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Forum Minireview

New Approaches to Blockade of the Renin–Angiotensin–Aldosterone System: Characteristics and Usefulness of the Direct Renin Inhibitor Aliskiren

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Abstract. Since renin inhibition interferes with the first and rate-limiting steps in the renin–angiotensin system, the renin step is a very attractive target for lowering blood pressure and minimizing target-organ damage. The newly developed direct renin inhibitor aliskiren has several attractive characteristics: it definitively reduces plasma renin activity among inhibitors of the renin–angiotensin system, is remarkably specific for human renin, exhibits a long half-life in plasma comparable to that of amlodipine, and has a high affinity for renal glomeruli and vasculature. Although these characteristics suggest the clinical usefulness and safety of aliskiren, several problems remain unsolved. Why does aliskiren have beneficial effects on the heart and kidneys of patients treated with angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II type 1–receptor blockers (ARBs)? Is the blood-pressure–lowering effect of aliskiren dependent on the plasma renin activity? Does aliskiren exert a possible adverse effect via (pro)renin receptor–dependent intracellular signals? Here, we review the characteristics and usefulness of aliskiren and discuss the current issues associated with this direct renin inhibitor.

Keywords: diabetes, hypertension, kidney, plasma renin activity, (pro)renin receptor, angiotensin

1. Introduction

Renin belongs to the aspartic protease family, which includes pepsin, cathepsin D, and chymosin. Each enzyme has two aspartic acid residues in its active site that are necessary for catalytic activity. Based on the x-ray crystal structures of other aspartic proteases, the active site appears as a long, deep cleft, as shown in Fig. 1. The enzyme also contains a mobile flap (prosegment of prorenin) that, when closed, lies across the cleft and holds the substrate (angiotensinogen) within the active site. Thus, the development of renin inhibitors typically involved one of two different pathways. The first approach was based on the hypothesis that the prosegment of prorenin is capable of inhibiting enzyme activity by preventing access to angiotensinogen. The second approach was to synthesize peptic analogs of the N-terminal amino acid sequence of angiotensinogen. However, these pathways so far led to the development of only weak inhibitors with low bioavailabilities. In contrast, the novel direct renin inhibitor (DRI) aliskiren was developed using an alternative approach based on x-ray crystallography and the reconstruction of the active site's structure. The DRI aliskiren has several unique characteristics, and numerous clinical studies have reported its usefulness and safety.

2. Definitive reduction in plasma renin activity

Plasma renin activity (PRA), even in the presence of angiotensin-converting enzyme (ACE) inhibitors (which increase PRA), was used as a prognostic marker in the Val-HeFT study (1). Because elevated PRA is capable of generating angiotensinogen-derived peptides even in the presence of ACE inhibitors or angiotensin II type 1–receptor blockers (ARBs), some angiotensinogen-derived

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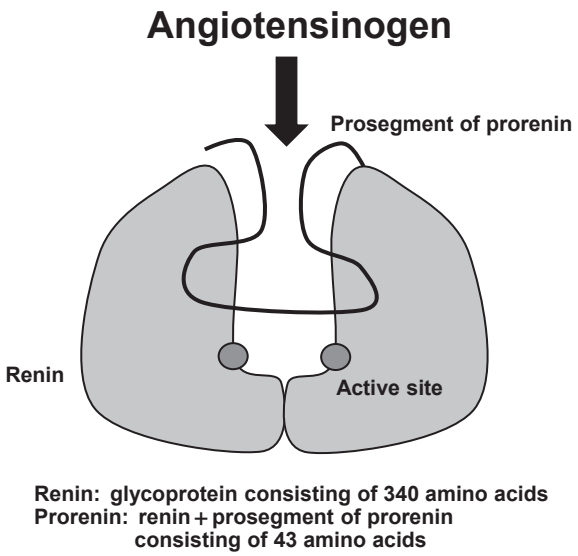

Fig. 1. Structure of renin and its active sites.

peptides may be harmful. Among the renin–angiotensin system (RAS) inhibitors, DRIs are the only drugs that inhibit PRA. *β*-Adrenergic blockers are capable of decreasing PRA but are incapable of inhibiting the synthesis and secretion of renin caused by decreases in pressure, sodium levels, and angiotensin II. Thus, DRIs are the only antihypertensive drugs capable of definitively reducing PRA.

