Results of a Comparative, Phase III, 12-Week, Multicenter, Prospective, Randomized, Double-Blind Assessment of the Efficacy and Tolerability of a Fixed-Dose Combination of Telmisartan and Amlodipine Versus Amlodipine Monotherapy in Indian Adults with Stage II Hypertension

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ABSTRACT

Objective: The aim of this study was to evaluate the efficacy and tolerability of a new fixed-dose combination (FDC) of telmisartan 40 mg + amlodipine 5 mg (T+A) compared with amlodipine 5-mg monotherapy (A) in adult Indian patients with stage II hypertension.

Methods: This comparative, Phase III, 12-week, multicenter, prospective, randomized, double-blind study was conducted in Indian patients aged 18 to 65 years with established stage II hypertension. Patients were treated with oral FDC of T+A or A QD before breakfast for 12 weeks; blood pressure (BP) and heart rate were measured in the sitting position. Primary efficacy end points were reduction in clinical systolic BP (SBP)/diastolic BP (DBP) from baseline to study end and number of *responders* (ie, patients who achieved target SBP/DBP <130/<80 mm Hg) at end of study. Tolerability was assessed by treatment-emergent adverse events, identified using physical examination, laboratory analysis, and electrocardiography.

Results: A total of 210 patients were enrolled in the study; 203 patients (143 men, 60 women) completed the study while 7 were lost to follow-up (4 patients in the T+A group and 3 in the A group) and considered withdrawn. At study end, statistically significant percentage reductions from baseline within groups and between groups were observed in SBP (T+A [–27.4%]; A [–16.6%]) and DBP (T+A [–20.1%]; A [–13.3%]) (all, $P < 0.05$). Response rates were 87.3% (89/102) in the T+A group and 69.3% (70/101) in the A group ($P < 0.05$). The prevalences of adverse events were not significantly different between the 2 treatment groups (T+A, 16.0% [17/106]; A, 15.4% [16/104]). Peripheral edema was reported in 8.5% patients (9/106) in the T+A group compared with 13.5% (14/104) in the A group, and cough was reported in 3.8% patients (4/106) in the T+A group and 1.0% (1/104) patients in the A group; these differences did not reach statistical significance. The incidences of headache, dizziness, and diarrhea were similar between the 2 groups.

Conclusions: Among these Indian patients with stage II hypertension, the FDC of T+A was found to be significantly more effective, with regard to BP reductions, than A, and both treatments were well tolerated. (*Clin Ther*. 2007;29:2667–2676) Copyright © 2007 Excerpta Medica, Inc.

Key words: stage II hypertension, telmisartan, amlodipine.

INTRODUCTION

High blood pressure (BP) is a leading risk factor for cardiovascular morbidity and mortality.[1] Effective antihypertensive therapy is available, but recognition and proper management of hypertension and BP goal

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achievement are still poor. It has been reported that approximately one third of all hypertensive patients (all ages) achieve the BP goal of <140/<90 mm Hg.[1] Furthermore, of the 58% of treated hypertensive patients, half achieve goal.[1,2] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) recommends a BP goal of <140/<90 mm Hg in patients with hypertension and <130/<80 mm Hg in those with diabetes or chronic renal disease.[1] Achievement of BP goals is associated with significant benefits in cardiovascular morbidity and mortality.[1] Although evidence suggests these goals are attainable, only about one third of patients are successful in meeting them.[3]

Clinical trials[4,5] in hypertension suggest that single-drug therapy may not achieve the target BP goals and related reductions in cardiovascular morbidity and mortality. Likely candidates for initial combination therapy include patients with initial BP >160/>100 mm Hg or those with a BP goal lower than the recommended <140/<90 mm Hg (ie, patients with target organ damage, clinical cardiovascular disease, proteinuria, renal impairment, diabetes mellitus). An angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (ARB) may be recommended as first-line treatment and adding a diuretic or calcium channel blocker (CCB) to it is much more likely to result in achievement of the BP goal.[6]

It has been reported that, on average, a reduction in systolic BP (SBP) of 2 mm Hg translates into a 10% reduction in risk for fatal stroke and a 7% reduction in risk for fatal coronary events.[7] Furthermore, since hypertension has been associated with target organ damage, lowering the BP has the additional advantage of improving morbidity and mortality and, if intervention is initiated early enough, preventing organ damage.[5,8–10] Trials such as the Hypertension Optimal Treatment study and the United Kingdom Prospective Diabetes Study have shown that diabetes-related end points benefited more from tight BP control than from tight glucose control.[5,8,9] Thus, attaining BP goal is crucial in the treatment of hypertension.

