Journal of the American Society of Hypertension 5(6) (2011) 489–497

Research Article

Comparative efficacy and safety of combination aliskiren/amlodipine and amlodipine monotherapy in African Americans with stage 2 hypertension and obesity or metabolic syndrome

Myron H. Weinberger, MD[a,*], Joseph L. Izzo Jr., MD[b], Das Purkayastha, PhD[c], Richard Weitzman, MD[c], and Henry R. Black, MD, FASH[d]

[a]*Indiana University Medical Center, Indianapolis, IN;*
[b]*State University of New York at Buffalo, New York, NY;*
[c]*Novartis Pharmaceuticals Corporation, East Hanover, NJ; and*
[d]*New York University School of Medicine, New York, NY*

Manuscript received June 29, 2011 and accepted August 9, 2011

Abstract

The renin-angiotensin system (RAS) is a common link between hypertension and comorbidities of obesity and metabolic syndrome (MetS). We evaluated the antihypertensive efficacy and safety of the combination direct renin inhibitor, aliskiren, with amlodipine versus amlodipine alone in self-identified African Americans with stage 2 hypertension in a subgroup of patients with obesity or MetS participating in the Aliskiren Amlodipine Combination in African AmEricans with Stage 2 HypertenSion (AACESS) trial. Subjects, newly diagnosed and treatment naive or taking three or fewer antihypertensive drugs with a mean sitting systolic blood pressure (msSBP) of 160–199 mm Hg were randomized to receive aliskiren/amlodipine 150/5 mg or amlodipine 5 mg for 1 week; force-titrated to aliskiren/amlodipine 300/10 mg or amlodipine 10 mg, for an additional 7 weeks. Overall, 292 obese (body mass index $\geq$30 kg/m^2) and 197 MetS subjects had baseline msSBP ranging from 167.0 to 167.5 mm Hg. Least-square mean reductions from baseline to 8 weeks in msSBP, the primary efficacy variable, were significantly higher with aliskiren/amlodipine than with amlodipine in both obese (−33.7 mm Hg vs. −27.9 mm Hg; $P < .001$) and MetS subjects (−36.4 mm Hg vs. −28.5 mm Hg; $P < .001$). Both treatments were well tolerated. Aliskiren/amlodipine 300/10 mg is more effective than amlodipine 10 mg in African Americans with stage 2 hypertension and obesity or MetS. J Am Soc Hypertens 2011;5(6):489–497.

Keywords: Direct renin inhibitor; calcium channel blocker; blood pressure; adverse events.

Both the study and the editorial assistance with the manuscript were supported by Novartis Pharmaceuticals Corporation. Drs. Weinberger, Izzo, and Black provided detailed verbal discussion and interpretation of the study data during the Publication Steering Committee meeting held in November 2009. Myron H. Weinberger has served on advisory boards and/or speakers bureaus for Daiichi-Sankyo, Forest, Merck, Novartis Pharmaceuticals Corporation and Takeda. Joseph L. Izzo has served as a consultant for Boehringer-Ingelheim, NicOx, Novartis Pharmaceuticals Corporation, Daiichi-Sankyo, and Takeda, and has received grant support from GlaxoSmithKline and Novartis Pharmaceuticals Corporation. Das Purkayastha and Richard Weitzman are employees of Novartis Pharmaceuticals Corporation. Henry R. Black has served as a consultant for Novartis Pharmaceuticals Corporation, Daiichi-Sankyo, Xoma, MSD, Boehringer-Ingelheim, Biosante, Servier, Johnson & Johnson, NicOx, Mitsubishi, BMS, Valeant, Arena, and Orexigen and has received grant support from Novartis Pharmaceuticals Corporation and AHRQ.

The data included in this manuscript were previously presented, in part, as a poster/abstract at the 25th Annual Scientific Meeting and Exposition of the American Society of Hypertension, New York, NY, May 1–4, 2010. Weinberger M, Izzo J, Purkayastha D, et al. Combination aliskiren/amlodipine provides greater blood pressure reduction than amlodipine monotherapy in African American subjects with stage 2 hypertension and obesity or metabolic syndrome. J Clin Hypertens. 2010;12(suppl 1):A45. Abstract PO-64.

ClinicalTrials.gov Identifier: NCT00853957.

*Corresponding author: Myron H. Weinberger, MD, Indiana University Medical Center, 135 Bow Lane, Indianapolis, IN 46220. Tel: (317) 253-7927; fax: (317) 274-7700.

