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Seated Cuff Blood Pressure-Lowering Efficacy of an Olmesartan Medoxomil-Based Treatment Regimen in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Hypertension is a common co-morbidity in patients with type 2 diabetes mellitus, and well tolerated, effective therapies are needed to achieve guideline-recommended blood pressure (BP) goals in these patients.
Objective: The aim of this study was to present the results of a prespecified analysis of key secondary endpoints from a 12-week, open-label, single-arm study evaluating the efficacy and safety of olmesartan medoxomil plus hydrochlorothiazide (HCTZ) in patients with hypertension and type 2 diabetes.
Study Design and Methods: After a placebo run-in period, 192 patients received olmesartan medoxomil 20 mg/day for 3 weeks. If BP remained ≥120/70 mmHg, patients were uptitrated at 3-week intervals to olmesartan medoxomil 40 mg/day, olmesartan medoxomil/HCTZ 40/12.5 mg/day, and olmesartan medoxomil/HCTZ 40/25 mg/day.
Main Outcome Measure: Endpoints evaluated in this analysis were the change from baseline in mean seated cuff BP (SeBP), proportions of patients achieving SeBP goals, and distribution of SeBP reductions.
Results: Mean SeBP was 158.1/90.0 mmHg at baseline. The mean ± standard error of BP reductions at 12 weeks for systolic and diastolic BP were 21.3 ± 1.1 mmHg and 9.8 ± 0.6 mmHg, respectively ($p < 0.0001$ for each). At the end of the study, the proportion of patients with diabetes achieving the recommended SeBP goal of <130/80 mmHg was 41.1%.
Conclusions: An olmesartan medoxomil ± HCTZ treatment regimen significantly reduced BP from baseline in patients with hypertension and type 2 diabetes.
Clinical Trials Registration: ClinicalTrials.gov identifier: NCT00403481

Introduction

Hypertension is a common co-morbidity of type 2 diabetes mellitus, affecting nearly 80% of patients.[1] The coexistence of these two conditions is particularly detrimental because of their demonstrated association with cardiovascular and renal disease. Each 5 mmHg increase in

seated cuff systolic blood pressure (SeSBP) or seated cuff diastolic blood pressure (SeDBP) increases the risk of cardiovascular disease by 20–30%.[2] Moreover, data from observational studies have shown that patients with both hypertension and diabetes have an approximately 2-fold greater risk of developing cardiovascular disease than patients with hypertension and no diabetes.[3] The United Kingdom Prospective Diabetes Study (UKPDS) was the first large-scale study to demonstrate a direct relationship between systolic blood pressure (SBP) and the complications of diabetes over time, and that intensive blood pressure (BP) lowering was associated with clinically important reductions in both diabetes-related, and cardiovascular morbidity and mortality in patients with type 2 diabetes.[4] Consequently, BP reduction was suggested to be at least as important as blood glucose control in patients with both hypertension and diabetes.

The assessment of BP control typically employs the seated cuff BP (SeBP) method, which has demonstrated both good practicality and clinical utility. The American Diabetes Association (ADA), the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), and the European Societies of Hypertension (ESH) and Cardiology (ESC) recommend that patients with diabetes should be treated to an SeBP goal of <130/80 mmHg, measured using an office cuff BP device.[5-7] In recent years, the use of ambulatory BP monitoring (ABPM) has increased. The ability to continuously assess BP over a 24-hour period during both normal daily activities as well at night-time can improve the prediction of cardiovascular risk and analyze BP loads as well as identify the presence of white coat and masked hypertension.[8-12]

The BENIFICIARY (BENIcar safety and efFICacy evaluatIon: An open-label, single-ARm, titration study in patients with hypertension and tYpe 2 diabetes) study assessed change from baseline in mean 24-hour ambulatory BP and achievement of ambulatory BP prespecified study targets in patients with type 2 diabetes and hypertension receiving an olmesartan medoxomil-based treatment algorithm.[13] In addition, efficacy of the olmesartan medoxomil-based therapy on SeBP levels was measured. We report herein the secondary efficacy endpoints from the BENIFICIARY study, which include the change from baseline in mean SeBP, the achievement of SeBP goals, and the distribution of SeSBP reductions.

