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Original Research Article

Comparative study to evaluate efficacy and safety of azilsartan and telmisartan in patients with grade I-II essential hypertension

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ABSTRACT

Background: Objectives of the study was to study the effect of Azilsartan 40mg once daily versus Telmisartan 40mg once daily in patients with Grade I-II essential hypertension.

Methods: A prospective study was conducted at MGM Medical college and Hospital which included 80 patients in each group with Grade I–II essential hypertension. The sex, age, presenting illness, and family history of the patients were recorded. Investigations such as blood sugar, urine analysis, kidney function test, lipid profile, and ECG were performed before starting the treatment. Any adverse effects during the treatment were noted. Blood pressure was recorded at baseline and during follow-up. One group received Azilsartan 40mg once daily and another group Telmisartan 40mg once daily. Patients were followed-up every week for 5 weeks.

Results: Patients receiving Azilsartan 40mg and Telmisartan 40mg showed a significant fall ($P <0.05$) in systolic (SBP) at the end of fifth week, when compared to baseline and diastolic blood pressure (DBP) significant fall at fourth and fifth week. The difference in fall in SBP and DBP was insignificant between the groups, after first, second and third week ($P >0.05$). Adverse effects such as Nasopharyngitis, Upper respiratory tract inflammation, Gastroenteritis, headache, dizziness, and fatigue were reported with both drugs.

Conclusions: Reduction of blood pressure with Azilsartan and Telmisartan was similar, but fall in blood pressure from baseline was highly significant in both groups.

Keywords: Angiotensin receptor blockers, Azilsartan, Blood pressure, Clinical trials, Efficacy studies, Safety, Telmisartan

INTRODUCTION

Essential hypertension is a common cardiovascular disorder with sustained increase in blood pressure ≥140/90 mmHg. The elevated arterial pressure causes pathological changes in the vasculature and hypertrophy of the left ventricle. Hypertension is the principle cause of stroke that is a major risk factor for coronary artery disease (CAD) and its attendant complications like myocardial infarction and sudden cardiac death. It is also a major contributor to cardiac failure, renal insufficiency and dissecting aneurysm of aorta.[1]

Hypertension is an increasingly prevalent chronic condition that is associated with serious morbidity and mortality. It is an important risk factor for the development and progression of cardiovascular disease (CVD), which is predicted to become the leading cause of death and disability worldwide by 2020.[2] As per the Registrar General of India and Million Death Study investigators (2001-2003), CVD was the largest cause of deaths in males (20.3%) as well as females (16.9%) and led to about 2 million deaths annually. In India, 23.10% men and 22.60% women over the age of 25 years suffer from hypertension.[3] Treating systolic blood pressure (SBP) and diastolic blood pressure (DBP) to targets that are <140/90 mmHg is

associated with a decrease in CVD complications.[4] Blood pressure (BP) reductions of 10 mmHg systolic or 5 mmHg diastolic are associated with a 33-48% reduction in stroke and a 17-27% reduction in coronary heart disease (CHD) events.[5]

Azilsartan is a new angiotensin II receptor blockers (ARB), and ARBs may reduce cardiac mortality rates in hypertensive patients.[6] In an *in vitro* study, azilsartan was shown to have higher affinity for and slower dissociation from AT 1 receptors than other ARBs, including olmesartan, telmisartan, valsartan, and irbesartan.[7] It has been reported that once-daily administration of azilsartan produced a more potent 24-h sustained antihypertensive effect than candesartan in Japanese patients with grade I-II essential hypertension, and it had an equivalent level of safety in a randomized, double-blind, comparative study.[8] It has also been reported that azilsartan provides greater BP reduction than candesartan over the entire 24-h monitoring period, as well as during the specific daytime, night-time, and early morning periods, by analysis of ambulatory blood pressure monitoring records.[9,10]

Hence, this study was undertaken to evaluate whether the above-mentioned theoretical benefits actually translate into clinically observable benefits in patients of Grade I-II essential hypertension.

