Clinical and Experimental Hypertension

ISSN: 1064-1963 (Print) 1525-6006 (Online) Journal homepage: https://www.tandfonline.com/loi/iceh20

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To cite this article: Keisuke Okamura, Yosuke Takamiya, Ken Mori, Kazuyuki Shirai & Hidenori Urata (2020): Add-on aliskiren treatment can decrease blood pressure but requires attention to risks of renal impairment and hyperkalemia Chikushi Anti-Hypertension Trial-Rasilez® (CHAT-Ras), Clinical and Experimental Hypertension, DOI: 10.1080/10641963.2020.1723618

To link to this article: https://doi.org/10.1080/10641963.2020.1723618

Published online: 08 Feb 2020.

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Add-on aliskiren treatment can decrease blood pressure but requires attention to risks of renal impairment and hyperkalemia Chikushi Anti-Hypertension Trial-Rasilez® (CHAT-Ras)

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ABSTRACT

Background: Renin is the starting point of the renin angiotensin (RA) system cycle. Aliskiren (AL), which is a direct renin inhibitor, suppressed the entire RA cycle. In the present study, the efficacy of add-on of AL treatment in patients with essential hypertension (HT) was investigated.

Methods: This study was a multi-center, open-label, prospective, observational study. Study subjects were patients with essential HT and poor blood pressure (BP) control, who had received calcium channel blocker monotherapy or angiotensin II receptor blocker monotherapy or had not received any BP lowering drugs. Following add-on of AL for 12 months, BP and additional laboratory findings were analyzed.

Results: A total of 150 subjects were enrolled. There were 50 dropout subjects including discontinuation. Dropouts were the highest in the ARB combination therapy group at 9 subjects due to adverse events, and 3 of them were due to hyperkalemia. A significantly higher number of patients with chronic kidney disease (CKD) dropped out compared to patients without CKD ($\varphi = 0.166$, $p < .05$). BP before add-on of AL was 155/88 mmHg. After add-on of AL, BP was significantly improved and this lowering was sustained for 3 months (136/78 mmHg, $p < .001$), 6 months (136/77 mmHg, $p < .001$) and 12 months (134/78 mmHg, $p < .001$). In contrast, add-on of AL increased the potassium level and decreased the estimated glomerular filtration rate.

Conclusion: While add-on AL treatment achieved a favorable and sustained decrease of BP in this study, caution is necessary with regard to elevation of potassium levels and renal impairment.

ARTICLE HISTORY
Received 4 December 2019
Revised 6 January 2020
Accepted 16 January 2020

KEYWORDS
Aliskiren; renin angiotensin system; direct renin inhibitor; hypertension; practitioner; multi-center prospective study

Background

Angiotensin II (AII) is produced by the renin angiotensin system (RAS) and is a potent pressor substance, meaning excessive elevation in vivo may result in organ damage. Many large-scale clinical studies investigating RAS inhibitors (RAS-I) such as angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) have demonstrated decreases in blood pressure (1) and organ protective effects. However, activated plasma renin activity (PRA) in the kidney by RAS-I feedback is considered one of the reasons for RAS-I non-responders. In addition, PRA elevation is correlated with the onset of myocardial infarction (MI) in patients with hypertension (HT) (2), which increases the incidence of cardiovascular events. Furthermore, an elevation of PRA in post-MI patients is a risk factor for severe heart failure, cardiovascular death, and complex cardiovascular events (3). Therefore, for patients with heart diseases, BP lowering therapy that does not elevate PRA is considered desirable.

Aliskiren (AL), a direct renin inhibitor (DRI), directly inhibits renin, the starting point of the RAS cycle. As such, it is the only renin angiotensin (RA) drug that decreases PRA and suppresses the entire RA cycle. The pharmacological characteristics of AL indicate that it is highly specific to substrates and demonstrates potent competitive inhibition against human renin. In addition, it has a low risk of adverse reactions (4). The blood concentration half-life of AL is 40 hours. This is the longest among the many already exiting RAS-I, indicating that a stable decrease in BP can be expected with AL treatment. Moreover, due to its high tissue affinity, organ protective effects can also be expected. Finally, as AL exhibits effects to expand afferent arterioles and therefore a potent increase in renal blood flow, the estimated glomerular filtration rate (eGFR) is unlikely to be decreased (5).

In the present study, patients with essential HT with insufficient BP control received add-on AL with various DRI characteristics. The impact on office BP and the results of blood tests were evaluated in order to investigate co-administration with AL. This study was named the Chikushi Anti-Hypertension Trial-Rasilez® (CHAT-Ras).

Methods

Study method

This study was conducted as a multi-center, open-label, prospective, observational study.

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Patient population

The inclusion criteria were patients visiting clinics of the Chikushi Cardiovascular Disease Clinical Research Network (Chikushi-JRN), who presented with poorly controlled BP (JSH2009 Guideline target values at study initiation (6)) and were receiving either ARB monotherapy, calcium channel blocker (CCB) monotherapy or no blood pressure lowering drugs. Informed consent was obtained from all patients.

Exclusion criteria were: Age < 20 years old, secondary HT patients, those whose condition was complicated with serious vascular complications requiring hospitalization in the past 6 months, patients with renal impairment (serum creatinine level ≥1.5 mg/dl), patients with hepatic impairment (alanine transaminase (ALT) ≥100 IU/L), patients with other serious disorders with poor prognosis, and patients who were considered inappropriate to participate in the study by their home doctor.

