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ORIGINAL ARTICLE

Comparison of the long-term effects of candesartan and olmesartan on plasma angiotensin II and left ventricular mass index in patients with hypertension

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In general, treatment with most angiotensin receptor blockers (ARBs) increases plasma angiotensin II (Ang II) level because of a lack of negative feedback on renin activity. Olmesartan is a potential ARB inducing activation of angiotensin-converting enzyme 2 (ACE2) that hydrolyzes Ang II to Ang 1–7, and has shown a beneficial effect on ventricular remodeling. Indeed, a previous study reported that olmesartan treatment resulted in decreased plasma levels of Ang II and aldosterone. However, there has not yet been a study showing the relationship of chronic effects of olmesartan on Ang II and the left ventricular mass index (LVMI) in comparison with those of other ARB. A total of 50 stable outpatients with essential hypertension who had received candesartan for more than 1 year were randomized into two groups: control group (n=25): continuous candesartan treatment at a stable dose; and olmesartan group (n=25): candesartan (8 mg day^{-1}) was changed to olmesartan given at a dose of 20 mg day^{-1}. There was no difference in the baseline characteristics between the two groups. In the control group, there were no significant changes in blood pressure, LVMI or biomarkers during 12 months of study. In the olmesartan group, blood pressure did not change and plasma levels of Ang II decreased during 12 months of study, whereas LVMI was significantly decreased after 12 months (135 ± 36 *vs.* 123 ± 29 g m^{-2}; $P<0.01$). These findings indicate that replacing candesartan with olmesartan decreased LVMI in association with a sustained decrease of plasma Ang II over a 12-month period without changing blood pressure or plasma aldosterone in patients with essential hypertension.
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Angiotensin receptor blockers (ARBs) are widely used for the management of hypertension and chronic heart failure (CHF). In general, treatment with ARBs increases the plasma angiotensin II (Ang II) level because of a lack of negative feedback on renin activity or competition of Ang II with AT1 receptor. Indeed, several types of ARBs have been shown to increase both plasma renin activity and plasma Ang II concentrations in hypertensive patients.[1–3] In contrast, Ichikawa *et al.*[4] reported that long-term treatment of hypertensive patients with olmesartan resulted in a reduction of the plasma Ang II level. The exact mechanism underlying the failure of olmesartan to increase the plasma Ang II levels remains uncertain.

Angiotensin-converting enzyme 2 (ACE2), a homolog of the ACE enzyme[5,6] expressed primarily in the vascular endothelium, removes a single amino acid from the carboxy-terminus of Ang II to generate Ang 1–7. Previous studies suggested that the ACE2–Ang 1–7 axis has an important role in hypertensive disease and CHF.[7–9] Takeda *et al.*[10] reported that treatment with candesartan increased *ACE2* mRNA level and decreased angiotensinogen mRNA level in the heart. Recently, it was shown that olmesartan increased ACE2 expression during the remodeling of the heart after myocardial infarction,[11] and olmesartan improved left ventricular remodeling with an increase in cardiac ACE2 expression in stroke-prone spontaneously hypertensive rats.[12] The ACE2 is a membrane-associated carboxy-peptidase that is highly expressed in the heart and kidney[13] and hydrolyzes Ang II to Ang 1–7, which inhibits the ACE C-domain and bradykinin by acting as an ACE inhibitor.[14] Therefore, olmesartan may be a potential ARB with an activating effect on ACE2 and an inhibitory effect on ACE.

We previously reported that plasma Ang II level was significantly increased in patients with CHF after chronic treatment with candesartan.[15] Therefore, we hypothesize that there is a difference in chronic effect on Ang II between candesartan and olmesartan in patients with essential hypertension. In this study, we compared the chronic effects of olmesartan on Ang II in comparison with those of candesartan, as well as the long-term effects of olmesartan on left ventricular mass index (LVMI) in comparison with those of candesartan. This study evaluated the long-term effects of olmesartan, after replacement of candesartan, on plasma levels of Ang II and aldosterone (ALD) and on left LVMI in patients with essential hypertension.

