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ORIGINAL ARTICLE

Efficacy and safety of aliskiren in Japanese hypertensive patients with renal dysfunction

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This 12-week, multicenter, open-label study assessed the efficacy, pharmacokinetics and safety of a once-daily aliskiren in Japanese hypertensive patients with renal dysfunction. Patients (n=40, aged 20–80 years) with mean sitting diastolic blood pressure (msDBP) $\geqslant$95 and $<$110 mm Hg and serum creatinine between $\geqslant$1.3 and $<$3.0 mg per 100 ml in males or between $\geqslant$1.2 and $<$3.0 mg per 100 ml in females were eligible. Patients began therapy with a once-daily morning oral dose of 75 mg of aliskiren. In patients with inadequate blood pressure control (msDBP $\geqslant$90 or mean sitting systolic blood pressure [msSBP] $\geqslant$140 mm Hg) and without safety concerns (serum potassium >5.5 mEq l^{-1} or an increase in serum creatinine $\geqslant$20%), the aliskiren dose was increased to 150 mg and then to 300 mg in sequential steps starting from Week 2. Efficacy was assessed as change in msSBP/msDBP from baseline to the Week 8 endpoint (with the last observation carried forward). The mean reduction from baseline to Week 8 endpoint was 13.9 $\pm$ 16.6 and 11.6 $\pm$ 9.7 mm Hg for msSBP and msDBP, respectively. At the Week 8 endpoint, 65% patients had achieved blood pressure response (msDBP $<$90 or a 10 mm Hg decrease or msSBP $<$140 or a 20 mm Hg decrease) and 30% had achieved blood pressure control (msSBP $<$140 mm Hg and msDBP $<$90 mm Hg). Aliskiren was well tolerated with no new safety concerns in Japanese hypertensive patients with renal dysfunction.
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Keywords: aliskiren; direct renin inhibitor; renal dysfunction; renin–angiotensin–aldosterone system

INTRODUCTION

Hypertension is a major modifiable risk factor for cardiovascular and renal disease that affects >25% of the adult population worldwide.[1] Despite the high prevalence of hypertension in patients with chronic kidney disease (81.8%), only 65.9% receive antihypertensive therapy and, in those that do receive treatment, only 23.3% achieve blood pressure control (systolic blood pressure/diastolic blood pressure <130/80 mm Hg).[2] Hence, optimal blood pressure management may improve clinical outcomes in these high-risk hypertensive patients, especially because some classes of antihypertensive drugs may offer renal protection independent of blood pressure lowering effect.[3]

The renin–angiotensin–aldosterone system (RAAS), a major regulator of blood pressure, is an important therapeutic target for antihypertensive therapy.[4] Although angiotensin I-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are effective in controlling blood pressure, these antihypertensives do not completely suppress the RAAS, leading to a reactive rise in plasma renin activity. In addition, the use of these antihypertensive agents slows renal deterioration, but does not completely stop the progression of renal disease.[5–7] Therefore, benefits in hypertensive patients with renal disease above and beyond that offered by ACEIs and ARBs may be achievable. Aliskiren, an oral direct renin inhibitor for treatment of hypertension, effectively reduces plasma renin activity, resulting in a more complete suppression of RAAS.[8] Further, aliskiren as a once-daily oral treatment (up to 300 mg per day) has shown dose-dependent reductions in both systolic and diastolic blood pressure in patients with essential hypertension.[9,10]

In Japan, adequate blood pressure control is achieved in <50% patients, and still fewer of those with co-morbidities such as diabetes mellitus.[11] Drugs that target RAAS are being increasingly used.[11] Although aliskiren has shown dose-dependent efficacy in Japanese patients with essential hypertension,[12] there is limited data regarding direct renin inhibitors in the high-risk population of hypertensive patients with renal dysfunction. This was the first study to evaluate the safety and efficacy of aliskiren in Japanese hypertensive patients with renal dysfunction.

