Original Research

A Randomized, Double-blind, Multicenter, Phase III Study to Evaluate the Efficacy and Safety of Fimasartan/Amlodipine Combined Therapy Versus Fimasartan Monotherapy in Patients With Essential Hypertension Unresponsive to Fimasartan Monotherapy

Kwang-il Kim[1]; Mi-Seung Shin[2]; Sang-Hyun Ihm[3]; Ho-Joong Youn[4]; Ki-Chul Sung[5]; Shung Chull Chae[6]; Chang-Wook Nam[7]; Hong Seog Seo[8]; Seong-Mi Park[9]; Moo-Yong Rhee[10]; Moo Hyun Kim[11]; Kwang Soo Cha[12]; Yong-Jin Kim[13]; Jae-Joong Kim[14]; Kook Jin Chun[15]; Byung-Su Yoo[16]; Sungha Park[17]; Eun-Seok Shin[18]; Dong-Soo Kim[19]; Doo Il Kim[20]; Kye Hun Kim[21]; Seung-Jae Joo[22]; Jin-Ok Jeong[23]; Jinho Shin[24]; and Cheol Ho Kim[1]

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [2]Division of Cardiology, Gachon University Gil Medical Center, Incheon, Republic of Korea; [3]Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Koreau, Bucheon, Republic of Korea; [4]Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [5]Division of Cardiology, Department of Medicine Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [6]Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea; [7]Department of Internal Medicine, Dongsan Medical Center, Keimyung University, Daegu, Republic of Korea; [8]Department of Internal Medicine, Korea University Guro Hospital, Seoul, Republic of Korea; [9]Division of Cardiology, Korea University College of Medicine, Seoul, Republic of Korea; [10]Cardiovascular Center, Dongguk University Ilsan Hospital, Goyang, Republic of Korea; [11]Department of Cardiology, Dong-A University Hospital, Busan, Republic of Korea; [12]Department of Cardiology, Pusan National University Hospital, Busan, Republic of Korea; [13]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [14]Division of Cardiology, Asan Medical Center, University of Ulsan, Seoul, Republic of Korea; [15]Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea; [16]Division of Cardiology, Wonju Severance Christian Hospital, Wonju, Republic of Korea; [17]Division of Cardiology, Yonsei Cardiovascular Hospital, Yonsei Health System, Seoul, Republic of Korea; [18]Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine,Ulsan, Republic of Korea; [19]Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Republic of Korea; [20]Department of Internal Medicine, Haeundae Paik Hospital, Busan, Republic of Korea; [21]Department of Cardiology, Chonnam National University Hospital, Gwangju, Republic of Korea; [22]Department of Internal Medicine, Jeju National University Hospital, Jeju,

http://dx.doi.org/10.1016/j.clinthera.2016.07.008
0149-2918/$ - see front matter

Republic of Korea; [23]*Department of Internal Medicine, Chungnam National University Hospital, Daejeon, Republic of Korea; and* [24]*Division of Cardiology, Hanyang University Hospital, Seoul, Republic of Korea*

ABSTRACT

Purpose: The goal of this study was to evaluate whether the blood pressure–lowering efficacy of fimasartan/amlodipine combination therapy was superior to that of fimasartan monotherapy after 8 weeks of treatment in patients with hypertension who had failed to respond adequately to fimasartan monotherapy.

Methods: This trial was a randomized, double-blind, multicenter, Phase III clinical study. Patients who failed to respond after 4 weeks of treatment with 60 mg daily of fimasartan (sitting systolic blood pressure [SiSBP]) ≥140 mm Hg) were randomized to receive either daily fimasartan 60 mg or fimasartan/amlodipine 60 mg/10 mg. The primary efficacy end point was the change in SiSBP from baseline to week 8. Secondary end points included the change in SiSBP from baseline to week 4, the changes in sitting diastolic blood pressure from baseline to weeks 4 and 8, and the response rate (SiSBP <140 mm Hg or decrease in SiSBP ≥20 mm Hg) or control rate (SiSBP <140 mm Hg) at week 8. Treatment-emergent adverse events were also assessed.

Findings: Of 143 patients randomized to treatment, 137 patients who had available efficacy data were analyzed. The mean age of patients was 59.1 (8.9) years, and 100 (73.0%) were male. Baseline SiSBP and sitting diastolic blood pressure were 150.6 (9.2) mm Hg and 91.7 (8.6) mm Hg, respectively. In the fimasartan/amlodipine combination group, a greater reduction in SiSBP from baseline to week 8 was observed compared with the fimasartan group (7.8 [13.3] mm Hg in the fimasartan group vs 20.5 [14.6] mm Hg in the fimasartan/amlodipine group; $P < 0.0001$). This reduction was observed after 4 weeks. The mean SiSBP changes from baseline to week 4 were 8.1 (15.8) mm Hg in the fimasartan group and 20.1 (14.7) mm Hg in the fimasartan/amlodipine group ($P < 0.0001$). At week 8, the response rate was significantly higher in the fimasartan/amlodipine (82.1%) group than in the fimasartan (32.9%) group ($P < 0.0001$). The control rate at week 8 was also higher in the fimasartan/amlodipine (79.1%) group than in the fimasartan (31.4%) group ($P < 0.0001$). Adverse drug reactions were observed in 9 patients (6.3%), with no significant differences between treatment groups. There were no serious adverse events associated with the study drugs.

