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RESEARCH ARTICLE

Antihypertensive efficacy and safety of the angiotensin receptor blocker azilsartan in elderly patients with hypertension

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Abstract

Objectives: The number of elderly patients with hypertension has been steadily increasing. However, there are limited data on the safety and efficacy of the new angiotensin type 1 receptor blocker (ARB) azilsartan in elderly patients with hypertension. We investigated the clinical efficacy and safety of azilsartan in this population. *Methods*: The study population comprised 56 ambulatory patients with essential hypertension. We evaluated the reduction in blood pressure and safety after 12 weeks of treatment with azilsartan in 29 hypertensive patients ≥65 years of age (aged group) in comparison with the findings in 27 patients <65 years of age (non-aged group). *Results*: Systolic blood pressure in the aged group declined significantly from 155 ± 18 mmHg at baseline to 138 ± 11 mmHg after 12 weeks of treatment with azilsartan, and that in the non-aged group also declined significantly from 152 ± 20 mmHg at baseline to 142 ± 13 mmHg after 12 weeks of treatment with azilsartan. There were no significant differences in the magnitude of change in blood pressures from pre-treatment to post-treatment with azilsartan between the non-aged and aged groups. There were no changes in clinical laboratory findings, including serum levels of creatinine, potassium, lipids, and other metabolic variables, after 12 weeks of treatment with azilsartan in both groups. *Conclusions*: Our findings suggest that azilsartan is effective in lowering blood pressure in elderly patients and may be safe. Therefore, azilsartan could be a valuable option for treating hypertension in elderly and non-elderly patients.

Keywords

Angiotensin type 1 receptor blocker, elderly, hypertension, safety

History

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Introduction

With the global prolongation of life expectancy, the number of elderly individuals, defined as those aged 65 years and older, is increasing, and consequently, the number of elderly patients with hypertension is also increasing (Turgut et al., 2013). In Japan, the prevalence of hypertension is 66% in the elderly population aged 65–74 years and 80% in the population older than 75 years (Shimamoto et al., 2014). In elderly patients, the number of deaths from stroke and ischemic heart disease has increased in proportion to systolic blood pressure (SBP) (Lewington et al., 2002). In the ESC/ESH guidelines published in 2013 (Mancia et al., 2013), antihypertensive treatment has been recommended in patients with SBP values ≥160 mmHg, with the goal of reducing SBP to <150 mmHg in elderly patients. In addition, antihypertensive treatment also may be considered in patients with SBP values >140 mmHg, with the goal of reducing SBP to <140 mmHg in elderly patients in good physical and mental condition with tolerability. Meanwhile, the JSH 2014 guidelines (Shimamoto et al., 2014) recommend initiating antihypertensive therapy in elderly patients with BP values >140/90 mmHg on principle, considering that the Japanese population has a high incidence of stroke.

During the past decade, angiotensin II type 1 receptor blockers (ARBs) have become widely used for the treatment of hypertension in Japan. Because Asians have a higher incidence of dry cough associated with angiotensin-converting enzyme inhibitors (ACEIs) (Cheung & Cheung, 2014), ARBs could be more suitable in Asian patients. In fact, ARBs are the second most commonly used antihypertensive drugs at present in Japan, following Ca channel blockers (Shimamoto et al., 2014). Azilsartan is a relatively new ARB that inhibits the actions of angiotensin II on the renin–angiotensin–aldosterone system (RAAS), and it has recently became available for the treatment of hypertension. In a previous study (Ojima et al., 2011), azilsartan was found to bind tightly to angiotensin II type 1 receptors, and it was also demonstrated to dissociate slowly from angiotensin II type 1 receptors in comparison with other widely used ARBs, including olmesartan, telmisartan, valsartan, and irbesartan. In fact, azilsartan has been reported to be more efficacious in

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lowering BP than other ARBs at their maximum approved doses in a series of comparative studies (Bakris et al., 2011; Rakugi et al., 2013; White et al., 2011). Azilsartan at a dose of 80 mg showed superior efficacy to both valsartan (320 mg) and olmesartan (40 mg) using ambulatory and semiautomated in-clinic BP monitoring without an increase in adverse events compared with other ARBs (White et al., 2011). Another study (Rakugi et al., 2013) reported that azilsartan produced more potent 24-h sustained antihypertensive activity than that of candesartan in Japanese patients with essential hypertension, and it had an equivalent level of safety.