METHODS

Study design

This was a 12-week, multicenter, single-arm, open-label study consisting of a 4-week placebo run-in period to wash out the effects of earlier antihypertensives, and an 8-week treatment period (Figure 1). The study was conducted according to the Declaration of Helsinki and in compliance with the Good Clinical

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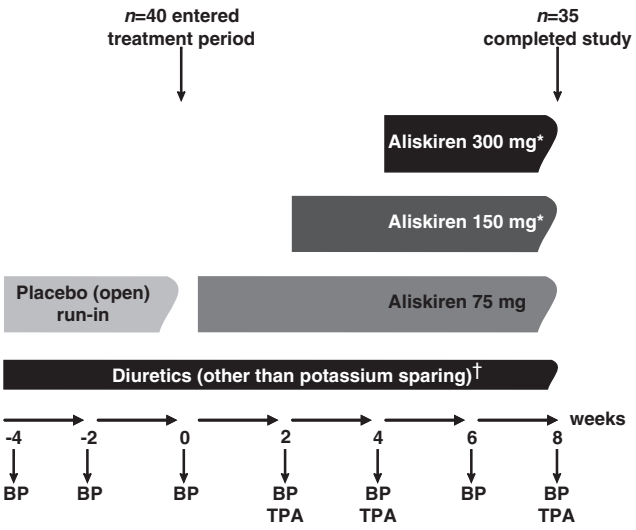

Figure 1 Study design. *Optional dose titration for inadequately controlled blood pressure (msDBP $\geqslant$90 mm Hg or msSBP $\geqslant$140 mm Hg) and no safety concerns (serum potassium level over 5.5 mEq l^{-1} or an increase in serum creatinine $\geqslant$20%). †Continued given that there was no change in drug or dosing regimen. BP, blood pressure; TPA, trough plasma aliskiren concentration.

Practice. This study was initiated only after obtaining institutional review board approval at each study center. Written informed consent was obtained from all patients.

Patients

Male or female Japanese outpatients (aged 20–80 years) with mild-to-moderate essential hypertension (mean sitting diastolic blood pressure [msDBP] $\geqslant$95 and $<$110 mm Hg) and renal dysfunction (serum creatinine levels $\geqslant$1.3 and $<$3.0 mg per 100 ml in males or $\geqslant$1.2 and $<$3.0 mg per 100 ml in females) were included in the study. Patients were excluded if they had severe hypertension (msDBP $\geqslant$110 and/or mean sitting systolic blood pressure [msSBP] $\geqslant$180 mm Hg), secondary hypertension (such as renovascular hypertension except renoparenchymal hypertension), malignant hypertension, type 1 diabetes mellitus or type 2 diabetes mellitus with poor glucose control (glycosylated hemoglobin [HbA_{1c}] $>$8% at the start of the run-in period), a history of cardiovascular disease or any condition (medical or surgical) that might affect the absorption, distribution, metabolism or excretion of the study drug. Women who were pregnant, nursing or those with child-bearing potential were excluded. Patients with a history of allergy or hypersensitivity to the study drug were also excluded.

Treatment

After a 4-week placebo run-in period, all eligible patients entered an 8-week optional dose-titration period during which they received aliskiren 75–300 mg once daily. As the Japanese Society of Hypertension guidelines for the management of hypertension[13] recommend that treatment with drugs acting on RAAS should be initiated at the minimum dose when serum creatinine is $\geqslant$2.0 mg per 100 ml, optional dose titration was used in stages to assess the safety of aliskiren in renal dysfunction. Eligible patients began therapy with a once-daily oral morning dose of 75 mg of aliskiren, except on the days of scheduled visits when aliskiren was administered after the completion of all assessments. The timing of food was not restricted and dosing could be pre- or post-prandial; however, on scheduled visit days, patients reported while fasting and without taking aliskiren and diuretics until the completion of all assessments. Patients who were on diuretics (other than potassium-sparing diuretics) before the initiation of the study continued to take them concurrently, as long as there was no change in the drug or the dosing regimen during the study. Concomitant use of other antihypertensive agents was not permitted from the start of the run-in period to end of treatment period.

