CONSISE REVIEW

Antihypertensive Efficacy of Combination Treatment with Olmesartan Medoxomil and Amlodipine

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Abstract: Because it increases the risk of cardiovascular disease, hypertension is one of most important causes of mortality. To achieve a target blood pressure of 140/90 mmHg, many patients with hypertension require combination therapy. One useful option is a fixed-dose combination of olmesartan and amlodipine. For example, the COACH trial showed that using these drugs in long-term combination therapy, rather than in monotherapy, had many advantages including a lower incidence of adverse events and stronger antihypertensive potency. Numerous other clinical trials have supported these findings for olmesartan and amlodipine combination therapy. Given these results, we conclude that combination therapy with olmesartan and amlodipine is clinically useful for the treatment of blood pressure control and may improve target organ protection.

Keywords: combination treatment, olmesartan, amlodipine, COACH, OSCAR

Introduction

Hypertension is a major contributor to worldwide cardiovascular mortality. Data from national surveys indicate that the prevalence of hypertension, defined as systolic blood pressure [SBP]/diastolic blood pressure [DBP] $\geq$140/90 mmHg or the use of any antihypertensive medication, is approximately 30% in Americans aged over 18 years[1] and approximately 40% in Europeans aged 35–64 years.[2] Compared with normotensive individuals, patients with hypertension have an increased risk of various cardiovascular diseases, including coronary artery disease (CAD) and cerebrovascular disease (CVD),[3] which together account for one-third of all global deaths.[4] The number of people with high blood pressure (BP) worldwide is expected to reach about 1.6 billion by 2025.[5] Despite our understanding of the close link between hypertension and mortality, however, BP control rates in hypertensive patients remain poor,[6] with approximately 55% of patients failing to reach recommended BP levels.[7] When antihypertensives are required, treatment should be initiated with thiazide diuretics, calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II type 1 receptor antagonists [angiotensin receptor blockers (ARB)] or beta adrenergic receptor blockers (β blocker).[8] The majority of patients with hypertension, however, require combination therapy.[9] Combination therapy has several advantages over monotherapy: in particular, the use of antihypertensive agents with complementary mechanisms of action has a greater BP lowering effect than that of individual agents, enabling patients to reach target BP levels.[10] Consequently, one of the more recent developments in antihypertensive therapy is the availability of fixed–dose combinations of ARB and CCB.[11] If its efficacy is confirmed, fixed-dose combination therapy would be considered a more attractive treatment option than non-fixed dose combination therapy or monotherapy with only ARB or CCB (Table 1).

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Olmesartan medoxomil (OLM), a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. OLM is an oral, once-daily angiotensin II type 1 receptor-selective ARB with high receptor affinity.[12] For OLM, the time to peak

Table 1. Large clinical trials.

The titles of the trials	Characteristics
COACH trial[11]	To compare the efficacy and tolerability of combinations of OLM and AML with those of the component monotherapies in patients with mild to severe hypertension
OSCAR study[30]	To compare the efficacy and safety of high-dose OLM monotherapy with that of an OLM plus CCB (including AML) combination therapy in elderly patients with high-risk hypertension
AZTEC study[31]	To evaluate the efficacy of a fixed-dose combination of OLM and AML over a 24-hour dosing interval using ambulatory blood pressure monitoring (ABPM).

effect of is 1 to 3 hours, elimination half-life is 12 to 18 hours, and time to reach steady state plasma levels is 7 to 10 days after consecutive daily dosing. Pharmacologically, OLM inhibits the actions of angiotensin II on the renin-angiotensin-aldosterone system (RAS), which plays a key role in the pathogenesis of hypertension, with linear pharmacokinetics and without cytochrome P450 interaction.[13,14]

OLM rapidly lowers blood pressure within 1 week of starting administration. Single daily oral administration at 20 mg olmesartan is considered optimum. In clinical trials and post-marketing studies, OLM has been shown to be safe and well tolerated with an adverse event profile similar to that of placebo.