Implications: Fimasartan/amlodipine combination therapy exhibited superior efficacy in reducing blood pressure, with no increase in adverse drug reactions, compared with fimasartan monotherapy. ClinicalTrials.gov identifier: NCT02152306. (*Clin Ther.* 2016;38:2159–2170)

Key words: amlodipine, angiotensin II type 1 receptor blockers, antihypertensive, blood pressure, combination, fimasartan.

INTRODUCTION

Hypertension is one of the most prevalent chronic medical conditions and is a major risk factor for cardiovascular and renal diseases. Remarkable advances in drug therapy have made it possible to control blood pressure (BP) in most patients with hypertension; however, hypertension continues to be a major global health issue.[1] Moreover, despite improvements in the awareness and treatment rate of hypertension, its control rate remains unsatisfactory, especially in middle- and low-income countries.[2] In particular, the rate of hypertension control remains largely unsatisfactory in the primary care setting, likely due to suboptimal treatment of higher risk patients, who may benefit the most from effective BP control.[3]

Therapeutic inertia, defined as the providers' failure to increase therapy when treatment goals are unmet, is believed to be one of the main reasons for the high prevalence of uncontrolled hypertension.[4] To overcome ineffective drug treatment, combination therapy is required to achieve the target BP. Previous data showed that combination therapy using ≥2 drugs that have mutually complementary mechanisms is more effective than monotherapy and can decrease the incidence of adverse events, which are usually dose dependent.[5,6] In addition, fixed-dose combination therapy is an effective and safe method for BP control that offers easier administration and better compliance.[7]

For this reason, many combination agents have been developed. Among the various combinations of antihypertensive agents, renin-angiotensin system (RAS) inhibitors plus calcium channel blockers are superior to other combinations or higher dose therapy

in the prevention of hypertension-related adverse clinical outcomes.[8,9] Fimasartan is an angiotensin II receptor blocker (ARB) with a selective type 1 receptor blocking effect.[10] Fimasartan at a dosage of 30 to 120 mg once per day has been shown to exert an effective BP-lowering effect in patients with mild to moderate hypertension.[11–14] Furthermore, excellent safety and tolerability were reported in a large observational study.[15]

A previous study confirmed that co-administration of fimasartan and amlodipine did not result in clinically relevant changes in the systemic exposure of either drug.[16] Thus, a fixed-dose combination of these 2 drugs can be used for patients with hypertension who require aggressive control of BP and who do not respond sufficiently to treatment with conventional drugs. Moreover, a Phase II study was conducted to evaluate the efficacy and safety of a fimasartan/amlodipine combination in patients with hypertension and to determine the optimal composition for a single-pill combination formulation. The combination of fimasartan/amlodipine at a dose of 60 mg/10 mg revealed the highest antihypertensive efficacy with no increased risk of adverse events.[17]

We thus performed a randomized, double-blind, multicenter, Phase III clinical study to confirm the maximal efficacy and safety of fimasartan/amlodipine combination therapy in Korean patients with hypertension who were unresponsive to fimasartan monotherapy.

PATIENTS AND METHODS

Study Design and Study Population

This clinical study was designed to evaluate the safety and efficacy of combination therapy of fimasartan/amlodipine compared with fimasartan monotherapy in patients with hypertension who failed to respond adequately to fimasartan monotherapy. It was a randomized, double-blind, multicenter, Phase III clinical study with a total treatment period of 12 weeks. This study was conducted at 25 hospitals in the Republic of Korea according to the Declaration of Helsinki and Good Clinical Practice guidelines. The institutional review board at each clinical site approved the study.

Patients were considered eligible for enrollment if they met the following criteria: male or female adults aged 20 to 75 years who signed the informed consent form and patients confirmed to have essential hypertension at a screening visit (visit 1) that was uncontrolled (sitting systolic blood pressure [SiSBP] $\geq$140 mm Hg) after the administration of fimasartan monotherapy (60 mg) for 4 weeks (visit 2). Patients were excluded from the study if they had secondary hypertension, severe hypertension (SiSBP $\geq$180 mm Hg or sitting diastolic blood pressure [SiDBP] $\geq$110 mm Hg), symptomatic orthostatic hypotension, symptomatic heart failure (New York Heart Association functional classes III and IV), significant structural heart disease or arrhythmia, uncontrolled diabetes mellitus (glycosylate hemoglobin levels $>$9%), or a history of any of the following within the past 6 months: ischemic heart disease (eg, angina pectoris, myocardial infarction), peripheral vascular disease, percutaneous coronary intervention, coronary artery bypass graft, or stroke. Furthermore, patients with severe organ dysfunction (as assessed by clinicians or according to laboratory abnormalities) or systemic diseases were also excluded. Patients already enrolled in other clinical trials or who had contraindications to fimasartan or amlodipine were also excluded.

Treatment

Patients who failed to respond after 4 weeks of treatment with fimasartan 60 mg (ie, SiSBP $\geq$140 mm Hg) were randomized in a 1:1 ratio to receive either fimasartan 60 mg or fimasartan/amlodipine 60 mg/10 mg. Randomized subjects were given the investigational drugs for another 8 weeks. Patients were instructed to take the assigned drug orally once a day at the same time after a meal in the morning. Patients were instructed to fast for 12 hours before the scheduled visit and to refrain from taking the study medication on the morning before the trough BP measurement. Patients were instructed not to take any other medications that may have effects on BP.

