Paper

Efficacy in angiotensin receptor blockade: a comparative review of data with olmesartan

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Key words: angiotensin receptor blocker, blood pressure, hypertension, olmesartan, renin-angiotensin-aldosterone system

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Journal of the Renin-Angiotensin-Aldosterone System (Including other Peptidergic systems)

September 2009 Volume 10 Number 3

Abstract

A range of angiotensin II receptor blockers (ARB) is available, and analyses suggest there are differences between agents in terms of antihypertensive efficacy and 24-hour blood pressure control. This review assesses the data comparing olmesartan with other ARBs in terms of blood pressure reductions, goal achievement, 24-hour control and speed of onset. Olmesartan seems to have a more favourable efficacy profile relative to standard doses of the ARBs used in comparative studies; results consistent with the high degree of blockade of the angiotensin II type 1 receptor for olmesartan. Taken together, there might be differences between ARBs regarding their blood pressure lowering efficacy, and these results may provide further support of the benefits of olmesartan therapy since choice of an effective agent is crucial in antihypertensive therapy.

Introduction

Current guidelines issued by the European Society of Hypertension (ESH) and European Society of Cardiology emphasise the importance of managing hypertension in order to reduce the substantial morbidity and mortality associated with cardiovascular events.[1] When initiating therapy in hypertensive patients, the guidelines recommend monotherapy, or combination therapy using low doses of each agent.[1]

Two classes of agents that are well suited to combination therapy are the angiotensin-converting enzyme inhibitors (ACE-I) and the angiotensin II receptor blockers (ARB). This is related to their favourable tolerability profile, which allows these agents to be used in combination with other agents without increasing the incidence of adverse events.[2] Treatment guidelines provide clear recommendations on the patient types and conditions for which treatment with ACE-Is and ARBs is suited.[1] Although ACE-Is and ARBs are well tolerated, certain undesirable effects, notably cough and angioedoema, are associated with the use of ACE-Is. Indeed, the incidence of each of these events was significantly higher with ramipril compared with telmisartan in the recent ONTARGET study.[3] Furthermore, the ONTARGET study specifically preselected ACE-I-tolerant patients by assigning ACE-I intolerant patients to the parallel TRANSCEND study.[4] The lower incidence of cough with ARBs may therefore explain the higher levels of persistence seen with ARB therapy relative to ACE-Is.[5]

The efficacy and tolerability of ARBs, as well as other ancillary benefits, have led to their rapid uptake and widespread use. Results from clinical studies have demonstrated the efficacy of ARBs as antihypertensive agents, and large-scale clinical investigations have shown that their efficacy is paralleled by reductions in the risk of cardiovascular and renal events such as stroke, ischaemic heart disease and diabetic nephropathy.[6-11] The link between lower blood pressure (BP) and reduction in cardiovascular risk is well established. Moreover, this causal link is so strong that even a reduction in systolic BP (SBP) of as little as 2 mmHg can reduce the risk of death from stroke by 10% and of death from vascular disease by 7% in patients aged 40 to 69 years.[12] This highlights the importance of antihypertensive efficacy, and since several ARBs are currently available it raises the question of whether differences in efficacy exist among the members of this class.

Numerous studies have been conducted that have assessed the antihypertensive efficacy of ARBs. Although some ARBs have been directly compared in head-to-head trials, no single study has directly assessed the efficacy of all seven of

 10.1177/1470320309342735

the available ARBs. Two recent reviews, which looked at the potential differences among the ARBs based on office BP, did not demonstrate significant differences.[13,14] However, a review which was performed with the aim of analysing the antihypertensive activity of ARBs based upon ambulatory blood pressure monitoring (ABPM) and the factors that affect this has been published.[15] This emphasises the dose-dependence of not only the efficacy but also duration of action among the ARBs.

Compared with BP measurements made in the clinic or office, ABPM reduces measurement technique error, avoids 'white coat' hypertension, provides temporal information about daily BP fluctuations,[16] and has been shown to be a better predictor of cardiovascular mortality.[17] Since treatments like ARBs are dosed once daily, information about their antihypertensive efficacy over 24 hours is important in order to ensure that the antihypertensive effect is maintained throughout the dosing interval. In addition, ABPM measurements made during the night-time have been shown to more accurately predict cardiovascular events than measurements made over 24 hours. This may relate to subjects' general lack of physical activities during the night-time, which means that BP measurements made during this period are more reflective of the state of the vascular tree than those made at other times. Beyond these clinical benefits, ABPM is also useful because it allows the efficacy of different antihypertensive agents to be assessed.

An independent systematic review looked at published, peer-reviewed studies that had measured BP using ABPM. Meta-regression analysis was used to calculate the relationship between initial BP values and BP reductions, and analysis of variance to analyse the influence of drug and dosage on the size of clinic BP measurements and ABPM measurements made over 24 hours, daytime, night-time and the last 4–6 hours of the dosing interval. It was shown that there are substantial differences between the degree of BP reduction achieved with the different ARBs, and that this difference is significant when assessing clinic diastolic BP (DBP) and 24-hour DBP and SBP.[15] Comparing individual members of the ARB family with each other and identifying the agent with the greatest antihypertensive efficacy was beyond the scope of this review. However, from the data presented it appears that the newest member of the ARB class, olmesartan medoxomil, was consistently associated with a high level of antihypertensive efficacy, both in terms of BP reductions assessed using standard clinic measurements and using ABPM measurements (figure 1).

