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R E V I E W

Role of aliskiren in blood pressure control and renoprotection

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Abstract: Patients with chronic renal disease are at increased risk for the development of cardiovascular disease, which is the main cause of death in this growing population. Among the risk factors involved, hypertension and proteinuria are major contributors to kidney damage and, if not controlled, may eventually lead to the progression of renal failure and end-stage renal disease. Both proteinuria and hypertension can be primary pathologic events or can appear as complications of other disease processes. Initially, these two factors may operate separately but, as progression ensues, both processes generally combine, potentiating their effects and hastening renal damage. Therefore, strategies to reduce blood pressure and proteinuria are essential in order to slow the worsening of many nephropathies. Therapies that target the renin–angiotensin system offer particular benefit, as hypertension and proteinuria can be precisely reduced with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers. However, with this intervention, plasma renin activity remains high, and although primary endpoints may be controlled, elevated renin concentration can contribute to cardiovascular damage. Aliskiren, a direct renin inhibitor, is the first example of a novel class of antihypertensive drugs with potent antiproteinuric effects, which, alone or combined, can contribute to delaying the progression of kidney disease.

Keywords: aliskiren, proteinuria, hypertension, chronic kidney disease, renoprotection

Introduction to blood pressure management and renoprotection

Hypertension and diabetes mellitus account for over 50% of cases of chronic kidney disease. High blood pressure itself is a major risk factor for the progression of renal disease, affecting approximately 30% of the adult population in Western countries.[1] As pointed out by Ritz[2] in an editorial regarding the 2007 World Kidney Day, "High blood pressure, not necessarily the 'disease' hypertension according to current definitions (JNC7), is a major killer …" If a subject presents a blood pressure of 140 mm Hg systolic, the risk of stroke or myocardial infarction is double that of someone with a blood pressure of 120 mm Hg systolic. However, with a systolic blood pressure of 120–130 mm Hg, rather than 120 mm Hg or lower, the risk of end-stage renal disease is approximately 62% and rises to nearly 160% with a pressure of 130–140 mm Hg.[3] Therefore, an aggressive approach to blood pressure reduction is mandatory. However, it is estimated that only a small percentage of hypertensive patients have adequate blood pressure control. This situation can, in part, explain the growing number of cases of chronic renal failure. According to the recently published United States Renal Data System (USRDS) report, in the general population, 31% of hypertensives are unaware

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41

of their diagnosis, 11% are aware but not treated, 24% are treated but uncontrolled, and only 34% of subjects are aware, treated, and well controlled. Surprisingly, in patients with chronic kidney failure stages 3–4 (glomerular filtration rate 15–60 mL/min), 24% are unaware of being hypertensive, 6% are aware but not treated, 50% are aware but poorly controlled, and only 20% have their blood pressure controlled (<130–180 mm Hg).[4] In the same report, it is shown that 91.4% of chronic kidney patients are hypertensive.[5] This grim reality may partially explain why the adjusted rate of prevalent cases of end-stage renal disease in the US rose 1.9% in 2008 (the same rate growth as that seen in 2007) to 1699 per million population. This rate is nearly 20% higher than that seen in 2000. The annual rate of increase has remained stable between 1.9% and 2.3% since 2003.[6]

Proteinuria is another relevant target, as it is a major risk factor for renal disease progression.[7–9] Proteinuria can be due to primary glomerulopathies (focal and segmental glomerulonephritis, membranous nephropathy, minimal change disease, Berger's disease, membranoproliferative glomerulonephritis), which are the third most likely cause of end-stage renal disease in the adult population and an important cause of secondary hypertension, or to secondary glomerular damage as a result of primary hypertension, diabetes mellitus, reflux nephropathy, or other causes of renal disease. A coexistent diagnosis of hypertension and diabetes increases the risk of adverse cardiovascular and renal outcomes. This increased risk extends to a diastolic blood pressure of ≥83 mm Hg and a systolic blood pressure of ≥127 mm Hg.[10,11] Reduction of proteinuria by >30% within the first 6–12 months of treatment in patients with chronic kidney disease has been shown to predict long-term renal and cardiovascular outcomes.[8,12] Moreover, the management of albuminuria in normotensive or hypertensive patients with diabetes may slow progression of diabetic nephropathy.[13] Microalbuminuria itself, an early marker of kidney vascular dysfunction, is a strong prognostic indicator of mortality and cardiovascular disease in hypertension and diabetes mellitus.[14,15] Therefore, one of the main goals to slow the progression of renal disease is an adequate and not unusually aggressive control of blood pressure and the reduction of proteinuria to its lowest possible level.