CCBs are a chemically heterogeneous group of substances that effectively reduce elevated BP in all age groups and have been found to have organoprotective properties.[11] Amlodipine, a peripheral arterial vasodilator, inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle and acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and BP.[12]

The ARB telmisartan has been approved by the US Food and Drug Administration for the treatment of hypertension.[13] Telmisartan has a long half-life (~24 hours) and duration of action.[13] Significantly greater mean changes in SBP and diastolic BP (DBP) were seen with telmisartan 40 mg (–14.21/–8.61) and 80 mg (–15.0/–9.71) during the 24-hour dosing period and during the last 6 hours (–10.7/–6.8 and –12.2/–7.1, respectively) before dosing compared with losartan 50 mg (–10.3/–6.0 and –6.0/–3.7) (all, $P < 0.05$).[14,15]

Based on a literature search from January 2003 through August 2007 using MEDLINE (terms: *telmisartan*, *amlodipine*, and *hypertension*), 1 study was identified that compared the efficacy and tolerability of a fixed-dose combination (FDC) of telmisartan + amlodipine with that of amlodipine monotherapy in 300 hypertensive patients with type 2 diabetes and microalbuminuria.[15] In that comparative, randomized, placebo–run-in, prospective study, reductions from baseline in urinary albumin excretion rates were 34.6 mg/24 h ($P < 0.05$ vs baseline), 62.9 mg/24 h ($P < 0.01$ vs baseline and $P < 0.05$ vs amlodipine monotherapy), 86.5 mg/24 h ($P < 0.001$ vs baseline and $P < 0.01$ vs amlodipine) and 102 mg/24 h ($P < 0.001$ vs baseline and vs amlodipine monotherapy) with telmisartan/amlodipine 40, 80, 120, and 160/2.5 mg/d, respectively. Reductions from baseline in urinary albumin excretion rates were 35.1 mg/24 h ($P < 0.05$ vs baseline), 46.3 mg/24 h ($P < 0.03$ vs baseline) 50.3 mg/24 h ($P < 0.03$ vs baseline), and 45 mg/24 h ($P < 0.03$ vs baseline) with amlodipine/telmisartan 2.5, 5, 7.5 and 10/40 mg/d, respectively. Both drugs were well tolerated, and the difference in reported adverse events (AEs) was not significant (10 patients [10%] in the telmisartan group; 15 [14%] in the amlodipine group). Reported AEs were dizziness (n = 5), nausea (n = 3), asthenia (n = 2), and headache (n = 1) in the telmisartan + amlodipine group and leg edema (n = 7), headache (n = 3), hot flushes (n = 3), and palpitations (n = 2) in the amlodipine group.

An open-label, noncomparative, postmarketing surveillance study by Gokhale et al[16] was conducted with the FDC of another ARB, losartan potassium, and amlodipine besylate in 719 Indian patients with mild to moderate hypertension. Mean SBP was significantly ($P < 0.05$) reduced by 33.8 mm Hg (19.1%), from baseline, while mean DBP also was significantly ($P = 0.05$) reduced, by 18.6 mm Hg (17.7%), from baseline after 20 days of treatment. This combination was well tolerated, with the most common AEs re-

ported being edema of the feet (5.1%) and ankle (2.0%). Other AEs included palpitation, constipation, muscular pain, weakness, generalized swelling, giddiness, headache, and insomnia. Thus, an FDC of a CCB and an ARB has been found to be effective and reasonably well tolerated when used as directed in the treatment of Indian hypertensive patients.[16]

