DRUG CORNER

Azilsartan: Novel Angiotensin Receptor Blocker

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Abstract

Objective: To describe the efficacy and safety profile of the new angiotensin receptor blocker (ARB), "Azilsartan Medoxomil", reviewing data available from both clinical and pre-clinical studies.

Material (Data Source): We completed a review of the English literature from PubMed using the keywords- azilsartan medoxomil, angiotensin receptor blockers (ARB), angiotensin converting enzyme inhibitors (ACEi) and hypertension.

Data Evaluation: Many clinical trials have been conducted comparing the efficacy of azilsartan with other ARB's and also with the ACEi ramipril. The trials have shown azilsartan to be more effective in reducing the mean 24-hour systolic blood pressure compared to its counterparts.

Conclusion: Azilsartan is a recently approved ARB and appears to be more efficacious in reducing blood pressure (BP) than the other ARBs with a similar safety and tolerability profile. Azilsartan's very high affinity to and slow dissociation from the angiotensin 1 receptor (AT_1R) along with its inverse agonistic properties make it a very good candidate for clinical effects beyond simple BP control, potentially counteracting cardiac hypertrophy, cardiac fibrosis and insulin resistance, together with improved reno-protection and atherosclerotic plaque stabilization.

Introduction

Inspite of the availability of numbers of drugs for hypertension, it still remains poorly controlled. There is always a search for potent and safer new anti-hypertensive drugs. Drugs that modulate the renin-angiotensin-aldosterone system (RAAS) are used because of their efficacy and excellent tolerability profile. Azilsartan was discovered through the efforts of scientists from Takeda, a Japanese pharmaceutical company, to find a new class of angiotensin receptor antagonists by modifying the tetrazole ring present in candesartan. The chemical structure of azilsartan is very similar to the structure of candesartan and differs only by replacement of candesartan's 5 member tetrazole ring with the oxo-oxadiazole ring of azilsartan (Figure 1). This modification makes azilsartan less acidic and more lipophilic than candesartan. More than 15 years after the clinical introduction of losartan, the US Food and drug administration (FDA) approved azilsartan medoxomil as the 8th ARB for the treatment of hypertension in 2011.[1] Azilsartan medoxomil has been currently approved for use in the United States, Japan and Europe.

Mechanism of Action

Angiotensin II receptor antagonists, also known as angiotensin receptor blockers (ARBs), are a group of pharmaceuticals that modulate the RAAS. By blocking the binding of angiotensin-II to its receptor (AT_1R), these agents inhibit the vasoconstriction effects of angiotensin-II and prevent the angiotensin-II-mediated release of aldosterone. Aldosterone promotes sodium and water retention. By inhibiting the production of aldosterone, ARBs indirectly inhibit fluid volume increases that result from the actions of aldosterone (Figure 2).

Azilsartan medoxomil (previously named TAK-491), an orally administered pro-drug, is hydrolyzed into azilsartan (TAK-536) in both the gastrointestinal tract and plasma.[2] Azilsartan and candesartan are structurally very similar, which may explain their similar AT_1R affinity. Azilsartan is a highly selective antagonist for AT_1R, exhibiting a >10,000 fold higher affinity for the AT_1R than for the AT_2R. Antihypertensive effect of Azilsartan is not disrupted by renin secretion fluctuations, primarily due to its AT_1R inhibition.

Pharmacokinetics

Azilsartan achieves its peak plasma concentration 1.5 to 3 hours

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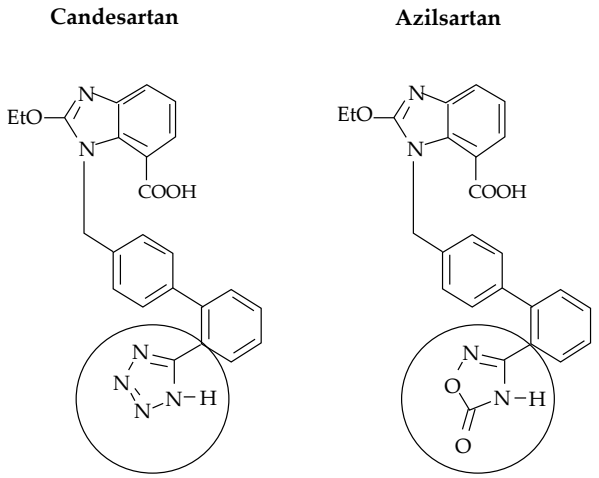

Fig. 1: Chemical structure of azilsartan compared to candesartan. The structures are identical except that azilsartan has a 5-oxo-1, 2, 4-oxadiazole ring in place of the tetrazole ring found in candesartan and other angiotensin receptor blockers

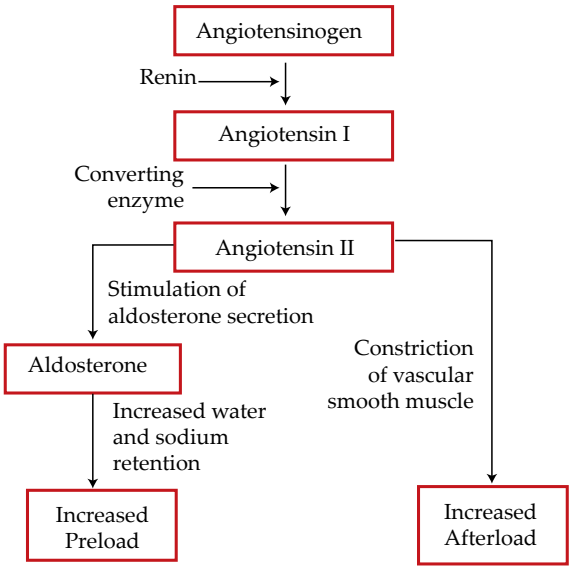

Fig. 2: The renin-angiotensin-aldosterone system (RAAS)