3. Specificity for human renin

DRIs have a remarkable inherent specificity. Although renin is a type of aspartic proteinase, aspartic proteinases other than renin, such as pepsin and cathepsin-D, are far less responsive to direct renin inhibitors (2). Thus, DRIs only inhibit the enzymatic activity of renin, and this inherent specificity has clinical implications, as it reduces the risk of possible side effects, such as dry cough, caused by ACE inhibitors. In addition, the DRI aliskiren has a high specificity for human renin. The IC_{50} values of aliskiren for the inhibition of renin originating from humans, dogs, rabbits, rats, pigs, and cats were 0.6, 7, 11, 80, 150, and 8500 nM, respectively (3). The inherent- and species-specificity of aliskiren is based on its unique structure. The active site of human renin has been newly discovered to contain an S3SP pocket not found in other aspartic proteinases or other species of renin, and the methoxyalkoxy side-chain of aliskiren is capable of occupying the S3SP pocket (3); consequently, aliskiren has a strong specificity for human renin and a long half-life, as described below.

4. Long half-life

As shown in Table 1, compared with other antihypertensive drugs, aliskiren has a mean terminal half-life of between 34 and 41 h after multiple dosing. This long half-life allows aliskiren to be used as a once-daily treatment for hypertension and related cardiovascular diseases. Only the calcium-channel blocker amlodipine has a similar half-life to aliskiren, enabling once-daily dosing. Recently, Palatini et al. performed a randomized, double-blinded study examining whether the blood-pressure–lowering effects were maintained following a missed dose of aliskiren, irbesartan, or ramipril (4). Aliskiren (300 mg) provided a sustained blood-pressure–

Table 1. Half-life of antihypertensive drugs in the plasma

Class	Drug	Half-life (h)	Administration
DRI	Aliskiren	34 – 41	single daily
ARB	Irbesartan	11 – 15	single daily
	Losartan	2 (parent), 6 – 9 (metabolite)	single daily
	Valsartan	6	single daily
	Telmisartan	24	single daily
ACEI	Enalapril	11	single or twice daily
	Lisinopril	12	single daily
CCB	Amlodipine	30 – 50	single daily
β-Blocker	Carvedilol	7 – 10	single or three times daily
	Atenolol	6 – 7	single daily
Diuretic	HCTZ	5.6 – 14.8	single or twice daily

DRI, direct renin inhibitor; ARB, angiotensin II type 1–receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium-channel blocker; HCTZ, hydrochlorothiazide.

lowering effect beyond a 24-h dosing interval, with a significantly smaller loss of the blood-pressure–lowering effect during the 24 – 48 h period after dosing than irbesartan (300 mg) or ramipril (10 mg).

5. High affinity for glomeruli and renal vasculatures

Feldman et al. showed that aliskiren accumulated in the glomeruli and vasculatures of rat kidneys with a high affinity (5). This observation may explain why the renal vasodilator response to DRIs exceeds the response to ACE inhibitors (6) and why the addition of aliskiren treatment further decreased albuminuria in patients treated with the ARB losartan (7).

6. Clinical usefulness and safety

In hypertensive patients, aliskiren significantly lowered the blood pressure in a dose-dependent manner, with safety and tolerability profiles comparable to those of irbesartan and a placebo; in fact, aliskiren (150 mg) was as effective as irbesartan (150 mg) for lowering blood pressure (8). A randomized, double-blinded study demonstrated that the combination of aliskiren and valsartan at the maximum recommended doses enabled significantly greater reductions in blood pressure than monotherapy with either drug in hypertensive patients, with safety and tolerability profiles similar to those of aliskiren and valsartan alone (9). Similar results have been reported by many clinical studies.

