Phase IV, 8-Week, Multicenter, Randomized, Active Treatment–Controlled, Parallel Group, Efficacy, and Tolerability Study of High-Dose Candesartan Cilexetil Combined With Hydrochlorothiazide in Korean Adults With Stage II Hypertension

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ABSTRACT

Objective: The objective of this study was to evaluate the efficacy and tolerability of high-dose (32 mg) candesartan in Asians.

Methods: In Korean adult patients with stage II hypertension, we evaluated the efficacy and tolerability of candesartan 16 mg/hydrochlorothiazide (HCT) 12.5 mg and candesartan 32 mg/HCT 12.5 mg compared with candesartan 16-mg and 32-mg monotherapy, respectively. This Phase IV, 8-week, multicenter, randomized, active treatment–controlled, parallel group, efficacy, and tolerability study, named CAESAR (Candesartan Effect in Second Stage Arterial Hypertension), enrolled 253 patients with stage II hypertension. Treatment started with either candesartan 16 mg or candesartan 16 mg/HCT 12.5 mg. After 4 weeks, the candesartan dose was forced titrated to 32 mg in both groups. The primary and secondary objectives were to compare the blood pressure (BP) changes after 4 weeks and 8 weeks between candesartan-HCT combination therapy and candesartan monotherapy. The proportion of patients achieving target BP (systolic blood pressure [SBP] <140 mm Hg, but <130 mm Hg for patients with diabetes mellitus or chronic kidney disease; diastolic blood pressure (DBP) <90 mm Hg, but <80 mm Hg for those with diabetes mellitus or chronic kidney disease) after 4 and 8 weeks of therapy was also evaluated. Adverse events were investigated both by spontaneous report by the patient and by the investigators' evaluations in each visit. Laboratory tests were performed at the end of the study to evaluate drug tolerability.

Results: Study patients were all Asians, mostly male (65.7%), with a mean (SD) age of 49.4 (10.6) years and a mean body weight of 68.9 (12.1) kg; there were no between-group variances in demographic profiles except that the mean age in the candesartan-HCT group (51.0 [10.2] years) was about 3.2 years higher than that in the candesartan monotherapy group (47.8 [10.7] years; $P = 0.02$) despite random allocation. A total of 80.4% of the study patients had not been treated before, whereas 19.6% were previously treated and enrolled after 2 weeks of washout period. Baseline sitting systolic/diastolic BPs (SBP/DBP) were 160.7 (13.0)/104.6 (9.5) mm Hg. After 4 weeks, patients

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treated with candesartan 16 mg/HCT 12.5 mg showed significant decreases in SBP/DBP of 28.7 (17.5)/17.8 (10.2) mm Hg, and those in the candesartan 16 mg monotherapy group showed decreases of 20.5 (14.5)/14.1 (10.1) mm Hg ($P < 0.01$ between treatments for both SBP and DBP). After forced titration of candesartan from 16 mg to 32 mg at week 8, there was an additional reduction in SBP/DBP of 4.1 (12.7)/3.8 (8.3) mm Hg in the candesartan-HCT combination therapy group and 4.0 (11.6)/2.0 (8.5) mm Hg in the candesartan monotherapy group ($P < 0.001$ for SBP and DBP in both groups compared with values at week 4). A greater proportion of patients (70.6%) attained the target BP in the candesartan-HCT combination therapy group than in the candesartan monotherapy group (53.2%, $P = 0.014$). A total of 32 mg of candesartan was well tolerated both in combination therapy with HCT and in monotherapy. Dizziness was the most common adverse event in both groups (5 and 2 patients, respectively).

Conclusions: The candesartan-HCT combination was associated with a statistically significant lowering of BP compared with candesartan monotherapy. Clinicaltrials.gov: NCT00621153. (*Clin Ther.* 2011; 33:1043–1056)

Key words: candesartan, combination, hydrochlorothiazide, hypertension.

INTRODUCTION

Most hypertensive patients do not reach the target blood pressure (BP) when treated with a single drug.[1] Thus, initial combination therapy for hypertensive patients, with BPs of 20/10 mm Hg or higher than their treatment goals, is recommended both in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the European Society of Cardiology/European Society of Hypertension guidelines.[1,2] The combination of an angiotensin receptor blocker (ARB) and a low-dose diuretic exerts a synergistic effect not only in potentiating the efficacy but also in minimizing the side effects owing to the complementary mechanisms of action.[3]

ARBs are known to reduce BP in a dose-dependent manner without an increment in adverse effects.[4] Moreover, many reports have suggested that higher doses of ARBs exert better organ-protecting effects than its usual doses.[5,6] Among ARBs, candesartan cilexetil (candesartan) has been reported to have a more pronounced increase in its effect following cumulative dosing than losartan potassium, valsartan, or irbesartan.[7] Furthermore, the combination of the usual dose (16 mg) of candesartan with hydrochlorothiazide (HCT) 12.5 mg has been reported previously to be effective and well tolerated in hypertensive patients.[8] Although 1 previous study reported that the administration of candesartan 32 mg and HCT 25 mg in combination provided the full additive antihypertensive effects of each component,[9] the efficacy and tolerability of the high-dose (32 mg) candesartan-HCT combination compared with the usual dose (16 mg) candesartan-HCT combination remained unclear.

In this study, we assessed the efficacy and tolerability of the combinations, candesartan 16 mg/HCT 12.5 mg and candesartan 32 mg/HCT 12.5 mg, compared with those of each monotherapy (candesartan 16 mg and candesartan 32 mg) in patients with stage II hypertension.

PATIENTS AND METHODS

Patients

Male and female outpatients, aged 18 to 70 years, who were untreated or taking the maximum of 2 classes of antihypertensive drugs at the time of screening, were eligible. In addition, patients were required to have a mean sitting diastolic BP (DBP) of ≥100 mm Hg and/or a systolic BP (SBP) of ≥60 mm Hg at the time of randomization. During the 2-week washout period, no antihypertensive medication was given to the patients.

Eligibility was established based on the patient's medical history, physical examination, and laboratory examination; 12-lead electrocardiography results; blood cell counts; serum biochemistry findings; and routine urinalysis test results. Exclusion criteria included any serious disorders that could bar the patients from participating in the study, for example, significant cardiovascular diseases (angina, myocardial infarction, cerebrovascular disease, or significant arrhythmia within the preceding 6 months), uncontrolled diabetes mellitus with glycosylated hemoglobin (HbA_{1c}) >9%, azotemia with serum creatinine >3 mg/dL, hyperkalemia >5.5 mmol/L, known bilateral renal artery stenosis, significant liver disease with serum alanine aminotransferase >3-fold higher than the upper normal limit, and secondary hypertension. Women of childbearing age were required