After the CHAT-Ras study was initiated, the interim results of the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) study was reported in 2012, which investigated ACE-I or ARB therapy in combination with AL in high risk patients with type 2 diabetes mellitus (DM) and a history of renal impairment or cardiovascular disorder (7). The interim results of this placebo-controlled, double-blind study indicated that combined treatment with AL 300 mg/day had a significantly higher incidence of events such as heart arrest, hyperkalemia, and hypotension compared to the placebo group. Consequently, the ALTITUDE study was discontinued prematurely.

It was clear therefore that for DM patients with a high risk of renal impairment, the efficacy of combination therapy of AL and RAS-I was unsafe and raised concerns regarding adverse effects. As a consequence, administration of AL is now contraindicated in DM patients receiving ACE-I or ARB in Japan, and careful administration was instructed for patients with renal impairment (eGFR < 60/min/1.73m^2).

The current CHAT-Ras study was consequently changed in January 23, 2012 to add further exclusion criteria for patients with DM orally receiving ACE-I or ARB, patients with an eGFR < 60/min/1.73 m^2 orally receiving ACE-I or ARB, and patients with hyperkalemia (serum potassium level ≥5.0 mEq/l).

Study design

The HT patients who met the new criteria including above further exclusion criteria after ALTITUDE study in terms of insufficient BP control were grouped into patients already receiving ARB (Group 1), patients already receiving CCB (Group 2), and patients naïve to antihypertensive therapy (Group 3). For all 3 groups, the effect of add-on AL (150 mg) on decreasing BP and safety were evaluated (Figure 1). When the target BP could not be achieved, AL was increased to 300 mg.

The observation period was 12 months, with no change in the drugs administered for 3 months. However, BP lowering drugs and medications for complications could be changed during this time at the discretion of the home doctor. Office BP and pulse rate (PR) were measured at baseline and every month up to 3 months, then at 6 and 12 months. Both BP and PR were measured in a sitting position (resting) by the usual procedure employed at each clinical site. A standard panel of blood and urine tests were conducted at baseline and at 3, 6, and 12 months.

Endpoints

The primary endpoints were the change in systolic BP (SBP), diastolic BP (DBP), and PR at 3, 6 and 12 months versus baseline. The secondary endpoints were adverse events and blood and/or urine test results of renal functions (eGFR and urine albumin).

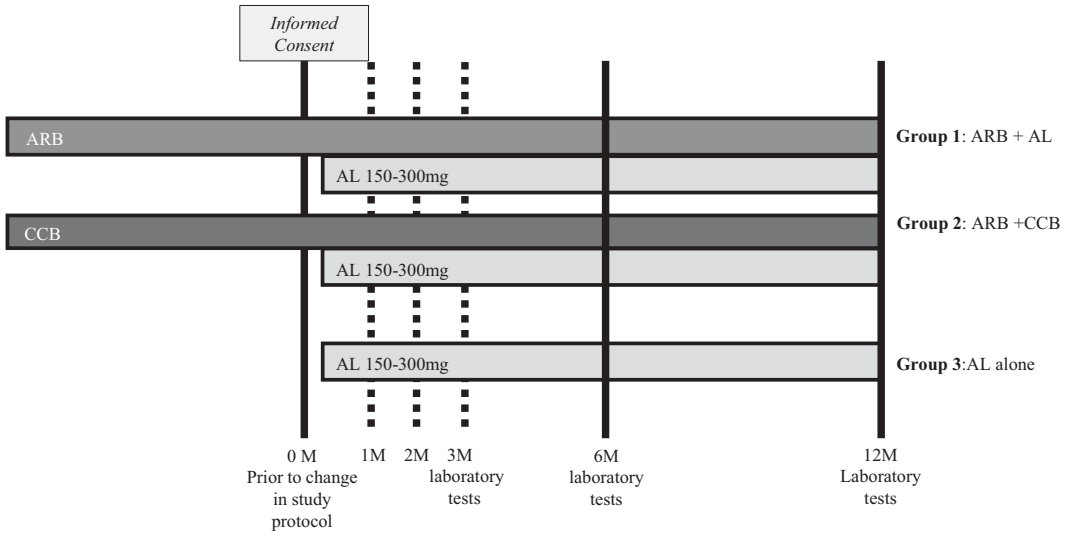

Figure 1. Study design.

Patients were grouped into 3 groups: Group 1 ARB + AL; Group 2 CCB + AL, and Group 3 AL alone. Office BP and pulse rate (PR) were measured at baseline and every month up to 3 months, then at 6 and 12 months after add-on of AL. A standard panel of blood and urine tests were conducted at baseline and at 3, 6, and 12 months after add-on of AL.

Criteria for discontinuation

The criteria for discontinuation included: the onset of excessive BP decline after add-on of AL; difficulty to continue investigation due to adverse events; very poor adherence by the patient to medications; patients meeting the aforementioned additional exclusion criteria, and other reasons as determined by the doctors.

Target sample size

The investigation of BP decreasing effects by add-on AL at 150–300 mg/day in Japanese HT patients with poor BP control despite ARB monotherapy or CCB monotherapy is still exploratory.

It was anticipated that CCB combination therapy would be more effective in decreasing BP than ARB combination therapy, and it was assumed that the lowering of the BP by AL add-on to ARB monotherapy and CCB monotherapy would be −15 mmHg vs −20 mmHg (δ: ± 15). When the risk ratio is considered to be 5% and power of detection is 90%, the minimum number of patients to detect a significant difference between these two add-on therapy groups was 190 patients/group, or a total of 380 patients.

Accordingly, taking into consideration the number of patients needed for statistical analyzes of the decrease in BP and the expected number of dropouts, it was decided to enroll a total of 400 patients including ARB non-responders, CCB non-responders, and those starting AL monotherapy.

