

Critical evaluation of the efficacy and tolerability of azilsartan

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Abstract: Appropriate control of blood pressure (BP) in hypertensive patients still represents the major therapeutic goal in the treatment of hypertension. Despite the growing attention and wide range of antihypertensive agents available in the clinical scenario, the target of BP below the advised thresholds of 140/90 mmHg is, unfortunately, often unreachd. For this reason, the search for new antihypertensive agents is still ongoing. Azilsartan medoxomil, a new angiotensin receptor blocker that has been recently introduced in the clinical arena, represents the eighth angiotensin receptor blocker currently available for BP control. The aim of this paper is to describe the efficacy and safety profile of this new compound, reviewing available data obtained from both pre-clinical and clinical studies.

Keywords: azilsartan medoxomil, angiotensin receptor blocker, hypertension

Introduction

Chronically elevated blood pressure (BP) is a highly heterogeneous, complex disease and a major global health issue.¹ Hypertension affects approximately one quarter of the world's adult population, and is predicted to increase in prevalence alongside the urbanization of economically developing countries.^{2,3} Hypertension has been recognized by the World Health Organization as the leading cause of global mortality, accounting for 7.6 million deaths and 92 million disability-adjusted life-years worldwide.^{4,5} Such sinister statistics are reflected in cardiovascular data showing that two-thirds of all cerebrovascular disease cases and 50% of all ischemic heart disease cases are attributable to non-optimal BP.^{5,6}

Among the many antihypertensive agents, drugs that modulate the renin-angiotensin-aldosterone system (RAAS) are more commonly used because of their efficacy and their excellent tolerability profile. Specifically, those agents able to inhibit the action of angiotensin II by binding directly to the angiotensin type 1 (AT₁) receptor, such as angiotensin receptor blockers (ARBs), are the most tolerated.⁷ In addition, aside from their well-known renoprotective effects,^{8,9} some ARBs have shown efficacy in reducing mortality in patients with heart failure and post-myocardial infarction.¹⁰⁻¹²

For these reasons, the search for novel antihypertensive agents – a novel ARB in particular – is still ongoing. The aim of this review is to focus attention on a novel ARB recently introduced in the clinical arena: azilsartan medoxomil.

Why and how we need to target the RAAS system

The pathophysiology of essential hypertension is complex and, although genome-wide association studies have delineated multiple common variants associated

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with essential hypertension, no firm hypothesis has yet been established.¹³ Multiple signaling pathways regulating BP have previously been elicited through physiological experiments. Of these, the discovery and accurate characterization of the neurohumoral pathway of the RAAS has enabled the production of pharmacological agents that assist in reducing a patient's BP.¹⁴ Figure 1 recapitulates the RAAS. Briefly, the RAAS cascade converts angiotensinogen to angiotensin II through an intermediate substrate, angiotensin I. The rate-limiting step within the cascade requires renin, a hormone synthesized and released from juxtaglomerular cells within the kidney's afferent arterioles, to convert angiotensinogen to angiotensin I.¹⁴ Angiotensin I is then enzymatically converted into angiotensin II, a pleiotropic hormone able to target the angiotensin type 1 receptor (AT₁R), which is located throughout the vasculature of multiple organs.¹⁴ Angiotensin II causes systemic vasoconstriction, increased sympathetic output, increased arginine vasopressin production, and increased aldosterone release. Consequently, an increase in angiotensin II results in increased peripheral vascular resistance, fluid retention, and increased cardiac output, thus contributing to elevated BP.

The conversion of angiotensin I to angiotensin II is mediated by the angiotensin converting enzyme (ACE). Competitive inhibition of the ACE, a relatively non-specific enzyme, with ACE inhibitors can assist in reducing BP. Meta-analysis demonstrated a reduction in both systolic and diastolic pressures in patients with essential hypertension, with a mean reduction of 6–9 mmHg and a 4–5 mmHg, respec-

tively.¹⁵ Despite these advantages, some limitations exist relating to ACE inhibitors. On one hand, substrate accumulation of renin and angiotensin I may attenuate the desired blockade. On the other hand, concomitant tachykinin accumulation frequently incites side effects, including dry cough and angioedema, thus reducing the compliance of the patient with respect to its prescribed regimen, which in turn contributes to sub-optimal BP control. In addition, angiotensin II formation is not entirely dependent upon the action of the ACE, with formation occurring through alternative pathways.

