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Efficacy and Safety of Combination Therapy Using High- or Low-Dose Hydrochlorothiazide With Valsartan or Other Angiotensin-Receptor Blockers

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ABSTRACT

Only a minority of patients treated for hypertension achieve controlled blood pressure (BP) levels. Therapy with fixed-dose combinations of an angiotensin-receptor blocker (ARB) and low-dose hydrochlorothiazide (HCTZ) is commonly prescribed but not always sufficient to achieve the target BP. The efficacy and safety of the fixed-dose combination of valsartan 160 mg and HCTZ 25 mg was evaluated in patients in whom BP had not been controlled with a fixed-dose combination of another ARB and low-dose HCTZ (12.5 mg) in a multicenter trial. After a wash-out period for antihypertensive drugs, patients with a mean sitting diastolic BP (DBP) at trough ≥100 mm Hg but <110 mm Hg were treated with candesartan cilexetil 16 mg plus HCTZ 12.5 mg or telmisartan 80 mg plus HCTZ 12.5 mg for 4 weeks (phase 1). Patients whose BP was still uncontrolled (DBP ≥90 mm Hg) after 4 weeks of therapy were then given valsartan 160 mg plus HCTZ 25 mg for an additional 4 weeks (phase 2). The primary efficacy parameter

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was the reduction in DBP between week 4 and week 8 in the intention-to-treat (ITT) population. BP reduction during phase 1 was –14.3±11.3/–7.5±3.9 mm Hg. DBP was controlled in 26% of the patients after phase 1. In patients treated with valsartan 160 mg plus HCTZ 25 mg during phase 2, DBP decreased by an additional 10.3±6.5 mm Hg and the mean sitting systolic BP (SBP) by an additional 11.0±11.7 mm Hg. The additional decrease was significant ($P<.0001$) for both parameters and independent of the fixed-dose combination used during phase 1. Among patients whose BP remained uncontrolled during phase 1, 74% achieved a controlled DBP after phase 2. The incidence of adverse events during both phases was comparably low and the results of laboratory tests were unremarkable. Treatment with valsartan 160 mg/HCTZ 25 mg offered a substantial benefit for patients with hypertension not controlled with the combination of candesartan cilexetil 16 mg or telmisartan 80 mg and low-dose HCTZ, while maintaining a comparable safety and tolerability profile.

Keywords: valsartan; hydrochlorothiazide; combination therapy; dose-related effects; hypertension; candesartan; telmisartan

INTRODUCTION

The global burden of hypertension is constantly increasing. It was estimated that in 2000, 26.4% of the global adult population had hypertension. It has been predicted that the number of adults with hypertension will increase by about 60% to a total of about 1.56 billion in 2025.[1] Hypertension is well known to be directly associated with an increased risk for stroke, coronary heart disease, myocardial infarction, heart failure (HF), and kidney disease,[2] and various trials—including the Hypertension Optimal Treatment (HOT) trial,[3] Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[4] Study on Cognition and Prognosis in the Elderly (SCOPE),[5] the Losartan Intervention for Endpoint (LIFE) trial,[6] and the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial[7]—have extensively demonstrated the benefit of antihypertensive therapy in terms of risk reduction.

Nevertheless, currently, up to 81.3% of patients in Europe and North America who are being treated for hypertension do not achieve adequate blood pressure (BP) control (ie, <140/90 mm Hg)[2,8]; this has significant implications for the cost of care in the healthcare systems of each region. For the US population with hypertension, inadequate BP control has been estimated to result in direct medical expenditures of $964 million.[9] In France, Germany, Italy, Sweden, and the United Kingdom, healthcare costs could be reduced by a total of 1.26 billion if patients undergoing antihypertensive therapy achieved their target BP.[10]

In large scale trials,[3-7,11] investigators have demonstrated that most patients require 2 or more antihypertensive drugs to reach their target BP. Ambitious BP goals, especially for patients with an elevated risk for cardiovascular disorders (eg, patients with diabetes), increase the need for intensive treatment strategies. Recent guidelines have taken this problem into account and include the recommendation to use combination therapy as first-line therapy,[12,13] such as in patients whose BP is 20/10 mm Hg above the goal.[2]

