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ORIGINAL ARTICLE

Telmisartan *vs* losartan plus hydrochlorothiazide in the treatment of mild-to-moderate essential hypertension—a randomised ABPM study

JM Neutel[1] , RE Kolloch[2], PF Plouin[3], TW Meinicke[4] and H Schumacher[5] for the OTELLOH Study Group

[1]*Orange County Heart Institute & Research Center, Orange, CA, USA;* [2]*Krankenanstalten Gilead, Bielefeld, Germany;* [3]*Hôpital Broussais, Paris, France;* [4]*Clinical Research Boehringer Ingelheim Pharma KG, Biberach, Germany;* [5]*Medical Data Services Boehringer Ingelheim Pharma KG, Ingelheim, Germany*

The objective of this prospective, randomised, open-label, blinded-end point parallel-group, multicentre study was to show that telmisartan 80 mg is not inferior to a fixed-dose combination of losartan 50 mg/hydrochlorothiazide (HCTZ) 12.5 mg in patients with mild-to-moderate hypertension. The criterion for noninferiority was a treatment difference of $\leqslant$3.0 mmHg in the reduction of 24-h mean ambulatory diastolic blood pressure (DBP) from the end of the 4-week placebo washout period to the end of the 6-week active treatment period. In the intent-to-treat analysis, the mean reduction in 24-h DBP was 8.3 $\pm$ 6.7 mmHg among telmisartan-treated patients (n = 332) and 10.3 $\pm$ 6.3 mmHg among losartan/HCTZ-treated patients (n = 350). The mean adjusted difference in 24-h DBP between the two treatment groups was 1.9 mmHg, allowing rejection of the *a priori* null hypothesis of a treatment difference of $>$3 mmHg. The reduction in mean 24-h systolic blood pressure was 13.2 $\pm$ 10.2 mmHg with telmisartan and 17.1 $\pm$ 10.3 mmHg with losartan/HCTZ. Both drugs provided effective control over the 24-h dosing interval. Analyses of morning (0600–1159) ambulatory blood pressure monitoring DBP means and trough cuff DBP confirmed the noninferiority hypothesis of the protocol for telmisartan 80 mg *vs* losartan 50 mg/HCTZ 12.5 mg. The reductions in office blood pressures measured at trough in patients treated with telmisartan were −16.3/−9.6 and −18.5/−11.1 mmHg in the patients treated with losartan/HCTZ (difference −2.4/−1.2 mmHg). There were no differences between the side-effect profiles of the two treatments.
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Keywords: telmisartan; losartan/hydrochlorothiazide; AT_1 receptor antagonist; combination therapy; ABPM

Introduction

It has been clearly demonstrated that adequate control of blood pressure in hypertensive patients is critical in order to reduce coronary artery disease.[1–3] Despite this knowledge, worldwide data have demonstrated that adequate blood pressure control is achieved in fewer than 30% of patients with hypertension.[4,5] Multiple factors contribute to these poor control rates, including socioeconomic factors, patient compliance and changing blood pressure goals. However, the efficacy of antihypertensive agents and response rates achieved with these agents remain critical components in the battle to achieve goal blood pressures. It is for this reason that there is a continued interest in developing new antihypertensive agents that have greater bioavailability, higher volumes of distribution, longer half-lifes and are more effective in interrupting physiologic pathways in an attempt to achieve greater efficacy. In addition, since hypertension is a multifactorial disease,[6] there is a move towards much earlier use of low-dose combination therapy in order to achieve greater efficacy.[7]

Telmisartan is a newly available angiotensin receptor blocker. It has a high bioavailability (40–60%), a half-life of 24 h, a volume of distribution of approximately 500 l, binds tightly and specifically to AT_1 receptors and may have some inherent natriuretic activity.[8] It has been shown in previous studies to be an extremely effective antihypertensive agent,

Correspondence: Dr JM Neutel, Orange County Heart Institute & Research Center, 505 South Main Street, Suite #1025, Orange, CA 92868, USA.
E-mail: JMNeutel@aol.com
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producing high response rates when compared with other commonly used antihypertensive agents.[9–11] It has also been shown to result in greater reductions in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) when compared with losartan.[10] Furthermore, telmisartan has a pharmacokinetic profile that differentiates it from other angiotensin receptor blockers.

