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The Comparative Study of Azilsartan with Telmisartan in Terms of Efficacy, Safety and Cost - Effectiveness in Hypertension

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Abstract

Introduction: Hypertension (HT) represents the most common cardiovascular risk factor amongst the cluster group of Cardiovascular Diseases (CVD). Clinically, HT might be defined as that level of Blood Pressure (BP) at which the institution of therapy reduces the BP-related morbidity and mortality. Azilsartan (AZL) is a relatively new Angiotensin Receptor Blocker (ARB) available for the treatment of any stage of HT. **Aim:** To compare the efficacy, safety and cost-effectiveness of AZL 40-80 mg once daily versus telmisartan 40-80 mg once daily in patients of stage-I HT. **Methods:** A prospective, open, randomized parallel group comparative study of AZL versus telmisartan was done in patients of stage-I HT. The study included 80 patients, 40 in each group (group I and group II) coming to the department of Medicine, Rajindra Hospital attached to Government Medical College, Patiala. The study was conducted over 8 weeks. Group I, patients received Azilsartan 40-80 mg per day in divided doses and group II, patients received telmisartan 40-80 mg per day in divided doses according to severity of hypertension. The therapeutic efficacy of drugs was evaluated by monitoring BP. Adverse drug reactions were monitored in patients. The daily cost for each medication was noted and total cost of drugs taken over 8 weeks was calculated. Effectiveness of the drugs was calculated in terms of mm Hg fall in mean BP. All the observations thus made were statistically analyzed using appropriate tests. **Results:** Patients receiving AZL 40mg and telmisartan 40mg showed a significant fall ($p<0.05$) in systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at 4 weeks and 8 weeks, when compared to baseline. The difference in SBP and DBP between Group I (AZL) and II (Telmisartan) was statistically significant at 4 weeks ($p<0.05$) and was highly significant at 8 weeks ($p<0.001$). Adverse effects such as nasopharyngitis, upper respiratory tract infection, gastroenteritis, headache, dizziness, and fatigue were reported with both drugs. **Conclusions:** Reduction of BP with AZL was more as compared to telmisartan at 4 weeks and 8 weeks. Safety and tolerability was similar in both groups.

Key words: Angiotensin Receptor Blocker (ARB), Azilsartan, Hypertension, Telmisartan

1. Introduction

HT is defined as a sustained increase in BP ≥140/90 mmHg, a criterion that characterizes a group of patients whose risk of HT-related CVD is high enough to get medical attention[1]. Clinically, the definition of HT is that level of BP at which the institution of therapy reduces BP related morbidity and mortality[2]. The most common contributor

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of morbidity and mortality in underdeveloped and developing countries including South Asian countries is CVD[3]. HT represents the most common CardioVascular (CV) risk factor amongst the cluster group of CVDs. Pathological changes in vasculature and hypertrophy of the left ventricle occur due to raised arterial pressure[1].

Around 12.8% of the total deaths per year (7.5 million) are due to HT. Adults of age 25 years or more have 40% prevalence of raised BP in year 2008[4]. 20.6% and 20.9% of Indian men and women respectively, were suffering from HT in year 2005. The percentage rate of HT is projected to go up to 22.9 for Indian men and 23.6 for Indian women by year 2025[5]. Recently, the studies done in India have shown that the prevalence of HT in urban and rural people of India is 25% and 10% respectively[6].

Studies have shown associations between HT and Coronary Artery Disease (CAD), Myocardial Infarction (MI), stroke, Congestive Heart Failure (CHF), and Peripheral Vascular Disease (PVD) and reduction in BP significantly reduces the CV morbidity and mortality[7].

A number of randomized controlled clinical trials have proved that antihypertensive therapy is associated with 35% to 40% mean reductions in stroke incidence; 20% to 25% in MI; and more than 50% in HF[8]. Thus, the goal of antihypertensive therapy is to reduce SBP and DBP to less than 140/90 and less than 130/80 in patients with coexisting diabetes mellitus and renal disease[9]. This can be achieved by non-pharmacological (lifestyle measures) as well as pharmacological means.