In this regard, the pharmacological manipulation of the renin–angiotensin–aldosterone system (RAAS) is an important tool to employ, as renin, angiotensin II, and aldosterone are important molecules with hemodynamic and inflammatory effects both systemically and locally, particularly in the kidney. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce proteinuria and blood pressure, either alone or combined.[16] However, by attenuating feedback inhibition of renin release, ACEIs and ARBs effects lead to an increase in plasma renin concentration and activity, rendering incomplete inhibition of the RAAS system.[17,18] Moreover, inhibition of ACE causes an increase in angiotensin I, which is then available for conversion to angiotensin II by ACE-independent pathways not blocked by ACEIs, namely cathepsins and tonins.[19–21] Consequently, despite adequate blood pressure control, angiotensin II levels increase aldosterone levels to certain degrees, rendering these inflammatory molecules free to play an active role in tissue remodeling and scarring. Henceforth, it is tempting and reasonable to assess the effects of a different pharmacologic strategy that blocks the RAAS upstream completely. Aliskiren is the first known representative of a new class of nonpeptide orally active renin inhibitors that block the RAAS at its rate-limiting step and induce a net reduction in plasma renin activity and angiotensin II and aldosterone levels.[22–24] Aliskiren has been assessed in recent years as an efficient antihypertensive drug, either alone or in combination with other drugs. Its antiproteinuric effects are notorious and may be independent of its antihypertensive effects, showing that aliskiren alone or combined can further decrease proteinuria and the risk of renal disease progression.[25] This suggests that renin- or angiotensin-independent pathways may be involved in inflammatory processes of which proteinuria is a disease activity marker and that aliskiren can abrogate.

Review of aliskiren pharmacology, mode of action, pharmacokinetics, and effects on renal hemodynamics

The direct renin inhibitor aliskiren is an octanamide and a nonpeptide piperidine with high affinity and specificity for human renin,[25] and it inhibits the enzyme renin by binding to its catalytic site, thus blocking the RAAS at its point of activation.[26] In this respect, angiotensin I, angiotensin II, and aldosterone levels decrease, and their hemodynamic and inflammatory effects are abolished. Therefore, aliskiren impedes efferent arteriolar vasoconstriction and diminishes the glomerular filtration fraction, salt and water absorption, and angiotensin II-induced inflammatory actions. Moreover, it blocks renin and prorenin activity while renin and prorenin levels remain high.[22,24,25]

A recently discovered (pro)renin receptor activates when exposed to either renin or prorenin, the inactive form of renin.[27] The (pro)renin receptor, in turn, enhances renin catalytic activity and allows prorenin to display catalytic activity without its proteolytic conversion to renin. This (pro)

