Original Paper

Results of Treatment With Telmisartan-Amlodipine in Hypertensive Patients

Thomas W. Littlejohn, III, MD;[1] Claudio R. Majul, MD;[2] Rafael Olvera, MD;[3] Mary Seeber, MD;[4] Maureen Kobe, MSc;[5] Robert Guthrie, MD;[6] Wille Oigman, MD;[7] On behalf of the study investigators

This randomized 4×4 factorial study determined the efficacy and safety of telmisartan (T) plus amlodipine (A) in hypertensive patients. Adults (N=1461) with stage 1 or 2 hypertension (baseline blood pressure [BP]: 153.2[12.1]/101.7[4.3] mm Hg) were randomized to 1 of 16 treatment groups with T 0, 20, 40, 80 mg and A 0, 2.5, 5, 10 mg for 8 weeks. In-clinic BP reductions were greater with combination therapy than respective monotherapies. The greatest least-square mean systolic/diastolic BP reductions were observed with T80 mg plus A10 mg (−26.4/−20.1 mm Hg; P<.05 compared with both monotherapies). BP control was also greatest in the T80-mg plus A10-mg group (76.5% [overall control] and 85.3% [diastolic BP control]), and BP response rates >90% with this combination. Peripheral edema was most common in the A10-mg group (17.8%); however, this rate was notably lower when A was used in combination with T: 11.4% (T20/A10), 6.2% (T40/A10), and 11.3% (T80/A10). J Clin Hypertens (Greenwich). *2009;11:207–213.* ©*2009 Wiley Periodicals, Inc.*

From Piedmont Medical Research Associates, Winston-Salem, NC;[1] the Hospital Santojanni, Buenos Aires, Argentina;[2] the Clinica de Estudios Medicos SC, Mexico City, México;[3] the Mediclinic Heart Hospital, Pretoria City, South Africa;[4] the Department of Cardiovascular and CNS Medicine, Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT;[5] Ohio State University, Columbus, OH;[6] and Rio de Janeiro State University, Rio de Janeiro, Brazil[7]
Address for correspondence:
Maureen Kobe, MSc, Department of Cardiovascular Medicine, Medical Affairs, Boehringer Ingelheim Pharmaceuticals Inc, 900 Ridgebury Road, Ridgefield, CT 06877
E-mail: maureen.kobe@boehringer-ingelheim.com
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The majority of hypertensive patients, especially those with target organ damage, are likely to require multiple drug therapy in order to reach blood pressure (BP) targets and reduce their risk of adverse vascular outcomes.[1,2] The rationale for combination therapy with agents that block the renin-angiotensin-aldosterone system (RAAS) and a calcium channel blocker (CCB) or diuretic is well founded.[2–5] Recent landmark studies, such as the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) and the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA), have demonstrated the antihypertensive benefits associated with angiotensin-converting enzyme (ACE) inhibitor/CCB combinations.[6,7] More recently, the combination of an angiotensin receptor blocker (ARB), such as valsartan or olmesartan and amlodipine have been introduced and tested in stage 1 and 2 hypertensive patients as well as those not controlled by monotherapy.[6,8–10] Besides the increased antihypertensive efficacy, the addition of an RAAS blocker has been shown to reduce the incidence of amlodipine-related edema.

Telmisartan has a different pharmacokinetic profile when compared with other ARBs,[11] and there are few studies examining telmisartan/CCB combinations in hypertensive patients.[12]

Against this background, the aim of the current study was to determine the clinical and safety profile of telmisartan (20–80 mg) plus amlodipine (2.5–10 mg) in stage 1 or 2 hypertension, and to establish the optimal doses using a rigorous factorial design involving 9 telmisartan-amlodipine combinations.

