Brief Report

Comparison of Fixed-Dose Combinations of Telmisartan/Hydrochlorothiazide 40/12.5 mg and 80/12.5 mg and a Fixed-Dose Combination of Losartan/Hydrochlorothiazide 50/12.5 mg in Mild to Moderate Essential Hypertension: Pooled Analysis of Two Multicenter, Prospective, Randomized, Open-Label, Blinded–End Point (PROBE) Trials

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ABSTRACT

Background: High incidences of cardiovascular events coincide with a surge in blood pressure (BP) that occurs in the early morning hours at the time of arousal. Thus, control of BP at this time of day, using oral fixed-dose combinations (FDCs) as required, is important in reducing cardiovascular risk in hypertensive patients.

Objective: The aim of this analysis was to compare the antihypertensive efficacy in the early morning hours and tolerability of oral FDCs of telmisartan/hydrochlorothiazide (HCTZ) (40/12.5 mg [T40/H12.5] and 80/12.5 mg [T80/H12.5]) versus a low-dose FDC of losartan 50 mg/HCTZ 12.5 mg (L50/H12.5).

Methods: Data from 2 similarly designed prospective, randomized, open-label, blinded–end point (PROBE) studies were pooled and analyzed. The studies were conducted at 72 centers across the United States, and 70 centers in Canada, Europe (9 countries), and the Philippines. Adult male and female patients with mild to moderate essential hypertension (24-hour mean ambulatory diastolic BP [DBP], ≥85 mm Hg; seated cuff DBP, 90–109 mm Hg) were enrolled. Patients were randomly assigned to receive T40/H12.5, L50/H12.5, or T80/H12.5, QD (morning) for 6 weeks. Antihypertensive efficacy was assessed using 24-hour ambulatory BP monitoring (ABPM) and cuff sphygmomanometry at trough, performed at baseline and on completion of active treatment. The primary end point was the reduction from baseline in mean ambulatory DBP over the last 6 hours of the dosing interval. Secondary end points included other ABPM- and clinic-derived changes in DBP and systolic BP (SBP), and control and response rates (*SBP response* defined as 24-hour mean SBP <130 mm Hg and/or reduction from baseline ≥10 mm Hg; *DBP response* defined as 24-hour mean DBP <85 mm Hg or reduction from baseline ≥10 mm Hg; *DBP control* defined as 24-hour mean DBP <85 mm Hg). Tolerability was assessed using patient interview, spontaneous reporting, and clinical evaluation.

Results: A total of 1402 patients were enrolled (876 men, 525 women; mean [SD] age, 53.1 [9.9] years) (T40/H12.5, n = 517; L50/H12.5, n = 518; and T80/H12.5, n = 367). With T40/H12.5, the mean reduction in last-6-hour mean ambulatory DBP was 1.8 mm Hg greater compared with that achieved with L50/H12.5 (–11.3 [0.4] vs –9.4 [0.4] mm Hg; $P < 0.001$), and with T80/H12.5, the mean reduction was 2.6 mm Hg greater compared with that achieved with L50/H12.5 (–12.0 [0.4] vs –9.4 [0.4] mm Hg; $P < 0.001$). Analysis of secondary end points found that greater BP reduction occurred with T40/H12.5 and T80/H12.5 com-

Accepted for publication August 30, 2005.
doi:10.1016/j.clinthera.2005.11.014
0149-2918/05/$19.00

pared with L50/H12.5. ABPM SBP control and response rates were similar between the 3 groups, but the ABPM DBP control and response rates were significantly higher with T80/H12.5 compared with L50/H12.5 (46.6% vs 34.0% [$P < 0.002$] and 69.4% vs 55.0% [$P < 0.001$], respectively). Clinic SBP and DBP control and response rates were higher with T40/H12.5 and T80/H12.5 compared with L50/H12.5 (SBP response, 80.4% and 80.8% vs 68.5% [both, $P < 0.001$]; DBP response, 66.1% and 67.4% vs 54.4% [both, $P < 0.001$]; DBP control, 56.5% and 56.4% vs 44.1% [both, $P < 0.001$]). The 2 most commonly recorded adverse events (AEs) were headache (T40/H12.5, 2.9%; L50/H12.5, 3.3%; and T80/H12.5, 3.0%) and dizziness (1.2%, 2.1%, and 3.0%, respectively). Most AEs were mild to moderate.