Treatment compliance was assessed by clinicians at each follow-up visit (week 4 and week 8). The number of medication doses that remained when the patient returned was counted to determine the number of administered tablets. The medication compliance rate was calculated by dividing the number of administered tablets by the total number of prescribed tablets and multiplying the result by 100.

Measurements

At the screening visit, the patient was interviewed by a clinician regarding medical history, medication history, and concomitant medications. Anthropometry, vital sign measurements, and a routine physical examination were also performed. Screening

laboratory examinations included ECG, complete blood cell counts, and routine chemistry tests. BP was measured by using a semi-automated sphygmomanometer (HEM-7080IT; Omron Corporation, Kyoto, Japan) in accordance with the recommendation for BP measurements.[18] At the screening visit, the BP of both arms was measured. The arm with the higher average of 3 SiSBP values was selected for subsequent measurements. BP was measured 3 times, at an interval of >2 minutes between measurements, and the average of the 3 measurements was calculated.

Primary and Secondary Efficacy End Points

The primary end point of the study was the mean change in SiSBP from the baseline visit (visit 2) to week 8. Secondary end points were as follows: (1) changes in SiSBP from baseline to week 4; (2) changes in SiDBP from baseline to week 4 and week 8; and (3) proportions of the response rate (SiSBP <140 mm Hg or decrease in SiSBP ≥20 mm Hg after 8 weeks of treatment) and control rate (SiSBP <140 mm Hg) after administration of the investigational drug for 8 weeks.

Safety Assessment

The safety assessment was conducted in patients who had received the investigational drug at least once after the baseline visit (visit 2). The numbers and percentages of treatment-emergent adverse events (TEAEs), adverse drug responses, and serious adverse events were assessed. Adverse events were coded and organized by using the Medical Dictionary for Regulatory Activities. All adverse events were organized according to severity, and TEAEs and serious adverse events were assessed separately.

Sample Size Calculation

To determine the size of the study population, we assumed a potential difference of 6.7 mm Hg in the weighted mean change of SiSBP, with an SD of 13 mm Hg, according to previous studies.[19,20] With a significance level of 5% (2-sided) and a statistical power of 80%, the number of required participants would be 59 subjects for each of the 2 treatment groups; thus, the total number of subjects needed was 118. However, after taking into account a dropout rate of 15%, it was calculated that 140 total subjects needed to be enrolled, with 70 subjects per treatment group.

Statistical Analysis

For the efficacy analysis, the full analysis set (FAS) was used for the main analysis, whereas the per-protocol analysis set was used for the additional analysis. The FAS population included all patients for whom efficacy assessments were made at least 1 time after randomization. Among the FAS population, the per-protocol analysis set included patients who completed the study without major or serious protocol violations. To perform analysis for the primary end point in patients who withdrew from the study before week 8, the last-observation-carried-forward approach was taken. The safety analysis set included all patients who received at least 1 dose of a study medication.

The comparisons of BP changes between the fimasartan monotherapy and the fimasartan/amlodipine combination therapy groups were made by using an ANCOVA analysis, with the baseline BP values as the covariates and the treatment groups as the factors. The comparisons between the fimasartan monotherapy and fimasartan/amlodipine combination therapy groups were analyzed by using the 2-sample t-test or the Wilcoxon rank sum test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. A 2-tailed P value <0.05 was considered significant. Statistical analyses were conducted by using SAS 9.2 software (SAS Institute, Inc, Cary, NC).

RESULTS

Study Population

Of the 355 patients with hypertension who agreed to participate in this study, 143 patients were randomized to treatment (fimasartan 60-mg group, n = 73; fimasartan/amlodipine 60-mg/10-mg group, n = 70) (Figure 1). Fourteen patients dropped out during the study period for the following reasons: withdrawal of consent (n = 5), protocol violation (n = 4), adverse events (n = 2), lack of efficacy (n = 1), and other reasons (n = 2). A total of 129 patients completed the study. The mean age of the patients was 59.1 (8.9) years, and 100 (73.0%) were male. Baseline SiSBP and SiDBP were 150.6 (9.2) mm Hg and 91.7 (8.6) mm Hg, respectively. There were no significant differences in baseline characteristics between groups, except for pulse rate (P = 0.0457) (Table I).

