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Aliskiren in the treatment of renal disease; a narrative review

Bijan Roshan¹, Tella Sadighpour^{2*}

Abstract

The renin–angiotensin–aldosterone system (RAAS) cascade has a significant effect on several systems. Angiotensin II (AngII) has appeared as not only a vasoactive peptide but also as a multifunctional cytokine that displays several non-hemodynamic properties beyond renal hemodynamic properties. The kidney includes total components of the RAAS such as aldosterone and AngII not only adjust renal hemodynamics and reabsorption of sodium but also activating various inflammatory and fibrotic responses. Inhibition of the RAAS is one of the most potent methods to impede the development of renal diseases such as chronic kidney disease (CKD) and its related problems such as high blood pressure and heart disorders. Aliskiren, an octanamide, nonpeptide piperidine, orally, active, first commercially available, and direct renin inhibitor (DRI), impedes RAAS and operates by attaching to the active sites of renin and may be effective for the management of renal disease because of blocking the RAAS at its point of start and most sensitive step. Based on numerous studies, aliskiren is the greatest powerful inhibitor of AngII extents among RAAS inhibitors, even though it is unable to prevent the (pro) renin receptor-mediated extracellular signal-regulated kinase 1 and 2 (ERK1/2) activations. In this review, it is described renoprotective effects of aliskiren against different types of nephropathy such as acute kidney injury, diabetic nephropathy, and hypertensive nephropathy.

Keywords: Renin–angiotensin–aldosterone system, Angiotensin II, Direct renin inhibitor, Chronic kidney disease, Acute kidney injury, Hypertensive nephropathy, Aliskiren

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Introduction

The renin–angiotensin–aldosterone system (RAAS) cascade takes a significant part in numerous pathophysiologic systems are combined with hypertensive, proteinuria, fibrosis, inflammation, production of reactive oxygen species, induction of chemokine and growth factors, apoptosis, and inhibition of nitric oxide (NO) synthesis. Angiotensin II (AngII) has appeared as not only a vasoactive hormone but also as a multifunctional cytokine which displays several non-hemodynamic properties beyond renal hemodynamic characteristics, for example, capable of prompting cellular growth, proliferation, cellular differentiation and renal fibrogenic that is mediated by other factors, such as transforming growth factor beta (TGF- β) (1). The kidney includes total components of the RAAS such as aldosterone and AngII not only adjusting renal hemodynamics and renal reabsorption of sodium but also activating numbers of inflammatory and fibrotic responses. Inhibition of the RAAS is one of the most potent methods to impede the development of renal diseases such as chronic kidney disease (CKD) and its related problems such as high blood pressure and heart disorders (cardiovascular). Numerous medical follows up have proved that suppression of RAAS

by angiotensin I-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) could impede the development of renal diseases (Figure 1).

Methods

Search strategy

For this review, we searched Web of Science, EBSCO, Scopus, PubMed/Medline, DOAJ (Directory of Open Access Journals), Embase, and Google Scholar, using various keywords including renin–angiotensin–aldosterone system, angiotensin ii, direct renin inhibitor, chronic kidney disease, acute kidney injury, hypertensive nephropathy and aliskiren

Direct renin inhibitor and its role of in progressive nephropathy

Previous studies suggested that aliskiren, an octanamide, a nonpeptide piperidine, orally, active, first commercially available, and direct renin inhibitor (DRI), impedes RAAS and performs by attaching bonds to the active S2 and S3 subsites of renin and may be impressive for the controlling of CKD and its related problems. Really, the reaction between renin and angiotensinogen is the rate-limiting stage of the RAAS and is extremely controlled

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■ Implication for health policy/practice/research/medical education

Aliskiren may have protective effects against different types of nephropathy such as acute kidney injury, diabetic nephropathy and hypertensive nephropathy.

