Aliskiren – an orally active renin inhibitor. Review of pharmacology, pharmacodynamics, kinetics, and clinical potential in the treatment of hypertension

Kristina Allikmets

Department of Drug Development and Medical Affairs, Nycomed Group, Roskilde, Denmark

Abstract: The importance of renin-angiotensin-aldosterone system (RAAS) in diseases such as hypertension, congestive heart failure and chronic renal failure has long ago been recognized. It has also been established that inhibition of RAAS, using inhibitors of the angiotensin-converting enzyme (ACE) or angiotensin II receptor blockers (ARB), is an effective way to intervene with the pathogenesis of these disorders. Renin inhibitors block the RAAS at the highest level, at its origin, and might thus offer a new exciting approach for pharmacotherapy of arterial hypertension. Aliskiren is the first in a new class of orally active, non-peptide, low molecular weight renin inhibitors, and so far the only renin inhibitor that has progressed to phase III clinical trials. This review summarizes the available data on the pharmacokinetic and pharmacodynamic properties of aliskiren and its clinical development for treatment of arterial hypertension.

Keywords: aliskiren, hypertension, renin-angiotensin-aldosterone system, renin inhibition, essential hypertension

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 (Ruggenenti et al 1999; Flather et al 2000; Turnbull 2003).

Secretion of renin is the first step in RAAS cascade and, importantly, also the rate-limiting step (Skeggs et al 1957). Renin 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 reabsoption and release of catecholamines from the adrenal medulla and prejunctional nerve endings (Kim and Iwao 2000).

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. Angiotensin-II receptor blockers (ARBs) specifically block the AT-1 receptors (Brunner et al 1974),

Correspondence: Kristina Allikmets
Senior Director, Medical Scientific Strategy & Medical Marketing, Nycomed Group, Langebjerg 1, DK-4000 Roskilde, Denmark
Tel +45 4677 1655
Fax +45 4675 5999
Email kta@nycomed.com

leaving the other types of AT receptors (eg, AT_2R and AT_4R) that might be involved in some important regulatory functions of the endothelium, unopposed to potential stimulation by Ang II (Watanabe et al 2005). Importantly, along with the incomplete blockade of RAAS, both ACE inhibitors and ARBs lead to a substantial compensatory raise in the circulating active renin and angiotensin peptides that may eventually limit their therapeutic potential (Stanton 2003).

Renin is the rate-limiting step of the RAAS and has unique specificity for its substrate, angiotensinogen. Inhibition of renin has long ago been recognised as an attractive 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 first renin inhibitors were synthesized already more than 30-years ago (Gross et al 1971). First orally active compounds were developed in the 1980s, including enalkiren (A 64662; Abbott, Abbott Park, IL, USA), CGP38560A (Ciba-Geigy, Basel, Switzerland), remikiren (Ro 425892; Hoffmann-La Roche, Basel, Switzerland), and zankiren (A 72517; Abbott). However, poor absorption from the gastrointestinal tract (with bioavailability of less than 2%), short half-life and low potency prevented further development of these compounds (Staessen et al 2006).

Aliskiren is the first in a new class of orally active, nonpeptide, low molecular weight renin inhibitors, and so far the only renin inhibitor that has progressed to phase III clinical trials. Aliskiren (formerly CGP 60536) was discovered in Ciba-Geigy (now Novartis, Basel, Switzerland) through a combination of molecular modeling and crystallographic structure analysis (Wood et al 2003). The synthetic pathway at that time was not suitable for large-scale manufacturing and the compound was out-licenced to Speedel AG (Basel, Switzerland) where a new cost-effective manufacturing method for aliskiren (SPP 100) was developed and preclinical and early clinical testing successfully performed. Novartis exercised its call-back option for further development of aliskiren in phase III trials (Wood et al 2003). Aliskiren was approved in 2007 by regulatary bodies both in Europe and in the US, for use alone as with others agents in the treatment of arterial hypertension.

