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Review Article

Azilsartan: the novel ARB with unique mechanism of action

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ABSTRACT

Hypertension is attributed to be one of the major risk factors in the pathophysiology of ischemic heart disease, stroke, heart failure and renal dysfunction. Angiotensin receptor blockers (ARBs) are one of the first line drugs recommended for clinical use in hypertension by JNC 8. Azilsartan is the recent addition to this family of ARBs and is perceived as one of the potent antihypertensive drugs today. Azilsartan was developed by replacing the tetrazole ring in candesartan with a 5 member oxo-oxadiazole ring. In India Azisartan was recently approved by DCGI in December 2016 for use in hypertension. In various randomized, double blind clinical studies Azilsartan was found to be to be superior in terms of clinical efficacy over other ARBs like Candesartan, Olmesartan and Valsartan and angiotensin converting enzyme inhibitor like Ramipril. In terms of safety profile Azilsartan appears to be equivalent to the currently available ARBs. Azilsartan due to its superior efficacy and comparative safety profile appear to be a new addition to the armamentarium in the treatment of hypertension.

Keywords: ARBs, Azilsartan, Angiotensin, Hypertension, Mas

INTRODUCTION

Hypertension is considered to be one of the leading risk factors involved in ischemic heart disease, stroke, heart failure and renal dysfunction.[1] Hypertension management should aim not only to control the blood pressure (BP) but also to reduce the overall cardiovascular (CV) and renal morbidity and mortality.[2] Angiotensin receptor blockers (ARBs) due to their beneficial effects on CV and renal morbidity and mortality has emerged as a valuable therapeutic option in the treatment of hypertension.

Losartan was the first ARB to be approved in US in 1995. Since then various ARBs were developed. Azilsartan is the latest addition to this armamentarium.[3]

AZILSARTAN: THE 8th ARB

Azilsartan medoxomil is a new addition to the ARB class of antihypertensive agents. Azilsartan is approved in USA, Europe and Japan in the treatment of hypertension. It is recently been approved by DCGI (09/12/2016) for use in hypertension.[4]

PHARMACOLOGY OF AZILSARTAN

Azilsartan was developed by replacing the tetrazole ring in candesartan with the 5 member oxo-oxadiazole ring. This modification has made Azilsartan less acidic and more lipophilic than candesartan. It has also rendered the molecule an unusual capacity to persistently block AT1 receptors for longer periods of time than most ARBs. Thus Azilsartan has an IC_{50} of 2.6 nM which is much lower than other potent ARBs Olmesartan (6.7 nM) and

Telmisartan (5.1 nM). This is the reason for higher potency of Azilsartan when compared to other agents.[5]

PHARMACODYNAMICS (PD)

Azilsartan medoxomil is a prodrug which upon rapid hydrolysis produces Azilsartan which is the active entity. Azilsartan acts by blocking the angiotensin II mediated activation of AT1 receptors. Azilsartan has also been hypothesized to act by stimulating the Mas receptors and thereby offering pleiotropic benefits. Studies suggest that

Azilsartan reduces vascular inflammation, cellular proliferation, fibrosis etc. through Ang (1-7) mediated Mas receptor activity. Azilsartan is also found to modify atherosclerotic lesions, insulin sensitivity and glucose metabolism. In a recent study by Carroll et al it was observed that the treatment with Azilsartan completely antagonized the elevation of BP induced by Angiotensin II, prevented cardiac hypertrophy and reduced renal damage.[6]