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METHODS

A total of 50 stable outpatients with essential hypertension who had received candesartan for more than 1 year were randomized to two groups using the envelope method: control group (n=25): continuous candesartan treatment at a stable dose; and olmesartan group (n=25): candesartan (8 mg day^{-1}) was changed to olmesartan given at a dose of 20 mg day^{-1}, which is a comparable antihypertensive dose. Patients with renal insufficiency (serum creatinine 1.5 mg 100 ml^{-1}), angina pectoris or moderate to severe CHF (New York Heart Association functional class (NYHA) III or IV) were excluded from this study. Patients who received ACE inhibitors and other ARBs were excluded. Although the use of other drugs was allowed, the doses of these agents were not changed during the study period. The general condition of each patient had been stable for more than 6 months before the study.

In the outpatient clinic, resting heart rate was determined from electrocardiogram and blood pressure measurements and data were independently confirmed by attending physicians. Blood samples were collected from the antecubital vein after rest in a seated position for at least 20 min at baseline, after 3 months, after 6 months and after 12 months. Echocardiography was performed at baseline and after 12 months by the same sonographer. Left ventricular ejection fraction (LVEF) was measured by echocardiography at the same time. The LVMI value was calculated from M-mode echocardiograms according to the formula derived by Devereux *et al*.[16]

Blood samples were assessed for plasma renin concentration (PRC), plasma levels of Ang II, ALD and brain natriuretic peptide (BNP). The attending physicians were blinded to the neurohumoral and echocardiographic data. Informed consent was obtained from all patients before participation in the study, after the approval of the protocol by the Committee on Human Investigation at our institution.

Measurement of neurohumoral factors

Blood samples were collected from the antecubital vein after rest in a seated position for at least 20 min. Blood sampling was performed in the afternoon. Blood was centrifuged at 3000 r.p.m. for 15 min at 4 °C, and the plasma thus obtained was stored at −30 °C until assay. The plasma levels of PRC, Ang II and ALD were measured using commercial radioimmunoassay kits as previously reported.[15,17] Samples for the assay of plasma BNP concentrations were transferred to chilled disposable tubes containing aprotinin (500 kallikrein inactivator units ml^{-1}). The blood samples were immediately placed on ice and centrifuged at 4 °C, and then the plasma was frozen in aliquots and stored at −30 °C until assay. Plasma BNP concentrations were measured by a immunoradiometric assay specific for human BNP using a commercial kit (Shionogi, Osaka, Japan) as previously reported.[18]

Statistical analysis

All results are expressed as the mean ± s.d. Univariate analysis was performed using Student's *t*-test. Categorical data were compared against a chi-squared distribution. Comparisons between groups were performed by analysis of variance with Fisher's test for continuous variables. A P-value <0.05 was regarded as significant.

RESULTS

Table 1 lists the characteristics of the subjects. The study subjects were 50 patients with essential hypertension. There was no difference in baseline characteristics, including LVEF and LVMI and plasma levels of PRC, Ang II, ALD and BNP between the two groups (Table 1). A total of 17 patients had CHF (NYHA class I or II) and there was no difference in the incidence of CHF complication between the two groups. Concomitant therapy other than candesartan was maintained for at least 12 months and there was no difference in baseline medication between the two groups.

There were no significant changes in either the control or olmesartan groups with regard to blood pressure or heart rate over the 12-month observation period (Table 2). In the control group, plasma

Table 1 Clinical characteristics of patients in the control and olmesartan groups

