Efficacy of combination therapy with telmisartan plus amlodipine in patients with poorly controlled hypertension

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There is accumulating evidence that blood pressure (BP) control significantly reduces the risk of future cardiovascular events in patients with essential hypertension. However, strict BP control is often difficult to maintain, and half of hypertensive patients fail to attain BP goals on single-drug therapy. Therefore, current guidelines recommend combinations of drugs that have complimentary mode of actions for treatment of patients with moderate hypertension. In this study, we examined in hypertensive patients uncontrolled by the combination treatment with 5 mg amlodipine plus 80 mg valsartan or 8 mg candesartan whether additional BP lowering could be achieved by switching to 5 mg amlodipine plus 40 mg telmisartan. Forty-seven patients with essential hypertension who failed to achieve a target BP level by the treatment of 5 mg amlodipine plus 80 mg valsartan or 8 mg candesartan for at least 2 months were enrolled. Replacement of valsartan or candesartan by telmisartan showed a significant reduction in both mean clinic systolic and diastolic BP at 4, 8 and 12 weeks; BP level decreased from 143.7/82.3 mmHg at baseline to 135.4/77.5 mmHg at 12 weeks. Furthermore, in 8 patients of valsartan group, switching to telmisartan significantly reduced central BP by 11.8 mmHg. Our present study suggests that combination therapy with telmisartan plus amlodipine may be more beneficial than valsartan or candesartan plus amlodipine treatment for controlling brachial and central BP, which could lead to more favorable cardiovascular outcomes with this drug combinations.

Introduction

There is a growing body of evidence that blood pressure (BP) level is one of the major determinants of cardiovascular morbidity and mortality in individuals.[1,2] A recent analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) revealed that any commonly used BP-lowering regimen reduced the risk of total major cardiovascular events, and larger lowering in BP level produced larger reductions in the risk.[3] These observations suggest that most of the differences among treatment regimens in their effects on cardiovascular outcomes could be explained by the differences in achieved BP level. However, it may also be true that some treatment regimen is superior or inferior to others with regard to the risk reduction of cardiovascular events.[4-6] Indeed, in Avoiding Cardiovascular Events through Combination Therapy in Patients with Living with Systolic Hypertension (ACCOMPLISH) trial, combination of the inhibitor of renin-angiotensin system (RAS) with amlodipine, one of the most widely used dihydropyridine calcium channel blocker (CCB), demonstrated a significant risk reduction in cardiovascular events in patients with hypertension compared to the RAS inhibitor-hydrochlorothiazide combination.[6]

Angiotensin II (Ang II) is a physiologically active major substance of the RAS; it not only acts as a vasopressor by inducing vasoconstriction, but also elicits water and sodium absorption in the proximal renal tubule by stimulating secretion of aldosterone.[5,7] Furthermore, Ang II exerts various biological effects in blood vessel, kidney and heart via the interaction with type 1 receptor.[5,7] Therefore, inhibition of the RAS by angiotensin-converting enzyme inhibitors (ACEIs) and/or Ang II type 1 receptor blockers (ARBs) may be a therapeutic target for the organ protection in patients with hypertension.[8]

