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REVIEW ARTICLE

ARB-Based Combination Therapy for the Clinical Management of Hypertension and Hypertension-Related Comorbidities: A Spotlight on Their Use in COVID-19 Patients

Vivianne Presta[1] · Ilaria Figliuzzi[1] · Barbara Citoni[1] · Giovanna Gallo[1] · Allegra Battistoni[1] · Giuliano Tocci[1] · Massimo Volpe[1]

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Abstract
Essential hypertension is the most common cardiovascular (CV) risk factor, being primarily involved in the pathogenesis of CV disease and mortality worldwide. Given the high prevalence and growing incidence of this clinical condition in the general population in both high and low-income countries, antihypertensive drug therapies are frequently prescribed in different hypertension-related CV diseases and comorbidities. Among these conditions, evidence are available demonstrating the clinical benefits of lowering blood pressure (BP) levels, particularly in those hypertensive patients at high or very high CV risk profile. Preliminary studies, performed during the Sars-COVID-19 epidemic, raised some concerns on the potential implication of hypertension and antihypertensive medications in the susceptibility of having severe pneumonia, particularly with regard to the use of drugs inhibiting the renin–angiotensin system (RAS), including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). These hypotheses were not confirmed by subsequent studies, which independently and systematically demonstrated no clinical harm of these drugs also in patients with Sars-COVID-19 infection. The aim of this narrative review is to critically discuss the available evidence supporting the use of antihypertensive therapies based RAS blocking agents in hypertensive patients with different CV risk profile and with additional clinical conditions or comorbidities, including Sars-COVID-19 infection, with a particular focus on single-pill combination therapies based on olmesartan medoxomil.

Keywords Hypertension · Blood pressure control · Combination therapy · Angiotensin receptor blockers · Olmesartan medoxomil · COVID-19

1 Introduction

Essential hypertension still remains the major driven of cardiovascular (CV) events and complications in the world, and one of the leading contributory cause to premature death and CV diseases, including ischaemic heart disease and stroke, at global level [1]. Furthermore, persistently high BP levels may lead to development and progression of chronic pathological conditions, such as end-stage renal disease, atrial fibrillation, dementia, peripheral artery disease and congestive heart failure, thus causing impairment of quality of life and bearing on health care costs [2].

Over the last few decades, substantial progress has been made in the pharmacological treatment of hypertension. Consistently, several scientific evidence demonstrated that lowering blood pressure (BP) levels can reduce both CV morbidity and mortality [3, 4]. However, despite the large number of highly effective drug treatment strategies and the improved patients' awareness on the clinical consequences of uncontrolled hypertension, the attained BP control rates under antihypertensive therapy remain poor in most western countries [5–8].

One of the main causes of unsatisfactory BP control, which was estimated to be of only 35% [8], has been ascribed to the persistently high rate prescription of monotherapy. Indeed, previous guidelines on hypertension had

✉ Massimo Volpe
massimo.volpe@uniroma1.it

[1] Chair and Division of Cardiology, Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, University of Rome "Sapienza", Sant'Andrea Hospital, Via di Grottarossa 1035-9, 00189 Rome, Italy

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suggested as a first step the prescription of monotherapies, and then up-titrating the prescribed drug for achieving the recommended BP targets [9]. However, such strategy, even when given at the full dose, has proven to be unsuccessful in most cases, and more than one drug is often needed in the majority of hypertensive patients to achieve an effective and sustained BP control [10–12]. Furthermore, increasing the dose of single agent may increase the risk of adverse effects, cause time-consuming dose adjustments and promote poor adherence and self-treatment withdrawal, with deleterious consequences on CV protection in treated uncontrolled hypertensive outpatients [13].

The evidence of low BP control rates attained under monotherapies led the most recent guidelines to suggest a new stepped-care approach, by initiating treatment with different classes of antihypertensive drugs in (fixed) combination therapies or formulations. Both European [14] and North American [15] hypertension guidelines promote, alongside to lifestyle changes, the use of combination therapies, especially in form of single-pill combination, with the aim at ameliorating patients' adherence, therapeutic efficacy and consequently BP control. Such approach, based on the use of combination therapy even from the first therapeutic steps, resulted in about 80% of patients achieving BP target levels at the end of different randomized controlled clinical trials [16–18], and, more recently, in the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [19], which firstly adopted fixed combination therapy in a single pill formulation from the beginning of the trial.