This review summarizes the available data on the pharmacokinetic and pharmacodynamic properties of aliskiren and its clinical development for treatment of arterial hypertension.

Pharmacokinetic properties

Aliskiren is a transition-state mimetic, with favourable physico-chemical properties including high aqueous solubility (>350 mg/ml at pH 7.4) and high hydrophilicity (log Poct/water = 2.45 at pH 7.4). These properties are important prerequisites for improved oral bioavailability (Wood et al 2003).

Aliskiren pharmacokinetics has been studied in marmosets. After a single oral dose of 10 mg/kg, peak plasma concentrations were reached in 1–2 hours. The calculated bioavailability was 16.3% and mean half-life 2.3 h (Wood et al 2005).

The single and multiple-dose oral pharmacokinetics of aliskiren have been investigated over the dose range 40–1800 mg in healthy male subjects (Azizi et al 2006). Study in healthy volunteers (n = 18) showed that the plasma concentration increased dose-dependently after oral aliskiren in doses of 40–640 mg/day, with peak concentrations reached in 3–6 h. The mean plasma half-life was 23.7 h (with SD of 7.6h and range 20–45 h). The oral bioavailability of the hard gelatine 75 mg capsule was 2.6%. Plasma steady-state concentrations were reached after 5–8 days of treatment (Nussberger et al 2002).

Aliskiren accumulates following multiple once-daily administration as indicated by the accumulation ratios of between 1.4 and 3.9, with the accumulation being more pronounced at higher doses (Azizi et al 2006). Aliskiren pharmacokinetics is dependent on food intake. Thus, aliskiren 150 mg orally with food results in mean C_{max} and $AUC_{0-\infty}$ values by 81 and 62% lower, respectively, when compared to the fasting state (Azizi et al 2006).

Aliskiren pharmacokinetics after a single dose of 300 mg has been examined in type-2 diabetic patients (n = 30) versus healthy volunteers (n = 30) and no significant differences were observed. Also, no significant correlation between glycaemic control (% glycosylated haemoglobin) and any of the measured pharmacokinetic parameters were detected (Zhao et al 2006).

Aliskiren demonstrated similar pharmacokinetic and pharmacodynamic properties in Japanese and Caucasian subjects (Vaidyanathan, Jermany et al 2007). At steady state, peak PRC level and AUC for the concentration-time plot were not significantly different ($p = 0.64$ and $p = 0.80$, respectively) and PRA was reduced to a similar extent (by 87.5% and 85.7%, respectively, compared with baseline; $p < 0.01$). Aliskiren was well tolerated by both ethnic groups.

Aliskiren is mainly eliminated unmetabolized via biliary excretion, with less than 1% excreted in the urine (de Gasparo et al 1989). Aliskiren binds only moderately to plasma proteins (mean protein-bounding level of 49.5%), with the

binding concentrations being independent over the range of 10–500 ng/ml (Azizi et al 2006).

Interactions with other drugs

Aliskiren 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). Aliskiren 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), hydrochlorthiazide (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).

Pharmacodynamic properties

Aliskiren is a highly potent inhibitor of human renin in vitro (IC_{50} = 0.6 nmol/L), this compares favourably with the earlier renin inhibitor compounds. Thus, the IC_{50} for enalkiren (A-64662) is 14 nmol/L (Rongen et al 1995), IC_{50} for remikiren (Ro 42-5892) and zankiren (A-72517) are 0.8 nmol/L and 1.1 nmol/L, respectively (Kleinbloesem et al 1993; Menard et al 1995). 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. Renin displays high specificity for its substrate and this species specificity complicates the preclinical experimental studies with renin inhibitors. Special transgenic model that over-expresses both renin and angiotensinogen (ie, double transgenic rats) has been developed and has provided an alternative to primate models for the evaluation of renin inhibitors (Ganten et al 1992; Fukamizu et al 1993).

