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## Aliskiren: A new renin inhibitor as anti-hypertensive

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### ABSTRACT

Hypertension or high blood pressure (BP) is usually defined as a systolic BP > 90 mm Hg. It is a serious condition affecting millions of people every year. The prevalence varies with age, race, education and many other variables. Although number of techniques have been employed for control of blood pressure, still a lot needs to be done in this regard. Lifestyle changes (including weight loss, increased physical activity, and decreased salt and alcohol intake) are the first step in treating hypertension. Hypertension is closely linked to the renin-angiotensin-aldosterone system (RAAS). Drugs that inhibit renin have been available for many years but have been limited by low potency, bioavailability and duration of action. Aliskiren is the most advanced of a new class of non-peptide, low-molecular weight, orally active inhibitors introduced recently. In healthy subjects, it produces a dose-dependent reduction in plasma renin activity, angiotensin I and II and aldosterone concentrations. In patients with essential hypertension, aliskiren suppresses plasma renin activity and causes dose-related reductions in blood pressure. The safety and tolerability of aliskiren appears to be comparable to angiotensin antagonists and placebo. Aliskiren has, therefore, a considerable promise for the treatment of hypertension and other cardiovascular and renal diseases.

**Key words:** Hypertension, Angiotensin, Aliskiren, Renin inhibitor, Antihypertensive.

### 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 (Turnbell, 2003). Secretion of renin is the first step in RAAS cascade and happens to be the rate-limiting step (Skeggs et al., 1957). It is secreted, in response to a variety of stimuli, from the juxtaglomerular cells in the kidneys. 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 octapeptide Ang 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 reabsorption and release of catecholamines from the adrenal medulla and prejunctional nerve endings (Kim et al., 2000). Pharmacological agents at various sites may block RAAS. 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. ACE inhibitors are not specific for RAAS thereby 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. Angiotensin-II receptor blockers

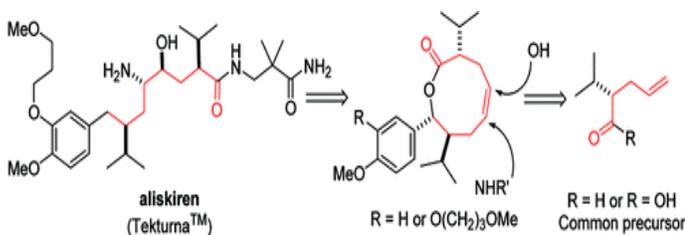
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(ARBs) specifically block the AT-1 receptors (Brunner et.al., 1974), leaving the other types of AT receptors (eg, AT<sub>2</sub>R and AT<sub>4</sub>R) that might be involved in some important regulatory functions of the endothelium, unopposed to potential stimulation by Ang II (Watanabe et.al., 2005). However, 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 (Stanton et.al., 2003).

Renin is the rate-limiting step of the RAAS and has unique specificity for its substrate, angiotensinogen. Inhibition of renin has been the main option that would block the RAAS at the highest level, at its origin. Thus, the 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 (Nussberger, et.al, 2002; Azizi et.al., 2004).

The concept of blocking the RAAS at its origin by inhibiting renin has existed for at least 50 years. The first synthetic renin inhibitor was pepstatin, which was followed by first-generation agents that were active but required parenteral administration. Oral agents that were subsequently developed, such as enalkiren, remikiren, and zankiren, had limited clinical use because they demonstrated poor bioavailability (<2%), short half-lives and weak antihypertensive activity (Satoskar et.al., 2003).

