REVIEW ARTICLE

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Aliskiren – an antihypertensive renin inhibitor in the treatment of patients with chronic kidney disease

Krzysztof Łukawski[1,2], Iwona Baranowicz-Gąszczyk[3]

[1] *Department of Physiopathology, Institute of Rural Health, Lublin, Poland*
[2] *Department of Pathophysiology, Medical University, Lublin, Poland*
[3] *Department of Nephrology, Medical University, Lublin, Poland*

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Abstract

Introduction. The renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathogenesis of hypertension, cardiovascular diseases (CVDs) and chronic kidney disease (CKD). Drugs affecting the RAAS system, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), are commonly used in the treatment of hypertension and heart failure. These drugs are also effective in reducing proteinuria and may, at least, delay end-stage renal disease in both diabetic and non-diabetic proteinuric CKD. However, novel drugs are needed to more effectively suppress the RAAS system and the progression of CKD. Aliskiren is the first direct renin inhibitor which has been approved for the treatment of hypertension. Additionally, a number of clinical studies have shown the antiproteinuric effect of aliskiren.

Objective. This review focuses on the antihypertensive and antiproteinuric effects of aliskiren in patients with CKD. The pharmacology of aliskiren in these patients is also provided.

Conclusions. Aliskiren-based hard endpoint large trials in non-diabetic nephropathy are needed in order to clarify the use of aliskiren in CKD patients.

Key words

aliskiren, chronic kidney disease, clinical studies

INTRODUCTION

According to the World Health Organization (WHO), more people die annually from cardiovascular diseases (CVDs) than from any other cause. Risk factors for CVDs are tobacco use, unhealthy diet and obesity, physical inactivity, hypertension, diabetes and raised lipids. Preventing or treating these factors can reduce the cardiovascular risk [1]. Cardiovascular disease is a major cause of morbidity and mortality among patients with chronic kidney disease (CKD) [2]. In 2012, CKD has been defined by Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group as abnormalities of kidney structure or function, present for > 3 months, with implications for health, and CKD has been classified based on cause, GFR (glomerular filtration rate) and albuminuria category [3]. CKD with prevalence ranging from 8% to 16% worldwide and its complications including increased all-cause cardiovascular mortality, kidney-disease progression, acute kidney injury, cognitive decline, anaemia, mineral and bone disorders, is a global public health issue, but awareness is low among patients and health-care providers [4].

It is widely accepted that the activity of the renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathogenesis of hypertension, CVD and CKD. Actually, a lot of hypertensive patients suffer from increased arterial blood pressure as a result of increased activity of the RAAS [5]. Renin, an aspartyl protease enzyme, is produced by the juxtaglomerular apparatus of the kidney and cleaves its substrate, angiotensinogen, forming the inactive decapeptide angiotensin I (ANG I). Renin is considered a key enzyme of the RAAS due to the rate-limiting nature of its hydrolytic activity on the precursor angiotensinogen [6]. From circulating ANG I, angiotensin-converting enzyme (ACE), a zinc metalloprotease, catalyzes the formation of angiotensin II (ANG II), a potent vasoconstrictor [7]. In kidney, ANG II basically induces vasoconstriction in the efferent glomerular arteries leading to glomerular hypertrophy [8] and vasoconstriction of glomerular capillaries, which affects the glomerular filtration rate [9]. ANG II has multiple biological effects in addition to causing vasoconstriction of arteries and modulating blood pressure, including acting as a proinflammatory mediator at all stages of the cardiovascular and renal disease [10]. The actions of ANG II are mediated by AT_1 and AT_2 receptors, which are seven transmembrane glycoproteins with 30% sequence similarity [11]. ANG II induces acute vasoconstriction by binding mainly to AT_1 receptors while AT_2 receptors activation is thought to have the opposite effects of those mediated by the AT_1 receptors, which are beneficial to the cardiovascular system and help protect target organs from damage [10]. By blocking the formation of ANG II in blood, ACE inhibitors significantly lower systemic vascular resistance, lower blood pressure, and improve cardiac function [12]. Apart from blocking the actions of ANG II that are mediated by AT_1 receptors, angiotensin II receptor blockers (ARBs) may induce end-organ protection by leaving AT_2 receptors free to be activated by ANG II [10]. ACE inhibitors and ARBs are routinely used drugs in the treatment of hypertension and heart failure [10, 12]. Furthermore, these drugs are also effective in reducing