Pharmacological measures include Diuretics, Beta blockers, Alpha blockers, Calcium Channel Blockers (CCB), Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin II Receptor Blockers (ARBs), centrally acting sympatholytics and vasodilators[10].

Practically, ARBs are now the first line pharmacological treatment for HT without any comorbidity and also in hypertension with renal disease, Heart Failure (HF) and diabetic patients who cannot tolerate ACE inhibitors[11].

AZL which is a new ARB, has high affinity for AT-I receptors, thus, inhibits the binding of angiotensin II to AT-I receptors. In the gastro-intestinal tract hydrolysis of prodrug, AZL-M occurs into active form i.e. AZL. The drug is available in 40mg and 80 mg once daily doses. At the recommended dose of 80 mg once a day, the BP lowering effect of AZL-M is more than the maximal doses of valsartan and Olmesartan[12].

Antihypertensive drug therapy is a common target of cost-cutting efforts as HT is so common and its treatment often requires the use of more than a single medication. The most common type of cost analysis is the cost-effectiveness calculation[13]. Thus, cost effectiveness is measured by dividing therapy's total cost by its therapeutic effectiveness.

As HT is affecting a large population worldwide and very few studies have been done till now to compare the new ARB i.e. AZL with a comparatively older ARB i.e. telmisartan, the present study was designed to look for efficacy, safety and cost effectiveness of AZL as compared to that of telmisartan in stage-I HT patients.

2. Methods

The present study was conducted by the Department of Pharmacology, Government Medical College, Patiala, in association with Out Patient Department of Medicine of Government Medical College and Rajindra Hospital, Patiala.

Total 80 patients with HT were evaluated after having fulfilled the inclusion and exclusion criteria, in the parallel group, comparative, randomized, prospective and open labelled study.

2.1 Inclusion Criteria

- New patients with HT i.e. not on any antihypertensive therapy.
- Adult males and females of age 21 years or more.

2.2 Exclusion Criteria

- Patients already on anti-hypertensives.
- Patients who were hyper-sensitivity to AZL or telmisartan.
- Women who were pregnant, lactating or were planning to get pregnant.
- Evidence of severe renal disorder.
- Patients with hepatic insufficiencies.
- Patients who were not willing or were not able to comply with the proceedings of the study.
- Patients with severe bradycardia, cardiogenic shock, heart block, sick sinus syndrome, decompensated HF, bronchial asthma, hypothyroidism, hyperthyroidism, CVA, CAD.

Patients were randomly allocated into 2 groups from time to time i.e. 40 cases in each group. The study was conducted over 8 weeks. The study protocol was approved by institutional ethics committee.

A written informed consent was taken from patients after explaining them about study drugs. Patients in group I were given AZL 40 mg once daily and subsequent titration was carried out up to maximum recommended dose of 80 mg/d depending on therapeutic response. Patients in group II were given telmisartan 40mg once daily and subsequent titration was carried out up to maximum dose of 80mg/d depending on therapeutic response. BP was measured on day 0, 4th week and then on 8th week.

Following base line investigations were carried out at the commencement of treatment—Hemoglobin (Hb), Total Leucocyte Count (TLC), Differential Leucocyte Count (DLC), Fasting Blood sugar (FBS), Blood Urea, uric acid, Serum Creatinine, serum electrolytes, Liver Function Test (LFT), Lipidogram, Echocardiography (ECG) and urine Routine Examination (R/E). At the end of the treatment the investigations were repeated and compared with the previous ones. Adverse effects as reported by patients were recorded and compared. For cost-effectiveness analysis, mean cost of drugs in both the treatment groups was calculated for 8 weeks, by noting the Maximum Retail Price (MRP) of all the study drugs. Effectiveness was calculated as mean change in Mean Blood Pressure (MBP) from baseline to 8 weeks in both the treatment groups. Data was statistically analyzed using t-test. The results were eventually tabulated and graphically represented.