Another recent review, based upon a pharmacological approach, appears to support this observation.[18] Randomised, placebo-controlled studies with comparable designs and dose ranges were used to extract dose-response data for several ARBs which were then fitted to a simplified E_{max} model. The E_{max} model was based on a calculation of expected maximal antihypertensive efficacy by using placebo-subtracted mean BP reductions fitted for DBP and SBP. The BP-lowering efficacy of olmesartan (defined as maximal effect) was found to be larger than that seen with irbesartan, valsartan and losartan, and larger than candesartan for DBP reductions.

Such findings raise the possibility that olmesartan might possess a greater degree of antihypertensive

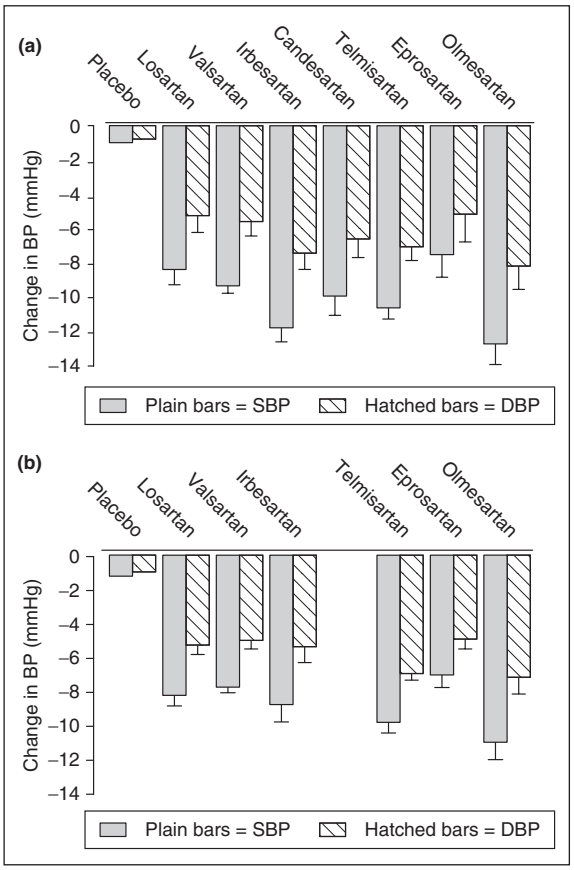

Figure 1
Mean changes in systolic and diastolic blood pressure (SBP; DBP) assessed by ambulatory blood pressure monitoring over (**a**) 24 hours (**b**) the last four hours of the dosing interval. Values are adjusted by initial dose, age, number of patients, clinic blood pressure. Error bars denote standard error. Figure reproduced with permission adapted from Fabia *et al.*[15]

activity than other ARBs at standard doses. The aim of the present review is to assess available data relating to the efficacy and tolerability of olmesartan in relation to other ARBs.

Olmesartan versus other ARBs

The most robust data relating to the comparative effects of ARBs come from head-to-head studies in which the efficacy and/or safety endpoints have been prospectively defined.

BP reduction – monotherapy

Several head-to-head studies have been performed in which the antihypertensive efficacy of olmesartan has been compared with that of other ARBs.[19-25] The majority of these studies involved hypertensive patients without other significant cardiovascular disease. Two studies have been performed, however, in hypertensive patients with mild-to-moderate renal impairment,[24] and with early-stage type 2 diabetes.[25] It should be noted that the majority of the published studies was supported by the respective manufacturers.

The designs of the double-blind head-to-head studies are summarised in table 1. Most studies assessed the standard dose of olmesartan (20 mg). However, one study was initiated with the lower dose (10 mg)[20] and one with a forced dose-titration step, so that the effects of the higher (40 mg) dose could be assessed.[23] The majority of the studies had primary efficacy variables related to reductions in DBP, assessed using cuff BP measurements or 24-hour ABPM.

All the studies utilised parallel-group designs with a placebo run-in phase, with the exception of the study by Nakayama *et al.*,[25] which used ABPM and a crossover design in which all patients received valsartan 80 mg prior to taking study medication.

