Original Paper

Antihypertensive Efficacy of the Oral Direct Renin Inhibitor Aliskiren as Add-On Therapy in Patients Not Responding to Amlodipine Monotherapy

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This study investigated the addition of the direct renin inhibitor aliskiren to amlodipine in patients with mild to moderate hypertension that was inadequately controlled with amlodipine alone. Following once-daily treatment with amlodipine 5 mg for 4 weeks, patients whose hypertension responded inadequately to therapy (mean sitting diastolic blood pressure [DBP] 90–109 mm Hg) (n=545) were randomized to 6 weeks of double-blind treatment with amlodipine 5 mg plus aliskiren 150 mg, amlodipine 5 mg, or amlodipine 10 mg. At the study's end, mean systolic blood pressure and DBP reductions with the combination of aliskiren 150 mg and amlodipine 5 mg (11.0/8.5 mm Hg) were significantly greater (P<.0001) than with amlodipine 5 mg (5.0/4.8 mm Hg)—the comparator group—but similar to amlodipine 10 mg (9.6/8.0 mm Hg). All treatments were well tolerated. Edema occurred more frequently with amlodipine 10 mg (11.2%) than with combination therapy (2.1%) or amlodipine 5 mg (3.4%). In conclusion, aliskiren 150 mg plus amlodipine 5 mg shows similar but not better blood pressure–lowering efficacy when compared with amlodipine 10 mg in patients not completely responsive to amlodipine 5 mg; less edema was noted with combination therapy. (J Clin Hypertens. 2007;9:742–750) ©2007 Le Jacq

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Monotherapy with antihypertensive agents is insufficient to control blood pressure (BP) in many patients with hypertension (HTN).[1,2] Most guidelines for the management of HTN recognize that patients, especially those with more severe degrees of HTN or evidence of target organ involvement, will require therapy with at least 2 antihypertensive drugs for effective BP control.[1,2] It has been shown that even in the controlled setting of a clinical trial, combination therapy with 2 or 3 different antihypertensive agents is often required to achieve BP level targets.[3] Despite the availability of a range of antihypertensive therapies, approximately 50% to 60% of patients with HTN have BP levels that are not at goal.[4]

For patients in whom BP targets are not achieved with antihypertensive monotherapy, physicians have the choice of titration of the single agent to a higher dose or addition of a second antihypertensive medication to improve treatment response. Guidelines for the treatment of HTN recommend the use of antihypertensive agents with differing mechanisms of action,[2,5] as this increases the

likelihood of achieving BP control.[2] Thus, combining an agent that blocks the activity of the renin-angiotensin system (RAS) (an angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB]) with either a calcium channel blocker (CCB) or a diuretic would be expected to provide additional BP reductions. Both CCBs and diuretics reduce BP independent of the RAS; CCBs reduce BP by directly inducing vasodilation, while diuretics are also effective as vasodilators over the long term.

Further rationale for using CCBs with RAS blockers comes from their complementary effects on the autonomic system, RAS, and endothelium. The CCB amlodipine, as well as other CCBs, has been shown to increase sympathetic activity and decrease parasympathetic activity, whereas ACEIs and ARBs enhance parasympathetic activity but have little effect on sympathetic activity.[6,7] This suggests that the autonomic effects of amlodipine are likely to be mitigated by concomitant administration of medications that affect the RAS.[6] CCBs also cause reflex activation of the RAS, so use of these with a medication that blocks the activity of the RAS is a logical choice.[8] CCBs, ACEIs, and ARBs may also exert beneficial effects on the endothelium, such as improved nitric oxide availability. It has been suggested that these agents may have complementary effects on the vascular wall.[9–13]

These complementary actions may help explain the beneficial effects of a CCB combined with an ACEI that were recently reported in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).[14] Although the primary end points of coronary heart disease events were no different than in a β-blocker–based group, there was a lower incidence of overall cardiovascular events and all-cause mortality with the CCB/ACEI combination. Previous studies have demonstrated that therapy with CCBs and ACEIs provides significantly greater BP reductions when compared with CCB or ACEI monotherapy, with a significantly lower incidence of edema than with amlodipine alone.[15–17] When combined with an ACEI or ARB, diuretics have also been found to be as effective in reducing BP as an CCB/ACEI combination.[18]

