Renin inhibitor in hypertension treatment: from pharmacological point of view

Johannes Hudyono

Clinical Study Unit – Faculty of Medicine, University of Indonesia

Abstrak

Penggunaan obat yang menghambat sistem renin-angiotensin adalah salah satu cara efektif dalam mengintervensi patogenesis kelainan-kelainan kardiovaskular dan ginjal khususnya dalam terapi hipertensi. Ide untuk menhambat sistem renin pada muaranya dengan renin inhibitor telah dimulai sejak lebih dari 30 tahun yang lalu. Renin inhibitor menghambat perubahan angiotensinogen menjadi angiotensin, yang selanjutnya mengurangi pembentukan peptida aktif angiotensin II. Generasi pertama (enalkiren) dan generasi kedua (remikiren) dari renin inhibitor yang secara oral aktif, tidak pernah digunakan secara klinis karena rendahnya bioavailabilitas oral dan lemahnya aktivitas anti hipertensinya. Saat ini aliskiren, non-peptida renin inhibitor pertama yang secara oral aktif dari generasi ketiga telah melalui uji klinik di fase III dan telah disetujui oleh U.S. Food and Drug Administration (FDA) pada bulan Maret 2007. Obat ini merupakan renin inhibitor pertama dengan indikasi hipertensi di Indonesia, suatu obat dengan bioavailabilitas oral, spesifisitas dan efikasi yang lebih baik. Makalah ini membahas perkembangan serta aspek farmakologi dari aliskiren. ***(Med J Indones 2011; 20:232-7)***

Abstract

The use of drugs that inhibit the renin-angiotensin system is one of the effective way to intervene in the pathogenesis of cardiovascular and renal disorders, especially in hypertension treatment. The idea of blocking the renin system at its origin by renin inhibitor has existed for more than 30 years. Renin inhibitor supresses the covension of angiotensinogen into angiotensin, and further deacreases the generation of the active peptide angiotensin II. The first generation (enalkiren) and second generation (remikiren) of orally active renin inhibitors were never used clinically because of low bioavailability and weak blood pressure-lowering activity. At present, aliskiren is the first non-peptide orally active renin inhibitor of the third generation to progress to phase III clinical trials and was approved by U.S. Food and Drug Administration (FDA) in March 2007. Aliskiren becomes the first renin inhibitor with indications for the treatment of hypertension in Indonesia, a compounds with improved oral bioavailability, specificity and efficacy. This review summarises the development of oral renin inhibitors, pharmacological aspects, with a focus on aliskiren. ***(Med J Indones 2011; 20:232-7)***

Key words: *aliskiren, hypertension, renin inhibitor, renin-angiotensin*

The use of drugs inhibiting the renin-angiotensin system (RAS) is one of effective ways to intervene in the pathogenesis of cardiovascular and renal disorders, especially in hypertension treatment. Renin has a strong specificity for its substrate, angiotensinogen. Therefore, this made it very interesting for a therapeutic target. Inhibition of renin will cause RAS inhibition without affecting other metabolic pathways. Blockade of renin activity specifically inhibits the renin-angiotensin system at its initial point of activation. The action of renin on its substrate and all step of pathways involved in the development of angiotensin II will also be prevented. Renin inhibitors have different therapeutic profile from both Angiotensin Converting Enzyme Inhibitor (ACEI) and Angiotensin Receptor Blocker (ARB) concerning low possibility of side effect.[1]

Renin-angiotensin system

Activation of renin system is initiated by renin production of the kidney. Renin is a proteinase enzyme that catalyzes the conversion of angiotensinogen to angiotensin I (Ang I). Ang I by itself is inactive, but biologically activated by angiotensin converting enzyme (ACE) into angiotensin II (Ang II). ACE is produced by vascular endothelium, mostly in the lung and in other vascular beds. Ang II binds to Ang II type 1 receptor (AT_1) on the peripheral vascular smooth muscle cells leading to vasoconstriction and thereby increases peripheral vascular resistance and blood pressure (BP). AT_1 receptor activation by Ang II also stimulates aldosterone release, a mineralocorticoid hormone, secreted from the zona glomerulosa of cortex of adrenal gland. Aldosterone causes Natrium (Na^+) and water retention, in the distal convoluted tubule of nephron, resulting further increased in BP. When the BP constantly increases as occurs in hypertension induced by the hormone aldosteron, it will lead to organ damage.[2,3] Aldosterone itself induces vascular remodelling and myocardial fibrosis, thus precipitates organ damage. Renin-angiotensin system is a classic endocrine system which has negative feedback mechanism. It produces Ang II through Ang I which is converted to Ang II and in turn the Ang II will have feedback cycle to the kidney and stop the renin production. In contrast to renin inhibitor, both ACE inhibitors and ARBs result in increased plasma renin activity (PRA). The increase in local and circulating renin activity leads to further generation of Ang I, which could overcome the effects of renin system blockers. In addition, Ang II may also be generated by ACE-independent pathways, leading