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. Its metabolism occurs mainly via the hepatic cytochrome P450, with no CYP system induction or inhibition properties.[3] Azilsartan's inactive metabolites (M-I and M-II) are excreted through the kidney at a rate of 2.3 mL/min. According to single and multiple-dose pharmacokinetic studies, area under the curve (AUC) and maximum concentration of the drug (Cmax) are both modestly affected by age, sex, race, renal impairment and hepatic impairment, although the pharmacokinetic properties of azilsartan have not been studied in patients with severe hepatic impairment. No dosage adjustment of azilsartan is suggested on the basis of a patient's age, gender, race, or degree of renal/hepatic impairment.[4]

Drug Interaction

No major drug interaction studies on azilsartan have been reported to date. Drug interactions with a daily 80 mg azilsartan doses 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) co-administration with an antacid or oral digoxin.[4] No significant pharmacokinetic or international normalized ratio differences were in evidence. Although no evidence specifically evaluating azilsartan with non-steroidal anti-inflammatory agents or cyclooxygenase-2 inhibitors exists, Takeda pharmaceuticals issued a warning about their combined usage with azilsartan.[5]

Preclinical Trials

Studies have demonstrated that azilsartan is superior to other ARBs in lowering 24-hour BP. This response is due to its property of high affinity to and slow dissociation from AT_1R. This characteristic attenuates the angiotensin II derived effects more persistently than previous ARB's leading to a prolonged functional effect.[6,7]

Aside from blocking AT_1R, preclinical studies have investigated the pleiotropic effects of this new compound. The functional effects demonstrated by Azilsartan are dependent on two key factors of the molecule: its high affinity to and slow dissociation from AT_1R and its inverse agonistic properties. These factors make azilsartan a possible therapeutic agent in angiotensin II-dependent cardio-metabolic diseases, cardiac hypertrophy, unstable atherosclerotic plaque, cardiac fibrosis, insulin resistance and reno-protection.

Several studies have investigated the anti-proliferative properties of Azilsartan within vascular endothelial cells compared to traditional ARBs and azilsartan has been shown to be superior in inhibiting the proliferation of rabbit aortic endothelial cells compared to valsartan.[6,7] The mechanism attenuating proliferation is not entirely AT_1R-dependent and pleiotropic effects are largely attributable to azilsartan's inverse agonist properties.

Azilsartan can stabilize atherosclerotic plaque and reduce cardiac fibrosis following myocardial infarction in mice. It also suppresses angiotensin II-mediated plasminogen activator inhibitor type-I, causing increased collagen deposition, thus stabilizing atherosclerotic plaque.[8]

Azilsartan also demonstrates

improved insulin sensitivity in rats, mice and dogs in a superior fashion compared to olmesartan. It has also been investigated in animal models with nephropathy and was shown to be superior in reducing albuminuria in rats compared to olmesartan.[9]

Clinical Trials

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. 80 mg doses of azilsartan were more effective in reducing the mean 24-hour systolic pressure compared to 40 mg of olmesartan. Moreover, azilsartan was very well tolerated.[10]

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 (-1.7 mmHg). The tolerability profile was not significantly different compared to 320 mg of valsartan.[11]

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 clinic systolic and diastolic BP at 16 weeks and ambulatory BP at 14 weeks, with a similar safety profile. 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.[12]

In another clinical trial, 884 patients were randomized to 20 mg azilsartan - medoxomil or 2.5 mg ramipril once daily for two weeks, then force-titrated to 40 or 80 mg azilsartan - medoxomil or 10 mg ramipril for 22 weeks. The study demonstrated that azilsartan - medoxomil at doses of 40 to 80 mg OD was significantly superior to 10 mg ramipril OD in reducing clinic and ambulatory systolic and diastolic BP and the safety profile was similar to ramipril with fewer discontinuations due to adverse events like dry cough.[13]

Conclusion

Azilsartan is a very recently approved ARB that will be available in the clinical arena 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. The functional properties of azilsartan mentioned above make it a very attractive candidate for clinical effects beyond simple BP control, potentially counteracting cardiac hypertrophy, cardiac fibrosis and insulin resistance, together with improved reno-protection and atherosclerotic plaque stabilization. However, unlike other ARB's, azilsartan is not backed up by clinical data supporting its ability to affect improvement in cardiovascular outcomes and is not approved for diabetic nephropathy or heart failure.

Azilsartan medoxomil is the only ARB that has been approved for use in a fixed dose combination with the diuretic chlorthalidone.[14] Time course studies of the ability of different ARB's to persistently block angiotensin II binding to AT receptors after drug washout have also indicated that Azilsartan dissociates from AT receptors more slowly than other ARB's including olmesartan, telmisartan and valsartan. It is more effective than other ARB's in persistently inhibiting angiotensin II-induced increases in BP, contraction of aortic vascular strips, cellular accumulation of inositol 1-phosphate, or activation of mitogen activated protein kinase (MAPK) in smooth muscle. Thus, this drug appears as a promising aspect for the management of hypertension and other related conditions in the future and with this review, we aim to enhance the awareness of this new ARB among physicians.

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