Patients and Methods

The methodology for the BENIFICIARY study has been described previously[13] and is summarized here.

Study Design

BENIFICIARY was a prospective, open-label, multicenter, single-arm titration study. Patients underwent a 12-week, open-label, active treatment period beginning with olmesartan medoxomil 20 mg/day following a 3- to 4-week placebo run-in phase.[13] During the active treatment period, patients received olmesartan medoxomil alone or as a fixed-dose combination with hydrochlorothiazide (HCTZ) and were uptitrated if BP remained ≥120/70 mmHg according to the following schedule: olmesartan medoxomil 20 mg (weeks 1–3); olmesartan medoxomil 40 mg (weeks 4–6); olmesartan medoxomil/HCTZ 40/12.5 mg (weeks 7–9); olmesartan medoxomil/HCTZ 40/25 mg (weeks 10–12). If SeBP was <120/70 mmHg, patients entered a maintenance phase continuing on the same dosage. If SeBP was ≥130/80 mmHg in patients in the maintenance phase during subsequent visits, the titration schedule was resumed, and patients continued to be uptitrated at 3-week intervals, as necessary, if SeBP remained ≥120/70 mmHg.

Patients

Main inclusion criteria included the patient having hypertension (mean SeSBP of 140–199 mmHg and mean SeDBP ≤114 mmHg at two consecutive study visits during the placebo run-in phase, with a difference in SeSBP of ≤10 mmHg) and type 2 diabetes (current regular use of oral antidiabetes agents; documented diabetes according to the ADA and/or WHO criteria; or diagnosis of diabetes after 40 years of age [non-insulin-dependent]). Patients were also included in the study if they

were stable on oral antidiabetes agents for ≥4 weeks or if they had newly diagnosed or existing hypertension (>130/80 mmHg) that was uncontrolled on current antihypertensive therapy. Finally, patients needed to have a mean daytime (8am to 4pm) ambulatory SBP >130 and ≤199 mmHg, and mean daytime ambulatory diastolic BP (DBP) ≤114 mmHg, as assessed by mean 24-hour ABPM during the placebo run-in phase for inclusion in the active treatment phase of the study.

The presence of any serious disorder, including cardiovascular, renal, pulmonary, hepatic, gastrointestinal, endocrine/metabolic (note: patients with non-insulin-dependent type 2 diabetes were allowed in the study), hematologic, oncologic, neurologic, and psychiatric diseases, overt proteinuria, or non-dominant arm circumference <24 cm or >42 cm, was exclusionary. Patients were removed from the study and treated with appropriate antihypertensive therapy at the discretion of the investigator if at any time SeBP either became >199/114 or <120/70 mmHg with symptomatic hypotension. Also, patients with a fasting serum glucose level of >300 mg/dL or a serum creatinine level of >1.7 mg/dL at screening were excluded from the study.

Cuff Blood Pressure Protocol

Following a 5-minute rest period, three separate measurements were taken using an automatic Omron BP-monitoring device (HEM-705CPII; Omron Healthcare, Inc., Bannockburn, IL, USA), with a full 2-minute interval between SeBP measurements and with the cuff fully deflated between measurements. The mean of the three SeBP measurements constituted the SeBP value for that visit.

Efficacy Assessments

ABPM and safety data for the BENIFICIARY study have been reported previously.[13] Secondary endpoints reported here include changes from baseline in mean SeSBP and mean SeDBP at the end of each titration period; the overall change at the end of the 12-week active treatment period; the number/percentage of patients achieving SeBP goals of <130/80 and <120/80 mmHg; and the number/proportion of patients achieving mean SeSBP reductions of ≤15 mmHg, >15 and ≤30 mmHg, >30 and ≤45 mmHg, or >45 mmHg.