In an 8-week, open-label study,[17] adding amlodipine to a regimen containing telmisartan in patients with newly diagnosed (within 6 months without medication) stage I or II hypertension was associated with significant BP reductions from baseline ($P < 0.001$). However, statistically significant reductions between both treatments were not seen in ambulatory BP (ABP) during day (9.3/6.0 and 14.7/9.4 mm Hg, respectively) or night (12.4/7.7 and 13.3/8.6 mm Hg) readings after 8 weeks of treatment. That study found that low-dose combination therapy with telmisartan + amlodipine was associated with significant reductions in ABP during each 24-hour interval compared with high-dose telmisartan monotherapy in hypertensive patients whose BP was not controlled with low-dose monotherapy. Moreover, patients receiving monotherapy with a CCB (amlodipine, felodipine, lacidipine) more often experienced AEs and required therapy to be discontinued or modified. While the study did not mention the number of patients who discontinued treatment, it is mentioned that 11.4% of patients (4/35) treated with the high-dose CCB (amlodipine, felodipine, lacidipine) required treatment modification in comparison to 4.8% of patients (2/42) treated with the high-dose ARB (telmisartan, irbesarten, candesarten, losarten, valsartan) and 6.7% of patients (4/60) treated with telmisartan + amlodipine ($P < 0.05$).[17]

The present study was undertaken to evaluate the efficacy and tolerability of a new FDC of telmisartan 40 mg + amlodipine 5 mg (T +A) and that of amlodipine 5-mg monotherapy (A) in adult Indian patients with stage II hypertension.

PATIENTS AND METHODS

Study Design

This comparative, Phase III, 12-week, multicenter, prospective, randomized, double-blind study was undertaken in India. Study protocols were reviewed and approved by the review boards of the participating institutions. The study was conducted in compliance with the principles set forth in the Guideline for Good Clinical Practice[18] and the Declaration of Helsinki and its amendments.[19]

Inclusion and Exclusion Criteria

Indian male and female patients aged 18 to 65 years with established stage II uncomplicated essential hypertension (SBP, 160–179 mm Hg; DBP, 100–109 mm Hg) were eligible for participation in the study.

Patients hypersensitive to telmisartan, amlodipine, other ARBs, and/or other dihydropyridine CCBs, or who were pregnant (as determined by a positive serum β-human chorionic gonadotropin test and urinalysis) or breastfeeding were excluded from the study. Additional reasons for exclusion included severe hypertension, malignant hypertension, or secondary hypertension; history of acute myocardial infarction; coronary revascularization; unstable angina pectoris; arrhythmia requiring treatment during the previous 6 months; New York Heart Association class IV heart failure or severe aortic or mitral valvular disease requiring medical treatment or causing hemodynamically significant disturbances; stroke or transient ischemic attack within the previous 6 months; significant cardiac, hepatic, renal, or cerebrovascular disease; uncontrolled diabetes mellitus; and/or other serious illness (eg, malignancy, HIV). Patients with concurrent use of other hypertensives, including diuretics, α-blockers, β-blockers, or CCBs, and those with a serum potassium concentration <3.0 mEq/L and >5.0 mEq/L were also excluded, as were those with malignancy, severe chronic systemic diseases, or any condition likely to hamper compliance with the study protocol (eg, remote location, inability to follow study instructions) or those unwilling to maintain a daily diary or who had participated in a new drug study in the previous 3 months.

All eligible patients were provided an oral explanation about the nature of the study and about the study drugs by the investigator at each center. An information sheet was provided in a language understood by the patient, and written informed consent was obtained from each participant prior to any study-related procedure.

Treatment

All antihypertensive treatments were discontinued and placebo was administered for 2 weeks before the start of the study. Lifestyle modifications (exercise: light aerobic physical activity [eg, brisk walking for ≥ 30 min/d most days of the week] and diet [sodium intake <240 mg/d as per the JNC7 guideline[8]]) were recommended during the 2-week placebo run-in peri-

od and continued throughout the study period. Compliance with lifestyle modifications was assessed through questioning patients at follow-up regarding the modifications and through patient entry on the adherence to the instructions regarding diet and exercise in the diary card.

