Effects of Olmesartan on the Renin-angiotensin-aldosterone System for Patients with Essential Hypertension after Cardiac Surgery—Investigation Using a Candesartan Change-over Study—

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Background: Various angiotensin II receptor blockers are widely used for the treatment of hypertension in recent years. The results of large-scale clinical studies have shown that they have various efficacies: not only hypotensive effects but also organ protective effects. In this study, the effects of a change-over from candesartan to olmesartan on renin-angiotensin-aldosterone system, cardiomegaly and peripheral circulation were studied.

Methods: Participants enrolled in this trial were outpatients with essential hypertension after cardiac surgery who had received candesartan for more than one year. Fifty-six patients switched from candesartan to olmesartan. The primary endpoints were 1) renin activity, angiotensin II, aldosterone, and 2) left ventricular mass index (LVMI).

Results: It was clear that angiotensin II and aldosterone are decreased by the potent hypotensive effects of olmesartan in a change-over from candesartan to olmesartan. Since LVMI and BNP were decreased, inhibitory effects on myocardial hypertrophy were also confirmed.

Conclusion: In the present study, left ventricular hypertrophy and on arterial compliance were inhibited by a decrease in angiotensin II and aldosterone due to the change-over to olmesartan. In the future, protective effects on organs will be clarified by long-term observations.

Keywords: angiotensin, renin, hypertension

Introduction

Various angiotensin II receptor blockers (ARBs) are widely used in the treatment of hypertension, and in recent years, the results of large-scale clinical studies have shown that they have various efficacies, not only hypotensive effect but also organ protective effects.1-3 In its chemical structure, olmesartan has a carboxyl group (COOH group) and hydroxyl group (OH group). These groups form strong bonds with AT1 receptors to form a...
double chain domain. Olmesartan shows the most potent hypotensive effects among ARBs because it exhibits potent inverse agonist action (other ARBs do not have a hydroxyl group) and increasing action on Ang-(1-7).\textsuperscript{4, 5} Various studies on the effects of ARBs on the renin-angiotensin-aldosterone system (RAAS) have been reported. Aoki et al. reported that telmisartan increased renin activity after administration, but angiotensin II and aldosterone showed no change before and after its administration.\textsuperscript{6} Goldberg et al. reported that losartan increased renin activity after administration, while aldosterone was decreased.\textsuperscript{7} The effects differ depending on the type of ARB. With angiotensin-converting enzyme inhibitors (ACE-I), aldosterone, which had decreased, is increased by the long-term administration (aldosterone breakthrough),\textsuperscript{8} and the same cases are also observed with ARB.\textsuperscript{9} Yoneda et al. reported that this occurred in 23\% of cases given candesartan.\textsuperscript{10} Few reports have appeared on the effects of olmesartan on the RAAS. Many patients who undergo cardiac surgery have essential hypertension, and use of ARB is important not only for reducing blood pressure but also from the standpoints of left ventricular function, organ protection and long-term prognosis. In this study, the subjects had undergone cardiac surgery with essential hypertension, and the effects of a change-over from candesartan to olmesartan on RAAS, cardiomegaly and peripheral circulation were studied.

**Methods**

**Study protocol**

This trial was a prospective open, blinded end-point study of patients who had essential hypertension. In this trial, essential hypertension was defined as an office blood pressure $>$140 and/or 90 mmHg, and patients with secondary hypertension were excluded. The diagnosis and medical therapy of essential hypertension were decided according to the guidelines of The Japanese Society of Hypertension.

The details of the study were explained to patients and informed consent was obtained. This study was registered with the University Hospital Medical Information Network (UMIN) (study ID: UMIN00000 3518).

Participants enrolled in this trial were stable outpatients with essential hypertension after cardiac surgery who had received candesartan for more than one year. Patients who had consented in the present study switched from candesartan to olmesartan. The patients receiving candesartan at a dose of 4 mg/day were changed to olmesartan at a dose of 10 mg/day, and the patients receiving candesartan at a dose of 8 mg/day were changed to olmesartan at a dose of 20 mg/day (Fig. 1). Other drugs were not changed after administration of olmesartan. Patients treated for cardiac-related events within 6 months, patients using ACE-I, patients with poorly-controlled diabetes (HbA\textsubscript{1c} $>$6.5\%), and patients with renal insufficiency (serum creatinine $>$1.5 mg/dl), arteriosclerosis obliterans or left ventricular dysfunction (left ventricular ejection fraction $<$40\%) were excluded.

