ORIGINAL ARTICLE

Strong suppression of the renin–angiotensin system has a renal-protective effect in hypertensive patients: High-dose ARB with ACE inhibitor (Hawaii) study

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The principal means for reducing proteinuria in patients with chronic kidney disease are strong blockade of the renin–angiotensin system and strict regulation of blood pressure (BP). This study compared the efficacy of the maximum permissible doses of two common angiotensin receptor blockers (ARBs), namely valsartan (maximum dose=160 mg per day) and olmesartan (maximum dose=40 mg per day). We also investigated whether a high-dose ARB or the combination of an angiotensin-converting enzyme inhibitor with a high-dose ARB would be more renal protective. We recruited 87 poorly controlled hypertensive patients. In the first study, 50 patients without proteinuria were switched from valsartan (160 mg per day) to olmesartan (40 mg per day) for 4 months. In the second study, 37 patients with proteinuria were randomized to either switch from valsartan 160 mg per day to 40 mg per day olmesartan (n=19; Olm-G) or addition of 2.5–10 mg per day imidapril (stepped up by 2.5 mg per month) to valsartan at 160 mg per day (n=18; Imi-G). After 4 months, the BP level decreased (first study) from 157/88 mm Hg to 145/82 mm Hg (P<0.001) and (second study) from 149/86 mm Hg to 135/77 mm Hg and 145/82 mm Hg for Olm-G and Imi-G, respectively. Furthermore, in the second study, urinary protein/creatinine excretion was reduced from $2.0 \pm 1.8 \, \mathrm{g \, g^{-1}}$ to $0.8 \pm 0.8 \, \mathrm{g \, g^{-1}}$ (P=0.0242) in Olm-G and from $1.4 \pm 1.3 \, \mathrm{g \, g^{-1}}$ to $0.9 \pm 1.0 \, \mathrm{g \, g^{-1}}$ (P=0.0398) in Imi-G. The significance persisted after adjustment for BP or other risk factors. Our results suggested that the maximum dose of olmesartan was more effective than that of valsartan and comparable with the combination of valsartan and imidapril for reducing BP and proteinuria in poorly controlled hypertensive patients.

INTRODUCTION

Chronic kidney disease (CKD) has received considerable attention in the management of hypertension,[1] and it is an independent risk factor for cardiovascular disease in patients with hypertension.[2] Proteinuria is one of the clinical parameters for diagnosing renal damage, particularly glomerular hypertension, and it is a risk factor and predictor for cardiovascular events.[3] Reducing glomerular pressure is a principal strategy for reducing proteinuria in patients with hypertension.[4] To reduce glomerular pressure, blood pressure (BP) must be decreased, typically by reducing arteriolar resistance in the efferent renal arterioles.[5–6] Angiotensin II type 1 receptors are localized to both afferent and efferent renal arterioles.[5–6] Several multicenter randomized clinical trials have shown that both angiotensin II receptor blockers (ARBs)[7] and angiotensin-converting enzyme inhibitors (ACEIs)[8] can reduce proteinuria. On the basis of those results, ARBs and ACEIs are the drugs of choice for managing hypertensive patients with CKD, according to JSH2009 (Japanese Society of Hypertension Guidelines for the Management of Hypertension,

2009). The recommended BP for patients with CKD is lower than that for older patients with hypertension alone with no complications.