To overcome the limitations of ACE inhibitors, the strategy to directly inhibit the binding of angiotensin II to the AT₁R through ARBs has been shown to provide an effective pharmacologic strategy for inhibiting the AT₁R and diminishing angiotensin II-derived effects, through both ACE-dependent and alternate pathways.¹⁴ Eight ARBs (losartan, valsartan, candesartan, irbesartan, olmesartan, telmisartan, eprosartan, and azilsartan) have been approved for the treatment of hypertension. Their main characteristics are summarized in Table 1. Clinically, ACE inhibitors and ARBs are prescribed interchangeably for the first-line treatment of hypertension.¹⁶

In addition to ACE inhibitors and ARBs, there is an increasing number of additional agents, which modulate the RAAS, to lower BP and prevent cardiovascular events, including aldosterone antagonists, renin inhibitors, and neutral endopeptidase inhibitors.^{17–19} As this specific review will focus on azilsartan medoxomil, we refer the reader to specifically focused articles.^{20–24}

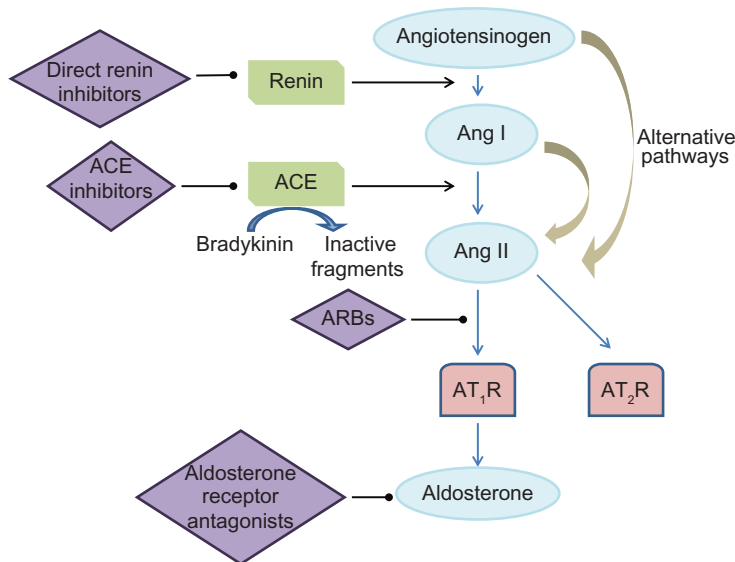


Figure 1 The renin-angiotensin-aldosterone system.

Table 1 Comparison of the eight currently available angiotensin-receptor blockers

Generic name	Brand name	Dose (mg)	Cost (28-tab pack)	Metabolism	Half-life (h)	Primary function	Dosing	AT ₁ /AT ₂ receptor selectivity	Pressor inhibition at 24 hours
Azilsartan	Edarbi (Takeda)	40 80	£54.19 £54.19	Hepatic: mainly CYP2C9 (also CYP2B6 and CYP2C8); no CYP inhibition; inhibits p-glycoprotein	11	Hypertension	80 mg once daily for hypertension	>10,000-fold	32 mg 60%
Candesartan	Atacand	4 32	£9.78 £16.13	Ester hydrolysis within gastrointestinal wall	9	Hypertension, heart failure	8–32 mg once daily over 4-(for hypertension) or 2-(for heart failure) week intervals	>10,000-fold	8 mg 50%
Eprosartan	Teveten	300 600	£7.31 £14.31	Not metabolized and eliminated unchanged	20	Hypertension	400–800 mg once daily, increase after 2–3 weeks	1000-fold	350 mg 30%
Irbesartan	Aprovel (Bristol-Myers Squibb) (Sanofi-Aventis)	75 300	£9.69 £15.93	Hepatic: glucuronidation and oxidation by CYP2C9	11–15	Hypertension, diabetic nephropathy	150–300 mg once daily for hypertension and renal disease in hypertensive type 2 diabetes mellitus	>8500-fold	150 mg 40% 300 mg 60%
Losartan	Losartan Potassium, Cozaar	25 100	£1.45 £16.18 £1.47 £16.18	Hepatic: CYP2C9 and CYP3A4	2	Hypertension, diabetic nephropathy	25–100 mg once daily over several weeks for hypertension and diabetic nephropathy; 12.5–150 mg once daily over weekly intervals for chronic heart failure	1000-fold	100 mg 25%–40%
Olmesartan	Olmetec	20 40	£12.95 £17.50	Ester hydrolysis within gastrointestinal wall	13	Hypertension	10–40 mg once daily for hypertension	>12,500-fold	20 mg 61% 40 mg 74%
Telmisartan	Micardis (Boehringer Ingelheim)	40 80	£8.00 £17.00	Minimally conjugated, no CYP450 activation	24	Hypertension	40–80 mg once daily after 4 weeks for hypertension; 80 mg once daily to prevent cardiovascular events	>3000-fold	80 mg 40%
Valsartan	Diovan (Novartis)	40 160	£13.97 £18.41	Minimal metabolism (CYP2C9) and eliminated largely unchanged	6	Hypertension, heart failure, myocardial infarction	80–320 mg once daily over 4 weeks for hypertension; 40 mg twice daily, up to 160 mg twice daily, over 2-week intervals for heart failure; 20 mg twice daily, up to 160 mg twice daily, over 2-week intervals for myocardial infarction	20,000-fold	80 mg 30%

