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Will Azilsartan - An Eight ARB Bring Paradigm Shift in Hypertension Management Practices in India?

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Hypertension, a common cardiovascular disease, should take the most accountability for the morbidity and mortality caused by disease in the world every year. Hypertension is the prime cause of Cardiovascular Disease (CVD) and deaths worldwide [1]. Almost three-quarters of people with hypertension (639 million people) live in developing countries with restricted health resources and where people have a very low awareness of hypertension and poor blood pressure control [2,3]. Chronic hypertension is a powerful risk factor for CVD in India. Epidemiological studies conducted in India in the last six decades suggest an escalating prevalence of hypertension both in the urban and rural areas and in both the genders. Some observational studies indicate that the incidence of hypertension is anywhere between 30% and 40% of the adult population [4].

Regional Estimates for the Prevalence of Hypertension

In India about 33% urban and 25% rural Indians are hypertensive. Out of these 25% rural and 42% urban Indians are aware of their hypertensive status. Only 25% rural and 38% of urban Indians are being treated for hypertension. One-tenth of rural and one-fifth of urban Indian hypertensive population have their BP under control (Figure 1) [5].

The target BP advocated in current treatment guidelines is generally <140/90 mmHg, with a lower target (<130/80 mmHg) for patients with diabetes mellitus or heart or renal disease [6]. A meta-analysis of 61 prospective, observational studies has shown that a 10 mmHg lower SBP would be associated over the long term with a 40% lower risk of stroke death and a 30% lower risk of death from IHD or other vascular causes. Even a small, 2 mmHg falls in mean SBP would be associated with large reductions in stroke mortality (10%) and death due to IHD and other vascular diseases (7%) in middle age [7].

Prompt initiation of suitable Anti-hypertensive therapy is crucial for those affected in order to avoid the development of progressive disease and reduce the risk of mortality. Even though major advances have been made in the treatment of hypertension, it remains inadequately managed. In India physicians are facing multiple challenges to optimum blood pressure goals. For better understanding classified into Physician Related Challenges includes: Multiple Guidelines to refer, Acceptance of BP targets, Willingness to achieve targets, Therapeutic Inertia. Patient related challenges includes: long term adherence and persistence to treatment, asymptomatic nature of disease, loss of motivation to take medication over time, no immediate benefit of treatment, cost.

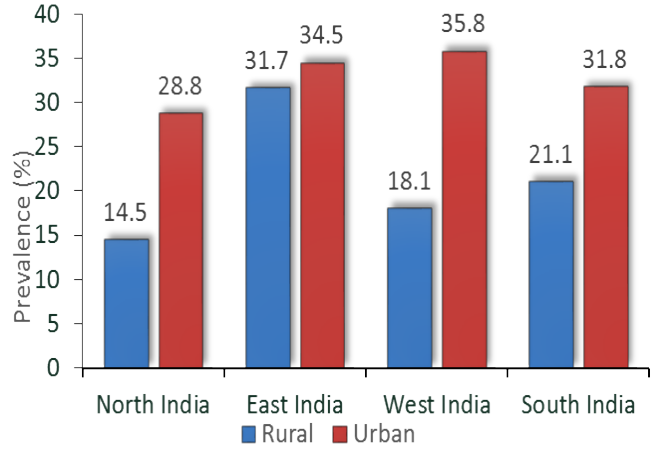

Figure 1: Regional estimates for the prevalence of hypertension.

Numerous guidelines for the effective management of hypertension have been published. Selection of a suitable antihypertensive drug is dependent on a number of factors, including concurrent diseases, such as renal disease, tolerability profile, and efficacy of drug, twenty four hours blood pressure control, and cost.

Several classes of drugs are available in India for the treatment of patients with essential hypertension. These include drugs, such as diuretics, beta adrenergic antagonists (blockers), alpha-adrenergic blockers and calcium channel blockers, and other drugs that affect the Renin-Angiotensin System (RAS), such as the direct renin inhibitors, the Angiotensin- Converting Enzyme (ACE) inhibitors and the angiotensin II receptor antagonists (blockers), also known as ARBs. But adequate blood pressure control is still a great challenge in India. In spite of the availability of numbers of drugs for hypertension, it still remains poorly controlled. There is always a search for potent and safer new antihypertensive. Ability of ARBs to protect against target organ damage and improve clinical outcomes is still considered to be largely mediated by their ability to decrease BP. Despite the fact that all approved AT1 receptor blockers can lower BP, many patients treated with currently available ARBs do not achieve BP treatment goals [8].

Azilsartan medoxomil is a recent addition to the angiotensin II receptor antagonist class of drugs and is the eighth approved drug in this class will be very soon available in India.