We hypothesized that patients with hypertension and CKD would benefit from treatment with an ARB that sufficiently reduced BP, on the basis of previous results obtained from meta-analyses and the IRMA2 multicenter clinical trial.[9] However, the initial, standard and maximum doses for ARBs are under government regulation in Japan. We previously reported that the administration of valsartan at 160 mg per day was more effective for reducing BP and proteinuria than the administration of candesartan at 12 mg per day in patients with hypertension.[10] The Val-HeFT[11] and VALIANT[12] trials demonstrated that 320 mg per day of valsartan had beneficial effects on the prognoses for chronic heart failure and ischemic heart disease. However, in Japan, the permitted maximum doses of candesartan and valsartan are lower than the doses used in those clinical trials. No studies have compared the BP-lowering and renal-protective effects of the permitted maximum doses of ARBs. Head-to-head comparisons of olmesartan with each of the other ARBs, administered at the

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label-recommended doses, showed that olmesartan was most effective at decreasing BP.[13] This study focused on hypertensive patients who had not achieved optimal BP after at least 3 months of treatment with the maximum permitted valsartan dose. We had two aims: (1) to determine whether BP would be better controlled by switching from valsartan to the maximum permitted olmesartan dose; and (2) to determine, in patients with hypertension and CKD, whether BP and urinary protein excretion (UPE) would be better controlled by switching from valsartan to the maximum permitted olmesartan dose or by adding an ACEI to valsartan. Thus, we called this study the high-dose ARB with ACEI study (Hawaii) study.

METHODS

Study population

We recruited 90 hypertensive outpatients of the Osaka University Hospital who had received 160 mg valsartan per day for at least 3 months. At the onset of this study, patients had not achieved optimal BP recommended by the JSH2009. According to the JSH2009, optimal BP was <130/80 mm Hg for managing hypertensive patients with diabetes or CKD; <130/85 mm Hg for patients <65 years of age without major complications; <140/90 mm Hg for patients >65 years of age; and <125/75 mm Hg for patients with proteinuria or >1.0 g per day UPE. Patients were excluded from the study when they had experienced a stroke or cardiovascular event during the previous year; had grade 2 or higher congestive heart failure, according to the New York Heart Association scale; had >3.0 mg per 100 ml serum creatinine; and/or had a history of dry cough when taking ACEIs. The use of other antihypertensive drugs was permitted, except ACEIs. The doses of concurrent drugs remained unchanged throughout the study. The protocol for this study was approved by the hospital ethics committee, and informed consent was obtained from all patients before switching from valsartan to olmesartan or before adding imidapril.

Study protocol for study 1

A total of 53 patients without CKD who had been taking 160 mg per day valsartan were recruited for study 1. Two patients were excluded because their average BP level was lower than optimal on the day of switching to olmesartan. Thus, 51 hypertensive patients were switched to 40 mg per day olmesartan. One month before the switch, we measured the cholesterol profile, uric acid, fasting blood glucose, as well as renal and liver functions. BP and pulse rate (PR) were evaluated 1 month before, the day of and 1 and 2 months after the switch. One patient left the study because of unpleasant side effects; thus, a total of 50 hypertensive patients were analyzed.

Study protocol for study 2

A total of 37 patients without CKD who had been taking 160 mg per day valsartan were recruited for study 2. All patients were randomly classified into two groups: 19 patients were switched to 40 mg per day olmesartan (Olm-G) and 18 patients had imidapril added to their valsartan regimen (Imi-G). Imidapril was gradually increased, from 2.5 mg per day for the first month to 5 mg per day for the second month, 7.5 mg per day for the third month and 10 mg per day for the fourth month. All other antihypertensive drugs were not modified. On the first day of the switch, we measured the cholesterol profile, uric acid, fasting blood glucose and liver function. Every month after initiation, we evaluated BP, PR, serum creatinine and UPE. All patients participated throughout the study.

BP and renal function measurements

Two BP and PR measurements were taken while the patient was seated and had rested for 10 min. BP was measured using BP-103iII (Nippon Colin, Tokyo, Japan). Averages of the two BP and PR measurements were automatically calculated, recorded and used in subsequent analyses. On the mornings of these hospital visits, subjects refrained from taking valsartan, olmesartan and imidapril.