	Control (n=*25*)	*Olmesartan* (n=*25*)	P-*value*
Age (years)	67.7 ± 7.8	68.2 ± 12.3	0.880
Sex (male/female)	16/9	15/10	0.999
Chronic heart failure, *n* (%)	8 (32)	9 (36)	0.999
Heart rate (beats per min)	72 ± 8.0	75 ± 10.7	0.262
Systolic blood pressure (mm Hg)	130 ± 21	134 ± 15	0.434
Diastolic blood pressure (mm Hg)	73 ± 7.5	77 ± 9.7	0.104
LVDd (mm)	51.5 ± 7.5	51.3 ± 6.6	0.919
IVS (mm)	10.3 ± 1.8	10.8 ± 2.4	0.377
LVPW (mm)	9.7 ± 1.6	10.5 ± 2.0	0.127
LVEF (%)	59 ± 10	61 ± 9.8	0.377
LVMI (g m^{-2})	121 ± 36	135 ± 36	0.185
Serum creatinine (mg 100 ml^{-1})	0.89 ± 0.27	1.0 ± 0.29	0.07
eGRF (ml min^{-1} 1.73 m^{-2})	63 ± 15	53 ± 13	0.012
Renin concentration (pg ml^{-1})	21 (9.3, 78)	47 (15.7, 132)	0.109
Angiotensin II (pg ml^{-1})	28 (13, 84)	34 (7.7, 145)	0.999
Aldosterone (pg ml^{-1})	86 ± 43	108 ± 131	0.432
BNP (pg ml^{-1})	73 ± 78	73 ± 68	0.998
Potassium (mEq l^{-1})	4.3 ± 0.35	4.5 ± 0.32	0.102
Baseline therapy			
Candesartan, *n* (%)	25 (100)	25 (100)	—
Duration of candesartan therapy (years)	2.5 ± 1.1	2.4 ± 1.4	0.923
Ca-blockers, *n* (%)	10 (40)	10 (40)	0.999
β-blockers, *n* (%)	10 (40)	14 (56)	0.396
Spironolactone, *n* (%)	16 (64)	15 (60)	0.999
Loop diuretics, *n* (%)	7 (28)	11 (44)	0.377

Abbreviations: BNP, brain natriuretic peptide; IVS, intraventricular septum; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall.
Values are shown as mean ± s.d. or median (25 percentile, 75 percentile).

Table 2 Clinical and neurohumoral data during 12 months

	Treatment	*Baseline*	*3 months*	*6 months*	*12 months*
HR (beats per min)	Control	72 ± 8.0	71.5 ± 9.0	72.4 ± 8.2	73 ± 8.6
	Olmesartan	75 ± 10.7	73.4 ± 7.9	74 ± 8.4	74.5 ± 9.2
SBP (mm Hg)	Control	130 ± 21	130.7 ± 20	127 ± 16	128 ± 14.5
	Olmesartan	134 ± 15	130 ± 15	129 ± 15.5	131.4 ± 15
DBP (mm Hg)	Control	73 ± 9.5	74 ± 10.4	74 ± 10.4	75 ± 9.4
	Olmesartan	77 ± 9.7	73 ± 9.8	75 ± 9.8	75 ± 11.4
LVEF (%)	Control	59 ± 10	—	—	61 ± 7.7
	Olmesartan	61 ± 9.8	—	—	62 ± 9.3
LVDd (mm)	Control	51.5 ± 7.5	—	—	51.3 ± 6.6
	Olmesartan	51.3 ± 6.6	—	—	51.2 ± 7.7
IVS (mm)	Control	10.3 ± 1.8	—	—	10.2 ± 2.0
	Olmesartan	10.8 ± 2.4	—	—	10.2 ± 2.0
LVPW (mm)	Control	9.7 ± 1.6	—	—	9.8 ± 1.7
	Olmesartan	10.5 ± 2.0	—	—	10.0 ± 1.7
LVMI ($g\,m^{-2}$)	Control	121 ± 39	—	—	120 ± 37
	Olmesartan	135 ± 36	—	—	123 ± 29*
Creatinine ($pg\,ml^{-1}$)	Control	0.89 ± 0.27	0.89 ± 0.23	0.89 ± 0.22	0.89 ± 0.20
	Olmesartan	1.0 ± 0.29	1.04 ± 0.24	1.02 ± 0.23	1.08 ± 0.33
eGRF ($ml\,min^{-1}\,1.73\,m^{-2}$)	Control	63 ± 15	62 ± 14	61 ± 14	61 ± 13
	Olmesartan	53 ± 13	52 ± 13	51 ± 14	51 ± 15
Serum K ($mEq\,l^{-1}$)	Control	4.3 ± 0.35	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.35
	Olmesartan	4.5 ± 0.32	4.5 ± 0.4	4.3 ± 0.4	4.5 ± 0.36
BNP ($pg\,ml^{-1}$)	Control	73 ± 78	79 ± 99	81 ± 101	72 ± 81
	Olmesartan	73 ± 68	78 ± 71	89 ± 81	82 ± 67
PRC ($pg\,ml^{-1}$)	Control	21 (9.3, 78)	21 (10.3, 56.5)	29 (13, 78)	40 (13.5, 85)
	Olmesartan	47 (15.7, 132)	21 (8, 96)	36 (9, 112)	23 (10, 91)
Ang II ($pg\,ml^{-1}$)	Control	28 (13, 84)	29 (13.7, 83.7)	50 (13, 120)	41 (12, 94)
	Olmesartan	34 (7.7, 145)	19 (5.7, 64)**	13 (4.7, 43.5)**	12 (5, 22.5)**
ALD ($pg\,ml^{-1}$)	Control	86 ± 43	85 ± 45	85.6 ± 49	86.7 ± 48.7
	Olmesartan	108 ± 131	89 ± 75	90 ± 95	92 ± 94