Aliskiren is a new nonpeptide, low molecular weight, orally active inhibitor that has recently been developed (Stanton et.al., 2003). It is a direct human-renin inhibitor that blocks the conversion of angiotensinogen to Ang I (Nusberger et.al., 2002). Aliskiren, a 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-methoxypropoxy-] phenyl)-octanamide, is the only orally active renin inhibitor that has successfully progressed to phase III trials and extensive clinical use (Lin et.al., 1996; Raheul et.al., 2000). The US Food and Drug Administration's approval in March 2007 of aliskiren for the treatment of hypertension met with great enthusiasm. Despite the notable absence of human clinical data for this agent, many clinicians have doubted aliskiren as the ideal agent to achieve additional suppression of the RAAS as a means to reduce the morbidity and mortality of chronic diseases of the cardiovascular and renal systems (Stanton, 2003).



It was discovered by Ciba-Geigy (now Novartis, Basel, Switzerland) through a combination of molecular modeling and crystallographic structure analysis (Wood et.al., 2003). It was approved in 2007 by regulatory bodies both in Europe and in the

US, for use alone as with others agents in the treatment of arterial hypertension.

## MECHANISM OF ACTION

Renin is an aspartyl protease that is synthesized as prorenin, a proenzyme that is transformed into renin by cleavage of a 43-amino-acid segment from the N-terminal end. Receptor binding induces a 4-fold increase in the catalytic conversion of angiotensinogen to Ang I, suggesting that the cell surface is an important site of Ang generation. Once bound, renin triggers a series of intracellular events that culminate in activation of the mitogen-activated protein kinases ERK1 (p44) and ERK2 (p42), which are involved in cell hypertrophy and proliferation (Satoskar et.al., 2003). Aliskiren has a high binding affinity for renin and appears to bind to both the hydrophobic S1-/ S3- binding pocket and to a large, distinct sub pocket that extends from the S3-binding site toward the hydrophobic core of the enzyme. It is a potent competitive inhibitor of purified renin, but very poorly inhibits related aspartic peptidases. It is one of the most potent known renin inhibitors with high specificity for primate rennin (Nurberger et.al., 2002).

## FATE

Aliskiren possesses high aqueous solubility (>350 mg/ml at pH 7.4) and high hydrophilicity (log P<sub>oct</sub>/water = 2.45 at pH 7.4) leading to improved oral bioavailability (wood et.al., 2003). It is mainly eliminated unmetabolized via biliary excretion, with less than 1% excreted in the urine (Gasparo, 1989). It binds only moderately to plasma proteins (mean protein-binding level of 49.5%), with the binding concentrations being independent over the range of 10–500 ng/ml (Azizi, 2006).

It is not metabolized by cytochrome P450 and is not bound extensively to blood proteins therefore having a low potential for drug interactions. It has been shown that multiple doses of aliskiren have no detectable effects on the pharmacodynamics or pharmacokinetics of a single dose of warfarin (Dieterle et.al., 2004).

## Adverse Effects

The adverse effects of aliskiren are uncertain due to its 10,000-fold higher affinity for renin than for other aspartic peptidases. Most common adverse effects reported are headache, dizziness, diarrhoea, hypotension, hyperkalemia, nasopharyngitis, laryngopharyngitis, fatigue, back pain, gastrointestinal disorders, rashes and renal stones (Stanton 2003; Gradman et.al., 2005). In some studies edema involving the face, lips, tongue, hands and whole body have been reported. It has no clinically important effects on total cholesterol, HDL, fasting triglycerides or fasting glucose.

## Benefits

a) As renin inhibitors prevent the formation of both angiotensin I and angiotensin II, they may offer a therapeutic profile distinct from both ACE inhibitors and ARBs (Gradman et.al., 2005).

b) ACE inhibition causes an increase in angiotensin I, which is then available for conversion to angiotensin II by ACE independent pathways not blocked by ACE inhibitors (Hollenberg et.al., 1998). Further, renin inhibitors also do not affect kinin metabolism and hence would not be expected to cause dry cough or angioneurotic edema, which are characteristic side effects of ACE inhibitors (Karlberg, 1993).

c) Although the AT<sub>2</sub> receptor generally is conceptualized as a cardiovascular protective receptor, its activation may contribute to cardiac fibrosis (Ichihara et.al., 2001). ARBs increase levels of angiotensin II and indirectly stimulate angiotensin II subtype 2 receptor (AT<sub>2</sub>), an effect that does not occur with renin inhibitors and thus prevents unexpected effects of AT<sub>2</sub> receptor stimulation (Jackson, 2001; Gradman et.al., 2005).

d) No evidence of withdrawal effect (Gradman et.al., 2005).

e) Aliskiren possesses synergistic potential when compared with a thiazide diuretic, an ACE inhibitor and with an ARB.