Correspondence email to: Jhudyono@csufkui.com

to 'escape' from ACE inhibition and increase in Ang II level.[2-6]

Aliskiren – the first direct renin inhibitor

Before aliskiren was discovered, various types of peptide-like renin inhibitors, analogs of angiotensinogen were synthesized. Such substances in preclinical models, have shown to reduce renin activity and lowered blood pressure when given intravenously but with low efficacy. Moreover, low oral bioavailability due to first-pass elimination by the liver and biodegradation by gastrointestinal peptides, short half-life and high cost of synthesis, precluded further development of such drugs for clinical use. [5,7-13] Aliskiren is a small sized non-peptide molecule with molecular weight of 609.8 g/moL as aliskiren hemifumarate. It was developed by using molecular modeling technique and structure crystallographic analysis with molecular formula of $C_{30}H_{53}N_3O_6$. Aliskiren is a hydrophilic molecule with water solubility >350 mg/mL at pH 7.4 and *a partition coefficient* (log $P_{octanol/water}$) 2.45 at pH 7.4, which made aliskiren suitable for oral route with improved pharmacokinetic profile compared with previous generation of renin inhibitors.[12,13]

Important features of the various generations of renin inhibitors

The 1st generation peptides such as Enalkiren has high molecular weight, short duration of action (< 4 hours) and no oral bioavailability, and very high cost of production, while the 2nd generation peptidomimetic such as Remikiren has medium molecular weight, short duration of action (2-6 hours) with < 2% oral bioavailability and also very high cost of production. The 3rd generation synthetic non-peptidic such as Aliskiren has small molecular weight, long duration of action (> 24 hours) with > 4% oral bioavailability and high cost of production.[12]

Aliskiren binds to the S1 and S3 pocket on renin molecule, inhibit the activity of catalytic aspartate residues, Asp32 and Asp215. Therefore, it blocks the conversion of angiotensinogen to angiotensin I.[13]

Mechanism of action of aliskiren

Aliskiren is the first of orally active, non-peptide, highly potent and selective direct renin inhibitor which was approved by the U.S. Food and Drug Administration (FDA) in March 2007 for the treatment of hypertension either as monotherapy or in combination with other anti-hypertensive agents. Aliskiren binds to both hydroxyl group and aspartic residues of renin via hydrogen binding, inhibiting the ability of renin to catalyze the conversion of angiotensinogen into angiotensin I.[4,8,14]

It demonstrates more than 10,000-fold higher affinity to renin than other related aspartic peptidase enzymes such as pepsin and cathepsin D or E in vitro. It has no effect on adrenergic, serotonergic, histamine, opiate, benzodiazepine or adenosine receptors and does not show any effect on bradykinin level or its activity. The binding of aliskiren to renin is followed by an effective reduction in PRA and compensatory rise in plasma renin concentration (PRC). Although PRC rises during treatment with aliskiren, the levels of angiotensin I and II remain low due to inhibition of PRA, when used as monotherapy or in combination with other agents. The inhibition of PRA appears to persist for approximately 10 hours with low dose aliskiren (40-80 mg/day or less) and for more than 24 hours with high dose (160 mg/day or higher) in healthy volunteers. PRA reductions in clinical trials ranged from 50% to 80% and were not dose-dependent.[4]

Pharmacokinetics of aliskiren absorption and bioavailability

Aliskiren is rapidly absorbed following oral administration in healthy subjects with peak plasma concentration (C_{max}) reached within 1-3 hour(s) following the administration. An absolute bioavailability of 75 mg single-dose oral aliskiren (relative to intravenous dose) as observed in 9 healthy male subjects is 2.6%.