For patients whose blood pressure was not adequately controlled with the initial dose (msDBP $\geqslant$90 or msSBP $\geqslant$140 mm Hg) and who had no safety concerns (serum potassium was not $>$5.5 mEq l^{-1} and serum creatinine had not increased by $\geqslant$20% from baseline), aliskiren was up-titrated to 150 and then to 300 mg in sequential steps starting from Week 2.

Efficacy assessments

The primary efficacy outcome was the change in msSBP/msDBP from baseline (Week 0) to Week 8 (last observation carried forward). Blood pressure was measured three times at all scheduled visits (Weeks -4, -2, 0, 2, 4, 6 and 8), taken at 1- to 2-min intervals after resting for at least 5 min in the sitting position. The reported blood pressure for the visit was the average of all three measurements. Additional assessments included the following: (i) msDBP responder rate (defined as the proportion of patients with an absolute msDBP $<$90 or a $\geqslant$10 mm Hg reduction from baseline to Week 8), (ii) msSBP responder rate (defined as the proportion of patients with an absolute msSBP $<$140 or a $\geqslant$20 mm Hg reduction from baseline to Week 8), (iii) msDBP or msSBP responder rates and (iv) control rate (defined as the proportion of patients with msDBP $<$90 mm Hg and msSBP $<$140 mm Hg).

Pharmacokinetic assessments

Trough plasma aliskiren concentrations were measured at Weeks 2, 4 and 8 in the treatment period. Blood samples were drawn from a forearm vein using heparinized blood sample tubes and were centrifuged at 800 *g* for 15 min. Plasma was stored at $-70\,^{\circ}C$ or below until measurement of the drug concentration. The concentration of aliskiren in plasma was determined by liquid chromatography/mass spectrometry. The lower limit of quantification was 0.5 ng ml^{-1}.

Safety assessments

Safety and tolerability of aliskiren treatment in hypertensive patients with renal dysfunction was assessed by monitoring and recording adverse events, performing laboratory tests for hematology, blood chemistry and urinalysis, and monitoring vital signs, ECG and body weight. At all scheduled visits, adverse events were recorded and rated as mild, moderate or severe, and were assessed for relationship to study medication. Serious adverse events were reported up to 4 weeks after completion of the study. Standard laboratory tests were performed at baseline (Week 0) and at Weeks 4 and 8 in the treatment period. In addition, serum creatinine, blood urea nitrogen and serum electrolytes (sodium, potassium, chloride, calcium and phosphorous) were measured at Weeks 2 and 6 in the treatment period. The Cockcroft–Gault equation was used to calculate creatinine clearance (C_{Cr}).

Body weight was measured during all scheduled visits in the treatment period and a 12-lead ECG recording was obtained at Week -4 in the run-in period and at Week 8 of treatment. Change in orthostatic blood pressure (a decrease of $\geqslant$20 mm Hg in systolic blood pressure or $\geqslant$10 mm Hg in diastolic blood pressure when changing from a supine to a standing position) was also assessed. Treatment compliance was assessed at all visits using pill counts and information provided by the patients. Compliance was defined as taking the medication correctly on at least 70% of the days.

Data analysis

A target sample size of 30 patients was considered sufficient to evaluate the overall safety and tolerability of aliskiren treatment with 95% power to detect the incidence of adverse event (10%) in at least one patient. However, at least 38 patients had to be enrolled to allow for a 20% drop out rate. Efficacy and safety analyses were performed on all patients who received at least one dose of aliskiren. Patients with major protocol violations were excluded from the analyses. No statistical inference was performed in this study, and descriptive statistics were used for all efficacy and safety variables. The last observation carried forward method was used to assess the changes from baseline to Week 8 endpoint.