Active comparative studies have demonstrated that the efficacy of OLM is equivalent or superior to that of other ARBs.[15–19] Indeed, recent studies suggest that OLM may inhibit ACEs in addition to blocking Ang II receptors, preventing an increase in Ang II level, and protecting cardiovascular remodeling through an increase in cardiac nitric oxide and endogenous blood depressor peptides Ang-(1-7) production. This last effect acts via the over-expression of ACE2, which hydrolyzes Ang II to Ang-(1-7).[20,21]

Amlodipine (AML) is a third-generation, long-acting dihydropyridine CCB that decreases the influx of extracellular calcium into cardiac and arterial smooth muscle cells via L-type calcium channels[22] This prevents actin and myosin from interacting, resulting in vasodilatation. In contrast to first- and second-generation short-acting dihydropyridine CCBs, AML

exerts a gradual and sustained antihypertensive effect over 24 hours in patients with mild to moderate hypertension.[23] The time to peak effect of AML is 6 to 8 hours, elimination half-life is 40 to 60 hours, and time to reach steady state plasma levels is 7 to 10 days after consecutive daily administration.[24,25] AML does not cause first-dose hypotension, postural hypotension, tachycardia, or rebound hypertension when treatment is discontinued abruptly, and the normal circadian BP rhythm is preserved. In addition, AML does not block L-type calcium channels and thus has little or no effect on heart rate, plasma lipid level, insulin sensitivity, blood glucose level, plasma catecholamine level, plasma rennin activity, or aldosterone level.[26] AML also increases renal blood flow, decreases renovascular resistance, and increases glomerular filtration rate without affecting proteinuria or filtration fraction.[27] Recent clinical data support the idea that treatment of hypertensive patients with AML leads to a reduction in the incidence of cardiovascular events. In the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT), amlodipine reduced the progression of carotid intima-medial thickening and the incidence of unstable angina and revascularization in patients with coronary artery disease.[28] In the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA), cardiovascular events were optimally prevented in patients who were randomly assigned to amlodipine treatment.[29]

Since the pharmacological effects of these two drugs differ considerably, their combination use in for patients who require more than one medication appears rational. Total OLM and AML systemic exposure after administration of OLM/AML was dose-dependently proportional over a range of 10 mg/5 mg to 40 mg/10 mg.[23]

Clinical Studies
COACH trial
The Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High BP (COACH) trial was an 8-week, multicenter, randomized, double-blind, and factorial design study. Inclusion criteria were as follows: patients were aged ≥18 years and had mild to severe hypertension, defined as a seated DBP of 95–120 mmHg at two separate visits with a difference of <10 mmHg

between the two measurements.[11] Exclusion criteria were as follows: a history of cardiovascular disease; DBP > 120 mmHg; uncontrolled diabetes; glycosylated hemoglobin (HbA1c > 9.0%); history of alcohol or drug abuse; smoking more than one pack of cigarettes per day; and any medical condition which could jeopardize the evaluation of efficacy and safety of therapy as determined by the investigators. Patients were randomized to 1 of 12 treatment groups for 8 weeks of double-blind treatment with placebo, OLM monotherapy (10, 20 or 40 mg/day), AML monotherapy (5 or 10 mg/day), or combination therapy comprised of possible combinations of OLM plus AML. Patients who were treatment-naive were immediately randomized to receive study therapy, while those already receiving antihypertensive therapy at screening underwent a 2-week washout period prior to assessment for eligibility and randomization.

Patients were instructed to take their medication at the same time each day (± 2 hours), regardless of the assigned treatment. Clinic visits were scheduled to measure trough BP at 24 hours after the normal dosing time. The primary efficacy endpoint was the change in mean DBP from baseline to the end of double-blind treatment.[11] Statistical analyses for the primary endpoints were on an intention-to-treat (ITT) basis with last-observation-carried-forward (LOCF) imputation. The ITT population included patients who had a BP measurement at baseline and at least one BP measurement after taking at least one dose of study medication. Secondary efficacy endpoints included changes in mean SBP from baseline to 8 weeks and the proportions of patients with and without diabetes who achieved a prespecified BP goal (<130/80 mmHg for patients with diabetes, <140/90 mmHg for patients without diabetes). Therapeutic efficacy and safety were evaluated at 2, 4, 6, and 8 weeks after starting treatment. The study also included a 44-week open-label phase after completion of the 8-week double-blind phase, the results of which will be reported separately. Safety and tolerability were also evaluated, with a particular focus on the incidence and severity of edema.

For the total study cohort, 4234 patients were screened, 1940 were randomized, and 1689 completed the 8-week double-blind portion of the study. A total of 1940 and 1923 patients were included in the safety and intention-to-treat populations, respectively.