Ethical considerations

This study was performed according to the Declaration of Helsinki. The study protocol was approved by the Institutional Review Committee of Fukuoka University Chikushi Hospital (Approval No.: R10-026), and written informed consent was obtained from each patient before enrollment. The study period was from November 5, 2010 (the day approval was provided by the IRB) through December 31, 2012.

Statistical analysis

Numerical results are expressed as the mean (standard deviation [SD]), median (interquartile range [IQR]), or frequency (%). Statistical analysis was performed at Fukuoka University using IBM SPSS Statistics 23 software. The t-test was performed to determine the significance of differences for variables with a normal distribution. In addition, Levene's test was used to assess the equality of variance, and Welch's test was employed if equal variance was not confirmed. If the data did not show a normal distribution, the Wilcoxon signed rank test was used for continuous variables and the Mann-Whitney test was performed for independent variables.

For comparison of 3 groups, 1-way analysis of variance (ANOVA) was used. Variation over time was analyzed by repeated ANOVA and the chi-square test was performed to investigate associations between categorical variables. In all analyses, $p < .05$ was considered to indicate significance.

Results

The target number of subjects was 400 patients, but the number of enrolled patients at the end of the study was: Group 1 (ARB+AL combination): 59 patients; Group 2 (CCB+AL combination): 81 patients, and Group 3 (AL monotherapy): 10 patients, resulting in a total of 150 patients. Therefore, the number of enrolled patients was considerably lower than the original target number.

The protocol of the study was revised on January 23, 2012 as per recommendations based on the ALTITUDE study. During the 500 days from September 10, 2010 to before the protocol revision (January 22, 2012), a total of 137 patients (Group 1: 57 patients, Group 2: 77 patients, and Group 3: 3 patients) were enrolled. During the 280 days from after the protocol revision (January 23, 2012) to the last enrolled patient on October 28, 2012, a total of 13 patients were enrolled (Group 1: 2 patients, Group 2: 4 patients, and Group 3: 7 patients).

The dose of AL was increased to 300 mg for 11 patients (Group 1: 6 patients, Group 2: 1 patient, and Group 3: 4 patients).

Table 1 shows the patient demographics. The age of Group 1 was higher compared to Groups 2 and 3. Cases of dyslipidemia (DL) was high in Group 2 and cerebrovascular disease

Table 1. Patient demographics.

	All cases (n = 150)	SD, %	Group 1 ARB + AL (n = 59)	SD, %	Group 2 CCB + AL (n = 81)	SD, %	Group 1 vs Group 2 P-value	Group 3 AL alone (n = 10)	SD, %	1-way ANOVA P-value
Age, years, mean (SD)	69	12	71	10	68	12	0.088	58	16	0.036
Male Gender, male, n (%)	74	49	29	49	43	53	0.648	2	20	0.096
BMI, kg/m2, mean (SD)	24.1	3.9	24.0	3.9	24.1	4.0	0.824	25.4	3.8	0.605
Dyslipidemia, n (%)	65	43	19	32	43	53	0.013	3	30	0.047
DM, n (%)	23	15	7	12	16	20	0.202	0	0	.
Ischemic heart disease, n (%)	12	8	3	5	9	11	0.187	0	0	.
Cerebrovascular disease, n (%)	10	7	1	2	8	10	0.031	1	10	0.101
Current smoker, n (%)	25	17	8	14	16	20	0.341	1	10	0.531
Drinking alcohol, n (%)	61	41	21	36	37	46	0.232	3	30	0.401
SBP, mmHg, mean (SD)	155	16	158	15	151	15	0.009	162	19	0.013
DBP, mmHg, mean (SD)	88	13	87	12	87	12	0.950	100	16	0.007
PR/bpm, mean (SD)	75	11	74	9	76	14	0.546	71	4	0.062

Patient demographics were compared among Group 1 (ARB + AL), Group 2 (CCB + AL), and Group 3 (AL monotherapy). Comparison was conducted between Groups 1 and 2 and among the 3 groups (1-way ANOVA).

(CVD) was higher in Group 2 compared to Group 1. Group 3 had the lowest number of DL cases compared to both Groups 1 and 2, and no patient had DM or ischemic heart disease.

The number of dropouts including discontinuation was as follows: Group 1: 31/59 patients (53%), Group 2: 19/81 patients (23%), and Group 3: 0/10 patients (0%). The dropout rate was highest in Group 1 (Figure 2).

Comparison of the ARB and CCB combination groups showed that significantly more patients dropped out in the ARB combination group ($\varphi = -0.300$, $p < .001$) (Table 2). Adverse events were the most common reason for dropout in Group 1 (ARB combination), with 9 patients dropping out due to this. The most common adverse event was hyperkalemia with 3 patients out of the 9. The cases of hyperkalemia were not critical. There were 10 patients who were discontinued due to the protocol revision. Adverse events were the most common reason for dropout in Group 2 patients, with 4 patients dropping out due to this, and the most frequent adverse event was excessive BP lowering at 2 patients. There were 3 patients who were discontinued due to the protocol revision.

A correlation between chronic kidney disease (CKD) and DM and dropout was investigated using the chi-square test. The number of patients with CKD was significantly associated with dropout ($\varphi = 0.166$, $p < .05$) (Table 2). There was no significant correlation between the number of patients with DM and dropout ($\varphi = 0.092$, $p = .262$) (Table 2).