Reductions in DBP after 8 or 12 weeks of treatment are shown for the double-blind head-to-head studies in figure 2a. The results of the study starting with low-dose olmesartan (10 mg) demonstrated significantly greater reductions in

Table 1
Head-to-head double-blind studies comparing the antihypertensive efficacy of olmesartan with other angiotensin receptor blockers when administered as monotherapy

Study	Duration	Study population	Mean baseline BP (SBP/DBP mmHg)	Daily dose and comparator	Primary outcome variable
Oparil *et al.*[19]	8 wks	Hypertensive patients (n=588)	157/104	Olmesartan 20 mg; losartan 50 mg; valsartan 80 mg; irbesartan 150 mg	Cuff DBP at wk 8
Stumpe and Ludwig[20]	24 wks	Hypertensive patients (n=316)	DBP: 102 mmHg	Olmesartan 10 mg; losartan 50 mg; dose doubled at week 4 in non-responders	Cuff DBP at wk 12
Brunner *et al.*[21]	8 wks	Hypertensive patients (n=643)	146/92*	Olmesartan 20 mg; candesartan 8 mg	DBP assessed by ABPM at wks 1, 2 and 8
Liau *et al.*[22]	12 wks	Chinese hypertensive patients (n=126)	149/103	Olmesartan 20 mg; losartan 50 mg	Cuff BP at wk 12
Giles *et al.*[23]	12 wks	Hypertensive patients (n=696)	155/103	Forced titration study: olmesartan 20 mg to 40 mg; valsartan 80 mg to 320 mg; losartan 50 mg to 100 mg; placebo	Cuff DBP at wk 8
Agabiti-Rosei[24]	52 wks	Hypertensive patients with renal impairment (n=393)	157/97	Olmesartan 20 mg; losartan 50 mg (both in combination with furosemide 20 or 40 mg)	Cuff DBP at wk 12
Nakayama *et al.*[25]	16 wks†	Japanese hypertensive patients with early-stage type-2 diabetes (n=20)	134/76* (with valsartan therapy)	Olmesartan 20 mg; telmisartan 40 mg	Not stated

Key: †Crossover study (each study period: 8 wks); *assessed using 24-hour ABPM. ABPM = ambulatory blood pressure monitoring; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

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DBP than losartan after 12 weeks' treatment.[20] Olmesartan 20 mg was shown to provide significantly greater DBP reductions than losartan 50 mg, valsartan 80 mg, irbesartan 150 mg and candesartan 8 mg after 8 weeks' treatment.[19,21] Olmesartan 20 mg was also associated with significantly greater DBP reductions than losartan 50 mg after 12 weeks' treatment in hypertensive patients with and without renal impairment.[22,24] Results from the up-titration study showed that,

