Three-Year Safety and Effectiveness of Fixed-Dose Losartan/Hydrochlorothiazide Combination Therapy in Japanese Patients with Hypertension Under Clinical Setting (PALM-1 Extension Study)

Toshihiro Kita, Naoto Yokota, Yoshinari Ichiki, Takao Ayabe, Takuma Etoh, Noboru Tamaki, Johji Kato, Tanenao Eto, Kazuo Kitamura

Division of Circulatory and Body Fluid Regulation, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan, Yokota Naika, Miyazaki, Japan, Ichiki Naika Geka Iin, Miyazaki, Japan, Ayabe Iin, Miyazaki, Japan, Etoh Clinic, Nichinan, Japan, Tamaki Clinic, Aya, Japan, Frontier Science Research Center, University of Miyazaki, Miyazaki, Japan, Miyazaki Prefectural Health Foundation, Miyazaki, Japan

Abstract

Concerns about metabolic complications often disturb prolonged use of diuretics in Japan. We investigated 3-year safety and efficacy in Japanese patients with hypertension who were uncontrolled with angiotensin receptor blocker or angiotensin-converting enzyme inhibitor regimens and then switched to losartan (50 mg)/hydrochlorothiazide (12.5 mg; HCTZ) combinations. Blood pressure decreased favorably and maintained a steady state for 3 years (157 ± 16/88 ± 11 mm Hg to 132 ± 13/75 ± 9 mm Hg, P < .0001). Metabolic parameters maintained a limited range of changes after 3 years, and adverse events were markedly decreased after 1-year treatment. The losartan/HCTZ combination minimized diuretic-related adverse effects and thus may be useful for the treatment of Japanese patients with hypertension.

Keywords: losartan, hydrochlorothiazide, Japanese, uric acid, hypertension

INTRODUCTION

Strict blood pressure (BP) control as recommended in guidelines for hypertension treatment, including those of the Japanese Society of Hypertension (JSH) (1,2), is crucial for the prevention of cardiovascular and renal accidents. However, considerable numbers of patients with hypertension have not achieved recommended BP goals in clinical practice (3). Appropriate combinations of antihypertensive drugs are required for such cases, and in particular, low-dose (quarter to half dose) diuretics are recommended as important candidates for satisfactory BP control (1).

Recently, several fixed drug combinations consisting of angiotensin receptor blocker (ARB) and hydrochlorothiazide (HCTZ) have come to the Japanese market. We and others (4–7) reported remarkable effectiveness of this drug combination in patients with uncontrolled hypertension in Japan. These studies also reported acceptable safety of the drug combination taking into account the metabolic complications of HCTZ treatment (4–7). However, observational periods were limited, namely, up to 1 year, and thus, concerns about metabolic complications still remain due to prolonged use of the drug combination. Here, we have extended our study and evaluated the safety and efficacy over 3 years of the fixed combination of losartan 50 mg/HCTZ 12.5 mg (Preminent®, MSD, Tokyo, Japan) in patients with essential hypertension.

METHODS

Study Subjects

This study was conducted at 43 centers for the Preminent® Assigned League in Miyazaki by primary care physicians: the PALM-1 study group (4). Patients with essential hypertension (20–89 years old) were considered for screening and potential recruitment into the trial. They had visited the attending clinics from
February 2007 to March 2008 and had not reached BP goals over 1 month with antihypertensive therapy regimens including ARBs or angiotensin-converting enzyme inhibitors (ACEIs), but not including diuretics. Patients were excluded from the study if there was any evidence of secondary hypertension, renal failure (serum creatinine ≥ 2.0 mg/dL), severe liver dysfunction, or symptomatic heart failure (New York Heart Association functional class III or IV for dyspnea at exertion). Patients with concomitant use of two or more ARBs and/or ACEIs and any type of diuretic were also excluded.

### Study Protocol

The study was conducted in accordance with the principles of the Helsinki declaration. The investigational protocol was approved by the ethics committee for human studies at the University of Miyazaki. Informed consent was obtained from all patients prior to recruitment.

The detailed protocol for 1-year follow-up has been reported previously (4). Briefly, patients whose baseline BP measurements were over the recommended BP goals of JSH 2004 under antihypertensive treatment with regimens including ARBs or ACEIs were enrolled. Then, ARBs or ACEIs were switched to a fixed dose combination of losartan/HCTZ and patients were followed for 1 year. The modified prescription was continued for the initial 3 months, and then, if needed, adjustments of antihypertensive drugs were permitted, except for ARBs, ACEIs, and diuretics. After 1-year follow-up, only patients who continued the drug combination for 1 year were re-enrolled for the extended study. The same parameters, namely, symptoms, sitting BP, pulse rate, and blood tests including potassium, uric acid (UA), lipid profile, creatinine, glucose, and hemoglobin A1c (HbA1c, diabetic patients only) were evaluated for another 2 years. Major complications were also evaluated. The criteria for diabetes and dyslipidemia were as follows: diabetes, using antiglycemic drugs or fasting blood glucose ≥ 126 mg/dL; dyslipidemia, using lipid-lowering drugs or total cholesterol ≥ 220 mg/dL and/or high-density lipoprotein-cholesterol < 40 mg/dL, and/or triglyceride ≥ 150 mg/dL. The criterion for chronic kidney disease was estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73 m².