Changes in BP and PR after add-on of AL are shown in Figure 3. For all cases, after the addition of AL, both SBP and DBP significantly decreased over time ($p < .001$ for both) (Figure 3a). In Group 1, SBP and DBP significantly decreased over time ($p < .001$ and $p < .05$, respectively) (Figure 3b). In Group 2, SBP and DBP were significantly decreased over time ($p < .001$ for both) (Figure 3c). In Group 3, SBP and DBP were significantly decreased over time ($p < .001$ for both) (Figure 3d). There was no change in PR in any patients. When we analyzed Group 1 and Group 2 together, SBP and DBP were significantly decreased over time ($p < .001$ for both). And decreased PR was observed throughout (Figure 3e).

If cases with SBP less than 130 mmHg and 140 mmHg after 3 months were defined as achieved BP cases, respectively, there was no difference between the ARB combination and the CCB combination with the achievement rate of less than 130 mmHg. But the achievement rate of less than 140mmHg was higher with the CCB combination (63%) than that with the ARB combination (41%) ($p = .009$).

Changes in serum potassium after the addition of AL are shown in Figure 4. The addition of AL increased serum potassium in all cases. However, the change in serum potassium was not significant when each group was analyzed individually.

Changes in eGFR after the addition of AL are shown in Figure 5. The addition of AL decreased eGFR in all cases. When the groups were individually analyzed, however, the decrease in eGFR was only significant in Group 1.

In the majority of patients, urine albumin was not measured in a consistent manner and was therefore excluded from the analysis.

Table 2. Correlation between patient demographics and dropout rate.

	Drop out (-)	Drop out (+)
Correlation between Group 1 (ARB + AL) or Group 2 (CCB + AL) and dropout rate		
ARB (n = 59)	28 (47%)	31 (53%)
CCB (n = 81)	62 (77%)	19 (23%)
	p < 0.001	φ = −0.300
Correlation between CKD and dropout rate.		
CKD (-) (n = 114	81(71%)	33 (29%)
CKD (+) (n = 36)	19 (53%)	17 (47%)
	p = 0.043	φ = 0.166
Correlation between DM and dropout rate.		
DM (-) (n = 127)	87 (69%)	40 (31%)
DM (+) (n = 23)	13 (57%)	10 (43%)
	p = 0.262	φ = 0.092

Each category was tested by the chi-square test.
Compared to the CCB + AL group, the number of dropouts was significantly higher in the ARB + AL group ($\varphi = -0.300$, $p < 0.001$).
The number of patients with CKD correlated significantly with a higher number of dropouts ($\varphi = 0.166$, $p = 0.043$).
The number of patients with DM was not significantly correlated with a higher number of dropouts ($\varphi = 0.092$, $p = 0.262$).

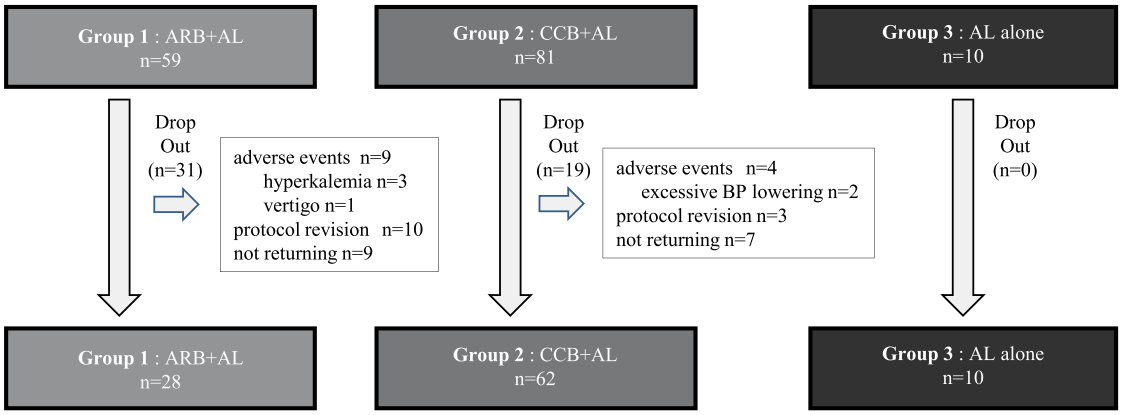

Figure 2. Patient dropout.

The number of dropouts including discontinuation was as follows: Group 1: 31/59 patients, Group 2: 19/81 patients, and Group 3: no patients. Adverse events were the most common reason for dropout in Group 1. The most common adverse event was hyperkalemia. There were 10 patients who were discontinued due to the protocol revision. Adverse events were the most common reason for dropout in Group 2 patients and the most frequent adverse event was excessive BP lowering. There were 3 patients who were discontinued due to the protocol revision.