With regard to the study population, mean age was 54.0 years, 19.8% were aged $\geq$ 65 years, 54.3% were male, 71.4% were white, mean BP at baseline was 164/102 mmHg, and 79.3% of patients had stage 2 hypertension (BP $\geq$ 160/100 mmHg).

Combination therapy with OLM and AML was associated with dose-dependent reductions in DBP (from −13.8 mmHg with OLM/AML 10/5 mg to −19.0 mmHg with OLM/AML 40/10 mg) and SBP (from −23.6 mmHg with OLM/AML 20/5 mg to −30.1 mmHg with OLM/AML 40/10 mg), which were significantly greater than those with the corresponding component monotherapies ($P < 0.001$). At week 8, the number of patients achieving the BP goal was between 57 of 163 (35.0%) and 84 of 158 (53.2%) in the combination-therapy groups; between 32 of 160 (20.0%) and 58 of 160 (36.3%) in the OLM monotherapy groups; between 34 of 161 (21.1%) and 53 of 163 (32.5%) in the AML monotherapy groups ($P < 0.005$, combination therapies vs. component monotherapies); and 14 of 160 (8.8%) in the placebo group. Crossing BP thresholds was highest in the combination-therapy groups, with 56.3% and 54.0% of patients achieving a BP $< 140/90$ mmHg with OLM/AML 20/10 and 40/10 mg, respectively. The combination of OLM and AML was effective and well tolerated in this adult population with hypertension.

OSCAR study

The Olmesartan and Calcium Antagonist Randomized (OSCAR) study is the first large-scale [check] clinical trial to compare the efficacy and safety of high-dose OLM monotherapy with that of an OLM plus CCB combination therapy in elderly patients with high-risk hypertension.[30]

The study was conducted under a multicenter, active-controlled, two-arm parallel group comparison design, using the prospective randomized open-blinded end-point method. Elderly ($\geq$65 year-old and $<$85 year-old) hypertensive patients with diabetes or cardiovascular disease received monotherapy with OLM at an optimal dose of 20 mg/day. After confirming eligibility using an enrollment sheet sent by facsimile, the OSCAR data center randomly assigned patients to a high-dose (40 mg/day) OLM group or an OLM plus CCB (AML or azelnidipine) group. After randomization, any earlier antihypertensive medication was switched to OLM at a dose of 20 mg/day in the 'Step 1' period. If the target blood pressure control (less than 140/90 mmHg) was not achieved by OLM monotherapy, the patient was randomized to receive either 1) an increased dose of OLM at 40 mg/day (high-dose OLM monotherapy) or 2) the addition of a CCB (AML or azelnidipine) to OLM at 20 mg/day (OLM plus CCB combination therapy) in the 'Step 2' period. The follow-up duration was 3 years. The primary efficacy endpoints were the composite of fatal and non-fatal cardiovascular events and death from any cause. Of the 1164 elderly patients who were included in the analysis, 578 patients were randomly assigned to the high-dose OLM group and 586 to the OLM plus CCB group. Interestingly, this study used two kinds of CCBs, AML and azelnidipine, on the basis that both are considered preferable for the treatment of hypertension in terms of preventing cardiovascular diseases. The results of this study are expected to provide novel insights into therapeutic strategies for hypertension using high-dose ARB monotherapy and standard-dose OLM plus CCB combination therapy.

AZTEC study

An oral antihypertensive medication which combines the two antihypertensive agents OLM and AML in a film-coated tablet was recently launched in the United States. This new compounding agent, AZOR®, is available in several different OLM/AML doses, namely 20/5, 20/10, 40/5 and 40/10 mg.[31] The AZOR Trial Evaluating Blood Pressure Reductions and Control Study (AZTEC study) was conducted to evaluate the efficacy of a fixed-dose combination of OLM and AML over a 24-hour dosing interval using ambulatory BP monitoring (ABPM). This 12-week, titrate-to-goal study was conducted in 185 patients with hypertension. Patients were initially treated with AML 5 mg/day and titrated up to OLM/AML 20/5, 40/5, and 40/10 mg/day at 3-week intervals if mean seated BP (SBP) was $\geq$120/80 mmHg.