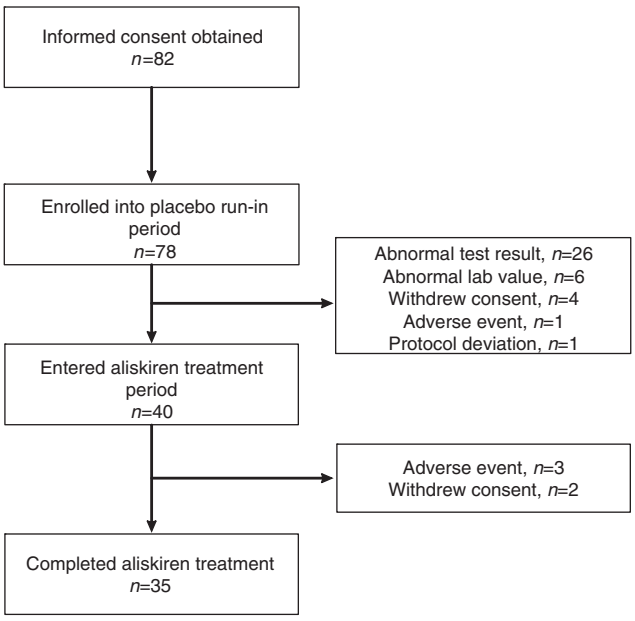

Figure 2 Patient flow chart.

RESULTS

Informed consent was obtained from 82 patients, and 78 patients entered the 4-week, placebo run-in period. Of these 78 patients, 38 discontinued the study before receiving the study drug. Of 40 patients who entered the treatment period, 35 completed aliskiren treatment and five discontinued treatment because of an adverse event or withdrew consent (Figure 2). All 40 patients were evaluable for efficacy, pharmacokinetic and safety analyses.

Patient baseline characteristics are presented in Table 1. The mean duration of hypertension was 9.2 years and 15.0% patients had concomitant diabetes mellitus and 42.5% had hyperlipidemia. Concomitant renal disease was diagnosed in 30 patients (75.0%), with chronic glomerulonephritis being the most common occurring disorder in 19 patients (47.5%), followed by diabetic nephropathy in four patients (10.0%). Prior antihypertensive medication was used by 30 patients (75%), with dihydropyridine derivatives (21 patients), Ang II antagonists (20 patients) and ACEIs (6 patients) being the most common ones. During the study, six patients (15%) used non-potassium-sparing concomitant diuretics (with no change in drug or dosing regimen), the most common being furosemide by four patients and indapamide by two patients.

Efficacy

The antihypertensive effect of aliskiren on msDBP was evident during the first 2 weeks of treatment, msDBP (±s.d.) fell from 99.3 ± 3.7 mm Hg at baseline to 90.3 ± 8.8 mm Hg at Week 2, followed by a further decrease to 88.3 ± 10.2 mm Hg at Week 4 and 87.8 ± 9.8 mm Hg at Week 6. After Week 6, msDBP was stable at 87.4 ± 10.0 mm Hg until Week 8. Mean (±s.d.) decrease in msDBP from baseline to Week 8 endpoint was 11.6 ± 9.7 mm Hg (Figure 3). At Week 2, msSBP (±s.d.) fell from 163.3 ± 11.7 mm Hg at baseline to 153.6 ± 15.1 mm Hg, followed by a further decrease to 149.5 ± 15.2 mm Hg at Week 4. After Week 4, msSBP remained stable at Week 6 (148.9 ± 16.6 mm Hg) and at Week 8 (149.1 ± 18.4 mm Hg). The mean (±s.d.) decrease in msSBP from baseline to Week 8 endpoint was 13.9 ± 16.6 mm Hg (Figure 3).