3. Results

A total of 80 patients with stage-I HT were enrolled in the study and were randomly allocated into 2 groups i.e. 40 cases in each group. There were 19 (47.5%) males and 21 (52.5%) females in group I and 21 (52.5%) males and 19 (47.5%) females in group II. Statistical analysis showed that the difference between the 2 groups was not significant.

The mean age in group I was 54.83(8.12) years and the mean age in group II was 54.63(8.95) years. Maximum number of individuals was in age group of 46-55 years. Statistically, there was no significant difference in mean age of both the groups.

Table 1 shows, that in group I, the mean SBP prior to treatment was 149.00 ± 3.87 mmHg but after treatment, the SBP reduced to 137.80 ± 2.71 mmHg, and 132.00 ± 1.81 mmHg at 4th week and 8th week respectively. The reduction in SBP was found to be statistically significant ($p<0.001$) at 4th week and 8th week of therapy on comparing with the baseline readings.

In the Telmisartan-treated group, the mean SBP prior to treatment was 149.45±3.95 mmHg. After treatment, the SBP reduced to 139.35±3.41 mmHg and 135.30±3.25 mmHg at 4th week and 8th week respectively. The reduction in the mean SBP was found to be statistically significant ($p<0.001$) at 4th week and 8th week of therapy when compared with the baseline readings.

On comparing the mean SBP in patients on AZL and Telmisartan at baseline, 4 and 8 weeks, the mean difference at baseline was 0.45 mmHg, at 4 weeks was 1.55 mmHg and mean difference at 8 weeks was 3.3 mmHg.

Table 1. SBP at different visits in group I and group II

Time Intervals	Groups	N	Mean	SD	Std. Error Mean	Mean Difference	t-test	p value
Baseline	Group I	40	149.00	3.87	0.61	0.45	0.515	0.608
	Group II	40	149.45	3.95	0.62			
After 4 Weeks	Group I	40	137.80	2.71	0.43	1.55	2.254	0.027
	Group II	40	139.35	3.40	0.54			
After 8 Weeks	Group I	40	132.00	1.81	0.29	3.3	5.607	0.001
	Group II	40	135.30	3.25	0.51			

The difference in mean SBP between Group I (AZL) and II (Telmisartan) was statistically significant at 4 weeks ($p<0.05$) and was highly significant at 8 weeks ($p< 0.001$).

Table 2, the mean DBP before AZL treatment was 91.20±1.86 mmHg. After treatment, the DBP reduced to 85.20±1.86 mmHg and 80.70 ± 1.32 mmHg at 4th week and 8th week respectively. The reduction in DBP was found to be statistically significant ($p<0.001$) at 4th week and 8th week of therapy when compared with the baseline readings.

The mean DBP before Telmisartan treatment was 92.00±1.92 mmHg. After treatment, the DBP reduced to 86.05±1.78 mmHg and 83.20±2.11 mmHg at 4th week and 8th week respectively. The reduction in the DBP with Telmisartan was found to be statistically significant ($p<0.001$) at 4th week and 8th week of therapy when compared with the baseline readings.

On comparing, the mean DBP in patients on AZL and Telmisartan at baseline, 4 and 8 weeks, the mean difference at baseline was 0.8 mmHg, at 4 weeks was 0.85 mmHg and at 8 weeks was 2.5 mmHg. The difference in mean DBP between Group I (AZL) and II (Telmisartan) was statistically significant at 4 weeks ($p<0.05$) and was highly significant at 8 weeks ($p< 0.001$).

Figure 1 shows in group I the incidence of dizziness was 5(12.5%), fatigue was 2(5%), headache was 2(5%), nasopharyngitis was 3(7.5%), upper respiratory tract infection 3(7.5%) and gastroenteritis was 1(2.5%). In group II the incidence of dizziness was 4(10%), fatigue was 2(5%), headache was 2(5%), nasopharyngitis was 4(10%), upper respiratory tract infection 3(7.5%) and gastroenteritis was 2(5%).