Endpoints: The primary endpoints were 1) plasma renin activity, angiotensin II, aldosterone, and 2) left ventricular mass index (LVMI). The LVMI was evaluated by echocardiography (VIVID 7, GE Yokokawa Medical Systems Co, Tokyo, Japan) according to the formula derived by Devereux et al.,\textsuperscript{11} which was operated by a specialist in echocardiography.

The secondary endpoints were 1) systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), 2) atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), 3) serum creatinine (sCr), high sensitivity-C-reactive protein (hs-CRP), 4) ankle brachial pressure index (ABI), pulse wave velocity (PWV), and 5) side effects. The ABI and PWV were measured by Form ABI/PWV (BP-203RPE II, Omron-colin Inc, Tokyo, Japan). Persons performing the measurements were blinded. Each measurement time is shown in Fig. 1. Side effects in this study included hypotension, renal dysfunction, hepatic dysfunction, hyperkalemia and hypoglycemia. Administration was discontinued at the discretion of the physician in charge. Data on RAAS, ANP, BNP, LVMI, ABI, PWV were blinded for the attending physicians. Renin activity, angiotensin-II and aldosterone were measured by a radioimmunoassay method; the ANP and BNP were by the Chemiluminescence enzyme immuno assay method.

![Fig. 1 Study protocol.](image-url)
Statistical analysis

For parametric data, the results were expressed as the mean ± standard error of the mean (SEM). The data were analyzed by repeated measures ANOVA with Fisher’s Protected Least Significant Difference. Spearman’s correlation coefficients were used for the correlation test. A p value less than 0.05 was considered statistically significant.

Results

Patient enrollment: Fifty-six patients were enrolled in this trial; there were no cases of discontinuation of administration and no cardiac events or deaths. All patients could be followed up for one year.

Baseline characteristic (Table 1): Patient characteristics are shown in Table 1. Forty-two patients were changed to olmesartan 10 mg/day from candesartan 4 mg/day and fourteen patients were changed to olmesartan 20 mg/day from candesartan 8 mg/day. Concomitant drugs included calcium antagonists in 38 cases (amlodipine, 36 cases; nifedipine, 2 cases), beta blocker in 5 cases ( carvedilol: 4 cases, metoprolol: one case) and statins in 20 cases (atorvastatin, 13 cases; pravastatin, 3 cases; rosvastatin, 3 cases; Simvastatin, one case).

Primary endpoints:

1) Plasma renin activity, angiotensin II, aldosterone (Fig. 2): Renin activity tended to increase after olmesartan administration but the difference was not statistically significant (p = 0.7181). Angiotensin II showed a significant decrease from after 3 months of administration of olmesartan (3 months: p = 0.0059, 6 months: p = 0.0027, one year: p <0.0001). After administration, a significant decrease was found after one year administration when compared with after one month of administration (p = 0.0201). Aldosterone showed a significant decrease from after one month of administration compared with immediately before the olmesartan administration (1 month: p = 0.0011, 3 months: p = 0.0001, 6 months: p = 0.0001, one year: p <0.0001). After administration, a significant decrease was found after one year of administration when compared with after one month of administration (p = 0.0218).

2) LVMI (Figs. 3 and 4): LVMI showed significant decreases at 141.1 ± 4.7 g/m² after 6 months and 128.5 ± 4.6 g/m² after one year when compared with 159.5 ± 5.4 g/cm² before the administration of olmesartan (6 months: p = 0.0158, one year: p <0.0001). After the administration, a significant decrease was found after the one-year administration, when compared with the after 6-month administration (p = 0.0461). The correlation between angiotensin II or aldosterone and LVMI after one year of olmesartan administration was tested. Although there was not found between angiotensin II and LVMI with a correlation coefficient (r = 0.184, p = 0.1754), a strong correlation was found between aldosterone and LVMI with a correlation coefficient of 0.613, p <0.0001.

Secondary endpoints: 1) Blood pressure and heart rate (Fig. 5): systolic blood pressure was 134.0 ± 2.5 mmHg before and 127.3 ± 1.8 mmHg after 1 month, 125.4 ± 1.6 mmHg after 3 months, 127.7 ± 2.3 mmHg after 6 months and 126.1 ± 1.8 mmHg after one year of olmesartan administration; diastolic blood pressure was 76.7 ± 1.3 mmHg before and 72.6 ± 1.0 mmHg after 1 month, 72.5 ± 0.9 mmHg after 3 months, 71.8 ± 1.2 mmHg after 6 months and 70.3 ± 1.2 mmHg after one year of olmesartan administration;
**Fig. 2** Profile of the renin-angiotensin-aldosterone system before and after the olmesartan administration.

