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A Direct Renin Inhibitor Aliskiren: Re-Evaluation of Effectiveness

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Abstract

The RAAS is an important pharmacologic target as the system is involved in cardiovascular (CV) and renovascular disease. Ang II is the key component of RAAS. The intervention to the RAAS can be achieved in different stages. While angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are two big groups that target the RAAS, aliskiren a direct renin inhibitor that became clinically feasible in 2007 with the launch of aliskiren. In this review, we will discuss direct renin inhibition as a new concept for pharmacotherapy of hypertension and aliskiren, the first oral direct renin inhibitor, as a new class of antihypertensive drug based on new evidence.

Keywords: Hypertension; Renin-angiotensin-aldesterone system; Aliskiren; Direct renin inhibitor; RAAS inhibitor

Introduction

Pivotal role of the renin angiotensin aldosterone system (RAAS) both in the progression as well as the pathogenesis of cardiovascular disease such as hypertension, atherosclerosis, chronic heart failure, is undeniable [1]. The activation of the RAAS, which is initially regulatory and compensational, becomes disproportionate and uncontrollable by time, and hence triggers emergence of cardiovascular diseases. Key factor that determine the activation of the RAAS system is renin protease, which control the synthesis of angiotensin II (Ang II) from angiotensinogen. Ang II, produced from angiotensin I (Ang I) by angiotensin converting enzyme (ACE), is responsible for the complications mediated by Ang II receptor in the end organs such as vasoconstriction, hypertrophy and growth in vascular smooth muscles in the cardiovascular diseases.

Although the activity of renin is the basic rate-limiting step in the RAAS, the initial drug development goals have been directed to the subsequent steps and successful clinical results were obtained from clinical studies conducted with angiotensin converting enzyme inhibitors (ACEIs) and then angiotensin receptor blockers (ARBs) [2]. Numerous studies have shown that ACEIs and ARBs lead to significant decrease in morbidity and mortality of cardiovascular diseases, such as hypertension and heart failure. However, it is not possible to say that the final point is reached in the RAAS blockade. A complete blockade of the RAAS is not provided with ACEIs and ARBs. Such agents cause increase in renin activity by "feedback" mechanism. On the other hand, the effects of ACEIs on bradykinin negatively affect the side effect profile of these agents. Above all, the clinical benefits with both ACEIs and ARBs are significant, yet insufficient. Considering that the renin activity is the main controlling step of the RAAS, inhibition of the renin will theoretically provide a more complete and effective inhibition of RAAS. In this review pharmacokinetic and clinical data regarding Aliskiren, the first direct renin inhibitor (DRI) with accepted clinical utility, will be reviewed based on new evidence.

Renin Angiotensin Aldosteron System

Basically, RAAS is a coordinated hormonal cascade that governs the cardiovascular, renal and adrenal functions by regulating fluid and electrolyte balance as well as arterial pressure [3, 4].

Secretion of renin is the first step in RAAS cascade and, importantly, also the rate-limiting step, Figure (1) [5, 6]. Renin is secreted, in response to a variety of stimuli, from kidneys but the only known physiological substrate for renin in the plasma is angiotensinogen. Renin acts on the angiotensinogen to form angiotensin I (Ang I) that is subsequently converted to the biologically active angiotensin II (Ang II) by the help of angiotensin converting enzyme (ACE) [7].

Ang II is the effector enzyme of the cascade and most biological actions of Ang II are mediated primarily through type-1 (AT_1), and type II (AT_2) receptors. In human activation of AT_1 receptor causes vasoconstriction via activation of phospholipase and inhibition of adenylate cyclase. Increased blood pressure, promotes adrenal aldosterone secretion, renal sodium reabsorption and release of catecholamine from the adrenal medulla and prejunctional nerve endings [8]. In contrast activation of AT_2 receptor causes vasodilation via cGMP dependent pathway [9].