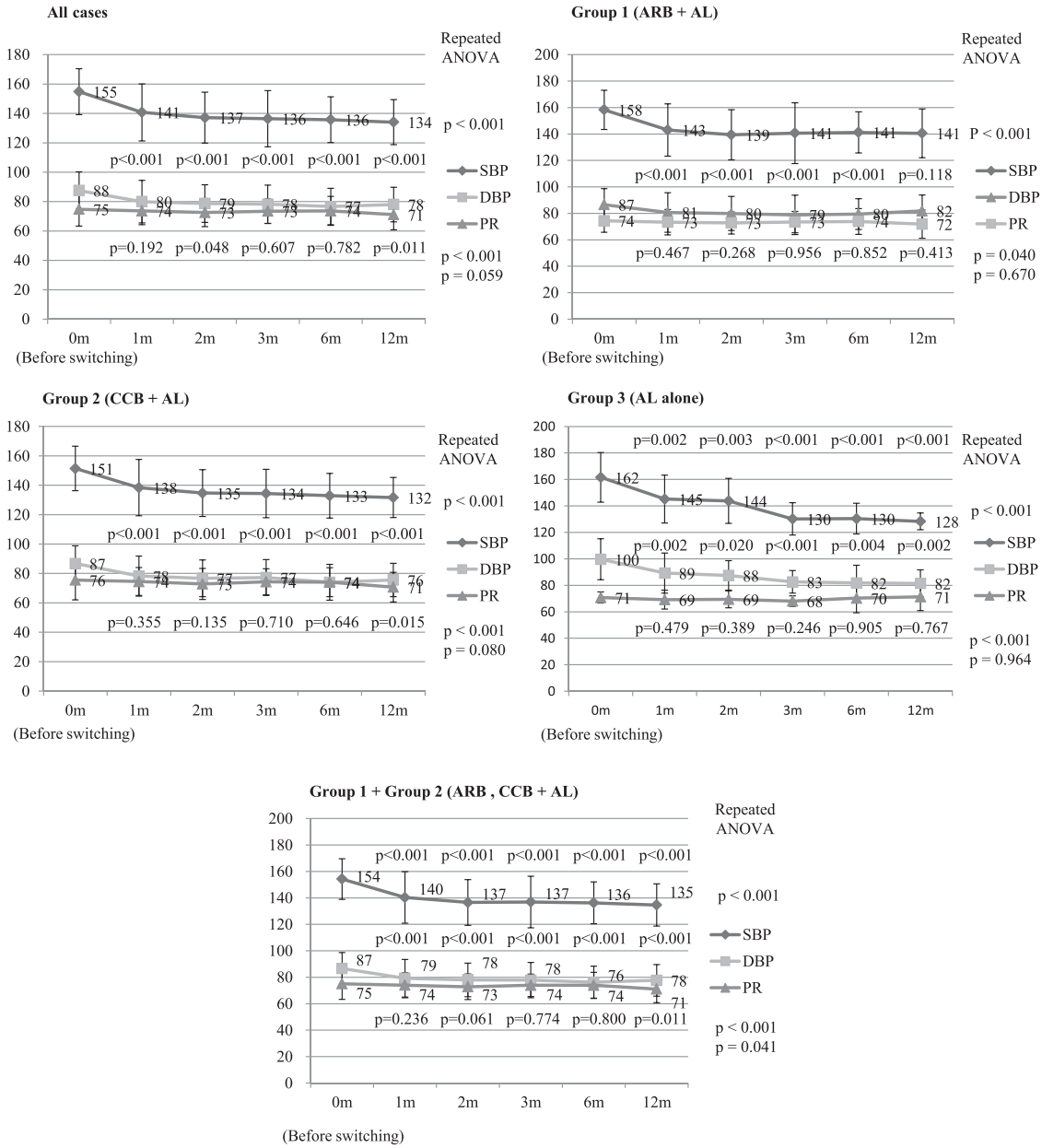

Figure 3. Changes of BP and PR after add-on AL.

T-test was performed to compare data at baseline and at 1, 2, 3, 6, and 12 months. Changes during the follow-up period was analyzed by repeated ANOVA. (a) All cases. (b) Group 1 (ARB+AL). (c) Group 2 (CCB+AL). (d) Group 3 (AL alone). (e) Group 1 + 2 (ARB, CCB + AL)

Discussion

The major findings of this study include: a favorable decrease in BP over time following addition of AL; a significant association between the addition of AL and the number of dropouts in the ARB combination group compared to the CCB combination group; a significant association between AL and the number of dropouts in patients with CKD, and an increase in serum potassium but a decrease in eGFR following addition of AL.

Based on patient demographics, baseline BP was higher and the patient age was younger in the AL monotherapy group (Group 3). This is most likely due to the fact that this study was not randomized, and the young patients who were enrolled in this trial were allocated to AL monotherapy as their first treatment for HT. Group 2 had a high number of cases with DL and had a higher number of patients with CVD compared to Group 1. It is likely that Group 2 had many patients requiring stronger BP lowering effects and used CCB in combination.

In this study, favorable BP lowering effects over time were observed in all patients and for each patient group. Many clinical studies have demonstrated potent BP lowering effects by AL monotherapy and combination therapy with another BP lowering drug.

The Japanese population in general have a higher salt intake compared to Western populations, and therefore hypo-renin hypertension may occur more frequently in this population. Consequently, it is considered that the BP lowering effects of

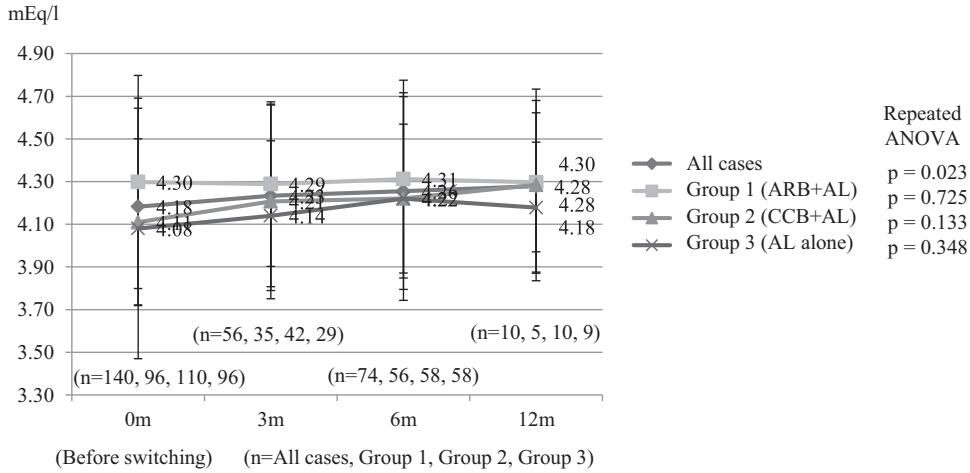

Figure 4. Changes in potassium levels after add-on AL.
Changes in potassium levels after add-on AL treatment in the follow-up period was analyzed by repeated ANOVA.

