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Regression of Left Ventricular Hypertrophy With Moexipril, an Angiotensin-Converting Enzyme Inhibitor, in Hypertensive Patients

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Left ventricular hypertrophy (LVH) is a common complication of essential hypertension and an independent risk factor for the development of cardiovascular disease. Therefore, antihypertensive treatment should decrease blood pressure (BP) and reverse LVH. However, antihypertensive drugs have been shown to have different effects on LVH despite similar effects on BP reduction. Although lowering BP produces a beneficial effect on LVH per se, metaanalyses of clinical trials have indicated that angiotensin-converting enzyme (ACE) inhibitors decrease left ventricular mass (LVM) to a greater extent than do some other antihypertensives. The aim of this study was to evaluate the effect of a 24-week treatment with the ACE inhibitor moexipril (15 mg once daily) on the regression of LVH in hypertensive patients. This was a multicenter, international, single-blind, single-group, nonrandomized study. After a wash-out placebo period of 2 weeks, 15 mg moexipril once daily was administered for 24 weeks followed by a 2-week follow-up placebo period. Subjects with mild to moderate essential hypertension were screened; those with LVH [defined as an LVM indexed for body surface area (LVMIs) >111 g/m^2 in men and LVMIs >106 g/m^2 in women] were eligible to participate in this study. Echocardiograms were recorded on videotape and sent to a centralized laboratory for reading by 2 independent experts blinded for treatment, center, and visit; the mean values of these readings were calculated and used for analysis. Valid echocardiographic data were obtained from 72 patients (50 males, 22 females) with a mean age of 49 ± 11 years. Analysis showed significant decrease of LVMIs (121 ± 20 versus 103 ± 17 g/m^2; $P < 0.001$) and BP (152 ± 12/96 ± 9 versus 140 ± 13/86 ± 9 mm Hg; $P < 0.001$) with moexipril. For patients who met LVMI inclusion criteria after centralized, blinded readings, the decrease from baseline in LVMIs was 23.4 g/m^2. The decrease in LVMIs was independent from the regression to the mean phenomenon as observed from the follow-up placebo period. Moexipril 15 mg once daily administered for 24 weeks resulted in a significant reversal of LVH in patients with essential hypertension. The result compares favorably with results previously obtained in trials of similar duration with other ACE inhibitors.

Keywords: left ventricular hypertrophy, angiotensin converting enzyme inhibitor, moexipril, hypertension, echocardiography

INTRODUCTION

Left ventricular hypertrophy (LVH) is associated with a higher risk of the development of coronary artery disease, heart failure, stroke, and other cardiovascular complications.[1] LVH is a common complication of essential hypertension and develops in most patients with untreated hypertension. The prognostic value of LVH regression is not well established; however, reversal of LVH has been associated with beneficial effects, such as fewer arrhythmias and improvement in coronary reserve.[2] Accordingly, current guidelines for the treatment of hypertension should take into account all cardiovascular risk factors including LVH when treating hypertension.[3,4]

Although lowering blood pressure (BP) produces a beneficial effect on LVH per se,[5] metaanalyses of clinical trials have indicated that pharmacologic treatment with the angiotensin-converting enzyme (ACE) inhibitors decreases LV mass more effectively than other

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classes of antihypertensive drugs.[6,7] Therefore, antihypertensive treatment should decrease BP and potentially reverse target-organ damage including LVH.

Moexipril hydrochloride (Univasc; Schwarz Pharma, Mequon, WI) is a non–sulfhydryl-containing, nonpeptide, orally active ACE inhibitor. It is a prodrug and is deesterified to the active agent moexiprilat. Moexipril produces clinically important BP reductions comparable with other antihypertensives when given once daily in doses between 7.5 and 30 mg.[8–10] The aim of this study was to evaluate the effect of moexipril (15 mg once daily for 24 weeks) on the regression of LVH in patients with essential systolodiastolic hypertension or isolated systolic hypertension.

PATIENTS AND METHODS

Study design

The study was designed as a multicenter (France, Poland, and Portugal), single-group, single-blind, nonrandomized trial. The trial consisted of 3 phases: a 2-week placebo run-in phase, a 24-week active treatment phase in which patients were treated with 15 mg moexipril once daily, and, last, a 2-week placebo follow-up phase. Echocardiography was performed at study entry (W 2), end of placebo run-in (W 0), end of treatment (W 24), and completion of placebo follow-up (W 26). Measurements of BP and heart rate were performed at all visits; laboratory tests were performed at W –2, W 2, and W 24 and ECG at W –2 and W 24. Information on adverse events was collected at all visits.