Aliskiren is the first in a new class of orally effective direct renin inhibitors approved for the treatment of HTN and is a potent inhibitor of human renin.[19,20] The elimination half-life of aliskiren is approximately 40 hours,[21,22] making it suitable for once-daily dosing. Aliskiren monotherapy has been shown to provide effective BP reductions in short-term placebo-controlled studies,[23–26] providing comparable reductions to the ARB irbesartan[23] and the diuretic hydrochlorothiazide (HCTZ).[26] Unlike most other antihypertensive agents, aliskiren reduces plasma renin activity (PRA) from baseline, both as monotherapy and when combined with antihypertensive agents that elevate PRA.[24,26] Aliskiren has been shown to have a good safety profile, with adverse event rates similar to those observed with placebo at doses of ≤300 mg.[23,26]

Given that adequate BP control is not achieved in many hypertensive patients with a single antihypertensive agent, it is interesting to evaluate the effects of the addition of aliskiren in cases that involve an inadequate response to antihypertensive monotherapy. Based on the rationale of combining treatments that have complementary mechanisms of action, a logical approach might be to add aliskiren to a CCB in patients not responding to CCB monotherapy. The objective of the present study was to evaluate the effect on BP when once-daily aliskiren 150 mg was added to once-daily amlodipine 5 mg in patients with mild to moderate HTN that responded only partially to once-daily amlodipine 5 mg monotherapy. The safety and efficacy of administering this combination was compared with maintaining patients on once-daily amlodipine 5 mg or increasing the amlodipine dosage to 10 mg once daily. In addition, the effects of each treatment on PRA were assessed in a subset of patients.

METHODS

Patients

Eligible patients were men and women aged 18 years or older with mild to moderate HTN (mean sitting diastolic BP [DBP] level ≥95 to <110 mm Hg at baseline if untreated or DBP level <110 mm Hg if treated). Patient exclusion criteria included the following: severe HTN (DBP level ≥110 mm Hg and/or mean sitting systolic BP [SBP] level ≥180 mm Hg); a history or evidence of secondary HTN; hypertensive retinopathy (Keith-Wagener grade III or IV); a history of hypertensive encephalopathy or cerebrovascular accident; a transient ischemic cerebral attack in the previous 12 months; heart failure (New York Heart Association classes II–IV); a history of myocardial infarction, coronary bypass surgery, or percutaneous coronary intervention in the previous 12 months; angina pectoris requiring pharmacotherapy; second- or third-degree heart block without a pacemaker; life-threatening or symptomatic arrhythmia; clinically significant valvular heart disease or severe aortic stenosis; type I or type II diabetes mellitus with poor

glycemic control (hemoglobin A_{1c} >9%); upper arm circumference >42 cm; serum sodium less than normal and serum potassium <3.5 mmol/L or ≥5.5 mmol/L; evidence of renal impairment (serum creatinine level >1.7 mg/dL in women or >2.0 mg/dL in men at screening or a history of dialysis or of nephrotic syndrome) or hepatic disease (serum glutamic oxaloacetic transaminase or serum glutamic pyruvic transaminase values >3 times the upper limit of normal at screening, or a history of hepatic encephalopathy, esophageal varices, or portocaval shunt); and any condition that may affect the evaluation of efficacy or safety data or alter the absorption, distribution, metabolism, or excretion of study drugs. Patients were therefore relatively healthy except for the presence of HTN.

Patients were recruited at 81 centers in Denmark, Germany, Greece, Korea, Malaysia, Slovakia, South Africa, and the United States. All patients provided written informed consent. The study design was approved by the appropriate local ethical review boards and conducted in accordance with the principles of the 1996 Declaration of Helsinki of the World Medical Association.