ARBs have less adverse reactions; they are unlikely to cause dry cough and angioedema associated with ACEIs.[9] Since risk of cough from ACEIs is relatively high in East Asian compared with white patients,[10] ARBs are now a more popular RAS inhibitor in Japan. Although CCBs and ARBs are one of the recommended combinations in order to achieve target BP level,[11] optimal combination regimen is not well established. Valsartan, candesartan and telmisartan are effective and well-tolerated ARBs, and their usual dosages
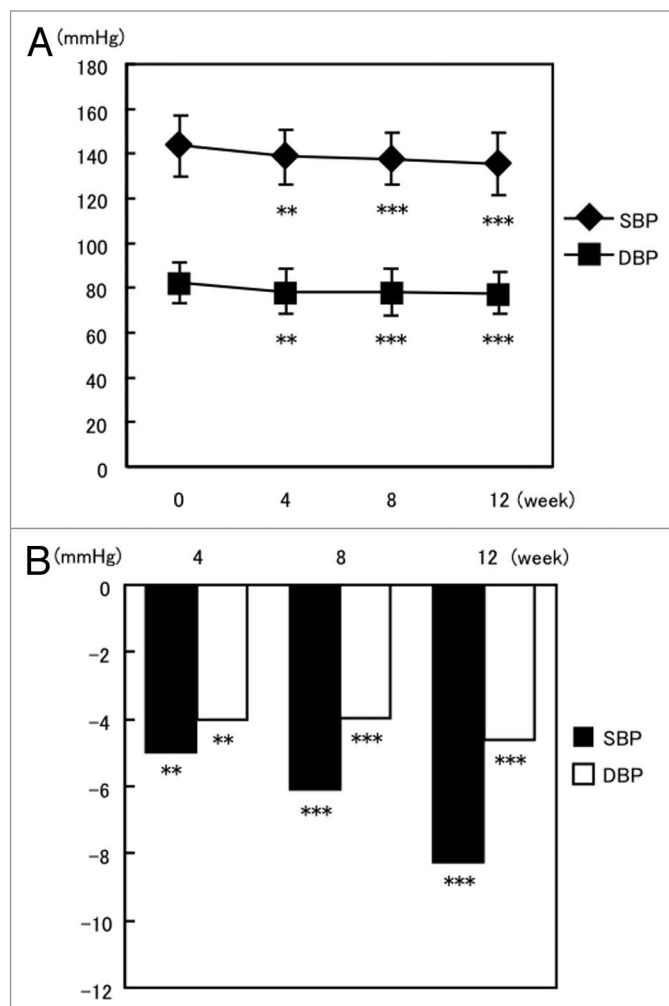
Figure 1. BP levels in whole patients. Replacement of valsartan or candesartan by telmisartan showed a significant reduction in both mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 4, 8 and 12 weeks. Forty-seven patients (36 males and 11 females) with poorly controlled hypertension were assigned to replace 80 mg valsartan or 8 mg candesartan with 40 mg telmisartan. All patients were taking 5 mg amlodipine. (A) SBP and DBP at baseline (0 week) and at 4, 8 and 12 weeks after telmisartan treatment. (B) Mean changes in SBP and DBP from baseline. ** and ***, p < 0.01 and p < 0.001 compared to the values of baseline, respectively.

are 80 mg, 8 mg and 40 mg once daily, respectively in Japan.[12] Therefore, we examined in hypertensive patients whose BP level was uncontrolled by combination treatment with 5 mg amlodipine plus 80 mg valsartan or 8 mg candesartan for at least 2 months whether additional BP lowering could be achieved by switching to 5 mg amolodipine plus 40 mg telmisartan. We also investigated whether combination therapy with telmisartan and amlodipine was more effective in reducing central aortic pressures compared with valsartan or candesartan plus amlodipine treatment.

Results

Demographical data of the subjects are presented in **Table 1**. As shown in **Figure 1**, replacement of valsartan or candesartan by

telmisartan in amlodipine-treated hypertensive patients showed a significant reduction in both mean clinic systolic BP (SBP) and diastolic BP (DBP) at 4, 8 and 12 weeks; BP level decreased from 143.7/82.3 mmHg at baseline to 135.4/77.5 mmHg at 12 weeks after the telmisartan treatment. When valsartan and candesartan group was separately analyzed, switching from valsartan to telmisartan had more beneficial BP-lowering effects (**Figs. 2 and 3**); replacement of valsartan by telmisartan reduced mean SBP and DBP by 7.1 and 6.5 mmHg at 4 weeks, 6.9 and 5.0 mmHg at 8 weeks, 10.5 and 7. mmHg at 12 weeks, respectively. Furthermore, although central BP (cBP) and augmentation index (AI) were evaluated in only 8 patients of valsartan group, switching to telmisartan significantly reduced cBP by 11.8 mmHg (**Table 2**). There were no significant differences among low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), fasting plasma glucose (FPG), glycosyalted hemoglobin (HbA1c), insulin, homeostasis model assessment of insulin resistance (HOMA-IR) index, creatinine (Cr), estimated glomerular filtration rate (eGFR) values and AI before and after the treatment of telmisartan (**Tables 1 and 2**).

