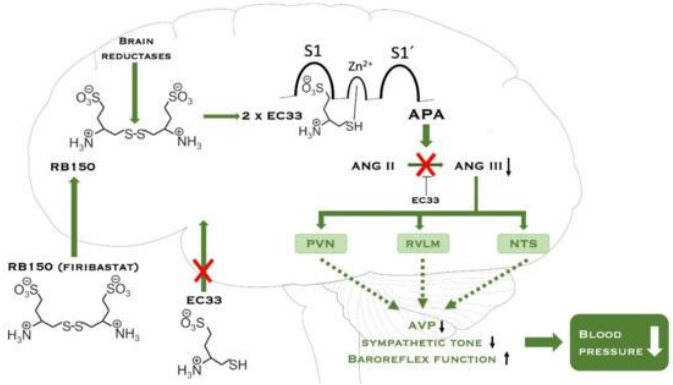

Fig 3. Crossing the blood–brain barrier after oral administration because of the disulfide bridge

Although Ang-II and Ang-III have similar effects, studies in murine brains have attempted to define their respective roles in relation to cardiovascular function. An in trace rebroventricular injection of EC33 in hypertensive rats showed a decrease in blood pressure due to the inhibition of APA. An intravenous injection, however, showed no decrease, indicating that EC33-induced BP decrease is a central but not systemic effect. These findings suggest that Ang-III is an important effector peptide of the brain RAS and in the control of BP. The conversion from Ang-II to Ang-III is central to increase BP, therefore it is a potential therapeutic target whereby this conversion is inhibited. A possible explanation for the fact that Ang-II does not induce a BP increase under brain APA blockade might be that in the presence of an APA inhibitor, alternative pathways of Ang-II are activated via other peptidases such as ACE2, aminopeptidases or endopeptidases, leading to Ang3–8, Ang1–5, Ang4–8, and Ang1–7, all of which do not activate the AT1receptor. This hypothesis is further supported by observations by Feng et al., and Yamazato et al., who showed that ACE2 overexpression in the brain can prevent low-dose Ang-II-induced hypertension, and reduces BP in SHR rats, respectively.

IV. INTERACTION

Firibastat is a new drug and is therefore still being tested in various clinical trials phase III. Therefore, there is currently not much knowledge about the interactions between firibastat and other drugs. Firibastat study that was performed before phase 1 where the effect of firibastat was tested in rats and dogs. This study gives the result that none of the human recombinant cytochrome P450 enzymes were significantly inhibited by either RB150or EC33. The human recombinants involve CYP1A2, CYP2C9, CYP2C19, CYP2D6 andCYP3A4 and were all tested in vitro at 10 µmol/L in fluorimetric substrate assays. Based on this experiment, strong inducers of these specific human recombinant cytochrome P450enzymes will not interact with firibastat.

V. CONCLUSION

Firibastat is the novel antihypertensive drug approved by the FDA recently. In clinical trials firibastat shows none of adverse effects on rat and dog as per investigation. Firibastat newly first in class drug Centrally acting on Aminopeptidase A inhibitor. Pharmacologically, firibastat prevents the conversion of angiotensin-II to angiotensin-III, one of the main effector peptides of the brain Renin–angiotensin system that exerts central stimulatory regulation over blood pressure. firibastat may constitute a potential alternative therapy in the management of high-risk patients with difficult to treat or resistant high blood pressure.

REFERENCES

[1] Ahmed Abu-Zaid,Firibastat, the first-in-class brain aminopeptidase a inhibitor, in the management of hypertension: a review of clinical trials, Avicenna Journal of Medicine / Volume 11 / Issue 1 / January-March 2021.

[2] Hansen, E.; Grimm, D.Wehland, M. Current Knowledgeabout the New Drug Firibastat inArterial Hypertension. Int. J. Mol. Sci.2022, 23, 1459.

[3] Marc, Y.; Hmazzou, R.; Balavoine, F.; Flahault, A.; Llorens-Cortes, C. Central antihypertensive effects of chronic treatment withRB150: An orally active aminopeptidase A inhibitor in deoxycorticosterone acetate-salt rats. J. Hypertens. 2018, 36, 641–650.