After the placebo run-in period, patients were randomly assigned (in a 1:1 ratio using SPSS version 10.2 software [SPSS Inc., Chicago, Illinois] computer-generated randomization list) to receive an oral tablet formulation of an FDC of telmisartan 40 mg + amlodipine 5 mg (T+A) or amlodipine 5 mg (A), once daily before breakfast for 12 weeks. To maintain blinding of the investigators and patients, the study drugs were identical in appearance and were provided in identical sealed containers. The randomization code was broken only after analyses were completed. Treatment compliance was monitored throughout the study using a count of the unused medication at each visit.

The use of antihypertensive treatment (other than the exercise and dietary modifications) was not permitted during the study period. However, the use of medications for concomitant conditions (eg, antidiabetic agents, acetylsalicylic acid) and any other treatments (eg, multivitamins, antioxidants, mineral supplements) that would not interfere with the study drugs was permitted.

After the end of the study, treatment with either study drug and/or any other antihypertensive agent at an appropriate dose was continued at the discretion of the attending physician.

Efficacy Assessments

The primary efficacy end points were reductions in clinical SBP and DBP from baseline (week 0) to study end (week 12) and the number of *responders* (those who achieved clinical SBP/DBP <130/<80 mm Hg).

The methods for measuring BP and heart rate (HR) were standardized at each center: at each visit, BP was measured in the morning, ~24 hours after the previous drug administration and after 5 minutes of rest, using a standard 6-inch cuff mercury sphygmomanometer (Diamond Mercurial Deluxe, IEAP, Pune, India) that was calibrated prior to use. Patients were sitting upright in a chair with their feet on the floor and 1 arm supported at heart level. Sitting BP was measured 2 times with an interval of ~5 minutes, and the mean of the 2 measurements was calculated. Elevated BP was confirmed by measuring the BP in the other arm (mean of 2 measurements). HR was determined using palpation of the radial pulse in the wrist for 1 minute.

Tolerability Assessments

At the screening visit (before placebo run-in), each patient underwent a physical examination and medical history, including measurements of SBP, DBP, and HR, and demographic data were recorded. Laboratory analysis (including hematology, biochemistry, and urinalysis), chest radiography, and electrocardiography were performed at this visit. Follow-up visits were carried out at 2, 4, 8, and 12 weeks of treatment and included BP and HR measurements. Peripheral edema was identified on physical examination. Laboratory parameters were tested using standardized procedures at the centralized laboratory of each institution. At each visit, AEs were also collected using patient reports, patient questioning, and investigator observation and were recorded on case-report forms.

Statistical Analysis

The sample size calculation was based on the number of responders and the percentage of patients with a reduction in clinical SBP and DBP of ≥5 mm Hg at study end in each group. It was determined that a sample of 100 patients per group was needed to provide 80% power to detect a 5-mm Hg between-group difference and ≥20% response rate in the primary end points (reduction in clinical SBP and DBP from baseline to week 12 and number of responders) at a significance level of $\alpha = 0.05$ for 2 comparisons.

All randomized patients who received all doses of study medications and completed the study were included. Between-group differences in baseline demographic data and changes in HR, laboratory parameters, and clinical SBP/DBP were analyzed using analysis of variance, whereas response rate and AE profile in each group were analyzed using the χ^2 test.

The per-protocol (PP) population included all patients who received ≥1 dose of study medication, and the PP assessment consisted primarily of incidences of AEs, withdrawals attributable to AEs, and serious AEs.

Data analyses were performed using SPSS version 10.2 software. Differences were considered statistically significant if $P \leq 0.05$. Data are expressed as mean (SD).