Pre-clinical and clinical studies have shown that aliskiren effectively inhibits RAAS, along with dose-dependent decrease in BP. In a double-blind, randomised, crossover study in normotensive volunteers (n = 18), aliskiren was administered in two oral doses (either 40 mg and 80 mg or 160 mg and 640 mg once daily) and compared to enalapril 20 mg/day, or placebo (Nussberger et al 2002). Aliskiren dose-proportionally decreased PRA and plasma Ang I and Ang II concentrations. Compared with placebo, the highest dose of aliskiren reduced plasma Ang II by about 80%, although the plasma concentration of renin rose by more than ten times. Inhibition was still significant after repeated dosing, with maximal decreases in Ang II levels by 89% and 75% on days 1 and 8, respectively. The inhibitory effects of aliskiren (160 mg) on Ang II were comparable to the effects of enalapril (20 mg). Decreases in plasma and urinary aldosterone levels were detected with aliskiren at daily doses of 80 mg or more but not at 40 mg (Nussberger et al 2002).

The effects of aliskiren on plasma renin activity (PRA) were assessed in an open-label, 8-week dose escalation study in patients with mild-to-moderate essential hypertension (n = 8). Aliskiren, 75 mg for 4-weeks, reduced PRA to 34 ± 7% of baseline levels, with 4-weeks of further treatment with 150 mg of aliskiren giving an additional reduction to 27 ± 6% of baseline activity (Wood et al 2003).

Importantly, the rapid rise in plasma immunoreactive renin levels observed following aliskiren administration, caused by the removal of the normal feedback inhibition of Ang II on renin release, did not compromise the ability of aliskiren to provide sustained PRA inhibition and BP lowering (Wood et al 2003). This is in accordance with the sustained inhibition of Ang II production observed over 8-day period with once-daily oral administration of aliskiren in doses of 40–640 mg in healthy volunteers (Nussberger et al 2002).

In a small pilot trial with a four-period randomised crossover design, single doses of 300 mg aliskiren, 160 mg valsartan, the combination of 150 mg aliskiren plus 80 mg valsartan, or placebo were given to 12 male volunteers with mild sodium depletion (Azizi et al 2004). Aliskiren reduced PRA and plasma levels of Ang I and II for 48 h. Compared with valsartan, aliskiren more strongly stimulated the release of active renin into the circulation (about 10 times compared with about 15 times) while inhibiting PRA, and reduced the urinary aldosterone excretion for a longer period (8 vs 48 h). The effects of the combination of the lower doses of aliskiren and valsartan were similar to those of 300 mg aliskiren and larger than those of 160 mg valsartan. Aliskiren also blunted the valsartan-induced rise in plasma renin activity and in plasma concentration of angiotensin I and II (Azizi et al 2004). These findings suggest that, at lower doses, renin inhibitors and angiotensin-receptor blockers might have synergistic effects on the renin system.

Similar findings were obtained In 3 open-label studies in which BP was assessed with ambulatory measurement (O'Brien et al 2007). Aliskiren was administered to patients with mild-to-moderate hypertension in combination with hydrochlorothiazide (n = 23), ramipril (n = 21), or irbesartan (n = 23). Aliskiren (150 mg) alone significantly inhibited plasma renin activity by 65% ($p < 0.0001$) while ramipril and irbesartan monotherapy caused 90% and 175% increases in plasma renin activity, respectively. By contrast, when aliskiren was co-administered with hydrochlorothiazide, ramipril, or irbesartan, plasma renin activity did not increase but remained similar to baseline levels or was decreased, alon with improved 24-hour blood pressure control (O'Brien et al 2007).

Clinical studies with aliskiren in essential hypertensive patients

Early phase II trials with aliskiren compared the BP-lowering effects and safety of aliskiren with placebo, with losartan and irbesartan.

Aliskiren (at doses 37.5, 75, 150, and 300 mg once daily) and losartan (100 mg once daily) were compared in a 4-week trial in 226 patients with mild-to-moderate essential hypertension. Aliskiren showed dose-dependent reduction in BP, with the changes in patients getting 75–300 mg of aliskiren similar to those receiving 100 mg of losartan (Stanton et al 2003).