Azilsartan medoxomil with brand name Ipreziv & Edarbi, is a prodrug of azilsartan, a nonpeptide angiotensin II receptor type 1 (AT1) antagonist, and has been approved in the EU and the US for the treatment of patients with essential hypertension aged more than 18 years.

In Japan, the drug is available as the active metabolite (azilsartan)

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that differs from the licensed compound in Europe and the US (Azilsartan medoxomil), which is the prodrug formulation [6].

Azilsartan created by modifying thetetrazole ring present in candesartan. Azilsartan less acidic and more lipophilic than candesartan-which potentially increases its oral bioavailability [8]. Azilsartan is highly selective for AT1 receptors and has more than a 10,000-fold greater affinity for AT1 versus AT2 receptors. Ojima et al., Azilsartan was found to be approximately twice as potent as either olmesartan or telmisartan. Azilsartan was found to be about 5-20 times more potent than irbesartan and valsartan, respectively. The greater potency of Azilsartan for AT1 receptor blockade could help explain why Azilsartan lowers BP more than maximum approved doses of other ARBs such as olmesartan and valsartan [8].

Following oral administration, Azilsartan medoxomil is hydrolyzed into Azilsartan in both the gastrointestinal tract and plasma. Peak plasma concentrations of Azilsartan are reached within 1.5-3 hours post-dose. The elimination half-life is 11 hours. Azilsartan medoxomil, Oral prodrug of azilsartan, an AT1 receptor antagonist (blocker). Azilsartan produces greater AT1 receptor blockade activity than several other angiotensin II receptor antagonists, including valsartan and olmesartan *in vitro*. Azilsartan dissociates from AT1 receptors more slowly than other ARBs including olmesartan, telmisartan, and valsartan. Demonstrates pleiotropic cardioprotective effects *in vivo* and *in vitro*. Pharmacokinetic profile allows for once-daily oral administration. More effective in reducing 24 h mean SBP than maximum approved dosages of olmesartan or valsartan over 6 weeks or valsartan over 24 weeks in randomized phase III trials. Generally well tolerated with headache and dizziness among the most common adverse events. Low rate of treatment discontinuation due to adverse events in the 24 week trial. Contraindicated during pregnancy [6]. No major drug interaction studies on Azilsartan have been reported to date.

Azilsartan medoxomil, acts independently by lowering BP, offers preventive and therapeutic vasculoprotection in diabetes-induced cerebrovascular remodeling and myogenic dysfunction [9] also Azilsartan is also said to have renoprotective effects in reducing the proteinuria, albuminuria and nephrinuria along with reduced tubular cast formation and glomerular injury.

The recommended starting dosage in the EU is 40 mg once daily, increased to a maximum of 80 mg once daily for patients who do not achieve adequate BP with the lower dose. Azilsartan medoxomil may be consumed with or without food. After 2 weeks of treatment, a near maximal antihypertensive effect is expected; maximal antihypertensive effects are achieved after 4 weeks of treatment with the drug [10]. For patients with inadequate control of BP after treatment with Azilsartan medoxomil, additional reduction of BP may be achieved by co-administration with other antihypertensive agents, including diuretics (e.g. chlorthalidone and hydrochlorothiazide) and calcium channel blockers. Dosage adjustment of Azilsartan medoxomil is not required for patients with mild or moderate renal impairment [9]. In the EU, close monitoring of patients with mild to moderate hepatic impairment receiving Azilsartan medoxomil is recommended and a starting dose of 20 mg should be considered. A starting dose of 20 mg may be considered for very elderly (aged more than 75 years) patients who may be at risk of hypotension [9]. Treatment of hypertensive patients using Azilsartan appears to be more effective in younger than in older patients [11,12].

In conclusion, Azilsartan will be soon introducing in Indian market for the treatment of Hypertension. Once-daily Azilsartan medoxomil effectively lowers BP in patients with essential hypertension and has shown better antihypertensive efficacy than maximum therapeutic dosages of olmesartan medoxomil or valsartan in major trials of up to 24 weeks' duration. Azilsartan provide greater BP reduction than candesartan over 24-h monitoring period as well as during specific daytime, night-time and early morning period. Azilsartan medoxomil is generally well tolerated and low rates of discontinuation reported over a 24-week period, suggesting that patients are likely to persist with long-term treatment [8,13]. Azilsartan medoxomil is therefore a useful and attractive new option for lowering BP in Indian patients with essential hypertension (Mild to Moderate Hypertension), particularly for those not able to tolerate other antihypertensive drugs. Azilsartan also improved the non-dipping pattern in nocturnal hypertension. Also can be combine with other anti-hypertensives like Chlorthalidione and or Amlodipine [12]. 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 till date [14]. This drug appears as a promising aspect for the management of hypertension for Indian hypertensive patients.

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