Monotherapy and a combination therapy with angiotensin-receptor blockers (ARBs) and diuretics have been found to be effective and well tolerated; therefore, both are recommended in current guidelines.[2,12,13] It has been shown in clinical trials

that the ARB valsartan 80 mg or 160 mg in combination with hydrochlorothiazide (HCTZ) 12.5 mg or 25 mg is significantly more effective than either drug alone. Moreover, combination therapy resulted in a significant benefit in terms of BP reduction in patients who did not respond adequately to monotherapy with one of its components.[7,14-20] In addition, compliance and persistence in patients being treated with valsartan and other ARBs have been shown to be significantly higher than that with angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, β-blockers or thiazide diuretics.[21-23] This is of particular importance because most patients with hypertension require treatment for decades and are more likely to adhere to therapy longer with a preferred agent.

Low-dose (12.5 mg) ARBs are available in fixed-dose combinations with high-dose HCTZ (25 mg). Currently, the use of fixed-dose combinations with low-dose HCTZ (12.5 mg) seems to be more common, perhaps in part because of uncertainty regarding the safety and tolerability profiles of higher doses of HCTZ, which produces effects on glucose and lipid metabolism as well as on blood chemistry (hypokalemia, hyperuricemia, etc).[24,25] Nevertheless, in some patients, the target BP is not achieved with fixed-dose combinations that include low-dose HCTZ. One potential therapeutic approach is a fixed-dose combination with high-dose HCTZ.

The aim of this trial was to investigate the efficacy and safety of the fixed-dose combination of valsartan 160 mg and HCTZ 25 mg (valsartan 160/HCTZ 25) in patients whose BP had not been controlled with fixed-dose combinations of other ARBs and low-dose HCTZ.

METHODS

Patients

Enrolled in the study were patients aged 18 years or older who had uncomplicated moderate essential hypertension, which is defined as a mean sitting diastolic BP (DBP) ≥100 mm Hg but <110 mm Hg. Ineligible for the trial were women who were pregnant, nursing, or of childbearing potential and not using an effective method of birth control. Also ineligible were patients who had evidence of severe (World Health Organization [WHO] grade III) or a secondary form of hypertension, severe hypertensive retinopathy, heart failure (New York Heart Association class II-IV), a history of clinically significant cardiovascular or cerebrovascular events or diseases, allergy or hypersensitivity to the study medication, diabetes mellitus (type 1 or inadequately controlled type 2), or clinically significant renal or hepatic disease.

The study protocol complied with the Declaration of Helsinki and the Good Clinical Practice guidelines. It was approved by the Ethics Committee at each site. All patients provided written informed consent prior to being enrolled.

Study Design

This prospective, open-label, multicenter trial was conducted at 20 centers throughout Germany. All antihypertensive medications being taken at enrollment were withdrawn during a 2-week washout phase. Subsequently, patients were given a fixed-dose combination of either candesartan cilexetil 16 mg plus HCTZ 12.5 mg (candesartan 16/HCTZ 12.5) or telmisartan 80 mg plus HCTZ 12.5 mg (telmisartan

80/HCTZ 12.5) once daily for 4 weeks (treatment phase 1). Patients in whom adequate BP control (DBP <90 mm Hg) was not achieved by the end of treatment phase 1 were then given the fixed-dose combination of valsartan 160/HCTZ 25 once daily for the following 4 weeks (treatment phase 2).

Efficacy and Safety Evaluations

BP was measured using a sphygmomanometer 24 hours after the dose (between 7:00 and 10:00 AM) at each visit according to the recommendations of the American Society of Hypertension[26,27] and the American Heart Association[28]: after each patient had been seated for at least 5 minutes, the pulse rate was counted for 30 seconds, then BP was measured in triplicate every 1 to 2 minutes. The mean of the 3 BP measurements was used for the statistical analyses.

All adverse events (AEs) and serious adverse events (SAEs) were recorded to assess drug safety. Hematologic and biochemical parameters were measured at a central laboratory. Vital signs and the physical condition of each patient were assessed regularly. A 12-lead electrocardiogram (ECG) and a pregnancy test were conducted at visit 1. At every visit, a semiquantitative urinalysis was conducted to identify patients with microalbuminuria (Chemstrip® Micral®, Roche Diagnostics, Indianapolis, Ind). Compliance was checked by counting pills.