renin receptor-induced prorenin activation could explain how prorenin exerts pathological effects in diabetic patients, where prorenin represents approximately 95% of total circulating renin.[28] Interestingly, recent data have shown that renin and prorenin induce activation of the extracellular signal-regulated kinase (ERK) pathway, independent of angiotensin II. In this respect, aliskiren has no (pro)renin receptor-blocking action. Therefore, ACEIs, ARBs, and aliskiren all increase renin concentration, which could conceivably induce (pro)renin receptor signaling without the involvement of angiotensin II, suggesting that blockade of the (pro)renin receptor might be an alternative or an adjunct to renin–angiotensin system inhibition, particularly in conditions with high renin and/or prorenin levels.[28] High prorenin levels are closely associated with the severity of diabetic complications. In this respect, in diabetics, increased prorenin levels have been shown to be associated with microalbuminuria and with the development of nephropathy.[29,30] However, aliskiren still blocks the tissue renin–angiotensin system, because at the (pro)renin receptor level, activated prorenin can immediately be blocked by aliskiren. The result would be angiotensin II production not occurring.[28] Interestingly, renin bound to the (pro)renin receptor presents much more enhanced catalytic activity than soluble renin.[31] The cloning of a functional receptor for both renin and prorenin suggests that renin and prorenin may exert direct angiotensin II-independent tissue-damaging effects by increasing the expression of profibrotic pathways and molecules, such as transforming growth factor-β.[32] Additionally, the receptor may amplify renin-induced angiotensin II-dependent effects. Plasma renin activity is blocked only by aliskiren. Elevated baseline plasma renin activity in untreated patients has been associated with end-organ damage, such as left ventricular hypertrophy and renal dysfunction,[33,34] probably due to high angiotensin II levels. Renin inhibition with aliskiren therefore offers the chance of enhanced RAAS suppression and improved end-organ protection either alone or in combination with other antihypertensive drugs.[35]

Aliskiren is poorly absorbed, with an absolute oral bioavailability of 2.5% with maximum plasma aliskiren concentrations reached within 1–3 hours of oral administration.[36,37–39] Although food has a big effect on the pharmacokinetics of aliskiren, the resulting decreases in aliskiren exposure are not considered clinically relevant.[40] Steady-state plasma concentrations are reached 5–8 days after once-daily oral administration of aliskiren.[36,41] The half-life of oral aliskiren is around 24 hours;[40] it is approximately 50% protein bound in human plasma, and protein binding is independent of aliskiren plasma concentration.[41] Hepatic and renal metabolism are

not major routes of aliskiren elimination.[40,41] Following a single oral 300 mg dose, aliskiren has an elimination half-life of 40 hours in healthy volunteers.[42] Excretion is almost completely by the fecal route (91.5%), with 77.5% of the dose excreted as unchanged drug.[43] The pharmacokinetics of aliskiren are not affected by sex,[36,41] body mass index,[36,41] or race and are similar in Chinese, Japanese, and Caucasian[44–46] patients. The pharmacokinetics of aliskiren in patients with hepatic impairment, mild to severe renal disease,[36,41] or type 2 diabetes[42] are no different from those of healthy volunteers. Thus, initial dosage adjustments are not necessary in patients with renal or hepatic impairment.[36,41]

Aliskiren has a low potential for clinically relevant interactions with other drugs.[40,41] However, coadministration of aliskiren with irbesartan decreased the aliskiren maximum concentration by 50% after multiple dosing.[36,41] The exposure to aliskiren was not altered by coadministration of furosemide.[47] However, furosemide decreased by 28% and 49% with concomitant aliskiren administration. Although the clinical significance of this is unclear, the effects of furosemide should be monitored.[41] When aliskiren was coadministered with rifampicin, the latter reduced aliskiren concentration by 39%.[48] Coadministration of aliskiren with potent P-glycoprotein inhibitors (cyclosporine, quinidine, and verapamil) is virtually contraindicated because aliskiren plasma concentrations significantly increase, and aliskiren and moderate P-glycoprotein inhibitors (ketoconazole, itraconazole, clarithromycin, telithromycin, erythromycin, and amiodarone) should be coadministered with caution. Grapefruit juice should not be taken together with aliskiren.[41]