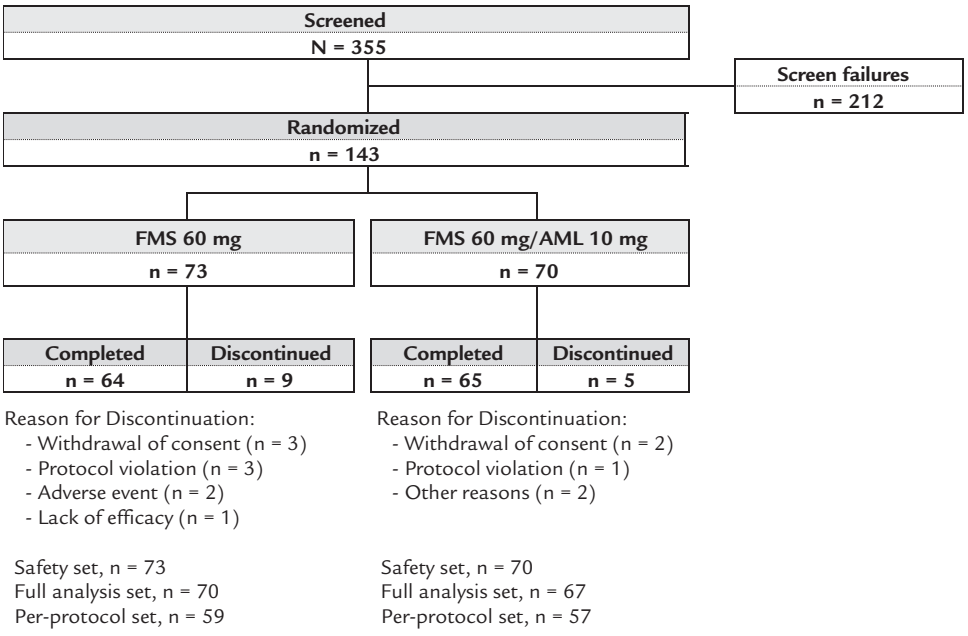

Figure 1. Subject disposition and reasons for dropout. FMS = fimasartan; FMS/AML = fimasartan/amlodipine.

Efficacy Outcome

In the FAS group (n = 137), the mean reductions in SiSBP from baseline to week 8 were 7.8 (13.3) mm Hg in the fimasartan group and 20.5 (14.6) mm Hg in the fimasartan/amlodipine group ($P < 0.0001$). The least squared mean (SE) difference between the fimasartan and fimasartan/amlodipine groups was –13.3 (2.2) mm Hg (95% CI, –17.7 to –8.9; $P < 0.0001$). The

Table I. Demographic and baseline characteristics of the study population. Unless otherwise indicated, values are given as mean (SD).

Characteristic	FMS 60 mg (n = 70)	FMS 60 mg/AML 10 mg (n = 67)	Total (N = 137)	*P*
Age, y	60.2 (8.8)	57.9 (9.0)	59.1 (8.9)	0.1282
Male sex, n (%)	51 (72.9)	49 (73.1)	100 (73.0)	0.9709
Weight, kg	71.6 (12.0)	72.9 (9.2)	72.2 (10.7)	0.2817
Height, cm	166.3 (7.6)	165.6 (8.2)	166.0 (7.9)	0.7845
Body mass index, kg/m^2	25.8 (3.1)	26.6 (2.7)	26.2 (2.9)	0.1249
SiSBP, mm Hg	151.1 (9.6)	150.1 (8.9)	150.6 (9.2)	0.5682
SiDBP, mm Hg	92.2 (8.7)	91.3 (8.5)	91.7 (8.6)	0.5284
Pulse rate, beats/min	73.9 (10.8)	69.9 (10.1)	71.9 (10.6)	*0.0457*
Current smoker, n (%)	14 (20.0)	15 (22.4)	29 (21.2)	0.1949
Alcohol drinking, n (%)	47 (67.1)	45 (67.2)	92 (67.2)	0.9979
Drug allergy, n (%)	2 (2.9)	0	2 (1.5)	0.4966

FMS = fimasartan; FMS/AML = fimasartan/amlodipine; SiSBP = sitting systolic blood pressure; SiDBP = sitting diastolic blood pressure.

findings were similar in the per-protocol analysis set (n = 116).

This change in SiSBP was observed after 4 weeks. The mean reductions in SiSBP from baseline to week 4 were 8.1 (15.8) mm Hg in the fimasartan group and 20.1 (14.7) mm Hg in the fimasartan/amlodipine group ($P < 0.0001$). The least squared mean (SE) difference between the fimasartan and fimasartan/amlodipine groups was −12.6 (2.4) mm Hg (95% CI, −17.5 to −7.8; $P < 0.0001$). In addition, there were significant decreases in SiDBP with fimasartan/amlodipine combination therapy at weeks 4 and 8 (Table II).

At week 8, the response rate (defined as SiSBP <140 mm Hg or a decrease in SiSBP ≥20 mm Hg after week 8) was significantly higher in the fimasartan/amlodipine (82.1%) group than in the fimasartan (32.9%) group ($P < 0.0001$). In addition, the control rate at week 8 (defined as SiSBP <140 mm Hg) was also higher in the fimasartan/amlodipine (79.1%) group than in the fimasartan (31.4%) group ($P < 0.0001$) (Figure 2).

Comparison Between Responders and Nonresponders to the Study Drug

There were no significant differences in baseline clinical characteristics between responders and nonresponders at week 8. However, the BP profiles were significantly different after week 4, and this difference was maintained throughout the study period (Figure 3). Interestingly, there were no significant further decreases in BP between weeks 4 and 8 in any of the 4 groups.

Table II. Change in mean sitting systolic and diastolic blood pressure (BP) at weeks 4 and 8 in the fimasartan (FMS) monotherapy group and in the fimasartan/amlodipine (FMS/AML) combination group.