### Statistical Analysis

All data were expressed as mean ± SD. The significant differences were evaluated by one-factor ANOVA with repeated measures on time course of variables followed by Bonferroni/Dunn post hoc comparison tests. Comparisons of parameters among subgroups were made using unpaired Dunnett’s C test or ANOVA followed by Scheffe’s post hoc comparison test. A P-value < .05 was the criterion for statistical significance.

### RESULTS

This study commenced with 278 eligible patients. At the original end point, namely, 1 year later, 240 patients had continued the drug combination. Among the 240 patients, we could not collect additional data from 23 patients due to later technical problems, including those caused by computer difficulties. The remaining 217 patients were therefore enrolled in the extended study and followed-up for another 2 years. These 217 patients were considered to be subjects for full analysis. Finally, 166 patients had continued the drug combination for 3 years and were used for the evaluation of efficacy.

The basal characteristics of the starting population and the 166 patients who completed the 3-year study are indicated in Table 1. Essentially, there were no remarkable differences between the two groups. Also, there were no remarkable differences between patients who completed the 3-year study and dropout patients (Table 1). Additionally, the distribution of pre-prescribed ARBs or ACEIs and average dosage of each drug were similar in these two groups (data not shown).

BP levels over time in 166 patients are illustrated in Figure 1. After switching to the drug combination, steady levels of BP were maintained for 3 years. Six patients underwent change of antihypertensive agent after 1-year follow-up: two patients, additional Ca channel blocker (CCB); two patients, increase in dose of

| Table 1. Background characteristics |
|-------------------------------------|
| **Patients (n)** | All | Completed | Dropout | **P-value** |
| Age (y) | 65.2 ± 11.2 | 65.8 ± 10.6 | 64.5 ± 12.6 | n.s. |
| Male (n) | 151 (54.3%) | 85 (51.2%) | 52 (58.4%) | n.s. |
| Body mass index (kg/m²) | 25.0 ± 5.4 | 25.3 ± 6.2 | 24.7 ± 3.5 | n.s. |
| Obesity (n) | 119 (42.8%) | 71 (42.8%) | 41 (46.1%) | n.s. |
| Diabetes (n) | 76 (27.3%) | 40 (24.1%) | 26 (29.2%) | n.s. |
| Dyslipidemia (n) | 101 (36.3%) | 65 (39.2%) | 27 (30.3%) | n.s. |
| Heart disease (n) | 49 (17.6%) | 33 (19.9%) | 15 (16.9%) | n.s. |
| CKD (n) | 75 (27.0%) | 46 (27.7%) | 22 (24.7%) | n.s. |
| **Antihypertensives (n)** | | | |
| One drug | 109 (39.2%) | 62 (37.3%) | 39 (43.8%) | n.s. |
| Over two drugs | 169 (60.8%) | 104 (62.7%) | 50 (56.2%) | n.s. |

Abbreviation: CKD – chronic kidney disease.
CCB; one patient, additional beta-blocker; one patient, decrease in dose of alpha-blocker. There were no remarkable changes if we excluded these six patients from the data presented in Figure 1. The average decrease in systolic BP was $-24.9 \pm 18.4$ mm Hg and in diastolic BP was $-12.6 \pm 11.0$ mm Hg after 3 years. The respective goals of BP were achieved by 51% of the patients for systolic BP and 78% of the patients for diastolic BP in the final assessment 3 years later. There were no changes in pulse rate at any check points (data not shown).