Notes: Data drawn from Zalken K, Cheng JW. Azilsartan medoxomil: a new angiotensin receptor blocker. *Clin Ther.* 2011;33(11):1577–1589.²³

Azilsartan medoxomil: pharmacodynamic and pharmacokinetic profile

Following the introduction in the clinical arena of azilsartan medoxomil in early 2011, eight ARBs are now recognized in Europe and by the United States Food and Drug Administration for the treatment of hypertension.

Mechanism of action

Azilsartan medoxomil (previously named TAK-491), an orally administered prodrug, has recently become the eighth ARB to achieve Food and Drug Administration approval for the treatment of hypertension. Following oral administration, azilsartan medoxomil is hydrolyzed into azilsartan (TAK-536) in both the gastrointestinal tract and plasma.²⁵ Azilsartan, a selective AT₁R antagonist, prevents angiotensin II binding, specifically within vascular, smooth muscles and the adrenal gland, and produces vasodilation and attenuated aldosterone effects.²⁶ Azilsartan and candesartan are structurally very similar, which may explain their similar AT₁R affinity. Indeed, azilsartan is a highly selective antagonist for AT₁R, exhibiting a >10,000-fold higher affinity for the AT₁ receptor than for the AT₂ receptor.²⁴ This effect is significant; however, valsartan, olmesartan, and candesartan all demonstrate equivalent or greater AT₁ selectivity (see Table 1). The manufacturer suggests that the antihypertensive effect of azilsartan is not disrupted by renin secretion fluctuations, primarily due to its AT₁R inhibition.²⁶

Pharmacokinetics

Azilsartan achieves its peak plasma concentration 1.5 to 3 hours following oral administration, with bioavailability (approximately 58%) unaffected by co-administration with food. Azilsartan demonstrates a half-life of approximately 11 hours and achieves a steady-state concentration 5 days following consecutive oral administration.^{25,26} Reports from healthy subjects suggest that the volume of distribution is approximately 30 L, with >99% circulating attached to plasma proteins.^{25,26}

Azilsartan metabolism occurs mainly via the hepatic cytochrome P450, with no CYP system induction or inhibition properties. Azilsartan does, however, inhibit p-glycoprotein, an efflux transporter. A major inactive metabolite (MI) forms through CYP2C9, while an additional minor, inactive metabolite (MII) is generated through CYP2B6 and CYP2C8. The MII has approximately 50% systemic exposure, and MI has <1% systemic exposure.^{21,23}

Azilsartan's inactive metabolites (MI and MII) are excreted by the kidney at a rate of 2.3 mL/min. Animal studies

recording 14C-radiolabeled orally administered azilsartan recovered approximately 97% of the administered dose within 14 days. Specifically, 55% was traced to fecal excretion, and urine accounted for 42%, of which 15% was excreted as azilsartan.²³