In a comparative trial with the ARB irbesartan, 652 hypertensive subjects were randomized to receive either irbesartan (150 mg) or aliskiren (150, 300 and 600 mg). At a dose of 150 mg, aliskiren was as effective as irbesartan (150 mg) in lowering blood pressure with similar safety and tolerability over the short term (Gradman et al 2005).

The BP-lowering effects of aliskiren (75, 150, or 300 mg) alone or in combination with the ARB valsartan (80, 160, or 320 mg) were compared in a multicenter, randomized, placebo-controlled, 8-week trial in 1123 patients with mild-to-moderate hypertension (Pool et al 2007). In an additional comparator arm, patients were receiving a combination of valsartan/hydrochlorothiazide (160/12.5 mg). The results indicated that co-administration of aliskiren and valsartan produced a greater antihypertensive effect than either drug alone, comparable in magnitude to the effect of valsartan/hydrochlorothiazide, with similar tolerability to the component monotherapies and to placebo (Pool et al 2007).

In subsequent trials, aliskiren has been compared with other antihypertensive drugs. Aliskiren (in doses 75 mg, 150 mg, 300 mg once daily) was compared with HCTZ (in doses 6.25, 12.5, and 25 mg once daily), and with the combination of the two agents in an 8-week placebo-controlled, factorial design trial in 2776 hypertensive patients (published so far only as an abstract). This study demonstrated that HCTZ significantly potentiates the antihypertensive efficacy of aliskiren. The greatest mean reduction in BP (21.2/14.3 mmHg in systolic and diastolic BP, respectively) was observed with the combination of aliskiren 300 mg and HCTZ 25 mg. The responder rates for aliskiren monotherapy were betweem 51.9% (75 mg) and 63.9% (300 mg), and similar to those observed with HCTZ (Villamil et al 2006).

Data for safety and efficacy of aliskiren over long-term use has recently become available. Thus, the efficacy of aliskiren with optional addition of HCTZ was studied in a 12-month open-label study (Sica et al 2006; published so far only as an abstract). Patients with mild-to-moderate essential hypertension were randomized to aliskiren 150 mg (n = 1178) or 300 mg (n = 773) once daily. Dose titration (aliskiren 150 mg titrated to 300 mg) or addition of HCTZ (12.5 mg titrated to 25 mg if required) to aliskiren 300 mg was permitted in patients with BP $\geq$140/90 mmHg after Month 2. A subgroup of patients remaining on aliskiren monotherapy at Month 11 were randomized to continued aliskiren (n = 132) or placebo (n = 129) during a 4-week double-blind withdrawal phase. In total, 868 patients (45%) required addition of HCTZ, the BP reductions at study end were comparable in these patients (BP reduction of 18.7/12.1 mmHg) and the patients who had responded adequately to aliskiren monotherapy (BP reduction of 17.4/13.3 mmHg). Following treatment withdrawal, BP rose gradually with no evidence of rebound (Sica et al 2006).

Rebound hypertension has not emerged as a problem with aliskiren. Theoretically it is conceivable that long-term renin-inhibition therapy could induce pharmacologic tolerance with renin hypersecretion as well as the phenomenon of rebound hypertension after abrupt cessation of chronic therapy. However, clinical experience with aliskiren does not confirm this, as shown in the long-term study reported recently by Sica et al 2006. In another study in 672 patients with mild-to-moderate essential hypertension, aliskiren withdrawal after 8-week therapy (in doses 150, 300 or 600 mg) was not associated with blood pressure or PRA rebound, despite elevated plasma renin concentration at the time of withdrawal, BP and PRA remained suppressed for 2-weeks after discontinuation of therapy (Herron et al 2006).

