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Research Article

Comparison of the effects of aliskiren/valsartan in combination versus valsartan alone in patients with Stage 2 hypertension

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Abstract

The extent to which the combination of a renin inhibitor with an angiotensin receptor blocker (ARB) lowers clinic and ambulatory blood pressure (BP) versus an ARB alone in stage 2 hypertension is not well known. Hence, we performed an 8-week, randomized, double-blind study in 451 patients with stage 2 hypertension to compare the efficacy of the combination of aliskiren/valsartan 300/320 mg versus valsartan 320 mg. The primary endpoint was change in seated systolic BP from baseline to week 8 analyzed on the intent-to-treat (ITT) population using the last-observation-carried-forward (LOCF) approach; patients completing the entire treatment period (per-protocol completers) were similarly analyzed. For the predefined primary analysis, systolic BP reductions for aliskiren/valsartan (n = 230) and valsartan (n = 217) were −22.1 and −20.5 mm Hg, respectively ($P = .295$). In per-protocol completers, aliskiren/valsartan (n = 201) lowered BP significantly greater than valsartan (n = 196); −23.7 mm Hg versus −20.3 mm Hg, respectively ($P = .028$). Although limited by a small sample size (n = 76) using ambulatory BP monitoring, aliskiren/valsartan lowered the 24-hour BP significantly more than valsartan alone (−14.6/−9.0 mm Hg versus −5.9/−4.2 mm Hg; $P < .01$). Safety and tolerability were similar for the two treatment groups. These data demonstrate the importance of multiple modalities to assess BP changes in clinical trials of antihypertensive therapies, particularly in stage 2 hypertension. J Am Soc Hypertens 2012;6(2):142–151.

Keywords: Aliskiren; valsartan; combination therapy; ambulatory blood pressure; stage 2 hypertension.

Introduction

Dual blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) has been used for years in hypertension care despite the absence of long-term clinical outcomes data. The incremental blood pressure (BP) lowering seen with the combination of an ACE inhibitor and an ARB is only modestly greater than with

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monotherapy with either drug class.[1–3] Combined use of ACE inhibitors and ARBs,[4–6] as well as the direct renin inhibitor, aliskiren, in combination with ARBs,[7,8] has been shown to incrementally lessen proteinuria in patients with proteinuric chronic kidney disease (CKD) and continues to be a rationale for selected patients to receive these drugs as combination therapy.

Aliskiren, a direct renin inhibitor, lowers BP to a similar or greater extent than other inhibitors of the RAS.[9,10] Safety analyses conducted in more than 12,000 patients from controlled clinical trials of aliskiren showed a tolerability profile similar to those of ARBs (and placebo) and superior to ACE inhibitors.[11,12] There is a logical rationale for combining an AT1 receptor antagonist and a direct renin inhibitor. The RAS plays a substantive role in BP regulation and target-organ injury. However, blockade of the RAS is incomplete with AT1 receptor blockade (reactive hyperreninemia). The addition of a direct renin inhibitor to an ARB can confer more complete blockade of the RAS accounting for incremental BP reduction as well as the potential for greater target-organ protection. A previous trial of aliskiren in combination with the ARB, valsartan in stage 1 to 2 hypertensive patients showed superior clinic BP reductions compared with each agent alone.[13] In the present study, we compared the antihypertensive efficacy and general safety of the combination of aliskiren/valsartan compared with valsartan alone in patients with stage 2 hypertension. Furthermore, recent findings of potential disparities in antihypertensive efficacy based on ambulatory versus clinic BP[14] highlights the importance of assessing treatment efficacy using both clinic and ambulatory BP monitoring. In our study, we also analyzed results of ambulatory BP recordings in a subset of the stage 2 patient population.

Methods

Patients

Eligible patients were men and women ≥18 years of age with stage 2 systolic hypertension defined as mean sitting systolic BP ≥160 mm Hg and <180 mm Hg at randomization. Key exclusion criteria included; systolic BP ≥180 mm Hg and/or mean sitting diastolic BP ≥110 mm Hg; treatment with three or more antihypertensive agents; evidence or a history of secondary hypertension or resistant hypertension (BP >140/90 mm Hg despite optimal-dose triple-drug therapy including a diuretic); poorly controlled type 1 or type 2 diabetes (defined as fasting glycosylated hemoglobin >9.0 % at screening visit); and history of cerebrovascular accident, transient ischemic attack, hypertensive encephalopathy, heart failure (New York Heart Association Class II to IV), myocardial infarction, unstable angina pectoris, coronary bypass graft surgery, or percutaneous coronary intervention within the past 12 months, and the use of aliskiren or participation in an aliskiren clinical trial within 30 days of screening. Other exclusion criteria included a serum sodium level <135 mEq/L and serum potassium level <3.5 mEq/L or ≥5.3 mEq/L. Premenopausal women who were pregnant, nursing, or not using an effective form of contraception were also excluded. Additional exclusion criteria specific for patients participating in the ambulatory blood pressure measures (ABPM) substudy were arm circumference >42 cm, night shift workers, and sleep apnea.

This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board at each site. All participants provided written informed consent.

Study Design and Procedures

This was an 8-week, prospective, multicenter, randomized, double-blind, double-dummy, active-control, parallel-group study (Figure 1) conducted at 72 centers in the United States in 2009 (Clinical trials.gov NCT00809926). After a 1- to 4-week washout period, eligible patients were randomized to receive either a daily combination of aliskiren/valsartan 150/160 mg or valsartan monotherapy 160 mg for 2 weeks followed by forced titration to aliskiren/valsartan 300/320 mg or valsartan 320 mg for the remaining 6 weeks.

An ABPM substudy was performed at 29 of the 72 sites. After the washout period, patients meeting the eligibility criteria and willing to participate in the ABPM study had an ambulatory BP (ABP) recording (Spacelabs, Inc, Issaquah, WA) the day before randomization. On the day of randomization, if ABPM was successful, they were randomized into the substudy. If ABPM study was unsuccessful, randomization was postponed and the ABPM device was reapplied within 48 hours. After two unsuccessful attempts of ABP measurement, the patient was discontinued from participation in the ABPM substudy but was allowed to continue in the study using clinic BP measurements. Hence, ABPM recordings were performed at the end of study only in those patients with a successful baseline ABP measure.

Study drug was supplied as valsartan (160 mg) capsules or matching placebo capsules and aliskiren (150 mg) tablets or matching placebo tablets. Patients were instructed to take each dose of the medication with water in the morning between 7:00 AM and 10:00 AM. On the day of the clinic visit, study medication was administered at the clinic after completion of procedures. To adequately blind the study, patients were required to take a total of two tablets and two capsules of study medication per day. Patients were closely monitored throughout the study and those experiencing office SBP ≥200 mm Hg or office DBP ≥110 mm Hg at any time during the study were permanently discontinued from the study. Patients with signs or symptoms of hypotension (defined as seated BP <100/60 mm Hg) at any time during the study were evaluated by the