The urgent need to improve BP control is also linked to the new recommended BP treatment targets to be achieved under antihypertensive therapy (less than 130/80 mmHg in the overall population and less than 140/90 mmHg in older hypertensive people) [14]. Although different combinations of antihypertensive drug are recommended, specific advantages can be brought by the availability of some combination therapies to be adopted on an individualized basis, according to the presence of hypertension-mediated organ damage (HMOD), concomitant risk factors, and associated clinical conditions [20, 21].

On the basis of these considerations, the aim of this narrative review is to critically discuss the available evidence in favor of the combination therapies based on ARBs, with a particular focus on those combination based on olmesartan medoxomil (OLM), which provide a wide choice of therapeutic options to cover the specific features of hypertensive patients at different CV risk profile and with additional clinical conditions and comorbidities [22, 23]. A special section of this article briefly discusses the safety of ARB-based therapies in SARS-COV-2 infection, since initial studies during the COVID-19 pandemic had generated conflicting data and opened an active scientific and clinical debate [24, 25].

1.1 Olmesartan-Based Monotherapies

ARBs have been available for the clinical management of hypertension and hypertension-related CV diseases since 1995. Within this antihypertensive drug class, OLM is one of the agents characterized by long-lasting efficacy and a documented profile of tolerability and safety [26, 27]. Indeed, the higher efficacy of OLM compared to other ARBs, proved also by the persistent BP reductions over the 24-h BP period, confers to OLM additional therapeutic benefits [28]. This has particular relevance, since high 24-h BP values, mostly during the night-time period, strongly and significantly correlate with the risk of major CV outcomes, particularly stroke, myocardial infarction and CV death [29, 30]. The mechanism through which OLM provides long-lasting BP-control is related to its pharmacologic dynamic properties, namely the high affinity prolonged binding to the AT1 subtype receptors, with a consequent long-lasting inhibition competitive towards angiotensin II [31, 32]. This property has important clinical implications, representing an option for the first-line antihypertensive therapy based on this drug [31, 32].

Several trials demonstrated the clinical effectiveness for the OLM-based monotherapies at different dosages in hypertensive outpatients with different CV risk factors. As an example, a multicenter, randomized, double-blind trial [33] compared the efficacy of once-daily treatment with the OLM at the dosage of 20 mg daily with either losartan (50 mg), valsartan (80 mg), or irbesartan (150 mg) in 588 patients with diastolic BP between 100 and 115 mmHg and a mean daytime diastolic BP between 90 and 120 mmHg. The reduction of clinic diastolic BP with OLM (11.5 mmHg) was significantly greater than that obtained with losartan, valsartan, and irbesartan (8.2, 7.9, and 9.9 mmHg, respectively), whilst no significant differences were found regarding systolic BP reductions among groups. Similarly, the reduction in mean 24-h diastolic BP with OLM (8.5 mmHg) was significantly greater than the reductions achieved with either losartan or valsartan (6.2 and 5.6 mmHg, respectively), greater but not statistically significant with irbesartan (7.4 mmHg; $P = 0.087$). Furthermore, the reduction in mean 24-h systolic BP achieved with OLM (12.5 mmHg) was significantly greater than the reductions observed in other groups treated with losartan and valsartan (9.0 and 8.1 mmHg, respectively) and equivalent to the reduction obtained with irbesartan (11.3 mmHg).

Another aspect that should be considered when choosing the first-line antihypertensive drug is the fact that in most hypertensive patients prevalence of metabolic disorders, such as obesity, dyslipidemia, metabolic syndrome and type 2 diabetes, is higher than that observed

in normotensive individuals [34]. In this regard, previous studies and meta-analyses demonstrated the detrimental effects of high-dose diuretics or beta-blockers in term of increased risk of new-onset diabetes, particularly in hypertensive patients with metabolic disorders [35]. Thus, combination therapies based on drug classes with neutral or even favorable metabolic profile may have additional beneficial effects, beyond the BP reduction, which should be considered in view of a personalized antihypertensive strategy and in order to improve the long-term prognosis in treated hypertensive outpatients. Among different antihypertensive drug classes, ARBs are reported to exert a favorable effect on insulin resistance and to reduce incidence of new-onset diabetes [36, 37], as well as left ventricular hypertrophy and dysfunction [38], albuminuria and progression towards chronic kidney disease [39]. According to these premises, the available evidence support the clinical efficacy and safety of ARB-based antihypertensive therapies, including those based on OLM-based monotherapies, in hypertensive patients with metabolic abnormalities, diabetes and HMOD [40, 41].