Address for correspondence: Krzysztof Łukawski, Department of Physiopathology, Institute of Rural Health, Jaczewskiego 2, 20-090 Lublin, Poland
E-mail: lukaw@mp.pl.

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proteinuria and may delay or even prevent end-stage renal disease (ESRD) in both diabetic and non-diabetic proteinuric CKD [13]. Clinical studies showed a correlation between reduction in proteinuria and renal or cardiovascular events, and some of them reported that stronger RAAS inhibition obtained by ACE inhibitors and ARBs combination therapy could reduce proteinuria and delay ESRD even more effectively than monotherapy with these drugs [14]. However, the concept of using dual RAAS blockade is currently under scrutiny following recent disappointing results from major hard endpoint trials [14, 15].

OBJECTIVE

As the blockade of the RAAS system with ACE inhibitors or ARBs has been proven to be a powerful tool for treating hypertension and heart failure [10], and slow or prevent progression of chronic proteinuric nephropathies [14], the research on drugs affecting the RAAS system continues. Aliskiren is the first orally bioavailable direct renin inhibitor approved for the treatment of hypertension [16]. By inhibiting renin, aliskiren blocks the conversion of angiotensinogen to ANG I, which subsequently results in a reduction in ANG II concentrations. Unlike ACE inhibitors and ARBs, which reactively stimulate an increase in plasma renin activity, aliskiren suppresses the effects of renin and leads to a reduction in plasma renin activity [17]. This review focuses on the pharmacology and therapeutic approach to aliskiren in patients with CKD.

DISCUSSION

Pharmacology of aliskiren. Aliskiren has the chemical structure 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-methoxypropoxyl-]phenyl)-octanamide, with a molecular weight of 551.8 g/mol. The active substance of aliskiren is a hemifumarate salt [18]. Aliskiren is a highly potent inhibitor of human renin *in vitro* (concentration of aliskiren that produces 50% inhibition of renin- 0.6 nmol/L) [16]. Aliskiren appears to bind to both the hydrophobic S1/S3-binding pocket and to a large, distinct subpocket that extends from the S3-binding site towards the hydrophobic core of renin [18]. Aliskiren is rapidly absorbed following oral administration, with maximum plasma concentrations reached within 1–3 hours and its bioavailability is 2.6% in humans [16]. The plasma half-life of aliskiren showed a slow terminal elimination at 23–70 h, depending on the duration of the post-dose sampling period [18]. Aliskiren achieves its steady state blood levels in around 7 days with once daily administration [18]. The binding of aliskiren to plasma proteins is moderate (47–51%) and is independent of the concentration. Aliskiren is eliminated through the hepatobiliary route as unchanged drug and, to a lesser extent, through oxidative metabolism by cytochrome P450 (CYP) 3A4 [16]. It is available as 150 mg and 300 mg tablets (trade names: Rasilez, Tekturna).

In patients with mild, moderate or severe renal impairment (creatinine clearance [CL_{CR}] 50–80, 30–49 and <30 mL/minute, respectively) receiving oral aliskiren 300 mg once daily, the aliskiren AUC (area under the plasma concentration-time curve) and C_{max} (maximum plasma drug concentration) values at steady state were 1.5- to 2-fold higher than the values in matched healthy subjects. Changes in exposure did not correlate with the severity of renal insufficiency, as assessed by CL_{CR} [19]. The accumulation of aliskiren at steady state (indicated by the AUC from 0 and 24 hours [AUC_{24}] on day 7 vs day 1) was similar in healthy subjects (1.79) and each subgroup of subjects with renal impairment (1.39–1.99). The authors conclude that exposure to aliskiren is increased by renal impairment, but does not correlate with the severity of renal insufficiency (CL_{CR}); therefore, adjustment of the starting dose of aliskiren is not required in patients with renal impairment [19]. However, caution is advised in patients with severe renal impairment, especially those with sodium depletion [16]. Some clinical studies have reported symptomatic hypotension in patients with CKD following aliskiren treatment [20].