Characteristic	FMS 60 mg (n = 70)	FMS 60 mg/AML 10 mg (n = 67)	LS Mean (SE) Difference	95% CI	*P*
Systolic BP					
Baseline, mean (SD)	151.1 (9.6)	150.1 (8.9)			
Week 4, mean (SD)	143.0 (15.7)	130.0 (13.5)			
Week 8, mean (SD)	143.3 (13.8)	129.6 (13.2)			
Change from baseline at week 4					
Mean (SD)	−8.1 (15.8)	−20.1 (14.7)			
LS mean (SE)*	−7.8 (1.7)	−20.4 (1.7)	−12.6 (2.4)	−17.5 to −7.8	<0.0001
Change from baseline at week 8					
Mean (SD)	−7.8 (13.3)	−20.5 (14.6)			
LS mean (SE)*	−7.5 (1.6)	−20.8 (1.6)	−13.3 (2.2)	−17.7 to −8.9	<0.0001
Diastolic BP					
Baseline, mean (SD)	92.2 (8.7)	91.3 (8.5)			
Week 4, mean (SD)	88.4 (8.9)	80.1 (9.1)			
Week 8, mean (SD)	88.2 (8.4)	79.8 (9.6)			
Change from baseline at week 4					
Mean (SD)	−3.8 (7.9)	−11.1 (8.2)			
LS mean (SE)*	−3.7 (0.9)	−11.3 (0.9)	−7.7 (1.3)	−10.2 to −5.2	<0.0001
Change from baseline at week 8					
Mean (SD)	−3.9 (6.8)	−11.5 (9.0)			
LS mean (SE)*	−3.8 (0.9)	−11.7 (0.9)	−7.9 (1.2)	−10.4 to −5.5	<0.0001

LS mean = least squared mean.
*Difference between treatment groups; ANCOVA model using baseline as covariates.

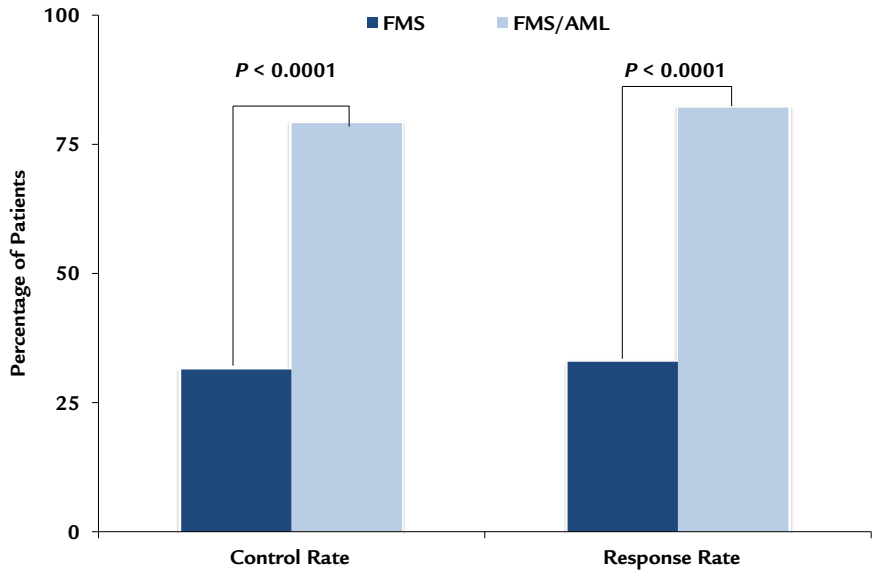

Figure 2. Comparison of the response rate and control rate between fimasartan (FMS) and fimasartan/amlodipine (FMS/AML) at week 8. Control rate: proportion of participants whose sitting systolic blood pressure (SiSBP) was <140 mm Hg after 8 weeks of treatment. Response rate: proportion of participants whose SiSBP was <140 mm Hg or had a decrease in SiSBP ≥ 20 mm Hg after 8 weeks of treatment.

Safety Outcome

Safety analysis was performed for a total of 143 patients who had been treated with a study drug at least once. A total of 47 TEAEs were identified in 32 patients (22.4%). There were no significant differences in TEAEs between the fimasartan and fimasartan/amlodipine groups ($P = 0.3485$). Adverse drug responses were observed in 9 participants (6.3%), and there were no significant differences in adverse drug responses between the 2 groups ($P = 0.4944$) (Table III). No serious adverse events were associated with the study drugs.

DISCUSSION

In this study, we confirmed the efficacy of fimasartan/amlodipine combination therapy in reducing BP among patients with hypertension whose BP was uncontrolled with fimasartan monotherapy. Interestingly, BP-lowering efficacy was apparent after 4 weeks of treatment and was maintained throughout the study period. Noticeably, with the combination of fimasartan/amlodipine, we can expect an increase in the BP response rate of $\sim$50% in fimasartan monotherapy-resistant patients with hypertension. The impact of hypertension on cardiovascular morbidity and mortality is well known, and controlling BP is the most important and cost-effective measure for improving health outcomes in patients with hypertension. Furthermore, recent clinical evidence has shown an additional benefit of lowering SBP to <130 mm Hg, especially in high-risk patients.[21,22] In practice, however, it is difficult to control BP with only monotherapy; thus, most patients require >2 medications. In addition, combining medications that have different mechanisms of action provides an additive BP-lowering effect through complementary mechanisms.[23] Moreover, a fixed-dose combination therapy can enhance patient compliance and improve convenience for the patient by reducing the necessary number of pills and visits for the titration of each drug, and it can lower BP within a shorter period of time.[5,24,25] For this reason, current guidelines recommend low-dose combination therapy or adding another class of drug at low doses for better BP control.