Statistical Analysis

All patients who received at least one dose of the active study drug and had at least one post-baseline BP measurement were included in the efficacy analysis dataset. All data are reported as mean ± standard error of the mean (SEM) unless otherwise specified. The last observation carried forward method was used to assess the changes from baseline in mean SeSBP and mean SeDBP. Baseline characteristics were summarized using descriptive statistics conducted at a two-sided significance level of 5%. A one-sample *t*-test was used for within-group change from baseline to end of study, and the resultant mean change, standard error, two-sided 95% confidence interval, and p-value were provided. Summary statistics for the primary efficacy variable were presented. Secondary efficacy variables were analyzed in a similar way to the primary efficacy variable. Statistical analyses were carried out using SAS software version 6.12 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient Disposition and Baseline Characteristics

Of the 329 patients screened, 267 received at least one dose of placebo run-in medication and 192 received at least one dose of active study medication, and were considered part of the efficacy and safety cohorts. By study end, 192 patients (100%) had received olmesartan medoxomil 20 mg/day, 182 (94.8%) had received olmesartan medoxomil 40 mg/day, 173 (90.1%) had received olmesartan medoxomil/HCTZ 40/12.5 mg/day, and 144 (75.0%) had received olmesartan medoxomil/HCTZ 40/25 mg/day. Baseline demographic data are summarized by treatment regimen in table I.

Efficacy

The mean 24-hour ambulatory BP data for the BENIFICIARY trial has been previously presented.[13] In the BENIFICIARY study, for the

Table I. Baseline demographics, clinical characteristics, and baseline blood pressure (BP) information[a,b]

Parameter	Value
Age [y]	58.1 ± 10.3
Race [n (%)]	
Caucasian	145 (75.5)
Black	43 (22.4)
Asian	3 (1.6)
native Hawaiian/Pacific islander	1 (0.5)
Gender [n (%)]	
male	107 (55.7)
female	85 (44.3)
Height [cm]	168.0 ± 11.3
Weight [kg]	95.2 ± 23.0
HTN stage[c] [n (%)]	
stage 1	101 (52.6)
stage 2	91 (47.4)
SeBP[d] [mmHg]	
SeSBP	158.1 ± 12.6
SeDBP	90.0 ± 10.0

a Demographics were identical for efficacy and safety cohorts (n = 192).

b All data are mean ± standard deviation, unless otherwise specified.

c HTN stage determined by mean cuff BP at baseline.

d Data are the average of the mean office cuff BP from last visit before active therapy initiation (presented as mean ± standard error of the mean).

HTN = hypertension; **SeBP** = seated cuff blood pressure; **SeDBP** = seated cuff diastolic blood pressure; **SeSBP** = seated cuff systolic blood pressure.

primary endpoint, the change from baseline in mean 24-hour ambulatory SBP at week 12 was 20.4 mmHg.

Seated Cuff Blood Pressure Measurement

At week 12, the reductions (± SEM) in mean SeSBP and mean SeDBP were 21.3 ± 1.1 mmHg and 9.8 ± 0.6 mmHg, respectively, for the total cohort (both $p < 0.0001$ vs baseline).

Mean SeSBP was significantly decreased from baseline by week 12 for each treatment regimen, with reductions ranging from –9.5 ± 1.0 mmHg to –21.8 ± 1.2 mmHg (figure 1). Mean SeDBP also significantly decreased, with reductions ranging from –4.0 ± 0.6 mmHg to –9.9 ± 0.7 mmHg (figure 1).

SeSBP and SeDBP reductions were significantly increased when HCTZ 12.5 mg was added to olmesartan medoxomil 40 mg in all treatment groups (figure 1). Patients also had significant increases in SeSBP and SeDBP reductions when titrated from olmesartan medoxomil/HCTZ 40/12.5 mg to olmesartan medoxomil/HCTZ 40/25 mg (figure 1).

At study end, the cumulative percentages of patients achieving SeBP goals of <130/80 mmHg and <120/80 mmHg were 41.1% and 24.0%, respectively. Overall, each uptitration increased SeBP goal achievement in the total cohort (figure 2).

The proportions of patients who achieved mean SeSBP reductions of ≤15 mmHg, >15 and ≤30 mmHg, >30 and ≤45 mmHg, and >45 mmHg were 16.1%, 34.9%, 19.3%, and 4.7%, respectively, for the maximum dose of the treatment algorithm (figure 3). There was a non-statistically significant trend between treatment and the proportion of patients achieving defined SeSBP reductions (i.e. increasing the dose of olmesartan medoxomil and olmesartan medoxomil/HCTZ resulted in more patients achieving >15 mmHg reductions in SeSBP).