The daily cost of AZL and telmisartan was Rs. 7.4 and 6.3 respectively. The cost for 8 weeks was Rs. 414.40 for AZL and Rs. 352.80 for telmisartan. The cost per year was Rs. 2701.00 for AZL and Rs. 2299.50 for telmisartan.

Table 3 shows, Group I MBP at baseline were 110.43±1.91 and 96.90±1.74 at 8 weeks. In Group II the MBP at baseline was 110.10±1.82 and 100.00±1.21 at 8 weeks. There was a statistically significant difference in the MBP in group I & group II.

In group I fall in MBP at 8 weeks was 13.53±0.17 mmHg whereas it was 10.10±0.61 mmHg in group II. In group I, the 8 weekly costs was Rs. 414.40 and in group II, the 8 weekly cost was Rs. 352.80. Therapy in group I was more effective and more expensive than therapy in group II.

Table 4 shows the cost effectiveness analysis in group I and group II. In group I, the average cost of treatment was Rs. 414±14.74 and was Rs. 352.80±12.51 in group II.

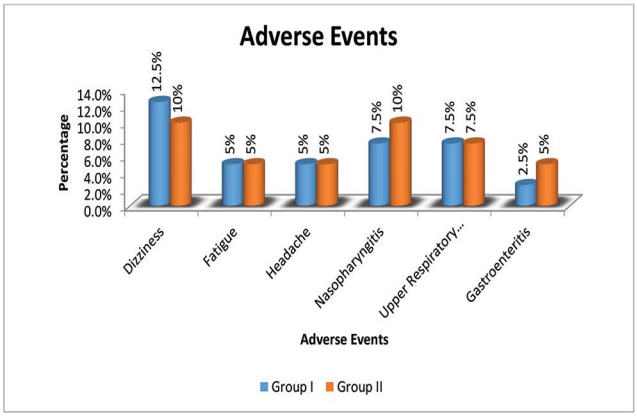

Figure 1. Comparison of adverse events in group I and group II.

Table 2. DBP at different visits in group I and group II

Time Intervals	Groups	N	Mean	SD	Std. Error Mean	Mean Difference	t-test	p value
Baseline	Group I	40	91.20	1.86	0.29	0.8	1.894	0.062
	Group II	40	92.00	1.92	0.30			
After 4 Weeks	Group I	40	85.20	1.86	0.29	0.85	2.089	0.040
	Group II	40	86.05	1.78	0.28			
After 8 Weeks	Group I	40	80.70	1.32	0.21	2.5	6.337	0.001
	Group II	40	83.20	2.11	0.33			

Table 3. Mean blood pressure in group I and group II

Group	MBP±SD (Baseline)	MBP±SD (8 Weeks)	Mean Difference	t-test	p value
Group 1	110.43±1.91	96.90±1.74	13.53±0.17	12.011	0.001
Group 2	110.10±1.82	100.00±1.21	10.10±0.61		

Table 4. Cost effectiveness analysis

Parameters	Group 1	Group 2	Difference in Cost C1-C2	Difference in Effectiveness	ICER
Cost (Rs.)	414.40±14.74	352.80±12.51	61.60±2.23	3.43±0.44	17.96
Fall in MBP (mmHg)	13.53±0.17	10.10±0.61			

13.53±0.17 mmHg was the fall in MBP in group I was and 10.10±0.61 mm Hg in group II. 61.60±2.23 Rs was the difference in cost of treatment of both the groups. 3.43±0.44 was the difference in the effectiveness in reduction of BP of both the groups. The ICER value comes out to be Rs 17.96 i.e. in AZL group, to reduce the mean MBP by one mmHg, the patient has to pay the additional cost of Rs 17.96. Calculation of ICER was done by dividing the cost of treatment of both the groups by the difference in effectiveness in reduction of blood pressure of both the groups.

