Efficacy and Tolerability of Amlodipine Camsylate/Losartan 5/100-mg Versus Losartan/Hydrochlorothiazide 100/12.5-mg Fixed-Dose Combination in Hypertensive Patients Nonresponsive to Losartan 100-mg Monotherapy

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ABSTRACT

Purpose: The aim of this study was to determine whether the efficacy and tolerability of amlodipine camsylate/losartan 5/100 mg/d (AML/LOS) are noninferior to those of losartan/hydrochlorothiazide 100/12.5 mg/d (LOS/HCTZ) fixed-dose combination in hypertensive patients unresponsive to losartan 100-mg/d monotherapy.

Methods: Male and female patients aged ≥18 years with hypertension despite 4-week, stable treatment with losartan 100-mg/d monotherapy were eligible for inclusion in this multicenter, randomized, double-blind study. Patients were randomly assigned to receive AML/LOS or LOS/HCTZ once daily for 8 weeks. The primary end point was the change from baseline to week 8 in sitting diastolic blood pressure (ΔsiDBP), and the secondary end points were the changes from baseline to 4 weeks in siDBP and sitting systolic BP (ΔsiSBP) and changes from baseline to 4 and 8 weeks in BP response rate. Tolerability was evaluated by physical examination, including vital sign measurement; laboratory analysis; and ECG.

Findings: Of 275 patients screened at 9 cardiovascular centers, 199 were enrolled (AML/LOS, n = 101; LOS/HCTZ, n = 98), and 183 completed the study. The demographic characteristics were similar between the 2 groups (mean age, 51.56 [9.97] years; men, 70.53%). At 8 weeks, the mean ΔsiDBP values were –11.54 (7.89) and –9.05 (6.57) mm Hg in the AML/LOS and LOS/HCTZ groups, respectively (both, $P < 0.0001$ vs baseline). The mean difference between the 2 groups was –2.57 mm Hg, a nonsignificant difference, meaning that AML/LOS was noninferior to LOS/HCTZ with regard to the primary end point. At 8 weeks, the mean uric acid level was changed significantly from baseline in the LOS/HCTZ group (+0.41 [0.80] mg/dL; $P < 0.0001$) but not in the AML/LOS group (–0.12 [0.82] mg/dL), representing a significant intergroup difference ($P < 0.0001$). Nineteen patients each in the AML/LOS (18.81%) and LOS/HCTZ (20.00%) groups experienced ≥1 adverse event, with 4 (3.96%) and 3 (3.16%) patients, respectively, experiencing 1 or more events considered by the investigators to have been treatment related.

Implications: The efficacy and tolerability of AML/LOS 5/100 mg/d was found to have been noninferior to those of LOS/HCTZ 100/12.5 mg/d in these hypertensive patients nonresponsive to losartan 100-mg/d monotherapy. (*Clin Ther.* 2014;36:1402–1411)

Key words: amlodipine, hypertension, losartan.

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INTRODUCTION

The current European Guidelines for the Management of Hypertension acknowledge that most hypertensive patients at high risk for cardiovascular disease require a combination of antihypertensive drugs.[1] Losartan and amlodipine are frequently used as first-line therapies in hypertensive patients, and in combination, these 2 drugs have also been reported to be effective in lowering blood pressure (BP).[2–4] In general, polytherapies based on agents with different mechanisms of action have greater efficacy and tolerability and thus potentially prevent the occurrence of the cardiovascular events associated with the corresponding monotherapies. Due to the beneficial effects of renin–angiotensin system RAS blockade combined with calcium channel blockade, as reported in the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension)[5] and ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trials Blood Pressure Lowering Arm)[6] studies, this strategy has become an attractive combination therapy for patients with hypertension and cardiovascular comorbidities. Amlodipine, a dihydropyridine calcium channel blocker (CCB) with a long half-life, is effective for the treatment of hypertension and has been studied extensively in BP control and cardiovascular-outcomes studies.[6,7] Amlodipine camsylate has pharmacokinetic and pharmacodynamic characteristics similar to those of amlodipine besylate; however, this amlodipine formulation has improved drug stability due to the substitution of the camsylate salt.[8] Fixed-dose combinations (FDCs) of losartan plus amlodipine camsylate or hydrochlorothiazide have recently become available.[9,10]

The aim of the present study was to determine whether the efficacy and tolerability of the amlodipine camsylate/losartan 5/100-mg FDC are noninferior to those of the losartan/hydrochlorothiazide 100/12.5-mg FDC in hypertensive patients unresponsive to losartan 100-mg/d monotherapy.

PATIENTS AND METHODS

This 8-week, multicenter, randomized, double-blind study was conducted at 9 cardiovascular centers in the Republic of Korea. Male and female patients aged $\geq$20 years with hypertension were screened for eligibility from August 2010 to January 2013. Exclusion criteria were familial or secondary hypertension, uncontrolled diabetes (fasting glucose >200mg/dL or HbA1c > 9.0%), past history of severe cerebrovascular event (within 6 months), transient ischemic to attack (within 1 year), severe heart failure (NYHA class III, IV), previous myocardial infarction, unstable angina (within 6 months), second and third degree AV block and clinically significant cardiac valve disease and previous angioplasty or coronary artery bypass graft surgery, moderate to malignant retinopathy, kidney dysfunction with a serum creatinine level >2.0mg/dL, hyperkalemia or hypokalemia, past history of liver disease, autoimmune disease, malignancy, alcohol abuse, definite possibility of pregnancy. After a 4-week run-in period of treatment with losartan 100-mg/d monotherapy, patients nonresponsive (sitting diastolic blood pressure [siDBP], $\geq$90 mm Hg) to losartan were randomly assigned to receive treatment with the amlodipine camsylate/losartan 5/100-mg FDC tablet (AML/LOS group) or the losartan/hydrochlorothiazide 100/12.5 mg/d FDC tablet (LOS/HCTZ group), once daily for 8 weeks. Patients were followed up for 8 weeks without dose adjustment.

The study protocol was approved by the local ethics review board at each hospital.

Efficacy Assessment

The primary end point was the mean change from baseline (Δ) in siDBP after 8 weeks of treatment. The secondary end points were the mean changes in sitting systolic BP (ΔsiSBP) after 4 and 8 weeks of treatment, ΔsiDBP after 4 weeks of treatment, and the rate of *response,* defined as achieving target BP (SBP $<$140 mm Hg or DBP $<$90 mm Hg) or achieving ΔSBP or ΔDBP of $>$20 or $>$10 mm Hg, respectively.

Tolerability Assessment

The safety profile evaluation was performed on data from enrolled patients administered $\geq$1 dose of the products that had been investigated. Tolerability was evaluated as adverse events obtained from laboratory tests (including hematology, blood chemistry, and urinalysis); physical examination, including vital sign measurement; and ECG findings.

Compliance was checked and recorded at each visit after randomization. Actual doses were recorded by counting the numbers of tablets remaining. If a patient's compliance was $<$80%, the data from that