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A Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and the Tolerability of a Triple Combination of Amlodipine/Losartan/Rosuvastatin in Patients With Comorbid Essential Hypertension and Hyperlipidemia

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ABSTRACT

Purpose: The objective of this study was to evaluate the efficacy and tolerability of a triple combination of amlodipine/losartan/rosuvastatin in patients with hypertension and hypercholesterolemia.

Methods: A randomized, multicenter, double-blind, placebo-controlled study was conducted. Eligible patients with hypertension and a sitting diastolic blood pressure (SiDBP) of >90 mm Hg and LDL-C levels <250 mg/dL were screened. After a 4-week run-in period with therapeutic lifestyle changes and losartan potassium 100 mg once daily, patients who met both blood pressure criteria (80 mm Hg ≤ SiDBP < 110 mm Hg) and the LDL-C level criteria (defined in the National Cholesterol Education Program Adult Treatment Panel III cardiovascular risk categories) were randomized to 1 of 3 groups and treated once daily

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for 8 weeks: losartan potassium 100 mg + rosuvastatin 20 mg treatment (L/R 100/20) group, amlodipine camsylate 5 mg + losartan potassium 100 mg treatment (A/L 5/100) group, and amlodipine 5 mg + losartan potassium 100 mg + rosuvastatin 20 mg (A/L/R 5/100/20) group. The primary efficacy variables were the percent change in LDL-C in the A/L/R 5/100/20 and A/L 5/100 groups and the mean change of SiDBP in the A/L/R 5/100/20 and L/R 100/20 groups after 8 weeks of treatment, relative to baseline values.

Findings: A total of 146 patients were enrolled and the demographic characteristics were similar among the 3 treatment groups. After 8 weeks of treatment, the mean (SD) percent change in LDL-C was significantly greater in the A/L/R group than in the A/L group (–48.40% [2.77%] vs –6.70% [3.00%]; $P < 0.0001$). Moreover, the mean change in SiDBP was significantly greater in the A/L/R group than in the L/R group (–9.75 [0.92] mm Hg vs –1.73 [1.03] mm Hg; $P < 0.0001$). SiDBP and LDL-C reductions in the A/L/R group were comparable to reductions in the A/L and L/R groups, respectively. Ten adverse events were reported in 7 patients (4.83%), and 1 patient from the A/L group (0.69%) experienced 2 adverse drug reactions (tachycardia and face edema), which were mild and resolved without specific treatment. There were no clinically significant tolerability issues during the treatment period.

Implications: Triple combination therapy with amlodipine/losartan/rosuvastatin can be an effective therapeutic strategy in patients with hypertension combined with dyslipidemia. These findings will form the foundation of the future development of a single-pill triple combination. ClinicalTrials.gov identifier: NCT02899455. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮)

Key words: angiotensin receptor blocker, calcium channel blocker, HMG-CoA reductase inhibitor, hypercholesterolemia, hypertension.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, resulting in a growing interest in associated issues, such as a decline in productivity and elevated medical costs, as well as in CVD risk factors, prevention, and treatment.[1] Hypertension and dyslipidemia are 2 of the most important risk factors for the development of CVD.[1–3] Furthermore, hypertension and dyslipidemia act synergistically to accelerate CVD progression,[4] and more than one half of patients with hypertension have dyslipidemia.[5,6] Many studies have also shown a positive correlation between blood cholesterol levels and CVD; thus, a reduction in cholesterol levels can significantly reduce the CVD risk.[7] Therefore, the goal of hypertension management is no longer blood pressure (BP) control alone but attenuation of overall CVD risk.[5,8]

In a majority of the hypertensive population, a combination of at least 2 drugs is required to achieve BP control.[9] Single-pill combination (SPC) therapy, in which ≥2 drugs are combined into a single dosage form, is an emerging concept aimed at ensuring adherence to the drug regimen by reducing the patients' "pill burden."[10] The safety and effectiveness of SPC, as well as consequent improvements in patient compliance, have already been demonstrated.[11] Among antihypertensive drug combinations, combinations of renin-aldosterone system inhibitors and calcium antagonists are the preferred treatment regimens because these 2 drug classes have complementary mechanisms of action, which reduce side effects.[12,13] In addition, a combination of angiotensin receptor blockers and statins has been shown to decrease oxidative stress, possibly through associated antioxidant activity.[14]

To establish the basis for the development of an SPC containing amlodipine, losartan, and rosuvastatin, the present clinical trial was designed to assess the efficacy and the tolerability of these 3 drugs in patients with hypertension and dyslipidemia whose BP was not adequately controlled with a single agent and who consequently needed an additional antihypertensive medication with a different mechanism. The aim of the study was to determine whether amlodipine/losartan/rosuvastatin therapy is superior to an amlodipine/losartan combination in treating dyslipidemia and superior to a losartan/rosuvastatin combination in treating hypertension, and to confirm the tolerability of this triple combination in patients with hypertension and dyslipidemia.

PATIENTS AND METHODS

Study Population

Eligible participants were male or non-childbearing female patients aged 19 to 75 years, with hypertension