The pharmacokinetics of aliskiren indicated a moderate to high level of interindividual variability, ranging from 40% to 70% for area under the plasma concentration-curve (AUC) and 30% to 50% for the $C_{max.}$ The variability is thought to reflect differences between individual subjects on the fraction of dose absorbed and elimination via hepatobiliary route. Despite the interindividual variations in pharmacokinetics, aliskiren has demonstrated consistent BP-lowering efficacy and inhibition of PRA in clinical trials. This is likely related to the potency and high binding affinity of aliskiren to human renin.

In a single-dose study in 32 healthy subjects, aliskiren demonstrated over-proportional increases in plasma concentration with increasing dose across the extended dose range from 75 to 600mg. Within the clinically approved dose range of 150-300 mg, increases of 2 to 3-fold and 2.6-fold were observed for Aliskiren AUC and C_{max}, respectively.[4,15]

Metabolism

In vitro studies of aliskiren metabolism by human liver microsomes demonstrated that aliskiren has a low hepatic clearance (41 μL/mg/minute). This suggests that liver metabolism is unlikely to be the major role in drug elimination. Less than 1% of an orally administered

dose is excreted in the urine as unchanged drug.[4,15,16] Incubation experiments with a series of 22 recombinant human cytochrome P450 (CYP) isoenzymes showed that only small proportion of aliskiren is metabolized. CYP3A4 responsible as the major isoenzyme. The CYP3A4 inhibitor, ketoconazole, almost completely inhibited aliskiren metabolism in human liver microsomes, and aliskiren did not induce CYP3A4 activity.[15,16]

Elimination

In healthy subjects, the excretion of radioactivity following administration of single dose 300 mg [^{14}C]-aliskiren was quite complete (91.5 ± 4.5%) after 7 days. The excretion of aliskiren was nearly complete through biliary/fecal route (91%), with most of the dose (77.5%) excreted as unchanged drug. Overall, oxidized metabolite in the excreta amounted to approximately 1.4% of the orally administered radioactive dose. Renal excretion accounted for only 0.6% of the radioactive dose, of which 0.4% (70% of the recovered radioactivity in urine) was unchanged aliskiren. In a study of 17 healthy subjects, renal clearance of aliskiren was approximately 1.3 L/hour.[15]

Accumulation and steady state pharmacokinetics

Steady-state Cmax value typically range from 200 to 400 ng/mL (330-660 nmol/L) following administration of aliskiren 300 mg; while trough plasma concentrations range from 15 to 30 ng/mL (25-50 nmol/L), greatly exceed the aliskiren concentration that produces 50% inhibition (IC_{50}) of renin (0,6 nmol/L).[15]

Patients with hepatic impairment

The disposition of aliskiren is not affected by hepatic impairment. Following a single oral 300 mg dose of aliskiren, the AUC and Cmax of aliskiren in patients with stable mild, moderate or severe hepatic impairment (based on Child – Pugh score) did not show significant difference from exposure in matched healthy subjects.[15] Pooled AUC and Cmax values for the three hepatic impairment subgroups were 12% and 19% higher, respectively compared with healthy subjects. There was no correlation between aliskiren level, as assessed by either Cmax or AUC values, or the severity of hepatic impairment. Therefore, no adjustment of the aliskiren starting dose is necessary in patients with mild to severe hepatic impairment.[15]

Patients with renal impairment

Following once-daily oral administration of aliskiren, steady state is reached after 7-8 days of dosing. The AUC and Cmax value at steady state were approximately 2-fold higher than those following single-dose administrations; hence, the accumulation factor for aliskiren is 2. A clinical trial in patients with mild, moderate and severe renal impairment (creatinine clearance [CL_{CR}] of 50-80, 30-49 and <30 mL/minute, respectively) showed no significant difference of accumulation between the three subgroups and healthy subjects.[15,16] Aliskiren may have renoprotective effects that are independent of its bloodpressure−lowering effect in patients with hypertension, type 2 diabetes, and nephropathy who are receiving the recommended renoprotective treatment.[17]

Pharmacokinetic drug interactions
In vitro studies of aliskiren

In vitro studies showed drugs that aliskiren is unlikely affect the pharmacokinetics of drugs that are substrates for CYP isoenzymes or efflux transporter protein. Experiments in human liver microsomes showed very low hepatic metabolic clearance of aliskiren. Other in vitro experiments with recombinant human CYP isoenzymes demonstrated that there was no significant inhibition of CYP isoenzyme with concentration of 10-fold greater than the therapeutic plasma concentration observed in human.[15]

Effect of other drugs on aliskiren

Based on in vitro studies, aliskiren is metabolized by CYP 3A4. Co-administration of lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amlodipine did not cause significant increases in aliskiren exposure.