Patients

Subjects aged 18 to 70 years with essential hypertension were eligible to participate in the study if they were untreated (DBP 95–14 mm Hg/SBP <180 mm Hg) during the month prior to the screening visit or if they had received antihypertensive monotherapy (excluding ACE inhibitor or angiotensin II receptor blocker use for longer than 1 month) and had uncontrolled BP (DBP 90–99 mm Hg/SBP <160 mm Hg). Patients with isolated systolic hypertension who had DBP <90 mm Hg and SBP 140–159 mm Hg (if

ly untreated) were also eligible. Patients with reproducible echocardiograms (<10% difference between the LVMIs values at W –2 and W 0) and LVMIs >111 g/m^2 in men and >106 g/m^2 in women[11] as determined by the local investigator at the site were included in the study. Exclusion criteria included secondary hypertension, history of stroke, severe cardiac disease, renal or hepatic disease, and any condition that would have increased the risk to the subject or compromise study objectives. All participants provided written informed consent; the study was approved by each local ethical committee and conducted in accordance with the declaration of Helsinki.

Echocardiography

All the investigators underwent training to standardize echocardiographic technique and evaluation prior to enrolling patients in the study. Echocardiography was performed according to guidelines current at the time of study initiation.[12]

Echocardiograms were recorded on separate VHS videotapes for each examination. Each videotape included parasternal long- and short-axis scans each showing the M-mode cursor, an apical 4-chamber 2-D view including the left ventricular long-axis and an apical 2-chamber aortic view. Readings were made during 3 to 5 successive cardiac cycles to eliminate influences of respiratory movement on the measurement of left ventricular dimensions. The following parameters were used in end diastole: end-diastolic internal diameter of the left ventricle (LVDD), interventricular septal thickness (IVST), and posterior wall thickness (PWT) according to the Penn convention. In end systole, the internal diameter of the left ventricle (LVSD) was measured. Using the Doppler, the ratio of the left ventricular inflow velocity in the early rapid filling and late atrial contraction phases and the isovolumetric relaxation time were measured. The endocardial echoes were excluded from the measurement of the septal and posterior wall thickness and included in the measurement of the left ventricular internal diastolic dimension.

LVM was calculated using the Devereux formula[13] and LVMIs was calculated as LVM/body surface area. Videotapes of visits W 0, W 24, and W 26 were sent to the central laboratory for reading by 2 independent cardiologists blinded for site, visit, and treatment. The mean values of the blinded readings were used for the efficacy analysis.

BP measurements

BP measurements were performed after 10 minutes

dard mercury sphygmomanometer and adapted cuff size according to the WHO recommendations.[4] Three successive measurements were performed at 1-minute intervals; the mean values were used for statistical analysis.

BP was monitored continuously during each echocardiography with 1 BP reading every 3 minutes.

Table 1. Baseline characteristics

	Patients (N = 72)	Men (n = 50)	Women (n = 22)
Age (y)	49 ± 11	47 ± 11	54 ± 9
Weight (kg)	77 ± 13	81 ± 13	70 ± 10
Height (cm)	169 ± 8	173 ± 6	161 ± 7
Body mass index (kg/m^2)	27 ± 4	27 ± 4	27 ± 3
AU5 Systolic BP (mm Hg)	152 ± 12	NA[1]	NA[2]
Diastolic BP (mm Hg)	96 ± 8	NA[3]	NA[4]
Heart rate (beats/min)	71 ± 10	NA[5]	NA[6]

Mean ± 1 SD.

Statistical analysis

The primary efficacy variable was the change in LVMIs from baseline (W 0) to the end of treatment with 15 mg moexipril once daily (W 24). Secondary efficacy variables were changes in the echocardiographic parameters [LVMI for height (LVMIh)], LVM, thickness of the interventricular septum, thickness of the posterior wall, left ventricular diastolic and systolic diameters), and changes in BP and heart rate. The effect of therapy withdrawal was evaluated by changes in echocardiographic parameters and BP at W 26.

Efficacy analysis was performed for all subjects who had valid echocardiographic measurements at baseline and at the end of active treatment. A correlation analysis related the change in LVMIs to the change in sitting BP after W 24 or treatment end point.

Safety assessment included physical examination, AU2 laboratory tests, and ECG. Safety analysis was performed in all subjects who received at least 1 dose of moexipril.

Analyses were performed using SAS software. Descriptive analysis for continuous variables included the mean values, standard deviation, and their ranges; for categorical variables, the frequency of occurrence of each category was described. Statistical tests included analysis of variance to analyze the possible site effect, 2-sided t test and correlation analysis; the SAS procedure GLM was used to analyze the change in LVMIs. A P value <0.05 was considered statistically significant.

RESULTS

Of the 104 subjects who entered the placebo run-in phase, 93 patients received at least 1 dose of moexipril and 72 patients completed the moexipril treatment phase with valid echocardiographic measurements at baseline and end of active treatment. Fifty-seven (57) patients completed the 2-week placebo follow-up phase.