4. Discussion

HT plays a major role in causing CVD and it is a leading cause of stroke, MI, HF and kidney disease. While the benefits of BP reduction have been well documented, the majority of patients of HT remain with poorly controlled BP. In developing countries, the high rate of undetected and untreated cases of hypertension is a major concern[14]. Since, HT is a chronic condition and its treatment is life long, it is important to ensure that the patient is compliant to antihypertensive therapy. Some of the major factors contributing to poor patient compliance are medication costs, side effects of the drugs and poor quality of life. Multiple classes of antihypertensive drugs are available for clinical management of hypertension like Diuretics, Beta blockers, Alpha blockers, Calcium Channel Blockers (CCB), Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin II receptor antagonist, centrally acting sympatholytics and vasodilators[10].

AZL is a new ARB which was discovered by modifying the tetrazole ring of candesartan[15,16]. In the present study, we have observed that both Azilsartan (40mg once daily) and Telmisartan (40mg once daily) are effective agents in reducing both SBP and DBP throughout the study period when measured at the baseline with 4th and 8th week in stage-I hypertension. When efficacy of Azilsartan was compared with Telmisartan, we found that Azilsartan was more effective than Telmisartan in reducing SBP and DBP.

The MBP in group I at baseline was 110.43 (2.87) and at 8 weeks was 96.90 (3.07). The MBP in group II at baseline was 110.10 (2.85) and at 8 weeks was 100.00 (3.11). Mean difference was 13.53 in group I and 10.10 in group II, which was statistically significant on comparing the two groups. There was more lowering of blood pressure in group I (AZL group).

White, Weber and Sica (2011) conducted a randomized trial on 1291 patients, whose mean age was 56 years and baseline mean SBP was 145 mm Hg. AZL-M at 80 mg was more efficacious than valsartan at 320 mg and olmesartan at 40 mg. There was greater lowering of mean SBP with AZL i.e. 14.3 mm Hg as compared to 10.0 mm Hg with valsartan and 11.7 mm Hg with olmesartan. It demonstrates that AZL-M at its maximal dose has higher efficacy than both olmesartan and valsartan at their maximal, approved doses without increasing the incidence of adverse events[17].

In the present study, both the therapies were equally well tolerated and there were no clear differences in incidences of AE between the two treatment groups.

The majority of AEs were mild in severity, and the most commonly reported events with both drugs were dizziness, nasopharyngitis and upper respiratory tract infection.

Barkis (2011) did a study to assess the antihypertensive efficacy and safety of the investigational ARB, azilsartan medoxomil (AZL-M), compared with placebo and the ARB olmesartan medoxomil (OLM-M). They assessed change from baseline in mean 24-hour ambulatory SBP following 6 weeks of treatment. The side effect profiles of both ARBs were similar to placebo. AZL-M is well tolerated and more efficacious at its maximal dose than the highest dose of OLM-M[18].

HT is a chronic disease and is a leading cause of stroke, MI, HF and kidney disease. Thus, it has huge implications in terms of economic burden on society. This stresses the need for pharmacoeconomic evaluations so that the best treatment options for patients with the lowest cost to the health care system are available and employed.

In the present study, the mean fall in BP in group I was 13.53±0.17 and in group II was 10.10±0.61. The mean cost in group I was Rs. 414.40 and in group II was Rs. 352.80. The ICER value comes out to be Rs 17.96 i.e. in AZL group, to reduce the mean MBP by one mmHg, the patient has to pay the additional cost of Rs 17.96.

5. Conclusion

Though AZL and Telmisartan belong to the same antihypertensive drug class i.e. ARBs and effectively reduce SBP and DBP, AZL is a better choice as compared to Telmisartan in my study because it caused more statistically significant decrease in BP with a similar safety and tolerability profile as telmisartan.

So, prevents future cardiovascular complications. However, the antihypertensive effects of azilsartan in hypertensive patients with serious comorbidities remain to be determined, as we have excluded patients having any comorbidities. Another limitation of this study is its limited sample size and short duration, as well as the follow ups could have more to look for the long-term adverse effects of azilsartan as not much studies have been done on it.

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