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REVIEW

Olmesartan-Amlodipine-Hydrochlorothiazide in Fixed Combination for the Treatment of Hypertension

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Abstract: The guidelines and consensus documents on hypertension management have emphasized the need for a better arterial hypertension (AH) control, and, thus, have recommended an optimized treatment, which usually requires the combined use of drugs that block different mechanisms responsible for blood pressure (BP) increase. For stage 2 and 3 hypertensives, the association of two drugs is mandatory, and if the BP goal is not attained, the association of a third drug is the preferential option. For high CV risk patients, the current tendency is to block the renin-angiotensin-aldosterone system (RAAS) with an angiotensin-converting-enzyme inhibitor (ACEI) or with an angiotensin II type 1 receptor blocker (ARB) or even with a direct renin inhibitor (DRI), associated with a calcium channel blocker (CCB). When the BP goal is not reached with this type of association, a diuretic compound is the drug to be added. The triple combination of Olmesartan (OM), amlodipine (AML), and hydrochlorothiazide (HCTZ) seems to be one of the most adequate choice, due to the complementary mechanisms of action of their agents. This study aimed at reviewing both the rationale for the combined use of drugs for controlling AH and the results of the clinical trials on the triple association of OM, AML, and HCTZ.

Keywords: hypertension treatment, fixed-dose combination drugs, olmesartan, amlodipine, hydrochlorothiazide
Introduction

Guidelines on hypertension management have emphasized the need for a better arterial hypertension (AH) control, and, thus, have recommended an optimized treatment, which usually requires the combined use of drugs that block different mechanisms responsible for blood pressure (BP) increase. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has drawn attention to the fact that over two thirds of the hypertensives do not achieve BP goals when treated with only one drug, requiring, thus, the use of two or more synergic drugs.

Despite the concentrated effort to improve AH control in the United States, with the National Health and Nutrition Survey (NHANES) 1999–2000 indicating that 34% of the hypertensives reach desirable goals, AH control worldwide is far from what is desired.

For stage I hypertension, the VI Brazilian Guidelines for Arterial Hypertension has recommended to start drug treatment with monotherapy, and then, if BP goal is not reached, titrate the dose or add a second drug. However, if the patient is at high or very high cardiovascular (CV) risk, or when the recommended goal requires a reduction of at least 20 mmHg in systolic blood pressure (SBP) and of 10 mmHg in diastolic blood pressure (DBP), drug association is already recommended, even for stage I hypertensives. Prior to the ACCOMPLISH Study, the preferential association of any drug would be that with a diuretic compound. For high CV risk patients, the current tendency is to block the renin-angiotensin-aldosterone system (RAAS) with an angiotensin-converting-enzyme inhibitor (ACEI) or with an angiotensin II type 1 receptor blocker (ARB) or even with a direct renin inhibitor (DRI), associated with a calcium channel blocker (CCB). When the BP goal is not reached with this type of association, a diuretic compound is the drug to be added. For stage 2 and 3 hypertensives, the association of two drugs is mandatory. And if the BP goal is not attained, the association of a third drugs is the preferential option.

Olmesartan medoxomil (OM) is one of the most recent and commercially available drugs of the ARB class. Amlodipine besylate (AML) is a CCB of the dihydropyridine class, which acts on smooth muscle, blocking calcium entry, and causing that musculature to relax.

Thiazide compounds, traditional drugs that have been safely used for several years, are the preferential therapy in the elderly and individuals with isolated systolic hypertension. Its use in monotherapy has been recommended in some guidelines as the preferential treatment, an indication supported by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The triple combination of OM, AML, and hydrochlorothiazide (HCTZ) seems to be a very useful choice, due to the complementary mechanisms of action of their agents.

This study aimed at reviewing both the rationale for the combined use of drugs for controlling AH and the results of the clinical trials on the triple association of OM, AML, and HCTZ.