Figure 1 represents the mas pathway.
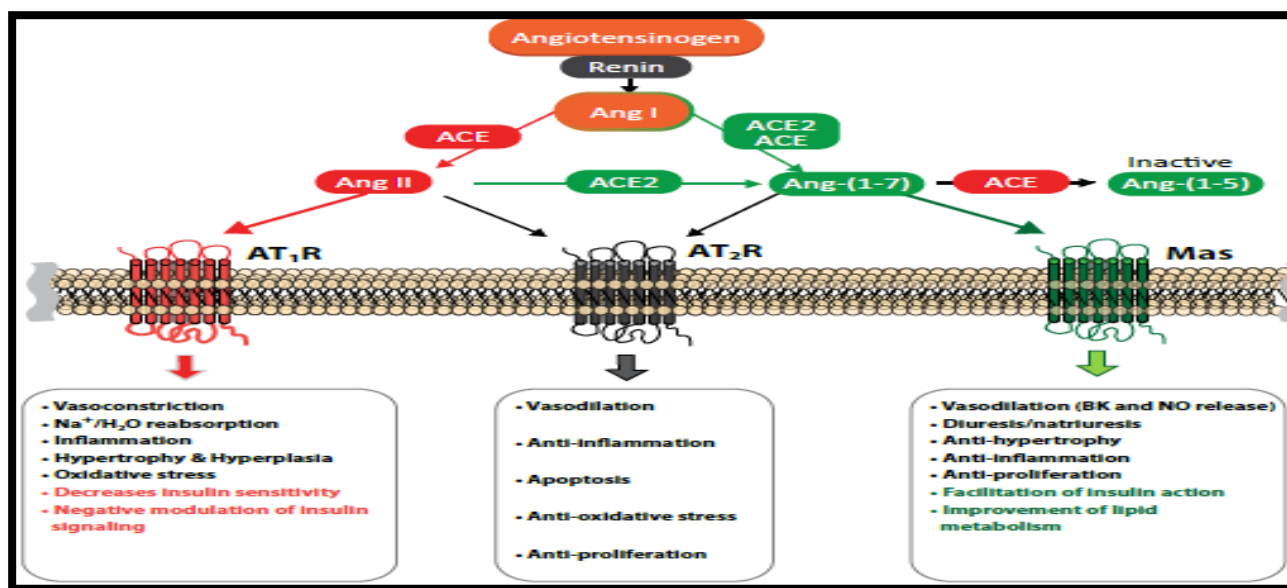
Figure 1: The Mas receptor pathway and the pleiotropic benefits.

The Renin Angiotensin Aldosterone System (RAAS) is the major pathway involved in the action of ARBs. In addition to the ACE/Ang II/AT1 receptor axis (classical), the RAAS possesses a counter-regulatory axis composed of ACE2, angiotensin-(1-7) [Ang-(1-7)] and the Mas receptor.[7] Recent investigations suggest new aspects in RAAS pathways with detailed exploration and consideration of ACE2/Ang-(1-7)/Mas pathway as an alternative protective pathway. Briefly each component of this alternate pathway is described below.

The ACE2 enzyme

ACE2 is a membrane-associated zinc metalloprotease and a homologue of the human ACE isoforms, which is highly expressed in several tissues such as human heart, kidney, lungs, and testes.[8] ACE2 is a catabolic enzyme and is essentially involved in the conversion of both Ang I and Ang II into smaller fragments. It has also been reported that ACE2 more efficiently hydrolyses Ang II than Ang I. ACE2 cleaves the C-terminal amino acid from Ang II and other peptides. The Ang-(1-7) peptide is mainly produced by ACE2 via action on Ang-II. ACE2 can also form Ang-(1-7) less efficiently by conversion of Ang I to Ang-(1-9) with subsequent Ang-(1-7) formation.

The mas receptor

Mas receptor was identified as a very hydrophobic protein, containing seven potential transmembrane domains were first cloned by Young and co-workers in 1986. Santos et al. established that Ang-(1-7) has limited interaction with AT1 or AT2 receptors and majorly it binds with Mas receptor.[9]

PHARMACOKINETICS (PK)

Table 1: Pharmacokinetic profile of Azilsartan.

PK Parameter	Finding
Bioavailability	60%
Effect of Food	No
T_{max}	1.5 - 3.0 hours
Steady state plasma concentration	5 d
$t_{1/2}$	11 hours
Elimination	Feces 55%, Urine 45%

Azilsartan is metabolized in the liver via cytochrome P450 (CYP) 2C9 producing two metabolites M-I and M-II which are inactive in nature. M-II is the major

metabolite formed whereas M-I is the minor metabolite. Key pharmacokinetic parameters are shown in Table 1.[10,11]

DRUG INTERACTIONS

As per the prescribing information of Azilsartan no clinically significant drug interactions have been observed in studies of Azilsartan medoxomil or Azilsartan given with amlodipine, antacids, chlorthalidone, digoxin, fluconazole, glyburide, ketoconazole, metformin, pioglitazone, and warfarin. Therefore, Azilsartan may be used concomitantly with this medications.[10]

