Original Research

Blood Pressure and Cholesterol-lowering Efficacy of a Fixed-dose Combination With Irbesartan and Atorvastatin in Patients With Hypertension and Hypercholesterolemia: A Randomized, Double-blind, Factorial, Multicenter Phase III Study

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ABSTRACT

Purpose: A fixed-dose combination of a stain and an antihypertensive drug may be useful for the treatment of patients with hypertension and hyperlipidemia. It may also improve patient drug compliance to help control risk factors of cardiovascular disease. This study was designed to evaluate the blood pressure–lowering and cholesterol-lowering effect of a fixed-dose

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combination of irbesartan-atorvastatin compared with monotherapy by either agent over an 8-week treatment period.

Methods: Patients with comorbid hypertension and hypercholesterolemia were screened for this randomized, double-blind, Phase III study. Eligible study patients were randomly assigned to test groups receiving a combination of irbesartan 300 mg and atorvastatin 40 mg or 80 mg (IRB300 + ATO40 and IRB300 + ATO80). Comparator groups comprised monotherapy groups with irbesartan 300 mg (IRB300) or atorvastatin 40 mg (ATO40) or atorvastatin 80 mg (ATO80), or placebo. Patients who were eligible at screening were subjected to a 4- to 6-week washout period before commencing 8 weeks of therapy per their assigned group. The primary efficacy end points were percent change in LDL-C and sitting diastolic blood pressure (DBP) levels from baseline to end of therapy. Tolerability profiles of combination therapy were compared with other groups.

Findings: A total of 733 patients with comorbid hypertension and hypercholesterolemia were screened for this study; 230 eligible patients were randomized to treatment. The mean age of patients was 58.9 (8.5) years, and their mean body mass index was 25.8 (3.2) kg/m^2. More than two thirds (70.9%) of the study patients were male. Mean LDL-C and sitting DBP levels at baseline were 149.54 (29.19) mg/dL and 92.32 (6.03) mm Hg, respectively. Percent reductions in LDL-C after 8 weeks were 46.74% (2.06%) in the IRB300 + ATO40 group and 48.98% (2.12%) in the IRB300 + ATO80 group; these values were 47.13% (3.21%) and 48.30% (2.98%) in the ATO40 and ATO80 comparator groups. Similarly, a reduction in sitting DBP after 8 weeks was −8.50 (1.06) mm Hg in the IRB300 + ATO40 group and 10.66 (1.08) mm Hg in the IRB300 + ATO80 group compared with 8.40 (1.65) mm Hg in the IRB300 group. The incidence rate for treatment-emergent adverse events was 22.27% and was similar between the monotherapy and combination groups.

Implications: A once-daily combination product of irbesartan and atorvastatin provided an effective, safe, and more compliable treatment for patients with coexisting hypertension and hyperlipidemia. ClinicalTrials.gov identifier: NCT01442987. (*Clin Ther.* 2016;38:2171–2184)

Key words: atorvastatin, combination, hyperlipidemia, hypertension, irbesartan.

INTRODUCTION

Hypertension and hyperlipidemia are 2 of the most important risk factors in the development of cardiovascular disease, and they often coexist.[1–3] These risk factors act synergistically in disease progression, and results from the Framingham Heart Study showed that even a moderate increase in blood pressure (BP) and cholesterol dysregulation has as much of a 10-year congestive heart disease risk as marked elevation of either factor alone.[4] Recent guidelines for the management of hypertension and hyperlipidemia, as recommended by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure 2014 (JNC VIII)[5] and the American College of Cardiology/American Heart Association 2013 blood cholesterol guideline,[6] respectively, emphasize the overall assessment of BP and serum lipid levels in evaluating cardiovascular risk rather than assessment of each risk factor individually.[7]

Presently, the drugs with a preferred mechanism of cardiovascular protection for antihypertensive therapy are those that inhibit the renin-angiotensin system (RAS).[8] Two classes of the drugs (the angiotensin-converting enzyme [ACE] inhibitors and the angiotensin II receptor blockers [ARBs]) have been discovered to have RAS inhibitory activity, albeit by different mechanisms. Although ACE inhibitors hinder the production of angiotensin II through the inhibition of ACE, ARBs prevent the interaction of angiotensin II with its receptor (AT_1), which subsequently prevents aldosterone secretion. However, ACE inhibitors may also lead to the production of certain immunomodulatory peptides such as bradykinin and substance P, which can result in dry cough and angioedema. In contrast, ARBs, owing to their specificity for AT_1, provide sufficient BP lowering without these side effects.[9–11]

Many studies have shown a positive correlation between blood cholesterol levels and cardiovascular disease, and thus a reduction in cholesterol levels can significantly reduce the risk.[12,13] Drugs belonging to the hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are the most commonly prescribed antihyperlipidemic agents. They act by inhibiting the formation of mevalonate, the rate-limiting step in the biosynthesis of cholesterol. Moreover, statins such as atorvastatin also increase LDL receptors on hepatocytes, thereby enhancing its uptake from blood. The latest, more potent statins such as atorvastatin can also