In addition to the Ang I and II, other bioactive angiotensin peptides have been determined in the last decade as: angiotensin III (Ang III), angiotensin IV (Ang IV) and angiotensin 1-7 (Ang 1-7), among of which Ang (1-7) is much more important [10]. Ang (1-7) opposes the vasoconstrictor actions of Ang II by stimulating vasodilator prostaglandins from vascular endothelial and smooth muscle cells [11, 12], releasing nitric oxide (NO) [13] and inhibiting vascular cell growth [14]. Furthermore, potentiation of bradykinin at its receptors by binding to the active site of ACE was shown [15]. In addition to vascular bed, Ang (1-7) is also formed in the kidney by the activation

of neutral endopeptidases, and its action depends on the state of sodium and water balance, renal nerve activity and RAAS activation [16]. According to the study conducted by Santos et al. Ang (1-7) participates in the control of hydroelectrolyte balance by influencing especially water excretion via both arginine vasopressin (AVP) dependent and independent pathways [17]. These effects of Ang (1-7) presumed to be mediated by a unique receptor known as the Mas receptor (Mas-oncogene) that does not bind to Ang II [18].

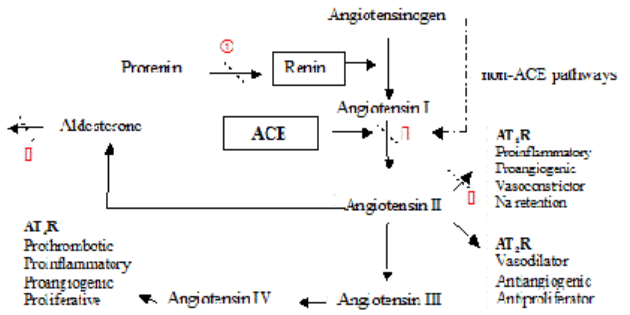

Figure 1: Site of action of four classes of antihypertensive drugs that block RAAS: ① Direct renin inhibitors, ② ACE Inhibitors, ③ARBs, ④ Aldosterone antagonists.

In recent years, in addition to the physiological role of systemic RAAS in in the regulation of fluid and electrolyte balance, arterial pressure together with pathological role in CV and renal diseases, studies have focused on the local tissue RAAS in the brain, heart, peripheral blood vessels, adrenal glands and kidney [19-23]. In these vital organs RAAS act as paracrine or autocrine systems both in physiological and pathophysiological conditions. For example, stimulation of intrarenal RAAS plays an important role both in minute-to-minute regulation of sodium reabsorption and in the pathophysiology of sodium retention states such as hypertension and congestive heart failure [24]. Again, inappropriate activation of RAAS in the kidney contributes the nephropathy in patients with diabetes [25, 26]. The role of vascular RAAS in the pathogenesis of inflammation, atherosclerosis, hypertrophy, remodeling, and angiogenesis is also known [27,28].

Therefore both circulatory and local RAAS inhibition is a key therapeutic approach to slow progression of chronic kidney disease (CKD) and to reduce CV risk through both blood pressure dependent and independent mechanisms.

RAAS Inhibitors and Need of Direct Renin Inhibition

As seen in the Figure 1 there are now 4 ways to inhibit the RAAS. Among two of them are ACEI and ARBs. Both of them target the Ang II as therapeutic effect, however their mechanisms of action are different. While ACEIs inhibit the ACE enzyme, which converts Ang I to Ang II, ARBs block Ang II to binds its receptors of AT_1. Therefore the differences in their mechanisms of action might have their therapeutic implications [29].