EXPERIMENTAL EVIDENCES

Data from various preclinical studies evaluated the pleiotropic benefits of Azilsartan in treating various pathological conditions underlying hypertension. A possible role of Azilsartan in metabolic syndrome has been suggested in a study in obese rats demonstrating its insulin sensitizing effect.[12,13] Beneficial effects like vasculoprotection, left ventricular remodelling has also been demonstrated in various animal studies.[14-16] Azilsartan is also claimed to have renoprotective effects in terms of reducing proteinuria, albuminuria and glomerular injury.[17]

CLINICAL EVIDENCES

Various double-blind randomized clinical trials were conducted to evaluate the efficacy and safety of Azilsartan in comparison to other ARBs. In all the clinical trials Azilsartan showed to be more efficacious than the comparator in terms of clinical efficacy. Safety profile was also found to be comparable with the existing ARBs. Below is an outline of the clinical trials conducted with Azilsartan as monotherapy and combination therapy (Table 2 and 3).

Table 2: Azilsartan Medoxomil (AZL-M) as monotherapy.

Study (year)	Study type	Patients	Duration	Study arms	Primary end point	Result
Bakris et al., 2011[18]	Double-blind RCT	1275	6 weeks	AZL-M 20,40,80 mg or OLM 40 mg or Placebo	Change from baseline in 24 hr mean SBP and clinic BP	AZL-M 80 mg reduced the 24 hours SBP by 14.6 mmHg and clinic SBP by 17.6 mmHg after 6 weeks. (P=0.038)
White et al., 2011[19]	Double-blind RCT	1291	6 weeks	AZL-M 40, 80 mg or VAL 320 mg or OLM 40 mg or Placebo	Change from baseline in 24 hr mean SBP	AZL-M 80 mg (-14.6 mmHg) vs. OLM 40 mg (-12.0 mmHg) (p=0.009) and VAL (-10.2 mmHg) (p<0.001)
Sica et al., 2011[20]	Double-blind RCT	984	24 weeks	AZL-M 40, 80 mg or VAL 320 mg	Change from baseline in 24 hr mean SBP	AZL-M 40 mg (-14.9 mmHg) and 80 mg (-15.3 mmHg) vs. VAL 320 mg (-11.3 mmHg) (p<0.001 for both)
Bonner et al., 2012[21]	Double-blind RCT	884	24 weeks	AZL-M 20-80 mg or RAM 2.5-10 mg	Change from baseline in sitting trough SBP	AZL-M 40 mg (-20.6 mmHg) & AZL-M 80 mg(-21.2 mmHg) vs. RAM (-12.2 mmHg) (p<0.001)

Table 3: Azilsartan Medoxomil (AZL-M) as combination.

Study (year)	Study type	Patients	Duration	Study arms	Primary end point	Result
Sica et al., 2012[22]	Double-blind RCT	1714	8 weeks	AZL-M 20, 40, 80 mg and/or CLD 12.5, 25 mg	Change from baseline in trough SBP by ABPM	Clinic SBP: AZL-M/CLD 40/25 and 80/25 mg (-39.8±0.88mmHg) vs AZL-M 80 mg (-24.2±1.23mmHg) and CLD 25 mg (-27.1±1.25 mmHg)
Weber et al. 2014[23]	Double-blind RCT	566	6 weeks	AZL-M/AML 40/5, 80/5 mg or AML 5 mg + Placebo	Change from baseline in 24 hr SBP by ABPM	AZL-M/AML 40/5 mg (SBP reduction by -24.8 mmHg by 24 hr ABPM vs. -13.6 mmHg reduction in 24 hr SBP by Placebo + AML 5 mg

Dosage

The recommended dose in India is 80 mg taken once daily. A starting dose of 40 mg for patients who are treated with high doses of diuretics to be considered. It may be administered with or without food. No dose adjustment is required in mild, moderate and severe renal failure and mild to moderate liver failure. However in other regions like Europe and UK the recommended dose is 40 mg once daily which may be increased to 80 mg once daily in patients whose blood pressure is not adequately controlled

