Hypertension: Focus on Olmesartan Medoxomil

Allison M. Bell¹ and Diane Nykamp²

¹Mercer University College of Pharmacy and Health Sciences, Atlanta, Georgia U.S.A. ²Department of Pharmacy Practice, Mercer University College of Pharmacy and Health Sciences, Atlanta, Georgia U.S.A; Clinical Pharmacist, St. Joseph’s Hospital Atlanta.

Abstract: Hypertension is the leading cause of stroke, heart failure, and ischemic heart disease. One of the key regulators of blood pressure is the renin-angiotensin aldosterone system (RAAS). Olmesartan medoxomil, an angiotensin receptor blocker (ARB), counteracts some of the primary effects of the RAAS by selectively and irreversibly binding to the type 1 angiotensin II receptor (AT₁-R). The pharmacokinetic profile of this ARB allows for the convenience of one a day dosing. The pharmacodynamic profile of olmesartan is favorable because it is neither metabolized by, induces, nor inhibits the CYP450 isozyme system. The metabolism of the prodrug to the active form occurs in the gut by the enzyme arylesterase. No further metabolism and a lack of interaction with the CYP450 isozyme system leads to very few drug interactions with olmesartan medoxomil.

Numerous studies have been conducted to evaluate the efficacy, safety, and tolerability of olmesartan medoxomil. Studies have been conducted to compare olmesartan medoxomil to other angiotensin receptor blockers. The efficacy of olmesartan medoxomil has been compared to other classes of antihypertensive agents. Results of all trials have proven non-inferiority of olmesartan medoxomil to other antihypertensive agents; some studies have shown superior blood pressure control provided by olmesartan medoxomil when starting dosages are evaluated. Overall, olmesartan medoxomil has the potential to facilitate the achievement of blood pressure goals, enhance compliance with a once daily dosing regimen, and is associated with minimal side effects. Olmesartan medoxomil has been proven to be a safe and effective antihypertensive drug when compared to other ARBs and other antihypertensive agents.

Keywords: Olmesartan, hypertension, ARB, angiotensin receptor blocker

Introduction

Hypertension is a disease which affects an estimated one billion people worldwide.¹ Hypertension is the leading cause of stroke, heart failure, and ischemic heart disease. There are many treatment regimens available to control high blood pressure yet many patients are not treated to goal. One reason for this lack of adequate treatment is that ideal blood pressure goals keep changing. This is due to the fact that as researchers learn more about hypertension and co-morbid conditions associated with hypertension the blood pressure goals get stricter.²

The renin-angiotensin aldosterone system (RAAS) is a very complex system that plays a pivotal role in regulation of blood pressure. The RAAS maintains vascular tone, electrolyte and water balance, and overall homeostasis of blood pressure and the vascular system.³ The RAAS is composed of a variety of complex steps; many of these steps serve as potential drug targets to suppress the RAAS system. Angiotensin II (Ang II) is the most biologically active product of the RAAS system, acting directly to constrict vascular smooth muscle cells, enhance myocardial contractility, stimulate the production of aldosterone, stimulate release of catecholamines from both the adrenal medulla and sympathetic nerve endings, and stimulate cravings for salt along with activating the thirst reflex.¹ Ang II can also induce inflammation, cell growth, mitogenesis, apoptosis, migration, and differentiation.⁴ It also has pro-thrombotic effects which can contribute to the rupture of atherosclerotic plaques and enhance thrombus formation.⁵ These effects potentially cause tissue damage which leads to the theory that Ang II has a prime role in the pathogenesis of hypertension and kidney injury due to inappropriate activation of the angiotensin II type 1 receptors.⁴

There are many antihypertensive drugs available, many which act on the RAAS system. Angiotensin receptor blockers (ARBs) are a class of antihypertensive medication that are growing in popular-
ity due to their excellent blood pressure control potential, low adverse event profile, and high patient tolerability. The once daily dosing interval of most ARBs helps enhance patient compliance which may lead to better patient outcomes. Olmesartan medoxomil is an ARB that has been proven to be an effective antihypertensive agent. Some studies have shown superiority of olmesartan medoxomil to agents in other classes as well as superiority of olmesartan medoxomil to other ARBs at starting dosages. The purpose of this review is to investigate the major studies associated with olmesartan medoxomil and investigate any limitations to claims resultant from these large clinical trials.