Although a number of reports support the efficacy and safety of azilsartan in patients with hypertension, data supporting the efficacy and safety of azilsartan in elderly patients are not substantial. ARBs should be used in elderly patients with attention paid to renal dysfunction, as ARBs cause an initial reduction in the glomerular filtration rate (GFR) or an increase in serum creatinine levels (Bakris & Weir 2000; Holtkamp et al., 2011; Lambers et al., 2014). Accordingly, we aimed to retrospectively evaluate efficacy and safety, particularly concerning renal function, of 12 weeks of treatment with azilsartan in elderly patients with hypertension in this study.

Methods

Study population

A total of 56 patients with essential hypertension (66 ± 11 years; 33 men and 23 women) were prescribed azilsartan at Fujita Health University Banbuntane-Hotokukai Hospital between May 2013 and August 2014. Hypertension was defined as sitting SBP $\geq$140 mmHg or diastolic BP (DBP) $\geq$ 90 mmHg on two consecutive measurements at the clinic or as the use of antihypertensive drugs. Nine patients were newly diagnosed with hypertension, and 47 patients were previously prescribed antihypertensive drugs including ACEIs/ARBs without achieving a target BP based on JSH 2014 (SBP $\geq$140 mmHg or DBP $\geq$ 90 mmHg at the clinic or early morning SBP $\geq$135 mmHg or DBP $\geq$85 mmHg at home) after at least 2 months of treatment. The exclusion criteria included known or suspected secondary hypertension, acute coronary syndrome, end-stage renal disease, and acute inflammation.

Study design

All patients were prescribed azilsartan at 20 mg once daily for the first time or switched from other traditional ACEI/ARBs in addition to their existing antihypertensive regimen. Patients visited the clinic every 4 weeks during the treatment period. At each visit to the clinic, physical examination was conducted, and sitting BP was measured. In the sitting position, two consecutive BP measurements were taken at 1-min intervals, and the average of these two measurements was taken as sitting BP. Clinical data and laboratory measurements including chest radiography, standard electrocardiography, and the results of blood sampling routinely performed before and after 12 weeks of treatment with azilsartan were obtained from the patients' medical charts.

Chronic kidney disease (CKD) was defined as baseline estimated GFR (eGFR) $<$ 60 ml/min/1.73 m^2, which was calculated using the Modification of Diet in Renal Disease formula modified for Japanese subjects as follows: $\text{eGFR} = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female) (Matsuo et al., 2009; Okumura et al., 2012). We defined end-stage renal disease as initiation of renal replacement therapy or death due to kidney disease. Diabetes was defined as having a diagnosis of diabetes and/or treatment with medication and/or diet or a fasting blood glucose level $\geq$126 mg/dl. Dyslipidemia was defined as follows: treatment with medication or a total cholesterol level $>$220 mg/dl, low-density lipoprotein level $\geq$140 mg/dl, or high-density lipoprotein level $<$40 mg/dl. Myocardial infarction was defined on the basis of typical electrocardiographic changes and increased serum activities of enzymes such as creatine kinase, aspartate aminotransferase, and lactate dehydrogenase together with the presence of wall-motion abnormality on left ventriculography and attendant stenosis in any of the major coronary arteries as documented by coronary angiography.

The primary endpoint for assessing efficacy was the change from baseline in the mean clinical SBP or DBP after 12 weeks of treatment with azilsartan. Safety measures included adverse events, clinical laboratory results, and physical examination findings. This study was conducted with the approval of the Human Investigations Committee of Fujita Health University and we obtained informed consent from all patients in this study.

Statistical analysis

The baseline characteristics of the two groups of patients were compared by Student's *t*-test for unpaired data or the Chi-square test for categorical data. The effects of 12 weeks of treatment with azilsartan were evaluated by a repeated measures analysis of variance (ANOVA). Numerical results are expressed as mean $\pm$ SD. In all analyses, $p < 0.05$ was considered significant.

Results

Clinical characteristics

We assigned subjects $\geq$65 years of age to the aged group ($n = 29$) and those $<$65 years of age to the non-aged group ($n = 27$). The clinical characteristics of each group are summarized in Table 1. There were a higher proportion of male patients in the non-aged group than in the aged group, but there were no significant differences in body mass index or the prevalence of diabetes mellitus, dyslipidemia, myocardial infarction, and CKD between the two groups. There were no significant differences in antihypertensive treatment prior to this study between the aged and non-aged groups summarized in Table 1. Concomitant antihypertensive medication use did not differ between the two groups.