The primary efficacy endpoint was the change in mean 24-hour systolic BP from baseline to week 12 as assessed by ABPM. Mean 24-hour ambulatory BP was 144.8/85.7 mmHg at baseline and decreased by 21.4/12.7 mmHg at week 12 ($P < 0.0001$ vs. baseline). Mean SBP was 158.2/92.8 mmHg at baseline and decreased by 24.1/12.1 mmHg at week 12 ($P < 0.0001$ vs. baseline). Proportions of patients achieving prespecified mean 24-hour ambulatory

BP targets were 70.9% (<130/80 mmHg), 48.3% (<125/75 mmHg), and 40.7% (<120/80 mmHg). Cumulatively, 76.8% of patients who uptitrated to OLM/AML 40/10 mg/day attained an SBP goal of <140/90 mmHg. All compounding doses were well tolerated, with a low incidence of anticipated adverse events (peripheral edema, 2.2%; dizziness, 1.1%). This study showed that an OLM/AML-based titration regimen effectively reduces BP in patients with hypertension.

Safety

Since adverse events with CCBs are generally dose-dependent and are far more prevalent at higher doses, their antihypertensive use at high doses is restricted. In contrast, ARBs, which have antihypertensive efficacy comparable to those of other classes of antihypertensive drugs, have placebo-like tolerability.[32] ARBs, therefore, reduce BP in hypertensive patients in a dose-dependent manner without increasing the incidence of adverse events at maximal doses.

It has been shown that combination therapy with an ARB or ACEI and a CCB may minimize the adverse effects of the CCB, such as peripheral edema.[33,34] ARBs also provide protection against renal and cardiac end-organ failure,[35] which is of particular importance in patients with diabetes and hypertension. A recent long-term clinical outcome study, ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension), has shown that the combination of a renin-angiotensin system blockade (ACEI-benazepril) and a CCB (amlodipine) is more effective in reducing cardiovascular complications than the combination of a renin-angiotensin system blockade (ACEI-benazepril) and a diuretic (hydrochlorothiazide).[36,37]

The safety of OLM/AML combination therapy has been demonstrated in multinational, randomized controlled clinical trials in patients with hypertension ranging from mild to severe.

In the COACH trial, combination therapy was generally well tolerated, and no unexpected safety concerns emerged during its course. The most common adverse event was edema (9.9% [OLM 20 mg], 23.5% [OLM/AML 40 mg/10 mg], 36.8% [AML 10 mg], 12.3% [placebo]). All combinations of AML 10 mg with OLM demonstrated less peripheral edema than AML 10 mg monotherapy. None of the treatments was associated with a significant increase in headache (ranging from 2.5% [OLM/AML 10/5 mg] to 8.7% [OLM 20 mg], 14.2% [placebo]).[38] In subgroup analysis, among all patients treated for another 44 weeks in an open-label extension at an OLM/AML dosage of 40 mg/5 mg, or an uptitrated dosage of 40 mg/10 mg per day, the adverse events profile was similar to that seen in the double-blind phase. In conclusion, the combination of OLM/AML in the total cohort showed no difference in the nature or incidence of adverse events from what would be expected for the component agents as monotherapies. The combination of OLM and AML does not appear to be associated with any new category of adverse events or have any clinically relevant effect upon the incidence of hypotension or edema in comparison to the component monotherapies.

Another randomized, double-blind, parallel-group multicentre study also demonstrated the safety of OLM/AML combination therapy in patients with moderate to severe hypertension who had failed to respond to open-label treatment with AML for 8 weeks[39] After 8 weeks of AML monotherapy (5 mg/day), non-responding patients were randomized to receive placebo plus AML (5 mg) or a combination of OLM (10–40 mg) and AML (5 mg) for 8 weeks. At week 16, all combination regimens were well tolerated.

In the AZTEC study, a fixed-dose combination of OLM and AML was well tolerated with few adverse events. Edema, the only adverse event to occur, had an incidence ≥3% in those who took OLM/AML and was more frequent than in those who took the placebo, in whom the incidence of edema was 12.3%. The placebo-subtracted incidence was 5.7% with OLM/AML at 20/5 mg, 6.2% at 40/5 mg, 13.3% at 20/10 mg, and 11.2% at 40/10 mg. Placebo-subtracted incidence refers to the difference between the total percentage of patients who had edema at each dosage and the percentage of patients who had edema and took the placebo. Patients who received OLM/AML had less common side effects at about the same or greater frequency than those receiving the placebo. These included hypotension, postural hypotension, rash, itchiness, palpitation, excessive frequency of urination, and excessive urination at night (peripheral edema, 2.2%; dizziness, 1.1%).