Discussion

Hypertension is one of the major risk factors of cardiovascular disease, and to control BP level appropriately is a therapeutic target for preventing future cardiovascular events in individuals.[1,2,13,14] However, strict BP control is often difficult to maintain, and BP level is not adequately controlled in more than 50% of hypertensive patients on single-drug therapy.[15] Therefore, current guidelines recommend combinations of drugs with different mode of actions for treatment of patients with moderate hypertension.[11,16] There are several papers to show that combination therapy with ARBs and amlodipine, one of the most popular CCBs is effective for BP control compared with high-dose monotherapy, although what types of ARBs in combination with amlodipine are more effective for achieving appropriate BP control is not well established.[17,18]

In this study, we demonstrated for the first time that in hypertensive patients uncontrolled by the combination treatment with 5 mg amlodipine plus 80 mg valsartan or 8 mg candesartan, additional BP lowering was achieved by switching to 5 mg amlodipine plus 40 mg telmisartan. BP level was significantly decreased at 4 weeks after the telmisartan treatment and remained low during the study periods. Furthermore, replacement of valsartan by telmisartan was found to significantly reduce cBP in our subjects as well. There are accumulating evidence that cBP is closely associated with coronary risk factors and future cardiovascular events in patients with hypertension.[19,20] Therefore, our present findings suggest that combination therapy with telmisartan plus amlodipine may be more beneficial than valsartan or candesartan plus amlodipine treatment for controlling brachial and cBP, which could lead to more favorable cardiovascular outcomes with this drug combinations.

We have previously found that telmisartan has the strongest binding affinity to Ang II type 1 receptor among various

ARBs, including valsartan and candesartan.[21] Further, telmisartan has a half-life of about 24 hours, which is longer than that of valsartan and candesartan (about 9 hours).[7] Among the ARBs, telmisartan is the most lipophilic compound as well.[22] Therefore, due to its strongest Ang II type 1 receptor antagonistic ability, longest half-life and lipophilicity, switching to telmisartan may have long-lasting BP lowering effects in our uncontrolled hypertensive patients who were treated with 5 mg amlodipine plus 80 mg valsartan or 8 mg candesartan. In support of this, it has been reported in clinical studies that telmisartan is significantly superior to valsartan in antihypertensive effect during the daytime and early morning,[23,24] and that it produces a sustained antihypertensive effect equal to or greater than amlodipine, a long-acting CCB.[25] Further, meta-analysis revealed that BP lowering effect of 40 mg telmisartan was stronger than that of 80 mg valsartan or 8 mg candesartan.[26]

Research Design and Methods

Subjects. This was a prospective, open-label, 12-week study. Forty-nine patients with essential hypertension not achieving a target clinic or home BP level were recruited from multiple centers in Japan.[27] All patients were taking 5 mg amlodipine plus 80 mg valsartan or 8 mg candesartan for at least 2 months. A screening period of up to 2–4 weeks was used to assess eligibility and to eliminate prior medications. Finally eligible 47 patients (36 males and 11 females, mean age; 64.8 ± 12.1 years old) were assigned to replace valsartan or candesartan with 40 mg telmisartan. During the study period, subjects were instructed not to change their lifestyles and to continue taking the same dose of any concomitant drugs. We excluded any patients with secondary hypertension, chronic liver disease, severe chronic heart failure, and those who had recent (<6 months) acute coronary syndromes, stroke and any acute infections. Patients whose age was younger than 20 years old, whose BP level was ≥ 180/110 mmHg, or whose serum Cr level was ≥ 1.5 mg/dL were also excluded. At baseline, 4, 8 and 12 weeks after the replacement, clinic BP level was monitored. Anthropometric and metabolic variables and serum chemistries were also measured at baseline and at 12 weeks after telmisartan treatment as described previously.[28] Only one male patient on switching from valsartan to telmisartan was dropped out at 8 weeks because of his personal reason. Informed consent was obtained from all the subjects, and the study protocol was approved by the Institutional Ethics Committee of Kurume University School of Medicine.

Table 1. Clinical variables at baseline and at 12 weeks after telmisartan treatment

| Clinical variables	Baseline	At 12 weeks	p-value
BMI (kg/m²)	24.8±3.5	24.7±3.6	0.37
Heart rate (beats/minute)	68.4±11.9	68.0±11.2	0.75
SBP (mmHg)	143.7±13.6	135.4±14.0	p < 0.001
DBP (mmHg)	82.3±9.4	77.5±9.4	p < 0.001
LDL-cholesterol (mg/dL)	112.6±29.4	111.4±27.0	0.46
Triglycerides (mg/dL)	159.9±167.9	132.0±74.4	0.23
HDL-cholesterol (mg/dL)	55.1±12.3	54.8±11.2	0.93
Fasting plasma glucose (mg/dL)	111.5±36.5	111.7±42.7	0.95
HbA1c (%)	6.0±1.1	6.0±0.8	0.63
Fasting insulin (µU/mL)	9.1±11.8	8.5±10.4	0.72
HOMA-IR	2.4±3.0	2.3±3.3	0.85
Creatinine (mg/dL)	0.7±0.2	0.7±0.2	0.32
eGFR (ml/min/1.73m²)	79.1±17.2	79.6±17.1	0.46
Diabetes mellitus (N)	12	12	-
Dyslipidemia (N)	27	27	-
Chronic kidney disease (N)	3	3	-
Cardiovascular disease (N)	4	4	-