Clinical studies on aliskiren in patients with CKD. There have been a number of studies evaluating the antihypertensive and antiproteinuric effects of aliskiren in patients with CKD. Persson et al. [21] reported that 15 patients with diabetic nephropathy (eGFR: 75.5 mL/min/1.73 m^2) receiving aliskiren (300 mg) and furosemide daily for 28 days, followed by a 4-week withdrawal period, exhibited reduced mean 24 h systolic blood pressure (SBP) by 6–8 mmHg on days 7, 14 and 28, compared with baseline. Aliskiren treatment was associated also with a significant decrease in the mean urinary albumin-to-creatinine ratio (UACR) throughout the treatment period, with a maximum reduction of 44% at the end of the treatment (days 26–28) [21]. The AVOID trial (Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy) showed that treatment with aliskiren (dose titrated to 300 mg daily) for 6 months, in addition to losartan (100 mg/kg), reduced the UACR by 20%, compared with placebo, with a reduction of 50% or more in 24.7% of the patients who received aliskiren, compared with 12.5% of those who received placebo [22]. The eGFR values for hypertensive patients with diabetic nephropathy enrolled for this study were as follows: 68.5 mL/min/1.73 m^2 (aliskiren group) and 66.8 mL/min/1.73 m^2 (placebo group). Differences in BP between the groups were small by the end of the study period; SBP was 2 mmHg and DBP was 1 mmHg lower in the aliskiren group [22]. Ito et al. [23] reported that in Japanese hypertensive patients with renal dysfunction (serum creatinine: 1.3–3.0 mg/dL in males, 1.2–3.0 mg/dL in females) treated with aliskiren (75–300 mg once daily), the mean reduction of BP from baseline to week 8 endpoint was 13.9 ±16.6 and 11.6±9.7 (mean ± S.E.M.) mmHg for SBP and DBP, respectively. Additionally, 65% patients achieved blood pressure response (mean DBP < 90 or a 10 mmHg decrease, or mean SBP < 140 or a 20 mmHg decrease), and 30% achieved blood pressure control (mean SBP < 140 mmHg and mean DBP < 90mmHg) at the week 8 endpoint [23]. Persson et al. [24] examined the antiproteinuric effect of increasing doses of aliskiren (up to 600 mg) in hypertensive patients with diabetic nephropathy (eGFR: 85 mL/min/1.73 m^2). Treatment with aliskiren 150, 300 and 600 mg daily reduced urinary albumin excretion rate by 36, 48 and 52%, and 24 h SBP by 4.5, 8.0 and 9.2 mmHg, respectively, compared with placebo. The authors found that there was no improved antiproteinuric effect of aliskiren at the dose 600 mg daily, compared with the maximal recommended antihypertensive dose of 300 mg

Table 1. Clinical studies on antihypertensive and antiproteinuric effects of aliskiren in patients with CKD