Nowadays, blockade of RAAS with ACEIs, ARBs or combination of these drugs underlies the current antihypertensive therapy. The beneficial effects of these agents are attributed to their preventative effects on Ang II mediated vasoconstriction, water and salt retention, aldosterone and vasopressin release, stimulation of sympathetic nervous system, inflammation and stimulation of cell growth [30]. However, inhibition of RAAS with ACEIs or ARBs has proven effective for controlling hypertension most important handicap of these agents is incomplete blockage of RAAS. A fundamental reason is reduced feedback inhibition of renin release, triggering a reactive rise in plasma renin activity [31, 32]. With an ACEIs, the reactive rise in plasma renin activity causes compensatory increase in Ang I, which partially restores Ang II production by both ACE-dependent and independent pathways (ACE-escape phenomenon) [33]. With an ARB, the reactive rise in plasma renin activity causes compensatory increases in both Ang I and II. This may partially restore AT_1, AT_2 and AT_4 receptors. In contrast, the direct renin inhibitor binds directly to the catalytic site of renin, thereby inhibiting its ability to convert angiotensinogen to Ang I, the rate-limiting step in the formation of angiotensin II Figure (1) [34, 35]. By this complete blockage of RAAS at its origin, decrease in both Ang I and Ang II levels can be achieved by DRIs. Although blocking feedback inhibition causes reactive rise in renin secretion, plasma renin activity (PRA), the enzymatic activity of renin is markedly reduced by the DRI [36]. Therefore, through this more complete RAAS inhibition, DRIs can offer greater protection from hypertensive complications [37].

A second issue with ACEIs and ARBs is that they may not provide effective inhibition of tissue RAAS activity [38,39]. Circulating renin can be taken up by cardiac and coronary tissues, leading to long lasting generation of Ang II via both ACE dependent and independent pathways that is only partially suppressed by ACEIs (Figure 1) [38,40]. While under physiological conditions, the function of the cardiac RAAS is to maintain cellular balance by inhibiting and inducing cell growth, and proliferation and mediation of adaptive responses to myocardial stretch [28] pathologic activation of cardiac RAAS has been proposed to contribute to the development of left ventricular hypertrophy. Similarly activation of vascular RAAS plays a role in the endothelial dysfunction, vascular smooth muscle cell growth, and production of reactive oxidative species that have been associated with inflammation, atherosclerosis, hypertrophy, remodeling, and angiogenesis [28].

Direct Renin Inhibitors: Aliskiren

In addition to being a rate-limiting step in the formation of Ang II, renin is also a good substrate for the inhibition of angiotensinogen. Moreover identification of renin receptors both in the glomerulus and in the artery gives additional advantages of renin inhibition for cardiovascular and renal protection [41]. On one hand binding of renin to its receptor starts the angiotensinogen cascade, on the other hand converts inactive prorenin to an active form. Binding of renin/prorenin to its receptors exerts physiological effects independent from Ang II including activation of intracellular signal pathways, enhanced synthesis of DNA, and stimulation of the release of plasminogen activator inhibitor 1, collagen 1, fibronectin, and transforming growth factor β-1 [42].

The first synthetic renin inhibitor was pepstatin, which was followed by first-generation agents that were active but required parenteral administration [43]. In 1980s, first orally active direct renin inhibitor (DRI) compounds were developed, such as enalkiren, remikiren, and zankiren. Because of their poor bioavability (less than 2%), short half-lives and weak antihypertensive activity they had

limited clinical use [44,45]. Later highly potent and selective, non-peptide, low molecular weight DRIs have been synthetized [46, 47]. Aliskiren is the first of this new non-peptide, orally effective DRI to be approved by the FDA and by EMEA in 2007 for the treatment of hypertension.

Preclinical development

Aliskiren acts as a competitive renin inhibitor (inhibitory concentration 50%: 0.6 nmol/L), by binding to the enzymatically active site of renin [35,48], which is highly specific for human and primate renin [49]. This makes it to difficult to carry out experimental studies. Therefore it was tested in marmosets and in transgenic rats. According to these studies the oral administration of aliskiren resulted in sustained decrease in mean BP, increase in plasma renin concentration (PRC) and strong inhibition of plasma renin activity (PRA) [50]. This BP lowering effect was also stronger and longer period than benazepril or valsartan [50] Beyond blood pressure lowering effect, end-organ protective effect of aliskiren was also shown in experimental settings. Experiments in a rat model of severe hypertension and organ damage, aliskiren administration reduced proteinuria, reversed cardiac hypertrophy and reduced macrophage infiltration in the heart and kidney. [49,51]. These results provide the proof of organ protective effects of aliskiren.