METHODS

The study was conducted in the Out-Patient Department of Medicine, Mahathma Gandhi Mission's Medical College and Hospital, Aurangabad, after the approval of the Institutional Ethics Committee. This was a prospective, comparative, parallel, open, randomized, controlled clinical trial.

A total of 80 patients were enrolled in the study as per the selection criteria. Patients with newly diagnosed with Grade I-II essential hypertension of either sex within the age group of 18–65 years with blood pressure of ≥140/90 mmHg were included in the study. The upper limit of blood pressure in both groups was 180/110 mmHg. Patients belonging to grade I-II essential hypertension were selected as per JNC VIII report. Only naïve newly diagnosed hypertensive patients without prior antihypertensive treatment and without any associated diseases mentioned earlier were included.

The following categories of patients were excluded from the study:

- Patients with sinus bradycardia,
- Sick sinus syndrome,
- Prinzmetal's angina,
- Heart block,
- Chronic heart failure,
- Myocardial infarction,
- Peripheral vascular disease

Patients with history of hypersensitivity or allergy to Azilsartan and Telmisartan were also excluded. Patients with diabetes mellitus, patients with impaired kidney function test confirmed by serum creatinine level >2 mg/dl, patients with impaired liver function test such as SGPT or SGOT >2 times than normal limit, patients with asthma, pregnant and lactating women, patients with history suggestive of obstructive biliary disease, cholestasis and those who had received other antihypertensive treatment were excluded from the study.

The patients meeting the inclusion criteria were explained in detail about the nature of the trial, its purpose, procedures, and follow-up. They were provided with detailed trial information in case report form. Written informed consent was obtained from those who volunteered to participate in the trial. Current medical history and diagnosis were noted during the first visit.

The patients were examined by the consultant physician to rule out Grade I-II Essential hypertension. Systolic and diastolic blood pressure was measured in right arm, sitting posture by auscultatory method using standard mercury sphygmomanometer. The pressure at which the sounds were first heard was taken as the systolic pressure and the pressure at which the sounds disappeared was taken as the diastolic pressure. Two recordings of blood pressure were taken at an interval of 15 min by the same physician. After initial screening, the demographic data, past medical history, family history, findings of physical examination, and clinical examination were recorded in the case report form. Diagnosed cases of essential hypertension were randomly allocated using random number table to either Group A (to receive tablet Azilsartan 40mg) or Group B (to receive tablet Telmisartan 40mg). All patients were instructed to take the tablet orally once a day with glass of water in the morning.

The patients were advised to report for follow-up every week for 5 week. On each visit, blood pressure was recorded. Blood sugar, urine analysis, renal function test, liver function test and ECG were assessed before starting the treatment.

Adverse Drug reaction (ADR) monitoring

The ADRs related to Azilsartan and Telmisartan were monitored and documented in suitably designed ADR documentation form after initial notification of the suspected ADR by physicians.

Additional details were collected by review of the patient case records and interview with patients. Severity and causality of the ADRs were assessed by using Modified Hartwig and Seigel scale and Naranjo's Algorithm, respectively. The Modified Hartwig and Seigel scale grades ADRs as Mild, Moderate, and Severe. Naranjo's Algorithm scale grades causality of ADRs as Definite, Probable, Possible and Unlikely.

Qualitative data on adverse-effects were analyzed by using the Z-test for difference between proportions. Quantitative data were analyzed by using the Z-test for difference between means. *P*-value <0.05 was taken as significant and *P*-value <0.001 was taken as highly significant, while *P* >0.05 was considered as insignificant.

RESULTS

Eighty patients were included in the study, of which Group 'A' 40 received tablet Azilsartan 40 mg and Group 'B' received tablet Telmisartan 40 mg once daily. The two groups were similar and comparable as regards systolic BP, diastolic BP before treatment and after every week for 5 weeks.