Abbreviations: ALD, aldosterone; ANOVA, analysis of variance; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; IVS, intraventricular septum; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall; PRC, plasma renin concentration; SBP, systolic blood pressure.
Values are shown as mean ± s.d. or median (25 percentile, 75 percentile).*$P<0.01$ *vs.* the baseline value.**$P<0.05$ *vs.* the baseline value by ANOVA with Fishers' s test.

levels of PRC, Ang II, ALD and BNP did not change during 12 months of observation. In the olmesartan group, plasma Ang II level was significantly decreased after 3 months and the decrease in Ang II was sustained during 12 months ($161 \pm 350\,pg\,ml^{-1}$ at baseline, $66 \pm 120\,pg\,ml^{-1}$ at 3 months, $68 \pm 101\,pg\,ml^{-1}$ at 6 months, $32 \pm 47\,pg\,ml^{-1}$ at 12 months; Figure 1) and plasma ALD level was slightly decreased after 3 months but there were no significant differences over the 12-month period ($108 \pm 131\,pg\,ml^{-1}$ at baseline, $89 \pm 75\,pg\,ml^{-1}$ at 3 months, $90 \pm 95\,pg\,ml^{-1}$ at 6 months and $92 \pm 94\,pg\,ml^{-1}$ at 12 months; Figure 2). In the olmesartan group, plasma levels of BNP did not change during 12 months but LVMI was significantly decreased after 12 months (135 ± 36 *vs.* $123 \pm 29\,g\,m^{-2}$; $P<0.01$; Figure 3). There was a significant positive correlation between the changes of LVMI (LVMI at baseline−LVMI after 12 months) and the delta changes in plasma Ang II (Ang II at baseline−Ang II after 12 months) in the olmesartan group ($r=0.521$, $P=0.0076$; Figure 4).

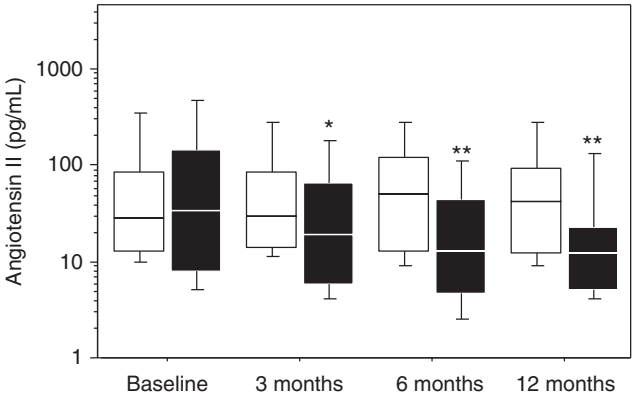

Figure 1 Changes in plasma angiotensin (Ang II) levels over 12 months. Closed columns represent patients who received olmesartan replaced by candesartan; open columns represent patients who continued receiving candesartan. *$P<0.05$, **$P<0.01$ *vs.* the baseline value by analysis of variance with Fisher's test.