ADVERSE DRUG REACTIONS

In a clinical study conducted by Bakris G et al, with 1275 patients over 6 weeks the common adverse effects reported were headache (3.2%-5.6%), dyslipidemia (3.5%-5.6%) and dizziness (2.1%-2.8%).[18] In another clinical study by White W et al, with 1291 patients over 6 weeks the adverse effects reported were headache (4.2%-6.4%), dizziness (1.8%-3.6%), urinary tract infection (1.1%-3.2%).[19] In the study conducted by Bonner G et al.[21] with 884 patients over 24 weeks, nasopharyngitis (4.4%-6.5%), cough (1.0%-1.4%) and headache (3.4%-4.1%) were the commonly reported adverse effects. Since these reactions are reported voluntarily from a population of uncertain size it is difficult to estimate their frequency or to establish a causal relationship to drug exposure.

DISCUSSION

The current review aims to focus on the efficacy and safety parameters of the new ARB Azilsartan in the treatment of hypertension.

(a) Azilsartan as monotherapy (Table 2)

In the clinical study by Bakris G et al, over 6 weeks there was an additional 2 mmHg reduction with Azilsartan 80mg in the 24 hour mean SBP in comparison to Olmesartan 40 mg (P=0.038) and 2.7 mmHg reduction in the clinic SBP (P=0.043).[18] There was also an additional 1.5 mmHg reduction in clinic DBP with Azilsartan 80mg over the Olmesartan 40mg (P=0.044). In another clinical study White WB et al, over 6 weeks Azilsartan 80mg additionally reduced the clinic SBP by 3.5 mmHg and 5.4 mmHg in comparison to Olmesartan 40mg (P=0.008) and Valsartan 320 mg (P<0.001) respectively.[19] The results were found to be similar for 24 hours mean SBP reductions from the baseline. Azilsartan 40mg dose was found to be noninferior to the Olmesartan 40 mg dose. The responder rate which was defined as the proportion of the population achieving a reduction in clinic SBP <140 mmHg and/or a reduction of ≥20 mmHg was larger for the Azilsartan 80mg group (58%) in comparison to Olmesartan 40mg (49%) and Valsartan (49%) 320mg groups. Statistically significant reductions in SBP/DBP were also found with Azilsartan in comparison to Valsartan in the study by Sica D et al.[20] Azilsartan was compared in a clinical study by Bonner G et al, with Ramipril for 24 weeks.[21] Fall in clinic SBP and DBP were significantly lower for Azilsartan 40mg and 80mg doses in comparison to Ramipril 10mg (P<0.001). In terms of safety profile cough was reported in 1.4% subjects in Azilsartan 80 mg groups versus 8.2% in the Ramipril 10 mg group. However dizziness and hypotension reported with Azilsartan was higher than Ramipril which might be related to greater BP reduction achieved with Azilsartan.

(b) Azilsartan in combination therapy (Table 3)

In the study by Sica D et al Azilsartan with Chlorthalidone (40/80 mg+25 mg) produced significantly higher clinic SBP reduction (-39.8±0.88 mmHg) in comparison to monotherapies with Azilsartan 80mg (-24.2±1.23mmHg) and Chlorthalidone (-27.1±1.25mmHg).[22] Similarly in the study by Weber MA et al, Azilsartan with Amlodipine (40mg+5mg) caused significant reductions in 24 hours mean SBP by -24.8 mmHg versus -13.6mmHg as seen with Placebo+Amlodipine 5mg.[23]

With the clinical data available till date Azilsartan appears to be a potent and well tolerated molecule in effectively lowering the BP. The high potency of this molecule can be attributed to its unique oxo-oxadiazole ring. Azilsartan is the only ARB which is approved in combination with chlorthalidone by US-FDA. In India, Azilsartan as a combination therapy is yet to be approved by DCGI.

CONCLUSION

Azilsartan medoxomil is the 8th ARB to be approved for the treatment of hypertension. With the clinical evidences available Azilsartan appears to be more effective than the other ARBs like Olmesartan, Valsartan and ACE inhibitor Ramipril. Azilsartan is the only ARB to be approved in combination with chlorthalidone by US-FDA. Currently monotherapy of Azilsartan in the treatment of hypertension is approved by DCGI in December 2016.

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