One concern is the potential adverse effect of high circulating renin concentrations after aliskiren therapy. As mentioned previously, aliskiren binds to the active site of renin, reducing its activity (plasma renin activity) and angiotensin II production. Diminished angiotensin II levels stimulate renin secretion (plasma renin concentration). The potential negative consequence of high renin concentration is that renin may bind to a renin receptor and trigger yet unknown events.[49] However, an important contributor to the exaggerated renin response is interference by the renin inhibitor in the renin assay causing overestimation of the renin concentration.[50] Thus, this renin response may not actually represent an increase in enzymatically active renin molecules in plasma. The question of whether this increase in renin concentration has any effect remains unanswered. Although aliskiren lowers plasma renin activity, renin concentration rises, and ACEIs and ARBs increase both.[51,52] As mentioned previously, high levels of renin can activate the prorenin/renin receptor,

which aside from activating prorenin, can possibly initiate ERK1/2 signaling and transform growth factor-β activation and other potentially serious complications.[25,53] However, ACEIs and ARBs also leave these issues unresolved with a partial inhibition of angiotensin II concentration, despite good blood pressure control. Some authors have argued against renin inhibition, because plasma renin concentrations attained after aliskiren are higher than those obtained after ARBs.[54] However, in some studies in mice, ARBs have caused higher plasma renin concentrations than aliskiren. This discrepancy could partly be due to the method employed to measure renin concentrations in mice and humans.[55]

Plasma renin activity is blocked only by aliskiren. Elevated baseline plasma renin activity in untreated patients has been associated with end-organ damage, such as left ventricular hypertrophy and renal dysfunction,[56,57] probably due to high angiotensin II levels.[58] Renin inhibition with aliskiren therefore offers the chance of enhanced RAAS suppression and improved end-organ protection, either alone or in combination with other antihypertensive drugs.[25,59] The kidney is an important site of the uptake of renin inhibitors, and aliskiren has been found in renal glomeruli, renal arteries, and capillaries.[60,61] Aliskiren may act directly on the renin-secreting juxtaglomerular cell to influence prorenin processing and renin release.[50]

Efficacy studies and organ protection
Efficacy studies
The therapeutic efficacy of aliskiren will be outlined in this section at a dosage of 150 mg/day or 300 mg/day alone and compared with placebo and ACEIs or ARBs and/or combined with hydrochlorothiazide, valsartan, valsartan plus hydrochlorothiazide, amlodipine, amlodipine plus hydrochlorothiazide, ramipril, and atenolol. In general, adult patients were enrolled in these trials with diastolic blood pressures >90–95 mm Hg and <110 mm Hg or mean systolic blood pressures between >160 mm Hg and <200 mm Hg. Patients with secondary hypertension, severe cardiovascular disease, uncontrolled diabetes mellitus, and hepatic or renal disease were excluded from most studies. A concise, thorough, updated review has recently been published.[62]

Monotherapy
In the 8-week, placebo-controlled trials, monotherapy with aliskiren 150 mg/day or 300 mg/day reduced baseline systolic and diastolic blood pressure to a significantly greater extent than placebo in patients with stage 1 to stage 2

hypertension.[63–67] The antihypertensive efficacy of aliskiren monotherapy was also demonstrated in subgroups of patients, including diabetic and obese patients and those with metabolic syndrome.[68]

Comparisons with other agents
Across a number of trials in patients with hypertension, aliskiren monotherapy was generally as effective as hydrochlorothiazide, ramipril, lisinopril, irbesartan, atenolol, valsartan, and losartan at reducing blood pressure in short-term studies. In long-lasting, double-blind trials, aliskiren-based therapy was at least as effective as ramipril-based therapy[69] and more effective than hydrochlorothiazide-based therapy.[70]

Aliskiren 150–300 mg/day was more effective than irbesartan 150–300 mg/day[71] and generally as effective as valsartan 160–320 mg/day[72] and losartan 100 mg/day[73] in lowering blood pressure. Aliskiren did not differ significantly from atenolol in lowering systolic blood pressure in a study in which patients received aliskiren 150 mg/day or atenolol 50 mg/day for 6 weeks followed by 6 weeks on double the initial dose of the agents.[74] However, reductions in diastolic blood pressure were significantly greater with atenolol than with aliskiren at both 6 weeks and 12 weeks.