We calculated the UPE adjusted for urinary creatinine. We estimated the glomerular filtration rate with a modified modification of diet in renal disease

equation: glomerular filtration rate (ml min^{-1} per 1.73 m^2)$=175\times$(serum creatinine)$^{-1.154}\times$(age)$^{-0.203}\times0.741$ ($\times0.742$ for females).[14]

Statistical analysis

Data were analyzed using commercially available statistical software (JMP version 5.1.1; SAS Institute, Cary, NC, USA). Differences in responses to treatment with olmesartan and valsartan were assessed with paired t-tests. Differences in low and high UPEs were assessed by one-factor ANOVA (analysis of variance) and Fisher's test. We used multiple regression analysis to evaluate influential factors for reducing UPE. P-values <0.05 were considered statistically significant.

RESULTS

Results are expressed as mean ± s.d.

Patient characteristics

Table 1 summarizes the characteristics of the 87 patients who completed studies 1 and 2. In study 2, the frequency of male patients was high (86%) and the mean age was slightly low compared with patients in study 1; however, these were not different between the Olm-G and Imi-G groups. Before entering this study, 68 participants had been taking anti-hypertensive drugs in addition to valsartan at 160 mg per day. These included calcium channel blockers ($n=62$, 71%), β-blockers ($n=27$, 31%), diuretics ($n=21$, 24%) and α-blockers ($n=6$, 7%). These 'other hypertensive drugs' were continued without change throughout the study. The mean number of concurrent anti-hypertensive drugs taken per patient was 2.3 ± 1.0. Common serum factors that indicate liver function (Table 1) did not change during the study. There were no significant differences between the Olm-G and Imi-G groups.

BP and PR changes in study 1

Both BP and PR measurements were comparable 1 month before and on the day of switching from valsartan to olmesartan (Table 2). However, after the switch to olmesartan, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean BP (MBP) levels were significantly lower (+1 month, +2 months; Table 2). After switching to olmesartan, the mean (averaged +1 and +2 month values) SBP was 144.7 ± 13.8 mm Hg and the mean DBP was 80.9 ± 10.1 mm Hg. These were significantly reduced compared with the mean values (averaged 1 month before and day of switch values) before the switch (SBP, 154.7 ± 10.0 mm Hg, $P<0.0001$; DBP, 86.9 ± 8.0 mm Hg, $P<0.0001$). In contrast, after the switch, the mean PR (73.9 ± 13.3 b.p.m.) was not different than the mean before the switch (PR, 72.9 ± 13.7 b.p.m., $P=0.2391$). A frequency analysis showed that after switching to olmesartan, 7 (14%) patients had elevations in SBP, 25 (50%) had <10 mm Hg reductions in SBP, 11 (22%) had 10–20 mm Hg reductions in SBP and 7 (14%) had >20 mm Hg reductions in SBP (data not shown).

BP in study 2

The results of study 2 are shown in Table 3. In the Olm-G group, SBP was significantly reduced after 1 month (from 149 ± 19 mm Hg to 142 ± 20 mm Hg; $P<0.05$), and finally reached 135 ± 15 mm Hg after 4 months ($P<0.01$ vs. 0 month). In the Imi-G group, SBP was not significantly reduced after the first month (from 145 ± 17 mm Hg to 140 ± 20 mm Hg), but finally reached 138 ± 15 mm Hg after 4 months ($P<0.05$ vs. 0 month). The MBP value is also an important parameter for managing CKD; therefore, we also evaluated MBP in study 2. In the Olm-G group, MBP was significantly reduced at 1 month (from 107 ± 15 mm Hg to 102 ± 16 mm Hg; $P<0.01$), 2 months (102 ± 14 mm Hg; $P<0.05$ vs. 0 month), 3 months (101 ± 15 mm Hg;

Table 1 Baseline characteristics of hypertensive patients taking valsartan, with or without other anti-hypertensive drugs