Study Design

This was a randomized, double-blind, active-controlled, parallel-group multicenter study comparing the efficacy and safety of once-daily aliskiren 150 mg/amlodipine 5 mg combination therapy with continuation of once-daily amlodipine 5 mg or dose titration to once-daily amlodipine 10 mg in patients whose HTN did not adequately respond to initial treatment with amlodipine 5 mg. The study was designed to reflect the situation faced by many physicians in clinical practice: examining alternative approaches for improving treatment response (increasing the dose of current medication or adding a second antihypertensive agent) in patients in whom specific BP targets have not been achieved with antihypertensive monotherapy. Continued treatment with once-daily amlodipine 5 mg provided a control comparator group.

Newly diagnosed or currently treated hypertensive patients provided a complete medical history and list of concomitant medications and underwent a physical examination, BP and electrocardiographic (ECG) recordings, and evaluation of laboratory safety parameters (blood chemistry, hematology, and urinalysis). Premenopausal women underwent serum and urine pregnancy tests. Following a 2-week washout of all antihypertensive medications, patients with a DBP level ≥95 mm Hg and <110 mm Hg entered a 4-week, single-blind run-in period during which they received once-daily oral amlodipine 5 mg. At the end of the run-in period, screening assessments were repeated. Patients whose HTN had not adequately responded to once-daily amlodipine 5 mg (defined as those with a DBP level ≥90 mm Hg and <110 mm Hg) were randomized to receive 6 weeks of once-daily oral treatment with amlodipine 5 mg, amlodipine 10 mg, or aliskiren 150 mg/amlodipine 5 mg (using a 1:1:1 allocation ratio). The efficacy and safety of treatment were assessed in patients at 1, 3, and 6 weeks after randomization, as described below. Patients whose SBP level was ≥180 mm Hg and/or DBP was ≥110 mm Hg at any time were withdrawn from the study and appropriate therapy was instituted.

Assessments

Efficacy. The primary efficacy variable was the change in DBP from baseline (the end of the 4-week run-in period with once-daily amlodipine 5 mg) to the end of 6 weeks of double-blind treatment. The primary objective of the study was to compare once-daily aliskiren 150 mg/amlodipine 5 mg with once-daily amlodipine 5 mg monotherapy. Secondary efficacy measures included the change from baseline in SBP, comparison of reductions in DBP and SBP between the combination therapy and amlodipine 10 mg monotherapy, the proportion of patients in each treatment group who responded to treatment (defined as a DBP level <90 mm Hg at week 6 and/or a reduction of ≥10 mm Hg from baseline), and the proportion of patients in each treatment group in whom BP control was achieved (BP level <140/90 mm Hg).

Sitting and standing BP levels were measured at baseline and after 1, 3, and 6 weeks of the double-blind period of the trial. All BP measurements were obtained at trough (24±3 hours after drug dose) using an automated BP monitor (Omron HEM-705CP; Omron Corporation, Tokyo, Japan) in accordance with the Guidelines for Management of HTN: Report of the Fourth Working Party of the British HTN Society, 2004 (BHS IV).[5] Three BP measurements were obtained at 1- to 2-minute intervals and averaged to calculate mean DBP and SBP for that visit. Pulse rate was measured for 30 seconds immediately before measurement of sitting BP and standing BP at each visit.

In a subset of approximately 150 patients, PRA was measured by DiaSorin assay (DiaSorin, Saluggia, Vercelli, Italy) at baseline and after 6 weeks of treatment, and the change in PRA from baseline after 6 weeks' treatment was assessed.

Safety and Tolerability. Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs). Each AE was classified as mild, moderate, or severe; the investigator assessed any possible relationship with the study drug. SAEs were defined as any event that was fatal or life-threatening, resulted in persistent or significant disability, constituted a congenital abnormality, required in-patient hospitalization or prolonged hospitalization, or was considered in some other way medically significant.

Laboratory safety evaluations were performed at baseline and after 6 weeks' treatment (or at the last study visit) and included hematology, blood chemistry (urea, creatinine, glucose, bilirubin, aspartate aminotransferase, alanine aminotransferase, lactic dehydrogenase, alkaline phosphatase, electrolytes, total protein, albumin, and uric acid levels), and urinalysis. Physical examinations and ECG studies were performed at the screening visit before the washout period and at the start and the end of the double-blind treatment period.