[4] Lenkei, Z.; Palkovits, M.; Corvol, P.; Llorens-Cortès, C. Expression of angiotensin type-1 (AT1) and type-2 (AT2) receptor mRNAsin the adult rat brain: A functional neuroanatomical review. Front. Neuroendocrinol. 1997, 18, 383–439.

[5] Vazeux, G.; Iturrioz, X.; Corvol, P.; Llorens-Cortes, C. A glutamate residue contributes to the exopeptidase specificity inaminopeptidase A. Biochem. J. 1998, 334 Pt 2, 407–413.

[6] Marc, Y.; Llorens-Cortes, C. The role of the brain renin-angiotensin system in hypertension: Implications for new treatment. Prog.Neurobiol. 2011, 95, 89–103.

[7] Marc, Y.; Gao, J.; Balavoine, F.; Michaud, A.; Roques, B.P.; Llorens-Cortes, C. Central antihypertensive effects of orally active aminopeptidase A inhibitors in spontaneously hypertensive rats. Hypertension 2012, 60, 411–418.

[8] Doroszko A, Janus A, Szahidewicz-Krupska E, Mazur G, Derkacz A. Resistant hypertension. AdvClinExp Med 2016;25:173-83.

[9] Balavoine, F.; Azizi, M.; Bergerot, D.; De Mota, N.; Patouret, R.; Roques, B.P.; Llorens-Cortes, C. Randomised, double-blind, placebo-controlled, dose-escalating phase I study of QGC001, a centrally acting aminopeptidase a inhibitor prodrug. Clin. Pharm. 2014, 53, 385–395.

[10] Jordan, J.; Kurschat, C.; Reuter, H. Arterial Hypertension. Dtsch. Arztebl. Int. 2018, 115, 557–568.

[11] Staff, M.C. Overview: High Blood Pressure (Hypertension). Available online: https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/symptoms-causes/syc-20373410.

[12] Oxlund, C.; Jeppesen, J.; Christensen, K.L.; Bang, L.E.; Pareek, M.; Olsen, M.H. Arteriel Hypertension. Available online:https://nbv.cardio.dk/hypertension.

[13] Saavedra JM. Brain and pituitary angiotensin. Endocr Rev 1992;13:329-80.

[14] Xu Q, Jensen DD, Peng H, Feng Y. The critical role of the central nervous system (pro)renin receptor in regulating systemic blood pressure. PharmacolTher 2016;164:126-34.

[15] Llorens-Cortes C, Touyz RM. Evolution of a new class of antihypertensive drugs: Targeting the brain renin-angiotensin system. Hypertension 2020;75:6-15.

[16] Yamazato, M.; Yamazato, Y.; Sun, C.; Diez-Freire, C.; Raizada, M.K. Overexpression of angiotensin-converting enzyme 2 in the

[17] rostral ventrolateral medulla causes long-term decrease in blood pressure in the spontaneously hypertensive rats. Hypertension2007, 49, 926–931.

[18] Ferdinand, K.C.; Balavoine, F.; Besse, B.; Black, H.R.; Desbrandes, S.; Dittrich, H.C.; Nesbitt, S.D. Efficacy and Safety of Firibastat,A First-in-Class Brain Aminopeptidase A Inhibitor, in Hypertensive Overweight Patients of Multiple Ethnic Origins. Circulation2019, 140, 138–146.

[19] Boitard, S.E.; Marc, Y.; Keck, M.; Mougenot, N.; Agbulut, O.; Balavoine, F.; Llorens-Cortes, C. Brain renin-angiotensin systemblockade with orally activeaminopeptidase A inhibitor prevents cardiac dysfunction after myocardial infarction in mice. J. Mol.Cell. Cardiol. 2019, 127, 215–222.

[20] Aronow, W.S. Approaches for the Management of Resistant Hypertension in 2020. Curr. Hypertens. Rep. 2020, 22, 3.

[21] Bodineau, L.; Frugière, A.; Marc, Y.; Inguimbert, N.; Fassot, C.; Balavoine, F.; Roques, B.; Llorens-Cortes, C. Orally activeaminopeptidase A inhibitors reduce blood pressure: A new strategy for treating hypertension. Hypertension 2008, 51, 1318–1325.