**Fig. 3** LVMI and BNP before and after the olmesartan administration.
LVMI: left ventricular mass index; BNP, brain natriuretic peptide

**Fig. 4** Correlation between LVMI and angiotensin II or aldosterone after one year of the olmesartan administration.
LVMI: left ventricular mass index
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Significant decreases were found at all times after when compared with the before olmesartan administration. The heart rate showed no significant change after the olmesartan administration ($p = 0.9929$).

In the olmesartan 10-mg group, systolic blood pressure was $133.1 \pm 2.6$ mmHg before and $127.8 \pm 1.9$ mmHg after 1 month, $126.1 \pm 1.7$ mmHg after 3 months, $127.7 \pm 2.1$ mmHg after 6 months and $125.7 \pm 1.8$ mmHg after one year of olmesartan administration. In olmesartan 20mg, systolic blood pressure was $135.3 \pm 2.6$ mmHg before and $126.9 \pm 1.9$ mmHg after 1 month, $126.1 \pm 1.9$ mmHg after 3 months, $127.9 \pm 2.5$ mmHg after 6 months and $125.2 \pm 2.0$ mmHg after one year of olmesartan administration. There were no significant differences between olmesartan 10mg and olmesartan 20mg ($p = 0.8812$).

2) ANP, BNP (Fig. 3 and Table 2): Although ANP showed no significant change after olmesartan administration ($p = 0.9461$), BNP was $0.16 \pm 0.02$ before and $0.12 \pm 0.01$ after 1 month, $0.12 \pm 0.02$ after 3 months, $0.09 \pm 0.01^*$ after 6 months and $0.11 \pm 0.02$ after one year of olmesartan administration. There were no significant differences between 6 months and one year.

3) sCr, hs-CRP (Table 2): The sCr showed no significant change before and after the olmesartan administration ($p = 0.9553$). hs-CRP was significantly lower only after 6 months of the olmesartan administration when compared with before the olmesartan administration.

4) ABI, PWV (Table 2): Although the ABI showed no significant changes before and after the olmesartan administration ($p = 0.8654$), PWV decreased significantly after the olmesartan administration (6 month: $p = 0.0038$, one year: $p = 0.0024$). There was no significant difference between 6 months and one year.

5) Side effects: There were no side effects after the administration of olmesartan. All patients received it for one year.

Discussion

In this study, renin activity in relation to RAAS did not show any change after the olmesartan administration when a change-over was made from candesartan to olmesartan, but angiotensin II and aldosterone decreased significantly after when compared with the before administration of olmesartan. LVMI showed significant decreases after

![Fig. 5](image-url) Changes in hemodynamics after the olmesartan administration.

Table 2  Each measurements before and after administration of Olmesarten

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>1 month</th>
<th>3 month</th>
<th>6 month</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.93 ± 0.03</td>
<td>0.92 ± 0.03</td>
<td>0.91 ± 0.03</td>
<td>0.90 ± 0.03</td>
<td>0.92 ± 0.03</td>
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<tr>
<td>hs-CRP (mg/dl)</td>
<td>0.16 ± 0.02</td>
<td>0.12 ± 0.01</td>
<td>0.12 ± 0.02</td>
<td>0.09 ± 0.01*</td>
<td>0.11 ± 0.02</td>
</tr>
<tr>
<td>ABI</td>
<td>1.06 ± 0.02</td>
<td>-</td>
<td>-</td>
<td>1.06 ± 0.02</td>
<td>1.07 ± 0.02</td>
</tr>
<tr>
<td>PWV</td>
<td>1885.5 ± 77.8</td>
<td>-</td>
<td>-</td>
<td>1648.9 ± 42.4*</td>
<td>1636 ± 42.0*</td>
</tr>
</tbody>
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hs-CRP: high sensitivity C-reactive protein; ABI: ankle brachial pressure index; PWV: pulse wave velocity