In the table 1, Azilsartan -treated group, the mean systolic BP prior to treatment was 159.9 ± 7.85 mmHg. After treatment, the systolic BP reduced to 146.95 ± 2.35 mmHg, 139.60 ± 3.33 mmHg, 134.45 ± 3.46 mmHg, 129.85 ± 3.11 mmHg and 126.35 ± 1.80 mmHg at 1st week, 2nd week, 3rd week 4th week and 5th week respectively. The reduction in systolic BP was found to be statistically significant (*P* < 0.001) at 1st week, 2nd week, 3rd week 4th week and 5th week of therapy when compared with the baseline readings.

In the Telmisartan-treated group, the mean systolic BP prior to treatment was 158.95±9.06mmHg. After treatment, the systolic BP reduced to 147.3±4.71mmHg, 140.05±3.28mmHg and 135.05±2.96mmHg, 130.90±2.96mmHg and 127.40±2.31mmHg at 1st week, 2nd week, 3rd week 4th week and 5th week respectively. The reduction in the mean systolic BP was found to be statistically significant (*P* <0.001) at 1st week, 2nd week, 3rd week 4th week and 5th week of therapy when compared with the baseline readings.

The mean reduction in systolic BP in the Azilsartan/ Telmisartan group was 12.95±1.29/11.65±1.61mmHg, 20.30±1.35/ 18.90±1.52 mmHg, 25.45±1.35/ 23.90±1.50mmHg, and 30.05±1.33/ 28.05±1.50mmHg respectively, at 1st week, 2nd week, 3rd week and 4th week. When the reduction in systolic BP in the two groups was compared, there was no significant difference between the groups (*P* >0.05). But in 5th week 33.55±1.27/ 31.55±1.48 statistically significantly reduced (*P* <0.05).

In the table 2, the mean diastolic BP before Azilsartan treatment was 96.85±2.11mmHg. After treatment, the diastolic BP reduced to 93.75±2.22 mmHg, 91.85±1.59 mmHg, 89.05±2.26 mmHg, 86.75±2.50 mmHg and 84.30±2.37 mmHg at 1st week, 2nd week, 3rd week 4th week and 5th week respectively. The reduction in diastolic BP was found to be statistically significant (*P* <0.001) at 1st week, 2nd week, 3rd week 4th week and 5th week of therapy when compared with the baseline readings.

The mean diastolic BP before Telmisartan treatment was 96.70±2.00mmHg. After treatment, the diastolic BP reduced to 93.95±1.83mmHg, 91.40±2.08mmHg,

87.95±2.24mmHg 85.20±2.20 and 82.75±2.15mmHg at 1st week, 2nd week, 3rd week 4th week and 5th week respectively. The reduction in the diastolic BP with Telmisartan was found to be statistically significant (*P* <0.001) at 1st week, 2nd week, 3rd week 4th week and 5th week of therapy when compared with the baseline readings.

The mean reductions in diastolic BP in the Azilsartan / Telmisartan group were 3.10±0.48/2.75±0.42mmHg and 5.00±0.41/5.30±0.45mmHg, respectively, at 1st week, and 2nd week. When the values were compared in both the treatment groups, the difference was not statistically significant (*P* >0.05).

The mean reductions in diastolic BP in the Azilsartan / Telmisartan groups at 3rd week, 4th week and 5th week were 7.80±0.49/ 8.75±0.47mmHg and 10.10±0.51/ 11.50±0.47mmHg, and 12.55±0.50/13.95±0.46mmHg respectively.

The mean reduction in diastolic BP achieved with Azilsartan at 3rd week 4th and 5th week was statistically significant (*P* <0.05) than that achieved with Telmisartan at the corresponding Period.

Table 1: Comparative effect of Azilsartan and Telmisartan on systolic blood pressure.