RESULTS

Patient Population

A total of 210 patients (143 men, 67 women; mean age, 50.8 years; mean weight, 67.2 kg) met the inclusion criteria and were enrolled in the study (n = 106 for T+A, n = 104 for A). Medical social workers tracked patients for follow-up. However, 7 (n = 4 for the T+A group and n = 3 for the A group) patients were lost to follow-up: 5 due to relocation and 2 who were tracked after a gap of 4 weeks without medication and were therefore not included in the study. Thus, data from 203 patients (n = 102 for T+A, n = 101 for A) were included in the PP analysis. Data from all 210 patients were included in the tolerability analysis. The demographic and clinical characteristics at baseline were statistically comparable between the groups (**Table I**), including HR and SBP/DBP. Questioning of the patients at each follow-up visit helped to confirm their adherence to diet and exercise recommendations. All patients who completed the study reported adherence to the diet and exercise recommendations (101/102 [99.0%] and 98/101 [97.0%], respectively).

Effectiveness

Changes in SBP

From week 2 through week 12, significant reductions from baseline in mean (SD) SBP were found in the 2 groups (T+A, from 176.3 [10.6] to 128.0 [12.7] mm Hg;

Table I. Demographic and clinical characteristics of the study patients.*

Characteristic	Telmisartan + Amlodipine (n = 106)	Amlodipine (n = 104)
Age, y		
Mean (SD)	51.3 (8.7)	50.2 (9.9)
Range	32–80	26–70
Sex, no. (%)		
Male	71 (67.0)	72 (69.2)
Female	35 (33.0)	32 (30.8)
Weight, kg		
Mean (SD)	67.3 (10.3)	67.2 (14.6)
Range	40–96	40–110
Height, cm		
Mean (SD)	163.4 (7.8)	163.8 (7.8)
Range	145–180	146–180
Concomitant diseases, no. (%)		
Osteoarthritis	7 (6.6)	8 (7.7)
CHD	3 (2.8)	2 (1.9)
Peripheral vascular disease	2 (1.9)	1 (1.0)
History of MI/stroke	2 (1.9)	1 (1.0)
Comorbid type 2 diabetes, no. (%)	29 (27.4)	26 (25.0)
Prior therapy, no. (%)		
ARBs	29 (27.4)	31 (29.8)
CCBs	20 (18.9)	19 (18.3)
β-Blockers	7 (6.6)	8 (7.7)
ACEIs	6 (5.7)	8 (7.7)
Diuretics	2 (1.9)	3 (2.9)

CHD = coronary heart disease; MI = myocardial infarction; ARBs = angiotensin II–receptor blockers; CCBs = calcium channel blockers; ACEIs = angiotensin-converting enzyme inhibitors.
*No significant between-group differences were found.

A, from 171.8 [10.3] to 143.4 [12.1] mm Hg; both, $P < 0.05$ vs baseline) (**Table II**). The between-group difference in mean percentage reduction in SBP at 2 weeks was not significant (T+A, –9.0%; A, –6.8%). At the end of week 12, statistically significant mean percentage reductions from baseline in SBP were –27.4% and –16.6% in the T+A and A groups, respectively ($P < 0.05$ within group and between groups from baseline to week 12).

Changes in DBP

At week 2, significant reductions from baseline in mean (SD) DBP were found in the 2 treatment groups (T+A, from 100.9 [6.0] to 93.8 [5.8] mm Hg; A, from 99.7 [6.8] to 94.3 [7.3] mm Hg; both, $P < 0.05$). The percentage reductions from baseline in DBP were also statistically significant ($P < 0.05$) but similar between the 2 groups at 2 weeks (T+A, 7.1%; A, 5.4%). At the end of week 12, there was a 20.2% reduction in mean DBP in the T+A group, which was significantly greater compared with the reduction of 12.7% observed in the A group ($P < 0.05$ between groups and within both groups at week 12 vs baseline).

Response Rates

A total of 89/102 patients (87.3%) receiving T+A reached a target SBP/DBP of <130/<80 mm Hg at 12 weeks, which was statistically significant compared with 70/101 patients (69.3%) receiving A ($P < 0.05$) (**Figure**).