**Pharmacology, Mode of Action, and Pharmacokinetics**

Angiotensin receptor blockers inhibit the actions of the renin-angiotensin aldosterone system by blocking type 1 angiotensin II receptors (AT$_1$-R). Blockade of the AT$_1$-R can block vasoconstriction, reduce sodium and water retention, and decrease cellular proliferation and hypertrophy. Selectivity for the AT$_1$-R allows for the stimulation of the angiotensin II type 2 receptor (AT$_2$-R) by the circulating Ang II. Though the AT$_2$-R is not as abundant of a receptor as the AT$_1$-R in adults, it still plays an important role in the modulating of vascular homeostasis. The AT$_2$-R acts as a counterbalance to the effects mediated by activation of the AT$_1$-R. Effects of AT$_2$-R activation include inhibition of cellular hypertrophy, inhibition of cellular proliferation, and vasodilation via formation of nitric oxide. ARBs antagonize the effects of Ang II produced outside of the RAAS system. The renin escape phenomenon (where renin and AngII levels return to pre-treatment levels) can occur with chronic treatment of an ACE inhibitor. ACE inhibitors do not block the other enzymes in the body, such as chymase, which can convert Ang I to Ang II. This phenomenon is a result of the loss of the negative feedback inhibition from Ang II on the juxtaglomerular cells of the afferent arteriole. The effect of increased renin and AngII due to the renin escape phenomenon is nullified in patients taking an ARB due to the essentially irreversible binding of the ARB to the AT$_1$ receptor. An ARB also allows for the conversion of Ang I to Ang II; since kinase II is not inhibited bradykinin can be broken down. The breakdown of bradykinin eliminates the dry cough side effect commonly seen with ACE inhibitors that act at the rate limiting step of the RAAS.

Olmesartan medoxomil is a prodrug ester. In vivo, this prodrug is rapidly de-esterified via an enzyme, arylesterase. Arylesterase, located in both the intestine and plasma, rapidly converts the prodrug olmesartan medoxomil to the active olmesartan by breakdown of the medoxomil ester. Olmesartan has 100,000 times greater selectivity for the AT$_1$-R than it does for the AT$_2$-R$^6$ inhibiting the vasoconstricting and aldosterone secreting effects of Ang II while not interfering with the vasodilatory effects that occur with AT$_2$-R stimulation. This selective binding of olmesartan to the AT$_1$-R is coupled with a high degree of insurmountability and demonstrated a greater binding affinity than most of the other commercially available ARBs. In vitro studies of recombinant human AT$_1$ receptors olmesartan was shown to have a dissociation half life of 166 minutes. This shows a stronger binding affinity than candesartan (133 minutes), losartan (70 minutes), and valsartan (67 minutes). The only ARB that demonstrated stronger binding affinity was telmesartan which has a dissociation half life of 213 minutes. In addition to the tight binding to the AT$_1$-R, it is thought that the long anti-hypertensive effects of olmesartan may result from increased drug accumulation at the receptor site or from re-association of the olmesartan with the receptor after dissociation. Olmesartan medoxomil is indicated for hypertension in a range of 20 mg to 40 mg once daily.

Olmesartan has an oral bioavailability of 26% with a terminal half life of approximately 13 hours which makes it suitable for once a day dosing. It is highly bound to plasma proteins (99%) and has a volume of distribution of approximately 17 L. It demonstrates linear pharmacokinetics with single doses up to 320 mg following oral administration. In rats olmesartan medoxomil crosses the blood brain barrier poorly, if at all. Olmesartan is not further metabolized following its de-esterification in the gut; there is no cytochrome P450 metabolism of olmesartan. It neither inhibits nor induces CYP450 isozymes. Olmesartan is primarily eliminated in the feces via the hepatobiliary route (50%–65%) and also eliminated via the kidneys (35%–50%).

In elderly patients, mean AUC time to steady state was increased by 33% and the mean $C_{\text{max}}$ was increased by 14% in very elderly patients.
These changes were not considered clinically significant so dosage reductions are not necessary for elderly patients. In patients with moderate to marked renal impairment (CrCl < 40 mL/min) no initial dosage adjustment is necessary. For patients with mild to moderate hepatic impairment a dosage decrease is not needed though there have not been studies to recommend dosage adjustments for patients with severe hepatic dysfunction.