7. Why does aliskiren have beneficial effects on the hearts and kidneys of patients treated with ACE inhibitors and/or ARBs?

The Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study reported that the administration of 300 mg/day of aliskiren reduced the mean urinary albumin-to-creatinine ratio of diabetic patients who had been treated with 100 mg of losartan (7). In addition, the Aliskiren Observation of Heart Failure Treatment (ALOFT) study showed that 150 mg/day of aliskiren reduced the plasma levels of BNP and NT-proBNP and the urinary aldosterone levels in patients with NYHA II to IV heart failure who had been treated with an ACE inhibitor (or ARB) and β-blocker (10). The favorable effects of the addition of aliskiren treatment in patients treated with ACE inhibitors or ARBs can be explained by its characteristics described above: namely, that it enables a definitive reduction in PRA, is highly specific for human renin, and has a long half-life and a high affinity for glomeruli and renal vasculatures. The reduction in PRA induced by aliskiren might be particularly important because the elevation in PRA that occurs during treatment with ACE inhibitors and ARBs can lead to "aldosterone breakthrough" and an "overestimated reduction in tissue angiotensin II levels" via non-ACE pathways like chymase and cathepsin G or angiotensin II type 2 receptors (Fig. 2)

8. Is the blood-pressure–lowering effect of aliskiren dependent on the plasma renin activity?

There is an argument that PRA affects the blood-pressure–lowering effect of aliskiren. An analysis of

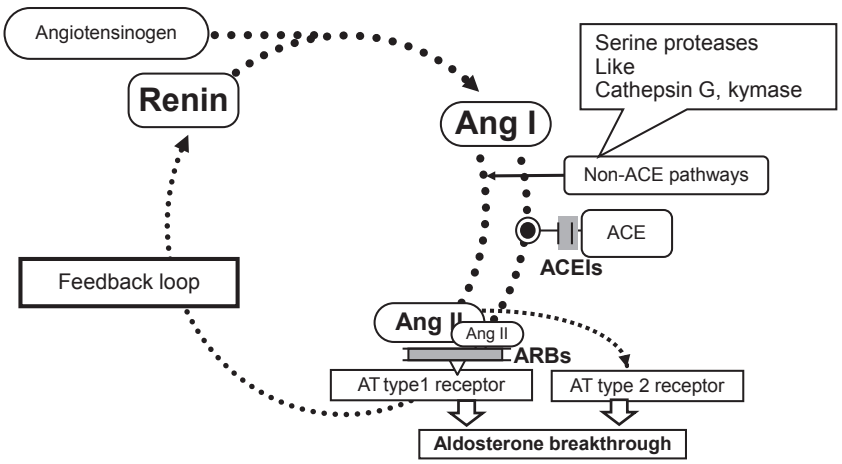

Fig. 2. "Overestimated reduction in tissue angiotensin (Ang) II levels" via angiotensin-converting enzyme (ACE)–independent pathways and "aldosterone breakthrough" via Ang II receptors (AT) type 2 during treatment with ACE inhibitors (ACEIs) and AT type 1–receptor blockers (ARBs), respectively.

three clinical trials (11 – 13) suggests that aliskiren does not lower the blood pressure of most hypertensive patients with low renin levels or those with medium or high renin levels, whose PRA levels do not fall sufficiently (14). However, this speculation was partially refuted by two authors of the three clinical trials (15). They found that neither the baseline PRA nor the change in PRA was associated with the blood-pressure–lowering effect during aliskiren therapy combined with ACE inhibitors or ARBs, although the change in PRA was correlated with the blood-pressure–lowering response during aliskiren monotherapy. Furthermore, a recent long-term (6-month) clinical study showed that the blood pressure reductions were independent of the baseline PRA and were greater in patients that received aliskiren-based therapy, rather than ramipril-based therapy (16). These findings suggest that the blood-pressure–lowering effect of aliskiren might not be influenced only by PRA derived from the juxtaglomerular apparatus, but also by other factors. Since aliskiren has a high affinity for renal tissues, renin activity in renal tissues other than the juxtaglomerular apparatus might also contribute to the effectiveness of aliskiren.