Mechanism of Action, Metabolism, and Pharmacokinetic Profile

Amlodipine belongs to the dihydropyridine class of CCBs. Its major mechanism of action involves a reduction in the arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through L-type calcium channels. Another possible mechanism of action is that AML inhibits carbonic anhydrase of the vascular smooth muscle. Amlodipine is a long-lasting CCB that has a good peak-trough ratio, and can be used in a single daily dose. It causes a slower and sustained vasodilation and no sympathetic activation, which account for the lower occurrence of adverse effects with that drug. It is metabolized in the liver, and around 90% are converted into inactive metabolites by the cytochrome P4503A4 isoenzyme. Although AML is well tolerated, a significant number of patients can have lower limb edema, requiring discontinuation of the drug. The AML-related edema results from vasodilation, with increased capillary pressure and venous transudation. The minimum and maximum doses of AML are 2.5 and 10 mg, respectively, and the usual posology consists of one daily administration. Amlodipine interacts mainly with the two following drugs: cyclosporine, whose serum level increases with the concomitant use of the CCB; and H2 blockers, which increase the serum levels of AML.
are as follows: plasma half-life of 30 to 50 hours; liver metabolism; renal excretion; no interaction with food; and increased plasma concentration with aging.18,19

Olmesartan is a prodrug that after being orally administered is rapidly esterified into its active form, in a reaction that does not depend on cytochrome P450. That active metabolite is a potent ARB with no agonist activity.9 The occurrence of adverse effects with OM is comparable with that with placebo, the major adverse effect being hyperpotassemia, mainly present in patients with renal failure. In patients whose renal function is highly dependent on the RAAS, OM should be carefully administered, because it can cause oliguria and acute renal failure. Olmesartan is potentially teratogenic, and should not be used during pregnancy. The major pharmacokinetic characteristics of OM are as follows: plasma half-life of 12 to 18 hours, which allows its administration in a single daily dose; preferential liver metabolism; renal excretion from 35% to 50%; the minimum and maximum doses of OM are 20 and 40 mg, with once-daily dosing.9

Hydrochlorothiazide inhibits the Na+/Cl− reabsorption in the distal convoluted tubules. In addition, it causes potassium loss and increases serum uric acid levels. Its antihypertensive effect does not necessarily result from its diuretic activity. Although the mechanism of action of thiazide diuretics has not been completely elucidated, those diuretics cause vasodilation by activating the calcium-activated potassium channels and by inhibiting the carbonic anhydrase in the vascular tissue. Hydrochlorothiazide inhibits water reabsorption in the nephron by inhibiting the Na+/Cl− transporter enzyme (SLC12A3) in the distal convoluted tubule, which accounts for 5% of the total sodium reabsorption. Hydrochlorothiazide is not metabolized, and is rapidly eliminated by the kidneys.20 Its minimum and maximum daily doses are 6.25 and 25 mg, in a single daily administration. Its plasma half-life is 12 to 18 hours. The thiazide diuretics have no therapeutic effect with creatinine clearance below 30 mL/min. The major adverse effect of HCTZ is hypokalemia, occasionally associated with hypomagnesemia, which can induce arrhythmias and hyperuricemia. Another adverse effect worthy of note is its potential to impair the glucose metabolism, increasing the risk for diabetes and alterations in the lipid profile, mainly hypertriglyceridemia. In some patients, sexual dysfunction may occur, being usually dose-dependent.20

Clinical Studies
Clinical studies have evidenced that the antihypertensive treatment has evolved regarding tolerability and the antihypertensive effect of the drugs. We are facing a very favorable scenario, although the challenge of controlling stage 2 and 3 hypertensives at high and very high CV risk, for whom more ambitious goals have been proposed, still requires more effort in the search for the most adequate association of two or more drugs.

Guidelines have recommended therapeutic strategy optimization by either increasing the dosages of the drugs used or adding more drugs until BP goals are attained. For that purpose, the combination of drugs has proved to be the best therapeutic option for most hypertensives.

