Aliskiren (Renin inhibitor)

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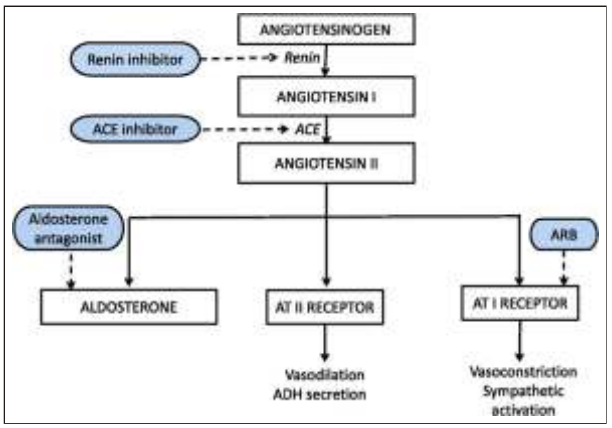
ABSTRACT

The renin-angiotensin-aldosterone system (RAAS) plays a key role in the pathogenesis of diseases such as hypertension, congestive heart failure and chronic renal failure and that the inhibition of RAAS is an effective way to intervene with the pathogenesis of these disorders. Different pharmacological agentsblock RAAS at different sites causing incomplete blockade of RAAS. Aliskiren is relatively a new drug in inventory of RAAS blockers. It has a novel mechanism of action. It inhibits enzyme renin that is the first step in RAAS cascade. It is approved for the treatment of hypertension and is taken once per day. It is effective as monotherapy and when used in conjunction with thiazide diuretics or ARBs, the antihypertensive effects are additive. It has a positive effect on end organ damage caused by essential hypertension (EH). In patients of chronic kidney disease (CKD) it leads to reduction in levels of proteinuria, tubulointerstitial fibrosis, oxidative markers, glomerular pressure, and podocytopathy. Also it causes regression of left ventricular hypertrophy (LVH), and can be a well-tolerated treatment option for patients with LVH.

Introduction

The renin-angiotensin-aldosterone system (RAAS) plays a key role in the regulation of blood pressure (BP) and volume homeostasis. Its importance in diseases such as hypertension, congestive heart failure and chronic renal failure has long ago been recognized and it has also been established that inhibition of RAAS is an effective way to intervene with the pathogenesis of these disorders.[1,2,3]

Secretion of renin is the first step in RAAS cascade and, importantly, also the rate-limiting step. Renin is secreted, in response to a variety of stimuli, from the juxtaglomerular cells in the kidneys. It is a proteolytic enzyme that is released by the kidneys in response to sympathetic activation, hypotension, and decreased sodium delivery to the distal renal tubule The only known physiological substrate for renin in the plasma is angiotensinogen. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I) which is then converted by angiotensin-converting enzyme (ACE) to the active octapeptideAng II, the effector enzyme of the cascade. Ang II interacts with type-1 angiotensin receptors (AT-1), inducing vasoconstriction and increase in blood pressure, promoting adrenal aldosterone secretion, renal sodium reabsoption and release of catecholamines from the adrenal medulla and prejunctionalnerve endings.[4]



Mechanism of action :

Aliskiren has an innovative mechanism of action for the treatment of hypertension and end organ damage. RAAS may be blocked by pharmacological agents at various sites. Inhibitors of the ACE block the formation of Ang II but also cause a respective increase in the concentrations of Ang I that can subsequently be converted to Ang II by other pathways, such as the chymase system. Also, ACE inhibitors are not specific for RAAS, preventing inactivation of bradykinin and substance P that are known to mediate some of the side-effects of ACE inhibitions such as cough and angioedema.

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Angiotensin-II receptor blockers (ARBs) specifically block the AT-1 receptors[5], leaving the other types of AT receptors (eg, AT_2R) that might be involved in some important regulatory functions of the endothelium, unopposed to potential stimulation by Ang II.[6] Importantly, along with the incomplete blockade of RAAS, both ACE inhibitors and ARBs lead to a substantial compensatory rise in the circulating active renin and angiotensin peptides that may eventually limit their therapeutic potential.[7]

Aliskiren inhibits enzyme renin and formation of both Ang I and Ang II is blocked, there is no activation of the AT receptors and no interference with bradykinin metabolism. It has been shown that a rise in circulating renin occurs, but the activity of the released enzyme is blocked in the presence of renin inhibitors[8,9]. Aliskiren significantly inhibits the RAS in a dose-dependent manner with maximum reductions in Ang II observed within one hour following oral administration.

