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Cardiovascular Disease: Role of Aliskiren

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Abstract

Literature surveys were shown that plasma renin activity (PRA) and the risk of cardiovascular disease. There is also evidence that angiotensin II exerts harmful effects on progression and in stabilization of atherosclerotic plaque. The renin-angiotensin system (RAS) can be inhibited through inhibition of angiotensin I (Ang I) generation from angiotensinogen by direct renin inhibitors, inhibition of angiotensin II (Ang II) generation from angiotensin I by angiotensin-converting enzyme inhibitors and finally by direct inhibition of the action of Ang II receptor level. Aliskiren, the first direct renin inhibitor to reach the market, is a low-molecular-weight, orally active, hydrophilic nonpeptide. Aliskiren blocks Ang I generation, while plasma renin concentration increases because the drugs block the negative feed-back exerted by Ang II on renin synthesis. Because of its long pharmacological half-life, aliskiren is suitable for once-daily administration. It's through-to-peak ratio is approximately 98% for the 300 mg/day dose. Because of its mechanism of action, aliskiren might offer the additional opportunity to inhibit progression of atherosclerosis at tissue level. Hypertension is an approved indication for this drug, which is also promising for the treatment of heart failure. The efficacy of this drug in reducing major clinical events is being tested in large ongoing clinical trials.

Keywords: Plasma Renin Activity; Renin Angiotensin System; Aliskiren; Angiotensinogen; Renin; Hypertension; Heart Failure; Diabetes

Abbreviations: PRA: Plasma Renin Activity; RAS: Renin-Angiotensin System; Ang I: Angiotensin I; Ang II: Angiotensin II; ACE: Angiotensin-Converting Enzyme; BP: Blood Pressure

Introduction

A link between plasma renin activity (PRA) and risk of cardiovascular disease has been demonstrated in several [1-4], but not all [5,6] epidemiological studies. Such a link is also supported by many experimental and clinical studies which provided convincing evidence that the renin-angiotensin system (RAS) is capable of stimulating atherosclerosis by triggering basic reactions which ultimately lead to growth, instability, and rupture of atherosclerotic plaques and facilitation of thrombosis [7,8].

Mechanisms Of Pharmacological Inhibition of the RAS

The pharmacological inhibition of the RAS can be achieved through 3 different basic mechanisms (Skeggs et al.):

- Inhibition of angiotensin I (Ang I) generation from angiotensinogen. This can be achieved by direct inhibition of renin, an aspartyl protease that releases the decapeptide Ang I from the α-2-globulin angiotensinogen.

- Inhibition of angiotensin II (Ang II) generation from angiotensin I. This can be achieved through inhibition of angiotensin-converting enzyme (ACE), a zinc dependent protease that generates the octapeptide hormone angiotensin II (Ang II) by cleaving 2 amino acids histidine and leucine) from Ang I. ACE is highly expressed in the kidney and pulmonary endothelium.

- Inhibition of the action of Ang II at the level of its receptor(s).

Circulating Renin and Prorenin

Circulating levels of renin are _1 pmol/L in humans and levels of prorenin are about 10-fold higher (Denser et al 1998). However, circulating levels of prorenin and rennin tend to be related. Under physiological conditions, less than 2% of prorenin is in the active conformation. Acute stimuli may cause a sudden increase in the release of active renin from the juxtaglomerular apparatus without any immediate rise in the prorenin levels, while chronic stimuli may lead to a rise in both renin and prorenin, with a higher rate of conversion of inactive prorenin into active renin [9]. Prorenin has a low intrinsic activity on angiotensinogen which is _3% than fully activated renin. Stimulation of AT1 receptors by Ang II inhibits rennin release. In contrast, inhibition of RAS

at any level increases renin release by attenuating the negative feedback effect by Ang II. In patients with diabetes mellitus, as well as during pregnancy, there is usually a rise in prorenin levels with an increased prorenin/renin ratio. In patients with diabetes, prorenin levels may even predict the occurrence of subsequent nephropathy [10,11].

Aliskiren

Aliskiren, a 2(S),4(S),5(S),7(S)-N-(2-carbamoyl- 2-methylpropyl)-5-amino-4-hydroxy-2,7 diisopropyl-8- (4-methoxy-3-[3-methoxypropoxy-] phenyl)-octan amide, is the only orally active renin inhibitor that successfully progressed to phase III trials and extensive clinical use.

Chemical properties

Aliskiren is a low-molecular-weight hydrophilic nonpeptide which exerts a potent and specific competitive inhibition on renin in primates (Wood et al.). The very high specificity for renin (10,000-fold higher affinity for rennin than for other aspartic peptidases) makes aliskiren unlikely to cause adverse effects potentially related to inhibition of other peptidases. Because renin is a water-soluble protein that can be studied with crystallographic analysis (Rahuel et al.), the opportunity arose to examine systematically the crystals of renin bond to renin inhibitors. Consequently, the development of aliskiren was the result of successive steps of molecular modeling on earlier peptide-like renin inhibitors (Wood et al.). These steps were aimed to improve the affinity for the active enzymatic sub pocket of renin and to prolong the duration of action of the drug. The high potency of aliskiren is reflected by the finding that the concentration at which this drug can inhibit 50% of renin activity is only 0.6 nmol/L (Wood et al.). After oral administration in healthy volunteers, the plasma concentration of aliskiren increases in a dose dependent fashion with peak concentrations after 3-6 hours, average plasma half-life of 23.7 hours (range 20-45 hours), oral bioavailability of about 5% (for 95% it is excreted unchanged in feces), and plasma steady-state levels after 5-8 days of treatment [12].