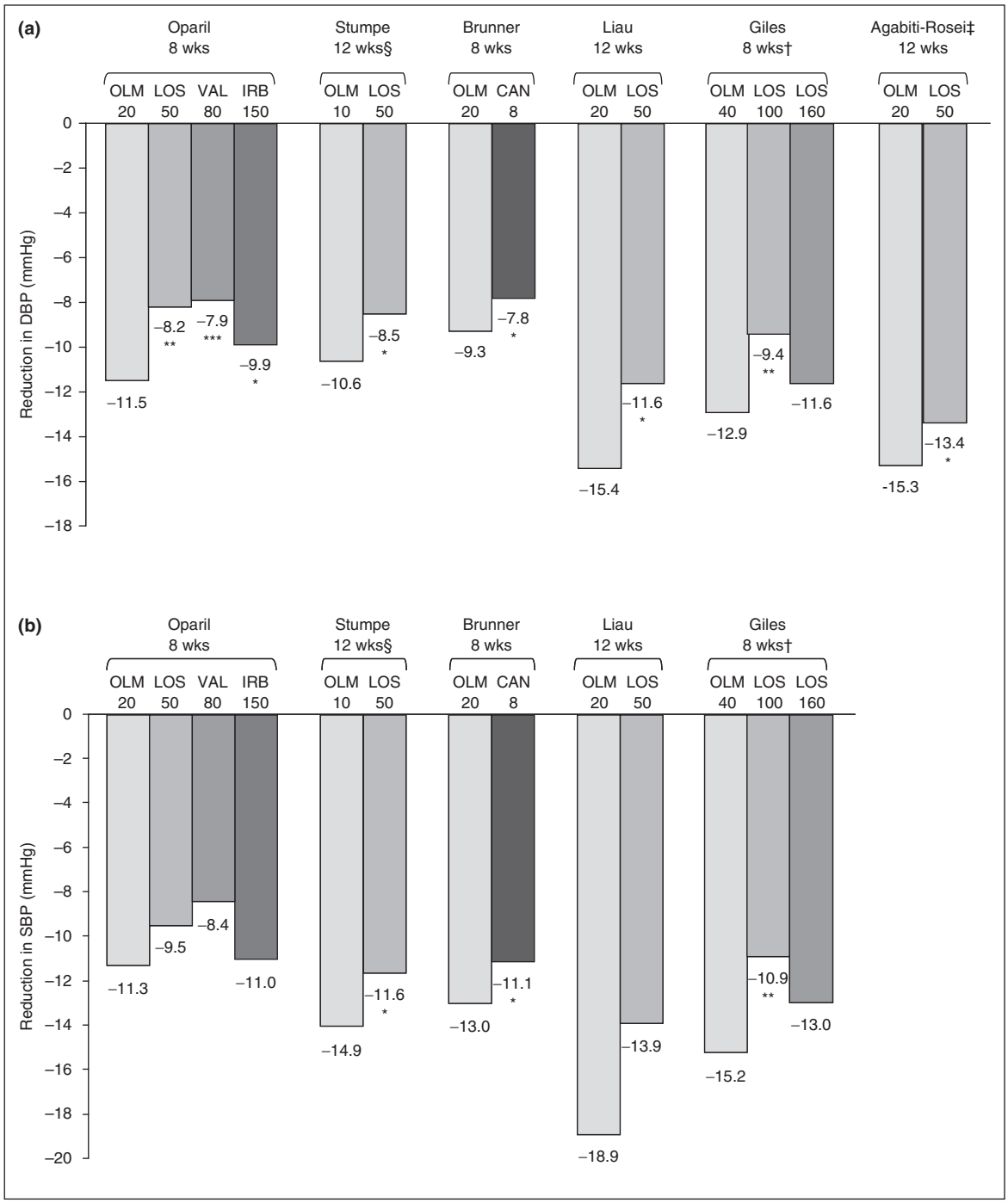

Figure 2
Change in (**a**) diastolic blood pressure (DBP) and (**b**) systolic blood pressure (SBP) after 8 or 12 weeks' treatment with olmesartan and other angiotensin receptor antagonists in head-to-head double-blind comparative studies. All doses are mg/day. All values were obtained with cuff measurements, with the exception of the study by Brunner *et al.*,[21] where the data relate to daytime ambulatory blood pressure monitoring. *p<0.05, **p<0.001, ***p<0.0001 *vs.* olmesartan. †Doses were up-titrated from half the amount shown after the first 4 weeks. ‡Results obtained in patients with renal impairment (no corresponding SBP data given). §Doses were doubled at 4 weeks in non-responders. CAN = candesartan; IRB = irbesartan; LOS = losartan; OLM = olmesartan; VAL = valsartan (Oparil *et al.*[19]; Stumpe and Ludwig[20]; Brunner *et al.*[21]; Liau *et al.*[22]; Giles *et al.*[23]; Agabiti-Rosei[24]).

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after 8 weeks of treatment, olmesartan 20 mg followed by 40 mg also provided significantly greater DBP reductions than losartan 50 mg followed by 100 mg, and was associated with a numerically greater DBP reduction than valsartan 80 mg followed by 160 mg.[23]

Similar reductions relative to comparator ARBs were also observed in SBP (figure 2b). The results from these studies demonstrated that olmesartan started at a dose of 10 mg provided significantly greater SBP-lowering efficacy than losartan started at 50 mg, after 12 weeks' treatment.[20] A titration of olmesartan 20 mg followed by 40 mg provided a greater SBP reduction than losartan 50 mg followed by 100 mg after 8 weeks.[23] Furthermore, olmesartan 20 mg provided significantly greater SBP reduction than candesartan 8 mg after 8 weeks.[21]

In addition to the double-blind studies discussed above, a small open-label study has also been performed which compared the effects of a standard maintenance dose of olmesartan (20 mg) with double the standard dose of valsartan (160 mg) in hypertensive patients (mean baseline BP 146/91 mmHg).[26] The results demonstrate that the higher dose of valsartan was associated with significantly greater reductions in certain parameters (e.g. DBP after 8 weeks, valsartan: 78.5 mmHg; olmesartan 79.6 mmHg; $p<0.05$), while for other BP assessments, there was no significant difference between treatments (e.g. SBP after 8 weeks, valsartan: 130.7 mmHg; olmesartan 131.4 mmHg). However, since no prespecified endpoints were stated, it is assumed that all analyses were exploratory. Further studies are therefore required to confirm these findings, and to determine if valsartan at this dose is associated with a greater risk of adverse events, relative to olmesartan 20 mg.

BP reduction – combination therapy

The efficacy of olmesartan combined with the thiazide diuretic hydrochlorothiazide (HCTZ) has also been compared with that of another ARB/HCTZ combination. In a multicentre, randomised, double-blind study in 629 patients with moderate-to-severe hypertension (mean BP 170/105 mmHg), the effects of 12 weeks' olmesartan 20 mg/HCTZ 12.5 mg were compared with losartan 50 mg/HCTZ 12.5 mg.[27] Although the difference between treatments in DBP reduction did not reach significance for the intent-to-treat analysis, an analysis of the per protocol set showed that olmesartan/HCTZ therapy was associated with significantly greater DBP reductions after 12 weeks (18.2 *vs.* 16.7 mmHg, $p<0.05$). The results also showed that olmesartan-based combination therapy resulted in a significantly greater reduction in SBP than losartan-based therapy after 12 weeks' treatment (29.3 *vs.* 24.9 mmHg, $p<0.001$).