Efficacy Parameters

The primary efficacy parameter was the change in mean sitting DBP at trough between week 4 (ie, after 4 weeks of treatment with candesartan 16/HCTZ 12.5 or telmisartan 80/HCTZ 12.5 once daily) and week 8 (ie, after 4 weeks of treatment with valsartan 160/HCTZ 25 once daily). Secondary parameters included the change in mean sitting systolic BP (SBP) at trough between weeks 4 and 8 and changes in mean sitting heart rate (HR), normalization rate (defined as mean sitting DBP <90 mm Hg), and responder rate (mean sitting DBP <90 mm Hg or a decrease of at least 10 mm Hg compared with week 4) at week 8.

Data Analysis

The change in mean sitting DBP at trough was calculated and tested for being equal to 0 by a 1-sample *t* test. Point estimates, *P* values, and 95% confidence intervals (CIs) were reported for the pooled sample as well as for each of the two phase 1 treatment groups. The 2-sided significance level was set at 5%. A comparison of the pooled sample with each phase 1 treatment group was of primary interest and was first tested hierarchically. Within-group comparisons provided confirmatory evidence, but only if the decrease in BP was significant in the overall population. The secondary efficacy parameters, change in mean sitting SBP, and change in pulse rate were analyzed analogously. Calculations of the responder and normalization rates included the 95% CI. The analysis of all secondary parameters was exploratory.

The primary and secondary efficacy analyses were based on outcomes for all patients who had at least 1 BP measurement after starting treatment with valsartan 160/HCTZ 25 (the intent-to-treat [ITT] population). Safety and tolerability analyses were performed on the safety populations. The safety population in phase 1 consisted of all patients who took at least 1 dose of candesartan 16/HCTZ 12.5 or telmisartan

80/HCTZ 12.5, and the safety population in phase 2 consisted of all patients who took at least 1 dose of valsartan 160/HCTZ 25.

RESULTS

Patients

Of the 220 patients screened for this study, 205 were enrolled in treatment phase 1. Only 26% of these patients achieved adequate BP with candesartan 16/HCTZ 12.5 or telmisartan 80/HCTZ 12.5. As a result, 148 patients entered treatment phase 2 (ITT population).

Four patients (2%) discontinued treatment prematurely in phase 1. Two patients withdrew because of AEs and 2 were lost to follow-up. Three patients (2.0%) discontinued therapy prematurely during phase 2 because of an AE (n=1), protocol violation (n=1), or abnormal test result(s) (n=1).

The baseline characteristics of patients in the safety population and in the ITT population were comparable (Table 1).

Compliance

Compliance—defined as intake of 80% to 120% of the prescribed dose—was similar during phase 1 (84.9% of patients) and phase 2 (89.2% of patients). An intake of <80% of the prescribed dose was recorded for only 2.0% of patients in phase 1 and 0.7% of patients in phase 2.

Efficacy

Treatment phase 1

Treatment with candesartan 16/HCTZ 12.5 (n=103) or telmisartan 80/HCTZ 12.5 (n=102) (ie, in the safety population in phase 1) resulted in a reduction in mean DBP of 11.2±7.5 mm Hg (103.4±2.3 mm Hg on day 1 to 92.2±7.7 mm Hg at week 4). The decrease observed for the mean SBP was 17.8±12.3 mm Hg (163.3±10.0 mm Hg on day 1 to 145.5±13.4 mm Hg at week 4). This resulted in a normalization rate of 26% and a responder rate of 48%. In the ITT population, the mean BP decreased by 7.5±3.9/14.3±11.3 mm Hg during phase 1 (Fig 1). The responder rate in this population was 31% (Fig 2). The HR remained largely unchanged.

Treatment phase 2

Treatment with valsartan 160/HCTZ 25 resulted in a reduction in the mean sitting DBP at trough of 10.3±6.5 mm Hg (from 96.0 mm Hg at week 4 to 85.8 mm Hg at week 8; 95% CI: 9.2, 11.3; $P<.0001$) (Fig 1). Similarly, the mean sitting SBP at trough was significantly reduced, by 11.0±11.7 mm Hg (from 149.2±11.8 mm Hg at week 4 to 138.2±12.4 mm Hg at week 8; 95% CI: 9.1, 12.9; $P<.0001$).