METHODS

Study Design

This was an 8-week, randomized, double-blind, double-dummy, placebo-controlled, international, multicenter, parallel-group, 4×4 factorial design trial that evaluated the efficacy and safety of telmisartan 20, 40, or 80 mg plus amlodipine 2.5, 5, or 10 mg in adults with hypertension (trial registration: NCT00281580). Patients were recruited from 150 centers in the United States, South Africa, Mexico, Argentina, and Brazil. The trial was conducted in accordance with the Declaration of Helsinki (1996), and was approved by each participating country's health authority and institutional review board or an independent ethics committee.

Following screening and a 21- to 28-day, single-blind, placebo run-in period, eligible patients were randomized to 1 of 16 treatment groups involving either telmisartan 20, 40, 80 mg or telmisartan placebo and/or amlodipine 2.5, 5, 10 mg or amlodipine placebo for 8 weeks. All patients randomized to a treatment group containing amlodipine 10 mg started with amlodipine 5 mg for the first 2 weeks and were then up-titrated to the higher dosage. Trial drug was taken orally as 3 tablets and 2 capsules with water at 8 AM (±1 hour). If a dose was missed, the patient was instructed to take the next dose as scheduled.

Participants and Medication Restrictions

Patients were men and women aged 18 years and older with stage 1 or 2 hypertension according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) diastolic BP ranges[13] (diastolic BP ≥95 mm Hg and ≤119 mm Hg) at baseline. Diastolic BP was chosen as this was the standard inclusion criteria used for drug approvals at the time the trial commenced. Consequently, change in diastolic BP was chosen as the primary end point. There were no inclusion criteria relating to systolic BP, and a change in systolic BP was included as a secondary end point as per protocol. All patients provided written informed consent prior to participation. Patients with prespecified renal or hepatic disorders, congestive heart failure (New York Heart Association class III or IV), clinically relevant cardiac arrhythmias (as determined by the investigator's clinical judgment on a patient-by-patient basis), severe obstructive coronary artery disease, unstable diabetes (glycated hemoglobin A_{1c} ≥10%), or any other condition that would not allow for safe completion of the protocol were excluded, as were nightshift workers, pregnant or nursing women, and women of childbearing potential not using medically approved means of contraception. Patients with known hypersensitivity to any component of the trial drugs, prior angioedema due to an ACE inhibitor or ARB, or those with a history of drug or alcohol dependency within the 6 months prior to signing the informed consent, were also excluded. Any antihypertensive or concomitant medications known to affect BP were not permitted during the study.

Assessments

Seated cuff BP and pulse rate were measured in the clinic prior to randomization, after 2 weeks of treatment, and then periodically until the end of the study. BP was recorded to the nearest 2 mm Hg using standard equipment, and the mean of 3 readings (taken 2 minutes apart) was used for the final measurement. Pulse rate was recorded during the 2-minute interval between the second and third BP recording. The primary end point was change in the in-clinic seated trough diastolic BP (ie, the diastolic BP measured 20–30 hours after the last drug dose from baseline to end of study [week 8]). Secondary efficacy end points included change from baseline in the in-clinic seated trough systolic BP, the percentage of patients achieving a diastolic BP response (defined as diastolic BP <90 mm Hg or a decrease in diastolic BP ≥10 mm Hg) or a systolic BP response (defined as systolic BP <140 mm Hg or a decrease in systolic BP ≥15 mm Hg) after 8 weeks of treatment, and the percentage of patients achieving BP control (defined as diastolic BP <90 mm Hg and systolic BP control <140 mm Hg) and diastolic BP control (<90 mm Hg) following treatment.

All adverse events that occurred after the first dose of randomized study drug until the follow-up visit, and adverse events that occurred up to 1 day after treatment discharge were defined as on-treatment. Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) Version 10. Laboratory tests were con-

ducted at screening, baseline, and end-of-study visits. Twelve-lead electrocardiography was performed at screening and at the end-of-study visit, and a physical examination was performed at screening. In addition, orthostatic changes in BP (defined as a decrease in diastolic BP >10 mm Hg and/or a decrease in systolic BP >20 mm Hg from a seated to standing position) were documented. Drug compliance was assessed by physical count of returned trial medication at each visit.