Combination therapy
The efficacy[75–77] of aliskiren in combination with other antihypertensives has been evaluated in randomized, double-blind or open-label, multicentre trials in which aliskiren 150–300 mg/day was administered in combination with hydrochlorothiazide, valsartan, valsartan plus hydrochlorothiazide, amlodipine, amlodipine plus hydrochlorothiazide, ramipril, and atenolol.

In patients with stage 1 to stage 2 hypertension, combined strategies of aliskiren plus hydrochlorothiazide were more effective than aliskiren, hydrochlorothiazide, or ramipril monotherapies, and at least as effective as amlodipine, in reducing blood pressure in patients with stage 2 hypertension, including patients with diabetes, patients with obesity, patients with metabolic syndrome, African American patients, and aged patients.[78–83] Patients who received aliskiren plus valsartan had significantly greater blood pressure reductions than with either an individual component or placebo.[84] The antihypertensive effect of the combination of aliskiren plus valsartan was similar in patients with or without diabetes.[36] The antihypertensive effects of the aliskiren plus valsartan combination were diminished in African American patients, as was the case with ACEIs, ARBs, and atenolol.[36]

Aliskiren in combination with amlodipine was effective in lowering BP in patients with stage 1 to stage 2 hypertension.[62] First-line therapy with combination aliskiren 150 mg/day or 300 mg/day plus amlodipine 5–10 mg/day provided significantly greater control than the respective monotherapies in patients with stage 2 hypertension.[85] Combination therapy was also more effective than amlodipine monotherapy as first-line therapy in African-American patients with stage 2 hypertension.[86] This was also observed irrespective of age, sex, and the presence of diabetes or obesity.[62] Finally, aliskiren in combination with ramipril led to a significantly greater reduction in blood pressure than with each individual component in hypertensive patients with type 1 or 2 diabetes.[84] In a study combining aliskiren 150 mg/day with atenolol 50 mg/day, there were greater reductions in blood pressure than with aliskiren monotherapy after 12 weeks' treatment.[87]

Safety and tolerability

Aliskiren was generally well tolerated at doses of 150 or 300 mg/day[62] and resulted in an incidence of adverse events similar to placebo.[41] Adverse events, including uncontrolled hypertension (2.2%),[36] have generally been mild and have infrequently led to discontinuation of therapy.[41] The most common adverse events reported are headache (5.8%), nasopharyngitis (2.6%), and diarrhea (1.4%).[62] Aliskiren was also associated with a few cases of cough (1.1%), although, compared with ACEIs, the rate of cough was approximately one-third to one-half that reported with ramipril or lisinopril.[36] Although aliskiren has rarely been associated with changes in laboratory parameters, it is still prudent to monitor hemoglobin concentration and serum levels of creatinine, urea, potassium, uric acid, and creatine kinase.[36,41,62]

Organ protection

In respect of organ protection, although blood pressure-lowering effects with aliskiren are well established, its effects on cardiovascular morbidity and mortality are yet to be determined. A clinical program is under way to assess the potential benefits of aliskiren in clinical outcomes. Details on studies on the renoprotective and cardioprotective effects of aliskiren in hypertensive, diabetic subjects with nephropathy (Aliskiren in the Evaluation of Proteinuria in Diabetes [AVOID]),[88] reduced left ventricular hypertrophy (Aliskiren in Left Ventricular Hypertrophy [ALLAY]),[89] symptomatic heart failure (Aliskiren Observation in Heart Failure Treatment [ALOFT]),[90] acute coronary symptoms,[91] and postmyocardial infarction with low ejection fraction (Aliskiren Study

in Post-MI Patients to Reduce Remodelling [ASPIRE])[92] are available in the literature.