Author/study	Year	Treatment group	Population	Ref.
Persson et al.	2008	aliskiren (300 mg) + furosemide	diabetic nephropathy	[21]
AVOID	2008	aliskiren (150–300 mg) + losartan (100 mg)	diabetic nephropathy	[22]
Ito et al.	2010	aliskiren (75–300 mg) + diuretics	hypertension in non-diabetic and diabetic nephropathy	[23]
Persson et al.	2010	aliskiren (150–600 mg) + furosemide	diabetic nephropathy	[24]
Morishita et al.	2011	aliskiren (150 mg) + existing ACE inhibitor, ARB, calcium blocker, ß-blocker, α-antagonist or centrally acting agents	hypertension in hemodialysis-dependent CKD	[25]
Siddiqi et al.	2011	aliskiren (300 mg) + diuretics	hypertension in non-diabetic nephropathy	[26]
Moriyama et al.	2012	aliskiren (150 mg) + olmesartan (10–40 mg)	non-diabetic nephropathy	[27]
Nakamura et al.	2012	aliskiren (150 mg) + olmesartan (40 mg)	non-diabetic nephropathy	[28]
Lizakowski et al.	2012	aliskiren (150–300 mg)	non-diabetic nephropathy	[29]
Tang et al.	2012	aliskiren (150–300 mg) + losartan (100 mg)	IgA nephropathy	[30]
Abe et al.	2013	aliskiren (150–300 mg) + existing antihypertensives	diabetic and non-diabetic nephropathy	[31]
ALTITUDE	2012	aliskiren (300 mg) + existing ACE inhibitor or ARB	diabetic and non-diabetic nephropathy	[32]
Woo et al.	2013	aliskiren (150 mg) + losartan (100 mg)	chronic glomerulonephritis	[33]
Ohsawa et al.	2013	aliskiren (average dose 176.5 mg) + existing antihypertensives	diabetic and non-diabetic nephropathy	[35]
Woo et al.	2014	aliskiren (150 mg) + losartan (100 mg)	chronic glomerulonephritis	[34]
Wu et al.	2014	aliskiren (150 mg) + ARB or ACE inhibitor	diabetic and non-diabetic nephropathy	[36]
Kuriyama et al.	2014	aliskiren (150 mg) + existing antihypertensives	hypertension in hemodialysis-dependent CKD	[37]
Soji et al.	2015	aliskiren (150 mg) + existing antihypertensives	diabetic and non-diabetic nephropathy	[38]
Tani et al.	2016	aliskiren (300 mg) + existing antihypertensives	hypertension in diabetic and non-diabetic nephropathy	[39]

Description and main results of the studies are provided in the text.

[24]. In 2011, Morishita et al. [25] published a paper on effects of aliskiren on BP and the predictive biomarkers for CVD in hemodialysis (HD)-dependent CKD patients with hypertension. Aliskiren (150 mg daily) added to other antihypertensives, after 8 weeks treatment, reduced SBP from 169.0 ± 20.1 to 153.7 ± 19.6 mmHg and DBP from 78.1 ± 12.0 to 73.0 ± 13.6 mmHg, and inhibited the following biomarkers: natriuretic peptide (BNP), high-sensitivity C-reactive protein (hs-CRP) and diacron-reactive oxygen metabolite (d-ROM) [25]. Siddiqi et al. [26] reported that in hypertensive CKD patients (eGFR: 57.6 mL/min/1.73 m^2), aliskiren (300 mg daily) lowered SBP and DBP from 147 ±10 to 120±8 mmHg and from 96±7 to 83±7 mmHg, respectively, after 6 weeks treatment. Aliskiren additionally reduced the sympathetic activity quantified by assessment of muscle sympathetic nerve activity [26]. Moriyama et al. [27] showed that daily 150 mg aliskiren addition to olmesartan (10–40 mg) after 16 weeks, decreased the urinary protein-to-creatinine ratio by about 40% in 10 CKD patients (eGFR: 30–90 mL/min) without affecting BP. The authors suggest that the antiproteinuric effect of aliskiren is independent from its antihypertensive effect [27]. On the other hand, Nakamura et al. [28] reported that the combined therapy with aliskiren (300 mg daily) and olmesartan (40 mg daily) for 6 months decreased SBP and SBP, proteinuria, and urinary excretion level of L-fatty acid binding protein (L-FABP), which is a marker of tubular injury, in non-diabetic stage I or II CKD patients more than olmesartan or aliskiren monotherapy. In turn, Lizakowski et al. [29] compared the antiproteinuric and hypotensive effects of aliskiren with perindopril in non-diabetic CKD patients. Monotherapy with aliskiren (150–300 mg daily) or perindopril (5–10 mg daily), in equivalent hypotensive doses, decreased proteinuria at a similar level. Aliskiren (150 mg) and perindopril (10 mg) caused equal hypotensive efficacy, whereas aliskiren (300 mg) was superior to perindopril (10 mg) for both SBP and DBP [29]. Tang et al. [30] reported that aliskiren (150 mg daily for 1 month, followed by 300 mg daily for 11 months) added to losartan (100 mg daily) in CKD patients (eGFR: 40.3 mL/min/1.73 m^2) with immunoglobulin A nephropathy (IgAN) and significant residual proteinuria, reduced the mean urinary protein-to-creatinine ratio by 26.3% after 12 months of treatment. Abe et al. [31] examined the antiproteinuric and hypotensive effects of aliskiren in patients with both diabetic and non-diabetic nephropathy taking other antihypertensive agents, e.g. calcium channel blockers, ARBs, ACE inhibitors, ß-blockers, α-antagonists, loop or thiazide diuretics. Subjects divided into 3 subgroups according to CKD stage (stage 1/2: eGFR ≥ 60 ml/min/1.73 m^2; stage 3: 60 > eGFR > 30 ml/min/1.73 m^2; stage 4: 30 > eGFR > 15 ml/min/1.73 m^2), were treated with aliskiren 150 mg/day, which was increased to 300 mg/day for a 24-week study period. Aliskiren effectively reduced albuminuria and both SBP and DBP, regardless of the presence or absence of diabetes mellitus or the stage of CKD [31].