The establishment of stricter BP goals should also contemplate the search for safer drug combinations. Combining drugs is not only adding different drugs, but finding synergic drugs capable of both blocking more than one mechanism responsible for BP increase, and inactivating mechanisms triggered by the drugs themselves. Doubling the usual dose of a drug does not often correspond to the expected BP reduction, but might double the incidence of adverse effects. The association of two drugs, followed by the association of a third one may provide therapeutic advantages, especially for fixed combinations, which have proved to improve patient’s adherence to treatment.21 Thus, the availability of so many drug associations in clinical practice is justified.

Most clinical studies designed to assess the therapeutic efficacy of a drug apply the concept of mean BP reduction from initial BP levels, and do not focus on the final BP levels attained. That way of analyzing the results of a clinical study allow patients to be considered responders, even when they do not meet the BP goals proposed by the major medical societies worldwide. From the clinical practice perspective, the efficacy of a drug should ideally mean the capacity to reduce BP levels to the recommended goal. The option for the fixed combination of three drugs has shown a higher capacity to make a greater number of patients attain their BP goals.1,4,22
European Society of Hypertension Guidelines have recommended the combination of a RAAS blocker, a CCB, and a diuretic when three drugs are required for BP control.23

Recently, evidence from the literature has suggested that the triple combination of OM, AML and HCTZ is an effective and safe treatment option, because it involves drugs whose mechanisms of action are complementary and synergic.24–34

Safety
In general, studies have shown that the triple combination of OM, AML, and HCTZ is safe and well tolerated. The incidence of adverse effects attributed to that triple combination is low, the most common being headache, hypotension, dizziness, and edema. The incidence of adverse effects does not significantly differ between the dual- and triple-combination therapies.

Analyzing the adverse effects of interest regarding each therapeutic class, the overall incidence of hypotension-related adverse effects is low.

The Triple Therapy With Olmesartan Medoxomil, Amlodipine Besylate, and Hydrochlorothiazide in Adult Patients With Hypertension: The TRINITY Multicenter, Randomized, Double-Blind, 12-Week, Parallel-Group Study,28 the major study on the triple combination of OM, AML, and HCTZ, has reported a low incidence of adverse effects. Peripheral edema occurred in 1% of the OM group as compared with 7% and 8% in the groups using the triple combination containing AML. Headache occurred in 6% to 7% in the three groups treated. Hypokalemia was observed in 4.5% of the AML + HCTZ group as compared with 0.3% and 0.7% in the other treatment groups. Hypotension was reported in 1.4% of the triple-combination group as compared with 0% and 0.5% of the dual-combination groups.

When comparing the triple- and dual-combination groups, no statistically significant difference was observed in the set of adverse effects. The occurrence of serum adverse effect was 1.5% in the population studied, and 1% of the patients discontinued the study drug during follow-up. In the triple-combination group, the major reasons for discontinuing the treatment were as follows: dizziness (1%); peripheral edema (0.9%); hypotension (0.7%); and headache (0.5%).

Efficacy
The efficacy of the combination of OM, AML, and HCTZ has been assessed in clinical trials, which have demonstrated the incremental benefit of BP reduction with the triple-combination treatment as compared with monotherapy and dual-combination treatment.25,26,28,33

One study assessing 197 patients using OM as the initial treatment agent, with the possibility of adding HCTZ, and, later, AML, has reported that 93.3% of stage 1 and 2 hypertensives achieved the goal of BP ≤ 140/90 mmHg, and that 87.7% of those reached the stricter goal of BP ≤ 130/85 mmHg.35 In another study,30 those same authors have reported that BP reduction increased as the drugs were added to the treatment. In stage 2 hypertensives, the use of the triple-combination instead of the dual-combination (OM and HCTZ) treatment caused a 15% increase in the number of patients achieving BP ≤ 140/90 mmHg, and a 27% increase in the number of patients achieving BP ≤ 130/85 mmHg. That suggests that most stage 2 patients need combined therapy to achieve BP goals (Table 1).30