In the current study, we used ambulatory blood pressure monitoring (ABPM) to compare telmisartan 80 mg with losartan 50 mg plus hydrochlorothiazide (HCTZ) 12.5 mg in patients with stages I and II (mild-to-moderate) essential hypertension. The objective of the study was to assess whether telmisartan, an angiotensin receptor blocker with a favourable pharmacokinetic profile, at a dose of 80 mg was not inferior to a fixed-dose combination of losartan 50 mg/HCTZ 12.5 mg in this patient population.

Patients and methods

Patients

Patients over 18 years of age were recruited into the study if they had mild-to-moderate essential hypertension, defined as a mean seated cuff blood pressure $\geqslant$140/95 and $\leqslant$200/114 mmHg (mean of three seated blood pressures taken 2 min apart following 5 min at rest), and 24-h ABPM mean DBP $\geqslant$85 mmHg at the end of a 4-week placebo washout period. Compliance to trial treatment was also required to be 80–120% during the placebo washout period, as assessed by counting tablets returned to the clinic.

Study design

This was a Prospective, Randomised, Open-label, Blinded-Endpoint (PROBE), parallel-group, multicentre study. Following initial screening, all patients entered a 4-week, single-blind placebo washout period, during which previous antihypertensive medication was discontinued according to prescribing information. At the end of the washout phase, 24-h ABPM was conducted and eligible patients were then randomised to once-daily, oral treatment with either telmisartan 80 mg or losartan 50 mg/HCTZ 12.5 mg (fixed-dose combination). These dosages were chosen since they represent the first recommended titration for each of these agents by their respective package inserts. Treatments were allocated according to enrolment order and a randomisation list held by a third party. Patients remained on active treatment for 6 weeks; 24-h ABPM was repeated at the end of this period. Patients were instructed to take their medication at approximately the same time each morning.

The study protocol was approved by the local Ethics Committee at each centre before initiation, and the study was conducted in accordance with the principles of the Declaration of Helsinki. All patients signed an informed consent approved by the local Institutional Review Board before enrolment.

Blood pressure measurements

A 24-h ABPM was performed using the SpaceLabs 90207 device (SpaceLabs Inc., Redmond, WA, USA). The device was placed at 0900 $\pm$ 1 h. Blood pressure was recorded at 20-min intervals throughout the whole 24-h recording period. The ABPM data were then transmitted via modem to a central data storage point for blinded analysis. Hourly means were calculated for each patient and used to calculate mean blood pressure values over the following prespecified intervals: the entire 24-h period, last 6 h of the dosing interval, daytime (0600–2159), morning (0600–1159) and night time (2200–0559). The mean of the individual hourly means in each treatment group was then calculated for each ABPM end point. Owing to the PROBE design of this study, data derived from the ABPM were used to provide an observer-independent tool for blood pressure assessment. Baseline measurements were those collected at the end of the placebo washout period.

Efficacy was also evaluated from cuff sphygmomanometry measurements based on the changes from baseline in trough SBP and DBP at the end of 6 weeks of active treatment.

Safety assessments

The incidence, severity and causal relationship to the study drug were recorded for all adverse events that occurred during the study. In addition, safety was assessed from physical examinations, standard laboratory tests, changes in heart rate and 12-lead ECGs.

Statistical analyses

The primary objective of this study was to show that telmisartan 80 mg was not inferior to the fixed-dose combination of losartan 50 mg/HCTZ 12.5 mg in reducing mean 24-h ambulatory DBP from baseline levels after 6 weeks of therapy. This was to be accomplished by rejection of an *a priori* null hypothesis that the differences between the two drugs would be >3 mmHg in mean 24-h ambulatory DBP using a one-sided 95% confidence interval, with an $\alpha = 0.05$ level of significance. If the upper limit of this interval was greater than 3 mmHg, the null hypothesis would not be rejected. In accordance with the PROBE study design, analyses of the primary end point data were completed before unblinding of the treatment groups to which patients had been assigned.

Secondary end points—the change from baseline in 24-h ABPM mean SBP and in SBP and DBP during the other prespecified intervals of the 24-h ABPM profile and in trough cuff SBP and DBP—were also compared.