Statistical Analysis

The statistical models were adjusted (1) for telmisartan-by-amlodipine interaction (this first analysis was designed to show whether there were significant differences across the dosages of telmisartan or amlodipine, but was not a comparison between the 2 agents); (2) by dosage, country/region, and baseline BP as a covariate; and (3) for all combination treatment groups vs respective monotherapies. Least square means were used to quantify treatment effects, and the mean squared error was used to evaluate differences between combination therapy and the respective monotherapies. Analysis of covariance using the 3 statistical models was also performed on the secondary end point of the change from baseline in systolic BP. Responder rates were evaluated using the Mantel-Haenszel test. A 2-sided significance level of 0.05 was used when evaluating the primary and all secondary end points.

The efficacy analyses were performed on the full analysis set, which consisted of all treated patients with at least 1 trough BP measurement at the baseline and at the target dosage. For the primary analysis, the last observation following titration to the randomized target dosage was used in evaluating the change from baseline. The safety analyses were performed on all patients who received at least 1 dose of active treatment. The incidence of peripheral edema in the amlodipine 10-mg monotherapy group was compared with the 4 key combinations of telmisartan 40 mg or 80 mg plus amlodipine 5 mg or 10 mg in a post hoc analysis.

RESULTS

Population

A total of 2607 patients were enrolled in the study between April 2006 and November 2006, and 1461 were randomized and treated for up to 8 weeks. The baseline demographics are shown in Table I. A total of 1344 (92%) patients completed the 8-week trial. The efficacy analyses were performed on all patients with a baseline value and at least 1 efficacy measurement at target dose (n=1423). The safety analysis was performed on all patients who received at least 1 dose of study medication (n=1461). Compliance with study medication was 98.4% with no appreciable differences between the treatment groups. A total of 117 patients (8%) prematurely discontinued the study; the main reasons were adverse events (n=38), consent withdrawn (n=27), lack of efficacy (n=16), noncompliance (n=13), lost to follow-up (n=10), and other (n=13).

Table I. Baseline Demographics and Clinical Characteristics of Randomized Population

Variables	Total (N=1461)
Age, y	53.1±11.1
Males	737 (50.4)
Blood pressure, mm Hg	
Systolic	153.2±12.1
Diastolic	101.7±4.3
Pulse rate, beats per minute	74.4±9.3
Race	
Caucasian	1160 (79.4)
Black	237 (16.2)
Asian	64 (4.4)
Body mass index, kg/m^2	31.3±6.4
Duration of hypertension	
<1 year	211 (14.4)
1–5 years	444 (30.4)
>5 years	806 (55.2)
Previous antihypertensives used	
0	307 (21.0)
1	531 (36.3)
≥2	623 (42.6)
Diabetes	238 (16.3)
Renal impairment[a]	12 (0.8)

Values are expressed as mean ± standard deviation or No. (%). [a]Renal impairment was defined as serum creatinine >3.0 mg/d.

Efficacy Assessments

Both telmisartan (irrespective of amlodipine dosage; P<.0001) and amlodipine (irrespective of telmisartan dosage; P<.0001) significantly lowered the in-clinic trough diastolic BP, without evidence of counterproductive telmisartan-by-amlodipine interaction at any dosage (not involving patients treated with placebo; P=.1777).

As expected, the greatest least-square mean reductions in in-clinic diastolic and systolic BP were observed with combination therapy compared with respective monotherapies (Figure 1). The greatest overall reduction in BP was observed with the telmisartan 80-mg plus amlodipine 10-mg combination (mean reduction in systolic BP/diastolic BP: −26.4/−20.1 mm Hg; P<.05 vs both monothera-

