

Management of Hypertension in Patients with Diabetes Using an Amlodipine-, Olmesartan Medoxomil-, and Hydrochlorothiazide- Based Titration Regimen

Objective:

- The purpose of this study was to evaluate the efficacy and safety after 12 weeks of treatment of amlodipine (AML) and olmesartan (OM) in patients with hypertension (HTN) and Type II Diabetes (T2DM)

Methods:

- **Design:** Prospective, open-label, multi-center, single-arm, titration study
- **Inclusion criteria:** noninstitutionalized men and women 18-80 years with T2DM and HTN on stable treatment for ≥ 3 months, FPG ≥ 126 mg/dl and document history of T2DM, mean daytime systolic BP of ≥ 130 and ≤ 199 mm Hg and diastolic BP of ≤ 114 mm Hg after placebo run-in
- **Exclusion criteria:** uncontrolled HTN with multiple antihypertensive medications, insulin therapy, T2DM with glycosylated HbA1c $\geq 9.0\%$, proteinuria of $> 1+$ on dipstick, serum creatinine > 1.7 mg/dl, fasting serum glucose of > 300 mg/dl, nondominant arm circumference of < 24 or > 42 cm, serious disorders that limit the ability to evaluate olmesartan safety, women who are pregnant, planning to get pregnant, breastfeeding, or not on approved birth control, receiving no other antihypertensive medications
- **Drug regimen:** Patients were started at 5 mg of amlodipine daily. At three week intervals patients were titrated to AML/OM 5/10, 5/20, 5/40, 10/40 mg/day if the target blood pressure (BP) goal of $< 130/80$ was not reached
- **Primary Outcome Measures:** Change from baseline in the mean 24-hour ambulatory systolic BP after 12 weeks of treatment
- **Secondary Outcome Measures:** Change from baseline in the mean 24-hour ambulatory diastolic BP, the change from baseline in the mean daytime and night time ambulatory BP, change from baseline in the mean ambulatory BP during the last 6, 4, and 2 hours of the 24-hour treatment interval after 12 weeks of treatment, change from baseline in the mean seated BP at each titration step up to week 18, the proportion of patients achieving the prespecified ambulatory and seated systolic and diastolic BP reductions, and the proportion of patients achieving the seated BP goals during the study
- **Safety Outcome Measures:** adverse events reported during the 18 week active treatment period and 14 days after were recorded and graded. Safety was also assessed by monitoring laboratory value and physical examination findings at screening, week 12, and week 18
- **Power:** Power of 99% with an alpha level of 0.05; this was calculated with 200 patients; this sample size was expected to allow approximately 150 patients to complete the first 12 weeks of the active treatment period
- **Data Handling:** All efficacy and safety analysis were based on the treated group (all subjects who received at least one dose of study medication). All ambulatory BP monitoring analysis was based on the ambulatory BP monitoring group (all treated subjects having both valid baseline and week 12 ambulatory BP monitoring data)

Results:

- 164 patients completed the study; 7 patients were in the 5/20 group, 5 in the 5/40 group, 14 in the 10/40 group, 38 in the 10/40+ 12.5 group, 101 in the 10/40+ 25 group
- **Primary Outcome Measures:** The overall change from baseline in the mean 24-hour ambulatory systolic BP was -19.9 mm Hg ($p < 0.0001$)
- **Secondary Outcome Measures:** The reduction in the mean \pm SEM 24 hour ambulatory diastolic BP was -11.2 ± 0.5 mm Hg ($p < 0.0001$); the ambulatory BP was reduced in the daytime and

nighttime and during the last 6, 4, and 2 hours of the dosing interval at week (all $p < 0.0001$); after 12 weeks of treatment, 70%, 46%, and 36% of patients had achieved the prespecified 24-hour ambulatory BP targets of $< 130/80$, $< 125/75$, and $< 120/80$; during the daytime, 50%, 29%, and 26% of the patients had achieved these thresholds compared to 83%, 72%, and 68% of the patients during the nighttime, all seated BP reductions from baseline were statistically significant for each dosing period ($p < 0.001$)

- **Safety Outcome Measures:** 117 patients treated with one or more doses of the study medications experienced a treatment-emergent adverse event during the study, 40 patients experienced a drug-related treatment-emergent adverse event; five serious adverse events were reported; 12 patients discontinued therapy due to treatment; the most common reason for discontinuation was peripheral edema; no significant changes in laboratory monitoring occurred
- **Author's Conclusions:** This amlodipine-, olmesartan –based titration regimen was well tolerated and effectively lowered BP throughout the 24-hour dosing interval in patients with HTN and T2DM

Strengths:

- Placebo run-in period
- Appropriate dosages and dosage titrations for study medications
- Available combination products of study medications easing the pill burden of patients

Limitations:

- Unblinded, non-comparative study design
- Medication adherence was not addressed
- No control over patient's lifestyle factors (diet, exercise, drug and alcohol use, etc.)
- Medications concurrently taken by patient for non-study purposes were not reported
- Study support and author affiliations with study drug manufacturer
- Inclusion and exclusion criteria did not allow for extrapolation to entire study population

Conclusion:

- Although the study found the amlodipine-,olmesartan- titration-regimen to be statistically significant it may not be the most clinically significant option for patients
 - It is hard to evaluate its place in therapy since this was not a comparative trial
 - ACE inhibitors are a integral component in treating patients with T2DM and HTN
 - Over three quarters of the study participants (76%) experienced an adverse event during the study
- Further study is warranted in this patient population comparing this regimen to other available therapies

References:

Ram, C. V., Sachson, R., Littlejohn, T., Qian, C., Shojaee, A., Stoakes, K., et al. "Management of hypertension in patient with diabetes using an amlodipine-, olmesartan medoxomil-, and hydrochlorothiazide- based titration regimen." American Journal of Cardiology. May 2011: 107 (9): 1246- 52.

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