The Benibest study (Efficacy and Safety of Olmesartan Medoxomil in Stage 1 and 2 Essential Hypertension Study)24 assessed 144 individuals for the use of OM in a treatment algorithm in four steps as follows: (i) monotherapy (20 mg); (ii–iii) association

<table>
<thead>
<tr>
<th>Goal</th>
<th>Monotherapy (OM)</th>
<th>Dual combination (OM + HCTZ)</th>
<th>Triple combination (OM + HCTZ + AML)</th>
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<tbody>
<tr>
<td><strong>Stage 1 AH</strong></td>
<td></td>
<td></td>
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<tr>
<td>≤140/90 mmHg</td>
<td>79.7%</td>
<td>93.7%</td>
<td>97.5%</td>
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<tr>
<td>≤130/85 mmHg</td>
<td>55.7%</td>
<td>88.6%</td>
<td>96.2%</td>
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<tr>
<td><strong>Stage 2 AH</strong></td>
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<td></td>
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<tr>
<td>≤140/90 mmHg</td>
<td>42.0%</td>
<td>75.0%</td>
<td>90.0%</td>
</tr>
<tr>
<td>≤130/85 mmHg</td>
<td>19.0%</td>
<td>54.0%</td>
<td>81.0%</td>
</tr>
</tbody>
</table>

**Abbreviations:** AH, arterial hypertension; OM, olmesartan; HCTZ, hydrochlorothiazide; AML, amlodipine.
of HCTZ (20/12.5 mg and 40/25 mg); and (iv) association of AML (40/25 mg + 5 mg). The stepwise treatment caused 86% of the patients to attain the BP goal of below 130/85 mmHg, in addition to a mean reduction of 44.4 mmHg in SBP and of 20 mmHg in DBP. The association of OM, HCTZ, and AML determined an additional 13% increase in BP goal attainment as compared with the therapy with OM and HCTZ 40/25.24

Volpe et al,25 assessing 692 stage 2 and 3 patients in a 28-week open-label study, have reported a 66.9% BP goal attainment. Of the patients resistant to OM + AML 40/10 mg, 47.1% achieved BP goals when receiving OM + AML + HCTZ 40/10/12.5 mg; of those resistant to OM + AML + HCTZ 40/10/12.5 mg, 33.3% achieved BP goals when receiving OM + AML + HCTZ 40/10/25 mg. The additional mean reduction obtained with the triple combination was 6.3 mmHg for SBP and 3.7 mmHg for DBP.25

The COACH extension study (Efficacy and Safety of Long-Term Treatment with the Combination of Amlodipine Besylate and Olmesartan Medoxomil in Patients with Hypertension),26 a 44-week open-label extension study assessing 1684 patients, has compared the following four therapeutic regimens: AML 5 mg; OM + AML 40/5 mg; OM + AML + HCTZ 40/10/12.5 mg; and OM + AML + HCTZ 40/10/25 mg. In that study, the greatest reductions (36.1 mmHg) in SBP were observed in the group on OM + AML + HCTZ 40/10/25 mg. Those patients also had the highest baseline BP levels (172.9/103.2 mmHg), and 46.3% of them reached BP goals. In addition, the combined therapy led to faster BP goal attainment, and some patients, who did not reach BP goal, did not undergo up titration in a stepwise fashion, showing clinical inertia, which can contribute with as much as 20% of failure in controlling BP in clinical practice.26

In a prespecified subanalysis of the population studied,26 at the end of treatment, 26.9% of the diabetic patients achieved their BP goals (BP < 130/80 mmHg) with the triple-combination treatment.