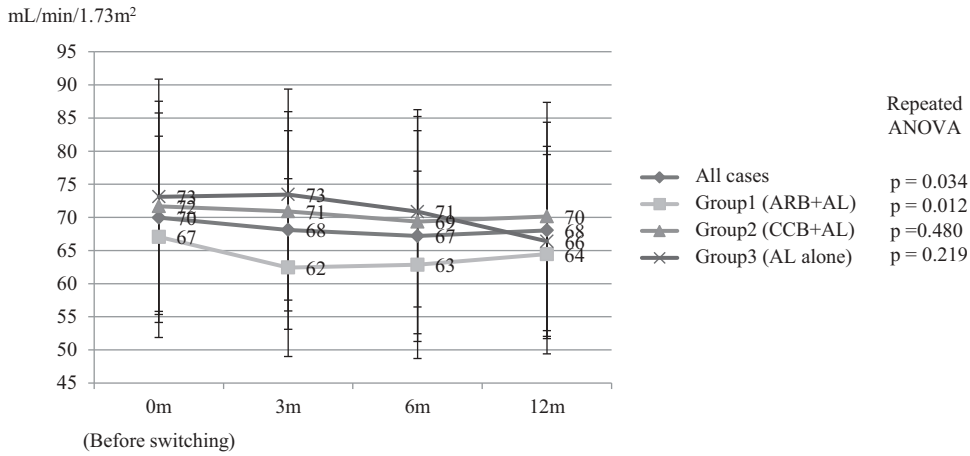

Figure 5. Changes in eGFR after add-on AL.
Changes in eGFR after add-on AL treatment in the follow-up period was analyzed by repeated ANOVA.

RA-I are lower in Japanese populations when compared to Western populations. However, a placebo-controlled AL study in Japanese patients demonstrated no difference in the incidence of adverse events. The BP of the AL group after subtracting the decrease of BP in the placebo group at Week 8 was −5.9/-4.5 mmHg at 150 mg and −11.2/-7.5 mmHg at 300 mg. The decrease of BP was dose-dependent and there was no difference in the incidence of adverse events (8). Dose-dependent BP lowering effects of AL have been observed in several studies (9). Although the maximum dose of AL at 300 mg is recommended to achieve good BP control, only 11 patients received this dose of AL in the present study, possibly due to fears of adverse reactions.

In the present study, the BP lowering effect of AL in Group 3 was −18/-12 mmHg at 2 months, larger than that observed in previous reports. This may be because this was not a placebo-controlled, comparative study, and there might have been considerable big-day bias at the enrollment of patients (10). The study protocol stipulates practicing doctors to enroll patients with poor BP control, however it is well known that the tendency to enroll patients becomes stronger when their BP is high. For ethical reasons, the study protocol enrolls patients with poor BP control. Care should be taken in future studies to establish a strict criteria for BP measurement prior to beginning a study. Moreover, with regard to study participation, the Hawthorne effect may also have played a role.

In this study, the 3-month BP in Group 1 (AL and ARB combination therapy) was −17/-8mmHg, indicating potent BP lowering effects. It has been reported that AL and valsartan combination therapy demonstrated additive, dose-dependent BP lowering effects without sacrificing safety (11,12). Therefore, this combination therapy, which inhibits the beginning and the end of the RAS by RAS-I, was shown to be effective.

In Group 2 (AL and CCB combination therapy), the 3-month BP was −17/-10mmHg, which indicated favorable BP lowering effects. It has been reported that combination with amlodipine rather than AL monotherapy could achieve potent BP lowering effects earlier. As there was no tolerability issue with this combination treatment, AL is considered a suitable drug for combination therapy with CCB (13,14).

A previous report has indicated that AL is the most potent agent to increase renal plasma flow among RAS-I. With

compensation by increased renal blood flow through the dilation of afferent arterioles, it is unlikely that eGFR will be decreased (5). In addition, in a renal ischemia model, AL delayed the progression of renal impairment by anti-inflammatory, anti-fibrosis, and anti-apoptosis effects (15,16). Finally, renal protective effects are synergistically achieved when combined with a BP lowering drug (17).

A longer duration of BP lowering effects are achieved by AL compared with ARB and ACE inhibitors, AL also suppresses the tissue RA system. As AL is accumulated in the kidney, renal protective effects have also been reported (18). In this study, the addition of AL decreased eGFR in all patients. When the groups were analyzed individually, there was only a significant decrease of eGFR in Group 1. It is important to note that the current study enrolled a number of elderly patients with high BP. In clinical practice, attention should be paid to the exacerbation of renal functions for AL and ARB combination therapy.

After the addition of AL, all patients demonstrated an increase in potassium level, however, there was no change in potassium levels in each group when the groups were analyzed individually. It is possible that the elevation of potassium in all patients was due to the dropout of patients by hyperkalemia, as these patients were excluded from the analysis. A study in CKD patients demonstrated an elevation of potassium in patients with an eGFR ≤ 30 mL/min/1.73m^2 following AL administration. However, patients with a history of hyperkalemia by ACE inhibitors and ARB were included (19).