Relatively few direct comparisons of the efficacy of different ARB/HCTZ combinations have been carried out. However, an analysis of factorial-design studies conducted with ARB/HCTZ combinations was undertaken with the aim of obtaining an insight into the relative efficacy of different ARBs, as monotherapy and in combination with HCTZ.[28] The results of this analysis demonstrated that all the ARBs in the analysis (olmesartan, irbesartan, telmisartan and valsartan), when used at the highest licensed doses as part of combination therapy with HCTZ, produced significantly greater reductions in SBP and DBP than monotherapy. The largest BP reductions were observed with the olmesartan 40 mg/HCTZ 25 mg combination (SBP 26.8 mmHg; DBP 21.9 mmHg). One study however, has observed that valsartan/HCTZ produced a higher BP reduction than olmesartan/HCTZ.[29]

BP goal achievement

BP goal achievement is an important factor in the selection of a hypertension treatment regimen. This is because BP has been repeatedly shown to be strongly and positively correlated to vascular and overall mortality, and meta-analysis of data from 61 prospective studies has shown that this is true from a BP threshold of 115/75 mmHg upwards.[12] In addition, BP goal achievement is directly relevant to physicians' daily practice since it can be used in the planning, monitoring and modification of a treatment regimen.

Current guidelines recommend that all hypertensive patients should have BP reduced to < 140/90 mmHg, and to < 130/80 mmHg in patients with diabetes and those at increased cardiovascular risk,[1] although the use of lower targets in such patients requires validation in randomised controlled trials. Since improved BP control has important cardiovascular benefits, it is therefore of interest to assess the efficacy of ARBs from the perspective of the proportion of patients who achieve BP goals.

In a retrospective analysis, using data from a multicentre, randomised, double-blind study,[19] the proportion of patients achieving the < 140/90 mmHg goal BP was compared for patients taking olmesartan 20 mg, losartan 50 mg, valsartan 80 mg or irbesartan 150 mg for 8 weeks. The

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results demonstrated that olmesartan 20 mg allowed a significantly (p<0.01) greater proportion of patients to achieve the < 140/90 mmHg threshold than losartan 50 mg or valsartan 80 mg (32.4% *vs.* 16.1% and 14.5%, respectively). Olmesartan 20 mg was also associated with a numerical advantage over irbesartan 150 mg (32.4% *vs.* 25.9%, respectively).[30]

Similar findings were also observed in a separate double-blind, randomised study in which goal rate achievement was a prespecified secondary endpoint. This study by Giles *et al.*[23] (discussed briefly above) utilised a forced titration design (table 1). The results showed that a significantly greater proportion of patients achieved the < 140/90 mmHg BP goal at week 8 with olmesartan therapy (39.7%), than with losartan (19.8%, p<0.001) or valsartan (29.0%, p<0.05).[23]

Olmesartan was also shown to be of greater benefit than valsartan and losartan in an analysis of 24-hour ABPM data obtained in the study by Oparil *et al.*[19] (table 1).[31] In this analysis, olmesartan 20 mg allowed a significantly greater proportion of patients to achieve the < 140/90 mmHg BP goal (52.9%) relative to losartan 50 mg (40.3%, p<0.05) or valsartan (35.4%, p<0.01). As with previous data, a numerical advantage was observed for olmesartan relative to irbesartan 150 mg (52.9% *vs.* 47.0%, respectively).[31]

A retrospective analysis has also been performed of goal rates achieved in the study by Brunner *et al.*[21] (table 1). Since this study utilised 24-hour ABPM, an analysis was performed of the proportion of patients achieving the 24-hour and daytime BP goals that were recommended by the European and Japanese guidelines. The results demonstrated that olmesartan 20 mg allowed a significantly greater proportion of hypertensive patients to achieve BP goal rates (using both guidelines' criteria and for both daytime and 24-hour assessments) than candesartan 8 mg.[32]

The approach of comparing the proportion of patients achieving BP goals has also been applied in a comparative study assessing the effects of olmesartan/HCTZ combination therapy. The study by Rump *et al.*[27] (discussed briefly above) demonstrated that olmesartan 20 mg/HCTZ 12.5 mg allowed a significantly greater proportion of patients to achieve the < 140/90 mmHg BP goal than losartan 50 mg/HCTZ 12.5 mg (43.2% *vs.* 32.1%, respectively; p<0.01).

BP-reducing efficacy over 24 hours

In order to provide maximum cardiovascular risk reduction with antihypertensive therapy, it is important that agents lower BP effectively over a 24-hour period. This is of particular importance for drugs such as ARBs that are taken once daily in the morning, since the final 4 hours of the inter-dosing period coincides with the 'early morning surge' – an increase in BP that occurs naturally as part of the circadian cycle. This early-morning increase is associated with an increase in the incidence of cardio-, and cerebrovascular (i.e. stroke) events and cardiac death.[33] The ability of antihypertensive drugs to act over the entire inter-dosing period is related to the pharmacokinetics of the various agents.[34] The current European guidelines stress that an antihypertensive drug should be chosen for which the BP-lowering effect lasts 24 hours.