Characteristic	Total	Study 1	Study 2 Total	Study 2 Olm-G	Study 2 Imi-G
N	87	50	37	19	18
Male/female	53/34	21/29	32/5	17/2	15/3
Age (years)	67 ± 11	69 ± 11	64 ± 11	64 ± 11	63 ± 11
Diabetes (n (%))	23 (26)	11 (22)	12 (32)	7 (37)	5 (28)
Hyperlipidemia (n (%))	40 (46)	22 (44)	18 (49)	12 (63)	6 (33)
Number of anti-hypertensive drugs[a]	2.3 ± 1.0	2.1 ± 0.9	2.7 ± 1.1	2.9 ± 1.1	2.6 ± 1.1
Valsartan only (n (%))	19 (22)	13 (26)	6 (16)	2 (11)	4 (22)
β-Blockers (n (%))	27 (31)	10 (20)	17 (46)	11 (58)	6 (33)
CCBs (n (%))	62 (71)	34 (68)	28 (76)	16 (84)	12 (67)
Diuretics (n (%))	21 (24)	8 (16)	13 (35)	5 (26)	8 (44)
α-Blockers (n (%))	6 (7)	2 (4)	4 (11)	2 (11)	2 (11)
TC (mg per 100 ml)	202 ± 30	201 ± 27	202 ± 36	206 ± 42	198 ± 30
TG (mg per 100 ml)	160 ± 93	149 ± 87	176 ± 99	188 ± 113	183 ± 115
HDL-C (mg per 100 ml)	54 ± 14	55 ± 14	51 ± 12	52 ± 14	50 ± 11
UA (mg per 100 ml)	6.2 ± 1.6	5.7 ± 1.7	6.8 ± 1.4	6.7 ± 1.5	6.8 ± 1.4
Serum creatinine (mg per 100 ml)	1.2 ± 0.7	0.8 ± 0.2	1.7 ± 0.9	1.7 ± 0.8	1.6 ± 0.9
AST (IU l^{-1})	25 ± 13	27 ± 13	21 ± 11	21 ± 12	21 ± 12
ALT (IU l^{-1})	26 ± 22	28 ± 22	24 ± 22	25 ± 22	23 ± 24
γ-GTP (IU l^{-1})	46 ± 46	38 ± 27	60 ± 66	70 ± 76	50 ± 66
FBG (mg per 100 ml)	121 ± 36	121 ± 38	122 ± 33	127 ± 38	116 ± 27

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCB, calcium channel blocker; FBG, fasting blood glucose; γ-GTP, γ-glutamyltranspeptidase; HDL-C, high-density lipoprotein cholesterol; Imi-G, patients who added imidapril to a valsartan regimen; Olm-G, patients who switched from valsartan to olmesartan; TC, total cholesterol; TG, triglyceride; UA, uric acid.
[a]The number of anti-hypertensive drugs is the mean number ± s.d. of drugs per patient that were taken concurrently with the drugs tested in this study.

Table 2 Study 1: blood pressure and pulse rate for patients who switched from valsartan to olmesartan

Measurement	−1 month	Day of switch	+1 month	+2 months
SBP (mm Hg)	154 ± 12	156 ± 10	145 ± 17[***, ###]	145 ± 13[***, ###]
DBP (mm Hg)	86 ± 8	88 ± 9	81 ± 11[***, ###]	82 ± 10[***, ###]
MBP (mm Hg)	109 ± 8	110 ± 8	102 ± 12[***, ###]	103 ± 10[***, ###]
PP (mm Hg)	68 ± 11	68 ± 11	64 ± 12[*, ##]	63 ± 11[**, ##]
PR (b.p.m.)	72 ± 14	74 ± 14	74 ± 13	75 ± 15

Abbreviations: b.p.m., beats per minute; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; PR, pulse rate; SBP, systolic blood pressure.
*$P<0.05$, **$P<0.01$, ***$P<0.001$ vs. −1 month; ##$P<0.01$, ###$P<0.001$ vs. day of switch.

