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ORIGINAL RESEARCH

Comparison of once daily versus twice daily olmesartan in patients with chronic kidney disease

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Background: The effects of olmesartan (OLM) on blood pressure and kidney function in Japanese patients with chronic kidney disease (CKD) were compared between 20 mg twice daily (BID) and 40 mg once daily (QD) treatments.

Methods: The subjects were Japanese CKD patients with concurrent hypertension who had been treated with OLM 20 mg BID for at least 3 months on an outpatient basis (n=39). After a change in the treatment regimen to 40 mg OLM QD (after breakfast), blood pressure (BP) (n=39), morning home BP (n=13), estimated glomerular filtration rate (n=39), and urinary albumin-to-creatinine ratio (n=17) were monitored for 2 months.

Results: No significant change in office (mean ± standard deviation [SD] [mmHg], $143.9 \pm 18.8/75.7 \pm 12.0$ to $141.6 \pm 16.1/74.7 \pm 11.7$, not significant [ns]) or early morning home (mean ± SD [mmHg], $133.8 \pm 15.9/71.2 \pm 11.5$ to $133.8 \pm 13.9/74.5 \pm 10.5$, ns) BP was observed 2 months after the change in dose. The estimated glomerular filtration rate increased significantly (mean ± SD, 49.0 ± 28.0 to 51.8 ± 27.0, $P<0.05$), whereas urinary albumin-to-creatinine ratio did not change significantly (mean ± SD, 0.551 ± 0.445 to 0.364 ± 0.5194, ns).

Conclusion: High-dose OLM administered BID and QD had similar effects on outpatient and early morning home BP in CKD patients, suggesting that the BID regimen can be safely changed to a QD regimen. For CKD patients with hypertension requiring continuous long-term treatment, the possibility that the QD regimen might bring a greater therapeutic effect was suggested. However, recognizing the best blood pressure control level for a CKD patient is still a matter of debate, and should ideally be personalized.

Keywords: high-dose angiotensin receptor blocker, hypertension, chronic kidney disease, compliance, olmesartan

Introduction

The renin–angiotensin–aldosterone system is activated in patients with chronic kidney disease (CKD), increasing the risk of cardiovascular events[1] and accelerating the transition to end-stage renal failure, in addition to being closely associated with hypertension.[2,3] Therefore, strict blood pressure (BP) control and treatment of underlying diseases is important.

However, strict BP control for 24 hours is challenging, even with once daily (QD) administration of an antihypertensive drug, and two divided doses are favorable in some cases. Because CKD is associated with decreased sodium excretion during the day and increased sodium excretion during the night in correlation with reduced kidney function, many patients have nondipper type hypertension in which nocturnal control of BP is frequently difficult.[4] Therefore, to achieve a more stable efficacy of

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angiotensin receptor blockers (ARBs), many patients with CKD receive drugs twice daily (BID), in the morning and in the evening.

On the other hand, in patients with hypertension who require long-term continuous treatment, a smaller number of tablets and lower daily dosing frequency lead to good compliance,[2] which improves the therapeutic efficacy and continuity of treatment. Therefore, drugs certain to control hypertension with a simple prescription are ideal.

In Japan, few studies have compared the effects of QD versus BID drug regimens on compliance, and no studies have compared the effects of QD versus BID olmesartan (OLM) administration.

OLM administered QD provides high continuity of treatment using ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring as compared with other ARBs,[5–8] making the QD regimen the most promising.

In the present study, we examined the effects of QD (morning) versus BID (morning and evening) OLM treatment on office BP, morning home BP, and renal function in patients with CKD complicated by hypertension.

Materials and methods
Patients and protocol

Thirty-nine consecutive Japanese outpatients (Tables 1 and 2) with CKD complicated by hypertension, treated with OLM 20 mg BID (after breakfast and supper) for more than 3 months, were switched to OLM 40 mg QD in the morning. Office BP and morning home BP were assessed, and renal function was examined by measuring serum creatinine levels to calculate estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR) to estimate proteinuria. The follow-up period for assessment of the stable antihypertensive efficacy of OLM was set at 2 months.[9] Antihypertensive drugs were not added during the follow-up period. This work was purely an observational study, and written informed consent was obtained from all patients.