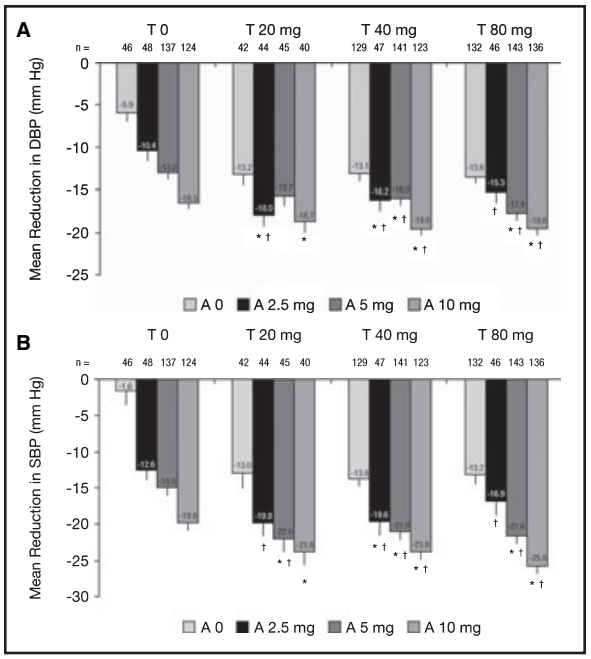

*Figure 1. Effect of 8 weeks of treatment with telmisartan (T) 0, 20, 40, 80 mg plus amlodipine (A) 0, 2.5, 5, 10 mg on the change from baseline in the in-clinic seated trough (A) diastolic blood pressure (DBP) (mm Hg) or (B) systolic blood pressure (SBP) (mm Hg). *P<.05 vs T monotherapy. †P<.05 vs A monotherapy. Data are least-square mean (SE) values adjusted for dosage, country/region, and baseline blood pressure.*

pies). When the mean reductions in diastolic or systolic BP were analyzed according to baseline categories, the 4 key combinations (telmisartan 40 mg or 80 mg plus amlodipine 5 mg or 10 mg) were all shown to consistently reduce BP even in patients with high baseline diastolic BP (≥110 mm Hg) (Figure 2A) and in patients with high baseline systolic BP (>160 mm Hg), achieving BP drops of more than 20 mm Hg diastolic BP and more than 30 mm Hg systolic BP with the combinations of telmisartan 40 mg or 80 mg and amlodipine 10 mg (Figure 2B).

The proportion of patients with BP control (diastolic BP <90 mm Hg and systolic BP <140 mm Hg) after 8 weeks of treatment is summarized in Table II. More than 50% of all patients treated with combination therapy achieved BP control, with the highest percentages (76.5% [overall control] and 85.3% [diastolic BP control]) being achieved by patients treated with telmisartan 80 mg plus amlodipine 10 mg. There was a clear relationship between dose and responder rate (Table II). Diastolic BP response and systolic BP response was achieved by 91.2% and 90.4% of patients in the telmisartan 80-mg plus amlodipine 10-mg group, respectively.

Safety Assessments

A total of 545 (37.3%) patients reported at least 1 adverse event during the 8-week study. When analyzed by treatment groupings, the percentage of patients reporting adverse events on specific treatment was comparable: placebo (39.1%, n=18), telmisartan monotherapy (36.8%, n=113), amlodipine monotherapy (36.1%, n=115), and combination therapy (37.9%, n=299) groups. The most commonly reported adverse events were headache (5.4%, n=79) and peripheral edema (4.4%, n=65). Headache was more frequent in the placebo group (10.9%, n=5) compared with the telmisartan monotherapy (5.9%, n=18), amlodipine monotherapy (6.0%, n=19), and combination therapy (4.7%, n=37) groups. The incidence of peripheral edema was highest in the amlodipine 10-mg group (17.8%, n=23); however, this rate was lower when amlodipine was used in combination with telmisartan: 11.4% (telmisartan 20 mg/amlodipine 10 mg), 6.2% (telmisartan 40 mg/amlodipine 10 mg), and 11.3% (telmisartan 80 mg/amlodipine 10 mg) (Figure 3). A total of 6 patients (2 in the amlodipine 10-mg group and 4 in the amlodipine 10-mg combination groups) discontinued the trial as a consequence of peripheral edema.