Results

Patients

This multicentre, international study was conducted in 10 countries (Belgium, Denmark, Finland, France, Germany, the Netherlands, Norway, South Africa, Spain and the UK) at 67 investigator sites. A total of 1285 patients were screened for the study, and 714 patients were randomised. Of the 571 patients who did not fulfil the randomisation criteria, the vast majority were excluded because mean 24-h DBP was less than 85 mmHg.

Of the 714 patients who fulfilled enrolment criteria, 351 were randomised to receive telmisartan and 363 were randomised to receive losartan/HCTZ. There were no significant differences in demographics or baseline characteristics between the treatment groups (Table 1). A total of 690 patients completed the study (338 in the telmisartan arm and 352 in the losartan/HCTZ arm). In all, 11 patients (eight treated with telmisartan and three treated with losartan/HCTZ) discontinued the study due to adverse events, three patients (two treated with telmisartan and one treated with losartan/HCTZ) discontinued due to lack of effective blood pressure control, and 10 patients (three treated with telmisartan and seven treated with losartan/HCTZ) either withdrew consent or were lost to follow-up. Evaluable ABPM data were available for 682 patients (332 in the telmisartan group and 350 in the losartan/HCTZ group), and trough cuff blood pressure measurements were available for 703 patients (334 in the telmisartan group and 359 in the losartan/HCTZ group).

Antihypertensive efficacy

Patients treated with telmisartan had clinically significant reductions in both systolic (−16.3 mmHg;baseline: 164.3 mmHg) and diastolic (−9.6 mmHg; baseline: 102.4 mmHg) office blood pressures. Similarly, patients treated with losartan/HCTZ had significant reductions in office SBP (−18.5 mmHg; baseline: 163.3 mmHg) and DBP (−11.1 mmHg; baseline: 102.8 mmHg) (Table 2).

Table 1 Patient demographics and baseline characteristics

	Telmisartan 80 mg (n=351)	*Losartan 50 mg/HCTZ 12.5 mg (n=363)*
Age (years)	54.2 ± 10.6	54.9 ± 10.5
Gender, *n* (%)		
Males	196 (55.8)	213 (58.7)
Females	155 (44.2)	150 (41.3)
Weight (kg)	82.8 ± 15.3	83.8 ± 15.2
Height (cm)	170.5 ± 9.4	170.5 ± 9.3
Body mass index (kg/m^2)	28.4 ± 4.5	28.8 ± 4.3
Baseline SBP (mmHg)	164.2 ± 14.5	163.2 ± 14.0
Baseline DBP (mmHg)	102.5 ± 5.7	102.8 ± 5.8

Figure 1 shows mean 24-h ABPM profiles of hourly DBP means measured at baseline and at the end of the active treatment period for both drugs. As is apparent, both drugs produced impressive reductions in DBP which were maintained throughout the dosing interval. The decrease in mean 24-h DBP was 8.3 ± 6.7 mmHg (baseline: 93.2 ± 6.7 mmHg) in telmisartan-treated patients and 10.3 ± 6.3 mmHg (baseline: 93.8 ± 6.6 mmHg) in losartan/HCTZ treated patients (Table 2). This amounted to a mean difference of −1.9 mmHg in 24-h DBP reductions between the treatment groups, adjusted for baseline values and country (one-sided 95% confidence interval: −2.7, α). As the 95% confidence interval excluded a treatment difference of more than 3.0 mmHg, the null hypothesis could be rejected, that is, the reduction in mean DBP with telmisartan 80 mg was not inferior to that with losartan 50 mg/HCTZ 12.5 mg.

The mean reduction in 24-h SBP was −13.2 ± 10.2 mmHg (baseline: 150.1 ± 14.1 mmHg) in the telmisartan treatment group and −17.1 ± 10.3 mmHg (baseline: 150.6 ± 13.3 mmHg) in the losartan/HCTZ treatment group (Table 2). The adjusted difference in mean 24-h SBP between the groups was −3.8 mmHg (−5.0, α). Neither of the drug regimens produced clinically meaningful changes in heart rate: 24-h mean heart rate increased by +0.1 ± 6.6 bpm in telmisartan-treated patients and by +1.1 ± 6.0 bpm in losartan/HCTZ-treated patients (Table 2).