Efficacy Studies

Many studies have been performed to demonstrate the efficacy of olmesartan medoxomil in controlling hypertension. Studies to compare the efficacy of olmesartan medoxomil as monotherapy vs. placebo have shown the antihypertensive benefits of this drug. Dosages ranging from 2.5 to 80 mg per day have shown good blood pressure response to treatment though the current recommended dosing range is from 20 mg to 40 mg a day.

Neutel et al. conducted a randomized, double blind, placebo controlled, parallel group study with randomization into seven different groups. This 8 week study investigated effective dosing amounts and schedule of olmesartan medoxomil. Treatment groups received either once a day dosing (5 mg, 20 mg, or 80 mg), twice a day dosing (2.5 mg, 10 mg, or 40 mg), or a placebo for control. Patients receiving once a day dosing also received a dummy placebo tablet to help with blinding. After a baseline sitting cuff blood pressure measurement, patients were measured on days 8, 15, 29, 43, and 57 of treatment. Ambulatory blood pressure was measured for 24 hours on days 1 and 58. The primary endpoint was the change in mean 24 hour diastolic blood pressure during treatment in the olmesartan medoxomil once a day treatment groups and placebo. Other endpoints were change in diastolic blood pressure in the twice a day dosing groups, change in systolic blood pressure in all of the treatment groups, and change in mean daytime and nighttime blood pressure in all treatment groups. Statistically significant changes in both diastolic blood pressure and systolic blood pressure were seen in all olmesartan medoxomil treatment groups. The reductions in blood pressure were independent of dosing schedule (once a day versus twice a day). This shows that olmesartan medoxomil maintains effective blood pressure control when dosed once a day.

Chrysant et al. report reductions in both systolic and diastolic blood pressure when olmesartan has been compared with placebo in many large clinical trials. Unger et al. also analyzed seven randomized, double blind, placebo controlled studies. These studies were large, with greater than 3000 participants, all with mild to moderate hypertension. The integrated analysis of data from these trials showed the dosage of 20 mg a day provided a sufficient anti-hypertensive effect. Similar reductions were seen with once a day dosing and twice a day dosing of olmesartan medoxomil regarding systolic blood pressure and diastolic blood pressure with ambulatory blood pressure monitoring. Stable reductions in diastolic blood pressure throughout the 24 hour period post drug administration confirmed that olmesartan medoxomil is effective with once a day dosing.

Giles and Robinson looked specifically at the effect of olmesartan medoxomil on systolic blood pressure and pulse pressure in the management of hypertension. Pulse pressure is an important factor to consider in the progression of hypertension. A wide pulse pressure occurs when there is a loss of proximal arterial compliance; drugs that block the RAAS may be effective in reducing pulse pressure.

Dosages of olmesartan medoxomil administered were 5 mg, 20 mg, and 40 mg each dosed once a day. A placebo group was also incorporated into the study designs. The study time from baseline to the primary time point of each trial ranged from 6 to 12 weeks. Each trial evaluated by Giles and Robinson included screening and placebo run-in periods. Change in trough seated diastolic blood pressure from baseline was used as a primary endpoint and secondary endpoints included the change from baseline in trough seated systolic blood pressure. Baseline characteristics for all treatment groups were very similar.

Significant dose dependent reductions in systolic blood pressure, diastolic blood pressure, and pulse pressure were shown in the groups who received olmesartan medoxomil. The treatment group that received the 40 mg olmesartan medoxomil demonstrated the greatest reductions in all three endpoints. Wide cohort analysis confirmed the previously mentioned findings. Olmesartan medoxomil was effective at reducing systolic blood pressure, diastolic blood pressure, and pulse pressure in subgroups ≥65 years of age and those <65 year old.