Efficacy

Barrios et al designed a randomized, double-blind, parallel-group, multicentre trial for patients with moderate to severe hypertension (SBP/DBP ≥ 160/100 mmHg).[40] They started therapy with OLM at the lowest recommended dosage (20 mg) and conducted follow-up for 8 weeks. 538 patients with SBP/DBP ≥ 140/90 mmHg were randomly assigned to 8 weeks of double-blind therapy with OLM/placebo, OLM/AML 20 mg/5 mg, or OLM/AML 20 mg/10 mg and evaluated for efficacy in BP reduction to the BP goal (<140/90 mmHg for patients without diabetes mellitus, <130/80 mmHg for patients with diabetes mellitus). After 8 weeks, the adjusted mean change in DBP from baseline was −7.6 mmHg for OLM/placebo, −10.4 mmHg for OLM/AML 20 mg/5 mg ($P = 0.0006$ vs. OLM/placebo) and −10.9 mmHg for OLM/AML 20 mg/10 mg ($P < 0.0001$ vs. OLM/placebo). Mean changes in SBP from baseline with OLM/AML 20 mg/5 mg and 20 mg/10 mg were −16.1 and −16.7 mmHg, respectively ($P < 0.0001$ for both dose regimens vs. OLM/placebo). Rates of achieving the BP goal were significantly higher with OLM/AML 20 mg/5 mg and 20 mg/10 mg (44.5% and 45.8%, respectively; $P = 0.0011$ and $P = 0.0004$, respectively) than with OLM/placebo (28.5%). These combination therapy regimes were well tolerated, with an incidence of drug-related adverse events of 8.9% for OLM/placebo, 7.7% for OLM/AML 20 mg/5 mg, and 11.3% for OLM/AML 20 mg/10 mg ($P = 0.490$). Most adverse events were mild in severity and were anticipated drug-class issues. The authors concluded that the combination of OLM and AML resulted in a significantly greater BP decrease in patients not achieving adequate BP control with OLM monotherapy, thus allowing a significantly greater proportion of patients to achieve their BP goal.

Volpe et al also demonstrated the efficacy of OLM/AML in age-, severity- and gender-based subgroups of patients with moderate to severe hypertension that was uncontrolled by AML monotherapy.[39] In this study, patients (n = 755) with uncontrolled BP after 8 weeks of AML (5 mg) monotherapy were randomized to continue taking AML (5 mg) or receive OLM (10–40 mg) plus AML (5 mg) for 8 weeks. Patients whose BP remained suboptimal were uptitrated to OLM/AML 20/5, 40/5 or 40/10 mg. Changes in BP and the number of controlled patients were calculated

after stratification by age (<65 or ≥65 years), severity of hypertension at baseline (moderate or severe), and sex. Results for the antihypertensive effects of OLM/AML were as follows: the two age groups showed no difference; patients with severe hypertension at baseline showed higher reductions in BP and lower BP goal achievement rates than those with moderate hypertension; and females showed greater mean reductions in DBP (1.61 mmHg; $P = 0.003$) and SBP (1.72 mmHg; $P = 0.053$) than males, independent of age and dose. Interestingly, this gender difference appeared to be higher and more consistent for patients aged <50 years, albeit without statistical significance ($P = 0.15$). These results suggest that OLM/AML is effective and safe in a wide range of patients, regardless of age or the severity of hypertension.

Schmieder reported that combination therapy with OLM and AML was associated with dose-dependent reductions in DBP (from −13.8 mmHg with OLM/AML 10/5 mg to −19.0 mmHg with OLM/AML 40/10 mg) and SBP (from −23.6 mmHg with OLM/AML 20/5 mg to −30.1 mmHg with OLM/AML 40/10 mg), which were significantly greater than those with the corresponding component monotherapies ($P < 0.001$).[41] At week 8, the number of patients achieving the BP goal was between 57 of 163 (35.0%) and 84 of 158 (53.2%) in the combination therapy groups; between 32 of 160 (20.0%) and 58 of 160 (36.3%) in the OLM monotherapy groups; between 34 of 161 (21.1%) and 53 of 163 (32.5%) in the AML monotherapy groups ($P < 0.005$, combination therapies vs. component monotherapies); and 14 of 160 (8.8%) in the placebo group. Reaching BP thresholds was highest in the OLM/AML 20/10 and 40/10 mg combination therapy groups, with 56.3% and 54.0% of patients achieving a BP < 140/90 mmHg, respectively.