The reductions in blood pressure were consistent throughout the 24-h dosing interval with both drug regimens. To compare the duration of action of the two agents, mean blood pressure reductions were calculated over the final 6 h of the dosing interval (Table 2). The mean reduction in DBP during this period was 7.2 ± 8.3 mmHg in the telmisartan treatment group and 9.3 ± 7.6 mmHg in the losartan/HCTZ treatment group. Similarly, SBP was reduced by 11.6 ± 12.0 mmHg among telmisartan-treated patients and by 15.5 ± 11.2 mmHg among losartan/HCTZ-treated patients. Thus, the decreases in blood pressure during the last few hours of the dosing interval were similar to those over 24 h, indicating smooth control throughout the entire period between doses.

Mean reductions in blood pressure during the morning hours (0600–1159) were also calculated (Table 2). Adequate blood pressure control is highly desirable over this period as it correlates with the time of peak incidence of non-embolic strokes and myocardial infarction. Mean SBP/DBP decreased by 14.0 ± 11.9/8.5 ± 7.8 mmHg in the telmisartan treatment group and by 16.9 ± 11.6/10.1 ± 7.3 mmHg in

Table 2 Mean changes from baseline in vital signs after treatment with telmisartan or losartan/HCTZ over various ABPM periods (24-h, last 6 h of the dosing interval, daytime (0600–2159), morning (0600–1159) and night time (2200–0559), and in trough cuff SBP and DBP (intent-to-treat population)

	Telmisartan 80 mg (n=*332*)	*Losartan 50 mg/HCTZ 12.5 mg* (n=*350*)	*Adjusted difference (one-sided 95% CI)*
24-h mean ABPM			
SBP (mmHg)	−13.2 ± 10.2	−17.1 ± 10.3	−3.8 (−5.0, α)
DBP (mmHg)	−8.3 ± 6.7	−10.3 ± 6.3	−1.9 (−2.7, α)
Heart rate (b.p.m.)	0.1 ± 6.6	1.1 ± 6.0	—
Last 6 h ABPM means (mmHg)			
SBP	−11.6 ± 12.0	−15.5 ± 11.2	−3.7 (−5.1, α)
DBP	−7.2 ± 8.3	−9.3 ± 7.6	−1.9 (−2.8, α)
Daytime ABPM means (mmHg)			
SBP	−14.0 ± 11.0	−17.6 ± 11.2	−3.6 (−4.9, α)
DBP	−8.7 ± 7.1	−10.5 ± 7.0	−1.8 (−2.6, α)
Morning ABPM means (mmHg)			
SBP	−14.0 ± 11.9	−16.9 ± 11.6	−2.9 (−4.3, α)
DBP	−8.5 ± 7.8	−10.1 ± 7.3	−1.6 (−2.5, α)
Night time ABPM means (mmHg)			
SBP	−11.8 ± 11.9	−16.0 ± 11.8	−3.9 (−5.3, α)
DBP	−7.7 ± 8.3	−9.9 ± 7.6	−1.9 (−2.9, α)
	Cuff sphygmomanometry parameters		
	(*n*=344)	(*n*=359)	
Trough cuff means (mmHg)			
DBP	−16.3 ± 15.2	−18.5 ± 15.6	−2.4 (−4.2, α)
SBP	−9.6 ± 9.0	−11.1 ± 8.6	−1.2 (−2.2, α)

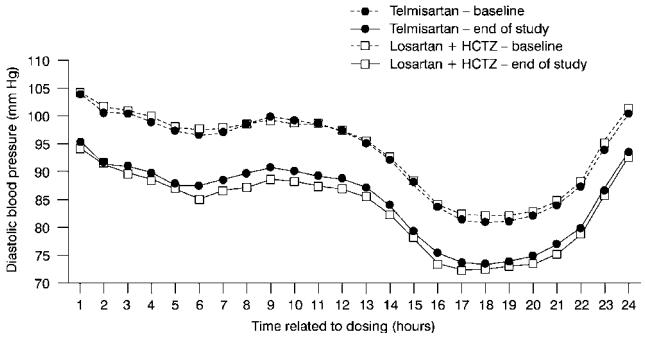

Figure 1 Mean 24-h ABPM profiles of hourly DBP means (related to dose time) at baseline and at the end of the study for telmisartan 80 mg and losartan 50 mg/HCTZ 12.5 mg.

the losartan/HCTZ treatment group. These blood pressure reductions were also similar to the 24-h mean reductions, indicating smooth and effective control over these critical hours.