Pharmacokinetic and pharmacodynamics of aliskiren

In the pharmacokinetic studies, after oral administration of aliskiren a dose dependent increase in the plasma concentration with a peak concentration after 3-6 hours was reported. Other reported pharmacokinetic parameters can be summarized as: the mean absolute bio-availability is 2.6% [52], the peak plasma concentration is reached 1–2 hours after dosing and steady state is reached after 5–8 days of once-daily administration [36], plasma half-life is 23.7 hours [49], and it is eliminated via biliary excretion as unmetabolized drug [45]

According to the pharmacodynamic studies carried out, in patients with hypertension, sustained BP reduction over the 24 h was reported by aliskiren [53]. This was attributed its long plasma half-life (approximately 40 h) [36]. Aliskiren is generally well tolerated, with a placebo like profile. Most commonly reported adverse effects are headache, diarrhea, dizziness, fatigue, and back pain; the frequencies of these effects are similar to both ARBs and placebo [54]. Furthermore because of having no interaction with metabolism of substance P and bradykinin, cough and angioedema like adverse effects caused by the use of ACEIs, do not occur with aliskiren treatment [55,56]. The hepatic elimination of aliskiren also makes it suitable for patients with impaired renal function [45]. Again aliskiren does not interfere with several agents, including warfarin, digoxin, statins and other antihypertensive agents [57,44,58].

Although aliskiren appears to be safe, serum potassium levels must be monitored in patients with renal impairment [49] especially in combination therapy with ACEI and/or ARBs [59] or in patients receiving cyclooxygenase (COX) inhibitors [60].

Clinical efficacy of aliskiren in the light of new evidences

Essential hypertension. Early phase II clinical trials with aliskiren compared the BP-lowering effect and safety of aliskiren with placebo, losartan and irbesartan [61,62].

According to the multicenter, randomized phase III clinical trials, combining aliskiren with drugs that produce a reactive increase in PRA, such as diuretics, ACEIs and ARBs, increases the antihypertensive efficacy of aliskiren [63-66]. In a study conducted by Villamil and colleagues combination therapy of HCTZ and aliskiren was superior to both monotherapies in reducing both systolic and diastolic blood pressure with a 46.1–63.5% decrease in PRA [65]. Moreover aliskiren/HCTZ combination showed similar tolerability to aliskiren monotherapy [67]. The efficacy, safety and tolerability of combination therapy with aliskiren and ACEIs have also been shown [59,63]. Again combination therapy with aliskiren and ARBs; the decrease in diastolic blood pressure was statistically significant than either monotheraphy alone without any increase in the rate of adverse effects. Furthermore incidents of hyperkalemia and increased serum creatinine levels were similar in all groups and did not demand discontinuation of treatment [63]. Similarly in the ACCELERATE trial, the decrease in the systolic blood pressure was significant when aliskiren combined with the amlodipine without additional adverse event [59].

Parallel with these findings; previous meta-analysis showed the safety and tolerability of aliskiren in combination with the ARBs, or diuretic, is similar to aliskiren, ARBs, or diuretics alone [68]. The analysis results confirmed that the combination therapy of aliskiren with ARB in adult patients with hypertension was associated with significantly better compliance, fewer hospitalizations and medical visits compared with ACEI/ARB combination [69]. On contrary according to the meta-analysis conducted by Harel et al, combination therapy of aliskiren/ACEIs or ARBs significantly increased the risk of hyperkalemia compared with monotherapy [70].

Prevention of end-organ damage. The cardio-renal protecting effects of aliskiren was evaluated with the ASPHIRE HIGHER program that consisted of 14 multicenter phase III clinical trials including more than 35.000 patients with hypertension, diabetes, HF, renal dysfunction, and previous MI [71].