Table 1 Patient baseline characteristics (*N*=40)

Parameter	*Statistics*
Age (years)	64.7 ± 13.4
Aged ⩾65 years, *n* (%)	25 (62.5)
Male, *n* (%)	38 (95.0)
BMI (kg/m^2)	24.3 ± 3.1
BMI ⩾30 kg/m^2, *n* (%)	2 (5.0)
msDBP (mm Hg)	99.3 ± 3.7
msSBP (mm Hg)	163.3 ± 11.7
C_{Cr} (ml min^{-1})	41.9 ± 16.4
C_{Cr} ⩾30 ml min^{-1}, *n* (%)	31 (77.5)

Abbreviations: BMI, body mass index; C_{Cr}, creatinine clearance; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.
Data presented as mean ± s.d. unless otherwise specified.
Baseline characteristics were established after a 4-week placebo run-in period.
BMI was calculated from Week −4 height and weight data.
C_{Cr} was calculated from Week −4 weight and serum creatinine using the Cockcroft–Gault equation.

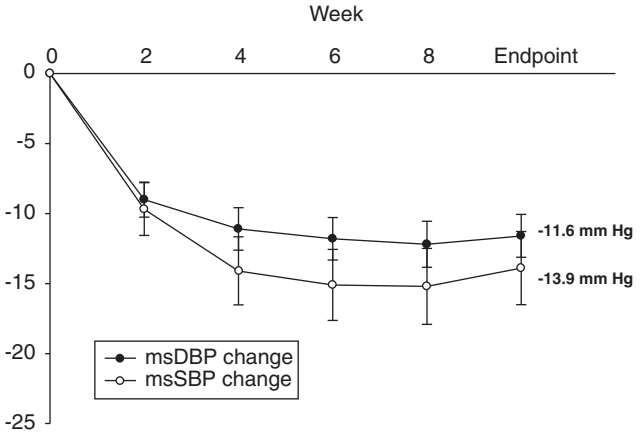

Figure 3 Mean change in mean sitting blood pressure from baseline to Week 8 endpoint. Endpoint is Week 8 using the last observation carried forward approach. msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.

Overall, 65.0% of patients had an msSBP or msDBP response at the Week 8 endpoint. The overall blood pressure control rate at each assessment increased over time and was 25.0% at Week 2, 25.6% at Week 4, 27% at Week 6 and 30% at the Week 8 endpoint. The majority of the patients (67.5%) in this study were on 300 mg of aliskiren at Week 8.

Pharmacokinetics

A dose-related increase in trough plasma aliskiren levels was observed, with trough levels reaching steady state 2–4 weeks after initiating aliskiren or increasing the dose. Mean (±s.d.) trough plasma aliskiren levels at Week 8 were 5.3 ± 2.8 for 75 mg, 20.3 ± 11.9 for 150 mg and 34.8 ± 23.6 ng ml^{-1} for 300 mg.

Safety and tolerability

Aliskiren was well tolerated in this study (Table 2). Adverse events were reported for 52.5% patients and 15.0% patients had adverse events that were suspected of being related to aliskiren. The most frequently reported adverse events were nasopharyngitis, back pain and dizziness (each in 5.0% patients). Most of the adverse events were mild-to-moderate in severity. Three patients (7.5%) discontinued the

Table 2 Safety and tolerability (*N*=40)

Adverse events	n *(%)*
Any adverse event	21 (52.5)
Serious adverse event	2 (5.0)
Death	0
Discontinuation because of adverse event	3 (7.5)
Adverse events occurring in ⩾3% of patients	
Nasopharyngitis	2 (5.0)
Back pain	2 (5.0)
Dizziness	2 (5.0)
Clinically notable changes in laboratory values	
Serum potassium >20% increase	6 (15.0)
BUN >50% increase	4 (10.0)
AST >150% increase[a]	1 (2.6)
ALT >150% increase[a]	1 (2.6)
Serum sodium >5% decrease	1 (2.5)
Serum chloride >10% increase	1 (2.5)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SAE, serious adverse event.
[a]Total number of patients was 39.

study because of the adverse events of increased blood pressure (n=1), cerebral infarction (n=1) and proteinuria (n=1).