Replacement of valsartan or candesartan by telmisartan showed a significant reduction in both mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 12 weeks. BMI; body mass index, LDL-cholesterol; low-density lipoprotein-cholesterol, HDL-cholesterol; high-density lipoprotein-cholesterol, HbA1c; glycosyalted hemoglobin, HOMA-IR; homeostasis model assessment of insulin resistance, eGFR; estimated glomerular filtration rate, N; number.

Table 2. Central BP at baseline and at 12 weeks after telmisartan treatment

Clinical variables	Baseline	At 12 weeks	p-value
Patients (N)	8	8	-
Age (years old)	55.1±8.7	-	-
Male/female (N)	7/1	7/1	-
BMI (kg/m²)	24.7±3.6	24.9±3.7	0.13
Heart rate (beats/minutes)	71.3±2.1	74.3±7.1	0.28
SBP2 (mmHg)	129.3±7.7	118.4±9.4	p < 0.05
Central BP (mmHg)	144.9±8.2	133.1±10.1	p < 0.05
AI (%)	71.8±16.5	72.9±20.0	0.82

Replacement of valsartan by telmisartan showed a significant reduction in central blood pressure (central BP) at 12 weeks. BMI; body mass index, SBP2; late systolic peak of blood pressure, BP; blood pressure, AI; augmentation index, N; number.