Pharmacodynamic Properties

Since important molecular differences exist in the structure of renin and angiotensinogen between different species, inhibitors of human renin are specific for primates and ineffective or scarcely effective in non-primates. In sodium depleted marmosets (which are primates), aliskiren at 3 mg/kg daily completely inhibited PRA for 24 hours [13]. The effect of aliskiren on blood pressure (BP) was dose-dependent, with a persistence of the effect for 24 hours. In marmosets, aliskiren was more effective than other renin inhibitors (zankirens and remikiren) in lowering BP. In order to obviate the specificity of aliskiren for primate renin, double transgenic rats were developed with human genes for renin and angiotensinogen [6,14]. In these rats, low and high doses of aliskiren and valsartan were compared with placebo to investigate their effects on left ventricular hypertrophy, creatinine, albuminuria, and mortality. In summary, both doses of aliskiren but only the higher dose of valsartan decreased all of the above endpoints compared with placebo. After 3 weeks, 74% of rats treated with the low valsartan dose, but 100% of rats treated with the high valsartan dose and both aliskiren doses survived, compared with none of the untreated rats [15]. A group of healthy normotensive volunteers put on a constant sodium diet (100 mmol/day) received aliskiren (40-80 mg/day or 160-640 mg/day), enalapril (20 mg/day) or placebo. Aliskiren decreased PRA, Ang I, and Ang II in a dose-dependent fashion. In comparison with placebo, the higher dose of aliskiren reduced Ang II by 80% and increased plasma renin concentration by more than 10 times.

The reduction in Ang II was comparable between enalapril 20 mg/day and aliskiren 160 mg/day. Neither BP nor heart rate were affected by aliskiren and enalapril in these normotensive subjects (Nussberger et al.). In a within-subject study, 12 sodium-depleted normotensive subjects were randomly given placebo, aliskiren 300 mg/day, valsartan 160 mg/day, and the combination of aliskiren and valsartan (150 mg/day +80 mg/day). As expected, aliskiren alone decreased PRA while valsartan alone increased PRA, Ang I and Ang II. The combination of aliskiren and valsartan completely eliminated the rise in

PRA elicited by valsartan [16-28].

Conclusion

Aliskiren, the first direct renin inhibitor to reach the market, is a low-molecular-weight, orally active, hydrophilic nonpeptide. Aliskiren blocks Ang I generation, while plasma renin concentration increases because the drugs block the negative feed-back exerted by Ang II on renin synthesis. Because of its long pharmacological half-life, aliskiren is suitable for once-daily administration. It's through-to-peak ratio is approximately 98% for the 300 mg/day dose. Because of its mechanism of action, aliskiren might offer the additional opportunity to inhibit progression of atherosclerosis at tissue level. Hypertension is an approved indication for this drug, which is also promising for the treatment of heart failure. The efficacy of this drug in reducing major clinical events is being tested in large ongoing clinical trials.

References

1. Brunner HR, Laragh JH, Baer L, Newton MA, Goodwin FT, et al (1972) Essential hypertension: rennin and aldosterone, heart attack and stroke. N Engl J Med 286(9): 441-449.
2. Alderman MH, Madhavan S, Ooi WL, Sealey JE, Laragh JH (1991) Association of the renin sodium profile with the risk of myocardial infarction in patients with hypertension. N Engl J Med 324(16): 1098-104.
3. Alderman MH, Ooi WL, Cohen H, Madhavan S, Sealey JE, et al. (1997) Plasma renin activity: a risk factor for myocardial infarction in hypertensive patients. Am J Hypertens 10(1): 1-8.
4. Campbell DJ, Woodward M, Chalmers JP, Colman SA, Jenkins AJ, et al (2005) Prediction of myocardial infarction by N-terminal-pro-B-type natriuretic peptide, C-reactive protein, and renin in subjects with cerebrovascular disease. Circulation, 112(1): 110-116.