Serious adverse events were reported in two patients (5.0%) and included cerebral infarction, which also led to discontinuation as stated above in one patient, and urinary retention and cystitis (cystitis reported after completion of study) in the other patient. A possible relation to the study drug could not be excluded for the cerebral infarction. No death was reported during the study.

The mean laboratory values for serum creatinine, C_{Cr}, and urinary protein/creatinine ratio from baseline to Week 8 endpoint were essentially unchanged with no apparent worsening. An elevated blood urea nitrogen (>50% increase from baseline) was observed in four patients and an elevated urinary protein/creatinine ratio (two-fold increase from baseline) was observed in two patients. For one of the patients with increased protein creatinine ratio, serum creatinine and blood pressure tended to higher levels from the start of the study. For the other patient, there were no significant changes in serum creatinine or C_{Cr}; however, the increase in urinary protein/creatinine ratio could have been due to a failure to control blood pressure or washout of prior therapeutic drugs (amlodipine besilate, perindopril erbumine, valsartan and dipyridamole). There were no reports of adverse events related to renal function. Serum potassium levels increased by ⩾20% in four out of six patients whose baseline C_{Cr} was $<30\,ml\,min^{-1}$.

Increases in serum potassium were observed in six patients; none of these changes were reported as adverse events. Serum potassium levels of >5.5 and $<6\,mEq\,l^{-1}$ were observed in three patients at some point during treatment, and returned to reference range at the endpoint. Three patients had serum potassium levels $\geqslant 6\,mEq\,l^{-1}$, of which one patient tended to $\geqslant 6\,mEq\,l^{-1}$ levels from the start of treatment (did not exhibit any related clinical symptoms), another had a history of hyperkalemia and was on calcium polystyrene and for the third, the value returned to reference range.

Four patients met the criteria for a decrease in orthostatic blood pressure at some point from baseline to Week 8 endpoint; all were asymptomatic. Throughout the treatment period, no changes were observed in pulse rate, body mass index and body weight. One patient exhibited an ECG abnormality (supraventricular extrasystole) at Week 8 that was suspected to be study-drug related, was mild in severity and required no treatment.

DISCUSSION

This was the first study to evaluate the efficacy, safety and tolerability of aliskiren in Japanese hypertensive patients with renal dysfunction. The antihypertensive effect of aliskiren (mean decrease from baseline to Week 8 endpoint of 11.6 mm Hg for msDBP and 13.9 mm Hg for msSBP) in this population was similar to that observed in Japanese hypertensive patients without renal dysfunction. In an earlier study by Kushiro *et al.*,[12] treatment with aliskiren for 8 weeks at doses ranging from 75 to 300 mg once daily resulted in mean decrease of 7.22–10.72 mm Hg for msDBP and 8.57–14.09 mm Hg for msSBP. Blood pressure reductions with aliskiren in this study were evident within 2 weeks of the first dose, consistent with earlier observations in other studies that evaluated the efficacy of aliskiren in Japanese and Caucasian hypertensive patients without renal dysfunction.[10,12,14]

In this study, a high proportion of patients (65%) achieved a treatment response by Week 8 endpoint (absolute msSBP <140 mm Hg or a decrease of ⩾20 mm Hg from baseline; or absolute msDBP <90 mm Hg or a decrease of ⩾10 mm Hg from baseline). Achieving target blood pressure is of utmost importance for improving renal outcomes, as reduction in blood pressure is known to exert a nephroprotective effect.[3,15,16]

In these patients with renal dysfunction, mean trough plasma aliskiren concentrations increased with dose and reached steady state 2–4 weeks after the start of dosing or up-titration of the dose. The results from an earlier study assessing the effects of renal impairment on pharmacokinetics of aliskiren (300 mg once daily) in patients with mild-to-moderate renal dysfunction and healthy volunteers showed that although exposure is increased by renal impairment, the increase in exposure does not correlate with the severity of renal impairment.[17] Moreover, healthy volunteer studies have shown that renal excretion has a minor role in aliskiren elimination, with only 0.1–1.0% of an oral dose being excreted in urine.[8] As renal clearance of aliskiren represents a small fraction of total clearance, adjustment of the initial dose is unlikely to be required in patients with moderate renal impairment. Therefore, aliskiren may be a useful alternative to other agents such as the majority of ACEIs, which require dose adjustment for patients with renal dysfunction.[18]