Among the former nonnormalizers, 74% (n=110) achieved normalization of mean DBP at week 4 and 80% of patients were responders (Fig 2). When the outcomes for treatment phase 1 were included, the overall normalization and response rates observed in this trial were 80% (n=163) and 88% (n=180), respectively.

Table 1. Baseline Characteristics

Variable	Safety Population Phase 1 (n=205)	ITT Population (n=148)
Age, y		
Mean (SD)	58.9 (12.4)	59.5 (12.6)
Range	23–91	23–91
<65 years, n (%)	136 (66.3)	96 (64.9)
≥65 years, n (%)	69 (33.7)	52 (35.1)
Sex, n (%)		
Male	101 (49.3)	75 (50.7)
Female	104 (50.7)	73 (49.3)
Race, n (%)		
Caucasian	204 (99.5)	148 (100.0)
Asian	1 (0.5)	
Weight (kg)		
Mean (SD)	81.9 (14.01)	82.0 (14.83)
Range	54.0–135.0	54.0–135.0
Body mass index (kg/m^2)		
Mean (SD)	28.3 (4.38)	28.1 (4.56)
Range	19.7–42.7	19.7–42.7
Sitting DBP (mm Hg)		
Mean (SD)	103.4 (2.25)	103.5 (2.45)
Range	100.0–109.3	100.0–109.3
Sitting SBP (mm Hg)		
Mean (SD)	163.3 (10.03)	163.5 (10.09)
Range	139.3–190.3	141.0–190.3
Sitting pulse (bpm)		
Mean (SD)	75.5 (9.34)	76.4 (9.19)
Range	52.0–111.0	58.0–111.0

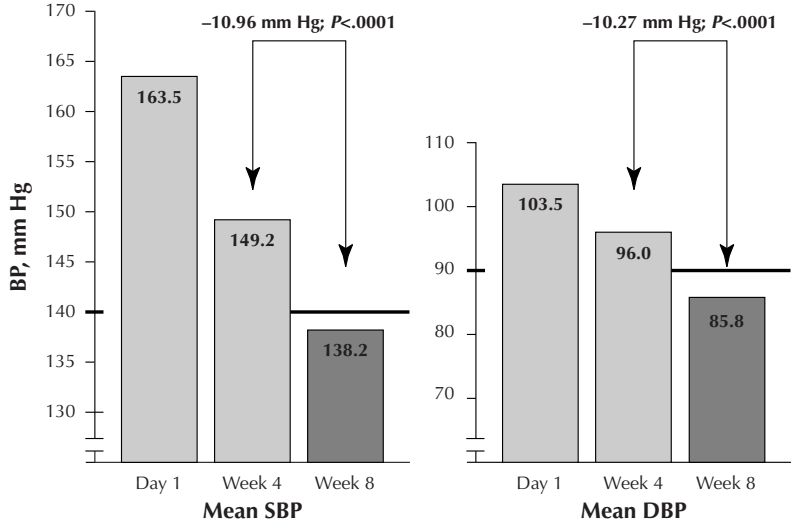
bpm=beats per minute

The decrease in BP observed during phase 2 was comparable in younger (<65; n=96) and older patients (≥65; n=52). Mean reductions in BP were 9.9±6.5/11.0± 6.6 mm Hg in younger patients and 11.0±11.8/10.9±11.6 mm Hg in older patients.

The higher the DBP measured at the beginning of phase 2, the more pronounced was the treatment effect. Patients entering phase 2 with a mean sitting DBP of <95 mm Hg showed a reduction in BP of 8.6±7.0/8.1±10.1 mm Hg. Patients with mean sitting DBPs ≥95 mm Hg and ≥100 mm Hg achieved reduction in BP of 11.5±5.2/12.2± 11.3 mm Hg and 11.8±7.1/15.7±11.5 mm Hg, respectively.