There were no remarkable changes in metabolic parameters over the 3 years of treatment with the drug combination (Table 2). Serum levels of UA were significantly increased at all evaluation points, but these increases were maintained within the normal range. In 166 patients who completed the 3-year treatment, UA levels over time in subgroups with high baseline UA levels and others with lower baseline levels are illustrated in Figure 2. As reported previously (4,6), UA was slightly increased in patients with relatively low levels of UA ($<7.0$ mg/dL). However, UA was significantly decreased in patients with a high level of UA ($\geq7.0$ mg/dL). Four patients (one with a high level of UA) had received additional alloprinol (100 mg) after 1-year follow-up, but there were no changes in the final results if we excluded these four patients. In addition, serum levels of creatinine were significantly increased at all evaluation points, and concomitantly, eGFR was significantly decreased. Interestingly, however, eGFR was significantly decreased only in patients with normal eGFR levels ($\geq60$ mL/min/1.73 m$^2$), and was maintained at steady levels in patients with lower eGFR (Figure 3). In diabetic patients, there were no changes in HbA1c; 6.35% ± 1.22% to 6.41% ± 1.11% after 1 year ($n = 56, P = .43$), 6.17% ± 1.06% to 6.15% ± 0.94% after 2 years ($n = 36, P = .85$), 6.19% ± 1.01% to 6.21% ± 1.11% after 3 years ($n = 38, P = .89$). There were no changes in drugs prescribed for patients with diabetes or dyslipidemia after 1 year of treatment.

Between years 1 and 3 of treatment, adverse events were observed in 9 of 217 patients (4.1%) who had continued with the losartan/HCTZ combination for at least 1 year; 6 of these (2.8%) discontinued the losartan/HCTZ combination, whereas the remaining 3 patients continued with the drug. Among the nine patients, six events were considered possibly, probably,

![Figure 1. Time course of blood pressure changes in all patients ($n = 166$). $^*P < .001$ compared to year 0.](image)

### Table 2. Changes in laboratory values

| Duration of treatment | 1 year | 2 years | 3 years |
|-----------------------|--------|---------|---------|
|                       | Before | After   | Before  | After   | Before  | After   |
| Potassium (mEq/L)     | 4.11 ± 0.49 | 4.13 ± 0.53 | 4.06 ± 0.46 | 4.01 ± 0.48 | 4.04 ± 0.46 | 3.97 ± 0.45 |
| $n$                   | 157    | 116     | 152     | 129     | 131     | 133     |
| $P$ value             | .67    | .25     | .07     | .43     | .43     | .56     |
| Total cholesterol (mg/dL) | 199.1 ± 33.0 | 190.9 ± 30.7 | 198.6 ± 31.3 | 193.2 ± 30.0 | 199.9 ± 29.4 | 195.2 ± 32.1 |
| $n$                   | 164    | 108     | 152     | 129     | 131     | 133     |
| $P$ value             | .001   | .09     | .07     | .43     | .43     | .56     |
| HDL-cholesterol (mg/dL) | 56.6 ± 14.6 | 55.2 ± 13.6 | 57.0 ± 14.5 | 56.2 ± 15.4 | 56.6 ± 14.4 | 55.6 ± 14.6 |
| $n$                   | 163    | 129     | 152     | 129     | 131     | 133     |
| $P$ value             | .99    | .43     | .07     | .43     | .43     | .56     |
| Triglyceride (mg/dL)  | 145.7 ± 95.2 | 145.6 ± 95.5 | 143.7 ± 97.8 | 154.2 ± 148.3 | 141.8 ± 96.7 | 146.9 ± 115.3 |
| $n$                   | 162    | 115     | 168     | 132     | 134     | 134     |
| $P$ value             | .33    | .75     | .016    | .23     | .016    | .016    |
| Glucose (mg/dL)       | 118.8 ± 47.6 | 121.3 ± 52.9 | 118.0 ± 43.6 | 116.9 ± 41.5 | 117.4 ± 43.4 | 119.7 ± 52.7 |
| $n$                   | 162    | 115     | 168     | 132     | 134     | 134     |
| $P$ value             | .33    | .75     | .016    | .23     | .016    | .016    |
| Uric acid (mg/dL)     | 5.40 ± 1.44 | 5.62 ± 1.43 | 5.44 ± 1.30 | 5.71 ± 1.36 | 5.35 ± 1.32 | 5.59 ± 1.34 |
| $n$                   | 168    | 132     | 168     | 132     | 134     | 134     |
| $P$ value             | .016   | .023    | .016    | .023    | .016    | .023    |
| Creatinine (mg/dL)    | 0.83 ± 0.29 | 0.88 ± 0.31 | 0.84 ± 0.29 | 0.91 ± 0.32 | 0.81 ± 0.27 | 0.89 ± 0.36 |
| $n$                   | 170    | 136     | 170     | 136     | 134     | 134     |
| $P$ value             | <.0001 | <.0001  | <.0001  | <.0001  | <.0001  | <.0001  |
| eGFR (mL/min/1.73m$^2$) | 68.9 ± 18.8 | 65.2 ± 19.4 | 67.2 ± 17.8 | 62.1 ± 18.2 | 69.5 ± 17.7 | 63.6 ± 18.6 |
| $n$                   | 170    | 136     | 170     | 136     | 134     | 134     |
| $P$ value             | <.0001 | <.0001  | <.0001  | <.0001  | <.0001  | <.0001  |