Statistical Analyses

A sample size of at least 168 patients per group (total, 504 patients) was chosen to ensure that the study was powered (90%) to detect a statistically significant difference in DBP of at least 3 mm Hg between the once-daily aliskiren 150-mg/amlodipine 5-mg group and the once-daily amlodipine 5-mg group, assuming a 10% dropout rate and a standard deviation of 8 mm Hg. Based on previous clinical trials, an estimated 60% of patients were expected to have poorly controlled BP with amlodipine monotherapy (and were therefore expected to be eligible for the double-blind period of this study). As a result, a sample size of 840 patients was planned for entry into the single-blind run-in period.

Efficacy analyses were performed on the intent-to-treat (ITT) population (all randomized participants who received ≥1 dose of the study drug, had a baseline assessment, and had ≥1 postbaseline assessment of efficacy). For each patient, the last postbaseline measurement for each variable assessed during the double-blind treatment period was carried forward and used as the week 6 end point measurement in the analyses. Changes in the primary efficacy variable were assessed using a 2-way analysis of covariance model with treatment and region as factors and baseline DBP values as a covariate. The null hypothesis was that there was no difference in the primary efficacy variable between once-daily aliskiren 150 mg/amlodipine 5 mg and once-daily amlodipine 5 mg; the alternative hypothesis was superiority of the combination over amlodipine 5 mg.

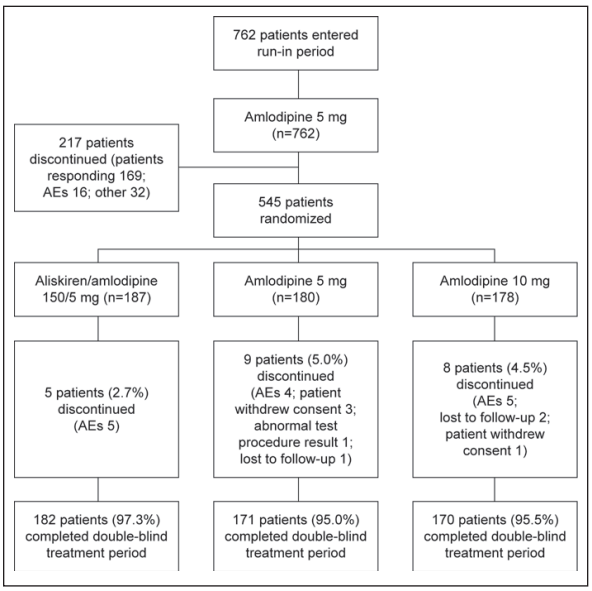

Figure 1. Patient flow. AEs indicates adverse events.

The secondary efficacy variables of change in SBP from baseline and comparison of SBP and DBP in the combination therapy group vs the once-daily amlodipine 10-mg group were analyzed in a way similar to the primary variable. The proportion of responders in each group was compared using a logistic regression model with treatment and region as factors and baseline DBP as a covariate. Pairwise comparisons of each treatment were made at a 2-sided significance level of <.05. The proportion of patients in whom BP control was achieved was analyzed in the same manner as the proportion of responders.

Safety and tolerability assessments were performed on the safety population, which was defined as all patients who received ≥1 dose of the double-blind study drug and had ≥1 postbaseline safety assessment.

RESULTS

Patients

A total of 762 patients were enrolled in the study. Of these, 169 responded to initial therapy with once-daily amlodipine 5 mg (DBP level <90 mm Hg) and 48 were not randomized for other reasons. The remaining 545 patients were randomized to double-blind treatment (187 received once-daily aliskiren 150 mg/amlodipine 5 mg, 180 received once-daily amlodipine 5 mg, and 178 received once-daily amlodipine 10 mg). In total, 541 patients were included in the ITT population (n=187, n=177, and n=177 for the aliskiren

Table I. Demographic and Baseline Clinical Characteristics of All Randomized Patients