Blood pressure measurement

Office systolic and diastolic BP was measured every 4 weeks with the patient in a sitting position after 5 minutes of rest. Each BP measurement was determined using a sphygmomanometer, and the average of two measurements was calculated. Home BP was also calculated as the average of two measurements. We had instructed patients to maintain a home BP diary. Home BP was measured before the oral administration of OLM and within 1 hour after waking in

Table 1 Baseline characteristics of the study population (n=39)

Parameter	Twice daily dosing n (%) or mean ± SD
Number of patients	39
Age (years)	69.7 ± 11.7
Women	16 (42.1)
Medical history	
Chronic kidney disease	39 (100)
Diabetic kidney	18 (46.1)
Benign nephrosclerosis	11 (28.2)
IgA kidney	4 (10.2)
Gouty kidney	4 (10.2)
Nephropathy of pregnancy	1 (2.5)
Hepatorenal syndrome	1 (2.5)
eGFR (mL/min/1.73 m^2)	49.0 ± 28.3
G1	
≥90	1 (2.5)
G2	
60–89	12 (30.7)
G3a	
45–59	10 (25.6)
G3b	
30–44	5 (12.8)
G4	
15–29	6 (15.3)
G5	
<15	5 (12.8)

Abbreviations: eGFR, estimated glomerular filtration rate; G, stages of chronic kidney disease; IgA, immunoglobulin A; SD, standard deviation.

the morning. We followed the Japanese guidelines for the treatment of hypertension[10] when assessing the patients' BP using the auscultation method and a mercury or automatic sphygmomanometer.

Renal function

Renal function was evaluated on the basis of the eGFR, which was calculated using an equation developed for the Japanese

Table 2 Antihypertensive treatment

	n (%)
Olmesartan	39 (100)
Number of antihypertensive drugs	
1	9 (23.0)
2	17 (43.5)
3	8 (20.5)
≥4	5 (12.8)
Drugs	
Calcium channel blocker	27 (71)
ACE inhibitor	8 (21)
Renin inhibitor	3 (7.9)
Aldosterone antagonist	2 (5.2)
Alpha blocker	1 (2.6)
Beta blocker	1 (2.6)
Diuretic	1 (2.6)

Abbreviation: ACE, angiotensin converting enzyme inhibitor.

population, as recommended by the Japanese Society of Nephrology[11] as,

$$eGFR = 194 \times sCrn - 1.094 \times age - 0.287$$
$$(\times\ 0.739,\ if\ female), \tag{1}$$

where sCrn is serum creatinine. The serum potassium concentration (K) was measured. Urinary samples and blood samples were collected at approximately the same time. UACR was expressed as g/gCr.

Statistical analysis

The changes in BP were expressed as mean ± standard deviation (SD) and analyzed using one-way analysis of variance. Serum creatinine and eGFR were expressed as mean ± SD. The changes in serum creatinine and eGFR were analyzed using the paired *t*-test. UACR (g/gCr) was expressed as mean ± standard error of the mean and analyzed using the paired *t*-test. All *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics

Table 1 shows the background characteristics of the patients who received OLM 20 mg BID. Table 2 shows the antihypertensive drug treatment regimens in these patients. A total of 39 patients with CKD complicated by hypertension, ranging in age from 41–90 years, were included in the study. Thirty patients used other antihypertensive drugs in addition to OLM.

Blood pressure

After 2 months of QD therapy, there was a small reduction in office BP, but the difference did not reach statistical significance. We had instructed all 39 patients to maintain a home BP diary, but only 13 of them adhered to this instruction during the follow-up period. Morning home BP did not differ significantly between QD and BID treatments (Figures 1 and 2; Table 3). Assessment of changes in BP up to 2 months after administration of OLM 40 mg QD revealed no significant difference between the baseline value and that obtained at month 1 or 2. No significant change in BP from baseline to that at month 1 or 2 was detected in the 13 patients whose early morning home BP was measured.