Although no studies regarding the pharmacokinetics of azilsartan are currently available on the PubMed website, the manufacturer has made available data reporting a dose proportionality following single- and multiple-dosing of azilsartan in the dose range of 20–320 mg. According to single- and multiple-dose pharmacokinetic studies, AUC and C_{max} are both modestly affected by age, sex, race, renal impairment (mild, moderate, severe, or end-stage renal disease), and hepatic impairment, although the pharmacokinetic properties of azilsartan have not been studied in patients with severe hepatic impairment. Accordingly, no dosage adjustment of azilsartan is suggested on the basis of a patient's age, gender, race, or degree of renal/hepatic impairment.²⁵

As with current ARBs, it is inadvisable to prescribe azilsartan during the first, second, or third trimesters of pregnancy. Although human studies have not been conducted, evidence has been gleaned from low levels of azilsartan being detected in lactating rats' milk.

Drug interactions

No major drug interaction studies on azilsartan have been reported to date; however, the manufacturer reports no significant pharmacokinetic disruptions for numerous drugs combined with either 40-mg or 80-mg doses of azilsartan. Drug interactions with a daily 80-mg azilsartan dose were investigated in 36 healthy volunteers against concomitant administration of a P450 probe cocktail (including 30 mg of dextromethorphan, 500 mg of tolbutamide, 200 mg of caffeine, 4 mg of midazolam, and 60 mg of fexofenadine) or coadministration with an antacid or oral digoxin.²⁵ Similarly, an orally administered 40 mg dose of azilsartan was investigated in 36 healthy volunteers, with concomitant delivery of warfarin, glyburide, metformin pioglitazone, chlorthalidone, and amlodipine. No significant pharmacokinetic or international normalized ratio differences were in evidence.²⁵

In addition, 36 healthy volunteers undertook a drug interaction study investigating 40 mg doses of azilsartan with co-administration of either 200 mg of fluconazole (a CYP2C9 inhibitor) or 400 mg of ketoconazole (a CYP3A4/5 inhibitor). The study described how concomitant CYP2C9 inhibition causes reduced renal clearance and increased the AUC by approximately 40%.²⁵ Concomitant CYP3A4/5 inhibition reduced the AUC by approximately 20%.

This initial study requires further investigation to fully evaluate the true clinical significance of this interaction.

Although no evidence specifically evaluating azilsartan with nonsteroidal anti-inflammatory agents or cyclooxygenase-2 inhibitors exists, Takeda issued a warning about their combined usage with azilsartan.²⁶ This concern stems from knowledge regarding non-steroidal anti-inflammatory agents and cyclooxygenase-2 inhibitors contributing to acute pre-renal failure through prostaglandins inhibition and a reduced glomerular filtration rate.

Preclinical trials

Preclinical studies have demonstrated that azilsartan is superior to alternative ARBs (ie, valsartan and olmesartan) in lowering 24-hour BP. Current evidence suggests that this response is due to its property of high affinity and slow dissociation to AT₁R. This characteristic attenuates angiotensin II-derived effects more persistently than previous ARBs, leading to a prolonged functional effect.^{24,27}

Aside from blocking AT₁R, ARBs have been shown to provide additional benefits in cardiovascular protection, and preclinical studies have investigated the pleiotropic effects of this new compound, in addition to BP control. Many of the functional effects demonstrated by azilsartan are dependent on two key factors relating to the molecule: its high affinity and slow dissociation from AT₁R, and its inverse agonistic properties. These factors make azilsartan a unique option as a possible therapeutic agent in a wide range of angiotensin II-dependent cardiometabolic diseases. These include cardiac hypertrophy, unstable atherosclerotic plaque, cardiac fibrosis, insulin resistance, and renoprotection.

Several studies have investigated the anti-proliferative properties of azilsartan within vascular endothelial cells compared to traditional ARBs. Azilsartan has been shown to be superior in inhibiting the proliferation of rabbit aortic endothelial cells compared to valsartan. Interestingly, the anti-proliferative properties demonstrated by azilsartan can be established at plasma concentrations of 1 μmol/L, similar to human oral drug-dosing concentrations.²⁴ The mechanism attenuating proliferation is not entirely AT₁R-dependent, and it has been suggested that the pleiotropic effects are largely attributable to azilsartan's inverse agonist properties. These inverse agonist properties are clinically relevant, as they could enable a new generation of ARBs, including azilsartan, to prevent cardiac hypertrophy.

Investigators have also demonstrated that azilsartan can stabilize atherosclerotic plaque and reduce cardiac fibrosis formation following myocardial infarction in mice.