$P<0.05$ vs. 0 month) and finally reached $97 ± 14$ mm Hg at 4 months ($P<0.01$ vs. 0 month). In the Imi-G group, MBP was not significantly reduced for the first 1–3 months, but finally reached $100 ± 11$ mm Hg at 4 months ($P<0.05$ vs. 0 month).

Influences of UPE in study 2

We evaluated renal function by analyzing UPE and the estimated glomerular filtration rate. The baseline (0 month) UPE was not statistically different between the groups. In the Olm-G group, UPE was significantly reduced after 1 month (from $2.0 ± 1.8$ g g^{-1} to $1.3 ± 1.2$ g g^{-1} creatinine; $P<0.05$), and finally reached $0.8 ± 0.8$ g g^{-1} creatinine after 4 months ($P<0.05$ vs. 0 month). In the Imi-G group, UPE was not significantly reduced after 1 month (from $1.4 ± 1.3$ g g^{-1} to $1.1 ± 1.0$ g g^{-1} creatinine), but finally reached $0.9 ± 1.0$ g g^{-1} creatinine after 4 months ($P<0.05$ vs. 0 month). However, there were no significant changes in the estimated glomerular filtration rate during follow-up in either group.

UPE reduction and other factors

To clarify the influence of other factors on UPE reduction, we used a multiple regression analysis to examine correlations between the fractional UPE reduction, defined as (UPE at 0 month-UPE at 4 months)/UPE at 0 month and other variables (Table 4). This showed that no other factors influenced the observed UPE reductions.

DISCUSSION

In this study, we first demonstrated in hypertensive patients without CKD that 40 mg per day olmesartan resulted in an enhanced reduction of SBP (10.1 mm Hg) and DBP (6.0 mm Hg) compared with 160 mg per day valsartan. A previous meta-analysis showed that several ARBs, such as losartan, irbesartan, candesartan, valsartan and olmesartan, had a placebo-corrected dose effect on BP. In that report, at the recommended maintenance dose (80 mg per day), the net effect of valsartan on SBP and DBP was very similar to that observed with olmesartan at 20 mg per day. However, at twice the recommended maintenance dose (160 mg per day), the net effect of valsartan on SBP and DBP appeared to be lower than that observed with olmesartan at 40 mg per day. On the basis of that evidence, we postulated that the BP-lowering effect of 40 mg olmesartan would be greater than that of 160 mg valsartan. However, there was no direct head-to-head study that showed an advantage of olmesartan over valsartan. Several current guidelines for managing essential hypertension[15–16] and many large, multicenter trials[17–18] have suggested that strict reduction of BP is the most important factor for preventing cardiovascular mortality and morbidity in hypertensive patients. The patients included in this study were hypertensive and could not achieve optimal BP with antihypertensive treatments, including 160 mg per day valsartan. We found that >80% of the study participants had

Table 3 Blood pressure, pulse rate and renal function for patients who switched from valsartan to olmesartan (Olm-G) or added imidapril to valsartan (Imi-G)

Measurement	Test group	0 month	1 month	2 months	3 months	4 months
SBP (mm Hg)	Olm-G	149±19	142±20*	144±18	142±21*	135±15**
	Imi-G	145±17	140±20	142±17	143±14	138±15*
DBP (mm Hg)	Olm-G	86±16	82±15**	81±16*	81±15*	77±15**
	Imi-G	86±12	83±17	83±14	84±14	82±11
MBP (mm Hg)	Olm-G	107±15	102±16**	102±14*	101±15*	97±14**
	Imi-G	105±12	102±17	104±13	104±13	100±11*
eGFR	Olm-G	41.8±24.0	39.0±21.9	38.2±24.9	33.1±21.0	38.4±23.4
	Imi-G	40.3±16.0	38.0±17.0	39.6±17.3	36.3±17.5	40.5±21.5
UPE (g per gcre)	Olm-G	2.0±1.8	1.3±1.2*	1.3±1.1	1.2±1.2	0.8±0.8*
	Imi-G	1.4±1.3	1.1±1.0	0.8±0.8	1.0±0.9	0.9±1.0*

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MBP, mean blood pressure; SBP, systolic blood pressure; UPE, urinary protein excretion.
*$P<0.05$, **$P<0.01$ vs. 0 month.