Saito et al. performed an open label, prospective, cohort study to evaluate the efficacy and safety of olmesartan medoxomil in elderly Japanese patients.
Patients involved in the study were age 65 or older; they were classified as either young-old (65–74 years old) or older-old (75 years or greater). Patients were also sub-classified as to whether they had both systolic and diastolic hypertension (SDH) or isolated systolic hypertension (ISH). Initial study daily dosages of 5 mg to 10 mg of olmesartan medoxomil were utilized; if necessary, the olmesartan medoxomil dosage could be increased to 20 mg then 40 mg per day during the 24 week period in which the study took place. Study participants were all olmesartan medoxomil naive. The main outcomes of the study were the efficacy and safety of olmesartan medoxomil. Non-compliant subjects were removed from the study.

The dosage of 10 mg a day was the most common dosage utilized both initially and throughout the 24 week study period. 5 mg and 20 mg, respectively, were the next most commonly used dosages. The 5 mg dosage was utilized more frequently in the older-old population than in the young-old group. Saito et al. suggests that a more conservative dosing approach should be utilized when treating older-old patients with hypertension. Approximately 76% of the young-old population was started on olmesartan medoxomil monotherapy; 67% remained on olmesartan monotherapy after 24 weeks. The most frequently used concomitant antihypertensive therapy was a calcium channel blocker, followed by diuretics, and beta blockers.

Efficacy was monitored through systolic blood pressure, diastolic blood pressure, and pulse pressure. Within two weeks of treatment both systolic and diastolic blood pressure were significantly reduced. The blood pressure lowering effects were maintained until the end of the study. Diastolic blood pressure reductions were significantly less in patients with ISH than those with SDH. This result is favorable for patients with ISH since a reduction in diastolic blood pressure is unnecessary and may lead to hypotensive side effects. Adverse drug reactions were similar among all subgroups and were primarily mild.

Olmesartan medoxomil has also been compared to other ARBs. One prime advantage of olmesartan medoxomil over other ARBs is the lack of hepatic metabolism of olmesartan. Table 1 lists comparable dosages and costs of ARBs. Other ARBs undergo metabolism via the CYP450 isozyme system. Both irbesartan and losartan undergo CYP450 metabolism; it is also thought that valsartan undergoes CYP450 metabolism though the exact enzymes for its metabolism are yet to be identified. Metabolism of a drug with the CYP450 isozyme system can lead to numerous drug-drug interactions; since olmesartan is not metabolized by this system it is unlikely to interact with other drugs. Another positive aspect of olmesartan medoxomil is that food does not affect its bioavailability. A head to head study of olmesartan medoxomil vs. valsartan utilized starting doses of 10 mg/day and 50 mg/day respectively. If study patients did not reach a diastolic blood pressure goal of ≤90 mmHg or a ≥10 mmHg decrease from baseline within 4 weeks then the dosage for the olmesartan medoxomil treatment group was increased to 20 mg/day and the dosage for the valsartan treatment group was increased to 100 mg/day. If the response was still inadequate after 12 or 16 weeks then hydrochlorothiazide (HCTZ) 12.5 mg or 25 mg was added. The results of the study demonstrated significantly greater antihypertensive efficacy of olmesartan medoxomil than valsartan at time points from 2 to 12 weeks. After the 16 to 24 weeks the olmesartan medoxomil still

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*Cost of medications for a 30 day supply from www.drugstore.com
**None of the ARBs are available generically in the U.S. although losartan will be available in 2010.
demonstrated greater efficacy than valsartan, though those results were not considered statistically significant. It is noted that the utilization of HCTZ was less frequently needed in the olmesartan medoxomil treatment group for patients to get to their goal blood pressure.\(^{18}\)

Oparil et al. have also compared the efficacy of olmesartan, losartan, valsartan, and irbesartan in a head to head study. The study was a randomized, double blind, parallel group, multicenter trial conducted at 68 different sites throughout the United States. A 4 week single blind placebo run-in followed initial screening. After the 4 week period an 8 week double blind active treatment was initiated.\(^{19}\) Blood pressure and heart rate were measured at the end of each week during the run-in period; those who were still eligible for the study received 24 hour ambulatory blood pressure monitoring prior to the start of the 8 week active treatment period. At the end of weeks 2, 4, and 8 sitting cuff blood pressure measurements were taken, heart rate was measured, and a pill count was conducted to assess patient compliance. Patients were also monitored for adverse effects.\(^{19}\)