Characteristic	Once-Daily Aliskiren 150 mg/ Amlodipine 5 mg (n=187)	Once-Daily Amlodipine 5 mg (n=180)	Once-Daily Amlodipine 10 mg (n=178)
Male sex, No. (%)	105 (56.1)	95 (52.8)	92 (51.7)
Age, y	52.7 (11.9)	53.7 (10.9)	54.0 (10.6)
Age 65 years or older, No. (%)	31 (16.6)	36 (20.0)	30 (16.9)
Race, No. (%)			
Caucasian	128 (68.4)	128 (71.1)	122 (68.5)
Black	34 (18.2)	33 (18.3)	29 (16.3)
Asian	21 (11.2)	18 (10.0)	22 (12.4)
Other	4 (2.1)	1 (0.6)	5 (2.8)
Duration of hypertension, y	8.5 (7.6)	8.0 (6.8)	8.2 (7.5)
DBP, mm Hg	95.7 (4.4)	96.2 (4.8)	96.5 (4.5)
SBP, mm Hg	150.5 (11.1)	150.5 (13.2)	150.8 (12.0)
BMI, kg/m^2	30.2 (5.5)	30.2 (5.7)	30.4 (5.7)
PRA, ng/mL/h[a]	1.0 (1.8)	1.2 (3.7)	0.7 (0.7)
Metabolic syndrome, No. (%)	80 (42.8)	71 (39.4)	74 (41.6)
Diabetes, No. (%)	26 (13.9)	26 (14.4)	27 (15.2)

Data are mean (SD) unless otherwise stated. [a]Evaluated in a subset of patients: amlodipine 150 mg/aliskiren 5 mg, n=56; amlodipine 5 mg, n=48; amlodipine 10 mg, n=49. Abbreviations: BMI, body mass index; DBP, mean sitting diastolic blood pressure; PRA, plasma renin activity; SBP, mean sitting systolic blood pressure.

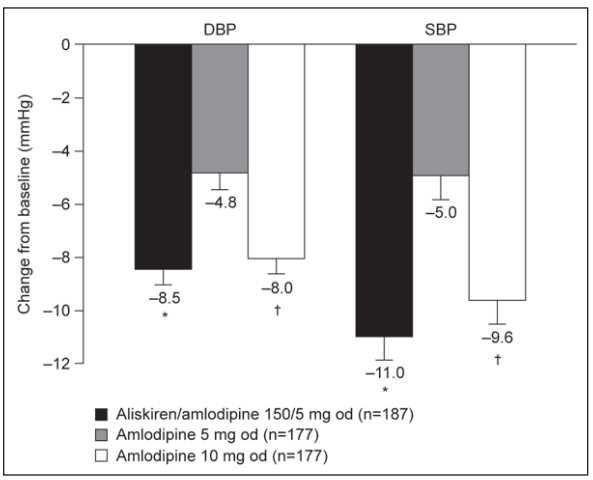

*Figure 2. Change from baseline in mean sitting diastolic blood pressure (DBP) and mean sitting systolic blood pressure (SBP) at study end with once-daily aliskiren 150 mg/amlodipine 5 mg, amlodipine 5 mg, and amlodipine 10 mg in hypertensive patients not responding (DBP ≥90 mm Hg and <110 mm Hg) to amlodipine 5 mg monotherapy (intent-to-treat population). *P<.0001 for aliskiren 150 mg/amlodipine 5 mg vs amlodipine 5 mg. †P=.0002 for amlodipine 10 mg vs amlodipine 5 mg (calculated retrospectively for completeness). Error bars indicate standard error of the mean.*

150-mg/amlodipine 5-mg, amlodipine 5-mg, and amlodipine 10-mg groups, respectively). A high proportion of patients (523; 96.0%) completed the double-blind treatment period (Figure 1).

Baseline and demographic characteristics were comparable among the 3 treatment groups (Table I). The mean age of patients was 53.4 years, with 17.8% aged 65 years or older, and the mean duration of HTN was 8 years. Most patients were Caucasian (69.4%) and 53.6% were men.

Efficacy

At study end, DBP level decreased from baseline by 8.5±0.60 mm Hg (least squares mean ± standard error of the mean) in the group receiving once-daily aliskiren 150 mg/amlodipine 5 mg combination therapy compared with 4.8±0.62 mm Hg in those continuing once-daily amlodipine 5 mg monotherapy (Figure 2). SBP level decreased by 11.0±0.88 mm Hg with combination therapy compared with 5.0±0.90 mm Hg in those receiving amlodipine 5 mg alone. The differences of 3.7 mm Hg in DBP level and 6.0 mm Hg in SBP level between the treatment groups were significant ($P<.0001$). Patients receiving amlodipine 10 mg had a DBP reduction of 8.0±0.62 mm Hg and a SBP reduction of 9.6±0.90 mm Hg from baseline, which was not statistically significantly different from the reductions achieved with combination therapy ($P=.6167$ and $P=.2666$, respectively) (Figure 2).