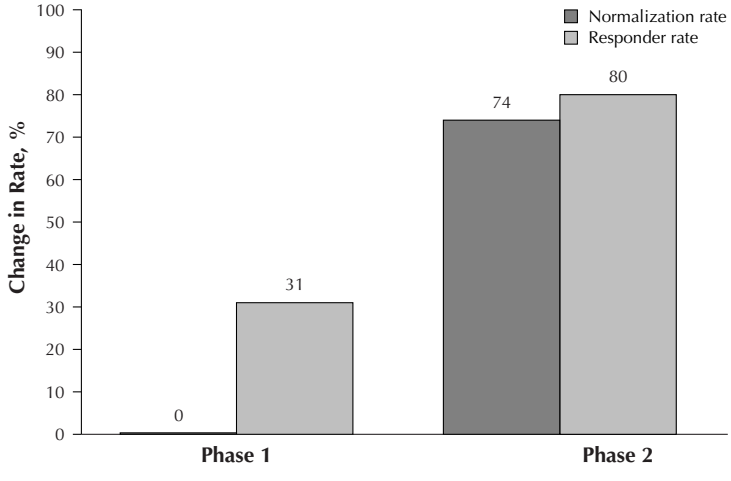
The HR remained largely unchanged during phase 2.

Fig 1. Mean systolic and diastolic blood pressure at baseline (day 1) and after 4 weeks of therapy with candesartan cilexetil 16 mg/HCTZ 12.5 mg, telmisartan 80 mg/HCTZ 12.5 mg, or valsartan 160 mg/HCTZ 25 mg.*



*Candesartan cilexetil 16 mg/HCTZ 12.5 mg or telmisartan 80 mg/HCTZ 12.5 mg was administered during weeks 1–4; valsartan 160 mg/HCTZ 25 mg was administered during weeks 4–8.

Fig 2. Normalization rate (mean DBP <90 mm Hg) and response rate (mean DBP <90 mm Hg or reduced by ≥10 mm Hg) after 4 weeks of treatment with candesartan cilexetil 16 mg or telmisartan 80 mg plus low-dose HCTZ (phase 1) or valsartan 160 mg/high-dose HCTZ (phase 2).*



*Candesartan cilexetil 16 mg/HCTZ 12.5 mg or telmisartan 80 mg/HCTZ 12.5 mg was administered during weeks 1–4; valsartan 160 mg/HCTZ 25 mg was administered during weeks 4–8.

Safety

Overall, the incidence of AEs was generally low and similar in both treatment phases, with 13.7% of patients in phase 1 and 16.9% of patients in phase 2 experiencing at least 1 AE (Table 2).

Table 2. Adverse Events Without a Suspected Causal Relationship to Study Drugs

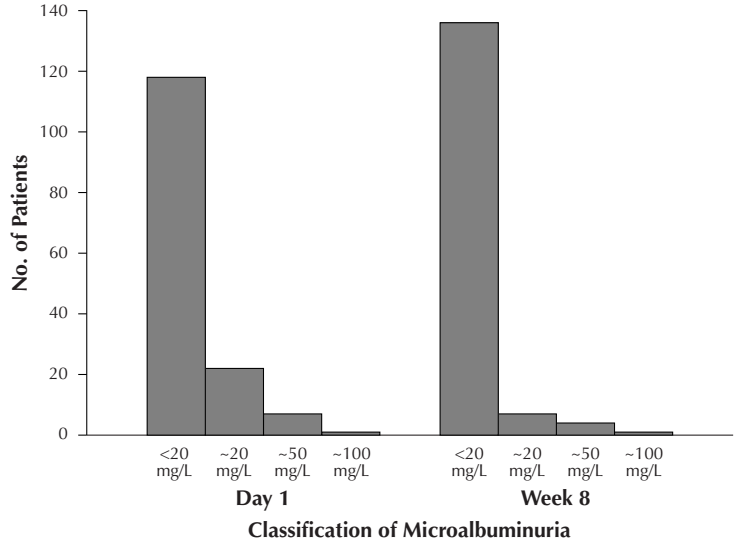
	First Occurrence of AE*	
	Treatment Phase 1 n (%)	Treatment Phase 2 n (%)
AEs overall		
Total no. of patients	205 (100.0)	148 (100.0)
Total no. of patients with AEs	28 (13.7)	25 (16.9)
Total no. of AEs	41	28
Patients with most frequent AEs		
Microalbuminuria	6 (2.9)	6 (4.1)
Back pain	2 (1.0)	2 (1.4)
Hypercholesterolemia	3 (1.5)	–
Influenza	1 (0.5)	2 (1.4)
Gastritis	1 (0.5)	2 (1.4)
Bronchitis	2 (1.0)	1 (0.7)
Nasopharyngitis	2 (1.0)	1 (0.7)
Gastroenteritis	2 (1.0)	–
Depression	2 (1.0)	–
Cervicobrachial syndrome	–	2 (1.4)