(2). Aliskiren prevents the activity of the renin enzyme by attaching bonds to its catalytic sites, thus hindering the RAAS at its spot of start and the most sensitive step that causes the largest shift in the general rate. Therefore, aliskiren offers advantages in the management of blood pressure and cardiovascular actions rather than other common RAAS-impeding mediators (3,4). This is an important outcome since many patients who get ARBs or ACEIs still have progressive renal disease. The suppression of renin by aliskiren could lead to more perfect prevention of the RAAS, and decrease renin secretion by negative feedback control by Ang II when compared with ACEI and ARB. Production of all angiotensin peptides such as angiotensin I (AngI), AngII, and aldosterone reduce, and their hemodynamic outcomes are suppressed by aliskiren while ARBs lead to a rise in all angiotensin peptides and ACEIs elevate the concentration of AngI and decrease the concentration of AngII in plasma. Aliskiren inhibits renal vasoconstriction, reduces the filtration fraction (FF: fraction of the glomerular filtration rate [GFR] to the renal plasma flow is normally about 20%), and decreases sodium and water absorption (5). Aliskiren directly inhibits plasma renin activity (PRA) by almost 50-80%, unlike the suppression of RAAS by ACEIs and ARBs which cause an active increase in PRA (2,6). Aliskiren has blood pressure reducing effect; however, the decrease in albuminuria was held after adjusting blood pressure. Aliskiren supplies antihypertensive potential alone (monotherapy) and in combination with other inhibitors of RAAS (7). Moreover, aliskiren in combination therapy can neutralize the addition in PRA prompted by ACEIs, ARBs, calcium channel blockers and diuretics. Additionally, it impedes prorenin and renin activity whereas prorenin and renin levels remain high (8).

(Pro)renin receptor

While aliskiren decreases PRA, the concentration of the renin enzyme increases to high levels (9). High renin

concentrations could likely interact with the (pro) renin receptor. This interaction could start extracellular signal-regulated kinase 1 and 2 (ERK1/2) signaling, activates TGF- β , and other possibly serious results. Attaching bonds of renin to (pro)renin receptor adds its catalytic activity. Above all, prorenin (inactive) becomes catalytically active after binding to this receptor and therefore can assist in AngII formation. This may have been of specific significance in syndromes for example diabetes where prorenin is expressively raised and shows 95% of plasma renin. Stimulation of the (pro) renin receptor in renal cells also triggers mitogen-activated protein kinase (MAPK), ERK 1/2 and numerous fibrosis/ atherosclerosis agents for instance TGF- β and plasminogen activating inhibitor (PAI-1) (10).

Is blocked binding of (pro)renin to (pro)renin receptor and finally AngII formation with aliskiren? Some of the studies, clearly display that preventing the active site of (pro)renin does not change their binding to (pro)renin receptor or following ERK1/2 activation while some other studies proposed that aliskiren through blocking the catalytic function of renin inhibits binding of the renin to (pro)renin receptor (11,12). In summary, there are much complexity and confusion relating to whether the aliskiren, reduces the binding of renin to the (pro) renin receptor and inhibits ERK activation. Based on many studies, aliskiren is the greatest powerful inhibitor of AngII extents among RAAS inhibitors, even though it is unable to prevent the (pro)renin receptor-mediated ERK1/2 activations (13).

Aliskiren is approved to induce the following properties:

A. blood pressure decreasing

Aliskiren was accepted as the medication for high blood pressure. This indicated the curative adjustment of blood pressure of aliskiren by preventing the RAAS at its start point and at the most sensitive step (14). Compared to placebo, aliskiren has a dose-dependent decreasing effect for both systolic blood pressure (SBP) and diastolic blood pressure (DBP). The quantity of blood pressure lowering effect is equal to that for ACEI and ARBs.