BP reductions compared with baseline were evident after 1 week of randomized treatment in all groups (Figure 3). The mean DBP level was below the recommended target of <90 mm Hg after 1 week of treatment in both the combination therapy group and the amlodipine 10-mg group. With combination therapy, mean SBP level was below the recommended target of <140 mm Hg by week 3 and remained below this threshold at study end; mean SBP level was >140 mm Hg at all time points

Table II. Overall Incidence of Adverse Events (AEs), Discontinuations Due to AEs, and AEs Occurring in ≥2% of Patients During the Double-Blind Treatment Period (Safety Population)

Adverse Events, No. (%)	Once-Daily Aliskiren 150 mg/ Amlodipine 5 mg (n=187)	Once-Daily Amlodipine 5 mg (n=179)	Once-Daily Amlodipine 10 mg (n=178)
All-cause AEs	59 (31.6)	51 (28.5)	55 (30.9)
Treatment-related AEs	14 (7.5)	17 (9.5)	27 (15.2)
Discontinuation due to AEs	5 (2.7)	3 (1.7)	5 (2.8)
All-cause AEs occurring in ≥2% of patients in any group			
Dizziness	2 (1.1)	0	5 (2.8)
Peripheral edema	4 (2.1)	6 (3.4)	20 (11.2)
Headache	5 (2.7)	9 (5.0)	3 (1.7)

in both the amlodipine 5-mg and 10-mg groups. DBP and SBP reductions from baseline were significantly greater by week 3 in the combination therapy group compared with the amlodipine 5-mg group ($P<.0001$ for both DBP and SBP), but not with the amlodipine 10-mg group.

The proportion of patients responding (defined as DBP level <90 mm Hg at study end and/or a reduction of ≥10 mm Hg from baseline) was significantly higher with combination therapy than with amlodipine 5 mg (64.2% compared with 45.2%; $P=.0005$). The difference in response rate between the aliskiren 150-mg/amlodipine 5-mg group and the amlodipine 10-mg group was not significant ($P=.6373$; 59.9% of patients responded in the amlodipine 10-mg group).

The proportion of patients in each group in whom both systolic and diastolic BP control (BP level <140/90 mm Hg) was achieved was significantly greater in the once-daily aliskiren 150-mg/amlodipine 5-mg group than in the once-daily amlodipine 5-mg group (42.8% vs 22.6%; $P<.0001$) but not significant when compared with the once-daily amlodipine 10-mg group ($P=.5229$; BP control was achieved in 37.9% of patients in the once-daily amlodipine 10-mg group).

In an exploratory analysis of a subgroup of patients in whom PRA was assessed (n=55), combination therapy produced a 74.4% reduction in PRA at study end compared with baseline, a finding consistent with the known pharmacology of aliskiren. Amlodipine 10 mg (n=48) increased PRA level by 58.0%, while in the amlodipine 5-mg group (n=48), PRA level remained similar to baseline (9.9% decrease from baseline measurement followed 4 weeks of initial treatment with amlodipine 5 mg) (Figure 4).

Safety and Tolerability

During the double-blind treatment period, the number of patients experiencing new or worsened

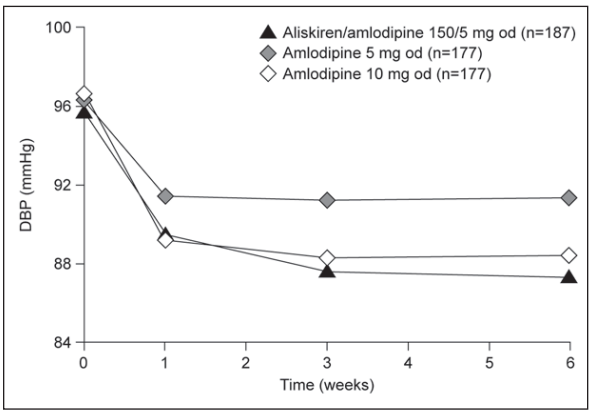

Figure 3. Time course of mean sitting diastolic blood pressure (DBP) with once-daily aliskiren 150 mg/amlodipine 5 mg, amlodipine 5 mg, and amlodipine 10 mg in hypertensive patients not responding to amlodipine 5 mg monotherapy (intent-to-treat population).