Study design. The medical history was ascertained by a questionnaire. Height and weight were measured, and body mass index (BMI: kilograms per meter squared) was calculated as an index of the presence or absence of obesity. Clinic BP was measured in the sitting position using an upright standard sphygmomanometer after at least 5 min of rest in the morning before taking anti-hypertensive agents. Three measurements were taken 1 min apart, and mean of the last two recordings was used as BP level. Using applanation tonometry (HEM-9000AI (Omron Healthcare, Kyoto, Japan), cBP was deduced noninvasively from the amplitude of the late systolic peak (SBP2) of the radial artery pulse waveform as
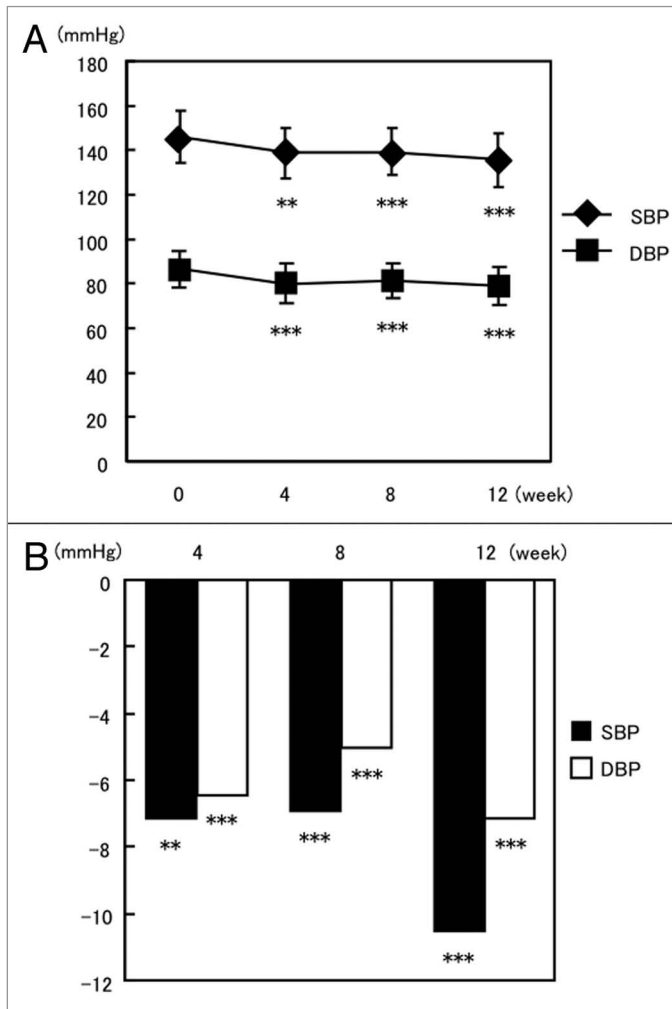
Figure 2. BP levels in patients on switching from valsartan to telmisartan. Replacement of valsartan by telmisartan showed a significant reduction in both mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 4, 8 and 12 weeks. Twenty-two patients (17 males and 5 females) with poorly controlled hypertension were assigned to replace 80 mg valsartan by 40 mg telmisartan. All patients were taking 5 mg amlodipine. (A) SBP and DBP at baseline (0 week) and at 4, 8 and 12 weeks after telmisartan treatment. (B) Mean changes in SBP and DBP from baseline. ** and ***, $p < 0.01$ and $p < 0.001$ compared to the values of baseline, respectively.
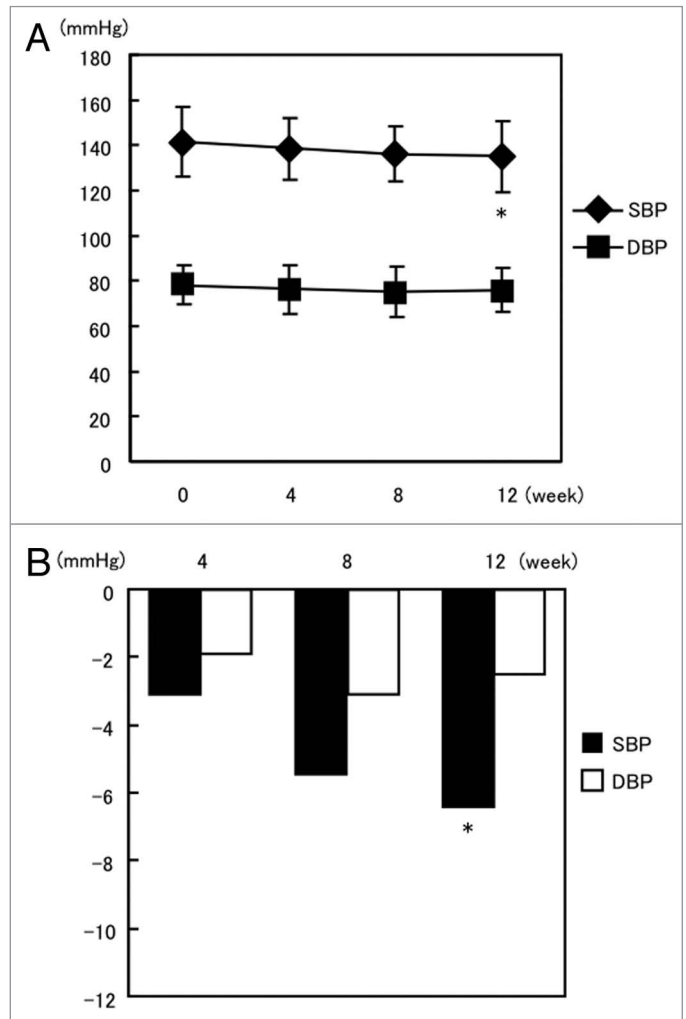
Figure 3. BP levels in patients on switching from candesartan to telmisartan. Replacement of candesartan by telmisartan showed a reduction in both mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 4, 8 and 12 weeks. Twenty-five patients (19 males and 6 females) with poorly controlled hypertension were assigned to replace 8 mg candesartan by 40 mg telmisartan. All patients were taking 5 mg amlodipine. (A) SBP and DBP at baseline (0 week) and at 4, 8 and 12 weeks after telmisartan treatment. (B) Mean changes in SBP and DBP from baseline. *, $p < 0.05$ compared to the values of baseline.

described elsewhere.[29] The AI was calculated as the ratio of the amplitude of SBP2 to the amplitude of the early systolic peak.

Blood was drawn from the antecubital vein in the morning after 12-hour fast for determinations of lipids (HDL-C, LDL-C, and TG), FPG, insulin, HbA1c, and Cr. Blood chemistries were measured at a commercially available laboratory (SRL Inc., Hachioji, Japan). The HOMA-IR index was calculated from the values of FPG (mg/dl) and insulin (µU/ml) using the following formula [(glucose x insulin)/405]. eGFR was calculated with the modified isotope dilution mass spectrometry (IDMS)-traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation for Japanese.[30]

Statistical methods. Data were expressed as mean ± standard deviation (SD). To compare the parameter changes between baseline and after the telmisartan treatment, we used the paired t-test. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed with the use of the SAS version 9.2 system (SAS Institute Inc., Cary, NC).

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