Drug-related adverse events were reported in 167 (11.4%) patients. These were lower in the telmisartan monotherapy group (6.5%, n=20) than in the placebo (13.0%, n=6), amlodipine monotherapy (12.2%, n=39), and combination therapy (12.9%, n=102) groups. The most frequent drug-related adverse events were peripheral edema (3.4%, n=50) and headache (2.1%, n=31). Adverse events associated with excessive BP lowering were reported at low rates in the placebo, telmisartan monotherapy, amlodipine monotherapy, and combination therapy groups; hypotension was reported in 0.0%, 0.0%, 0.0%, and 0.6%, respectively. There was no evidence of any dose-related trends in orthostatic changes (data not shown).

Serious adverse events were reported in 8 (0.5%) patients. Only one of the events (chest pain) in a patient in the telmisartan 80-mg plus amlodipine 2.5-mg group was considered related to study drug. There was one fatality (respiratory choking while eating dinner) during the study, which occurred in a patient who had been using telmisartan 80 mg. This was not considered drug-related and was not associated with any other condition. There were no clinically relevant changes on the electrocardiogram, in pulse rate, or in routine laboratory test results from baseline to end of study.

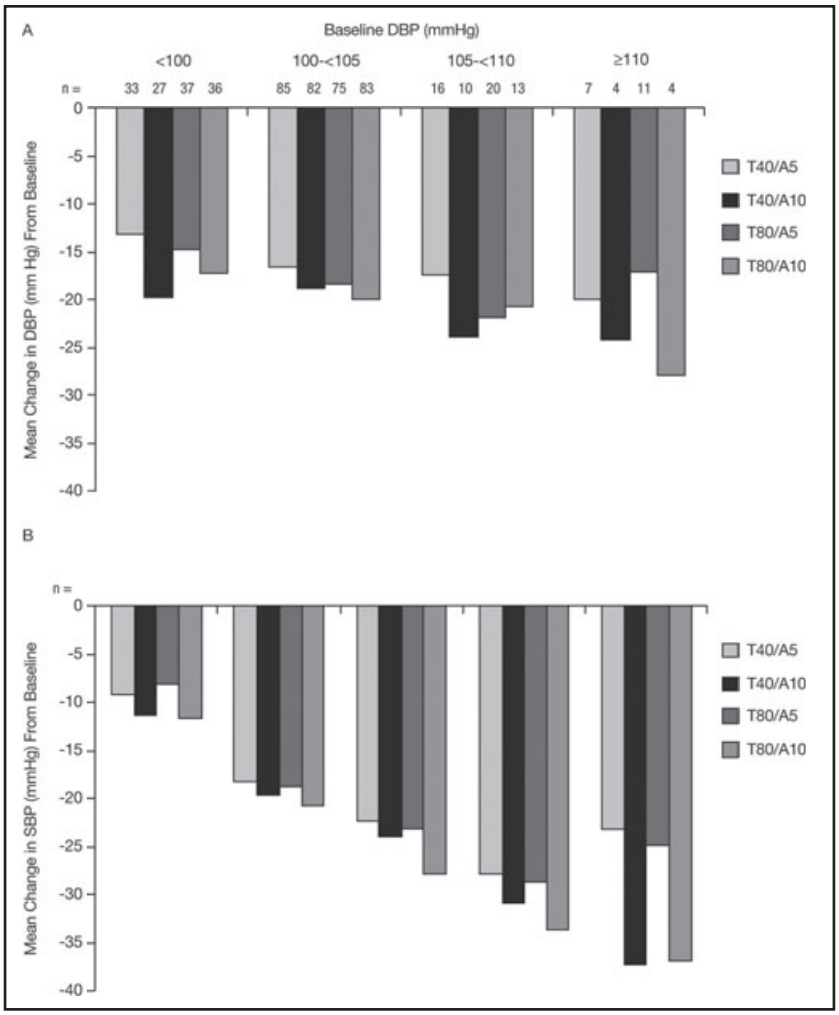

Figure 2. Effect of 8 weeks of treatment with the combinations of telmisartan 40 mg (T40) or 80 mg (T80) plus amlodipine 5 mg (A5) or 10 mg (A10) on the unadjusted mean change from baseline in the in-clinic trough (A) diastolic blood pressure (DBP) (mm Hg) or (B) systolic blood pressure (SBP) (mm Hg) according to baseline blood pressure categories.