AEs was similar among groups receiving aliskiren 150 mg/amlodipine 5 mg (31.6%), amlodipine 5 mg (28.5%), and amlodipine 10 mg (30.9%) (Table II). Overall, a higher proportion of patients receiving amlodipine 10 mg experienced AEs that were suspected to be study drug–related than those receiving aliskiren 150 mg/amlodipine 5 mg or amlodipine 5 mg (15.2%, 7.5%, and 9.5%, respectively). Peripheral edema was the most frequently reported AE, occurring in a higher proportion of patients receiving amlodipine 10 mg than in those receiving combination therapy or amlodipine 5 mg (11.2%, 2.1%, and 3.4%, respectively), although the study was not powered to compare AE rates between the treatment groups (Table II). There were no marked differences among groups with regard to other AEs.

AEs classified as gastrointestinal disorders were slightly more frequent in the combination therapy group (5.9%) than in the amlodipine 5-mg (4.5%) and 10-mg (2.8%) groups, although most individual gastrointestinal AE terms occurred in only 1 or 2 patients per group and showed a similar

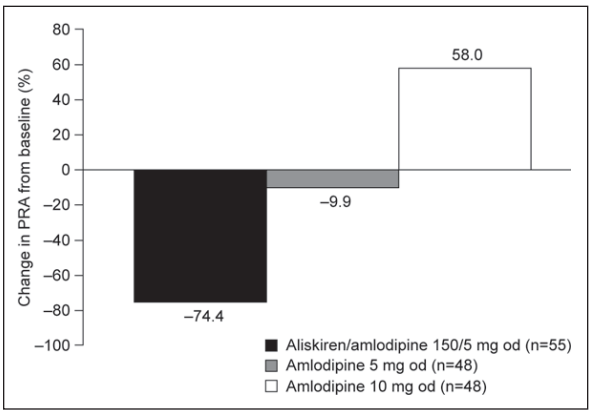

Figure 4. Change from baseline in plasma renin activity (PRA) at study end with once-daily aliskiren 150 mg/amlodipine 5 mg, amlodipine 5 mg, and amlodipine 10 mg in hypertensive patients not responding to amlodipine 5 mg monotherapy (preselected subsection of study population).

distribution across the 3 treatments. Infections and infestations were also more frequent in the combination group (7.5%) than in either amlodipine group (5 mg, 3.4%; 10 mg, 4.5%), although only upper respiratory tract infection (aliskiren 150 mg/amlodipine 5 mg, n=2; amlodipine 5 mg, n=2; amlodipine 10 mg, n=1) and sinusitis (aliskiren 150 mg/amlodipine 5 mg, n=2; amlodipine 5 mg, n=0; amlodipine 10 mg, n=1) were reported by more than 1 patient in any group. Overall, there were few discontinuations due to AEs, with a similar frequency in all 3 groups (Table II). The only AE to cause more than 1 patient to withdraw was peripheral edema, which occurred in the amlodipine 10-mg group (n=3).

There were 5 SAEs (1.1% [n=2], 0.6% [n=1], and 1.1% [n=2] of patients in the aliskiren 150 mg/amlodipine 5 mg, amlodipine 5 mg, and amlodipine 10 mg groups, respectively). These were diabetic hyperglycemic coma, diverticulitis, eye hemorrhage, myocardial infarction, and myocardial ischemia, none of which were considered to be related to study medication. No deaths were recorded.