B. Vasodilatory properties

Additionally, based on new information aliskiren advances NO bioavailability and upregulated endothelial

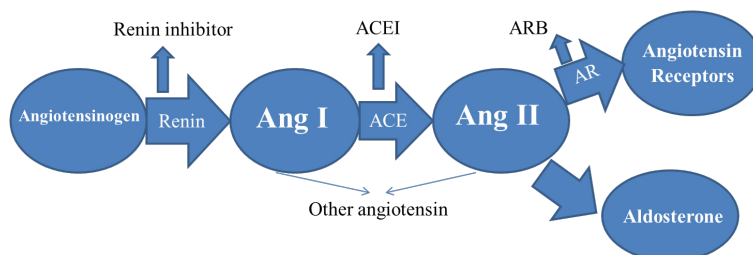


Figure 1. The scheme of renin–angiotensin–aldosterone system (RAAS) and RAAS inhibitors. Abbreviations: ACE: angiotensin-converting enzyme; ACEI: angiotensin-converting enzyme inhibitor, AR: angiotensin-II-receptor ARB: angiotensin-II-receptor blocker, AngI: angiotensin I, and AngII: angiotensin II.

nitric oxide synthase (eNOS) in atherosclerosis models and impedes efferent arteriolar vasoconstriction (15,16).

C. Suppressed inflammatory characteristics

Aliskiren restricted renal appearance of TGF- β , collagen I and likely the (pro)renin receptor. In this regard, AngI, AngII and aldosterone quantities decrease, and related inflammatory effects are suppressed. Additionally, aliskiren treatment in hydronephrosis increased water channel renal aquaporins (AQP2) expression, and expressively reduced gene expression of numerous proinflammatory cytokines, for example, TGF- β and tumor necrosis factor-alpha (TNF- α) (17).

D. Prevent progressive proteinuria

Aliskiren had an advantage in reducing proteinuria in diabetic patients having previously been medicated with ARB, recommending that aliskiren could have an additional effect beyond the suppression of the common RAAS. Aliskiren is shown dose-dependent antiproteinuric effects in diabetic and non-diabetic CKD patients (18). When patients with ACEIs or ARB have been treated, Ang II and aldosterone levels return to their pre-therapy levels. Possibly, this may be a substandard inhibition of RAAS activity inducing a deficient decrease of proteinuria. In comparison with before the start of treatment, aliskiren reduced both blood pressure and proteinuria more completely (7).

Aliskiren could have protective effects against different types of nephropathy that are summarized as follows.

Acute kidney injury

Substances-induced nephropathy has some RAAS

components. It is intended to study the effects of aliskiren for inhibition of acute kidney injury (AKI) because the RAAS biochemical reactions series begins with renin. Obtained outcomes recommended that aliskiren has renoprotective effects in contradiction to acute models (such as doxorubicin, adenine, calcineurin, gentamicin, contrast media, cyclosporine A and renal ischemia/reperfusion injury) that induced nephrotoxicity (Table 1). The mechanism of these renoprotective effects include inhibition of PRA, caspase-3 activity, hypoalbuminemia, anti-fibrotic, antihypertensive, anti-inflammatory, anti-apoptotic, decreased oxidative stress and reduced glomerular filtration damage.

Diabetic nephropathy

Medical trials have revealed that renal RAAS is stimulated initially in diabetic nephropathy, the most common reason for CKD. There is frequent PRA in diabetic patients (28). Diabetic nephropathy is regarded as one of the chief diabetic problems ($\geq 40\%$). These results recommend that the hyperglycemia state stimulated the renal RAAS, inducing progress of Ang II formation. In the high glucose condition, there is increased cleaved caspase-3. It is reported aliskiren reduced podocyte apoptosis in high glucose condition and suggesting a protective effect. Additionally, it is shown that aliskiren inhibited an increase in fibronectin mRNA and protein induced by high glucose condition in these cells. Short-range investigations have revealed that aliskiren, except for decreasing blood pressure, improves renal hemodynamics, increases the GFR, decreases arteriosclerosis, weakens endothelial damage and decreases proteinuria in diabetic nephropathy patients (29).