Renal function

Table 4 shows the changes in eGFR, serum creatinine, K, and UACR after 2 months of QD treatment.
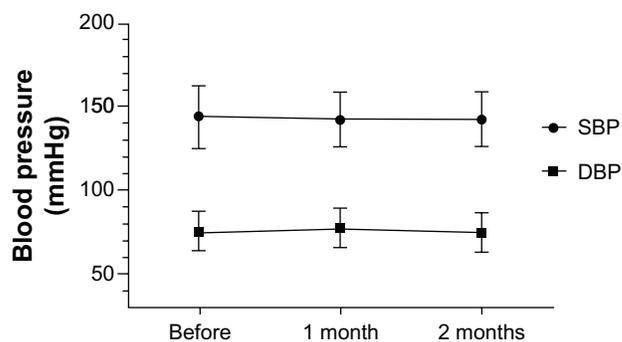

Figure 1 Changes in blood pressure during the course of treatment with high-dose olmesartan administered once daily.
Notes: One-way analysis of variance was used; results are expressed as mean ± standard deviation.
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

The eGFR significantly increased from the baseline value (Figure 3 and Table 4), whereas no significant change in creatinine or UACR was detected (Figure 4 and Table 4). These results indicated that the high-dose OLM BID regimen could be safely switched to the QD regimen in CKD patients with hypertension.

Adverse reactions

There was no withdrawal associated with hypotension or anemia while patients were on QD therapy, and no changes in laboratory values were observed. No significant change in K was detected (Table 4).

Discussion

In the present study, we showed that the high-dose OLM BID regimen could be safely switched to the QD regimen in CKD patients with hypertension. A high-dose BID regimen of ARBs is an effective approach for early-morning and evening control of BP and treatment-resistant hypertension in
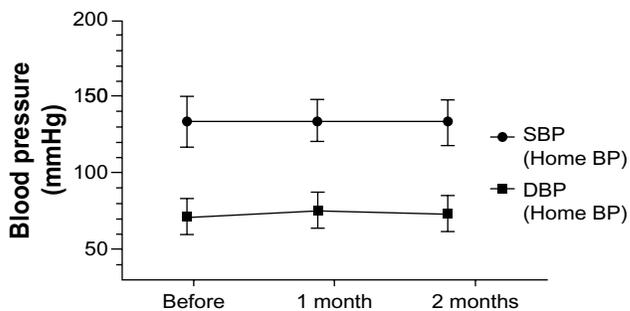

Figure 2 Changes of morning blood pressure during the course of treatment with high-dose olmesartan administered once daily.
Notes: One-way analysis of variance was used; results are expressed as mean ± standard deviation.
Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 3 Changes in office and home systolic/diastolic blood pressure (SBP/DBP) from baseline to after 1 and 2 months of once daily high-dose olmesartan treatment

Parameter	Baseline	1 month	2 months	P-value
Office SBP (n=39)	143.9 ± 18.8	142.0 ± 16.3	141.6 ± 16.1	0.826
Office DBP (n=39)	75.7 ± 12.0	77.3 ± 12.7	74.7 ± 11.7	0.650
Home SBP (n=13)	133.8 ± 15.9	134.0 ± 13.5	133.8 ± 13.9	0.999
Home DBP (n=13)	71.2 ± 11.5	75.6 ± 12.1	74.5 ± 10.5	0.621

Notes: One-way analysis of variance was used; results are expressed as mean ± standard deviation. Measurements mmHg.

CKD patients with increased renin–angiotensin–aldosterone system activity.

Nonetheless, a reduction in the number of daily tablets and the dosing frequency may improve treatment compliance[12–14] in CKD patients with hypertension requiring long-term continuous therapy, potentially improving the therapeutic effect in these patients.

On the basis of the meta analysis[15] that revealed a difference in treatment compliance between QD and BID regimens and reports that treatment compliance can be improved by the measurement of home BP,[16] it is plausible that switching to the QD regimen resulted in improved treatment compliance during the follow-up period. Although a home BP diary was maintained by 33% of the patients in this study, all patients were told of the importance of home BP measurements and instructed on how to measure home BP. Although there was no significant difference between regimens, a slight decrease in office BP was detected after switching to the QD regimen, indicating the possibility that the QD regimen might have contributed to decreased

Table 4 Renal function and potassium during once daily high-dose olmesartan treatment for 2 months