Among the various combinations of antihypertensive medications, RAS inhibitors and calcium channel

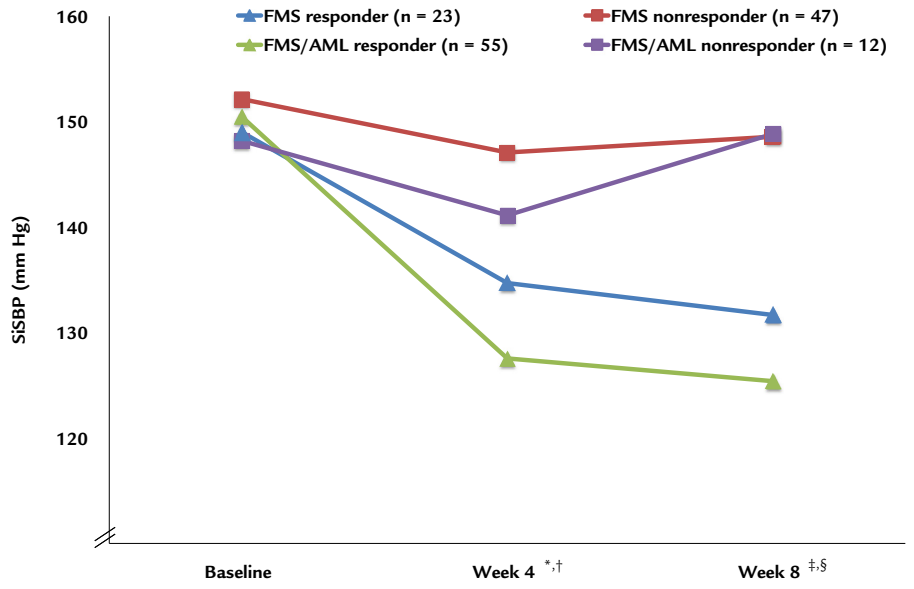

Figure 3. Comparison of sitting systolic blood pressure (SiSBP) in responders and nonresponders in the 2 treatment groups over the course of the study. FMS = fimasartan; FMS/AML = fimasartan/amlodipine. Responder: patients whose SiSBP was <140 mm Hg or had a decrease in SiSBP ≥20 mm Hg with the investigational drug. Nonresponder: patients whose SiSBP was ≥140 mm Hg and had a decrease in SiSBP <20 mm Hg despite use of the investigational drug. $^{*}P = 0.0015$ between responders and nonresponders in the fimasartan group, and $P = 0.0012$ between responders and nonresponders in the fimasartan/amlodipine group. $^{\dagger}P = 0.0296$ between the fimasartan and fimasartan/amlodipine groups among responders. $^{\ddagger}P < 0.0001$ between responders and nonresponders in the fimasartan group, and $P < 0.0001$ between responders and nonresponders in the fimasartan/amlodipine group. $^{\S}P = 0.0072$ between the fimasartan and fimasartan/amlodipine groups among responders.

blockers are most commonly used for fixed-dose combination therapy. Of the various available RAS inhibitors, angiotensin-converting-enzyme (ACE) inhibitors have been validated as beneficial drugs for the treatment of hypertension and heart failure, but their use has been limited because of well-known side effects, such as cough and angioedema. Furthermore, the incidence of cough has been reported to be >2-fold higher in East Asian patients than in white patients; thus, ACE inhibitors are rarely prescribed to BP control in Korea or other East Asian countries.[26]

In contrast, ARBs have good safety profiles, and patients for whom ARBs are prescribed seem to have the best level of adherence, followed by ACE inhibitors, calcium channel blockers, β-blockers, and diuretic agents.[27] Moreover, ARBs have also been proven to be effective in the treatment of heart failure as well as hypertension. Consequently, most fixed-dose combination therapies currently use ARBs instead of ACE inhibitors as a RAS inhibitor.

Amlodipine is a dihydropyridine-class calcium channel blocker that reduces peripheral vascular resistance, resulting in reduced BP. It is characterized by gradual and sustained antihypertensive efficacy. When amlodipine is administered concomitantly with other antihypertensive agents, it has the advantage of exhibiting even stronger antihypertensive efficacy. Furthermore, dose-dependent side effects of amlodipine, such as ankle edema, can be reduced by combining it with an ARB.[28] In this study, there were no significant differences in the overall safety profiles between fimasartan/amlodipine combination therapy and fimasartan monotherapy. In actuality, the combination of ARBs with calcium channel blockers

Table III. Treatment-emergent adverse events in the safety analysis group described according to the system organ class and preferred term. Treatment-emergent adverse events are displayed as number of subjects (percentage of subjects) [number of events].