Recently, Weir et al (2006) have reported a pooled analysis of data from 8 randomized multicenter studies with aliskiren, including 8570 patients with mild to moderate hypertension (published so far only as abstract). Treatment durations ranged from 6 to 52-weeks. The analysis showed

that aliskiren as monotherapy effectively reduces blood pressure in a dose-dependent fashion in doses of 75–600 mg, its effect was similar regardless of age or gender.

In summary, these clinical studies show that once-daily administration of aliskiren effectively lowers BP, being at least as effective as or possibly more effective than standard doses of established ACE inhibitors and ARBs. The long half-life of aliskiren can be expected to provide more reliable continuous BP control through the morning surge of BP that is known to be associated with increased cerebrovascular events (Kario et al 2003). Also, aliskiren possesses synergistic potential when combined with a thiazide diuretic, an ACE inhibitor, a calcium antagonist, and possibly also with an ARB.

Target organ protection with aliskiren

There is considerable evidence that inhibition of RAAS in essential hypertension is associated with prevention of cardiovascular complications (Dahlöf et al 2002, 2005; Julius et al 2004). However, in all these studies (and several others), the interpretation of the results has been difficult with regard to identifying the benefits that go beyond those of BP reduction per se. Moreover, it has been suggested that blood pressure lowering is the major determinant of cardiovascular events in primary and secondary prevention trials and the differences in outcomes can be ascribed to small differences in achieved systolic blood pressure (Staessen et al 2005; Wang et al 2005). Similarly, a recent meta-analysis of 127 clinical trials questioned the specific renoprotective effects of ACE inhibitors and ARBs beyond the effect related to blood pressure lowering (Casas et al 2005).

However, even though the underlying mechanisms of achieving cardiovascular protection may not be completely understood, establishing a new antihypertensive drug as a valuable addition to current therapeutic options requires proof of beneficial effects on mortality and morbidity. There is no long-term data available yet for aliskiren from studies with hard endpoints, but certain characteristics of the drug may point to cardioprotective and renoprotective properties.

The potential renoprotective effects of renin inhibitors were suggested already based on the studies with the earlier compounds. Studies on renal vasodilation with enalkiren and zankiren showed that renin inhibitors induce renal vasodilation to a greater extent than ACE inhibitors, despite the expectation that ACE inhibition might be superior due to additionally inducing vasodilation through kinin generation (Hollenberg et al 1998). These studies indicate that renin inhibitors might confer renoprotection possibly to larger extent than the ACE inhibitors.

Pilz et al studied aliskiren in relation to target-organ damage in the double transgenic rat model comparing the effects of aliskiren (0.3 mg/kg/day and 3 mg/kg/day) and valsartan (1 mg/kg/day and 10 mg/kg/day) with no treatment (Pilz et al 2005). Both aliskiren doses and the high valsartan dose lowered blood pressure and albuminuria more effectively than the low valsartan dose. Aliskiren and valsartan in high dose ameliorated markedly left ventricular hypertrophy. After 3-weeks, none of the untreated rats had survived, compared with 74% of the low-dose valsartan group, and 100% in all other groups (ie, high-dose valsartan and both aliskiren doses). In this animal model, renin inhibition therefore compared favourably with AT1-receptor blockade in reversing target-organ damage.

It has been speculated that direct inhibition of renin might have further advantage in cardiovascular protection by preventing activation of specific renin receptors (Azizi et al 2006). The renin receptor was identified in 1996 in the glomerular mesangium cells (Nguyen et al 1996), the receptor is also present in the subendothelium of coronary and renal arteries. Renin was found to bind to this receptor with high affinity, but binding of renin to this receptor was not attenuated by renin inhibitors, indicating that the renin catalytic site is distinct from the receptor binding site. It was further elucidated that binding of renin to this receptor resulted in significant increase in its catalytic efficiency in Ang I formation (Nguyen et al 2002). Receptor-bound renin will also induce a series of intracellular events that are distinct from the generation of Ang II. Moreover, this receptor also binds prorenin that, when bound to the receptor, would have renin-like action. Prorenin has been shown to be a powerful predictor of microvascular complications in diabetes mellitus, although the exact mechanism of this deleterious effect has not been elucidated (Fisher and Hollenberg 2005). It could be speculated that the activation of the renin receptor, in combination with the increased catalytic activity, might play a role in the pathogenesis of vascular complications, pointing to an attractive therapeutic potential for renin inhibition.