Mean changes in daytime (0600–2159) and night time (2200–0559) SBP and DBP are also shown in Table 2.

Systolic and diastolic loads

Systolic and diastolic load is defined as a measure of the number of SBP and DBP readings that are abnormally elevated over a 24-h period (SBP > 140 mmHg between 0600 and 2200 and > 130 mmHg between 2201 and 0559) and the number of DBP readings abnormally elevated over a 24-h period (DBP > 90 mmHg between 0600 and 2200 and > 85 mmHg between 2201 and 0559), expressed as a percentage. The systolic and diastolic loads of the patients in the telmisartan arm at baseline were 73 ± 23 and 64 ± 18%, respectively. However, treatment with telmisartan resulted in a reduction of 27 ± 24% in systolic load and of 25 ± 19% in diastolic load. Baseline values in the losartan/HCTZ arm were 76 ± 22% for systolic load and 66 ± 18% for diastolic load; treatment resulted in reductions of 37 ± 24 and 32 ± 20%, respectively.

Safety

Both treatment regimens were well tolerated. Over the 6 weeks of active therapy, the overall incidence of adverse events was 88/351 (25.1%) in the telmisartan group and 91/363 (25.1%) in the losartan/HCTZ group. Table 3 shows the adverse events occurring in > 1% of patients. The incidence of gastrointestinal adverse events was comparable between the two treatment groups: 3.1% for telmisartan and 2.8% for losartan/HCTZ. Adverse events

Table 3 Adverse events occurring in >1% of patients

Adverse event, n *(%)*	*Telmisartan 80 mg* (n=*351*)	*Losartan 50 mg/HCTZ 12.5 mg* (n=*363*)
Headache	7 (2.0)	10 (2.8)
Bronchitis	6 (1.7)	3 (0.8)
Household accident	4 (1.1)	6 (1.7)
Sweating	4 (1.1)	5 (1.4)
Eczema	4 (1.1)	2 (0.6)
Dizziness	3 (0.9)	6 (1.7)
Back pain	3 (0.9)	5 (1.4)

were considered to be drug related in 20/351 (5.7%) of the telmisartan-treated patients and 25/363 (6.9%) of the losartan/HCTZ-treated patients. The most common drug-related adverse events were headache, increased sweating, vertigo and dizziness.

Six patients experienced a serious adverse event during active treatment: five in the telmisartan group (arthritis, hemiparaesthesia, duodenal ulcer, multiple myeloma and ureterolithiasis) and one in the losartan/HCTZ group (urolithiasis deterioration). None of these serious adverse events was considered to be related to the study drug.

No clinically important changes from baseline in laboratory parameters were observed in either treatment group during the study.

Discussion

In this study, we have demonstrated that telmisartan 80 mg monotherapy and losartan 50 mg/HCTZ 12.5 mg fixed-dose combination therapy produce highly significant reductions in mean 24-h ambulatory DBP, which are maintained throughout the entire dosing interval. In addition, the reduction in mean 24-h ambulatory DBP among patients receiving telmisartan was only 1.9 mmHg less than the reduction among patients receiving losartan/HCTZ.

The exact definition of a clinically relevant difference in blood pressure in the general population is clearly open to debate. The objective of antihypertensive treatment, however, should be to achieve blood pressure control as stipulated in management guidelines. A difference of >3 mmHg in the reduction of mean 24-h ambulatory DBP as the definition for noninferiority between telmisartan 80 mg *vs* losartan 50 mg/HCTZ 12.5 mg (the primary object of this study) was chosen based primarily on what had been used in previous studies.[12,13] The results of some studies, such as the UK Prospective Diabetes Study (UKPDS) and the Hypertension Optimal Treatment Study (HOT)[1,3] indicate a particular benefit of more intensive blood pressure reduction in hypertensive diabetics. However, in the overall HOT population, no differences were observed in cardiovascular event or mortality rates among the three target groups (whose DBP was lowered by 20.3, 22.3 and 24.3 mmHg, respectively). On the other hand, an analysis of combined data from the Framingham Heart Study and the National Health and Nutrition Examination Survey (NHANES) II has also shown that a small reduction in DBP, of just 2-mmHg, would produce a substantial reduction in the incidence of primary cardiovascular events within the community.[14] Thus, even small differences in blood pressure reductions may have significant implications from a public health standpoint.

