Antihypertensive Efficacy of Olmesartan Medoxomil and Ramipril in Elderly Patients with Mild to Moderate Hypertension Grouped According to Renal Function Status

A Retrospective Analysis

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Abstract

Aim: The objective of this study was to compare the antihypertensive efficacy and safety of the angiotensin II antagonist olmesartan medoxomil and the ACE inhibitor ramipril in elderly patients with mild to moderate essential hypertension, grouped according to renal function.

Methods: We performed a post hoc analysis of pooled data from two randomized, double-blind, parallel-group, multicentre studies. After a 2-week placebo wash-out period, 1453 mild to moderate hypertensive subjects were randomized to a 12-week treatment with olmesartan medoxomil 10 mg/day or ramipril 2.5 mg/day. After 2 and 6 weeks, doses were increased up to a maximum of 40 mg/day (olmesartan medoxomil) and 10 mg/day (ramipril) in non-normalized subjects (office systolic blood pressure [SBP] ≥140 mmHg or diastolic blood pressure [DBP] ≥90 mmHg in non-diabetic subjects and office SBP ≥130 mmHg or DBP ≥80 mmHg in diabetic patients). Office blood pressure (BP) was measured at 0, 2, 6 and 12 weeks, 24-hour ambulatory BP at 0 and 12 weeks. 284 patients treated with olmesartan medoxomil 40 mg/day at the end of the double-blind period entered a 36-week, open-label follow-up. Renal function (Cockroft-Gault equation) was evaluated as normal or increased estimated glomerular filtration rate (eGFR) [≥90 mL/min/1.73 m²], mild eGFR reduction (60–90 mL/min/1.73 m²) and moderate or severe eGFR reduction (<60 mL/min/1.73 m²).

Results: 181 (12.7%) subjects had normal or increased eGFR, 840 (58.9%) mild eGFR reduction, and 405 (28.4%) moderate or severe eGFR reduction. Baseline-adjusted office BP reductions were superior with olmesartan medoxomil than with ramipril in normal or increased (olmesartan medoxomil – ramipril difference SBP: 5.0 mmHg [95% CI 1.9, 0.9], p = 0.018; DBP: 2.7 mmHg [4.8, 0.6], p = 0.011) and mildly reduced eGFR patients (SBP: 1.6 mmHg [3.5, 0.2], p = 0.080; DBP: 1.2 mmHg [2.3, 0.2], p = 0.022). In the group with moderately or severely reduced eGFR the two treatments were comparable (SBP: 1.9 mmHg [4.6, 0.9], p = 0.185; DBP: 0.8 mmHg [2.3, 0.7], p = 0.296). At 12 weeks, the rate of normalized patients was 46.1% with olmesartan medoxomil versus 23.9% with ramipril (p = 0.002) in the normal, and 49.9% versus 42.7% (p = 0.037) in the mild eGFR reduction group. No significant differences in normalization rate were observed in the moderately or severely reduced eGFR group (olmesartan medoxomil 49.5% vs ramipril 46.3%, p = 0.519). eGFR did not show any significant change during treatment.

Conclusions: Olmesartan medoxomil provides a more effective BP control, similar if not superior to that of ramipril, independently from the patient’s renal function status.

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Keywords: essential hypertension, elderly, olmesartan, ramipril, kidney disease, renal function, creatinine clearance.

Background

Achieving good blood pressure control in elderly patients with hypertension often represents a pharmacological challenge as such patients are more prone to developing kidney failure, and thus require special consideration when being assigned an antihypertensive treatment.[1]

Among antihypertensive agents currently in use, those known to have the best tolerability rate in older patients are ACE inhibitors and angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]).[2] These two classes of drugs also seem to reduce the risk of progression of kidney disease among hypertensive patients with renal dysfunction and, in fact, this protective effect on the kidneys has been demonstrated in previous studies on diabetic patients.[3,4] In addition to these properties, ARBs seem to slow or reverse the progression of microalbuminuria to macroalbuminuria and overt nephropathy,[5,6] an effect that appears to be independent of their blood pressure-lowering activity.[7]

As typical of ARBs, olmesartan medoxomil inhibits the action of the renin-angiotensin system at the level of the angiotensin type 1 (AT1) receptor.[8,9] The antihypertensive efficacy of olmesartan medoxomil in elderly patients with systolic and diastolic or isolated systolic hypertension has been well demonstrated throughout a number of large trials and clinical practice settings.[10,11] Recently, two large randomized, double-blind, parallel-group studies performed a head-to-head comparison of an ACE inhibitor and an ARB, demonstrating the superiority of olmesartan medoxomil 10–40 mg over the ACE inhibitor ramipril 2.5–10 mg in controlling both office and ambulatory blood pressure of elderly individuals (aged 65–89 years) with grade 1 or 2 essential hypertension.[12,13]

Here, we present a post hoc analysis of individual data from two pooled studies[12,13] in which the antihypertensive efficacy of olmesartan medoxomil is compared with that of the ACE inhibitor ramipril in elderly patients with essential hypertension, based on stratification of patients according to their renal function evaluated by means of estimated glomerular filtration rate (eGFR).

Participants and Methods

Study Design

This was a post hoc analysis of pooled data from two efficacy and safety multicentre studies with identical randomized, double-blind, parallel-group design. Subjects eligible for entering the studies were elderly outpatients (aged between 65 and 89 years) of both sexes, with grade 1 or 2 essential arterial hypertension (sitting clinic systolic blood pressure [SBP] 140–179 mmHg and/or sitting clinic diastolic blood pressure [DBP] 90–109 mmHg) or essential arterial hypertension not controlled with current treatment. Patients were enrolled from 102 centres in Italy and 31 across Europe (three centres in Austria, one in Belgium, two in France, ten in Germany, two in Greece, one in Ireland, six in Poland and six in Spain). The studies were performed in accordance with ethical principles stated in the Declaration of Helsinki and consistent with International Conference on Harmonisation/Good Clinical Practice. Written informed consent was obtained from all patients prior to their inclusion in the studies. The studies were approved by the independent institutional review boards of the centres involved. The main results of the original studies were reported in previous publications.[12,13]

Upon entering the study, patients underwent a 2-week placebo wash-out period followed by a 12-week treatment with olmesartan medoxomil or ramipril at the initial doses of 10 or 2.5 mg, respectively, given once daily between 9:00am and 11:00am. Patients were randomized in a ratio of 1 : 1. At the screening visit, medical history was collected and a full physical examination with haematological and biochemical analysis was performed. After the first 2 and 6 weeks of active treatment, the drug dose was doubled whenever office SBP was 140 mmHg or higher or office DBP was 90 mmHg or higher in non-diabetic patients and whenever office SBP was 130 mmHg or higher or office DBP was 80 mmHg or higher in diabetic patients, up to a maximum of 40 mg for olmesartan medoxomil or 10 mg for ramipril. At all visits, occurrence of adverse events was assessed. At the end of the 12-week treatment, all haematological and biochemical analyses were repeated.

At the end of the double-blind phase, a subgroup of patients under treatment with olmesartan medoxomil 40 mg continued an open-label follow-up for 36 weeks. During this open phase, non-diabetic patients not normalized at the end of the double-blind phase had to be treated with the addition of hydrochlorothiazide (HCTZ) 12.5 mg/day, which eventually was doubled to 25 mg/day at the subsequent visit in case of lack of blood pressure normalization. Diabetic patients not normalized (SBP ≥130 mmHg and DBP ≥80 mmHg) after the double-blind phase had to be treated with the addition of zofenopril 15 mg/day,