Table 1. Examined effect of aliskiren on numbers of substances induced AKI

Substances-induced AKI	Properties	Tested markers	Aliskiren effect	Ref.
Ischemia/reperfusion (I/R) injury	Sudden temporary impairment of the blood flow to kidney	Hemodynamic and tubular functions	Ameliorated the Ischemia/reperfusion effect on the renal blood flow, and reabsorption of sodium and gene expression of both NGAL and PAI-1	(19)
Gentamicin	Antibiotic used to treat several types of bacterial infections	Nephrotoxicity	Inhibition of inflammatory, profibrotic and apoptotic features like NF κ B and MAPK	(20)
Adenin	A purine derivative utilized in the synthesis of nucleic acids	Tubulointerstitial nephropathy	Prevention of PRA, weakening of oxidative stress, stimulation of gene expression of both NFE2L2 and eNOS, and inhibition of caspase-3	(21)
Tacrolimus or calcineurin	Immunosuppressive agent in kidney transplantation	Nephrotoxicity	Attenuated oxidative stress parameters for example malondialdehyde, glutathione and catalase	(22,23)
Contrast media	A substance used to increase the contrast of structures	Renal vasoconstriction	Reduced VEGF expression	(24)
Doxorubicin	Quinone-containing anthracycline antibiotic used to chemotherapy medication of cancer	Cardiotoxicity and nephrotoxicity	Decreased oxidative stress and prevention albuminemia, blood pressure and PRA	(25,26)
Cyclosporine A	An immunosuppressant medication and natural product	Hypertensive nephropathy	Antihypertensive, anti-inflammatory and anti-apoptotic behavior.	(27)

AKI, acute kidney injury; VEGF, vascular endothelial growth factor; PRA, plasma renin activity; NFE2L2, Nuclear factor erythroid-derived 2-like 2; eNOS, endothelial nitric oxide synthase; MAPK, mitogen-activated protein kinase.

Hypertensive nephropathy

Hypertensive nephropathy is located in the second degree after diabetic nephropathy in analytical incidences referred to induce end-stage renal disease. The RAAS plays an essential role in the pathogenesis of progress of arterial hypertension, CKD and cardiovascular disease. Increased afferent renal nerves and/or circulating AngII stimulate the sympathetic nervous system to increase hypertension. Several studies about hypertensive nephropathy are shown the renoprotective action of aliskiren, which might be because of its antihypertensive, anti-inflammatory and anti-apoptotic characteristics (21,30,31).

Inhibition of complement activation

Renin, in a manner identical to the C3 convertase, can cleave C3 into C3b and C3a (32). The cleavage into active C3b and C3a can be specifically blocked by aliskiren (32). This property of aliskiren can have potential therapeutic implications in complement-mediated renal diseases especially dense deposit disease and C3 glomerulonephritis (33). Multiple clinical trials are underway for this potential benefit.

Conclusion

The RAAS cascade performs main roles in many of the pathophysiologic systems associated with proteinuria, hypertensive, fibrosis, inflammation and etc. In monotherapy and combination therapy of RAAS, it seems spontaneously clear that suppression of RAAS at the most sensitive step is likely provided the probable best therapy. There are potent causes for performing medical trials that an ACEI or an ARB is associated with aliskiren in patients with proteinuria. Aliskiren could have protective effects against different types of nephropathy such as AKI, diabetic nephropathy and hypertensive nephropathy. Although for a period of time, it seemed that RAAS inhibitors development had been finished, it is now bright that the investigation for an orally bioaccessible renin inhibitor extends.

Authors' contribution

Conceptualization, Methodology, Validation, Formal Analysis, Research, Resources, Data Curation, Visualization, Supervision, Project Management: TS; Writing—Original Draft Preparation: BR and TS; Writing—Reviewing and Editing: BR and TS.

Conflicts of interest

The authors declare that they have no competing interest.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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