9. Does aliskiren exert a possible adverse effect via (pro)renin receptor–dependent intracellular signals?

The binding of renin and prorenin to the (pro)renin receptor triggers two major pathways: the angiotensin II–dependent pathway as a result of the enzymatic activation of renin and prorenin and the angiotensin II–independent intracellular pathway via the (pro)renin receptor (17). As shown in Fig. 3, although all RAS inhibitors including DRIs are capable of inhibiting the former pathway of the (pro)renin receptor, the latter pathway might be unaffected by the DRI aliskiren since aliskiren reportedly did not influence (pro)renin receptor–dependent p38MAPK signals in cardiomyocytes (18). Accordingly, the elevated levels of renin and prorenin during treatment with aliskiren should stimulate (pro)renin receptor–dependent intracellular signals. However, since ARBs and ACE inhibitors elevate plasma levels of renin and prorenin, the increased plasma levels of renin and prorenin by these drugs would also stimulate (pro)renin receptor–dependent intracellular signals. If the adverse effects occur with aliskiren, such adverse effects would be common to ARB and ACE inhibitors. In addition, there has been no direct evidence suggesting that (pro) renin receptor–dependent intracellular signals contribute to pathogenesis in patients. Only a study using angiotensin II type 1–receptor-deficient mice provided indirect evidence suggesting a contribution to the development of

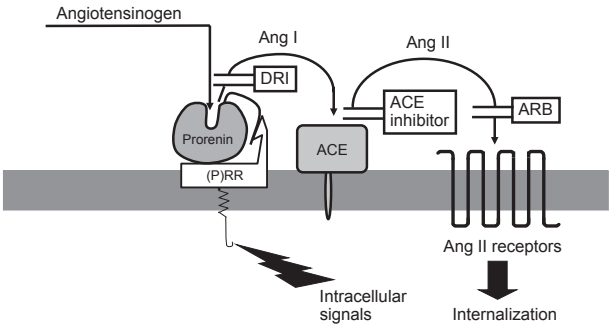

Fig. 3. Effects of direct renin inhibitor (DRI), angiotensin-converting enzyme (ACE) inhibitor, and angiotensin (Ang) type 1–receptor blocker (ARB) on the function of the (pro)renin receptor [(P)RR].

diabetic nephropathy (19). In addition, Feldman et al. showed that treatment with aliskiren significantly down-regulated the renal expression of the (pro)renin receptor in diabetic rats (5), probably because of its negative feedback regulation as a result of the elevated plasma levels of renin and prorenin (20, 21). However, the renal expression of the (pro)renin receptor was reported to be up-regulated under conditions with high plasma renin levels (22). Thus, the in vivo expression of the (pro)renin receptor is complicated and should be determined in each patient. Both development of the method to evaluate (pro)renin receptor expression and assessment of the relationship between (pro)renin receptor expression levels and cardiovascular mortality/morbidity will be required to clarify whether aliskiren exerts an adverse effect via the (pro)renin receptor in patients.

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References

1 Latini R, Masson S, Anand I, Salio M, Hester A, Judd D, et al. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. Eur Heart J. 2004;25:292–299.
2 Wood JM, Stanton JL, Hofbauer KG. Inhibitors of renin as potential therapeutic agents. J Enzyme Inhib. 1987;1:169–185.
3 Wood JM, Maibaum J, Rahuel J, Grutter MG, Cohen N-C, Rasetti V, et al. Structure-based design of aliskiren, a novel orally effective renin inhibitor. Biochem Biophys Res Commun. 2003;308: 698–705.
4 Palatini P, Jung W, Shlyakhto W, Botha J, Bush C, Keefe DL. Maintenance of blood-pressure-lowering effect following a missed dose of aliskiren, irebesartan or ramipril: results of a randomized, double-blind study. J Hum Hypertens. 2009;24: 93–103.
5 Feldman DL, Jin L, Xuan H, Contrepas A, Zhou Y, Webb RL,