DISCUSSION

In this study, (1) we evaluated the long-term effects of replacing candesartan with olmesartan on plasma levels of PRC, ALD, Ang II, ALD and BNP in patients with essential hypertension, (2) we also estimated the long-term effects of replacing candesartan with olmesartan on LVMI. Interestingly, despite significant changes in blood pressure and heart rate over the12-month observation period in both groups, LVMI was significantly decreased in the olmesartan group

only (Figure 3). In addition, the significant decrease in LVMI was associated with a decrease of Ang II (Figure 4) but not with changes in PRC, ALD or BNP level.

Whether the effects of several ARBs on ACE2 expression are same remains uncertain[10–12] especially in hypertensive patients. The present finding that the plasma Ang II level was decreased after replacement of candesartan with olmesartan without any changes in PRC suggests that the effect of olmesartan on ACE2 expression is more stimulating than that of candesartan. Ang 1–7 is an endogenous ligand for the G protein-coupled receptor Mas[19] and may have a beneficial effect on left ventricular remodeling. As experimental studies showed that olmesartan increased plasma Ang 1–7 levels through an increase in ACE2 expression, plasma Ang 1–7 level may be increased in association with the decrease in Ang II after replacement of candesartan with olmesartan. However, we could not measure the plasma levels of Ang 1–7 in this study. As the treatment with candesartan increases *ACE2* mRNA in Dahl salt-sensitive hypertensive rats[10] and local renin-angiotensin-aldosterone system (RAS) is independent of systemic RAS, further studies are needed to clarify this issue in a large number of patients.

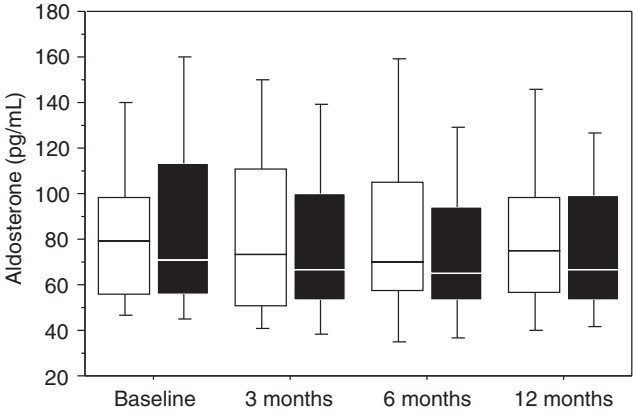

Figure 2 Changes in plasma aldosterone levels for 12 months. Closed columns represent patients who received olmesartan replaced by candesartan; open columns represent patients who continued receiving candesartan.

Long-term treatment with ACE inhibitors or ARBs does not necessarily induce significant decreases in plasma ALD levels (ALD breakthrough).[20–22] ALD breakthrough generally occurs in about half of the cases within 12 months.[23,24] Recently, ALD breakthrough was observed in 23% of hypertensive patients during candesartan treatment.[25] The elevation of Ang II after treatment with ARBs may contribute to ALD breakthrough due to the activation of AT type 2 receptor in the adrenal gland.[26] The finding that plasma ALD level was slightly decreased over the 12-month observation period in association with the significant decrease in Ang II may support findings in