Various outcomes studies over the past few years have shown that SBP is a powerful predictor of pending cardiovascular disease,[15] such that even small SBP reductions can produce an important clinical impact in specific patient populations. Consequently, there is now increased emphasis on lowering of pulse pressure, especially among the elderly. When the current study was designed (January 1998), systolic noninferiority was not included as a primary end point which, in retrospect, was unfortunate. However, the present study did not specifically include elderly patients or those at high risk of cardiovascular events. Therefore, further studies are required. Previous studies have chosen a mean 24-h SBP of <5 mmHg as a definition of noninferiority.[12,13] In the present study, the difference in mean 24-h SBP between the two treatment groups was 3.8 mmHg, which falls within this definition.

In this study, telmisartan, a newly available angiotensin receptor antagonist, produced reductions in mean 24-h DBP which were, according to the protocol definition, not inferior to those produced by a low-dose combination agent (losartan plus HCTZ). The findings in the current study may be related to the fact that telmisartan is a long-acting drug that binds tightly to AT_1 receptors. With a terminal elimination half-life of approximately 24 h, telmisartan has the longest half-life of any of the angiotensin II receptor blockers available for the treatment of hypertension.[16,17] Furthermore, telmisartan is highly lipophilic and consequently penetrates effectively into the tissues.

It is crucial in the management of hypertension to use agents that are administered on a once-daily basis. Compliance rates have been shown to be greater in patients treated with once-daily agents compared with those treated with drugs that require more frequent dosing. It is, however, essential to select once-daily drugs that provide effective control over the entire 24-h period. Several of the antihypertensive agents currently marketed and used as once-daily therapies tend to lose efficacy in the final 4–6 h of the dosing interval.[18,19] This coincides with the peak incidence of myocardial infarction and the time at which effective antihypertensive control seems most important. In the present study, we have shown that both telmisartan 80 mg and the losartan 50 mg/HCTZ 12.5 mg fixed-dose combination produced significant reductions in blood pressure that

persisted throughout the vulnerable morning hours (0600–1159), when the cardiovascular risk is greatest. The reductions in blood pressure during the morning period were similar to the mean 24-h blood pressure reduction, suggesting a smooth decrease in blood pressure that was maintained throughout the dosing interval.

There were no differences between the side effect profiles of the drugs. It is now well accepted that angiotensin receptor blockers are extraordinarily well-tolerated drugs, and it is interesting to note that the addition of a small dose of HCTZ to losartan did not have a negative impact on its side-effect profile. This demonstrates one of the benefits of low-dose combination therapy: it provides effective blood pressure control with fewer dose-dependent side effects because of the ability to achieve adequate blood pressure control with smaller doses of the component agent (HCTZ dosed at 12.5 mg). In a follow-up study with patients of the present study, addition of HCTZ 12.5 mg to telmisartan 80 mg was particularly effective in further enhancing antihypertensive efficacy.[20]

In conclusion, the current study has demonstrated effective reductions in mean ambulatory DBP over 24 h and other prespecified intervals of the ABPM monitoring period in patients treated with telmisartan 80 mg. The predefined protocol criteria for noninferiority of telmisartan 80 mg compared with the fixed-dose combination of losartan 50 mg/HCTZ 12.5 mg were achieved in this study. Both telmisartan and losartan/HCTZ provided effective blood pressure control over 24 h with once-daily dosing. In addition, both treatments were extremely well tolerated. Safety, efficacy and duration of action are critical factors required to achieve adequate blood pressure control. Thus, telmisartan, a newer angiotensin receptor blocker, is a very useful addition to our armamentarium for the management of patients with mild-to-moderate hypertension and an important alternative as first-line treatment of this disease.

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