There were 55 patients with comorbid type 2 diabetes mellitus, 29 of whom received therapy with T+A, 26 with A. At the end of 12 weeks, 15/29 patients (51.7%) in the T+A group and 9/26 patients (34.6%) in the A group achieved target BP. The difference between the groups was not statistically significant.

Tolerability

A total of 17/106 patients (16.0%) in the T+A group experienced AEs compared with 16/104 patients (15.4%) in the A group; this difference between the 2 groups was not statistically significant. All AEs were mild to moderate in severity (**Table III**).

The most common AEs in the T+A group were peripheral edema (9/106 patients [8.5%]), headache (6/106 patients [5.7%]), dizziness and cough (4/106 patients each [3.8%]), and diarrhea (2/106 patients [1.9%]). Sinusitis and upper respiratory tract infection (URTI) each occurred in 1/106 patient [0.9%].

The most common AEs in the A group were peripheral edema (14/104 patients [13.5%]), headache (5/104 patients [4.8%]), dizziness and diarrhea (3/104 patients each [2.9%]), vertigo (2/104 patients [1.9%]), and cough and URTI (1/104 patient each [1.0%]).

No statistically significant changes in HR were found with either treatment at follow-up visits. No significant changes from baseline were observed in hematology or biochemistry parameters. At baseline, mean (SD) concentrations of serum potassium were 3.7 (0.4) mEq/L in the T+A group and 3.7 (0.2) mEq/L in the A group; at study end, no significant changes in the mean (SD) potassium concentrations were found (3.9 [0.3] mEq/L and 4.0 [0.3] mEq/L in the T+A and A groups, respectively).

Table II. Systolic (SBP) and diastolic blood pressure (DBP) throughout the study with telmisartan + amlodipine (T+A) or amlodipine monotherapy (A) in adult Indian patients with stage II hypertension. Values are mean (SD) mm Hg.

	SBP, mm Hg		DBP, mm Hg	
Time Point	T+A (n = 102)	A (n = 101)	T+A (n = 102)	A (n = 101)
Baseline	176.3 (10.6)	171.8 (10.3)	100.9 (6.0)	99.7 (6.8)
Week 2	160.3 (11.3)*	160.0 (9.7)*	93.8 (5.8)*	94.3 (7.3)*
Week 4	147.1 (12.9)*	152.3 (11.9)*	86.8 (6.6)*	91.2 (6.6)*
Week 8	136.1 (14.1)*†	146.5 (12.6)*	83.9 (5.7)*†	88.7 (6.6)*
Week 12	128.0 (12.7)*†	143.4 (12.1)*	80.7 (5.5)*†	87.1 (7.0)*

*$P < 0.05$ versus baseline (*t* test).
†$P < 0.05$ between groups (*t* test).

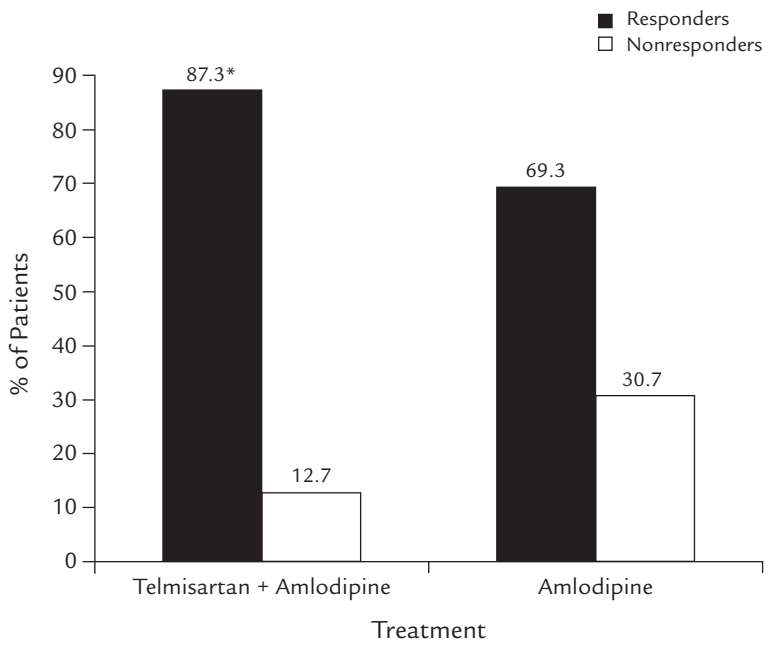

Figure. Response rates (percentages of patients achieving target blood pressure [<130/<80 mm Hg]) after 12 weeks of treatment with telmisartan + amlodipine or amlodipine monotherapy in adult Indian patients with stage II hypertension. *$P < 0.05$ versus amlodipine.