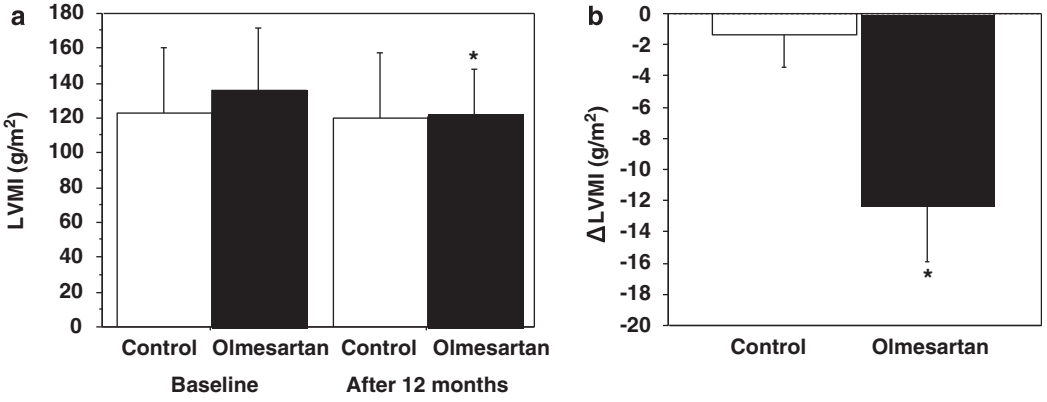

Figure 3 (**a**) Changes in left ventricular mass index (LVMI) before and after 12 months. (**b**) Delta changes in LVMI before and after 12 months. Closed columns represent patients who received olmesartan replaced by candesartan; open columns represent patients who continued receiving candesartan. $^*P<0.01$ *vs.* the baseline value.

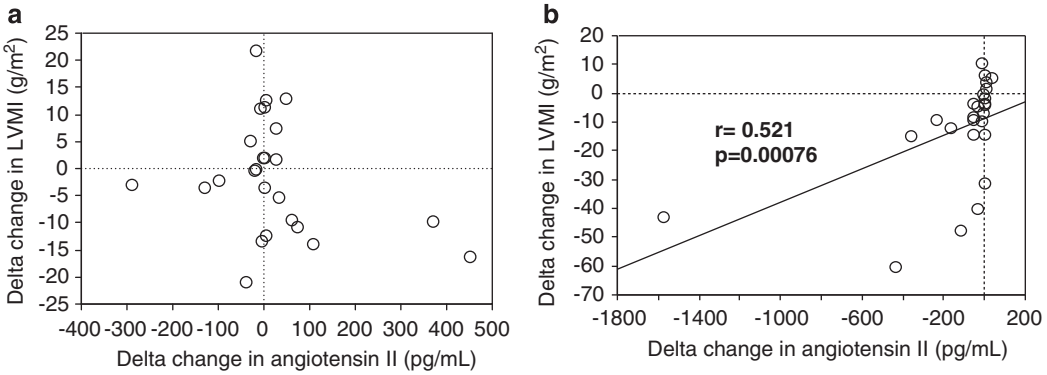

Figure 4 Correlation between the changes in LVMI (LVMI at baseline−LVMI after 12 months) and changes in angiotensin II (Ang II) (Ang II at baseline−Ang II after 12 months). (**a**) Control group, (**b**) olmesartan group.

previous experimental study,[26] but the decrease in ALD was not statistically significant, suggesting that multiple mechanisms may contribute to ALD breakthrough in patients with hypertension.

Although the significant decrease in LVMI, an important surrogate marker,[27] was observed in the olmesartan group, plasma level of BNP, a biomarker of hemodynamic overload did not change during 12 months. Therefore, hemodynamic changes, including blood pressure, may not contribute to the decrease in LVMI. In this study, 17 patients had CHF (NYHA class I or II). In patients with CHF, high plasma levels of PRC, Ang II, ALD and BNP were associated with poor prognosis.[17,18,28,29] Most biomarkers, except Ang II, did not change after replacement of candesartan with olmesartan. A high plasma Ang II level is a prognostic predictor in asymptomatic CHF patients[28] and in mild-to-moderate CHF patients.[29] Recently, it was reported that there may be differential effects of various ARBs on prognosis in patients with CHF.[30] Taken together with the improvement of LVMI, olmesartan may have a beneficial effect on surrogate markers for cardiac events in hypertensive patients with CHF.

This study has several limitations. First, we could not measure plasma level of Ang 1–7. Although we took blood samples after patients rested for at least 20 min in a seated position in this study and the attending physicians and sonographers were blinded to the neurohumoral data, the variability of biomarkers such as Ang II may have influenced the results. In addition, LVMI was slightly higher in the olmesartan group, which may have been reflected in the results. Further studies are needed to clarify this issue in a large number of patients.

Conclusions

At effective antihypertensive doses of candesartan and olmesartan, olmesartan significantly decreased the plasma Ang II level over the 12-month observation period. Furthermore, long-term olmesartan therapy decreased LVMI in patients with essential hypertension.

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