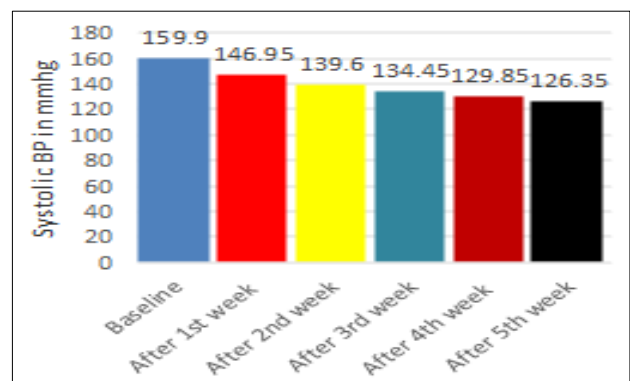| Parameters	Azilsartan systolic BP in mmHg (mean±SD)	Telmisartan systolic BP in mmHg (mean±SD)	P-value
Baseline	159.9±7.85	158.95±9.06	>0.05
After 1st week	146.95±2.35	147.3±4.71	>0.05
After 2nd week	139.60±3.33	140.05±3.28	>0.05
After 3rd week	134.45±3.46	135.05±2.96	>0.05
After 4th week	129.85±3.11	130.90±2.96	>0.05
After 5th week	126.35±1.80	127.40±2.31	<0.05

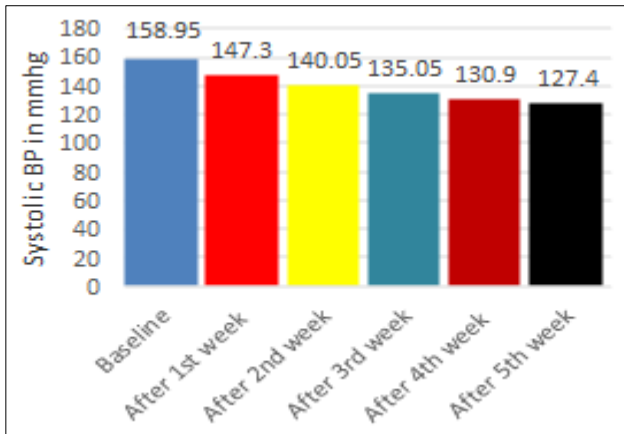**Figure 1: Effect of Azilsartan on systolic BP.**

Figure 2: Effect of Telmisartan on systolic BP.

Table 2: Comparative effect of Azilsartan and Telmisartan on diastolic blood pressure.

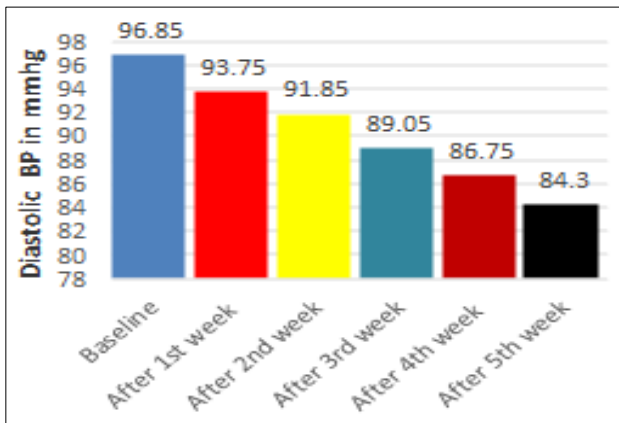| Parameters	Azilsartan diastolic BP in mmHg (mean±SD)	Telmisartan diastolic BP in mmHg (mean±SD)	P-value
Baseline	96.85±2.11	96.70±2.00	>0.05
After 1st week	93.75±2.22	93.95±1.83	>0.05
After 2nd week	91.85±1.59	91.40±2.08	>0.05
After 3rd week	89.05±2.26	87.95±2.24	<0.05
After 4th week	86.75±2.50	85.20±2.20	<0.005

Figure 3: Effect of Azilsartan on diastolic BP.