A prespecified subgroup analysis of patients with stage 1 and stage 2 hypertension showed that the proportion of patients achieving the JNC 7 recommended BP goal of <130/80 mmHg for patients with type 2 diabetes increased with upward titration of the treatment regimen. In patients with stage 1 hypertension, goal achievement rates were

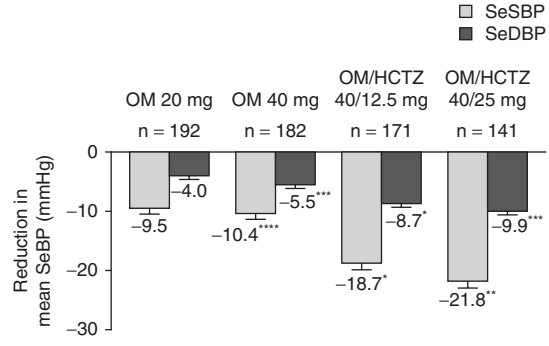

Fig. 1. Change from baseline in seated cuff blood pressure (SeBP) at week 12/last observation carried forward for the total cohort, patients with stage 1 hypertension, and patients with stage 2 hypertension. Data are mean ± standard error of the mean. $p < 0.0001$ for all reductions vs baseline. **HCTZ** = hydrochlorothiazide; **OM** = olmesartan medoxomil; **SeDBP** = seated cuff diastolic blood pressure; **SeSBP** = seated cuff systolic blood pressure; * $p < 0.0001$, ** $p < 0.001$, *** $p < 0.01$, **** p-value not significant vs preceding treatment regimen.

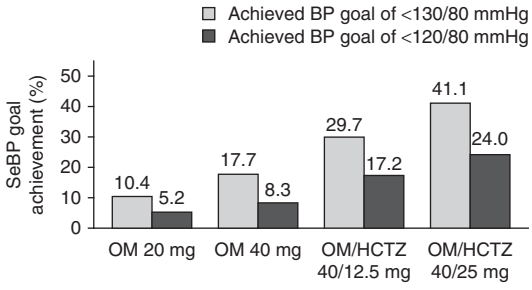

Fig. 2. Cumulative seated cuff blood pressure (SeBP) goal achievement at week 12/last observation carried forward. The SeBP measurements are calculated using the total number of subjects in the treatment cohort (n = 192) with the last observation carried forward for patients who did not have a measurement at end of study. **HCTZ** = hydrochlorothiazide; **OM** = olmesartan medoxomil.

16.8%, 29.7%, 44.6%, and 54.5% across the dosing range (olmesartan medoxomil 20 mg, olmesartan medoxomil 40 mg, olmesartan medoxomil/HCTZ 40/12.5 mg, and olmesartan medoxomil/HCTZ 40/25 mg), while the goal achievement rates for patients with stage 2 hypertension were lower at 3.3%, 4.4%, 13.2%, and 26.4%.

Discussion

In addition to recommended lifestyle changes to prevent or manage hypertension,[6] many patients with diabetes also require antihypertensive medication to achieve SeBP goals.[14] Monotherapy comprising a renin-angiotensin system inhibitor (either an angiotensin receptor blocker or an ACE inhibitor) is recommended as initial therapy.[5] The addition of agents such as a diuretic or calcium channel blocker is recommended if patients do not achieve the SeBP goal.[5] Adherence with therapy, and thus therapeutic efficacy, are improved through the use of fewer pills, and switching to fixed-dose combinations is a well proven strategy to ensure adherence.[15,16] The present study protocol comprised a treatment schedule similar to that recommended by hypertension treatment guidelines such as JNC 7 and ESH/ESC.[6,7] Dosing was intensified at 3-week intervals in a manner consistent with the recently revised guidelines of the American Society of Hypertension.[17]