Aliskiren-based therapy demonstrated positive effects on the markers of cardiovascular and renal damage in hypertensive patients with type 2 diabetes and nephropathy, reducing proteinuria independently of blood pressure control[88] in patients with reduced left ventricular hypertrophy[89] or in those with symptomatic heart failure and reduced plasma N-terminal probrain natriuretic peptide.[90] However, aliskiren therapy did not have a beneficial effect on left ventricular remodeling after myocardial infraction.[92] Add-on aliskiren 300 mg/day had no significant beneficial effect on left ventricular end-systolic volume compared with placebo (ASPIRE).[92] Further studies are currently under way to evaluate the effect of aliskiren on the following clinical outcomes: reduction of cardiovascular death and heart failure rehospitalization events within 6 months in patients with congestive heart failure hospitalized for an episode of acute decompensated heart failure (Aliskiren Trial on Acute Heart Failure Outcomes [ASTRONAUT]),[93] morbidity and mortality in patients with type 2 diabetes and pre-existing cardiovascular disease and/or kidney disease (Aliskiren Trial in Type 2 Diabetes Using Cardio-renal Disease Endpoints [ALTITUDE]),[94] and morbidity and mortality in patients with chronic heart failure (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure [ATMOSPHERE]).[95] The potential benefit of aliskiren on long-term outcomes is currently being evaluated as part of the larger ASPIRE HIGHER program (n = 35,000).

Patient-focused perspectives

Aliskiren can be employed in patients with hypertension, and in particular in subjects with proteinuria. Despite the possibility of an occasional forgotten dose (missing dose), it exerts protection beyond 24 hours due to its long half-life. This feature is not associated with a higher risk of hypotension.[41] An important advantage is that aliskiren does not need to be adjusted in patients with hepatic or renal disease. As an antihypertensive drug, aliskiren is equivalent to any other drug and may not present major differences in blood pressure control when used as monotherapy, particularly at 300 mg/day. However, in hypertensive patients with proteinuria, it may present some advantages. It can be used alone or in combination with other drugs to achieve low protein urinary excretion. Although aliskiren does not present a renal route of elimination and would potentially be useful at any stage of renal disease, there is still not enough information to recommend its use in chronic renal failure stages 4 or 5. Patients with

renin-dependent hypertension are a target population. In these cases, potassium levels must be monitored periodically. Diabetics appear to benefit from aliskiren, independently of being normotensive or hypertensive, normoalbuminuric, microalbuminuric, or proteinuric. Aliskiren can block prorenin activity, which is increased in diabetic subjects and associated with inflammatory processes systemically. Although plasma renin activity is suppressed by aliskiren, plasma renin concentration remains high, and the eventual consequences of this phenomenon are still unknown in the adult population.[25]

In patients with primary or secondary glomerulopathies, such as lupus nephritis, in which immunosuppression is the mainstay of treatment, once the acute process has been approached and renal function stabilized, aliskiren could be used alone or in combination with ARBs, ACEIs, or other anti-hypertensive drugs to inhibit angiotensin II-induced inflammatory processes (vascular remodeling, tissue fibrosis) to decrease proteinuria and the maintenance dose of immunosuppressants. In addition, in patients with glomerulopathies and moderate degrees of proteinuria (eg, immunoglobulin A, focal and segmental glomerulosclerosis), a first attempt to decrease protein excretion avoiding the use of immunosuppression could be the employment of aliskiren alone or in combination with other antihypertensive drugs, particularly ACEIs or ARBs.

Conclusion

Patients who could benefit most from aliskiren alone or in combination include glomerular proteinuric subjects and patients with moderate to high cardiovascular risk. As high plasma renin activity is regarded as a risk factor for myocardial infarction in untreated hypertensive and normotensive patients, this population could benefit from aliskiren prescription.[48] Diuretics, β-blockers, and calcium channel blockers appear to be good options for combinations. Associations with ACEIs or ARBs should be preferentially reserved for proteinuric patients and, in this case, combinations should be approached in a step-by-step fashion, increasing doses gradually. Severe vasodilatation must be avoided, salt-free diets must be encouraged, and serum creatinine and potassium levels must be followed initially until the full designed dose is achieved. Proteinuria and blood pressure are the main goals to control.

Disclosure

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