Effects on lowering BP

There were significant reductions in sitting SBP and DBP in the entire patient population after 12 weeks of treatment versus baseline, with the mean sitting SBP and DBP declining by 14 (154 mmHg versus 140 mmHg; $p < 0.01$) 7 mmHg (86 mmHg versus 79 mmHg; $p < 0.01$), respectively. In the

non-aged group, SBP and DBP at baseline were 152 ± 20 and 91 ± 13 mmHg, respectively, and these values decreased to 142 ± 13 and 84 ± 8 mmHg, respectively, after 12 weeks of treatment (Figure 1). Heart rate was not altered by treatment (73 ± 9 bpm at baseline versus 74 ± 11 bpm after 12 weeks of treatment). In the aged group, SBP and DBP at baseline were 155 ± 18 and 81 ± 10 mmHg, respectively, and these values decreased to 138 ± 11 and 75 ± 8 mmHg, respectively, after 12 weeks of treatment. Heart rate in this group was 73 ± 11 bpm at baseline and 73 ± 12 bpm after 12 weeks of treatment.

Table 1. Characteristics of the two patient groups at baseline.

Characteristics	Non-aged group ($n = 27$)	Aged group ($n = 29$)	p Values
Age (years)	57 ± 7.4	75 ± 5.4	<0.01
Male (n)	20	13	0.026
Body mass index (kg/m^2)	25 ± 4.4	24 ± 4.1	n.s.
Heart rate (beats/min)	73 ± 9	73 ± 11	n.s.
Diabetes mellitus (n)	3	8	n.s.
Dyslipidemia (n)	10	9	n.s.
History of myocardial infarction (n)	5	6	n.s.
Chronic kidney disease (n)	5	10	n.s.
Medication (n)			
ACEI or ARB	18	22	n.s.
Calcium-channel blockers	12	20	n.s.
Diuretics	6	6	n.s.
β-Blockers	8	7	n.s.

Date are means ± SD. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; n.s., not significant.

Reductions of SBP from baseline to post-treatment with azilsartan were 10 ± 17 mmHg in the non-aged group and 17 ± 17 mmHg in the aged group (Table 2). Reductions of DBP from baseline to post-treatment with azilsartan were 7 ± 10 mmHg in the non-aged group and 6 ± 10 mmHg in the aged group. There were no significant differences in the magnitude of change in SBP and DBP from baseline to post-treatment with azilsartan between the non-aged and aged groups.

Safety

No patients experienced adverse events of sufficient severity to warrant treatment discontinuation. The changes in laboratory measurements after 12 weeks of treatment with azilsartan versus baseline are shown in Table 2. There were neither

Table 2. Comparison of antihypertensive effect of azilsartan between the two groups.

	Non-aged group	Aged group	p Values
Systolic blood pressure (mmHg)			
Baseline	152 ± 20	155 ± 18	n.s.
After 12 weeks	142 ± 13*	138 ± 11*	n.s.
Change from baseline	10 ± 17	17 ± 17	n.s.
Diastolic blood pressure (mmHg)			
Baseline	91 ± 13	81 ± 10	<0.01
After 12 weeks	84 ± 8*	75 ± 8*	n.s.
Change from baseline	7 ± 10	6 ± 10	n.s.

Date are means ± SD; n.s., not significant; *p <0.05 versus baseline.