et al. Effects of aliskiren on blood pressure, albuminuria, and (pro)renin receptor expression in diabetic TG(mRen-2)27 rats. Hypertension. 2008;52:130–136.
6 Fisher NDL, Hollenberg NK. Renin inhibition: what are the therapeutic opportunities? J Am Soc Nephrol. 2005;16:592–599.
7 Parving H-H, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med. 2008;358:2433–2446.
8 Gradman AH, Schmieder RE, Lins RL, Nussberger J, Chiang Y, Bedigian MP. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. Circulation. 2005;111: 1012–1018.
9 Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. Lancet. 2007;370:221–229.
10 McMurray JJV, Pitt B, Latini R, Maggioni AP, Solomon SD, Keefe DL, et al. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. Circ Heart Fail. 2008;1:17–24.
11 Stanton A, Jensen C, Nussberger J, O'Brien E. Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. Hypertension. 2003;42:1137–1143.
12 Nussberger J, Gradman AH, Schmieder RE, Lins RL, Chiang Y, Prescott MF. Plasma renin and the antihypertensive effect of the orally active renin inhibitor aliskiren in clinical hypertension. Int J Clin Pract. 2007:61:1461–1468.
13 O'Brien E, Barton J, Nussberger J, Mulcahy D, Jensen C, Dicker P, et al. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. Hypertension. 2007;49:276–284.
14 Sealey JE, Laragh JH. Aliskiren fails to lower blood pressure in patients who have either low PRA levels or whose PRA falls insufficiently or reactively rises. Am J Hypertens. 2009;22: 112–121.
15 Stanton AV, Dicker P, O'Brien ET. Aliskiren monotherapy results in the greatest and the least blood pressure lowering in patients with high- and low-baseline PRA levels, respectively. Am J Hypertens. 2009;22:954–957.
16 Anderson K, Weinberger MH, Constance CM, Ali MA, Jin J, Prescott MF, et al. Comparative effects of aliskiren-based and ramipril-based therapy on the renin system during long-term (6 months) treatment and withdrawal in patients with hypertension. JRAAS. 2009;10:157–167.
17 Ichihara A, Sakoda M, Kurauchi-Mito A, Narita T, Kinouchi K, Itoh H. Drug discovery for overcoming chronic kidney disease (CKD): new therapy for CKD by a (pro)renin-receptor-blocking decoy peptide. J Pharmacol Sci. 2009;109:20–23.
18 Saris J, 'tHoen P, Garrelds I, Dekkers D, denDunnen J, Lamers J, et al. Prorenin induces intracellular signaling in cardiomyocytes independently of angiotensin II. Hypertension. 2006;48:564–571.
19 Ichihara A, Suzuki F, Nakagawa T, Kaneshiro Y, Takemitsu T, Sakoda M, et al. Prorenin receptor blockade inhibits development of glomerulosclerosis in diabetic angiotensin II type 1a receptor deficient mice. J Am Soc Nephrol. 2006;17:1950–1961.
20 Huang Y, Wongamorntham S, Kasting J, McQuillan D, Owens RT, Yu L, et al. Renin increases mesangial cell transforming growth factor-b1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms. Kidney Int. 2006;69: 105–113.
21 Huang Y, Noble N, Zhang J, Xu C, Border W. Renin-stimulated TGF-beta1 expression is regulated by a mitogen-activated protein kinase in mesangial cells. Kidney Int. 2007;72:42–52.
22 Krebs C, Hamming I, Sadaghiani S, Steinmetz OM, Meyer-Schwesinger C, Fehr S, et al. Antihypertensive therapy upregulates renin and (pro)renin receptor in the clipped kidney of Goldblatt hypertensive rats. Kidney Int. 2007;72:725–730.