At the end of week 8 a 24 hour ambulatory blood pressure monitoring was completed. The primary endpoint of this study was to assess the comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in regards to the reduction of elevated blood pressure.\(^{19}\) Starting dosages were used for each medication. Secondary endpoints included changes in sitting cuff diastolic blood pressure from baseline to week 2 and 4 visits, changes in sitting cuff systolic blood pressure from baseline to week 2, 4, and 8 visits, and change in mean 24 hour ambulatory blood pressure monitoring for both systolic and diastolic blood pressures from baseline to week 8.\(^{19}\)

All four ARBs showed statistically significant decreases in systolic and diastolic blood pressure; olmesartan medoxomil showed statistically significantly greater decreases in cuff diastolic blood pressure than the losartan, valsartan, or irbesartan groups. The reduction in systolic blood pressure for olmesartan medoxomil versus the other ARBs was not statistically significant at the 8 week time-point. Olmesartan medoxomil showed significantly greater reductions than the other treatment groups in both systolic and diastolic blood pressure at week 2; by week 4 olmesartan medoxomil only showed significant reductions over the other ARBs in regards to diastolic blood pressure.\(^{19}\)

There was no significant change in heart rate in any of the ARB treatment groups. The 24 hour ambulatory blood pressure monitoring revealed a statistically significant decrease in both systolic and diastolic blood pressures when comparing olmesartan medoxomil to losartan and valsartan, but the decrease was not statistically significant when compared to irbesartan.\(^{19}\)

A study performed by Liau et al. compared the efficacy and safety of olmesartan medoxomil for the treatment of mild to moderate essential hypertension in Chinese patients. This study was a multicenter, double blind, comparative trial conducted in three separate medical centers in Taiwan. Patients were randomized into treatment groups of once daily dosing of olmesartan medoxomil 20 mg or once daily dosing of losartan 50 mg. A corresponding placebo was also given to each study participant.

Baseline measurements were similar for both treatment groups; after treatment both study groups showed lower systolic blood pressure and diastolic blood pressure. When comparing the 20 mg olmesartan medoxomil treatment group to the 50 mg losartan treatment group the olmesartan medoxomil group showed a greater decrease which was statistically significant for both systolic blood pressure and diastolic blood pressure. Comparing both groups to baseline measurements the olmesartan medoxomil group demonstrated a significantly greater decrease than the losartan group at 4 weeks for both systolic blood pressure and diastolic blood pressure. The responder rate at the 4 week time point was 69.4% for the olmesartan group and only 38.6% for the losartan group. Data from Liau et al. suggests a faster antihypertensive effect with olmesartan medoxomil treatment.\(^{20}\) The olmesartan medoxomil group also demonstrated a greater decrease than the losartan group at 16 weeks for both systolic blood pressure and diastolic blood pressure at the 16 week time point that was statistically significant. A greater decrease in both systolic blood pressure and diastolic blood pressure at the 8 week time point, along with a greater decrease in systolic blood pressure for the 16 week time point were seen with the olmesartan medoxomil group but the difference was not statistically significant.\(^{20}\)

Olmesartan medoxomil was also compared to valsartan in a trial performed by Destro et al. A prospective, randomized, open-label, blinded endpoint, parallel arm study was used to determine whether olmesartan medoxomil 20 mg/day was
superior to valsartan 160 mg/day. Both trough and peak values were measured for each treatment group using ambulatory blood pressure monitoring. At the 2 week time point valsartan 160 mg was shown to be more effective than the olmesartan medoxomil 20 mg.\(^2^1\) The difference between the two groups was lessened at the 8 week time point but the valsartan still proved superior. Overall, this study showed that valsartan produced a greater blood pressure control and earlier blood pressure decrease than olmesartan medoxomil over a 24 hour period. Though both treatments were considered effective when compared to baseline the valsartan 160 mg proved to be superior in regards to 24 hour blood pressure control.\(^2^1\)