Hypertension and congestive heart failure. The ALOFT study conducted in patients with hypertension who had stable heart failure (HF) briefly showed that adding aliskiren to the standard therapy (ACEIs, ARBs and beta blockers (BBs) produces reduction in brain natriuretic peptide (BNP), N-terminal proBNP, aldosterone and renin levels, improvement in left ventricular (LV) function as well as comparable tolerability [72]. Similar results were also shown both in AVANT-GARDE trial for the aliskiren/valsartan combination [73] and in ALLAY trial for the aliskiren/losartan combination [74]. According to the ASPIRE study, with the addition of aliskiren to an ARBs or an ACEIs there was no differences in LV volume and function after MI. Furthermore higher rates adverse events were seen with aliskiren [74]. Same results were also shown for ARB/ACEI combinations both in ONTARGET and VAILANT trials [75].

Hypertension and diabetes. According to the AVOID study, addition of aliskiren to the losartan showed the renoprotective effect by reduction in proteinuria. This effect was also independent from BP reduction [76]. Similar cardio-renal protective effects were shown with the addition of aliskiren to ACEI or ARB conventional therapy in the ALTITUDE trial, in patients with II diabetes [77]. However the study was early terminated as a result of higher adverse events (renal complications, increased incidence of nonfatal stroke and hyperkalemia). After termination of the study both EMA and FDA contraindicated the use of dual RAAS blockade with aliskiren in

diabetic patients and patients with moderate-to-severe renal failure [78,79].

Hypertension and chronic disease. Early phase II studies showed the effectiveness of aliskiren in patients with CKD [64] unfortunately its use in the diabetic nephropathy gave disappointing results in the ALTITUDE study [77]. Here, we have to point out that there is no long-term comparative study evaluating the effect of direct renin inhibition in renal function with ACEI/ARBs especially in progressive renal injury.

Possible explanation for the controversial results of dual RAAS blockage with aliskiren

Controversial results were reported for the dual RAAS system blockage by ACEI and ARBs [80-83]. Similar controversy exists for aliskiren. While beneficial effect of aliskiren/losartan combination was shown in ALLAY trial [74], the result of ALTITUDE trial was disappointing [77]. According to Dr. Juncos, an investigator of ALTITUDE study, one possible explanation of this controversy is the unspecified use of dual RAAS blockage. For example using of dual RAAs blockage in patients with almost normal BP. The baseline BP values were: 142/82 mmHg and 137/74 mmHg for ONTARGET and ALTITUDE trials respectively. Dual RAAS inhibition with patients lower than basal BP levels could cause hypo perfusion of heart, brain or kidney. Observing of hypotensive episodes with the addition of aliskiren to the ACEI and/or ARB monotherapy in ALTITUDE trail, especially in patients with lower pulse pressure or patients who were older than 65 years of age supports this argument [84]. Again related to the hyperkalemia, a well-known complication of poor organ perfusion, similar argument can be done. In ALTITUDE trial, patients with the basal serum potassium concentration greater than 5mEq/l were randomized to the combination therapy arm. Although combination therapy significantly increased the risk of hyperkalemia (relative risk 1.58 %), this was clinically insignificant. (< 6 mEq/l) [70,84]. As a result, Dr. Junos claims that aliskiren could not be used as add-on therapy to ACEI or ARBs in patients with nearly normal BP and with serum potassium levels higher than 5mEq/l [84].

Regarding the increased stroke risk, through the analysis of ONTARGET database Mann and colleagues [75] showed the association of blood pressure lowering intervention with a reduction in stroke rate for diabetic patients. However, in patients with prior stroke it was suggested as a potential harm with BP below 120 mmHg systolic [85]. Parallel to this evidence, though the early results of ALTITUDE study showed an increase in nonfatal stroke (112 cases were in aliskiren and 85 cases were in placebo group, hazard ratio was 1.34, 95 % CI), all data analysis done by Harel showed a small relative difference (146 and 118 were in respectively, the hazard ratio was 1.25, 95 % CI) [70].