Conclusions: The results of this pooled analysis of 2 PROBE studies in adult patients with mild to moderate essential hypertension suggest that T40/H12.5 and T80/H12.5 conferred greater DBP and SBP control compared with low-dose L50/H12.5, including during the last 6 hours of the dosing interval. All 3 treatments were well tolerated. (*Clin Ther.* 2005;27:1795–1805)

Key words: hypertension, angiotensin II receptor blockade, telmisartan, losartan, hydrochlorothiazide, fixed-dose combination, ambulatory blood pressure monitoring.

INTRODUCTION

Hypertension remains a public health challenge, with prevalences of 26.6% in men and 26.1% in women in developed countries.[1] Data from the National Health and Nutrition Survey (NHNS)[2] showed that from 1999 to 2000, only 34% of adult patients treated with antihypertensives achieved the target blood pressure (BP) values recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (<140/<90 mm Hg).[3] The situation is worse in developing countries.[2] Although poor treatment compliance is assumed to explain inadequate control of BP, convincing empiric evidence to support this hypothesis is lacking.[4] A recently published systematic review of the literature found that studies of the association between achieved BP and compliance found inconsistent results.[4] Studies have found no evidence of a trend in compliance in patients categorized according to BP.[4] However, some studies have found evidence of improved BP control in patients categorized according to compliance.[4] The 34% response rate reported in the NHNS[2] might suggest that a large proportion of individuals diagnosed with hypertension are inadequately treated. Most patients require a combination of 2 or more antihypertensive agents to achieve target BP.[5,6] Persistently elevated BP (systolic BP [SBP]/diastolic BP [DBP] >140/>90 mm Hg) results in an enhanced risk for cardiovascular events.[5,6] Thus, ineffectively treated patients might face a risk for cardiovascular disease (CVD), a consequent decline in quality of life, and a risk for premature death.[7]

Evidence from cross-sectional[8] and longitudinal[9] studies suggests that 24-hour mean ambulatory BP predicts cardiovascular risk and end-organ damage more accurately compared with clinic values. Ambulatory BP measurement provides a way of monitoring the circadian changes in BP, which in ~65% of individuals is characterized by a reduction in BP at night and a sudden increase in the early morning at the time of arousal.[10] A large volume of circumstantial evidence suggests that the early morning surge in BP is associated with an elevated incidence of acute cardiovascular events.[9] Convincing evidence for the relationship between the early morning BP surge and asymptomatic cerebrovascular events such as stroke has been provided by Kario et al,[11] who observed that elderly (mean age, 72 years) Japanese hypertensive patients with the greatest early morning surge (≥55 mm Hg) experienced a 2.6-fold higher number of such events compared with other patients. These findings support the hypothesis that control of the rapid increase in BP during the early morning hours could be an important goal in managing hypertensive patients, particularly in the prevention of target-organ damage and subsequent cardiovascular events.

Outcomes studies have found that effective antihypertensive treatment reduces cardiovascular morbidity and mortality. For example, for a 12–mm Hg reduction, the number of patients with grade 1 hypertension (SBP/DBP 140–149/90–99 mm Hg) needed to treat ranged from 20 for patients with no other risk factors to 9 for patients with diabetes mellitus (DM), clinically manifest CVD, and/or target organ damage.[12] The mechanism of action of the antihypertensive agent may be particularly important, with two thirds of patients needing multiple agents targeting differing pressor mechanisms to achieve target BP.[13]