In the Table 3, the study drugs were equally well tolerated and there were no clear differences in the incidences of adverse events (AEs) between the two treatment groups. AEs were reported by 57.5% of patients (23/40) who received Azilsartan and 52.5% (21/40) who received Telmisartan. The vast majority of AEs were either mild or moderate in intensity in the two groups (23 in the azilsartan group; 21 in the Telmisartan group). No clear trend of

time- or dose-dependency in the incidence of AEs was evident in either treatment group. No deaths occurred during the study. Discontinuations due to adverse events and serious adverse events were infrequent in both groups.
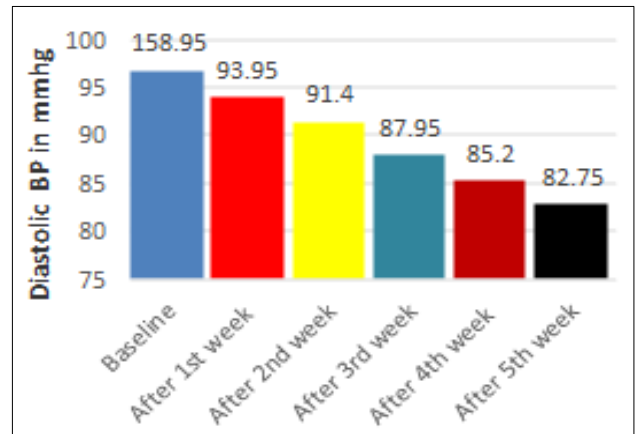

Figure 4: Effect of Telmisartan on diastolic BP.

The most common AEs occurring in 3% or more of the patients in the Azilsartan group were nasopharyngitis (20% in the azilsartan group vs. 17.5% in the Telmisartan group), upper respiratory tract inflammation (7.5% vs. 7.5%, respectively), and Gastroenteritis (2.5% vs. 5%, respectively). The overall incidence of hypotension-related events (dizziness, dizziness postural, syncope, vertigo and vertigo positional) was comparable to the two drugs- 5 of 40 patients (12.5%) who received Azilsartan as compared with 3 of 40 patients (7.5%) who received Telmisartan.

Table 3: Treatment-emergent adverse events (n, %) occurring in the Azilsartan and Telmisartan treatment groups (safety analysis sets).

Adverse event	Azilsartan (n=40)	Telmisartan (n=40)
Patients experiencing at least 1 AE	23 (57.5%)	21 (52.5%)
Mild	19 (47.5%)	17 (42.5 %)
Moderate events	3 (7.5 %)	2 (5%)
Severe events	1 (2.5%)	1 (2.5%)
Treatment-related AE	6 (15%)	5 (12.5%)
AE leading to drug discontinuation	2 (5%)	2 (5%)
Most common TEAEs		
Nasopharyngitis	8 (20%)	7 (17.5%)
Upper respiratory tract inflammation	3 (7.5%)	3 (7.5%)
Gastroenteritis	1 (2.5%)	2 (5%)

AEs considered treatment-related were infrequent in both groups, but were slightly more common with Azilsartan than with Telmisartan (15% vs. 12.5%; Table 3). This was mainly due to slightly higher incidences of postural dizziness (12.5% vs. 7.5%). However, this difference in

the frequency of adverse-effects between the groups was not statistically significant (*P* >0.05). Among these 44 ADRs were of possible category, followed by 23 ADRs were of probable category on the causality assessment scale.

DISCUSSION

Hypertension is defined as a SBP of 140mmHg or more or a DBP of 90 mmHg or more or taking antihypertensive medication.[11] Hypertension is classified as either essential hypertension (EH) or secondary hypertension, and EH accounts for about 90-95% of the cases characterized by high blood pressure with no obvious underlying medical causes.[12] In developing countries, it is a major medical concern that the high rate of undetected and untreated EH.[13] In clinical trials, antihypertensive therapy has been associated with reductions in (1) stroke incidence, averaging 35-40%; (2) myocardial infarction (MI), averaging 20-25%; and (3) HF, averaging >50%.[14] It is estimated that in patients with stage 1 hypertension (SBP 140-159mmHg and/or DBP 90-99mmHg) and additional cardiovascular risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated. In the added presence of CVD or target organ damage, only nine patients would require such BP reduction to prevent one death.[15]