*AEs that occurred in more than 1 patient per treatment phase.

With the exception of an SAE in phase 1, all AEs reported in this trial were mild to moderate. The most common AEs were infections and infestations, renal and urinary disorders, gastrointestinal disorders, metabolic and nutritional disorders, and musculoskeletal and connective tissue disorders.

Microalbuminuria, measured by the semiquantitative dipstick test, was the most frequently reported AE, affecting 6 patients in phase 1 and in 6 patients in phase 2; however, no relationship with the study drugs was suspected. In most of these patients, microalbuminuria was reported as an AE when the albumin level was at the detection limit of the dipstick (eg, an increase from "normal" [<20 mg/L] to ~20 mg/L); the level was in normal range at the following visit. More patients demonstrated normal or reduced urinary albumin levels, compared with baseline, at week 8 (Fig 3). At the day of inclusion, 20% of the ITT population showed urinary albumin levels above the normal range. This proportion decreased to 8% after 8 weeks of treatment.

Fig 3. Classification of microalbuminuria at baseline in phase 1 (day 1) and after 8 weeks of treatment with angiotensin II receptor blockers plus low- and high-dose HCTZ (week 8).



Levels <20 mg/L are defined as "normal," according to the dipstick.

The proportion of patients with suspected drug-related AEs was 0.5% in phase 1 (1 patient with glossodynia treated with candesartan 16/HCTZ 12.5) and 2.0% in phase 2 (2 patients with gastritis and 1 with dizziness and palpitations). Glossodynia and dizziness accompanied by palpitations led to permanent discontinuation of therapy. The patient with dizziness and palpitations had a BP of 164/89 mm Hg at the last visit.

With regard to SAEs, 1 patient experienced myocardial infarction during phase 1 that was determined by the investigator not to be drug related (candesartan 16/HCTZ 12.5). No SAEs were observed during phase 2.

Despite the use of high-dose HCTZ during phase 2, the incidence of laboratory changes during phase 2 was similar to that seen during phase 1 (Table 3). In patients with hypokalemia, potassium levels below the limit of normal were not observed in both treatment phases. In all cases of hyperkalemia, during both phases, the central laboratory had noted that the samples they received showed signs of hemolysis or improper handling. None of the patients discontinued therapy because of a change in electrolyte values.

Table 3. Changes in Laboratory Values After 4 Weeks of Therapy With Candesartan Cilexetil 16 mg or Telmisartan 80 mg Plus HCTZ 12.5 mg (Phase 1) and After an Additional 4 Weeks With Valsartan 160 mg Plus HCTZ 25 mg (Phase 2)

Parameter, Unit	Notable Definition*	Week 4 Safety Population Phase 1 (n=205) n (%)	Week 8 Safety Population Phase 2 (n=148) n (%)
ALT (SGPT), U/L	Increase >200%	0 (0.0)	0 (0.0)
AST (SGOT), U/L	Increase >200%	1 (0.5)	0 (0.0)
Chloride, mmol/L	Increase >10%	4 (2.0)	2 (1.4)
	Decrease >10%	4 (2.0)	2 (1.4)
Creatinine, mg/dL	Increase >50%	3 (1.5)	3 (2.0)
Glucose, mg/dL	Increase >50%	8 (3.9)	5 (3.4)
	Decrease >50%	3 (1.5)	4 (2.7)
Potassium, mmol/L	Increase >20%	8 (3.9)	12 (8.1)
	Decrease >20%	8 (3.9)	10 (6.8)
Sodium, mmol/L	Decrease >5%	12 (5.9)	8 (5.4)
Total bilirubin, mg/dL	Increase >100%	10 (4.9)	6 (4.1)
Urea, mg/dL	Increase >50%	16 (7.8)	14 (9.5)
Uric acid, mg/dL	Increase >50%	6 (2.9)	5 (3.4)

*Versus baseline
ALT=alanine aminotransferase; SGPT=serum glutamate pyruvate transaminase (alanine aminotransferase); AST=aspartate aminotransferase; SGOT=serum glutamate oxaloacetate transaminase (aspartate aminotransferase).