As part of their independent systematic review, Fabia *et al.*[15] assessed the effects of various ARBs during the last 4 hours of the inter-dose period. It was shown that the choice and dose of ARB influenced the BP-lowering effects of therapy when assessed during the last 4 hours of the inter-dose period (figure 1b). Indeed, the differences between doses and agents were more pronounced during this time. The results (figure 1b) show that telmisartan and olmesartan each produced a good degree of BP reduction during this period, indicating that these agents provide good 24-hour BP control. For telmisartan, such an observation is not surprising considering its long elimination half-life (approximately 24 hours).[35] However, olmesartan appears to provide 24-hour BP control which is at least as effective as that produced by telmisartan and this may be supported by data from a direct clinical comparison study that used ABPM. After weeks' treatment, olmesartan therapy led to a significantly greater reduction in night-time SBP (119.5 *vs.* 124.9 mmHg, p=0.028) and DBP (69.6 *vs.* 72.9 mmHg, p=0.032) relative to telmisartan. Olmesartan also reduced 24-hour SBP (129.4 *vs.* 132.7 mmHg, p=0.031) and DBP (74.6 *vs.* 77.3 mmHg, p=0.009) to a greater extent than telmisartan, and was associated with significant improvements in the inflammatory markers high-sensitivity C-reactive protein and interleukin-6.[25] However, another direct comparison study found that after 8 weeks' treatment, telmisartan produced greater reductions than olmesartan in 24-hour (p<0.05) and night-time BP (p<0.01), although the significance of these findings is harder to judge since the study was reported as an abstract without details of study design or patient characteristics.[36] Thus, although olmesartan may have a shorter half-life (approximately

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15 hours)[37] than telmisartan, it can be seen that dose and possibly potency exert an important influence on efficacy.

Looking again at the direct comparison of olmesartan with losartan, valsartan and irbesartan (discussed above), during the final 4 hours of the inter-dose period olmesartan was associated with numerically greater reductions in DBP and SBP than these other agents (figure 3a).[31] These differences translated into significantly greater DBP and/or SBP reductions with olmesartan 20 mg during the final 4 hours of treatment than losartan 50 mg, valsartan 80 mg, and irbesartan 150 mg (figure 3b).[31] In addition, olmesartan produced numerically greater DBP and SBP reductions during this final period of the dosing interval than candesartan 8 mg,[32] though the dose again needs to be taken into consideration.

Speed of onset

As hypertension is associated with significant cardiovascular risk, it is important that BP is normalised as quickly as possible following initiation of therapy. This was clearly seen in the VALUE study in which greater BP reductions with the calcium channel blocker amlodipine during the early months of the study relative to valsartan were associated with a significant lower rate of cardiac morbidity and mortality.[38] Here, it is interesting to note the results of a study that directly compared the efficacy of olmesartan 20 mg with amlodipine 5 mg.[39] A retrospective analysis showed that after 2 weeks' treatment, the reductions in DBP and SBP with olmesartan (10.6 and 12.8 mmHg, respectively) were similar to those produced by amlodipine (10.0 and 11.9 mmHg, respectively), although a greater proportion of patients achieved the BP goal < 140/90 mmHg with olmesartan (26.7% *vs.* 19.8%).[13]

The design of certain comparative studies with olmesartan has allowed the speed of onset to be compared with other ARBs. In the comparative study by Brunner *et al.*[21] (table 1), BP assessments (using ABPM) were taken at weeks 1 and 2 following initiation of therapy with olmesartan or candesartan. The results show that olmesartan 20 mg was associated with a significantly greater reduction in daytime DBP (the primary variable) than candesartan 8 mg after 1 week (6.7 *vs.* 5.3 mmHg, respectively; p<0.01) and 2 weeks of therapy (8.4 *vs.* 6.0 mmHg, respectively; p<0.001). A significant benefit with olmesartan 20 mg versus candesartan 8 mg was also observed for daytime SBP reduction and for reductions in 24-hour DBP and SBP after 1 and 2 weeks' therapy.[21]