#### **Drug Interactions**

It shows no clinically relevant pharmacokinetic interactions with lovastatin, atenolol, celecoxib, or cimetidine in healthy male volunteers (Dieterle et.al., 2005). No interactions with digoxin were observed in a pharmacokinetic study in 22 healthy volunteers (Dieterich et.al., 2006).

With regard to other antihypertensive medication, pharmacokinetic interactions between aliskiren 300 mg and valsartan (320 mg), hydrochlorothiazide (HCTZ; 25 mg), amlodipine (10 mg) and ramipril (10 mg) have been studied in healthy subjects and no clinically relevant effects were shown (Vaidyanathan et.al., 2006).

Aliskiren shows high specificity for human renin, with almost no inhibitory effect against other aspartic peptidases such as cathepsin D and pepsin. Although aliskiren also exhibits high affinity for primate renin, it is significantly less active against renin from dog, rat, rabbit, pig and cat (Wood et.al., 2003). This high potency for human renin compensates for the relatively low oral bioavailability of the drug. Pre-clinical and clinical studies have shown that aliskiren effectively inhibits RAAS, along with dose-dependent decrease in BP.

#### **ACE inhibitors (eg, captopril)**

Electrolytes and renal function need to be routinely monitored when these agents are coadministered, especially in diabetic patients.

#### **Atorvastatin**

Aliskiren C<sub>max</sub> and AUC may be increased approximately 50%, increasing the pharmacologic effects and risk of adverse reactions. Clinical response of the patient needs to be monitored and the aliskiren dose is to be adjusted as needed.

#### **Cyclosporine**

Aliskiren plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.

Coadministration of aliskiren and cyclosporine is not recommended.

#### **Drugs that increase potassium levels, potassium-sparing diuretics (eg, spironolactone), potassium supplements, salt substitutes containing potassium**

Increased serum potassium may occur. Use with caution. Monitor electrolytes.

#### **Food**

High-fat meals substantially reduce aliskiren absorption (eg, AUC and C<sub>max</sub> 71% and 85%, respectively). Patients should establish a routine pattern for taking aliskiren with regard to meals.

#### **Furosemide**

Blood concentrations may be reduced by aliskiren, decreasing furosemide efficacy. Monitor the diuretic response. Adjust the furosemide dose as needed.

#### **Irbesartan**

Aliskiren C<sub>max</sub> may be reduced up to 50%, decreasing the pharmacologic effect. Use with caution and monitor BP. Adjust the aliskiren dose as needed.

#### **Ketoconazole**

Aliskiren plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions. Monitor the clinical response of the patient and adjust the aliskiren dose as needed.

#### **Thiazide diuretics (eg, hydrochlorothiazide)**

Additive increases in serum uric acid levels may occur. It is to be used with caution, especially in patients at risk for hyperuricemia.

#### **CONCLUSION**

Aliskiren offers a promising new approach to the blockade of the RAS. It is the first representative of a new class of non-peptide, low molecular weight, orally active transition-state renin inhibitors. Its high potency against human renin compensates for its relatively low absolute bioavailability. Its long half-life makes it suitable for once daily administration. Aliskiren is effective in reducing blood pressure and is well tolerated, with a side-effect profile similar to placebo or ARBs. It exhibits synergistic effects when combined with drugs that lead to a reactive increase in the plasma renin activity, such as diuretics, ACE inhibitors or ARB.

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