Olmesartan has also been compared with calcium channel blockers for blood pressure control. Chrysant et al. compared the antihypertensive efficacy and safety of olmesartan medoxomil with amlodipine in patients with mild to moderate hypertension. The study was a randomized, double blind, placebo controlled, parallel group trial and was sponsored by Sankyo Pharmaceuticals. Patients were evaluated by 24 hour ambulatory blood pressure monitoring for 8 weeks. The primary endpoint was a change from baseline in mean 24 hour diastolic blood pressure at the 8 week time point. The secondary endpoint was a change in systolic blood pressure from baseline also at the 8 week time point. Both olmesartan medoxomil and amlodipine produced significantly greater reductions in blood pressure than the placebo. There was a statistically significant percentage of patients who reached the more strict diastolic blood pressure goal of $<85\text{ mmHg}$ more so with olmesartan medoxomil than with the amlodipine treatment ($48\%$ of the olmesartan medoxomil group vs. $34\%$ of the amlodipine group). There were also more patients in the olmesartan medoxomil group who reached a systolic blood pressure goal of $<130\text{ mmHg}$ than those who were in the amlodipine group ($34\%$ and $17\%$ respectively).\(^2^2\) According to this study, olmesartan medoxomil proves superior to amlodipine in regards to patients who strive to achieve a more stringent blood pressure goal of $<130/85\text{ mmHg}$.\(^2^2\)

Olmesartan medoxomil has also been compared to the calcium channel blocker nitrendipine. The study investigated the systolic blood pressure reduction potential of olmesartan medoxomil versus nitrendipine in elderly patients who had isolated systolic hypertension. Mallion et al. designed the study to be a phase III, multinational, randomized, double blind, double dummy, parallel group study which was also sponsored by Sankyo Pharmaceuticals. Patients enrolled were either elderly or very elderly and all had isolated systolic hypertension. After the placebo washout period of 2 weeks randomization occurred with patients in the olmesartan medoxomil group receiving 20 mg olmesartan once a day and patients in the nitrendipine group receiving 10 mg nitrendipine twice a day. All patients received dummy placebo tablets to help with the blinding; each patient took two tablets in the morning and one tablet in the evening. After 4 weeks those patients whose systolic blood pressure was not $<140\text{ mmHg}$ had their dose of either olmesartan medoxomil or nitrendipine doubled. After the 12 week time point the patients who still did not achieve a systolic blood pressure of $<140\text{ mmHg}$ had HCTZ added to their therapy. The primary endpoint of this study was the change from baseline of the systolic blood pressure at the 12 week time point. This was assessed by conventional blood pressure measurements. Secondary endpoints included change from baseline in both the mean sitting and standing systolic blood pressure and diastolic blood pressure over the 24 week total treatment period.\(^2^3\) The attainment of systolic blood pressure $\leq 135\text{ mmHg}$ (goal), time to goal systolic blood pressure attainment, proportion of participants who needed their original dosage of medication doubled or needed HCTZ, and effects of those medication changes were all secondary endpoints of this study.

Results of this study showed that olmesartan medoxomil was as effective as nitrendipine at the 12 week time point in decreasing sitting systolic blood pressure. Over the 24 week treatment period there were no significant differences noted between the treatment groups at any time for systolic blood pressure.\(^2^3\) There were also no significant differences between the treatment groups in regards to sitting diastolic blood pressure. No significant difference was noted between the groups in the time it to attain the systolic blood pressure goal of $\leq 135\text{ mmHg}$. As monotherapy the nitrendipine group had a slightly larger systolic blood pressure decrease while the olmesartan medoxomil combination therapy with HCTZ had a greater decrease in systolic blood pressure than the nitrendipine combination therapy group.\(^2^3\) Overall, both treatment groups experienced a lowered mean systolic blood pressure of approximately 30 mmHg at the
12 week time point for both the elderly and very elderly patients. This study proves the equal efficacy of olmesartan medoxomil and nitrendipine. An advantage noted by Mallion et al. was the benefit of once a day dosing in regards to patient compliance versus the twice a day dosing required by nitrendipine.

Olmesartan medoxomil has also been compared to the calcium channel blocker felodipine and non inferiority of olmesartan medoxomil was proven.24 Other studies have shown no significant difference between olmesartan medoxomil and atenolol in reducing mean trough diastolic blood pressure or response rates at a 12 week time point though olmesartan medoxomil did have a greater effect in reducing mean systolic blood pressure than did atenolol.24,25

Olmesartan medoxomil has also been compared to the ACE inhibitor captopril in a study performed by Ball et al. Once daily dosing of the olmesartan medoxomil resulted in a greater decrease from baseline in both systolic blood pressure and diastolic blood pressure than did twice a day dosing of captopril.25 One limitation with captopril is that captopril should be dosed three times a day. Twice a day dosing of captopril may have lead to decreased efficacy in terms of blood pressure lowering potential.