DISCUSSION

As anticipated, significant in-clinic BP reductions were observed following 8 weeks of treatment with telmisartan plus amlodipine in this randomized population of 1461 patients with stage 1 and 2 hypertension. Statistically significant reductions in both in-clinic systolic BP and diastolic BP were observed with the combinations of most clinical interest (ie, telmisartan 40 mg or 80 mg plus amlodipine 5 mg or 10 mg). There was evidence of a dose effect as the greatest reduction in systolic BP/diastolic BP (−26.4/−20.1 mm Hg; $P<.05$ compared with each monotherapy) was observed with telmisartan 80 mg plus amlodipine 10 mg. This also resulted in the greatest percentage of patients achieving BP control (76.5%) and diastolic BP control (85.3%). Diastolic BP and systolic BP responses were also high in the telmisartan 80-mg plus amlodipine 10-mg group (91.2% and 90.4%, respectively).

These results are consistent with other factorial studies where combination therapy with an ARB (valsartan or olmesartan) and amlodipine were more effective than respective monotherapies, in lowering BP. Philipp and colleagues[14] report findings from 2 valsartan/amlodipine studies in which 1911 and 1250 patients were randomized to the different treatments for 8 weeks. These studies showed that both monotherapies contributed to the overall efficacy of the combination and the biggest reductions were attained with the highest dose (valsartan 320 mg/amlodipine 10 mg). Similar reductions of more than 25 mm Hg in systolic BP and more than 18 mm Hg in diastolic BP were

Table II. Effect of 8 Weeks of Treatment With Telmisartan Plus Amlodipine on Blood Pressure Response and Control Rates (N=1423)

Treatment	DBP Response, %[a]	SBP Response, %[a]	Control, %[b]	DBP Control, %[c]
Telmisartan 0 mg/amlodipine 0 mg	39.1	32.6	19.6	30.4
Telmisartan 20 mg/amlodipine 0 mg	64.3	64.3	40.5	54.8
Telmisartan 40 mg/amlodipine 0 mg	69.8	63.6	42.6	53.5
Telmisartan 80 mg/amlodipine 0 mg	78.0	65.2	41.7	60.6
Amlodipine 2.5 mg/telmisartan 0 mg	52.1	47.9	25.0	33.3
Amlodipine 5 mg/telmisartan 0 mg	67.9	73.0	42.3	52.6
Amlodipine 10 mg/telmisartan 0 mg	85.5	82.3	62.9	73.4
Telmisartan 20 mg/amlodipine 2.5 mg	90.9	84.1	52.3	75.0
Telmisartan 20 mg/amlodipine 5 mg	80.0	77.8	51.1	64.4
Telmisartan 20 mg/amlodipine 10 mg	92.5	87.5	70.0	85.0
Telmisartan 40 mg/amlodipine 2.5 mg	87.2	83.0	66.0	72.3
Telmisartan 40 mg/amlodipine 5 mg	80.9	88.7	58.9	71.6
Telmisartan 40 mg/amlodipine 10 mg	91.9	91.9	75.6	82.1
Telmisartan 80 mg/amlodipine 2.5 mg	73.9	76.1	56.5	69.6
Telmisartan 80 mg/amlodipine 5 mg	88.8	83.9	65.7	74.8
Telmisartan 80 mg/amlodipine 10 mg	91.2	90.4	76.5	85.3

[a]Diastolic blood pressure (DBP) <90 mm Hg or ≥10 mm Hg reduction; systolic blood pressure (SBP) <140 mm Hg or ≥15 mm Hg reduction. [b]Trough DBP <90 mm Hg; trough SBP <140 mm Hg. [c]DBP <90 mm Hg.