Another open-label study, the APEX study33 (Efficacy and Onset of Antihypertensive Effects of an Amlodipine and Olmesartan Medoxomil-Based Titration Regimen in Patients with Hypertension and Type 2 Diabetes), has recruited 207 patients (80.7% with metabolic syndrome) for an 18-week active treatment followed by two weeks of additional follow-up. The APEX study has compared six different therapeutic regimens as follows: AML 5 mg; OM + AML 20/5 mg; OM + AML 40/5 mg; OM + AML 40/10 mg; OM + AML + HCTZ 40/10/12.5 mg; and OM + AML + HCTZ 40/10/25 mg. The results showed that treatment intensification was associated with a progressive reduction in BP. The BP goal of under 130/80 mmHg was achieved by 55.2% and 61.7% of patients treated with the two triple combinations, respectively, as compared with 21.0% to 42.8% of patients receiving the dual-combination therapy. In a prespecified analysis of the population with the metabolic syndrome, 39.8% of the patients achieved the BP goal of less than 120/80 mmHg, 59.6% achieved the BP goal of less than 130/80 mmHg, and 82.0% of the patients achieved the BP goal of less than 140/90 mmHg by the end of the study.

The BP CRUSH Study: Evaluation of the Efficacy and Safety of Amlodipine/Olmesartan Medoxomil in Patients who are Non-Responders to Antihypertensive Monotherapy34 has assessed a special group of uncontrolled patients, recruiting 999 individuals non-responsive to monotherapy over 20-weeks. At the end of the study, the triple combination (OM + AML + HCTZ 40/10/25 mg) resulted in 90.3% of the patients reaching the BP goal of less than 140/90 mmHg.

In the TRINITY Study,28 2492 patients with moderate-to-severe hypertension were randomized to one of the three different dual-combination strategies for four weeks: OM + AML 40/10 mg; OM + HCTZ 40/25 mg; AML + HCTZ 10/25 mg. After that, approximately 200 patients of each dual-combination treatment group received the triple combination of OM + AML + HCTZ 40/10/25 mg for eight more weeks, totalizing 12 weeks of follow-up. The group receiving the triple combination OM + HCTZ + AML 40/25/10 mg achieved the greatest reductions as compared to those of the dual-combination treatments. The mean reductions obtained with the triple combination were 37 mmHg in SBP and 22 mmHg in DBP. The mean reductions in the stage 2 hypertensive population using the triple combination were 36 and 21 mmHg for SBP and DBP, respectively, while in the stage 3 hypertensive population, the mean reductions were 47 mmHg and
24 mmHg, respectively.\textsuperscript{26} It is worth emphasizing that 64.3\% of the patients receiving the triple combination had already achieved BP goal (BP < 140/90 mmHg) at week 6 of treatment. In addition, 69.9\% of the patients treated with the triple combination had achieved the BP goal of below 140/90 mmHg at week 12. For lower BP goals, the triple combination has always provided greater percentages of control than the dual combination therapies (Figs. 1).

In a TRINITY Sub-Study,\textsuperscript{29} a prespecified subgroup analysis from TRINITY\textsuperscript{28} assessed the efficacy and safety of triple-combination treatment in patients with hypertension and diabetes. More participants with diabetes receiving triple-combination treatment reached BP goal (<130/80 mmHg) versus those receiving dual-combination treatments ($P \leq 0.0092$), and triple-combination treatment was well tolerated in both diabetes and non-diabetes subgroups.

**Patient Preference**

The major objective of treating AH is reducing BP levels to desired goals, thus, decreasing CV morbidity and mortality. That requires individualization of the therapeutic strategy according to risk stratification and BP goal.\textsuperscript{1,4,22}

The major medical societies have recommended that SBP be reduced to below 140 mmHg and DBP to below 90 mmHg in all hypertensive patients.\textsuperscript{1,4,22} Similarly, those societies have emphasized the benefits of a more intense BP reduction for SBP levels around 130 mmHg and DBP levels around 80 mmHg in high and very high CV risk patients.

Another important concept about that topic derived from the results of the VALUE trial,\textsuperscript{23} which has recommended that high-risk hypertensive patients reach BP goals in a maximum of six months.