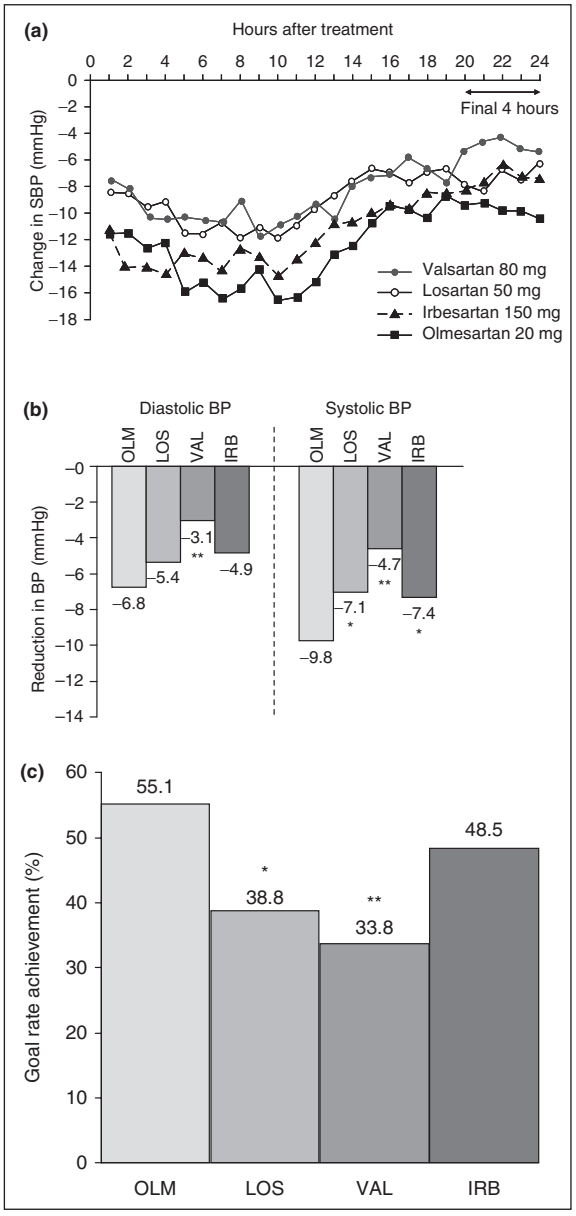

Figure 3
Twenty-four-hour blood pressure reducing effect with olmesartan 20 mg. (**a**) Change in systolic blood pressure (SBP) over the 24-hour period, assessed using ambulatory blood pressure monitoring after 8 weeks' therapy with olmesartan 20 mg (OLM), losartan 50 mg (LOS), valsartan 80 mg (VAL) or irbesartan 150 mg (IRB). Adapted from Smith *et al.*[31] (**b**) Change in diastolic and systolic blood pressure (BP) during the last 4 hours of the 24-hour dosing period.[31] (**c**) Proportion of patients achieving ambulatory blood pressure goal (< 140/90 mmHg) during the last 4 hours of the 24-hour dosing period.[31] *p<0.05, **p<0.001 *vs.* olmesartan.

In the study by Oparil *et al.*[19] (table 1), olmesartan 20 mg was also shown to have a faster speed of onset than the comparator ARBs. This was demonstrated by the results obtained after 2 weeks' therapy, when olmesartan 20 mg was associated with a significantly greater reduction in DBP (10.7 mmHg) relative to losartan 50 mg (7.6 mmHg, p<0.001), valsartan 80 mg (9.0 mmHg,

Journal of the Renin-Angiotensin-Aldosterone System
(Including other Peptidergic systems)

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p<0.05) and irbesartan 150 mg (9.0 mmHg, p<0.05). Olmesartan was also associated with significantly greater reductions in SBP after 2 weeks' therapy (13.0 mmHg) relative to losartan (8.9 mmHg, p<0.01), valsartan (9.2 mmHg, p<0.01) and irbesartan (10.8 mmHg, p<0.05).

The study discussed above,[27] which included analysis of BP reductions after 1, 2, 4 and 8 weeks of therapy, demonstrating the benefits of olmesartan therapy in terms of speed of onset, are also apparent when used as combination therapy with HCTZ. The results showed that a substantial proportion of the full BP reduction was achieved after just 1 week of olmesartan-based combination therapy: olmesartan 20 mg/HCTZ 12.5 mg led to a significantly greater reduction in DBP than losartan after 1 week of treatment (p<0.01), and in SBP after 1 and 2 weeks of treatment (p<0.001). Moreover, between-group differences significantly favoured olmesartan-based therapy at all time-points for SBP and at weeks 1, 4 and 8 for DBP.

Discussion

Quantifying the degree of benefit obtained with one ARB versus another is problematic since there are various factors that need to be considered when assessing the efficacy of antihypertensive therapy. These include BP-reducing efficacy, speed of onset, and degree of 24-hour BP control. In addition, there is controversy regarding which doses of ARBs are comparable.[40] However, the data reviewed here consistently show differences in the efficacy of olmesartan compared with certain other ARBs – notably losartan and valsartan. In this respect, these data support the observation made by Fabia *et al.*[15] that the antihypertensive effect achieved during ARB treatment depends upon the agent used but also on its dose.

The reviewed data relating to olmesartan raise the question of why this particular ARB should possess such a high degree of antihypertensive efficacy? Mechanistic studies have elucidated a number of differences among ARBs, which may help to explain the greater BP reductions observed with olmesartan relative to other ARBs. In one analysis, olmesartan 40 mg provided a greater reduction in plasma renin activity (a marker of the degree of blockade of the renin-angiotensin-aldosterone system [RAAS]) than valsartan at doses up to 320 mg and irbesartan 300 mg. Moreover, although there was a dose-dependent increase in the reduction of renin activity with olmesartan therapy, no such dose-dependency was observed with valsartan.[41] These results suggest that among those ARBs which produce insurmountable repression of the RAAS through tight binding to the angiotensin II type 1 (AT_1) receptor (olmesartan, valsartan and irbesartan), olmesartan provides a high degree of prolonged receptor binding.