At the end of 2012, the important report on ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) study was published [32]. Aliskiren (300 mg daily), when added to an ACE inhibitor or ARB in patients with type 2 diabetes and CKD, did not reduce cardiovascular or renal outcomes, compared with placebo, and resulted in an increased number of adverse events, i.e. an increased incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension after 18–24 months of treatment [32]. Woo et al. [33], based on their retrospective analysis, suggested that the findings of the ALTITUDE study would also apply to non-diabetic CKD patients. Patients with chronic glomerulonephritis (eGFR: 48–49 mL/min/1.73 m^2) subjected to combined aliskiren (150 mg/day) with losartan (100 mg/day) therapy, showed reduced proteinuria and BP as efficacious as aliskiren (150 mg/day) or losartan (200 mg/day)

alone, but the incidence of hyperkalaemia was the highest (14.2%) in the combined aliskiren and losartan group [33]. Later, Woo et al. [34] repeated their suggestion about the lack of beneficial effects and possible adverse effects of the addition of aliskiren to standard therapy with RAAS system blockade in non-diabetic CKD patients, based on a randomised trial in 155 patients with non-diabetic CKD (47–49 mL/min/1.73 m^2). They examined the effects of aliskiren (150 mg/day) combined with losartan (100 mg/day), aliskiren (150 mg/day) alone, and losartan (100 mg/day) alone, on BP and proteinuria in CKD patients with chronic glomerulonephritis. The combination therapy with aliskiren and losartan was as efficacious as aliskiren alone and losartan alone. Moreover, the incidence of hyperkalaemia was the highest (37.2%) in the combined aliskiren and losartan group, and there was one patient who developed a non-fatal stroke in this group while the other two groups had none [34]. Ohsawa et al. [35] compared the effects of aliskiren (average dose of 176.5 daily) with benazepril, when added to ARB and other antihypertensives, on ambulatory BP and cardiorenal function in CKD (eGFR: 45.7–46.3 mL/min/1.73 m^2). The add-on therapy with either aliskiren or benazepril significantly decreased clinic BP in hypertensive CKD patients who had already been treated with ARB, but the aliskiren add-on therapy was more effective in decreasing albuminuria. The aliskiren add-on therapy was well-tolerated in all of the patients, without any significant adverse events [35].