In this study, the incidence of adverse events was low and the adverse event profile was similar to that observed in earlier studies in hypertensive patients with and without renal dysfunction.[8,12,17] There were no reports of adverse events related to renal function. Changes in serum creatinine, C_{Cr}, and the urinary protein/creatinine ratio were minimal during the study and none of these changes resulted in any adverse event related to the renal function.

In patients with renal dysfunction, inhibition of RAAS with ACEIs, ARBs or both often induce functional increases in serum creatinine levels in an early stage of the treatment.[19] This is generally attributed to decreased glomerular capillary pressure because of preferential vasodilation of efferent arteriole as compared with afferent arterioles. In this study, we did not observe such increases in serum creatinine. This observation of unchanged serum creatinine is consistent with earlier studies that used aliskiren.[20,21] The mechanism for the difference between aliskiren and either ACEIs or ARBs is not clear from this study. However, it may be related to unique features of aliskiren, namely strong accumulation in the renal tissue and very powerful renal vasodilatory action.[22] It has been shown that in human beings, renal blood flow increased more with aliskiren than with either ARBs

or ACEIs.[23] As renal blood flow is a powerful determinant of glomerular filtration rate (GFR), administration of aliskiren may have induced little change in GFR even in the presence of decreased glomerular capillary pressure because of decreased Ang II. However, clarification of the significance of these findings awaits further investigation.

In this study, transient increases in serum potassium levels were observed in five patients; none of these changes were reported as adverse events. Transient elevations in serum potassium levels ($>5.5\,mmol\,l^{-1}$) have been earlier observed with aliskiren treatment in hypertensive patients.[24,25] Mild increases in potassium levels were expected with agents that block the RAAS, as observed with ACEIs and ARBs, because of changes in both GFR and aldosterone secretion.[26,27] Therefore, it is recommended that serum potassium levels be monitored during aliskiren treatment in patients with severe renal dysfunction.

Beyond its antihypertensive effect, recent data suggest that aliskiren may have a beneficial effect on kidney function by slowing the decline in GFR and reducing the urinary albumin/creatinine ratio. In the AVOID study of hypertensive patients with type 2 diabetes and nephropathy, patients treated with aliskiren plus losartan combination therapy for 6 months had a smaller decline in GFR than patients treated with placebo plus losartan, even though blood pressure was similar and well controlled in both treatment groups.[21] In the aliskiren plus losartan group, 25% patients experienced a reduction in the urinary albumin/creatinine ratio of $\geqslant$50% compared with 12.5% patients in the placebo plus losartan group. Additional research has shown that RAAS blockade with direct renin inhibition can decrease albuminuria. In a study by Persson *et al.*,[28] aliskiren 300 mg once daily for 28 days was associated with a 44% decrease in the urinary albumin/creatinine ratio and a reduction in 24-h systolic blood pressure (after 7 days) in patients with type 2 diabetes and albuminuria. In this study, the urinary protein/creatinine ratio was essentially unchanged, which could be a consequence of the short treatment period of 8 weeks and majority (85%) of the patients being non-diabetic. Moreover, this study was designed only to assess the safety and tolerability of aliskiren in these hypertensive patients with renal dysfunction, and not its renoprotective effect.

In conclusion, results from this study show that treatment with aliskiren is effective and well tolerated in Japanese patients with mild-to-moderate hypertension and renal dysfunction. Monitoring of renal function and electrolytes during aliskiren therapy should be considered in patients with moderate or severe renal dysfunction, particularly in those with a history of hyperkalemia.

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