1.2 Olmesartan-Based Dual Combination Therapies

ARBs can be effectively combined with either diuretics, namely hydrochlorothiazide (HCTZ), or dihydropyridinic calcium-channel blockers (CCBs), in order to enhance their ability in lowering BP, as recommended by current European guidelines [14]. Also in this case, several randomized, controlled, clinical trials demonstrated the clinical efficacy and safety of OLM-based combination therapies with excellent tolerability profile and high adherence to prescribed antihypertensive regimen, due to its fixed single-pill formulation.

1.3 Olmesartan/Hydrochlorothiazide Combination Therapy

In a randomized, double-blind, controlled clinical trial [42], 502 hypertensive patients with a baseline mean diastolic BP between 100 and 115 mmHg were randomized to one of following 12 groups: placebo, OLM monotherapy (10, 20, or 40 mg/day), HCTZ monotherapy (12.5 or 25 mg/day), or one of six groups of OLM/HCTZ combination therapies at different dosages. After week 8 of treatment, all OLM/HCTZ combination therapies produced greater reductions in both systolic and diastolic BP than did monotherapy with single component [42].

The Effect of an OLM-based treatment algorithm on systolic blood pressure in patients with stage 1 or 2 hypertension (BENIFORCE) was a randomized, double-blind, placebo-controlled, titration dose trial in 276 patients with arterial hypertension stage 1 or 2 [43]. After a run-in period with placebo, patients were randomized to placebo or OLM for 12 weeks. If BP was ≥ 120/80 mmHg, patients were up-titrated in a stepwise fashion from monotherapy with OLM 20 mg (weeks 1–3), to OLM 40 mg (weeks 4–6), OLM/HCTZ 40/12.5 mg (weeks 7–9) and then to OLM/HCTZ 40/25 (weeks 10–12) [43]. At week 12, the OLM-based treatment regimen provided a significantly greater reduction of mean sitting BP values compared with placebo [43].

The Benicar Efficacy: New Investigation Shows OLM Treatment Increasingly Leads Various Elderly Populations to Safe BP Reductions (BENISILVER) trial confirmed the efficacy of OLM also in elderly patients (aged 65 years and older) with either newly diagnosed hypertension or uncontrolled hypertension while taking antihypertensive medication [44]. At the end of the active treatment period, BP reductions were statistically significant in all predefined subgroups; in particular, the BP reductions during day-time, night-time, and last 6, 4, and 2 h of the dosing interval at 12 weeks were all statistically significant ($P < 0.0001$) [44]. Progressively greater and significant reductions were also achieved with titration steps ($P < 0.0001$ vs baseline) [44].

As observed for the monotherapies, also OLM-based combination therapies provided evidence in favor of the persistently BP reductions over the 24 period. In a double-blind, placebo-controlled, phase III study designed to test the effects of adding HCTZ (12.5 or 25 mg) to OLM (20 mg) on 24-h BP values measured in hypertensive patients with clinic diastolic BP between 100 and 115 mmHg and clinic systolic BP more than 150 mmHg, mean 24-h diastolic BP more than 84 mmHg and at least 30% of diastolic BP daytime readings more than 90 mmHg, after four weeks of treatment with OLM 20 mg once daily, non-responders patients by 8 weeks of treatment with placebo or HCTZ (12.5 or 25 mg) once-daily, added to OLM treatment [45]. In the group treated with combination therapies, mean daytime diastolic BP decreased significantly compared to placebo plus OLM 20 mg group ($P = 0.0012$). Both mean 24-h diastolic and systolic BP were significantly lowered with OLM/HCTZ 20/12.5 mg and 20/25 mg than with OLM monotherapy.

Finally, evidence of the persistent antihypertensive efficacy of OLM derived from the BENIcar safety and efFICacy evaluatIon: an open-label, single-ARm, titration study in patients with hypertension and tYpe 2 diabetes (BENIFICIARY) trial, that assessed the safety and efficacy of OLM alone or in combination with HCTZ through ABPM [46]. By the end of the study, a reduction of 20.4 mmHg and 11.1 mmHg in mean 24-h ambulatory systolic and diastolic BP, respectively, was observed ($P < 0.0001$ vs baseline for both values). The OLM-based treatment regimen demonstrated sustained once-a-day efficacy and BP control, as shown by significant BP reductions during the last hours of the 24-h dosing [46].