Abbreviation: eGFR – estimated glomerular filtration rate.
DISCUSSION

Despite progress in antihypertensive treatments, the status of many patients with hypertension still remains uncontrolled in Japan (3). The proportion of patients with hypertension attaining below 140/90 mm Hg with monotherapy is limited to 34.0% with ARBs and to 40.3% with CCBs (8); thus, appropriate combination therapy is recommended by the guidelines for treatment of hypertension (1,2). Salt intake in the Japanese population is relatively high, and practical salt restriction is extremely difficult in Japan (9,10). This high salt intake contributes to resistance against hypertensive treatment, and conversely, adequate use of diuretics such as HCTZ is crucial for successful management of BP (11). However, the prescription rate of diuretics remains low in Japan, for example, 9.3% in the J-HOME study (12). The principal reason to avoid diuretics, especially their long-term use, in Japan is due to fear over their negative effects on metabolic parameters (8). A means to maximize the therapeutic benefit of diuretics with minimum adverse effects is needed in Japan; a fixed-dose combination of ARBs/HCTZ seems to be a promising candidate for supplying the means.

In Japan, potent and stable antihypertensive effects of losartan/HCTZ combinations have been reported in many studies with high reproducibility; however, observation periods were limited to 1 year at most (4–7,13,14). In this study, the favorable effect was extended up to 3 years (Figure 1). In addition, this synergistic effect of losartan/HCTZ is effective in a comprehensive range of patients, with most patients achieving the BP goals of the JSH guideline; thus, specific cases of resistance against the losartan/HCTZ combination were not detected (4–7). In fact, background characteristics of the patient groups in the initial and final stages were quite similar (Table 1), which may suggest that the losartan/HCTZ combination could be

or definitely drug-related. Drug-related adverse events included three cases of hypotension, two cases of hypokalemia, and one case of hyperuricemia. Uncertain adverse events included one case of fatal myocardial infarction, one case of nonfatal cerebral infarction, and one case of laboratory abnormality (increase in γ-GTP).

Table 3 shows the reasons for dropout over the whole observation period. We could not collect data from 23 patients and the remaining 255 patients were followed-up for 36 months. As indicated in Table 3, adverse events that led to the discontinuation of the losartan/HCTZ combination were markedly decreased after 1 year, and in particular, skin complications were observed only within the first 12 months. The drug combination was switched to other drugs in 17 patients after 1 year (Table 3): in 9 patients due to excess decreases of BP and in the remaining 8 patients due to insufficient decreases of BP. Limited numbers (three cases) of cardiovascular events were observed over the whole observation period (Table 3).

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suitable for most patients with hypertension in the clinical setting. Specific characteristics of dropout patients were not identified in this study (Table 1). Background characteristics of patients who dropped out due to drug alteration or adverse events \( n = 42 \); Table 3) were also similar to those of other groups (data not shown).

No adverse changes in metabolic parameters were observed at 3-year follow-up (Table 2), and the number of adverse events leading to discontinuation of the drug combination gradually decreased year on year (Table 3). This durability of the drug combination may constitute an advantage over the use of diuretics alone. For example, only 34.4% of elderly patients had continued diuretics alone for 2 years (15), whereas in this study 65.1% (166/255) of patients continued the losartan/HCTZ combination for 3 years (Table 3). Although there were significant (but within the normal range) increases in UA and decreases in eGFR (Table 2), these negative effects were only limited in patients with normal values of UA or eGFR (Figures 2 and 3). Although such negative effects are a common feature of HCTZ, the low dose of HCTZ in the combination with losartan may have minimal negative impact, as observed in this study. In particular, only losartan has specific ability to increase UA excretion in the urine at the dose commonly used to treat hypertension (16) and, thus, has an advantage over other ARBs in UA management in combination with diuretics (13,14). Despite these advantages, small numbers of patients could suffer adverse effects such as hypokalemia or hyperuricemia (Table 3). Therefore, careful monitoring of blood parameters is required.

There are limitations to our study. This study has been carried out by primary care physicians; 35 of 255 patients (13.7%; Table 3) were lost to follow-up and 23 patients could not enter the extended study. In addition, there were some losses of metabolic parameters (Table 2). Despite these limitations, our original study (4) has been confirmed by subsequent studies with high reproducibility (5–7), and our extended study appears to be consistent with previous investigations.

In conclusion, 3 years of treatment with a fixed dose combination of losartan/HCTZ in a clinical setting resulted in acceptable safety and sufficient and steady BP decrease in a majority of Japanese patients with hypertension. In addition, there was a very limited number of cardiovascular accidents over the 3-year period. Japanese patients with hypertension can be treated effectively with a losartan/HCTZ combination with minimal risk.

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