Specifically, it has been proposed that azilsartan suppresses the angiotensin II-mediated plasminogen activator inhibitor type-1, causing increased collagen deposition, thus stabilizing atherosclerotic plaque.²⁸

Hypertension is associated with insulin resistance, possibly due to excess angiotensin II. Candesartan has previously demonstrated improved insulin sensitivity in hypertensive patients.²⁹ Investigators have determined that azilsartan also demonstrates improved insulin sensitivity in rats, mice, and dogs in a superior fashion to olmesartan.^{30,31} Debates continue, however, regarding how ARBs generate this effect.

Finally, patients with metabolic syndrome have a poorer prognosis if there is documented proteinuria.^{32,33} Traditional ARBs have previously been shown to benefit the diabetic population, mainly offering a renoprotective effect related to a reduction of proteinuria.¹⁰ Azilsartan has been investigated in animal models with nephropathy, and Kusumoto et al showed azilsartan to be superior in reducing albuminuria in rats compared to olmesartan.³¹

The results from these pre-clinical trials are encouraging; however, validation and replication in humans is required. Azilsartan has demonstrated superior 24-hour control of systolic BP and offers a broad spectrum of possible clinical benefits associated with cardiometabolic disease, possibly making it superior to traditional ARBs.

Clinical trials

Several comparative studies have assessed the efficacy of azilsartan in the treatment of hypertension. In a double-blind, placebo-controlled trial of 1275 hypertensive patients, the efficacy of azilsartan was compared to placebo and olmesartan. The primary efficacy measure was the mean 24-hour ambulatory systolic pressure. The mean baseline systolic BP was 146 mmHg. Eighty-mg doses of azilsartan were more effective in reducing the mean 24-hour systolic pressure compared to 40 mg of olmesartan (a mean difference of 2.1 mmHg). In terms of tolerability, azilsartan was very well tolerated, as the incidence of the most commonly reported adverse events (ie, headache, dyslipidemia, and dizziness) were reported to be similar compared to the placebo and candesartan groups.³⁴

In another study of 1291 subjects, where the mean systolic BP before treatment was 145 mmHg, reduction was highest with 80 mg of azilsartan (−14.3 mmHg), compared to 320 mg of valsartan (−10.0 mmHg) and 40 mg of olmesartan (−11.7 mmHg).³⁵ BP control and response rates were higher than those observed in the valsartan arm, with an absolute rate of approximately 10% of patients reaching an acceptable BP

control according to actual guidelines. Again, the tolerability profile was not significantly different compared to 320 mg of valsartan, especially with regard to the number of adverse events, including those that were life-threatening or simply lead to a discontinuation of the drug.

The superiority of azilsartan was also confirmed when compared to other sartans. In a recently published study, 622 hypertensive Japanese patients with moderate hypertension were randomized for treatment with azilsartan (20–40 mg od) or candesartan (8–12 mg od). Azilsartan was more effective in reducing sitting systolic and diastolic BP at 16 weeks and ambulatory BP at 14 weeks, with a similar safety profile.²² The study concludes by stating that once-daily azilsartan use provides a more-potent, 24-hour antihypertensive effect than does candesartan, but with an equivalent safety threshold.

In summary, clinical trials of azilsartan have so far demonstrated promising results, and this new substance has the potential to become a very valuable drug in the treatment of hypertension.

Conclusion

Azilsartan is a very recently approved ARB that is now available in the clinical arena for the treatment of hypertension. Compared to the maximum doses of three other ARBs (valsartan, olmesartan, and candesartan), azilsartan appears to be more efficacious in reducing BP, with a similar safety and tolerability profile. Azilsartan's very high affinity and slow dissociation from AT₁R, together with its inverse agonistic properties, make it a very attractive candidate for further pushing its clinical effects beyond simple BP control, potentially counteracting cardiac hypertrophy, cardiac fibrosis, and insulin resistance, together with improved renoprotection and atherosclerotic plaque stabilization. However, unlike other ARBs, azilsartan is not backed up by clinical data supporting its ability to affect improvement in cardiovascular outcomes and is not approved for situations in which other ARBs may be used, such as diabetic nephropathy or heart failure.

Disclosure

The authors report no conflicts of interest in this work.

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