In the present study, patients with an eGFR ≤ 30 mL/min/1.73m^2 were not included, and consequently, a similar investigation could not be conducted. When stratified by eGFR at ≥ 60 mL/min/1.73m^2 or not, patients with eGFR < 60 mL/min/1.73m^2 were not associated with a significant elevation of potassium (data not shown).

The pharmacokinetics of AL is unlikely to be affected by renal impairment, but taken together with previous reports, careful attention should be paid for hyperkalemia in patients with a history of decreased eGFR or hyperkalemia.

For patients with type 2 diabetes and albuminuria, treatment with AL demonstrated a decrease in urinary albumin independent of BP lowering effects (20–23). Treatment with AL was reported to be comparable to that of treatment with perindopril (24).

Add-on of AL to ARB treatment was not associated with adverse events such as renal impairment and hyperkalemia, but rather a decrease in proteinuria, indicating that combination therapy of ARB and AL may decrease urinary protein (25,26).

This study originally planned to evaluate if AL affects urinary protein. However, measurements were not taken based on the decision of doctors. Currently, practicing doctors in Japan seldom measure urinary albumin. This may be due to a concern of potential rejection of health insurance claims in Japan, and it is necessary to improve the awareness of doctors on the necessity of urinary protein measurements. As it has been shown that AL treatment increases the risk of hyperkalemia, AL should not be co-administered with RA drugs for the purpose of improving surrogate endpoints such as albuminuria.

There were 25 dropout patients from March 14, 2011 through January 22, 2012 (just prior to the protocol revision as per the recommendation). After the protocol revision (January 23, 2012), there were 25 dropout patients in the period through March 14, 2013. In short, the number of dropout patients was 25 patients in 315 days (prior to protocol revision) and 25 patients in 417 days (after protocol revision), or 1 patient per 12.6 days or 16.7 days, respectively. Thus, there was no marked increase of the dropout rate after the protocol revision.

Interestingly, after the protocol revision of the current study, patient registration decreased from 1 patient every 3.6 days to 1 patient every 21.5 days. It is possible that this change in patient registration was as a result of the interim findings of the ALTITUDE study influencing the thoughts of practicing doctors. Many of the dropouts were for CKD cases, which may have been due to doctors having concerns about the effects of AL on renal function.

There were no dropouts in Group 3, and dropout often occurred after the addition of AL as the second drug in Groups 1 and 2. Moreover, it was more often seen when AL was added to ARB.

It has been reported that AL has the potential for long-lasting BP lowering effects, and potential organ protective attributes can be expected as an RAS-I. Moreover, combination with a Ca antagonist or diuretic can lower the BP further. Unfortunately, combination AL treatment with RAS-I such as ACE inhibitors and ARB have been recommended to be avoided (27).

Based on the results of the current study, AL is not suitable to be administered as add-on for BP lowering therapy, especially ARB. Consequently, AL will only be considered for monotherapy.

However, according to the Guidelines for the Management of Hypertension, AL is unlikely to be selected as the first choice for treatment, and as such, it is expected that AL will not play a key role except in special situations. In clinical practice, strong BP lowering effect could be obtained by administering aliskiren. However, this study performed without placebo control made it difficult to demonstrate the protruding benefits of aliskiren in hypertensive cases.

Conclusion

While add-on AL treatment achieved a desirable and sustainable decrease in BP patients enrolled in the CHAT-Ras study, caution is necessary with regard to potential adverse effects such as the elevation of potassium levels and renal impairment.

Acknowledgments

We thank Mrs. Nao Totake for her excellent technical assistance and the general practitioners participating in Chikushi-JRN for enrollment of their patients.

Conflicts of Interests

The authors have financial conflicts of interest (Novartis Pharma K.K.) to disclose concerning this study.

Funding

This work was supported by the Novartis Pharma [110477FK].

Study Limitations

There may have been considerable big-day bias at the enrollment of patients (10). Moreover, with regard to study participation, the Hawthorne effect may have also played a role. Ambulatory BP and home BP were not measured. The target sample size was not achieved, and the dropout rate was high. Basically, the content of antihypertensive drugs should not have changed after the addition of AL. But the exact details are unknown.