Most laboratory parameters did not show meaningful changes during the study. Low potassium level (<3.5 mmol/L) was reported in 5 (2.7%), 13 (7.3%), and 10 patients (5.6%) receiving aliskiren 150 mg/amlodipine 5 mg, amlodipine 5 mg, and amlodipine 10 mg, respectively. None of the low potassium values were reported as AEs. Only one case of hyperlipidemia in the amlodipine 10-mg group and 1 case of hypokalemia in the amlodipine 5-mg group were suspected as being related to the study drug.

DISCUSSION

As shown in this study, aliskiren is effective in combination with amlodipine in patients with mild to moderate HTN in whom adequate BP control is not achieved with low-dose amlodipine monotherapy, but no more effective than 10 mg of amlodipine. The addition of aliskiren 150 mg to amlodipine 5 mg provided further reductions in BP level over those seen with amlodipine 5 mg monotherapy. The effect of adding aliskiren was the attainment of BP control (BP level <140/90 mm Hg) in almost twice as many patients compared with continued amlodipine 5 mg monotherapy. In approximately 64% of patients in the combination therapy group, goal DBP level (<90 mm Hg) was reached or at least a 10-mm Hg reduction in DBP level was observed at the end of the study, which according to findings of numerous prospective studies, has been reported to reduce the risk of cardiovascular mortality.[27] As noted, BP level changes with combination therapy were not significantly different from those with amlodipine 10 mg.

Higher doses of amlodipine have been associated with increased peripheral edema.[28] The current study findings are consistent with this observation, with the incidence of peripheral edema increasing by more than 3-fold in patients taking amlodipine 10 mg compared with those taking the 5-mg dose (11% compared with 3%); the study was not, however, designed to compare adverse event rates among the treatment groups. The occurrence of peripheral edema may require CCB therapy to be withdrawn,[29] but it may not prove to be a major problem in many patients: 3 patients in this study discontinued amlodipine therapy because of peripheral edema. Aliskiren in combination with amlodipine was well tolerated, consistent with previous observations of good tolerability at doses of up to 300 mg with aliskiren monotherapy.[23,26]

Aliskiren monotherapy has previously been shown to reduce both DBP and SBP levels in patients with mild to moderate HTN; aliskiren 150 mg was comparable with irbesartan 150 mg.[23] In addition, in a 4-week study in patients with mild to moderate HTN, once-daily aliskiren 75 to 300 mg reduced BP level significantly compared with baseline and similarly to losartan 100 mg.[24] In an 8-week comparison study with HCTZ, aliskiren 150 and 300 mg produced significant BP reductions from baseline similar to those observed with HCTZ 12.5 and 25 mg, respectively.[26] To date, no study has compared the BP-lowering effects of aliskiren and CCB monotherapy.

Aliskiren has previously been investigated in combination with the diuretic HCTZ[26] and in combination with the ACEI ramipril.[30] Combination therapy with aliskiren and HCTZ or ramipril has provided significant additional reductions in BP level from baseline when compared with component monotherapies.[26,30] The current study demonstrates that combination therapy with aliskiren and a CCB provides additional BP reductions from baseline over those seen with low-dose CCB monotherapy.

Aliskiren has been shown to suppress PRA when given as monotherapy,[24,26] and this study confirms that this effect also occurs when aliskiren is given in combination with amlodipine. The results of this study also showed that the addition of aliskiren to amlodipine avoids the increase in PRA level observed with increasing the dose of amlodipine, while providing comparable improvements in BP level. While increasing the dose of amlodipine provided comparable BP reductions to aliskiren/amlodipine combination therapy, contrasting effects on PRA level were observed, with a 58% increase in PRA level in the amlodipine 10-mg group. Whether this is of clinical significance is still debatable. As noted, the use of agents such as ACEIs and ARBs increases renin levels but reduces BP levels and decreases cardiovascular morbidity and mortality.

CONCLUSIONS

The present study demonstrates that aliskiren, an orally active direct renin inhibitor, is effective in combination with amlodipine 5 mg in patients with mild to moderate HTN in whom sufficient BP control has not been achieved with amlodipine 5 mg monotherapy. The BP-lowering efficacy of combining these 2 agents that have complementary mechanisms of action is equivalent to that of the 10-mg dose of amlodipine, with some evidence of better tolerability. Additional studies to determine the outcome benefits of decreasing renin activity in hypertensive patients are under way.

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