The combined therapy with two or more classes of drugs has proved to be more effective than high doses of monotherapy.\textsuperscript{21} In addition, beginning treatment with a combination of drugs has shown a greater reduction in the risk of CV events than beginning with monotherapy.\textsuperscript{36}

Two important studies have been essential to settle those concepts: the HOT\textsuperscript{37} and UKPDS\textsuperscript{38} trials. In the UKPDS trial,\textsuperscript{38} 35\% of the patients required two drugs and 29\% required three drugs to control BP. In the HOT trial,\textsuperscript{37} 70\% of the patients required two or more drugs to achieve BP goals.

The following situations in clinical practice are associated with a higher difficulty in reaching the recommended BP goals: severe AH; secondary causes of AH; advanced age; black ethnicity; diabetes; obesity; excessive consumption of salt or alcohol;
use of other drugs that increase BP; left ventricular hypertrophy; renal disease; and obstructive sleep apnea. Such conditions will more often require the triple combination of drugs as a strategy to achieve BP goals.

**Place in Therapy**
The rationale for the association of drugs is based on the increment of the antihypertensive effect when distinct pathophysiological mechanisms are involved. In addition, the combination of drugs can inhibit the activation of counterregulatory mechanisms, increasing the efficacy of the drugs. Furthermore, the combination of drugs reduces the occurrence of adverse effects due to either the use of a lower dose of each drug involved in the combination or the capacity of one drug to counteract the adverse effects of the other drug, such as with the reduction in ankle edema that occurs with the use of a combination of dihydropyridine CCBs and RAAS blockers.1,4,22

To be cost-effective, the combined therapy of antihypertensive drugs should meet some requirements listed in Table 2.1,4,22

It is worth emphasizing that a combination of drugs since the beginning of treatment can be used with BP-lowering drugs in free or fixed-dose combinations.1,4,22

The fixed-dose combination of drugs has advantages and disadvantages as compared with the free combination of drugs.1,4,22 The antihypertensive drug combination strategy improves BP control as compared with monotherapy. In addition, an increase in tolerance is observed with the use of combinations, because of the lower incidence of adverse effects with the use of lower doses of each drug. The most important and significant advantage of using fixed-dose combinations of drugs is the reduction in the number of pills taken, and, in some cases, the reduction in the cost of treatment. All that simplifies the treatment and increases convenience to the patient, reduces the need for subsequent therapeutic adjustment, contributing to improve therapeutic adherence and success and to increase the percentage of BP goal attainment.1,4,22 A recent meta-analysis has confirmed that the fixed combination of drugs provides greater treatment adherence and persistence as compared with free combinations of the same drugs.39

Regarding disadvantages of fixed-dose combinations, it is worth noting the difficulty in titrating the dose of each drug in the presence of adverse effects, or when an increase in the dose of only one of the components is required. In such situation, one of the drugs may reach a dosage above that required, leading to the appearance of adverse effects. In both cases, the patient’s adherence to treatment may be jeopardized.1,4,22

**Conclusions**
Despite the significant advances obtained in the pharmacotherapy for AH, BP control rates remain unsatisfactory worldwide. Thus, the use of combined therapy has become an important strategy for managing AH. The combination of antihypertensive drugs of several classes has proved to be more effective in reducing BP than the option of doubling the dose of any agent in monotherapy. In addition, by using the combination of those drugs, a higher number of patients has reached the BP goals recommended by the major guidelines.

This literature review suggests that the fixed triple combination involving OM, AML, and HCTZ leads to additional reductions in BP as compared with different dual-combination strategies. It also suggests that the use of that triple combination allows a greater number of patients to achieve BP goals in a short period of time as compared with dual-combination regimens, with an excellent tolerability.

Thus, the fixed triple combination of OM, AML, and HCTZ is a rational and efficient option for BP management in patients whose BP goals have not been attained with dual combinations of drugs, in patients using multiple therapies, and in those at higher CV risk.

**Table 2. Ideal characteristics of drug combination.**

- Association of different mechanisms of action
- Synergism of action
- Counteraction of adverse effects
- Pharmacokinetic compatibility
- Proportional pharmacological properties
- Greater antihypertensive efficacy than that of monotherapies
- Clinical benefits confirmed by clinical trials
References