Parameter	Baseline Mean ± SD	2 months Mean ± SD	p-value
eGFR mL/min/1.73 m^2 (n=39)	49.0 ± 28.0	51.8 ± 27.0*	0.0424
Creatinine mg/dL (n=39)	1.53 ± 1.48	1.48 ± 1.38	0.279
K mEq/L (n=39)	4.48 ± 0.47	4.42 ± 0.46	0.686
Parameter	**Baseline Mean ± SD**	**2 month Mean ± SD**	**p-value**
UACR g/gCr (n=17)	0.551 ± 0.445	0.364 ± 0.5194	0.119

Note: *P<0.05 paired t-test.
Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio.
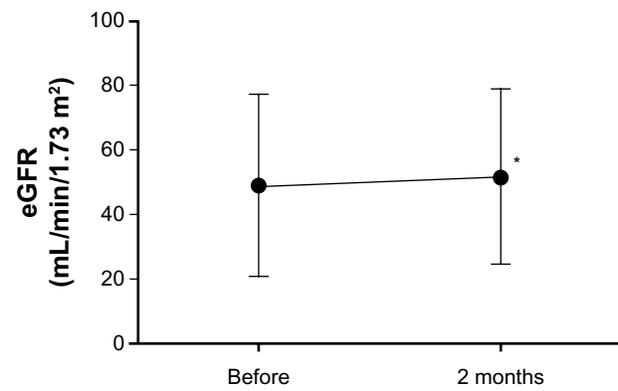

Figure 3 Changes of eGFR during administration of once daily high-dose of olmesartan.
Notes: Results are expressed as mean ± standard deviation; paired t-test.
Abbreviation: eGFR, estimated glomerular filtration rate. *P<0.05.

intraglomerular pressure and UACR (without any significant difference), and that increased GFR cannot be ruled out.

It is generally accepted that the inhibitory effect on proteinuria can be explained by the effects of ARB on decreasing intraglomerular pressure and reducing glomerular afterload. Although the results of this study did not show any significant difference, a slight decrease in office BP was detected, as is the case in decreased UACR. Undeniably, this decrease in office BP induced the decrease in UACR.

The superior continuous blood pressure-lowering effect of OLM compared with other drugs has recently been reported,[5–8] and the Japanese ABPM guidelines state that a sustained effect of OLM can be anticipated. In addition, a US study comparing the sustained effect of OLM administered BID using ABPM in outpatients with moderate to severe essential hypertension showed no significant difference in mean systolic or diastolic blood pressure during the final hour.[14] Our study showed that the blood pressure-lowering
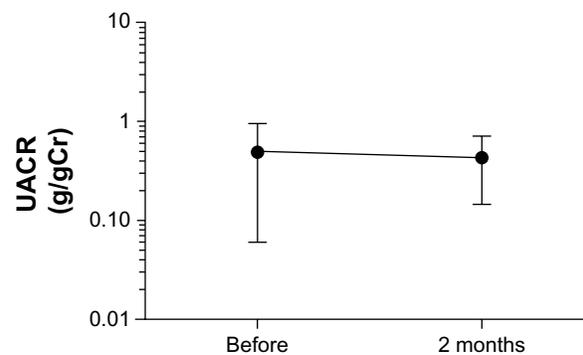

Figure 4 Changes of UACR during administration of once daily high-dose of olmesartan.
Notes: Results are expressed as mean ± standard deviation; paired t-test.
Abbreviation: UACR, urinary albumin-to-creatinine ratio.

and sustained effects of high-dose OLM administered QD and BID were similar. OLM administered in 40 mg tablets QD reduces the number of tablets prescribed to CKD patients and could therefore be expected to improve treatment compliance. Furthermore, we showed increased eGFR after 2 months of treatment. However, further examination is necessary to ascertain whether this improvement is attributable to mild decreases in blood pressure or whether it is associated with improved compliance.

Conclusion

OLM administered QD has a sustained effect and can control early morning blood pressure in CKD patients with hypertension. In addition, its effects are not likely to be influenced by clinical conditions or meals. Therefore, treatment with OLM can be adjusted to the lifestyles of patients to improve treatment compliance and enhance the antihypertensive effect in CKD patients with hypertension requiring long-term therapy. Recognizing the best blood pressure control level for a CKD patient is still a matter of debate and should ideally be personalized.

Disclosure

The authors report no conflicts of interest in this work.

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