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5. Doyle AE, Jerums G, Johnston CI (1973) Plasma renin levels and vascular complications in hypertension. Br Med J 2(5860): 206-207.
6. Fukamizu A, Sugimura K, Takimoto E, Sugiyama F, Seo MS, et al. (1993) Chimeric renin angiotensin system demonstrates sustained increase in blood pressure of transgenic mice carrying both human renin and human angiotensinogen genes. J Biol Chem 268(16): 11617-11621.
7. Donoghue M, Hsieh F, Baronas E, Gosselin M, Stagliano N, et al. (2000) A novel angiotensin converting enzyme-related carboxypeptidase (ACE_2) converts angiotensin I to angiotensin 1-9. Circ Res 87(5): E1-E9.
8. Jacoby DS, Rader DJ (2003) Renin-angiotensin system and atherothrombotic disease: from genes to treatment. Arch Intern Med 163(10): 1155-1164.
9. Danser AH, Batenburg WW, van Esch JH, Krop M (2008) Prorenin anno 2008. J Mol Med 86(6): 655-658.
10. James MN, Sielecki AR (1985) Stereochemical analysis of peptide bond hydrolysis catalyzed by the aspartic proteinase penicillopepsin. Biochemistry 24(14): 3701-3713.
11. Clausmeyer S, Sturzebecher R, Peters J. 1999. An alternative transcript of the rat renin gene can result in a truncated prorenin that is transported into adrenal mitochondria. Circ Res 84(3): 337-344.
12. Andersen K, Weinberger MH, Egan B, Constance CM, Ali MA, et al. (2007) Aliskiren-based therapy lowers blood pressure more effectively than ramipril-based therapy in patients with hypertension: a 6-month, randomized, double-blind trial J Am Coll Cardiol 49(Suppl A): A371.
13. Dieterle W, Corynen S, Vaidyanathan S (2005) Pharmacokinetic interactions of the oral renin inhibitor aliskiren with lovastatin, atenolol, celecoxib, and cimetidine. Int J Clin Pharmacol Ther 43(11): 527-535.
14. Ganten D, Wagner J, Zeh K, Bader M, Paul M, et al. (1992) Species specificity of renin kinetics in transgenic rats harboring the human renin and angiotensinogen genes. Proc Natl Acad Sci USA 89(16): 7806-7810.
15. Gradman AH, Schmieder RE, Lins RL, Nussberger J, Chiang Y, et al. (2005a) Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. Circulation 111(8): 1012-1018.
16. Azizi M, Menard J, Bissery A, Guyenne TT, Riviere AB, et al. (2004) Pharmacologic demonstration of the synergistic effects of a combination of the renin inhibitor aliskiren and the AT1 receptor antagonist valsartan on the angiotensin II-renin feedback interruption. J Am Soc Nephrol 15(12): 3126-3133.
17. Bader M, Ganten D (2008) Update on tissue renin-angiotensin systems. J Mol Med 86(6): 615-621.
18. Dahlof B, Anderson DR, Arora V (2007) Aliskiren, a direct rennin inhibitor, provides antihypertensive efficacy and excellent tolerability independent of age or gender in patients with hypertension. J Clin Hypertens 9(Suppl A): A157.
19. Danser AH, Derkx FH, Schalekamp MA, Hensen HW, Riegger GA, et al. (1998) Determinants of interindividual variation of renin and prorenin concentrations: evidence for a sexual dimorphism of (pro)renin levels in humans. J Hypertens 16(6): 853-862.
20. Danser AH, Dorpel MAVD, Deinum J, Derkx FH, Franken AA, et al. (1989) Renin, prorenin, and immunoreactive renin in vitreous fluid from eyes with and without diabetic retinopathy. J Clin Endocrinol Metab 68(1): 160-170.
21. Derkx FH, Alberda AT, de Jong FH, Zelimaker FH, Makovitz JW, et al. (1987) Source of plasma prorenin in early and late pregnancy: observations in a patient with primary ovarian failure. J Clin Endocrinol Metab 65(2): 349-354.
22. Derkx FH, Schalekamp MA (1988) Human prorenin: pathophysiology and clinical implications. Clin Exp Hypertens A 10(6): 1213-1225.
23. Dieterle W, Corynen S, Mann J (2004) Effect of the oral renin inhibitor aliskiren on the pharmacokinetics and pharmacodynamics of a single dose of warfarin in healthy subjects. Br J Clin Pharmacol 58(4): 433-436.
24. Gradman AH, Schmieder RE, Lins RL, Nussberger J, Chiang Y, et al. (2005b) Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. Circulation 111(8):1012-1018.
25. Huang Y, Wongamorntham S, Kasting J, Owens RT, Yu L, et al. (2006) Renin increases mesangial cells transforming growth factor-beta1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms. Kidney Int 69(1): 105-113.
26. Ichihara A, Suzuki F, Nakagawa T, Kaneshiro Y, Takemitsu T, et al. (2006) Prorenin receptor blockade inhibits development of glomerulosclerosis in diabetic angiotensin II type 1a receptor-defi cient mice. J Am Soc Nephrol 17(7): 1950-1961.
27. Itskovitz J, Rubattu S, Levron J, Sealey JE (1992) Highest concentrations of prorenin and human chorionic gonadotropin in gestational sacs during early human pregnancy. J Clin Endocrinol Metab 75(3): 906-910.
28. Itskovitz J, Sealey JE, Glorioso, Rosenwaks Z (1987) Plasma prorenin response to human chorionic gonadotropin in ovarian-hyper stimulated women: correlation with the number of ovarian follicles and steroid hormone concentrations. Proc Natl Acad Sci USA 84(20): 7285-7289.

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