Opposite conclusions to the ALTITUDE study [32] and the study by Woo and colleagues [34] were reached by Wu et al. [36] in their reports on CKD patients (eGFR: 37.4 mL/min/1.73 m^2). According to them, adding aliskiren to existing therapy with RAAS system blockade in both diabetic and non-diabetic CKD patients, had a favourable effect on reducing residual proteinuria and inadequately controlled BP, irrespective of CKD stage. Actually, the combined treatment with aliskiren (150 mg daily) and ACE inhibitor or ARB significantly reduced urine total protein-to-creatinine ratio by 23% and mean BP by 7.9 mmHg, and no significant changes in serum potassium level was noted after 6 months of treatment [36]. Kuriyama et al. [37] investigated the antihypertensive effect of aliskiren (150 mg/day) in comparison with amlodipine (5 mg/day) as add-on therapy in CKD patients undergoing HD. In contrast to other reports (e.g. [25]), aliskiren did not reduce BP effectively while amlodipine did so. On the other hand, there was a significant decrease in atrial natriuretic peptide (ANP) in the aliskiren group, but not in the amlodipine group, suggesting future studies on the role of aliskiren in improving cardiovascular events in HD patients [37].

Soji et al. [38] examined the efficacy of add-on therapy of aliskiren (150 mg daily) to ARB on renal outcomes in ESRD (eGFR: 13.7 mL/min/1.73 m^2). This study showed that aliskiren combined with ARB did not affect the incidence of starting dialysis or doubling of serum creatinine in patients with ESRD. The authors concluded that the add-on therapy of aliskiren to ARB is not beneficial in these patients [38]. In 2016, Tani et al. [39] reported that aliskiren (300 mg daily) is effective as add-on therapy in patients with poorly controlled hypertension, including patients with CKD. Furthermore, they suggested that by carefully monitoring the renal function and making adjustments to the drugs used, aliskiren can be safely used even in patients receiving other RAAS inhibitors to treat diabetes mellitus or CKD.

Other issues related to aliskiren treatment. Clinical studies showed that aliskiren lowers SBP and DBP both in younger and elderly hypertensive patients [40], and that greater antihypertensive effect is achieved when given aliskiren in combination with a thiazide diuretic, other blockers of the RAAS system, or a calcium antagonist [41]. The APOLLO trail (The Aliskiren Prevention of Later Life Outcomes) showed that the administration of the combination of aliskiren and hydrochlorothiazide or amlodipine, and used other background antihypertensive drugs (mean of 1.5 drugs), was associated with an anticipated SBP reduction of 10 mmHg and appeared to be safe in the elderly [42]. Recently, results from the ASTRONAUT trial (Aliskiren Trial on Acute Heart Failure Outcomes) were published. Among patients hospitalized for worsening chronic heart failure with reduced left ventricular ejection fraction, adding aliskiren (150–300 mg/day) to standard therapy did not reduce cardiovascular death or heart failure rehospitalization at 6 months or 12 months after discharge. Moreover, the rates of hyperkalaemia, hypotension, and renal impairment/renal failure were higher in the aliskiren group compared with placebo [43]. According to the European Society of Cardiology – Heart Failure Association, aliskiren is not presently recommended as an alternative to an ACE inhibitor or ARB in patients with heart failure [44]. Aliskiren also did not find a place in the recommendations of the Polish Society of Hypertension [45]. New recommendations for the use of aliskiren in kidney diseases from the nephrology point of view are awaited.

CONCLUSIONS

Although first studies on aliskiren suggested that the drug has beneficial effects for renoprotection and BP control in CKD, and that adding aliskiren to existing therapy with RAAS system blockade in patients with CKD may have a favourable effect on proteinuria or BP, the unexpected results of the ALTITUDE trial brought a new insight to the use of aliskiren in CKD. Based on these findings, the European Medicines Agency recommended that aliskiren-containing medicines should be contraindicated in patients with diabetes or moderate to severe renal impairment who take ACE inhibitors or ARBs [46]. Aliskiren-based hard endpoint large trials in non-diabetic nephropathy are needed in order to clarify the use of aliskiren in CKD patients.

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