Co-administration with irbesartan reduces the Cmax of aliskiren up to 50% after repeated dosing. Co-administration with atorvastatin increases the Cmax of aliskiren up to 50% after repeated dosing. [15]

Ketoconazole

Co-administration of 200 mg twice-daily dosing with aliskiren results in an approximate increase in plasma levels of aliskiren. A 400 mg once daily dosing has not been studied, but it may further increase aliskiren blood plasma levels.[15]

Effect of aliskiren on other drugs

Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP 3A) or induce CYP 3A4.

Co-administration with aliskiren insignificantly affects the pharmacokinetic of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.[15]

Warfarin

The effect of aliskiren on warfarin pharmacokinetics have not been evaluated in a well-controlled clinical trial.[15]

Furosemide

When aliskiren was co-administered with furosemide, the AUC and Cmax of furosemide were reduced by about 30% and 50%, respectively.[15,16]

Pharmacodynamic
Pharmacodynamic on healthy subjects

Effect of aliskiren on PRA and PRC. A study evaluating the effects of aliskiren on renin system in 18 healthy male subjects showed significant inhibition of PRA within 1 hour of oral dosing with aliskiren solution at single doses of 40-640 mg. The PRA inhibition by aliskiren was dose-dependent across the range dose studied and was sustained for at least 24 hours following administration of a single oral 640-mg dose of aliskiren. PRA reduction by aliskiren was associated with significant reduction both for angiotensin I and angiotensin II level, which showed effective inhibition of renin system. Aliskiren administration also resulted in dose-dependent increases in the PRC of up to 20-fold compared to placebo reflecting suppression of the negative feedback, by which angiotensin II inhibits renin release.[15]

Across-over study evaluated the effects of the administration of a single dose aliskiren, valsartan or combination of aliskiren and valsartan on renin system activity in healthy subjects. When aliskiren was administered in combination with valsartan, it inhibited the rise in PRA and angiotensin II which usually occur with administration of valsartan alone. Therefore, aliskiren provides effective inhibition of PRA even when used in combination with drugs that usually increases PRA.[7,18,19] The pharmacodynamic effects of aliskiren on renin system did not differ between healthy Caucasian and Japanese subjects, as well as between healthy subjects and patients with type 2 Diabetes Mellitus. In each group, administration of aliskiren was associated with significant inhibition of PRA and marked increase in PRC.[15]

Pharmacodynamics in patients with hypertension

Dose and Therapeutic Range for Blood Pressure Reduction Aliskiren has been approved by the FDA and the European Medicines Agency (EMEA) for the treatment of hypertension at once-daily oral doses of 150 and 300 mg. A study involving over 12,000 patients with hypertension has demonstrated that aliskiren reduced blood pressure effectively and persistently dose dependent, with a good safety and tolerability profile. A pooled analysis of placebo-controlled trials showed that 150 mg and 300 mg aliskiren treatment provided reductions in mean sitting systolic blood pressure (SBP)/ diastolic blood pressure (DBP) from baseline of up to 13.0/10.3 and 15.8/12.3 mg, respectively. Reduction in blood pressure with 75 mg aliskiren was inconsistently greater than those with placebo in these clinical trials; while aliskiren 600 mg did not exhibit extra reduction in blood pressure compared to the 300 mg dose.[15,20]

Aliskiren has a sustained 24-hour BP-lowering effect during ambulatory blood pressure monitoring. Responder rates for aliskiren monotherapy are between 51.9% (75 mg daily) and 63.9% (300 mg daily). Aliskiren further decreases BP in combination with hydrochlorothiazide (HCTZ), amlodipine, ramipril, or valsartan. Finally, aliskiren has a safety profile similar to placebo and to ARBs.[21]

Aliskiren also provides an effective PRA reduction when given in combination with antihypertensive agents that increase the PRA. In a pooled analysis, administration of hydrochlorothiazide, ramipril or valsartan alone were associated with increases in the PRC and PRA simultaneously. If aliskiren is given in combination with each of the above mentioned drugs, PRA is reduced to the same level as administration of aliskiren alone. This occurs despite much greater increase in the PRC during co-administration with aliskiren. For example, administration of 300 mg aliskiren and 25 mg hydrochlorothiazide resulted 1211% increase of the PRC compared with the 348% PRC increase with aliskiren alone.[15]