Although several previous head to head comparisons of ARBs in which clinical blood pressure was used as the primary efficacy variable have been published.[16-21] Azilsartan, an angiotensin type 1 (AT1) receptor blocker (ARB) was recently approved by regulatory clinical market. The development of AT1 receptor blockers (ARBs) can be traced back to the pioneer work of scientist at Takeda pharmaceutical who described a series of benzylimidazole compounds that inhibited the ability of angiotensin to stimulate the vascular contraction and increase blood pressure (BP).[22-25] More than 15 years after the clinical introduction of Losartan, the FDA approved Takeda's azilsartan medoxomil as the 8th ARB for the treatment of hypertension.[26]

Azilsartan was discovered by modifying the tetrazole ring present in candesartan.[27,28] Chemical structure of azilsartan is very similar to the structure of candesartan and differ only by replacement of candesartan's 5 member tetrazole ring with the 5 member oxa-oxadiazole ring of azilsartan. Unlike candesartan which must be orally administered as a prodrug candesartan cilexetil to ensure adequate bioavailability, azilsartan has been shown to be effective in reducing BP when orally administered as either the ester prodrug, azilsartan medoxomil or as the primary compound.[29-31] During gastrointestinal absorption, azilsartan medoxidil is rapidly hydrolyzed to azilsartan, the bioactive molecule that selectively and competitively blocks angiotensin induced activation of AT1 receptor in an insurmountable fashion.[32,33] Azilsartan in clinically approved doses as azilsartan medoxomil has been shown to lower 24-hour BP in hypertensive patients significantly more than the maximum approved dose of olmesartan medoxomil, the later being considered by some to be one of the most potent ARBs for lowering BP.[34-36] Given the close structural relationship between azilsartan and candesartan, head to head studies comparing the BP effects of these two drugs are of particular interest.[37]

In the present study, we have observed that both Azilsartan (40mg once daily) and Telmisartan (40mg once daily) are effective agents in reducing both systolic and diastolic BP throughout the study period when measured at the baseline with 1st 2nd 3rd 4th and 5th week in grade I-II essential hypertension. When efficacy of Azilsartan was compared with Telmisartan, we found that Azilsartan was as effective as Telmisartan in reducing systolic BP (Table 1), but Azilsartan is more effective in reducing diastolic BP when compared with Telmisartan (Table 2). In addition, the proportions of patients who were categorized as well-controlled at 4th and 5th weeks were significantly higher in reduction of BP in the Azilsartan group than in the Telmisartan group. When the time-courses of BP changes with two ARBs were evaluated at 5 weeks, Azilsartan was also found to provide a significantly greater reduction from baseline in mean SBP and DBP than Telmisartan group, indicating a more sustained duration of action.

The longer duration of antihypertensive efficacy of Azilsartan was not at the expense of diminished tolerability, as the two ARBs were equally well tolerated in this study. The majority of AEs were mild in severity, and the most commonly reported events with both drugs were nasopharyngitis, upper respiratory tract inflammation and Gastroenteritis. There was a slightly higher incidence of treatment-related AEs with Azilsartan than with Telmisartan (15% vs. 12.5%), mainly as a result of slightly higher incidences of postural dizziness (12.5% vs. 7.5%). However, these events were generally of mild intensity and resolved without intervention and, importantly, were not of clinical concern as they did not lead to syncope or gout. Overall, treatment-related AEs were infrequent in the two groups. There was no clear trend of time- or dose-dependency in the incidence of TEAEs with either treatment, and there were no remarkable findings of clinical concern in laboratory test results, vital signs, body weight and 12-lead electrocardiogram findings.

This study has two important limitations. First, the sample size is relatively small, which limits our ability to determine significance. Second, we applied a changeover, with switching from various ARBs to Azilsartan or Telmisartan. A crossover study would be preferable. However, the patients were divided into the two groups randomly, and this may have minimized any difference in BP.

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