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Efficacy and Tolerability of Telmisartan/Amlodipine + Hydrochlorothiazide Versus Telmisartan/Amlodipine Combination Therapy for Essential Hypertension Uncontrolled With Telmisartan/Amlodipine: The Phase III, Multicenter, Randomized, Double-Blind TAHYTI Study

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ABSTRACT

Purpose: This 8-week study in Korea aimed to evaluate the efficacy and tolerability of a telmisartan/amlodipine + hydrochlorothiazide (TAH) combination versus telmisartan/amlodipine (TA) combination in patients with essential hypertension that did

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not respond appropriately to 4-week treatment with TA.

Methods: All patients who met the inclusion criteria received TA (40/5 mg) during a 4-week run-in period (period 1). Patients who met the criteria for essential hypertension (mean sitting systolic blood pressure [MSSBP], ≥140 and <200 mm Hg, or ≥130 and<200 mm Hg in those with diabetes mellitus or chronic kidney disease) after period 1 were randomly assigned to receive TA 40/5 mg + hydrochlorothiazide 12.5 mg (test group) or TA only (control group). The test and control drugs were administered in each group for 2 weeks (period 2). Patients who completed period 2 underwent 6-week treatment (period 3) with a TAH and TA dose twice that in period 2. The primary end point was the change in MSSBP at week 8 of treatment. Secondary end points were the change in MSSBP at week 2 and MS diastolic BP, BP control rate, and BP response rate at weeks 2 and 8. Treatment tolerability was assessed based on adverse events (AEs), laboratory evaluations (chemistry, hematology, and urinalysis), 12-lead ECG, and physical examination including vital sign measurements.

Findings: We randomized 310 patients to the treatment groups. The mean (SD) ages of the TAH and TA groups were 62.0 (10.8) and 63.4 (10.4) years, respectively. The least squares mean change in MSSBP was significantly greater in the TAH group than in the TA group after 8 weeks (–18.7 vs –12.2 mm Hg; $P < 0.001$). Similar results were obtained on changes in MSSBP after 2 weeks and changes in sitting diastolic BP, BP control rate, and BP response rate at weeks 2 and 8 compared with the respective baseline values. The prevalences of treatment-emergent AEs (29.0% vs 16.3%; $P = 0.008$) and adverse drug reactions (20.0% vs 10.5%; $P = 0.020$) were significantly greater in the TAH group than in the TA group. Most treatment-emergent AEs were mild or moderate; none were severe. The most frequently reported AEs were dizziness and headache.

Implication: TAH triple therapy was more effective than was TA double therapy in reducing BP in these patients in Korea with essential hypertension that did not adequately respond to TA. ClinicalTrials.gov identifier: NCT02738632. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮)

Key words: amlodipine, blood pressure control, hydrochlorothiazide, hypertension, telmisartan, triple combination.

INTRODUCTION

According to the Korean National Health and Nutrition Examination Survey (KNHANES), the prevalence of hypertension in adults aged >30 years was 27.9% (men, 32.7%; women, 23.1%) in 2015. Hypertension is closely related to cerebrovascular and cardiovascular diseases, which are the most frequent causes of death among adults; thus, the prevention and management of hypertension greatly impact public health.[1,2]

Blood pressure (BP) management and the treatment of hypertension and can significantly reduce the risk for cardiovascular disease.[3,4] It has been suggested that, in hypertensive patients, the BP-lowering effect of combination therapy is greater than that of a dose increase in monotherapy.[5,6] The use of a combination of various antihypertensive agents has been shown to have significantly positive effects on BP control and the prevention of cardiovascular events in hypertensive patients.[5,6]

According to the 8th Joint National Committee's guideline on hypertension,[7] "In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes (thiazide-type diuretic, CCB, ACEI, or ARB)."[7] The European Society of Cardiology recommends initiating a low-dose combination therapy prior to single-dose treatments of hypertension.[8] Additionally, the guideline from the British Hypertension Society and the National Clinical Guideline Center recommends 3-drug combinations of an ACEI or ARB, a calcium antagonist, and a thiazide diuretic in cases in which a 2-drug combination does not yield effective BP control.[9,10]

DM and chronic kidney disease (CKD) are important causes of cardiovascular disease owing to their associations with hypertension, and because BP control is often difficult in practice, combination therapy might be useful in patients with these conditions.