System Organ Class Preferred Term	FMS 60 mg (n = 73)	FMS 60 mg/ AML 10 mg (n = 70)	Total (N = 143)	*P*
No. of subjects	14 (19.18) [19]	18 (25.71) [28]	32 (22.38) [47]	0.3485
Infections and infestations	4 (5.48) [4]	5 (7.14) [6]	9 (6.29) [10]	
Nasopharyngitis	3 (4.11) [3]	5 (7.14) [6]	8 (5.59) [9]	
Herpes zoster	1 (1.37) [1]	0	1 (0.70) [1]	
Nervous system disorders	2 (2.74) [3]	6 (8.57) [6]	8 (5.59) [9]	
Dizziness	2 (2.74) [2]	4 (5.71) [4]	6 (4.20) [6]	
Headache	1 (1.37) [1]	1 (1.43) [1]	2 (1.40) [2]	
Cognitive disorder	0	1 (1.43) [1]	1 (0.70) [1]	
Gastrointestinal disorders	3 (4.11) [3]	3 (4.29) [4]	6 (4.20) [7]	
Nausea	1 (1.37) [1]	1 (1.43) [1]	2 (1.40) [2]	
Dry mouth	1 (1.37) [1]	0	1 (0.70) [1]	
Dyspepsia	0	1 (1.43) [1]	1 (0.70) [1]	
Gingival disorder	0	1 (1.43) [1]	1 (0.70) [1]	
Periodontal disease	0	1 (1.43) [1]	1 (0.70) [1]	
Toothache	1 (1.37) [1]	0	1 (0.70) [1]	
General disorders and administration site conditions	2 (2.74) [2]	4 (5.71) [5]	6 (4.20) [7]	
Face edema	0	2 (2.86) [2]	2 (1.40) [2]	
Ankle edema	0	2 (2.86) [2]	2 (1.40) [2]	
Asthenia	1 (1.37) [1]	0	1 (0.70) [1]	
Chest pain	1 (1.37) [1]	0	1 (0.70) [1]	
Gait disturbance	0	1 (1.43) [1]	1 (0.70) [1]	
Investigations	2 (2.74) [3]	2 (2.86) [2]	4 (2.80) [5]	
Alanine aminotransferase levels increased	1 (1.37) [1]	0	1 (0.70) [1]	
Aspartate aminotransferase levels increased	1 (1.37) [1]	0	1 (0.70) [1]	
Blood triglyceride levels increased	0	1 (1.43) [1]	1 (0.70) [1]	
γ-Glutamyl transferase increased	0	1 (1.43) [1]	1 (0.70) [1]	
Weight decreased	1 (1.37) [1]	0	1 (0.70) [1]	
Cardiac disorders	2 (2.74) [2]	0	2 (1.40) [2]	
Palpitations	2 (2.74) [2]	0	2 (1.40) [2]	
Eye disorders	0	1(1.43) [2]	1 (0.70) [2]	
Eye discharge	0	1(1.43) [1]	1 (0.70) [1]	
Visual impairment	0	1(1.43) [1]	1 (0.70) [1]	
Metabolism and nutrition disorders	1 (1.37) [1]	0	1 (0.70) [1]	
Hypertriglyceridemia	1 (1.37) [1]	0	1 (0.70) [1]	
Musculoskeletal and connective tissue disorders	0	1 (1.43) [1]	1 (0.70) [1]	
Arthralgia	0	1 (1.43) [1]	1 (0.70) [1]	
Psychiatric disorders	0	1 (1.43) [1]	1 (0.70) [1]	
Insomnia	0	1 (1.43) [1]	1 (0.70) [1]	

(continued)

Table III. (continued).

System Organ Class Preferred Term	FMS 60 mg (n = 73)	FMS 60 mg/ AML 10 mg (n = 70)	Total (N = 143)	P
Skin and subcutaneous tissue disorders	1 (1.37) [1]	0	1 (0.70) [1]	
Hyperhidrosis	1 (1.37) [1]	0	1 (0.70) [1]	
Vascular disorders	0	1 (1.43) [1]	1 (0.70) [1]	
Flushing	0	1 (1.43) [1]	1 (0.70) [1]	

Medical Dictionary for Regulatory Activities, version 17.0.

has been shown to produce well-tolerated antihypertensive efficacy that is greater than that of monotherapy.[29] Accordingly, a fixed-dose combination of fimasartan/amlodipine 60 mg/10 mg, although not the initial choice, may be an appropriate option for patients with hypertension whose disease is uncontrolled with monotherapy.

The current study showed that BP-lowering efficacy was apparent after week 4 and that there was no further decrease in BP between weeks 4 and 8. In practice, the delay in dose titration is one of the reasons for therapeutic inertia, and a previous study showed the benefit of early goal achievement in preventing cardiovascular events in high-risk patients.[30] Accordingly, we should consider adding a new drug when the target BP goal is not achieved after week 4.

CONCLUSIONS

Combination treatment with fimasartan and amlodipine was effective in these patients with hypertension whose disease was not adequately controlled with fimasartan alone. The safety and tolerability of combined fimasartan and amlodipine treatment were comparable with those of fimasartan monotherapy.

ACKNOWLEDGMENTS

This research was initiated and financially supported by Boryung Pharmaceutical Co, Ltd. All authors acted as principal investigators at the study sites, recruited patients, and collected data. The manuscript was prepared, reviewed, and approved by all authors before publication

CONFLICTS OF INTEREST

The sponsor supported the supply of the study drugs, laboratory testing, and data collection and analysis. The funding body was not involved in data analysis, data interpretation, or writing the results.