1.4 Olmesartan/amlodipine combination therapy

Among the available ARB/CCB combinations, the fixed-dose OLM/amlodipine combination has the advantage to combine ideal pharmacodynamic properties of the two compounds, which are long-lasting and suitable for a once-a-day administration, thus providing a relevant antihypertensive efficacy and satisfactory safety profile.

The AZOR Trial Evaluating Blood Pressure Reductions and Control (AZTEC), a 16-week prospective, open-label, multicenter trial, tested the efficacy and safety of an OLM/amlodipine-based titration regimen in hypertensive patients after 12 weeks of active treatment [47]. OLM/amlodipine-based titration regimen significantly reduced 24-h BP, particularly during the last hours of the dosing interval, without affecting the normal diurnal oscillation of the BP profile [47].

The Combination of OLM and Amlodipine besylate in Controlling High Blood Pressure (COACH) trial was an 8-week factorial study with the goal of assessing the antihypertensive efficacy of the combination of OLM and AML at various doses compared with the respective monotherapy components in patients with mild to severe hypertension [48]. Eligible patients who had not been taking antihypertensive medications for at least 2 weeks before screening were immediately randomized to receive 1 of the following for 8 weeks: OLM monotherapy (10, 20, or 40 mg), amlodipine monotherapy (5 or 10 mg), combination therapy (including all possible combinations of the monotherapy doses of OLM and amlodipine), or placebo [48]. This trial demonstrated that all doses of the combination of OLM/ amlodipine were significantly more effective than single component of either monotherapies in reducing both seated systolic and diastolic BP levels ($P < 0.001$) [48]. In addition, 54.0% of patients receiving the highest dose of OLM/amlodipine achieved a BP < 140/90 mmHg by week 8 [48]. Furthermore, combination therapy was well tolerated and associated with a lower incidence of oedema compared to monotherapy with full dose amlodipine [48].

A randomized, double-blind, controlled trial designed to determine the additional antihypertensive efficacy gained by the combination of OLM 10 mg, 20 mg or 40 mg with amlodipine 5 mg in the treatment of patients affected by moderate to severe hypertension, whose BP was not adequately controlled after 8 weeks of open-label treatment with amlodipine 5 mg monotherapy confirmed high efficacy of OLM/ amlodipine [49]. After the first period during which patients were treated with AML 5 mg once daily, those who failed to respond adequately to this monotherapy were randomized to one of the four treatment groups during which they received 8 weeks of double-blind combination therapy: placebo/amlodipine 5 mg; OLM 10 mg/amlodipine 5 mg; OLM 20 mg/amlodipine 5 mg; OLM 40 mg/amlodipine 5 mg [49]. At the end of the period II (week 16), patients with BP ≥ 140/90 mmHg underwent up-titration at week 16 [49]. Patients who received 8 weeks of double-blind therapy with OLM (10, 20, 40 mg)/amlodipine 5 mg achieved additional and significant mean reductions in mean seated systolic and diastolic BP compared with patients who received amlodipine 5 mg and placebo [49].

1.5 ARB-Based Triple Combination Therapies

In those patients with difficult-to-treat hypertension or in those with treated uncontrolled hypertension under dual therapy, triple combination therapies should be adopted in order to achieve the recommended BP treatment targets [50, 51].

The clinical effectiveness and safaety of such therapeutic approach has been firstly demonstrated by the TRIple Therapy with OLM Medoxomil, Amlodipine, and Hydrochlorothiazide in HyperteNsIve PatienTs StudY (TRINITY) [52], a multicenter, randomized, double-blind trial, which compared triple combination therapy with dual combination therapies of the individual components in fixed-dose formulations, including OLM/amlodipine 40/10 mg, OLM/HCTZ 40/25 mg, and amlodipine/HCTZ 10/25 mg. After a 3-week wash-out period, patients with moderate to severe hypertension (n = 2492) were randomized to receive dual combination therapies or placebo for 2 weeks. Then, all patients, who were assigned to a dual combination treatment group, continued the assigned treatment until week 4, while all patients assigned to placebo were switched at week 2 to receive one of the dual combination treatments until week 4. All patients received either one of the potential dual combination therapies and none was treated with placebo at week 4. At this time patients continued dual combination treatment or switched to triple combination therapy until week 12. At the end of the study triple combination treatment showed to be associated with greater reductions in both systolic and diastolic BP levels as compared with dual combination therapies.