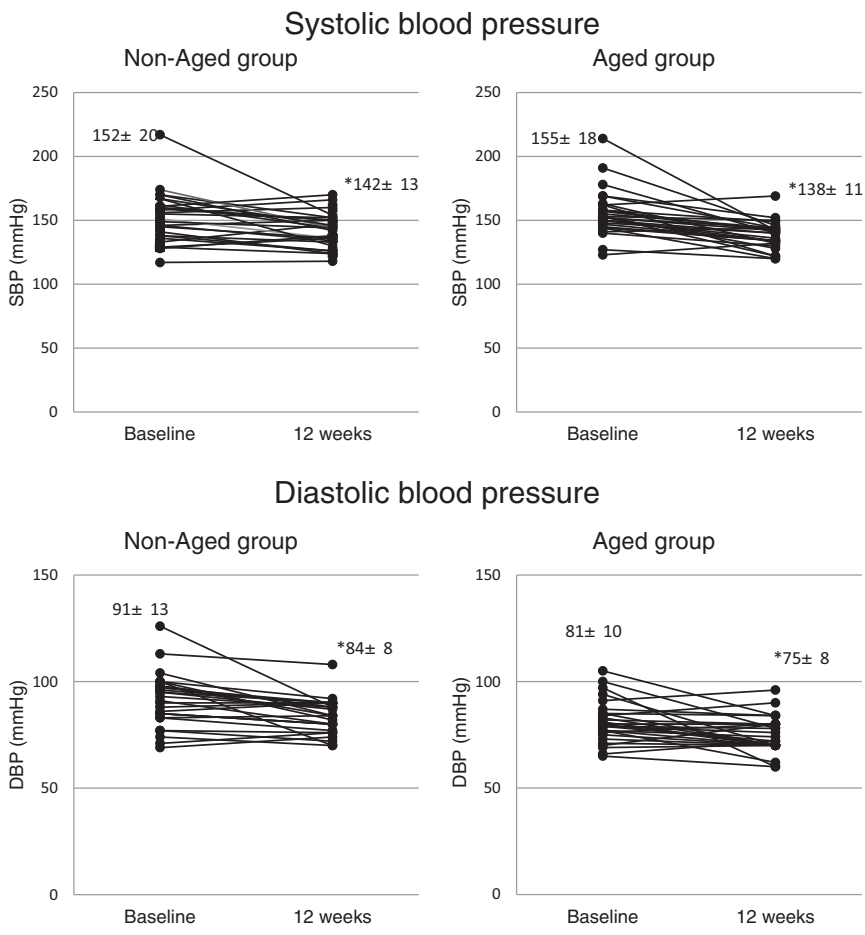

Figure 1. After 12 weeks of treatment, there were greater reductions in systolic (SBP) and diastolic blood pressure (DBP) in both the non-aged and aged groups. Reductions in SBP and DBP were similar in the two groups. *p <0.05 versus baseline.

differences in serum cholesterol, creatinine, uric acid, and potassium levels at baseline between the two groups nor were there any changes in the serum levels of these variables after 12 weeks of treatment with azilsartan in either group (Table 3). Although eGFR after 12 weeks of treatment with azilsartan in the aged group was lower than that in the non-aged group, there were no changes in eGFR after 12 weeks of treatment versus baseline in the aged group. Although the mean serum level of hemoglobin A1c at baseline in the aged group was higher than that in the non-aged group, there were no changes in the mean serum hemoglobin A1c level after 12 weeks of treatment with azilsartan in either group.

Discussion

This 12-week, open-label, real-world, single-center analysis revealed the efficacy and the safety of azilsartan in elderly and non-elderly patients with hypertension. We demonstrated that azilsartan at 20 mg significantly reduced both SBP and DBP in elderly hypertensive patients without adverse effects in the clinical setting.

Efficacy in lowering BP

Elevated BP is one of the most important cardiovascular risk factors in the population ranging from young adulthood to the elderly age group, and the final objective of treatment for hypertension is to prevent cardiovascular events, such as myocardial infarction, heart failure, and stroke (Pahor et al., 1995). In hypertensive patients without specific conditions, ARBs, ACEIs, Ca channel blockers, or diuretics are recommended as the first-choice treatment by the JSH 2014 guidelines (Shimamoto et al., 2014). Among these first-choice drugs, ARBs are among the most commonly used antihypertensive drugs in Japan, in addition to Ca channel blockers. ARBs improve the prognosis of heart failure (Granger et al., 2003), prevent the exacerbation of renal function in the long-term (Lewis et al., 2001), and reduce the incidence of stroke (TRANSCEND Investigators, 2008). These advantages of using ARBs for treating hypertension in addition to improvement in cardiovascular outcomes have also been confirmed in elderly hypertensive patients (Lithell et al., 2003; Winkelmayer et al., 2006). In this study, we demonstrated the efficacy of a new ARB, azilsartan, in lowering mean SBP and DBP by 17 and 6 mmHg, respectively, after 12 weeks of treatment in elderly Japanese hypertensive patients. These results are in accordance with those recently reported by White et al. (2011), who reported that reductions in SBP after 6 weeks of treatment with azilsartan from baseline were similar between 110 patients $\geq$65 years of age and 356 patients <65 years of age recruited from 141 centers in Guatemala, Mexico, Peru, Puerto Rico, and the United States. In the JSH 2014 guidelines (Shimamoto et al., 2014), BP should be gradually decreased to a target BP of <140/90 mmHg in patients aged 65–74 years and <150/90 mmHg in those older than 75 years. In addition, a more aggressive reduction in BP <140/90 mmHg is recommended in patients older than 75 years, if treatment is well tolerated. Accordingly, this study suggests that azilsartan could be useful in achieving the desired BP in elderly Japanese patients with hypertension.