Table III. No of patients with adverse events (AEs)* during 12-week treatment with telmisartan + amlodipine (T+A) or amlodipine monotherapy (A) in adult Indian patients with stage II hypertension.

	T+A (n = 106)			A (n = 104)		
AE	No. (%)	Mild, No.	Moderate, No.	No. (%)	Mild, No.	Moderate, No.
Peripheral edema	9 (8.5)	6	3	14 (13.5)	9	5
Headache	6 (5.7)	6	0	5 (4.8)	3	2
Dizziness	4 (3.8)	3	1	3 (2.9)	2	1
Cough	4 (3.8)	0	4	1 (1.0)	1	0
Diarrhea	2 (1.9)	2	0	3 (2.9)	3	0
Sinusitis	1 (0.9)	1	0	0	0	0
Vertigo	0	0	0	2 (1.9)	1	1
URTI	1 (0.9)	1	0	1 (1.0)	1	0
Total	17 (16.0)	–	–	16 (15.4)	–	–

URTI = upper respiratory tract infection.
*Some patients experienced >1 AE.

At baseline, mean (SD) serum creatinine concentrations were 1.1 (0.1) and 1.1 (0.07) mg/dL in the T+A and A groups, respectively; after treatment, no significant changes from baseline concentrations were found (1.0 [0.1] and 1.0 [0.1] mg/dL in the T+A and A groups, respectively).

DISCUSSION

The need for stricter BP control has been suggested because BP levels ≤130/<80 mm Hg provide additional benefits with regard to target organ protection (morbidity) and cardiovascular mortality.[5,9,11]

Among the antihypertensive drugs currently available, dihydropyridine CCBs and ARBs play an important role in hypertensive patients because they protect target organs and provide good tolerability.[20–23] Additionally, both groups of drugs have a favorable metabolic profile.[12,13]

The results of the present study indicate the antihypertensive efficacy of T+A and A. However, T+A (telmisartan 40 mg + amlodipine 5 mg) was found to be significantly more efficacious in reducing BP at the end of 12 weeks of treatment compared with A. The reductions in SBP and DBP were significantly greater in patients treated with T+A compared with those treated with A (27.4% and 20.1% vs 16.6% and 13.3%, respectively; both, $P < 0.05$). Moreover, a significantly greater number of patients in the FDC of T+A group achieved the target SBP/DBP <130/<80 mm Hg compared with those in the A group (84/102 [82.4%] vs 64/101 [63.4%]; $P < 0.05$).

Similar results were observed in a clinical study with the combination of losartan + amlodipine.[24] In that multicenter, randomized, double-blind, comparative study, 198 patients were followed for 12 weeks in the short-term study and 131 of the patients were followed up to 52 weeks in the long-term study. The authors observed that a low dose of losartan (100 mg) + amlodipine (5 mg) was more efficacious ($P < 0.04$) in lowering BP than monotherapy with losartan (100 mg) or amlodipine (5 mg). It was observed that 66.0% of patients treated with the combination of losartan + amlodipine maintained DBP <85 mm Hg compared with 63.6% in the amlodipine group and 51.7% in the losartan group. It was reported that although BP levels similar to those observed with the fixed combination were achieved by using amlodipine at high doses, a significant loss of efficacy and BP normalization end point was found in a significant number of patients treated with this monotherapy. Efficacy decreased from 79.3% to 51.7% with losartan monotherapy, from 97.7% to 75.0% with amlodipine monotherapy, and from 93.6% to 87.2% with the fixed-dose combination.