Co-administration of aliskiren with hydrochlorothiazide resulted in 62% reduction of PRA.[22,23] A study of aliskiren in combination with valsartan in 1797 patients with hypertension demonstrated similar results. Treatment with aliskiren 300 mg/valsartan 320 mg was associated with 44% reduction in PRA from baseline significantly despite increases in the PRC of 912%.[15,18]

Aliskiren in elderly patients

In elderly patients with systolic hypertension, aliskiren proved to be more effective and better overall anti-hypertensive therapy compared to ramipril. Aliskiren 150 and 300 mg provided significant, dosedependent reductions from baseline in msSBP and msDBP compared with placebo ($p < 0.0001$). Reductions in msSBP and msDBP were similar in men and women, and in patients ages < 65 years and those ages ≥ 65 years, for both aliskiren 150 and 300 mg.[24,25]

Plasma renin activity: A risk factor for myocardial infarction in hypertensive patients

A study done by Michael H. Alderman et al was very interesting. To determine whether pretreatment plasma

renin activity (PRA), without accompanying 24-h urine sodium, can predict myocardial infarction (MI), the PRA levels of 2,902 hypertensive patients [white (38%), male (65%), median age 55 years], with mean entry blood pressure (BP) of 150/97 mm Hg were examined. During an average 3.6 years follow-up (87% ≥ 9 months), there were 55 miocard infarks, 21 strokes, and 16 other cardiovascular disease (CVD) death.

In a Cox survival analysis only renin, age, sex, smoking, LVH, and cholesterol were significantly (*P* . .02) related MI occurrence. In this study it was concluded that there was, for every 2 unit increase in PRA, an overall 25% increase in MI disease (CVD) deaths.[26]

Safety

Based on the approval issued by the Drug and Food Control Agency of the Republic of Indonesia (BPOM-RI) dated November 21st, 2007, it is stated that aliskiren has been evaluated for safety in more than 7800 patients, including 2300 patients who had treatment for over 6 months, and more than 1200 patients for over than 1 year period. The side effects are usually mild and short-termed. The most common side effect is diarrhea. It was reported to occur in approximately 2% of patients at the 300-mg dose as approved compared to 1% in patients with placebo. Rarely, patients who take aliskiren may experience allergic reaction with swelling of face, lips or tongue and respiratory distress as seen in other hypertensive agents which act on the renin-angiotensin system.[15,16]

Usage during pregnancy and lactation
pregnancy

There are no data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits. Other substances that act directly on the RAS have been associated with serious foetal malformations and neonatal death. As for any medicine that acts directly on the RAS, Aliskiren should not be used during the first trimester of pregnancy or in women planning to become pregnant and is contraindicated during the second and third trimesters. Aliskiren is classified by the FDA as pregnancy category C for first trimester, and category D for second and third trimesters. However, aliskiren should be immediately discontinued when pregnancy is detected because, like other RAS-blocking drugs, it can cause fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Healthcare professionals prescribing any agents acting on the RAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, Aliskiren should be discontinued accordingly.[8,27]

Lactation

It is not known whether aliskiren is excreted in human milk. Rasilez was secreted in the milk of lactating rats. Its use is therefore not recommended in women who are breast-feeding.[8,27]

Paediatric patients: (below 18 years) Aliskiren is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy **Elderly patients** (over 65 years) : No adjustment of the initial dose is required for elderly patients. [24,27]

In conclusion, use of drugs that inhibit the renin-angiotensin system is one of effective ways for the treatment of hypertension. Renin inhibitor suppresses the generation of the active peptide, angiotensin I. The first generation of renin inhibitors (enalkiren) has no oral bioavailability and the second generation (remikiren), which is orally active has never been used clinically because of the low oral bioavailability and weak blood-pressure-lowering activity. At present, aliskiren is the first of orally active, non-peptide 3rd generation renin inhibitor have been numerously studied in phase III studies and has been approved by the U.S. Food and Drug Administration (FDA) in March 2007. The drug is the first renin inhibitor with indication for the treatment of hypertension in Indonesia, a drug with improved oral bioavailability, specificity, and efficacy than ACE inhibitors and Angiotensin Receptor Blockers. The development, mechanism of action, pharmacokinetics, pharmacodynamic, drug interaction as well as the safety/ side effects of aliskiren have been discussed in this review.

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