The main reasons for discontinuation were blood pressure outside the limits (7%), adverse events (9%), and withdrawal of consent (3%). Patient demographic and baseline characteristics are summarized in Table 1. Of the 72 patients enrolled based on LVMIs deter- T1 mined by the site investigator, 51 had an LVMIs value from the blinded reading at baseline that met the predefined inclusion criteria. These patients were analyzed as a subset of the total population.

Echocardiography

The overall change in LVMIs from baseline after 24 weeks moexipril treatment was –18.2 g/m^2 (P < 0.001) [95% CI (–22.4 g/m^2, –13.9 g/m^2)] (Table 2). Regres- T2 sion of LVMIs was slightly more pronounced in women (–20.0 g/m^2) than in men (–17.4 g/m^2). Similar results were observed for LVM (228 ± 43 g versus 193 ± 38 g, P < 0.001). Table 2 shows that regression of

Table 2. Echocardiographic parameters at baseline (W 0) after 24 weeks of 15 mg moexipril q.d. (W 24) and after 2 weeks of placebo follow-up (W 26)

	W 0 placebo (N = 72)	W 24 moexipril (N = 72)	W 26 placebo (n = 51)	P value W 0 vs. W 24
Interventricular septum (mm)	10.4 ± 1.1	9.1 ± 1.4	9.0 ± 1.3	<0.001
Posterior wall (mm)	9.2 ± 0.8	8.4 ± 0.9	8.3 ± 0.8	<0.001
Left ventricular diastolic diameter (mm)	52 ± 4	52 ± 4	53 ± 4	NS
Fractional shortening (%)	35 ± 3	35 ± 3	36 ± 4	NS
Cardiac output (l/m^2)	5 ± 0.9	5 ± 1.2	5 ± 1.0	NS
Left ventricular mass (g)	228 ± 43	193 ± 38	190 ± 38	<0.001
Left ventricular mass index (g/m^2)	121 ± 20	103 ± 17	101 ± 17	<0.001

Mean ± 1 SD.
NS, no significance.

Table 3. Reduction of LVMIs (g/m^2) in patients who met enrollment criteria with centralized, blinded readings

Patients	LVMI at W 0	LVMI at W 24	*P* value W 0 vs. W 24	% Change
Total (N = 51)	130 ± 16	107 ± 17	<0.001	18
Men (n = 36)	132 ± 12	109 ± 18	<0.001	17
Women (n = 15)	127 ± 22	103 ± 15	<0.001	19

Mean ± 1 SD.

the LVM is mainly related to a decrease in the interventricular septum and the posterior wall; no significant changes were observed for the left ventricular systolic or diastolic diameters.

The LVMIs of the 51 patients whose LVH met the inclusion criteria after the centralized, blinded reading at baseline showed similar changes: LVMIs decreased 23.4 g/m^2 [95% CI (−28.4 g/m^2, −18.3 g/m^2)] from baseline (130.3 g/m^2) to end of treatment (106.9 g/m^2). T3 (Table 3).

A final echocardiography was performed at the end of the follow-up placebo period (W 26, Table 2). There was a mean LVMIs change of −2.8 ± 12 g/m^2 [95% CI (−6.2 g/m^2, +0.6 g/m^2)] between W 24 and W 26, indicating no significant change of LVMIs after withdrawal of moexipril.

Blood pressure

Significant BP reduction was observed at the end of T4 the moexipril treatment (W 24) (Table 4). The corresponding mean changes were −12 ± 13 mm Hg for SBP and −10 ± 9 mm Hg for DBP. No significant correlation was observed between the changes of LVMIs and the changes of SBP ($r = -0.107$) or DBP ($r = -0.104$) at W 24.

At the end of the 2-week placebo follow-up period (W 26), significant increases of SBP (+8.9 ± 12.4 mm Hg) and DBP (+10.1 ± 10.2 mm Hg) were observed ($P < 0.001$).

Safety and tolerability

A total of 46 adverse events were reported by 29 patients (31.2%) of the safety population (n = 93). The most frequently reported events were pharyngitis (5.4%), anxiety, coughing, influenza-like symptoms (3.2% each), and bronchitis and allergy (2.2% each). Serious adverse events were reported for 4 subjects (4.3%); none were classified as related to moexipril (carcinoma of the tongue, lumbosciatica, acute cholecystitis, and myocardial infarction).

DISCUSSION

The aim of this study was to evaluate the effect of a 24-week treatment with 15 mg moexipril once daily on the regression of LVH in hypertensive patients. The results showed significant reduction of LVH and BP with moexipril, with no significant correlation between the reduction of LVMIs and the reduction of BP. Two weeks after withdrawal of moexipril, BP increased significantly, whereas LVMIs were unchanged.

