Azilsartan: New Angiotensin Receptor Blocker For Hypertension
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Hypertension is a leading global risk related to morbidity and mortality(1). It is a major risk factor responsible for cardiac, neurological, renal and peripheral vascular disease. As far as Indian scenario is concerned we are not far behind. In fact as we know India will be the diabetes capital by 2020, it seems India will also be hypertension capital and so will the morbidity related to hypertension(2). ICMR conducted study in four cities in Tamil Nadu, Jharkhand, Maharashtra and in Chandigarh. This revealed high prevalence of diabetes and hypertension in these cities(2). Diabetes along with hypertension and dyslipidemia contribute to high prevalence of cardiovascular diseases. Almost one third of adult population is having hypertension and only about 12.5% of these are controlled on medication(3). With each increment in blood pressure of 20/10 the cardiovascular mortality doubles. This undermines the importance of controlling blood pressure(4).

The treatment of hypertension is

1. Non-medicinal or what we call lifestyle modification i.e.
   Smoking cessation
   Weight reduction
   Reduction of excessive alcohol intake
   Physical exercise
   Reduction of salt intake
   Decrease in fat intake

2. Pharmacological treatment of hypertension is
   A. Angiotensin Converting Enzyme Inhibitors like Ramipril and Lisinopril
   B. Angiotensin Receptor Blocker (ARBs) like Losartan, Telmisartan, Olmesartan
   C. Beta Blockers like Atenolol, Metoprolol, Bisoprolol, Carvedilol
   D. Calcium Channel Blockers like Amlodipine, Cilnidipine
   D. Diuretics like Hydrochlorothiazide, Chlorthalidone

Angiotensin receptor blockers are now practically the first line pharmacological treatment for hypertension without any comorbidity and also in hypertension with renal disease, cardiac failure and diabetic patients who cannot tolerate ACE inhibitors.
Newer antihypertensive drugs are introduced with time to find the better molecule to control hypertension especially resistant hypertension. Recently there is addition of one more molecule in angiotensin receptor blocker (ARB) group i.e. Azilsartan which has been shown to have a few advantages over previous.

Various ARB’s available are Losartan (1986), Valsartan, Irbesartan, Candisartan (1990), telmisartan (1991) and Olmesartan (1995, marketed in 2002). Azilsartan was approved by FDA and has now been approved by DCGI in 2016. It has been approved for treatment of hypertension so far.

The principal reason for developing newer ARB’s is to have a comparatively better antihypertensive medication. It should be a potent drug with fewer side effects and should have positive effect in comorbidities especially cardiovascular outcomes. Azilsartan medoximal is a prodrug which is converted to azilsartan which is the active molecule. The active substance is less acidic and more lipophilic. Main advantages are that azilsartan is highly selective AT1 receptor and has very slow dissociation from the AT1 receptor. It has 10,000 times more affinity for AT1 receptor. It has also inverse agonistic effect. Assessment of inhibitory concentration 50 shows Azilsartan is low as compared to valsartan and olmesartan or else we can say Azilsartan is more potent than other ARBs(5). AT1 blocking action is sustained and consistent(5).

The pharmacokinetics shows it has high bioavailability and higher plasma concentrations are achieved at comparative doses. The following diagram (Fig. 1) shows the effects of Azilsartan and other ARB’s on Renin Angiotensin Aldosterone system (RAAS)(6).

RAAS is potent regulator of Blood Pressure and plays a significant role in the pathogenesis of cardiovascular diseases(7). Recently there has been evidence of angiotensin peptides other than angiotensin I and angiotensin II. Other members of system are Angiotensin III (Ang (2-8), Angiotensin IV (Ang (3-8) and Ang (1-7)(8). Ang (1-7) is distinct from ATI and ATII receptors. Vascular and baroreflex actions of Ang (1-7) counteract those of AT II(9). Endopeptidase pathway ACE2/Ang (1-7)/Mas axis is shown to have different actions as compared to ATII. It is a vasodilatory axis and has also vasoprotective effect. (10).
Azilsartan has been shown to increase Ang. (1-7) thus exert vasodilatory effect and vasoprotective effect also (11). (Fig. 2).

Azilsartan also modulates sodium hydrogen exchange system (NHE-3) in nephron. NHE-3 exchanges sodium for hydrogen in kidney. This leads to inhibition of sodium re-absorption. Azilsartan reduces NHE-3 expression thus sodium excretion. Azilsartan thus is effective in salt sensitive hypertension (12). Azilsartan has higher potential to suppress sympathetic nervous system and decrease noradrenaline levels (12). Azilsartan has been shown to decrease morning surge, improve dipping at night, 24-hour mean blood pressure (13). Thus as Telmisartan was better than earlier generation of ARBs and Olmesartan was found to be better than Telmisartan it seems Azilsartan might prove better than all ARBs as far as blood pressure control is concerned.

References:

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