Regarding the CKD, the risk of stroke is known to increase with CKD [86]. Furthermore, there is evidence with strong relationship of blood pressure and stroke in CKD [87]. Based on the evidence it would be argued that an antihypertensive therapy could be more protective for stroke in CKD [75]. Moreover, it is well known that increased protein excretion rate is a key parameter in the progression of kidney disease [88]. Therefore, in addition to blood pressure control, additional goal must be the reduction of proteinuria in CKD [84]. The renoprotective effect of aliskiren by reducing proteinuria is known. It is also shown that this effect is independent from BP reducing effect of aliskiren [76].

New Molecular Mechanisms of Aliskiren

Although clinical trials related to the organoprotective potential of aliskiren gave controversial results, new studies on molecular based show the organoprotective potential of aliskiren beyond its antihypertensive action.

As discussed earlier, renin catalyses the hydrolysis of angiotensinogen to form Ang I that is subsequently converted to the biologically active Ang II by the help of ACE. Renin is formed from the prorenin. Both prorenin and renin bind to the (pro) renin receptor (PRR) result in PRR-mediated effect of renin, independent from Ang-II [89]. The functional link of PRR to the vacuolar-H+-ATPase (v-H+-ATPase) that regulates pH of cellular and intracellular vesicles, and to Wnt/frizzled (Wnt/Fz) signalling is known. Moreover the physiological role of this signalling pathway in the cell survival and embryonic development together with the pathophysiological role in various disease like chronic kidney diseases, malignancy, infection, endocrine disorders, hypertension and diabetes was shown [90]. Hence PRR down regulatory potential of aliskiren opens up new areas of research beyond hypertension. Indeed aliskiren induced reduction induced reduction in PRR gene expression was shown in diabetic TG(mRen-2)27 rats [91] and cultured human aortic smooth muscle cells [92].

The peroxime proliferator-activated receptor (PPARγ) activated role of RAAS in the attenuation of the development of hypertension, endothelial dysfunction and inflammation has been shown [93, 94]. The endothelial nitric oxide (eNOS) activating effects of PPARγ in the prevention of cardiovascular disorders has also been shown [90]. Furthermore the Wnt/Fz mediated regulation of PPARγ transcription factor has been shown [95]. Therefore aliskiren might up regulate and activate PPARγ signaling via Wnt pathway resulted in increasing NO formation through eNOS activation. This in turn might afford CV protection and improve vascular endothelial function [90]. Improvement of impaired NO bioavailability and the protection against atherosclerotic changes in the vascular endothelium of Watanabe heritable hyperlipidemic rabbits was shown by aliskiren [96]. Again protective effect of aliskiren in the hypertensive organ injury caused by eNOS dysfunction was shown in eNOS-deficient mice [97]. Because these molecular mechanisms were shown in the in-vitro and/or in-vivo animal studies, they need to be proven in further clinical studies with larger sample size.

Conclusion

RAAS plays a vital role in the pathophysiology of hypertension and cardio-renal disorders. Ang II is the key component of RAAS. The intervention to the RAAS can be achieved in different stages. While ACEI and ARBs are the traditional blockers, aliskiren a direct renin inhibitor was launched as a new class of inhibitor. Although earlier small-scale clinical trials indicated a possible positive effectiveness, later large-scale trails were disappointing. As a consequence, both EMA and FDA terminated the use of dual RAAS blockage with aliskiren in diabetic patients and patients with moderate-to-severe renal failure. However, later metaanalysis showed evidence of the cardio-renal protective effect of aliskiren. Recently, the results of the invitro/in-vivo animal studies have also displayed new possible molecular mechanisms of aliskiren. With large size clinical trials to prove the new molecular mechanism of aliskiren, controversial results on the cardio-renal protecting effects of aliskiren would be solved.

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