The wide range of OLM-based combination therapies with 3 different dosages associated with two dosages of HCTZ and two dosages of amlodipine, beside the multiple choices offered by the triple single pill permit to adopt flexible strategies in relation to individual BP levels and to tailor the therapeutic choice on the basis of concomitant risk factors and comorbidities. We have previously proposed an OLM-based platform to personalize the treatment in hypertensive patients with diabetes, metabolic disorders, obesity, ischaemic heart disease, congestive heart failure, and other non-cardiovascular comorbidities [22, 23].

1.6 ARB-Based Therapies During COVID-19

As previously discussed, the favorable effects of RAS blocking agents, beyond their BP lowering properties, have been confirmed for many years in almost all patients across the CV continuum. In addition, both ACE inhibitors and, mostly, ARBs are among the most widely used antihypertensive drugs in different clinical conditions rather than hypertension and are associated with significantly lower treatment discontinuation rates than all other antihypertensive therapies [53, 54]. However, in the initial period of SARS CoV-2 pandemic some reports on small samples of patients with acute pulmonary disease suggested that these drugs might increase susceptibility to SARS CoV-2 infection and the likelihood of develop a severe illness [55]. These preliminary observations recognized a potential pathophysiological mechanism in the fact that ACE2, the enzyme that physiologically counters RAAS activation, is also the functional receptor to SARS CoV-2. Based on a claimed biological plausibility, some authors hypothesized that RAAS inhibitors may increase ACE2 expression, raising concern on their safe use in patients affected by COVID-19 [56].

This hypothesis, based on experimental studies, would have had dramatic consequences, since millions of people in the world are treated with ARBs and ACEI and an abrupt withdrawal of them, especially in high-risk patients, including those who have heart failure or previous myocardial infarction, may result in severe adverse events and hospitalizations [57].

In the early 2020, statements from the Italian Society of Hypertension (SIIA) on the clinical management of Hypertension during COVID-19 epidemic [24] firstly reported no evidence that people with arterial hypertension are overrepresented among those with COVID-19 infection and no clinical evidence in humans that associates the intake of ACE inhibitors or ARBs with COVID-19 disease. Other national scientific societies proposed similar recommendations [58].

In the subsequent months, three independent, large, observational studies tested the potential interactions between the use of ACE inhibitors or ARBs and the risk of COVID19-related death. These studies, published on New Engl J Med in May 2020, independently demonstrated that there are no evidence that the use of ACE inhibitors or ARBs is independently associated with the risk of Covid-19 [25, 59]. Though one study has been retracted on June 2020, due limited access to raw data by an independent to a third-party auditor [60], several other reports documented no clinically relevant relationships between the use of antihypertensive medications and increased susceptibility to Covid-19 infection [61–64]. In addition, several other trials are currently testing the clinical outcomes of hypertensive patients with SARS-Cov-2-related pulmonary disease continuing or suspending antihypertensive medications [65].

Thus, at the present time we can conclude that there are no clinical data that can confirm the harmful effect (not even a protective one) of ACEI and ARBs in relation to the COVID-19 pandemic. According to the latest available data ACEI and ARBs therapy should be continued in hypertensive patients and should not be suspended in those affected with COVID-19, with the exception of those who have specific known clinical contraindication for their prescription [24].

2 Conclusions

Arterial hypertension is still one of the major risk factor for major CV> outcomes and disability. Despite the progress made on antihypertensive therapies over the last few decades, several data showed persistently low rates of BP control worldwide.

To limit the gap between perceived and attained BP control, recent guidelines strongly support a more extended use of combinations therapies, especially in fixed single-pill formulation to be administered once daily. This strategy has shown to significantly and persistently reduce systolic/diastolic BP levels, improve patients adherence and ensure a good tolerability profile, thus reducing drug discontinuation, improving BP control and reducing the risk of major EV events and hospitalizations.

Among various antihypertensive therapies, those based on the use of OLM, alone or in combination therapies, could increase the percentage of treated hypertensive patients who achieve the recommended BP targets and to reduce the burden of CV diseases, when applied as part of a comprehensive approach that includes lifestyle changes, regular follow-up and timely therapy intensification, when needed.

Such therapeutic regimen can be safely and effectively maintained even during the COVID-19 pandemic, when appropriate, to maintain BP values within the recommended thresholds, reduce the risk of inappropriate hospitalization due to hypertension urgencies or emergencies and preventing the occurrence of coronary events, stroke or congestive heart failure.

Declaration

Conflict of interest Authors have no conflict of interest to disclose for the contents of the manuscript.

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