The degree of blockade of the RAAS obtainable with olmesartan was also demonstrated in a double-blind, randomised, crossover study in which volunteers took olmesartan (20, 40 or 80 mg), the ACE-I lisinopril 20 mg, or olmesartan (20 or 40 mg) plus lisinopril 20 mg combination therapy.[42] The results showed that the degree of 24-hour blockade of the SBP response to exogenously administered angiotensin was greatest with the highest olmesartan dose, and similar to that observed with the 40 mg dose given as combination therapy (76% *vs.* 83%, p=0.3). These data further support the dose-response of olmesartan inhibition of the RAAS, and demonstrate that at high doses olmesartan achieves almost complete 24-hour blockade of BP response to exogenous angiotensin.[42] These findings with olmesartan contrast to findings from the same research group obtained with losartan and telmisartan. Results from similarly designed studies showed that neither agent was able to provide 24-hour blockade of the RAAS even at their maximum recommended doses (54% inhibition with losartan 200 mg and 57% inhibition with telmisartan 160 mg).[43]

In a study using a range of pharmacological binding assays, the binding affinity for the AT_1 receptor was assessed for olmesartan and telmisartan.[44] Although both agents were shown to bind strongly to the AT_1 receptor, olmesartan had a higher affinity for the receptor, with a dissociation half-life of 72 minutes, compared with 29 minutes for telmisartan. This difference in binding characteristics is related to structural differences between olmesartan and telmisartan, with olmesartan able to stabilise the tightly bound receptor-ARB complex.[44]

The interaction between olmesartan and the AT_1 receptor has also been assessed using molecular binding assays with a range of mutated AT_1 receptors. Results from one study demonstrated that the strength of the interaction between olmesartan and the AT_1 receptor is mediated not only by the biphenyltetrazole group (also contained in other ARBs), but also by the position of the hydroxyl and carboxyl groups found in olmesartan but not other ARBs (figure 4).[45]

It should be noted that although olmesartan monotherapy provides effective BP control, it does not enable all patients to achieve guideline-recommended BP targets. This is especially true

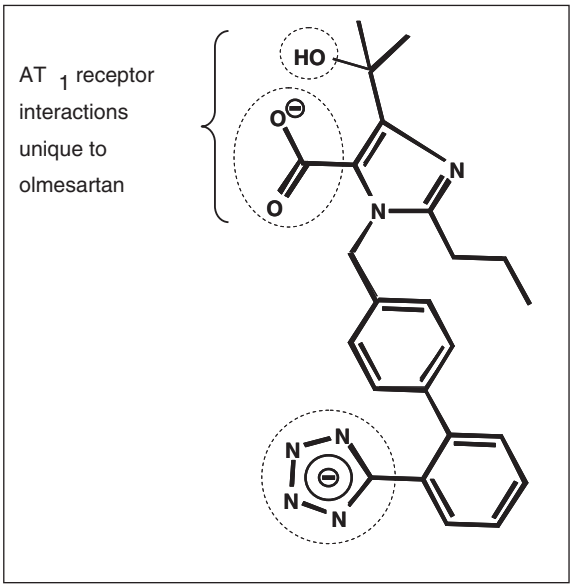

Figure 4
Structure of olmesartan showing which groups are important for binding the angiotensin II type 1 (AT_1) receptor.

for harder-to-treat patients, such as those with moderate-to-severe hypertension. However, when used in combination with other agents, such as HCTZ and amlodipine, treatment algorithms based upon olmesartan result in greater antihypertensive efficacy.[27,46] In a 24-week open-label forced titration study, 201 patients with stage 1 or 2 hypertension (seated DBP ≥90–≤109 mmHg, and seated SBP < 200 mmHg) initially received olmesartan (20 mg/day) for 4 weeks, after which the dosage was doubled for patients not achieving a BP target of ≤ 130/85 mmHg. From week 8, patients who had still not achieved this BP target also received HCTZ (12.5 mg/day) for 4 weeks, with a doubling of HCTZ dose for the subsequent 4 weeks for patients who did not achieve the target BP. At week 16, amlodipine (5 mg/day) was added, with dose doubling after another 4 weeks for patients with BP > 130/85 mmHg. At the end of the study (week 24), the proportion of patients who had achieved the primary study objective of SBP/DBP ≤ 130/85 mmHg was 87.7%, and the proportion who achieved the goal of ≤ 140/90 mmHg was 93.3%.[47] Further analysis of this study looked at patients according to their level of hypertension at baseline. In patients with stage 1 hypertension (SBP 140–159 mmHg, or DBP 90–99 mmHg; equivalent to ESH Grade 1, mild), the proportion who achieved the BP goals of SBP/DBP ≤ 130/85 mmHg and ≤ 140/90 mmHg at study end was 96.2% and 97.5%, respectively. For patients with stage 2 hypertension (SBP ≥ 160 mmHg, or DBP ≥ 100 mmHg; equivalent to ESH Grade 2/3, moderate-to-severe), the proportion who achieved these goals was 81.0% and 90.0%, respectively.[48] Thus, when treatment regimens are based upon an effective and well-tolerated ARB, the great majority of patients can achieve guideline-recommended BP goals. The implication of such findings is that the therapeutic tools required to treat hypertension are available and that hypertension control rates could be improved.

Conclusions

Meta-analysis of studies involving ARBs, looking at the effect upon ABPM, has shown that antihypertensive activity depends upon the agent used and its dose. Direct comparison studies indicate that olmesartan medoxomil provides a higher degree of antihypertensive efficacy than several other ARBs at the comparator doses, an observation which does not conflict with the meta-analysis of studies involving ARBs. These observations are of clinical relevance considering the generally poor level of BP control in most countries and the consistently high rates of cardiovascular events such as stroke and myocardial infarction.

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