Another limitation in many of these studies comparing olmesartan medoxomil to irbesartan, losartan, and valsartan is the claim of the superiority of olmesartan medoxomil in reducing blood pressure. This claim may not be valid in regards to overall superiority of the other ARBs since the studies were all performed with the starting dosage of irbesartan (150 mg), valsartan (80 mg), and losartan (50 mg), compared to the 20 mg starting dose of olmesartan medoxomil. Maximization of the dosage for each medication would give a clearer picture in regards to superiority of olmesartan medoxomil. Table 1 shows starting dosages and dosage ranges for each ARB. In 2006 the United States Food and Drug Administration issued a warning to Sankyo Pharmaceuticals about their pharmaceutical sales representatives making false claims about the superiority of olmesartan medoxomil.26

The OLMEPAS study evaluated the antihypertensive efficacy of olmesartan medoxomil in approximately 12,000 patients with hypertension over an 8 week period. The most common dose of olmesartan medoxomil utilized was 20 mg/day. Overall, the mean reduction from baseline in systolic blood pressure was 28.4 mmHg and the mean reduction in diastolic blood pressure from baseline was 14.2 mmHg.10 The OLMER3B study was a sub-study of the OLMEPAS that evaluated the responder rates and normalization in 4,000 patients. This sub-study showed a responder rate of 89% by the final visit and 49% of patients had achieved a normal blood pressure of <140/90 mmHg.10

The OLMEBEST study was conducted to determine the efficacy and tolerability of olmesartan medoxomil in patients with mild to moderate hypertension. This study was a prospective, parallel group, partially randomized double blind study which took place in nine European countries.27 Over 2300 adults (male and female) with mild to moderate essential hypertension received open-label olmesartan medoxomil 20 mg once a day for an 8 week time period. At the end of the 8 week time period patients who had not achieved their blood pressure goals were randomized to two groups. One group received olmesartan medoxomil 40 mg once daily while the other group received a combination of olmesartan 20 mg and hydrochlorothiazide 12.5 mg once daily. The subgroup was used to evaluate whether a higher dose of olmesartan medoxomil was non-inferior to a combination of olmesartan medoxomil and HCTZ to help patients achieve their diastolic blood pressure goals. This second part of the study took place over 4 weeks.

To ensure trough blood pressure measurements were obtained the patients were instructed to wait to take their medication on study visit days until their evaluations had been completed.27 Of the 2306 patients enrolled in the OLMEBEST study 76% of patients reached their diastolic blood pressure goal by week 8 of the study. Rapid improvements in both systolic blood pressure and diastolic blood pressure were seen within 2 weeks of the start of the trial.27 This larger than predicted group of patients who responded to the 20 mg olmesartan medoxomil treatment led to a smaller than expected study group for the second part of the study. This small sample size did not allow for statistical significance of the non-inferiority study. Though non-inferiority could not be demonstrated both treatment regimens (40 mg olmesartan medoxomil vs. 20 mg olmesartan medoxomil plus 12.5 mg of HCTZ) produced improvements in blood pressure control.27 Many patients who participated in the second part of the study also demonstrated
substantial improvement within two weeks of randomization into the treatment groups.

Safety and Tolerability
Numerous clinical trials have demonstrated the safety and tolerability of olmesartan medoxomil. In the analysis performed by Giles and Robinson of 7 major clinical trials comparing olmesartan medoxomil to placebo it was shown that olmesartan medoxomil is well tolerated. Dizziness was more common with the olmesartan medoxomil group than with placebo. It was noted that the incidence of dizziness (1.4%) was similar to the frequency of dizziness experienced with ARBs losartan, valsartan, and irbesartan found by Oparil et al. in 2001. Serious adverse effects were not attributed to the study medications. The adverse event profiles for olmesartan medoxomil and placebo were found to be similar. The tolerability profiles of olmesartan medoxomil and placebo showed no differences based on age, gender, or race.10