The time of dosing in BENIFICIARY was in the morning hours and correlated with the SeBP measurements.[13] It may be possible that evening dose administration may affect the efficacy of treatment with an olmesartan medoxomil-based treatment algorithm. This has previously been suggested by Tofe Povedano and Garcia De La Villa,[18] who conducted a crossover design ABPM study to determine the benefits of morning versus evening dosing of olmesartan medoxomil 40 mg on ambulatory BP, nocturnal BP fall, and albuminuria in patients with type 2 diabetes and newly diagnosed hypertension. These investigators demonstrated significantly greater reductions of night-time SBP (p = 0.007) and night-time mean BP (p = 0.012) following nocturnal dosing

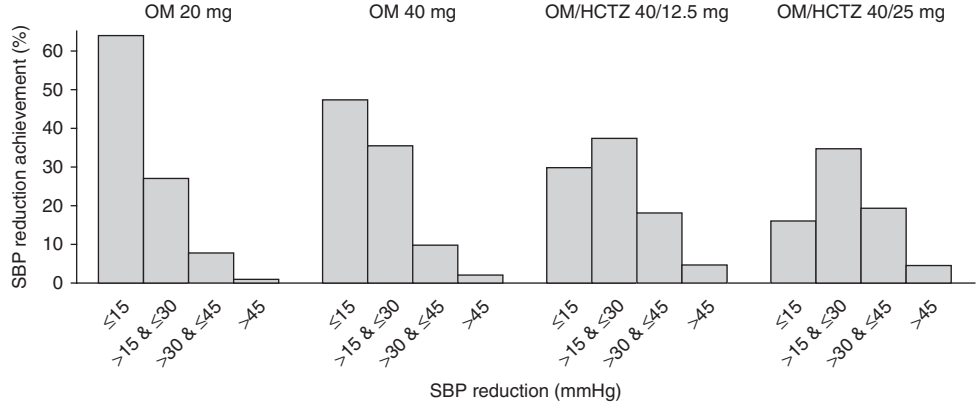

Fig. 3. The proportion of patients achieving prespecified systolic blood pressure (SBP) decreases at week 12. Percentages are calculated using the total number of subjects in the treatment efficacy cohort as the denominator. **HCTZ** = hydrochlorothiazide; **OM** = olmesartan medoxomil.

of olmesartan medoxomil compared with morning dosing.

The present study demonstrated that an olmesartan medoxomil-based treatment algorithm resulted in large SeBP reductions in a population of patients with diabetes and hypertension. For comparison, the most recent National Health and Nutrition Examination Survey showed that between 1999 and 2004, 42% of patients in the US who were diagnosed with diabetes and hypertension achieved an SeBP goal of <130/80 mmHg.[19]

The present study demonstrated a trend for dose response-related SeBP reductions with higher doses of olmesartan medoxomil and HCTZ when administered either alone or in combination. SeBP reductions were significantly greater following dose increments with the single exception of the SeSBP reduction observed following titration of olmesartan medoxomil 20 mg to olmesartan medoxomil 40 mg. More than one-half of these patients with diabetes and hypertension experienced a >15 mmHg SeSBP reduction in the olmesartan medoxomil/HCTZ 40/12.5 mg and 40/25 mg groups by end of study.

It has been well documented that tight BP control in patients with type 2 diabetes and hypertension significantly reduces the risk of cardiovascular and renal disease as well as associated mortality rates.[20-24] However, it has also been shown that two or more antihypertensive agents will be needed to achieve the SeBP goal of <130/80 mmHg in the majority of patients with diabetes and hypertension.[6] The results reported in the current analysis of the BENIFICIARY study data show that an olmesartan medoxomil-based combination therapy produced significant BP reductions in patients with type 2 diabetes. These results are similar to those of other studies involving angiotensin receptor blockers, which have demonstrated significant BP reductions and higher goal BP achievement with dose titration and concomitant use of HCTZ in this difficult-to-treat patient population.[25,26]

Conclusion

Olmesartan medoxomil ± HCTZ has been shown to effectively reduce BP in patients with hypertension and type 2 diabetes. The use of a fixed-dose combination of olmesartan medoxomil and HCTZ may improve BP control rates by enabling an increased proportion of these patients to achieve the currently recommended SeBP goal of <130/80 mmHg.

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