Renin inhibitors have actions, which are similar to those produced by ACEIs and ARBs :

Cardiorenal Effects of Renin Inhibitors

- Vasodilation (arterial & venous)
  - reduce arterial & venous pressures
  - reduce ventricular afterload & preload
- Decrease blood volume
  - natriuretic
  - diuretic
- Depress sympathetic activity
- Inhibit cardiac and vascular hypertrophy
- Dilate arteries and veins by blocking angiotensin II formation. This vasodilation reduces arterial pressure, preload and afterload on the heart.
- Down regulate sympathetic adrenergic activity by blocking the facilitating effects of angiotensin II on sympathetic nerve release and reuptake of norepinephrine.
- Promote renal excretion of sodium and water (natriureticand diuretic effects) by blocking the effects of angiotensin II in the kidney and by blocking angiotensin II stimulation of aldosterone secretion. This reduces blood volume, venous pressure and arterial pressure.
- Inhibit cardiac and vascular remodeling associated with chronic hypertension, heart failure, and myocardial infarction.[10]

Pharmacokinetics :

Aliskiren is administered orally. Its bioavailability is low (about 2.5%) due to active extrusion of absorbed drug by P glycoprotein. It appears that metabolism does not play a large role in elimination, as 91% of a radiolabeled dose is eliminated unchanged in the feces. It is unclear how much of the dose is metabolized, but hepatobiliary clearance seems to be the main route of elimination.[11] Based on in vitro studies, the major enzyme responsible metabolism is CYP3A4. Aliskiren has an approximate accumulation half life of 24 hours, allowing for once daily dosing. Aliskiren does not inhibit or induce any CYP450 isozymes, including CYP3A4. Aliskiren is a CYP3A4 substrate. It is also a substrate for P-glycoprotein.[12]

Special Populations

1. **Hepatic Impairment :**

   Pharmacokinetic parameters are not significantly affected in patients with mild to severe liver disease. Therefore, dosage adjustments are not recommended for patients with hepatic impairment; however, precautions do apply.

2. **Renal Impairment :**

   Dosage adjustments are not recommended for patients with renal impairment or in patients with ESRD receiving hemodialysis; however, precautions do apply.[12]

3. **Pediatrics :**

   Preclinical studies suggest a potential for a substantially increased aliskiren exposure in pediatric patients; therefore, aliskiren is contraindicated in children less than 2 years of age and should not be used in children 2 to 6 years of age.[12]

4. **Geriatric :**

   Elderly patients (65 years or older) included in pharmacokinetic assessments experienced an increase in drug exposure as measured by AUC; however, adjustments of the starting dose is not required.

Side Effects and Contraindications :

Aliskiren alone, like ACEIs and ARBs, has a relatively low incidence of side effects and is well-tolerated.

GIT : Aliskiren has dose-related gastrointestinal adverse effects in some patients; diarrhea is observed in less the 3% of patients.

Angioedema : Angioedema (life-threatening airway swelling and obstruction) can occur in patients taking aliskiren (as can occur with ACEI and ARB treatment), although fewer than 1% of patients develop this condition.

Hyperkalemia : When administered with an ACEI, aliskiren can produce hyperkalemia, especially in diabetic patients. Recent studies (ALTITUDE trial, 2011) have noted increased adverse events (non-fatal stroke, renal complications, hyperkalemia, hypotension) with no apparent additional benefits when added to treatment with an ACEI or ARB in diabetic patients[10].

Aliskiren is contraindicated in neonates, infants, and children less than 2 years and should not be used in children 2 to less than 6 years of age.

Aliskiren can cause fetal harm if administered to a pregnant woman. Once pregnancy is detected, discontinue aliskiren as soon as possible.

Drug interactions :

Aliskiren is a minor inhibitor of substrate CYP3A4 and, more importantly, P-glycoprotein :

1. It reduces furosemide blood concentration.
2. Atorvastatin may increase blood concentration, but no dose adjustment is needed.
3. Due to possible interaction with ciclosporin, the use of ciclosporin and aliskiren at the same time is contraindicated.
4. Caution should be exercised when aliskiren is administered with ketoconazole or other moderate P-glycoprotein inhibitors (itraconazole, clarithromycin, telithromycin, erythromycin, or amiodarone).
5. Recommendations have been made to stop prescribing aliskiren-containing medicines to patients with diabetes (type 1 or type 2) or with moderate to severe kidney impairment who are also taking an ACE inhibitor or ARB. Such patients should consider alternative antihypertensive treatment as necessary.[13]

Indication :

Hypertension

Aliskiren is a renin inhibitor that was approved for the treatment of hypertension by the U.S. FDA in 2007. It is taken once per day. Because of its relatively long half-life, it takes about 2 weeks of dosing to achieve a near maximal antihypertensive effect. It is effective as monotherapy. When used in conjunction with thiazide diuretics or ARBs, the antihypertensive effects are additive.[10] In clinical trials involving patients with mild-to-moderate hypertension, aliskiren provided antihypertensive efficacy that was comparable to that of an ARB. Combination therapy with aliskiren and an ARB may provide additional blood pressure-lowering effects compared with the respective monotherapies with each of the agents[14]

Oral dosage

1. Adults, Children and Adolescents weighing 50 kg or more : Initially, 150 mg PO once daily, may be increased to 300 mg once daily.
2. Children and Adolescents weighing 20 kg to 50 kg : Initially, 75 mg PO once daily, may be increased to 150 mg PO once daily.[12]

