Efficacy and Tolerability of Combination Therapy Versus Monotherapy with Candesartan and/or Amlodipine for Dose Finding in Essential Hypertension: A Phase II Multicenter, Randomized, Double-blind Clinical Trial

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ABSTRACT

Purpose: Intensive blood pressure (BP) lowering is important for the treatment of hypertension; however, it has been a challenge to achieve target BP in many patients. The purpose of this study was to explore the optimal dosage of a fixed-dose combination of candesartan cilexetil (CAN) and amlodipine besylate (AML), by examining the tolerability and efficacy of CAN/AML combination therapy compared with those of monotherapy with either drug in patients with essential hypertension.

Methods: This Phase II multicenter, randomized, double-blind clinical trial enrolled patients aged 19 years or older with essential *hypertension*, defined as a mean sitting diastolic BP (msDBP) between 95 and 115 mm Hg, and a mean sitting systolic BP (msSBP) of

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<200 mm Hg after a 2-week placebo run-in period. A total of 635 patients were screened, of whom 439 were randomized to receive treatment; 425 patients were included in the full analysis set (combination therapy, 212; monotherapy, 213). Participants were randomly assigned to receive 1 of 8 treatments: CAN (8 or 16 mg), AML (5 or 10 mg), CAN/AML (8 mg/5 mg, 8 mg/10 mg, 16 mg/5 mg, or 16 mg/10 mg), once daily for 8 weeks.

Findings: After 8 weeks of treatment, changes in msDBP were significantly greater in the groups receiving CAN/AML combination therapies compared with monotherapies at matched doses, with the exception of CAN 8 mg/AML 10 mg versus AML 10 mg. The response to treatment and the achievement of target BP (both msSBP and msDBP) at week 8 were significantly greater overall in the groups that received combination therapy versus monotherapy. All medications were relatively well tolerated in each group.

Implications: Eight-week administration of CAN/AML (8 mg/5 mg, 16 mg/5 mg, and 16 mg/10 mg) resulted in a significantly greater BP reduction than that with CAN or AML monotherapy, and was determined to be well tolerated. ClinicalTrials.gov identifier: NCT02944734. (*Clin Ther*. 2017;39:1628–1638) © 2017 Published by Elsevier HS Journals, Inc.

Key words: amlodipine, candesartan, combination, hypertension.

INTRODUCTION

Hypertension is the leading risk factor for cardiovascular disease and mortality worldwide.[1] On the basis of recent meta-analyses, major cardiovascular events and mortality have been significantly reduced by antihypertensive treatment.[2,3] However, achieving long-term success in hypertension control has been challenging. Most patients with hypertension need >1 antihypertensive drug to achieve target blood pressure (BP), but almost half of patients discontinue treatment, leading to poor BP control.[4,5] Recently published guidelines and meta-analyses recommend the use of single-pill combinations of 2 or 3 BP-lowering drugs at fixed doses, known as a fixed-dose combination, which reduces pill burden and thereby is expected to improve adherence and BP control with minimal adverse events.[4,6–8]

The antihypertensive drug amlodipine besylate (AML), a dihydropyridine calcium channel blocker, is highly efficacious in the reduction of BP. There is a substantial body of evidence that AML treatment results in better cardiovascular outcomes and BP control as a single or combination therapy compared with other classes of antihypertensive drugs.[9–13]

Candesartan cilexetil (CAN), a selective angiotensin II type 1 receptor blocker, is also an effective antihypertensive agent with a good tolerability profile and pleiotropic effects against cardiovascular morbidities.[14–17] An antihypertensive fixed-dose tablet combination of CAN and AML has been used as an effective first-line therapy in patients with mild to moderate hypertension. The purpose of this study was to establish the optimal dose of the CAN/AML combination by comparing the tolerability and efficacy of combination therapies to those of monotherapies in patients with essential hypertension in Korea (ClinicalTrials.gov Identifier: NCT02944734).

PATIENTS AND METHODS

Patients and Study Design

Male and female patients aged 19 years or older who were newly diagnosed with essential hypertension and/or had undergone antihypertensive treatment were screened. Patients with a mean sitting systolic BP (msSBP) of ≥200 mm Hg or a mean sitting diastolic BP (msDBP) of ≥115 mm Hg measured at screening, and those with a minimum–maximum difference in sitting SBP of ≥20 mm Hg or in sitting DBP of ≥10 mm Hg after 3 measurements in a chosen arm were excluded. Patients were also excluded if they had any of the following criteria: symptomatic orthostatic hypotension; a history of secondary hypertension or any disease that may induce secondary hypertension; severe symptomatic heart failure; acute coronary syndrome or significant peripheral arterial occlusive disease within 6 months before screening; clinically significant arrhythmias; type 1 diabetes or uncontrolled type 2 diabetes mellitus (hemoglobin A_{1c}, >9.0%); hemodynamically significant valvular heart disease; severe cerebrovascular disorder within 6 months before screening; severe eye disease; autoimmune or chronic inflammatory disease requiring continuous anti-inflammatory treatment; liver failure; chronic kidney disease with a creatinine clearance of <30 mL/min by Cockcroft-Gault equation; hypokalemia (serum potassium, <3.5 mmol/L) or