References

1. Ad-hoc working group of E, Fliser D, Laville M, Covic A, Fouque D, Vanholder R, Juillard L, Van Biesen W. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. Nephrol Dial Transplant. 2012;27:4263–72. doi:10.1093/ndt/gfs375
2. Alderman MH, Ooi WL, Cohen H, Madhavan S, Sealey JE, Laragh JH. Plasma renin activity: a risk factor for myocardial infarction in hypertensive patients. Am J Hypertens. 1997;10:1–8. doi:10.1016/S0895-7061(96)00301-9.
3. Rouleau J-L, Packer M, Moye L, de Champlain J, Bichet D, Klein M, Rouleau JR, Sussex B, Arnold JM, Sestier F, et al. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril. J Am Coll Cardiol. 1994;24:583–91.
4. Wood JM, Maibaum J, Rahuel J, Grutter MG, Cohen N-C, Rasetti V, Rüger H, Göschke R, Stutz S, Fuhrer W, *et al*. Structure-based design of aliskiren, a novel orally effective renin inhibitor. Biochem Biophys Res Commun. 2003;308:698–705.
5. Fisher NDL, Jan Danser AH, Nussberger J, Dole WP, Hollenberg NK, Dole WP, Hollenberg NK. Renal and hormonal responses to direct renin inhibition with aliskiren in healthy humans. Circulation. 2008;117:3199–205. doi:10.1161/CIRCULATIONAHA.108.767202.
6. Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, et al. The Japanese society of hypertension guidelines for the management of hypertension (JSH 2009). Hypertens Res. 2009;32:3–107.
7. Parving -H-H, Brenner BM, McMurray JJV, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, Persson F, Desai AS, Nicolaides M, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367:2204–13.
8. Kushiro T, Itakura H, Abo Y, Gotou H, Terao S, Keefe DL. Aliskiren, a novel oral renin inhibitor, provides dose-dependent efficacy and placebo-like tolerability in Japanese patients with hypertension. Hypertens Res. 2006;29:997–1005. doi:10.1291/hypres.29.997.
9. Kushiro T, Itakura H, Abo Y, Gotou H, Terao S, Keefe DL. Long-term safety, tolerability, and antihypertensive efficacy of aliskiren, an oral direct renin inhibitor, in Japanese patients with hypertension. Hypertens Res. 2009;32:169–75. doi:10.1038/hr.2008.21.
10. Howard JP, Francis DP. Overcoming the three biases obscuring the science of renal denervation in humans: big-day bias, check-once-more bias and I-will-take-it-now bias. Trends Cardiovasc Med. 2015;25:116–18. doi:10.1016/j.tcm.2014.10.011.
11. Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. Lancet. 2007;370:221–29. doi:10.1016/S0140-6736(07)61124-6.
12. Chrysant SG, Murray AV, Hoppe UC, Dattani D, Patel S, Hsu H, Zhang J. Long-term safety, tolerability and efficacy of aliskiren in combination with valsartan in patients with hypertension: a 6-month interim analysis. Curr Med Res Opin. 2008;24:1039–47.
13. Brown MJ, McInnes GT, Papst CC, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. Lancet. 2011;377:312–20. doi:10.1016/S0140-6736(10)62003-X.
14. Liu Y, Yan R, Song A, Niu X, Cao C, Wei J, Dong X, Gao D. Aliskiren/amlodipine vs. aliskiren/hydrochlorothiazide in hypertension: indirect meta-analysis of trials comparing the two combinations vs. monotherapy. Am J Hypertens. 2014;27:268–78.
15. Choi DE, Jeong JY, Lim BJ, Chang Y-K, Na K-R, Shin Y-T, Lee KW. Aliskiren ameliorates renal inflammation and fibrosis induced by unilateral ureteral obstruction in mice. J Urol. 2011;186:694–701.
16. Sun CY, Cherng WJ, Jian HZ, Hsu HH, Wu IW, Hsu HJ. Aliskiren reduced renal fibrosis in mice with chronic ischemic kidney injury–beyond the direct renin inhibition. Hypertens Res. 2012;35:304–11.
17. Sakuraya K, Endo A, Someya T, Hirano D, Murano Y, Fujinaga S, Ohtomo Y, Shimizu T. The synergistic effect of mizoribine and a direct renin inhibitor, aliskiren, on unilateral ureteral obstruction induced renal fibrosis in rats. J Urol. 2014;191:1139–46.
18. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK, Investigators AS. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med. 2008;358:2433–46. doi:10.1056/NEJMoa0708379.
19. Ito S, Nakura N, Le Breton S, Keefe D. Efficacy and safety of aliskiren in Japanese hypertensive patients with renal dysfunction. Hypertens Res. 2010;33:62–66. doi:10.1038/hr.2009.175.
20. Persson F, Lewis JB, Lewis EJ, Rossing P, Hollenberg NK, Parving HH. Aliskiren in combination with losartan reduces albuminuria independent of baseline blood pressure in patients with type 2 diabetes and nephropathy. Clin J Am Soc Nephrol. 2011;6:1025–31. doi:10.2215/CJN.07590810.
21. Persson F, Rossing P, Reinhard H, Juhl T, Stehouwer CD, Schalkwijk C, Danser AHJ, Boomsma F, Frandsen E, Parving -H-H, et al. Optimal antiproteinuric dose of aliskiren in type 2 diabetes mellitus: a randomised crossover trial. Diabetologia. 2010;53:1576–80.
22. Matavelli LC, Huang J, Siragy HM. Combined aliskiren and amlodipine reduce albuminuria via reduction in renal inflammation in diabetic rats. J Cardiovasc Pharmacol. 2012;59:281–87. doi:10.1097/FJC.0b013e31823fc3f5.
23. Persson F, Rossing P, Schjoedt KJ, Juhl T, Tarnow L, Stehouwer CD, Schalkwijk C, Boomsma F, Frandsen E, Parving -H-H, et al. Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes. Kidney Int. 2008;73:1419–25.
24. Kelly DJ, Zhang Y, Moe G, Naik G, Gilbert RE. Aliskiren, a novel renin inhibitor, is renoprotective in a model of advanced diabetic nephropathy in rats. Diabetologia. 2007;50:2398–404. doi:10.1007/s00125-007-0795-9.
25. Tang SC, Lin M, Tam S, Au WS, Ma MK, Yap DY, Ho YW, Lai KN. Aliskiren combined with losartan in immunoglobulin A nephropathy: an open-labeled pilot study. Nephrol Dial Transplant. 2012;27:613–18.
26. Moriyama T, Tsuruta Y, Kojima C, Itabashi M, Sugiura H, Takei T, Ogawa T, Uchida K, Tsuchiya K, Nitta K, et al. Beneficial effect of aliskiren combined with olmesartan in reducing urinary protein excretion in patients with chronic kidney disease. Int Urol Nephrol. 2012;44:841–45.
27. Riccioni G. Blood pressure control and favourable pleiotropic effects of aliskiren. Hypertens Res. 2013;36:102–03. doi:10.1038/hr.2012.202.