*p < 0.05
6 months and one year of the administration when compared with during the candesartan administration. Angiotensin-II and aldosterone are closely involved in the increase in blood pressure. In this study, after the change from olmesartan to candesartan, a significant drop in blood pressure was observed. This appeared to have happened because of further decreases in angiotensin-II and aldosterone. As time passed after the olmesartan administration, no differences in blood pressure were found, but immediately after the change from candesartan to olmesartan, the blood pressure dropped. The most important factor was the potent hypotensive effects of olmesartan. The blood pressure showed a difference, when compared to the before administration of olmesartan. However, the blood pressure showed no difference after the olmesartan administration, but since angiotensin II and aldosterone were significantly decreased after 1 year when compared with the after one-month administration, and LVMI was significantly decreased after 1 year when compared with the after the 6-month administration of olmesartan. It is possible that the hypotensive effect is not the only factor. Olmesartan has the strongest hypotensive effects among ARBs. The reason for this is that it increases Ang-(1-7) via ACE2 unlike with the other ARBs.\(^4\) Agata et al. reported that the long-term administration of olmesartan in an animal study caused an increase in renin activity, no differences in angiotensin II, and a decrease in aldosterone. This led to decreases in LVM, coronary arterial wall lumen ratio and perivascular fibrosis, and olmesartan had cardiovascular remodeling improvement effects.\(^12\) Igase et al. reported that olmesartan decreased the thickness of the tunica media of the abdominal aorta (cardiovascular remodeling improvement effects) and this led to an increase in Ang-(1-7).\(^13\) Yokoyama et al. reported that olmesartan showed definite inhibitory effects on left ventricular hypertrophy and fibrosis and these cardiovascular remodeling inhibitory effects were due to factors based on hypotensive effects and also factors not dependent on blood pressure.\(^14\) In a clinical study comparing candesartan and olmesartan, Tsutamoto et al. found no difference between the two drugs for aldosterone but angiotensin II was significantly lower in the olmesartan group from 3 months to one year of the administration. The decrease rate of LVMI was significantly higher after one year of the administration, and the decrease rates of angiotensin II and LVMI were correlated in the olmesartan group.\(^15\) In an acute stage study of healthy individuals, olmesartan significantly lowered aldosterone, significantly increased the renin activity and showed an improvement in arterial compliance.\(^4\) Few reports have appeared on the RAAS in relation to olmesartan, but as described previously, there have been reports on decreases in angiotensin II or aldosterone and also reports on decreases in both angiotensin II and aldosterone.\(^16\) There is no established opinion. In the present study, both angiotensin II and aldosterone decreased. The reason for this was that secretion of angiotensin II is inhibited by olmesartan, and this also inhibits the secretion of aldosterone. If Ang-(1-7) is measured, it is possible that the mechanism of inhibition of secretion of angiotensin II and aldosterone will become clinically clear. This research will continue in the future and this point must be clarified. However, the patient characteristics in each study (in this study, all subjects used candesartan and had cardiac surgery) are different, and the results are considered to be different.

In the present study, it was found that olmesartan has improvement effects on left ventricular hypertrophy and on arterial compliance. When the correlation among LVMI and angiotensin II or aldosterone was examined after the one-year administration of olmesartan, LVMI was correlated with aldosterone. Aldosterone is said to be involved in myocardial hypertrophy and fibrosis and in the present study, myocardial hypertrophy was inhibited by a decrease in aldosterone due to the change-over to olmesartan.

PWV is a measurement factor that shows a correlation with cardiovascular events. In the present study, PWV was significantly decreased by the administration of olmesartan, and this was effective in avoiding the onset of cardiovascular events. Furukawa et al. compared olmesartan and candesartan and reported that PWV was significantly decreased in patients taking olmesartan when compared with those taking candesartan.\(^17\) Since PWV is affected by blood pressure, it is possible that the result of this study only reflect changes in blood pressure; it will be necessary in the future to study in detail the relations between humoral factors and inflammatory markers. In the present study, hs-CRP was measured as an inflammatory marker, but it decreased significantly only after 6 months of administration of olmesartan when compared with candesartan, suggesting that olmesartan has a stronger anti-inflammatory action than does candesartan. Fliser et al. reported that inflammatory markers such as hs-CRP, TNF-alpha, interleukin-6 and MCP-1 were decreased more significantly in the olmesartan group when olmesartan or placebo was administered to hypertensive patients with microinflammation.
Olmesartan has pleiotropic effects such as organ protective effects in addition to hypotensive effects.\(^8\) In the future, it will be necessary to measure various inflammatory markers in addition to hs-CRP and clarify the anti-inflammatory effects of olmesartan.

**Conclusion**

In the present study, it was clear that angiotensin II and aldosterone are decreased by the potent hypotensive effects of olmesartan in a change-over from candesartan to olmesartan. Since LVMI and BNP were decreased, inhibitory effects on myocardial hypertrophy were also confirmed. With the decrease of PWV, effects in avoiding onset of cardiovascular events were also obtained. In the future, protective effects on organs will be clarified by long-term observations.

**Limitations**

The present study investigated the same patients, but the study was performed on patients taking other drugs such as Ca-blockers, concomitantly. The subjects were blinded but not randomized, because the study design was a single-direction, change-over study. The efficacy of olmesartan was clear, but the comparison with candesartan was not sufficiently detailed. In the present study, Ang-(1-7) was not measured. By measuring it, it should be possible to clarify the mechanism of inhibition of secretion of angiotensin II and aldosterone.

**References**