Chrysant et al. demonstrated that olmesartan medoxomil was associated with less edema than amlodipine. Olmesartan, along with other ARBs, have shown a placebo-like tolerability and no increase in adverse effects even when given at maximum doses. Mallion et al. again proved the safety and tolerability of olmesartan medoxomil when it was compared to nitrendipine. No serious adverse effects were attributed to study medications. The adverse event profiles for olmesartan medoxomil and placebo were found to be similar. The tolerability profiles of olmesartan medoxomil and placebo showed no differences based on age, gender, or race.10

The OLMEBEST study showed both safety and tolerability to 20 mg and 40 mg of olmesartan medoxomil given once a day. None of the three deaths that occurred during the trial were attributed to the medication given in the study. Adverse effects experienced were similar during the open label phase of the study and the randomized second phase of the study. There was a lower frequency of adverse events in the 40 mg olmesartan medoxomil group in the randomized second phase than with the combination of 20 mg olmesartan medoxomil and 12.5 mg of HCTZ. Serious adverse events only occurred in 6 patients and none were considered to be related to the study medication.27

Overall, olmesartan medoxomil, along with the other ARBs, has a safety and tolerability profile similar to placebo. ARBs have a decreased incidence of cough and angioedema when compared with ACE inhibitors. ARBs all have teratogenic potential similar to ACE inhibitors and should therefore be avoided in pregnant women. There may also be an increase in serum potassium with ARBs.3

Quality of Life, Patient Satisfaction/ Acceptability, Adherence and Uptake
Schmidt et al. specifically looked at quality of life in hypertension management when using olmesartan medoxomil in primary care. This study was an open label, prospective, non-interventional study to investigate how olmesartan medoxomil affected a patient’s quality of life. Patients were asked about previous antihypertensive therapies. Physical components investigated and rated by patients included description of general health, ability to do moderate to heavy work, ability to climb stairs, ability to accomplish tasks (based on health problems), and disability due to pain. The resultant ratings for each component were evaluated by gender. After a 6 week time point on olmesartan medoxomil therapy all values for both genders improved significantly. Mental components such as depression, ability to relax, energy levels, and social interactions were also evaluated and in all aspects improved significantly at the 6 week time point with olmesartan medoxomil treatment. Overall, this study showed high tolerability and patient compliance along with efficacy of olmesartan medoxomil for treating hypertension. Increased compliance decreases disease state progression. Schmidt et al. also notes that other studies have proved similar quality of life benefits with ARBs other than olmesartan medoxomil. This suggests that the increased quality of life when compared to ACE inhibitors, beta blockers, calcium channel blockers, and other blood pressure medications may be a class effect of the ARBs and not unique to olmesartan medoxomil. A limitation of this study was the short 6 week time period for which it was conducted; longer follow up time periods would help reinforce the enhance compliance and improved quality of life that this study infers.

Conclusion
Olmesartan medoxomil has been proven to be an effective drug for reducing both systolic blood pressure and diastolic blood pressure in the non-elderly and elderly population. Numerous large studies have shown the non-inferiority of olmesartan
medoxomil when compared to other ARBs, calcium channel blockers, beta blockers, and ACE inhibitors for treatment of hypertension and isolated systolic hypertension. The tolerability and safety of olmesartan medoxomil has also been documented, with an adverse event profile similar to placebo. The once daily dosing of olmesartan medoxomil helps to enhance compliance and facilitate achievement of blood pressure goals in patients. Many studies have shown that olmesartan medoxomil has more potent blood pressure lowering effects than other ARBs when given at the typical starting doses. Though the results were statistically significant in these studies further investigation, comparing maximum daily dosages of ARBs need to be performed to prove the superiority of olmesartan medoxomil over other agents in this class. Overall, olmesartan medoxomil has many benefits in hypertension. Blockade of the AT1, -R provides pleiotropic effects which benefit the patient in more ways than simply reducing blood pressure. It is an excellent choice for antihypertensive therapy due to its superior side effect profile and ability to provide great reductions in both systolic blood pressure and diastolic blood pressure.

Disclosure

The authors report no conflicts of interest.

References