Table 3. Blood parameters at baseline and after 12 weeks of treatment.

Parameter	Non-aged group	Aged group	*p* Values
Creatinine (mg/dl)			
Baseline	0.85 ± 0.20	0.88 ± 0.38	n.s.
After 12 weeks	0.87 ± 0.20	0.90 ± 0.33	n.s.
eGFR (ml/min/1.73 m^2)			
Baseline	68.4 ± 13.0	62.2 ± 20.2	n.s.
After 12 weeks	65.5 ± 11.4	58.1 ± 16.8	0.030
Uric acid (mg/dl)			
Baseline	6.1 ± 1.3	5.9 ± 1.6	n.s.
After 12 weeks	6.0 ± 1.4	5.8 ± 1.6	n.s.
Sodium (mEq/l)			
Baseline	142 ± 2.0	142 ± 2.6	n.s.
After 12 weeks	142 ± 2.0	142 ± 2.4	n.s.
Potassium (mEq/l)			
Baseline	4.1 ± 0.3	4.3 ± 0.4	n.s.
After 12 weeks	4.2 ± 0.3	4.3 ± 0.6	n.s.
Hemoglobin A1c (%)			
Baseline	5.8 ± 0.4	6.3 ± 1.1	0.018
After 12 weeks	5.8 ± 0.3	6.4 ± 1.3	0.016
LDL-C (mg/dl)			
Baseline	120 ± 37	116 ± 40	n.s.
After 12 weeks	123 ± 30	106 ± 38	n.s.
HDL-C (mg/dl)			
Baseline	62 ± 25	65 ± 17	n.s.
After 12 weeks	65 ± 31	65 ± 19	n.s.

Date are means ± SD; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; n.s. not significant.

Safety

Acute kidney injury and hyperkalemia are the potential adverse effects of RAAS blockers such as ARBs in elderly patients (Turgut et al., 2013). Generally, elderly patients use multiple medications, including diuretics or non-steroidal anti-inflammatory drugs for concurrent conditions, further increasing the risk of acute kidney injury and hyperkalemia. Accordingly, the use of RAAS blockers in elderly patients requires additional caution for adverse effects. We showed that azilsartan did not affect either serum creatinine or potassium levels after 12 weeks of treatment in elderly patients in this study. Based on a recent critical review of the literature on the use of RAAS blockers in patients with renal insufficiency (Bakris & Weir, 2000), it was demonstrated that RAAS blockers exerted long-term renoprotective effects in patients with an initial increase in serum creatinine levels of up to 30%, which stabilized within the first 8 weeks of treatment. In addition, a more recent review (Weir & Rolfe, 2010) indicated that hyperkalemia was minimal and clinically insignificant in patients treated with RAAS blockers. In consideration of these reviews, the use of RAAS blockers including ARB can be considered appropriate in patients if the increase in blood creatinine levels from baseline is within 30% within the first 8 weeks of treatment or if hyperkalemia develops (Turgut et al., 2010). However, these studies unfortunately were not designed for elderly patients. Future prospective studies are warranted to determine whether the limited initial increase in serum creatinine levels or hyperkalemia after treatment with ARBs such as azilsartan could result in long-term renoprotective effects and clarify the safety of these drugs in elderly patients with hypertension.

Study limitations

Limitations of this study should be acknowledged. The study population is relatively small size. And the relative number of males to females in the aged group increased compared with that in the non-aged group. Although these limitations still exist, we reported for the first time in Asian patients, that azilsartan could be an effective and safe antihypertensive drug in elderly patients. A future clinical prospective trial of adequate size and duration should be needed to confirm effects of azilsartan in Asian elderly hypertensive patients.

Conclusions

In this study, we demonstrated that a new ARB, azilsartan, had several benefits in elderly patients with hypertension, including potential BP-lowering effects, and the safety of the drug was possible. Accordingly azilsartan could be a valuable option for the treatment of elderly patients with hypertension.

Declaration of interest

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