Similar results were also observed in a randomized, comparative study in 302 patients.[17] The mean (SD) decreases 6 weeks after initiation of drug treatment from baseline in SBP were 19.6 (17.3) mm Hg in the group treated with the low-dose CCB (amlodipine, felodipine, lacidipine) (group A) and 16.2 (16.5) mm Hg in the group treated with the low-dose ARB (telmisartan, irbesartan, candesartan, losartan, valsartan) (group B); this difference did not reach statistical significance. The mean (SD) decreases in DBP were −10.8 (9.6) mm Hg in group A and −8.6 (9.4) mm Hg in group B which were not significant. Of the 137 subjects who failed on low-dose monotherapy, 35 (25.5%) were switched to a high-dose CCB (group A1), 42 (30.7%) were switched to a high-dose ARB (group B1), and 60 (43.8%) were switched to a low-dose combination of CCB+ARB (group C) for 6 weeks. At 6 weeks after the switch, the mean (SD) reductions in SBP were 9.8 (15.2), 8.7 (15.9), and 12.7 (16.2) mm Hg, respectively ($P < 0.05$ for group C vs groups A1 and B1) and in DBP, 6.8 (7.2), 6.9 (7.2), and 6.7 (9.3) mm Hg. The reduction in SBP was significantly higher in group C than in groups A1 and B1 ($P < 0.05$). In groups A1 and B1, 42.9% (15/35) and 40.5% (17/42) of patients achieved adequate BP control, while in group C, this rate was 61.7% (37/60) ($P < 0.05$ vs groups A1 and B1). Rates of drug withdrawal and treatment modification were significantly higher in group A1 than groups B1 and C, likely due to intolerability with high doses of the CCB. Specifically, 11.4% of patients (4/35) in group A1 required treatment modification in comparison to 4.8% (2/42) in group B1 and 6.7% (4/60) in group C (both, $P < 0.05$).[17]

In addition to reducing BP and maintaining it at controlled levels, an antihypertensive medication should also have a good tolerability profile because the presence of AEs may decrease patient compliance, ultimately leading to treatment discontinuation.[15,17] The most common AEs in the present study with the FDC of T+A and with A were peripheral edema and headache. Although this study was not powered to detect differences in the incidence of peripheral edema, the incidence of this AE was found to be numerically lower in the T+A group than in the A group (9/106 vs 14/104), but this was not statistically significant.

Amlodipine, a potent antihypertensive drug by virtue of its potent action as an arterial vasodilator, also has natriuretic, antiproliferative, and antisclerotic effects.[21,22,25] However, this antihypertensive drug class does not promote venodilation, and it facilitates fluid extravasation into the interstitial space, which enables the formation of peripheral edema due to the gravity force and is frequently regarded as the cause of treatment withdrawal.[21,22,25,26] However, clinical practice has found that a 50% reduction in the dose of amlodipine results in the loss of ≥20% of the hypotensive effect provided by the full dose, thus making the goal of controlling BP difficult to achieve.[27,28] By adding a drug that promotes venodilation to the CCB, it is possible to reduce or prevent CCB-induced peripheral edema.[23,24,26,29]

Patient compliance to treatment with antihypertensive agents is also known to be influenced by a number of factors, including the absence of symptoms, the development of AEs, and the number of tablets that need to be taken per day. In this study, all patients appeared to have complied with the therapeutic regimen as indicated by the return of empty containers at each follow-up visit.

Study Limitations

The exclusion criteria in this study limited the application of the results to the general population. Also, a third arm comprising patients treated with telmisartan monotherapy was not included for comparison with the other 2 groups, and the dosage of amlodipine was not titrated upward. Furthermore, a pill count is not a reliable estimate of true compliance. A long-term follow-up of the FDC of T+A in a larger group of hypertensive patients is warranted.

CONCLUSIONS

Among these adult Indian patients with stage II hypertension, the FDC of T+A was found to be significantly more effective, with regard to BP reductions, than A, and both treatments were well tolerated.

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