Dr. C.H. Kim has received lecture honoraria from GlaxoSmithKline; Hanmi Pharmaceutical Co, Ltd; and research grants from Merck Sharp & Dohme, LG Life Sciences Ltd, and Boryung Pharmaceutical Co, Ltd. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

REFERENCES

1. Chobanian AV. Shattuck Lecture. The hypertension paradox—more uncontrolled disease despite improved therapy. *N Engl J Med*. 2009;361:878–887.
2. Poulter NR, Prabhakaran D, Caulfield M. Hypertension. *Lancet*. 2015;386:801–812.
3. Kim KI, Kim Y, Kim HJ, et al. Current status and characteristics of hypertension treatment by primary physicians in Korea: data from Korean epidemiology study on hypertension (KEY study). *Am J Hypertens*. 2008;21:884–889.
4. Okonofua EC, Simpson KN, Jesri A, et al. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. *Hypertension*. 2006;47:345–351.
5. Egan BM, Bandyopadhyay D, Shaftman SR, et al. Initial monotherapy and combination therapy and hypertension control the first year. *Hypertension*. 2012;59:1124–1131.
6. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National

Health and Nutrition Examination Survey, 2001 to 2010. *Circulation*. 2012;126:2105–2114.
7. Kumagai N, Onishi K, Hoshino K, et al. Improving drug adherence using fixed combinations caused beneficial treatment outcomes and decreased health-care costs in patients with hypertension. *Clin Exp Hypertens*. 2013;35:355–360.
8. Ogawa H, Kim-Mitsuyama S, Matsui K, et al. Angiotensin II receptor blocker-based therapy in Japanese elderly, high-risk, hypertensive patients. *Am J Med*. 2012;125:981–990.
9. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–2428.
10. van Hoof J, Kort HS, Rutten PG, Duijnstee MS. Ageing-in-place with the use of ambient intelligence technology: perspectives of older users. *Int J Med Inform*. 2011;80:310–331.
11. Lee H, Kim KS, Chae SC, et al. Ambulatory blood pressure response to once-daily fimasartan: an 8-week, multicenter, randomized, double-blind, active-comparator, parallel-group study in Korean patients with mild to moderate essential hypertension. *Clin Ther*. 2013;35:1337–1349.
12. Lee H, Yang HM, Lee HY, et al. Efficacy and tolerability of once-daily oral fimasartan 20 to 240 mg/d in Korean patients with hypertension: findings from two Phase II, randomized, double-blind, placebo-controlled studies. *Clin Ther*. 2012;34:1273–1289.
13. Youn JC, Ihm SH, Bae JH, et al. Efficacy and safety of 30-mg fimasartan for the treatment of patients with mild to moderate hypertension: an 8-week, multicenter, randomized, double-blind, phase III clinical study. *Clin Ther*. 2014;36:1412–1421.
14. Lee SE, Kim YJ, Lee HY, et al. Efficacy and tolerability of fimasartan, a new angiotensin receptor blocker, compared with losartan (50/100 mg): a 12-week, phase III, multicenter, prospective, randomized, double-blind, parallel-group, dose escalation clinical trial with an optional 12-week extension phase in adult Korean patients with mild-to-moderate hypertension. *Clin Ther*. 2012;34:552–568. 568 e1-9.
15. Park JB, Sung KC, Kang SM, Cho EJ. Safety and efficacy of fimasartan in patients with arterial hypertension (Safe-KanArb study): an open-label observational study. *Am J Cardiovasc Drugs*. 2013;13:47–56.
16. Yi S, Kim TE, Yoon SH, et al. Pharmacokinetic interaction of fimasartan, a new angiotensin II receptor antagonist, with amlodipine in healthy volunteers. *J Cardiovasc Pharmacol*. 2011;57:682–689.
17. Lee HY, Kim YJ, Ahn T, et al. A randomized, multicenter, double-blind, placebo-controlled, 3 x 3 factorial design, Phase II study to evaluate the efficacy and safety of the combination of fimasartan/amlodipine in patients with essential hypertension. *Clin Ther*. 2015;37. 2581-2596 e3.
18. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*. 2005;111:697–716.
19. Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clin Ther*. 2007;29:563–580.
20. Sinkiewicz W, Glazer RD, Kavoliuniene A, et al. Efficacy and tolerability of amlodipine/valsartan combination therapy in hypertensive patients not adequately controlled on valsartan monotherapy. *Curr Med Res Opin*. 2009;25:315–324.
21. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2015.
22. Group SR, Wright JT Jr., Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
23. Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009;122:290–300.
24. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension*. 2010;55:399–407.
25. Neutel JM. Low-dose antihypertensive combination therapy: its rationale and role in cardiovascular risk management. *Am J Hypertens*. 1999;12:73S–79S.
26. McDowell SE, Coleman JJ, Ferner RE. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. *BMJ*. 2006;332:1177–1181.
27. Kronish IM, Woodward M, Sergie Z, et al. Meta-analysis: impact of drug class on adherence to antihypertensives. *Circulation*. 2011;123:1611–1621.
28. Makani H, Bangalore S, Romero J, et al. Effect of renin-angiotensin system blockade on calcium channel blocker-associated peripheral edema. *Am J Med*. 2011;124:128–135.
29. Parati G. Optimization of hypertension management: the role of angiotensin receptor blocker-calcium channel blocker combinations.

J Cardiovasc Pharmacol. 2009;53: 352–358.

30. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363: 2022–2031.

Address correspondence to: Cheol-Ho Kim, MD, PhD, Division of Geriatrics, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82, Gumi-ro 173 beon-gil, Bundang-gu, Seongnam, 463-707, Korea. E-mail: cheolkim@snu.ac.kr