Echocardiography is used most widely to measure LVM because of its wide availability and anatomic and prognostic validation; however, this technique is expertise dependent and may give erroneous results in the absence of standardized procedures.[12,13] In this study, echocardiography was conducted according to established guidelines.[12,14,15] Training for standardized methodology and evaluation was provided for all the investigators prior to enrolling patients in the study. Furthermore, because of the single-blind study design, centralized, blinded readings were conducted by 2 independent cardiologists at the principal investigation site. The mean values from these blinded readings were used for the efficacy analyses. Advantages of similar methodology have been shown in several studies.[16,17]

On the basis of distributions of indexed echocardiographic LV mass in normal populations, LVH has been identified using indices based on body surface area (BSA) or body height.[16,18,19] There are different definitions of LVH with different thresholds for the LVMIs: values range from 95 g/m^2 for both sexes[20] to 106 g/m^2 in women and 111 g/m^2 in men[11] or 120 g/m^2 and 134 g/m^2, respectively.[22,23] Inclusion criteria for LVH based on BSA (LVMIs) in this study were AU3

Table 4. Blood pressure at baseline (W 0), after 24 weeks of moexipril (W 24), and after 2 weeks of placebo

	W 0 placebo (N = 72)	W 24 moexipril (n = 70)	W 26 placebo (n = 53)	*P* value W 0 vs. W 24
Systolic BP (mm Hg)	152 ± 12	140 ± 13	146 ± 13	<0.001
Diastolic BP (mm Hg)	96 ± 8	86 ± 9	93 ± 10	<0.001

Mean ± 1 SD.

>106 g/m^2 in women and >11 g/m^2 in men.[11] Compared with other indices, these values are in the lower range. However, these criteria are valid for several reasons. The impact of different partition values on the prevalence of LVH and concentric geometry in a large hypertensive population was analyzed by Wachtell et al, who found no difference in prevalent cardiovascular disease in subjects identified by either criterion, suggesting a similar high risk.[17] A greater reduction of LVM is expected in patients with a higher initial LVM value; this is supported by a number of studies, including the metaanalysis[7] that showed that the higher the pretreatment LVMI value is, the greater the decrease in LVMI. Analysis of these study results using LVMIh showed similar results (data not shown).

BP is the strongest independent determinant for LVH; LVH has been observed in normotensive individuals as well as in all stages of hypertension.[24] Although lowering BP produces a beneficial effect on LVH and reduction of LVH can be achieved by most of the first-line antihypertensive drugs, a metaanalysis of randomized, double-blind studies showed that duration of treatment, the pretreatment LVMI, and the drug class determine the degree of reduction of LVMI.[7] In this metaanalysis, ACE inhibitors decreased LVM to a greater extent than other classes of antihypertensives: ACE inhibitors, 13.3%; calcium channel blockers, 9.3%; beta-blockers, 5.5%; and, diuretics, 6.8%. These findings are in accordance with the results of 2 other metaanalyses[6,25] and suggest that regression of LVH may be more strongly related to changes in the renin-angiotensin system than to BP reduction. The results of our study showed a decrease of LVMIs of about 15% after moexipril treatment of 24 weeks; these results are in agreement with results obtained from metaanalyses of previous trials of similar duration with other ACE inhibitors.[6,7,25]

SBP and DBP decreased markedly during the moexipril treatment phase and increased significantly during the placebo follow-up period. The observed mean reduction of systolic (–12 mm Hg) and diastolic (–10 mm Hg) BP was comparable with those found in other moexipril trials.[8–10,26] In the present study, no significant correlation was observed between the reduction of LVMIs and the BP changes. This is in accordance with other trials that showed that reduction is also in agreement with the metaanalyses findings[6,7,25] that suggest that regression of LVH may be more strongly related to changes in the renin-angiotensin system than to BP reduction.

Some limitations of the study have to be considered. The study was designed as a single-group, single-blind, nonrandomized trial. To overcome limitations related to the use of the single-group design and the regression to the mean phenomenon that may affect the results observed between W 0 and W 24, 2 placebo phases were included: a run-in placebo period and a wash-out placebo period. In this regard, changes of LVMIs and BP observed between W 0, W 24, and W 26 were not due to the regression to the mean phenomena because of their nonlinearity and the absence of significant correlation between changes of LVMIs and changes in BP. To overcome limitations related to the single-blind design, all readings used for the efficacy analysis were performed at the central investigation site by 2 independent cardiologists blinded for treatment, site, and visit.

CONCLUSION

The results of the study showed that 15 mg moexipril once daily administered for 24 weeks resulted in a significant reduction of LVMIs and BP in patients with essential systolodiastolic hypertension or isolated systolic hypertension. This reduction in LVMIs is consistent with the LVMIs reduction achieved with other ACE inhibitors, as shown in the metaanalysis by Schmeider et al.[7] Whether regression of LVH is directly associated with a decrease in cardiovascular morbidity and mortality, independent of BP reduction, remains to be demonstrated.

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