DISCUSSION

This study was designed to investigate the effect of treatment with the ARB valsartan in fixed-dose combination with high-dose HCTZ (25 mg) in patients in whom BP levels had not been controlled with other ARBs prescribed in fixed-dose combinations with low-dose HCTZ (candesartan 16/HCTZ 12.5 or telmisartan 80/HCTZ 12.5).

Treatment with an ARB in combination with low-dose HCTZ for 4 weeks resulted in similar and prominent reductions in both SBP and DBP. Unfortunately, these reductions were not sufficient to normalize DBP levels (DBP <90 mm Hg) in nearly three quarters of the patients. These patients benefited substantially from subsequent treatment with valsartan in combination with high-dose HCTZ for an additional 4 weeks, which led to further decreases in DBP (–10.3 mm Hg) and SBP (–11.0 mm Hg). This effect was similar in younger and older patients, which is important, because the prevalence of hypertension and the risk for cardiovascular events increases with age. The observations made in this study are in accordance with the trial by Lacourciere et al[29] and the large-scale randomized, parallel-group trial by Mallion et al,[30] in which greater reductions in BP were observed with valsartan 160/HCTZ 25 than with

valsartan 160/HCTZ 12.5 or valsartan 160 mg monotherapy in patients in whom BP had not been adequately controlled initially with valsartan 160 mg monotherapy. Similar observations were made in studies of other ARBs in combination with HCTZ.[31]

The impact of antihypertensive therapy on cardiovascular event rates has been evaluated in various trials (eg, HOT,[3] ALLHAT,[4] SCOPE,[5] LIFE,[6] VALUE[7]) in which even a minor reduction in BP was associated with a significant difference in outcome. A 5- to 6-mm Hg reduction in DBP with antihypertensive therapy was observed to reduce the risk for cardiovascular death by 21%.[32] A prolonged difference of 10 mm Hg in the usual DBP was associated with at least a 56% lower incidence of stroke and 37% lower incidence of coronary heart disease.[33] For individuals aged 40 to 70 years, each incremental increase of 10 mm Hg in DBP doubles the risk for cardiovascular disease across the BP range of 115/75 mm Hg to 185/115 mm Hg.[2] This is clearly related to the clinical benefit of reductions in BP, such as those observed in this study with valsartan plus high-dose HCTZ. It is well known that the benefit of antihypertensive therapy is more pronounced in patients with increased cardiovascular risk than in patients with a low-risk profile (based on the WHO risk stratification scheme).[34] Concomitant risk factors (eg, obesity or physical inactivity, age, diabetes mellitus, smoking, and elevated lipid parameters) increase cardiovascular risk, are common in the overall population, and are often even more frequently observed in the hypertensive population. Evidence of microalbuminuria (an independent predictor of all-cause and cardiovascular mortality)[35-37] was observed in 17% of the overall population in this study. After 8 weeks of therapy, the proportion of patients with microalbuminuria in the ITT population decreased from 20% to 8%. Thus, a nephroprotective effect has already been reported for valsartan,[38] as well as for other ARBs and ACE inhibitors.[36] Because BP reduction per se has an impact on the severity of microalbuminuria and because a parallel arm with a neutral antihypertensive drug is missing in this trial, the drug-specific effect on excreted albumin levels could not be determined.

Treatment with valsartan plus high-dose HCTZ in this trial led to the normalization of DBP in 74% of the former nonnormalizers; it also resulted in a responder rate of 80%. It should be taken into consideration that only selected patients—none of whom achieved a mean sitting DBP <90 mm Hg after the first 4 weeks of therapy—were included in the second treatment phase. Considering both treatment phases together, normalization and responder rates of 80% and 88% were achieved in this trial.