Clinical trial	Population	Period of observation	Comparison (successive numbers stand for successive groups compared in the trial)	Results
Oparil S, et al. Lancet 2007; 370: 2219	1797 patients with mild and moderate EH	8 weeks	1. Placebo 2. Aliskiren (150-300 mg) 3. Valsartan (160 - 320 mg) 4. Aliskiren + valsartan (150/160 → 300/320 mg)	Placebo < aliskiren = valsartan < aliskiren+ valsartan[1]

Villamil A, et al. J Hypertens 2007; 25: 217-26	2776 patients with mild and moderate EH	8 weeks	1. Placebo 2-4. Aliskiren (75-300 mg) 5-7. HCTZ (6.25-25 mg) 8-15. Aliskiren + HCTZ (75-300 mg/6.25-25 mg)	Placebo <aliskiren = HCTZ < aliskiren + HCTZ
Schmieder RE, et al. J Hypertens 2009;	1124 patients with mild and moderate EH	52 weeks	1. HCTZ (12.5 → 25 mg) ± amlodipine (510 mg) 2. Aliskiren (150 → 00 mg) ± amlodipine (510 mg)	HCTZ ± amlodipine <aliskiren ± amlodipine

Selected clinical trials ofaliskiren therapy among patients with mild and moderate EH 15

Other effects :

1. Diabetic kidney disease

Diabetic kidney disease (DKD) has been the leading cause of end-stage renal disease. Drugs such as ACEI and ARB have been the basis of management in DKD. On administration of aliskiren, a reduction in levels of proteinuria and hypertension has been noted. The use of aliskiren has been shown to decrease tubulointerstitial fibrosis, oxidative markers, glomerular pressure, and podocytopathy[16].

In a randomized, double-blinded, placebo-controlled, multinational study, the use of aliskiren for 24 weeks showed a 20% reduction in albuminuria with small differences in blood pressures. Five hundred and ninety-nine hypertensive patients with Type 2 diabetes and nephropathy on treatment with losartan (100 mg per day) were randomly selected for aliskiren treatment or placebo. The study concluded that aliskiren does have an additional renoprotective effect with mild lowering of blood pressure properties when used in combination to ARBs. Another similar study conducted to learn about the effectiveness of dual therapy over monotherapy in the management of the cardiovascular and renal system was stopped due to adverse effects, including hypotension, hyperkalemia, and acute renal injury, with the use of ACEI and ARB. This study has led to a debate ever since.[16]

Most recent analyses concerning renin inhibitors in nephroprotection emphasize that double blockade of the RAAS can be considered in cases of chronic nephropathy with albuminuria among patients who, despite treatment with an optimal dose of ACEI or sartan, do not achieve full and permanent albuminuria remission. The necessity to strictly monitor kalemia and renal function among these patients is stressed[17].

2. Cardioprotective effects :

Studies assessing cardioprotective effects of aliskiren, with other RAAS blockers, have been conducted. ALLAY (Aliskiren in Left-Ventricular Hypertrophy Study), which included 465 obese patients with EH and left ventricular hypertrophy, concluded that aliskiren and losartan have a comparable effect on left ventricular hypertrophy regression and similar hypotensive efficacy and safety of use. These findings suggest that aliskiren is an effective and well-tolerated treatment option for patients with LVH.ALOFT (Aliskiren Observation of Heart Failure Treatment) compared the effects of aliskiren and placebo on the brain natriuretic peptide (BNP) serum concentration in patients with heart failure. Three-month aliskiren therapy, as compared with placebo, statistically significantly decreased the concentration of BNP, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), aldosterone and SRA[15]. This trial shed light on the potential benefit of using DRI in patients with heart failure[16]. Trials are shown in the table.

Patients	N	Duration	Treatment (mg/d)	Results	References
Heart failure NYHA class IIIV heart failure	302	3 months	Aliskiren (150) or placebo (plus standard therapy including ACEIs and ARBs)	Aliskiren decreased plasma NT-proBNP and BNP	McMurray et al The ALOFT Study
Left-ventricular hypertrophy Hypertension with increased Left-ventricular wall thickness	465	9 months	Losartan (100) Aliskiren (300) Losartan / Aliskiren (100/300)	Left-ventricular mass reduced to a similar extent in all Treatment Groups	Solomon et al The ALLAY Study

3. Aliskiren - Metabollic syndrome

Aliskiren increased insulin sensitivity both in humans and in animals on a high-fructose diet, due to decreased AngII formation. It was observed that hypertension, hyperinsulinaemia, insulin resistance, hyperglycemia, hypercholesterolemia and hypertriglyceridaemia induced by persistent high-fructose diet in male Sprague-Dawley rats were prevented or reversed by aliskiren in the dose of 100 mg/kg/daily s.c. For 48 weeks. Reduction of plasma leptin levels and decreased insulin resistance following aliskiren administration in obese mice on a high-fat diet was also seen[15].

Conclusion :

The key, rate-limiting step reaction of the RAAS cascade can be inhibited pharmacologically by using aliskiren, which successfully decreases BP and has a positive effect on organ damage caused by EH. It is approved for treatment of hypertension but for other cardiac and renal conditions further long-term studies on large groups of patients are required to precisely determine the place of aliskiren.

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