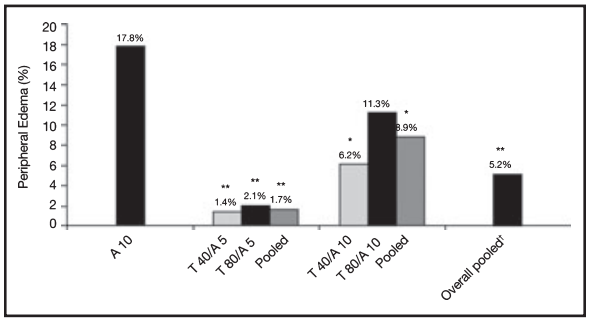

*Figure 3. Incidence of peripheral edema (%) in the amlodipine 10-mg (A10) group compared with combinations (telmisartan 40 mg [T40] or 80 mg [T80] plus amlodipine 5 mg [A5] or 10 mg). *P<.05. **P<.0001 vs A10. †Pooled for key combinations.*

observed by Chrysant and colleagues,[10] with the highest dose of olmesartan and amlodipine (40 mg/10 mg, respectively) in an 8-week factorial study in 1940 patients with higher baseline BP values.

The ACCOMPLISH study, which compared 2 different approaches of combination therapy suggests that the combination of an ACE inhibitor with amlodipine may provide better cardiovascular protection than an ACE inhibitor and diuretic at similar levels of BP control.[8,15] Although cumulative, mounting evidence supports the therapeutic equivalence between ARBs and ACE inhibitors, there are no studies to date that report the cardiovascular benefits of the combination of an ARB and a CCB. Nevertheless, the favorable tolerability profile of an ARB alone or in combination makes them an appealing alternative to ACE inhibitors.

The safety analysis showed that the number of patients experiencing an adverse event was comparable between combination therapy (37.9%) and the telmisartan (36.8%) and amlodipine (36.1%) monotherapies. Retention and drug adherence were high (92% and 98.4%, respectively). However, as expected, amlodipine 10 mg was associated with a high incidence of peripheral edema (17.8%) compared with all dosages of telmisartan monotherapy (range: 0.0%–0.8%). When telmisartan (all dosages) was used in combination with amlodipine 10 mg, the incidence of peripheral edema was notably reduced: 6.2% (telmisartan 40 mg/amlodipine 10 mg) and 11.3% (telmisartan 80 mg/amlodipine 10 mg). Although CCB-induced edema is not a new finding, the underlying mechanism is still not fully understood. It may involve pronounced vasodilation in precapillary vessels, which could result in abnormal intracapillary pressure or it could be linked to interference in local vasodilator control.[16,17] RAAS blockade is known to attenuate this effect, possibly via normalization of intracapillary pressure. However, the attenuation of edema has not been observed with some other combinations such as amlodipine plus hydrochlorothiazide.[18]

CONCLUSIONS

In conclusion, the findings in our study suggest that the combination of telmisartan plus amlodipine is associated with significant BP lowering after 8 weeks. The results of this factorial design study

are in line with the observations from factorial studies of other ARB/amlodipine combinations. However, head-to-head studies are needed to determine if the different pharmacokinetic profile of the individual ARBs, eg the longest half-life of telmisartan, are translated into clinically different pharmacodynamic effects among the 3 ARB/amlodipine combinations.

Overall, among the different combinations of telmisartan and amlodipine, it is clear that telmisartan 80 mg plus amlodipine 10 mg is the most effective combination and when treatment decisions have to take into consideration not only the antihypertensive efficacy but also the peripheral edema rates, the telmisartan and amlodipine combinations offer a very effective and tolerable option particularly in susceptible patients that require combination therapy.

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