Table 4 Multiple regression analysis results for factors that influenced the reduction of urinary protein excretion

Influencing factor	P-value
Age	0.4518
Sex (male)	0.4636
Diabetes	0.1161
Dyslipidemia	0.0944
Pre-SBP	0.4545
Pre-DBP	0.6958
Pre-PR	0.4282
SBP reduction	0.1236
DBP reduction	0.1153
Pre-GFR	0.0541
Pre-UPE	0.1236
Olmesartan/imidapril	0.8712

Abbreviations: DBP reduction, difference in diastolic blood pressure between 0 and 4 months; Pre-DBP, diastolic blood pressure at baseline; Pre-GFR, estimated glomerular filtration rate at baseline; Pre-SBP, systolic blood pressure at baseline; Pre-UPE, urinary protein excretion at baseline; SBP reduction, difference in systolic blood pressure between 0 and 4 months. Olmesartan/imidapril, a switch from valsartan to olmesartan or a combination of valsartan and imidapril.

reduced SBP after switching from 160 mg per day valsartan to 40 mg per day olmesartan.

We also found that 40 mg per day olmesartan more effectively reduced UPE than did 160 mg per day valsartan. Furthermore, olmesartan was as effective as the combination of valsartan 160 mg per day and imidapril 10 mg per day for reducing UPE after 4 months. These results were consistent with those from the modification of diet in renal disease study, which showed that the reduction in MBP was useful for decreasing UPE.[19] Other clinical data suggested that high doses of ARBs reduced UPE more effectively than did low doses; examples include 96 mg per day candesartan,[20] 640 mg per day valsartan[21] and 300 mg of irbesartan.[9] Thus, the UPE reduction observed in this study was not a specific effect of olmesartan, but of high doses of ARBs, in general.

There is no statistical difference in UPE and BP at baseline; however, UPE and BP in the Olm-G group showed higher tendency than those in the Imi-G group. To clarify factors that influenced the reduction of UPE, we also performed multiple regression analysis in Table 4. We did not find influenced factors, including BP and UPE at baseline, BP reduction and medication, such as switching to olmesartan or adding imidapril. According to these evidences, olmesartan 40 mg per day and valsartan 160 mg per day with imidapril 10 mg per day equally reduced UPE in patients with hypertension and CKD.

This study demonstrated that the maximum permitted dose of olmesartan produced a greater reduction in BP and UPE than did the maximum allowable dose of valsartan. Moreover, high-dose olmesartan reduced UPE with an efficacy comparable with that achieved with high-dose valsartan combined with imidapril. These results do not discount the efficacy of valsartan in preventing cardiovascular events and total mortality in many multicenter trials.[11–12,18] Our results suggested that a high dose of olmesartan is beneficial for managing hypertensive patients, especially those with impaired renal function.

Study limitations

This study had several limitations. The most important limitation was the protocol; only one switch was performed to compare two antihypertensive drugs in study 1. A crossover or randomized study would be necessary to properly compare olmesartan and valsartan treatments. From an ethical standpoint, it was not advisable to switch patients back to 160 mg valsartan after they had achieved optimal BP with 40 mg olmesartan. In study 2, although we randomized the participants into olmesartan and imidapril groups, BP and UPE in the olmesartan group were slightly higher, although the difference was not statistically significant. A study with a larger number of participants will be required to confirm our results. In this study, subjects were preferentially selected to create a group whose hypertension was poorly controlled with valsartan treatment. Thus, it was not surprising that the study patients did not respond well to valsartan.

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