E-mail: mweinbe@iupui.edu

1933-1711/$ - see front matter
doi:10.1016/j.jash.2011.08.005

Introduction

In the United States, the prevalence of hypertension in African Americans has remained at approximately 40% over the past decade compared with rates <30% in Caucasians and Hispanics.[1] Hypertension is more severe, develops at an earlier age, and leads to more target organ damage in African Americans than in Caucasians.[2] Moreover, hypertension in African Americans is often accompanied by obesity and/or metabolic syndrome (MetS),[3] which further increases cardiovascular (CV) risk in this population. Blood pressure (BP) goals are more difficult to achieve in subjects with these comorbidities versus those without them, with most individuals requiring a combination of antihypertensive agents.[4]

The updated International Society on Hypertension in Blacks (ISHIB) consensus statement recommends two-drug therapy when systolic BP (SBP) is >15 mm Hg and/or diastolic BP (DBP) is >10 mm Hg above goal (<135/85 mm Hg for primary prevention, <130/80 mm Hg for secondary prevention).[5] Primary prevention is applicable for subjects who have no target-organ damage, no history of CV disease, and no CV risk factors (specifically, MetS, Framingham risk score >20%, prediabetes, or diabetes mellitus [DM]), whereas secondary prevention is applicable for subjects with any of these characteristics. The statement further recommends use of a renin-angiotensin system (RAS) inhibitor plus either calcium channel blocker (CCB) or thiazide diuretic as the preferred initial combinations, the latter in edematous and/or volume overload states. The recommendation for RAS-based therapy stems from the wealth of clinical experience with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Direct renin inhibitors (DRIs) are the newest antihypertensive class to be indicated for the treatment of hypertension. Aliskiren, the first agent in this class, reduces plasma renin activity (PRA), unlike ACE inhibitors and ARBs, which increase PRA and thereby plasma levels of angiotensin I and angiotensin II.[6] This agent provides safe and effective BP lowering when administered alone or in combination with other agents, including a CCB (amlodipine) or thiazide diuretic (hydrochlorothiazide), although subjects studied to date have been predominantly Caucasian.[7,8] Previously, in the Aliskiren Amlodipine Combination in African AmEricans with Stage 2 HypertenSion (AACESS) study, we reported that combination aliskiren/amlodipine provided significantly greater BP lowering than amlodipine monotherapy in African Americans with stage 2 hypertension.[9] The objective of this post-hoc analysis of the AACESS study was to evaluate the antihypertensive efficacy and safety of these treatments in African Americans with hypertension and comorbid obesity or MetS.

Methods

Methods for the AACESS study have been previously described in detail[9] and are briefly summarized here. A research ethics board, ethics committee, or institutional review board at each center approved this study, and all subjects provided written informed consent before inclusion. The study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonized Tripartite Guidelines for Good Clinical Practice in conjunction with local regulations and the ethical principles of the current Declaration of Helsinki.

Subjects

Subjects were adult men or women who were self-identified as African Americans and who had newly diagnosed and treatment naïve stage 2 hypertension or were taking 3 or fewer antihypertensive drugs with a mean sitting systolic blood pressure (msSBP) ≥160 mm Hg and <200 mm Hg at randomization. Subjects with msSBP ≥200 mm Hg, mean sitting diastolic blood pressure (msDBP) ≥110 mm Hg, secondary hypertension, or a history of treatment with four or more antihypertensive agents were excluded. In addition, subjects could not have hypertension that was uncontrolled at screening (defined as msSBP >180 mm Hg on one or more antihypertensive agents) or refractory to treatment (>140/90 mm Hg on the maximum dose of three antihypertensive agents, including a diuretic). Subjects with CV disease, evidence of renal dysfunction, abnormal serum sodium or potassium, type I DM, or type II DM requiring insulin or associated with glycosylated hemoglobin >10% were also excluded. Premenopausal women who were pregnant, nursing, or not using two approved forms of contraception were not permitted to enter the study.

Study Design

This was an 8-week, prospective, multicenter (67 American centers), randomized, double-blind, parallel-group study. After screening, subjects underwent a 1- to 4-week washout period before being randomized 1:1 to receive either combination aliskiren/amlodipine 150/5 mg or amlodipine 5 mg alone for 1 week; subjects were then force-titrated to aliskiren/amlodipine 300/10 mg or amlodipine 10 mg, respectively, for 7 weeks (Figure 1).

Study drugs provided were aliskiren 150-mg tablets, amlodipine 5-mg capsules, and matching placebos. To ensure blinding, subjects were instructed to take 4 tablets/capsules of study drug per day with water in the morning between 7:00 a.m. and 10:00 a.m., except on the morning of clinic visits, when they were to be taken after the visit procedures were completed. Subjects were not permitted to take any nonstudy antihypertensives, nor were they permitted to take drugs that could affect BP, such as diuretics, certain classes of antidepressants and antipsychotics, oral corticosteroids, alpha adrenergic blockers, and antiarrhythmic drugs. Chronic use of sympathomimetic drugs or nonsteroidal