Tolerability and safety

Aliskiren has been shown to be well tolerated in healthy subjects and in patients with hypertension, when given as single and multiple oral doses. The incidence of adverse events with aliskiren and the number of study discontinuations as a result of adverse events during aliskiren treatment have been relatively low and were similar to results obtained in patients treated with wither placebo. The most common adverse effects reported were fatigue, headache, dizziness and diarrhoea (Stanton et al 2003, Gradman et al 2005; Weir et al 2006).

No dose-dependent increase in the number of adverse effects and no significant abnormalities in laboratory parameters have been observed with aliskiren doses up to 300 mg (Stanton et al 2003; Weir et al 2006). However, higher doses of aliskiren (600 mg) seem to be associated with higher rate of diarrhoea when compared to placebo. In the meta-analysis by Weir et al (published so far only as abstract), the incidence of diarrhoea with aliskiren 600 mg was 9.5% versus 1.2% in the placebo group, there was no increase with aliskiren doses of 150 mg or 300 mg (1.2% and 2.3% respectively), and diarrhoea was not associated with patient discontinuations (Weir et al 2006).

Aliskiren is a highly selective inhibitor of the RAS and does not interfere with the metabolism of bradykinin or substance P; therefore side-effects such as cough or angioedema that occur with ACE inhibitors are not likely to occur with aliskiren treatment. Aliskiren's side effect profile is rather comparable to that of ARBs (ie, similar to that of a placebo).

Aliskiren was well tolerated in patients with hepatic imparment (Vaidyanathan et al 2007). This open-label, nonrandomized, single-center, parallel-group study compared the pharmacokinetics and safety of a single 300 mg oral dose of aliskiren in patients with mild, moderate, or severe hepatic impairment to that in healthy subjects. Pooled analysis across subgroups was performed, with no significant differences detected between patients with hepatic impairment and healthy subjects in aliskiren $AUC_{0-\infty}$ (ratio of geometric means, 1.12; 90% confidence interval, 0.85, 1.48) or C_{max} (mean ratio, 1.19; 90% confidence interval, 0.84, 1.68). Also, there was no correlation between severity of hepatic impairment and either $AUC_{0-\infty}$ or C_{max}. In conclusion, hepatic impairment had no significant effect on the pharmacokinetics of aliskiren following single-dose administration, and dosage adjustment is unlikely to be needed in patients with liver disease (Vaidyanathan et al 2007).

Although aliskiren appears to be safe, additional data would be needed to assess the effects of aliskiren on renal function and biochemistry, especially serum potassium levels in patients with renal impairment, heart failure and diabetes mellitus (Azizi et al 2006). The potential hazards of a complete RAAS inhibition with combination treatment (aliskiren combined with ACE inhibitor and/or ARB) require careful evaluation, especially in situations in which blood pressure and renal function are renin dependent (such as in elderly or salt-depleted patients), in patients receiving COX inhibitors, patients with renal artery stenosis and patients placed under anaesthesia (Azizi et al 2006).

In summary, aliskiren appears to be well tolerated and safe based on the available clinical data. Future studies should further confirm the beneficial side-effect profile of aliskiren in specific patient populations such as patients with renal impairment or heart failure. The potential hazards of a complete RAAS inhibition when using aliskiren in combination with ACE inhibitors or ARBs need to be evaluated, especially in populations in whom BP and renal function are renin dependent, such as elderly, salt-depleted patients and patients with renal artery stenosis.

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. Aliskiren has demonstrated target organ protection in animal models and in clinical trials, future studies must show whether these properties translate into beneficial effects on long-term morbidity and mortality.

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