Patient Preference

Combination therapy with OLM and AML is indicated as initial therapy in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals. Initial therapy with OLM and AML in combination is not recommended in patients aged 75 years or older, or in patients with impaired hepatic function. Further, combination therapy with OLM and AML should not be used during pregnancy (http://www.azor.com/hcp/index.html).

Use in pregnancy

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. Use is also associated with a high risk of congenital malformations.[42] Given these results, this combination therapy should be discontinued as soon as pregnancy is detected.

Hypotension in volume- or salt-depleted patients

In human studies, the effects of OLM on BP parallel its effects on the RAS, and protect end organs that are affected by the pathological changes which occur during hypertension.[43] Patients with an activated RAS, however, such as those who are volume- and/or salt-depleted, including those with metabolic syndrome, symptomatic hypotension due particularly to the OLM component may occur after the initiation of combined treatment with OLM/AML. Physicians must take particular care when initiating treatment with OLM/AML in patients who are at high risk for postural hypotension, including elderly patients with hypovolemia or sodium depletion.

Vasodilatative effect

The vasodilatation attributable to AML in combination therapy is gradual in onset, and acute hypotension after oral administration has rarely been reported. As with any other peripheral vasodilator agent, physicians should closely monitor patients administered combinations of these medications, particularly those with severe aortic stenosis.

Impaired cardiac function

Patients, particularly those with severe coronary artery disease, may develop increased frequency, duration, or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or when dosages are increased. In general, calcium channel blockers should be used with caution in patients with heart failure.

Impaired renal function

Studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis have reported increases in serum creatinine or blood urea nitrogen (BUN).[44] Long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis has not been reported, but similar effects would be expected with OLM/AML because of the olmesartan medoxomil component.

Impaired hepatic function

Since AML is extensively metabolized by the liver and has a plasma elimination half-life (t1/2) in patients with severely impaired hepatic function of about 60 hours,[24,25] its use in patients with severe hepatic impairment is contraindicated.

Concomitant prescribing

OLM/AML should not be used concomitantly with potassium, including either supplements or agents affecting potassium levels, due to the potential for clinically important pharmacokinetic drug interactions with OLM/AML.

ARB and cancer

Recent meta-analysis published in Lancet Oncology suggesting an increased risk for cancer in patients treated with ARBs.[45] Patients randomly assigned to receive ARBs had a significantly increased risk of new cancer occurrence compared with patients in control groups (7.2% vs. 6.0%, risk ratio [RR] 1.08, 95% CI 1.01–1.15; $P = 0.016$). Although no statistically significant difference in cancer deaths was observed in patients randomly assigned to receive ARBs than in those assigned to receive control (1.8% vs. 1.6%, RR 1.07, 0.97–1.18; $P = 0.183$), these findings warrant further investigation.

Place in Therapy

The AZTEC study[24] analyzed the effect of OLM/AML on 24-hour ambulatory BP measurement (ABPM), which provides a 24-hour measurement of patient BP and is generally considered a better indicator of target organ injury than casual blood pressure measurement. ABPM provides physicians with information on BP control over a 24-hour period in patients with hypertension. According to the Seventh Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7), ABPM patients whose 24-hour BP is greater than 135/85 mmHg are nearly twice as likely to have a cardiovascular event as those with a BP less than 135/85 mmHg. Although no studies of OLM/AML

have demonstrated a decrease in cardiovascular events, BP control throughout a 24-hour period will achieve this goal. The results of this study demonstrate the ability of a stepwise OLM and AML-based titration regimen to maintain BP reductions over 24 hours. This study also showed that an LM and AML-based titration regimen can be an effective tool for treating hypertension in more challenging patient populations, such as those with type 2 diabetes and blacks. During the study, OLM/AML demonstrated significant reductions in SBP, also known as casual blood pressure. Unlike ABPM, however, SBP is recorded only once during the course of a day. OLM/AML 40/10 mg provided a mean reduction in SBP of –24.6 mmHg and in DBP of –12.3 mmHg.

Conclusions

In double–blind trials, OLM/AML combination therapy was more effective than OLM or AML monotherapy in reducing BP and achieved BP goals in patients with moderate to severe hypertension. In addition, the combination of OLM and AML was generally well tolerated in almost clinical trials. Given these results, for patients who do not experience adequate control by monotherapy with OLM or AML, a combination of these drugs are an effective option.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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