It could be argued that the high proportion of patients with inadequate BP reduction or control during phase 1 was due in part to the short duration of phase 1: too short to demonstrate the full BP-lowering capacity of the treatment. This is contradicted, however, by data from studies of candesartan cilexetil 16 mg and losartan 50 mg, in which the effect on DBP observed after 8 weeks of treatment did not differ from that after 4 weeks.[39] Other data on the effect of candesartan cilexetil on 24-hour DBP at weeks 2 and 8 show that about 80% of DBP reduction had already been achieved after 2 weeks.[40] Therefore, it may be inferred that 4 weeks of therapy is sufficient to observe most of the BP-lowering effect of the phase 1 treatment. In addition, it should be taken into account that BP reductions are more pronounced when BP levels are higher at the start of therapy. This factor clearly favors the types of treatments used during phase 1 in this study.

Because most patients require more than 1 antihypertensive drug to achieve BP control, fixed-dose combinations of ARBs and HCTZ offer the option of efficient antihypertensive treatment with 1 pill per day. In addition to convenience, patient compliance with therapy and excellent safety and tolerability are required for a drug's optimal therapeutic effect. Significantly better compliance and persistence has been observed with valsartan and other ARBs than with drugs from other classes, such as calcium channel blockers, β-blockers, diuretics, and ACE inhibitors.[21-23] This may be related to the excellent safety profile of the ARBs.

Currently, the combination of an ARB with low-dose HCTZ seems to be increasingly common because of uncertainty about the unfavorable effect of HCTZ on lipids, electrolytes (as in hyperuricemia or hypokalemia), and glucose (especially in susceptible populations such as those with impaired glucose tolerance or diabetes).[41-44]

In recent long-term studies, investigators demonstrated that patients taking thiazide diuretics at the doses used in this study were not at greater risk for diabetes. The VALUE[7] study included patients with hypertension who had an increased cardiovascular risk, and most patients in the valsartan group received treatment with HCTZ; however, the incidence of new-onset diabetes in the valsartan group was 23% lower than that in the amlodipine group. This result suggests a long-term, active, positive effect of valsartan on glucose metabolism. Similar effects were noticed in LIFE[6] and other trials.[45,46] The efficacy of thiazides in reducing cardiovascular morbidity and mortality in hypertensive patients with diabetes has been demonstrated in several endpoint studies[4,47]; therefore, thiazides are recommended as first-line therapy in such patients (according to the guidelines of the American Diabetes Association).[48]

This study demonstrates that the fixed-dose combination of valsartan 160 mg plus high-dose HCTZ (25 mg) was safe and well tolerated, as were the other ARBs (candesartan cilexetil 16 mg and telmisartan 80 mg) in combination with low-dose HCTZ (12.5 mg). The overall incidence of AEs and the incidence of drug-related AEs were low. Only 1 SAE was reported (during phase 1), and it was not considered drug related. All other AEs were mild to moderate, which supports the findings of previous trials. A similar incidence of AEs was observed during treatment with valsartan and high-dose HCTZ and with regimens including low-dose HCTZ; this result may have been caused by the synergistic effects of ARBs on thiazide activity, or vice versa.[31] Thus, the positive effect on BP observed during therapy with the combination of valsartan and the higher dose of HCTZ was not diminished by reduced tolerability.

CONCLUSION

The results of this trial indicate that the fixed-dose combination of valsartan 160 mg and HCTZ 25 mg once daily effectively reduces BP in patients with hypertension whose BP has not been adequately controlled with fixed-dose combinations of other ARBs and low-dose HCTZ (candesartan cilexetil 16 mg or telmisartan 80 mg plus HCTZ 12.5 mg). This remarkable additional benefit in BP reduction was accompanied by a low incidence of AEs and of changes in laboratory parameters similar to that seen with ARBs and low-dose HCTZ. Thus, the benefit-risk assessment of valsartan 160 mg plus HCTZ 25 mg is clearly positive. The combination of valsartan with HCTZ offers a useful treatment option for patients in whom BP is not adequately controlled with fixed-dose combinations of other ARBs and low-dose HCTZ.

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