Comparative Study of Efficacy and Safety of Azilsartan with Telmisartan in Hypertensive Patients

Sashidhar Reddy[1], Mary Rohini[2], Prasanna[3], Rakesh[4], Lokesh[5]

ABSTRACT

Introduction: Hypertension is defined as either a sustained systolic blood pressure of greater than 140 mm Hg or a sustained diastolic blood pressure of greater than 90 mm Hg. Chronic hypertension can lead to heart disease and stroke, the top two causes of death in the world. Angiotensin receptor blockers are more selective blockers of angiotensin and have the potential for complete inhibition of angiotensin than ACE inhibitors. The aim of this study was to compare safety and efficacy of newer ARB Azilsartan with Telmisartan.

Material and methods: This prospective study was carried out in patients attending the Department of Medicine, RVMIMS. Patients with newly diagnosed with stage 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. Severe hypertension >180/110 mm of Hg, hypersensitivity to ARBs, secondary hypertension with any other etiology, pregnant women, history of Drug/Alcohol abuse, cardiac arrhythmias were excluded. Patients who gave consent for the study were divided into 2 random groups 1 and 2 – the first received azilsartan and the second received telmisartan. Point of control was defined as blood pressure<140/90 mm of Hg after initiation of therapy.

Results: 204 patients were randomized into two groups. Out of 104 patients included in group 1 who received azilsartan, 3 were lost for follow up. Out of 100 patients included in group 2 who received telmisartan, 12 were lost for follow up. There was no significant difference between the two drugs in both mean systolic and diastolic blood pressure at 6hrs, 15 days, 1 month and 3 months. Mean diastolic blood pressure at 24 hrs was reduced more with telmisartan compared to azilsartan which is significant. Hypotension related adverse effects occurred in 3% of the patients in azilsartan group while it occurred in 8% of them in telmisartan group.

Conclusion: Azilsartan is an effective blood pressure lowering drug with its safety and efficacy comparable to that of telmisartan.

Keywords: Blood Pressure, Azilsartan, Telmisartan

INTRODUCTION

Hypertension is defined as either a sustained systolic blood pressure of greater than 140 mm Hg or a sustained diastolic blood pressure of greater than 90 mm Hg, according to Joint National committee (JNC VIII) on hypertension.

Although many patients may not have symptoms but chronic hypertension can lead to heart disease and stroke, the top two causes of death in the world. Hypertension is also an important risk factor in the development of chronic kidney disease.[1]

Effective control of blood pressure in patients with hypertension is required to produce a maximum reduction in clinical cardiovascular events[2,3] and expert consensus guidelines advocate BP levels <140/90 mm of Hg in patients lacking target organ involvement and <130/80 of mmHg in patient with diabetes mellitus, heart disease, or kidney disease[4,5].

Angiotensin II appears to exert a central role in both the pathophysiology of essential hypertension and arteriosclerosis- associated hypertension[6] and insulin resistance[7].

Angiotensin receptor blockers are more selective blockers of angiotensin and have the potential for complete inhibition of angiotensin than ACE inhibitors[8].

Among the angiotensin receptor blockers telmisartan has favourable pharmacokinetic profile, has longest plasma half-life and is the commonly prescribed ARB. After clinical introduction of losartan in 1995, US Food and Drug Administration (FDA) approved azilsartan medoxomil as the 8th ARB for the treatment of hypertension in 2018[9].

Azilsartan was discovered by modifying the tetrazole ring present in candesartan[10-11]. Azilsartan has been shown to be effective in reducing BP when administered orally as either the ester prodrug azilsartan medoxomil or as the primary compound[12-14].

The aim of this study was to compare safety and efficacy of newer ARB Azilsartan with Telmisartan.

MATERIAL AND METHODS

This Prospective, randomized open labelled parallel study was carried out in patients attending the Out-Patient and In-patient Department of Medicine, RVMIMS and RC after the approval of the Institutional Ethics Committee.

Inclusion criteria

Patients with newly diagnosed with stage I-II essential

[1]Assistant Professor, Department of General Medicine, [2]Assistant Professor, Department of Pharmacology, [3]Head of the Department, Department of Pharmacology, RVMIMS and RC, Telangana, [4]Junior Residents, Department of General Medicine, [5]Junior Residents, Department of General Medicine, India

Corresponding author: Dr. Sashidhar Reddy B, MBBS DNB, Assistant Professor, Department of General Medicine, RVM Institute of Medical Sciences, Laxmakkapally, Mulugu Mandal, Siddipet – 502279, Telangana, India

International Journal of Contemporary Medical Research
ISSN (Online): 2393-915X; (Print): 2454-7379 | ICV: 77.83 | Volume 5 | Issue 5 | May 2018

E51

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. Only naïve newly diagnosed hypertensive patients without prior antihypertensive treatment and without any associated diseases were included.

Exclusion criteria

Severe hypertension>180/110 mm of Hg, hypersensitivity to ARBs, secondary hypertension with any other etiology, history of Drug/Alcohol abuse, cardiac arrhythmias(atrial flutter, atrial fibrillation, ventricular tachycardia), Patients with sinus bradycardia, Sick sinus syndrome, Prinzmetal's angina, Heart block, Chronic heart failure, Myocardial infarction, Peripheral vascular disease, pregnant and lactating women, 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.

After taking approval from ethics committee, 204 patients who were willing to participate and give informed consent and fulfilled inclusion and exclusion criteria were enrolled in the study. Patients were randomly divided into 2 groups by computer generated numbers. Group 1 received AZILSARTAN 40 mg to 80 mg daily and Group 2 received TELMISARTAN 40 mg to 80 mg daily depending on the blood pressure.

Standard Conventional sphygmomanometer was used for BP measurement and the pressure at which the korotokoff 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 in sitting position. 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 and following investigations were done. ECG, serum electrolytes, serum creatinine, CBP and CUE.

Selection of patients was restricted to those who had a BP of >140/90 mm of Hg to <180/110 mm of Hg (stage I and stage II hypertension).

Telmisartan was started at a dose of 40 mg to 80 daily while Azilsartan was started at a dose of 40 to 80 mg daily depending on the blood pressure.

Point of control was defined as blood pressure<140/90 mm of Hg after initiation of therapy.

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.

Causality of the ADRs were assessed by using Naranjo's Algorithm.

STATISTICAL ANALYSES

The primary end point for assessing efficacy was the change

from baseline in mean systolic and diastolic BP after 8 weeks of treatment.

Data were entered in MS excel 2007, same were exported into STATA (version 10). For normally distributed continuous data, comparison for significance of difference were done by using 1) Student's paired t test for within group before and after treatment. 2) Student's unpaired t test was used for comparison of normally distributed continuous data between the two treatment groups. P value<0.05 was considered statistically significant.

RESULTS

This study was carried in the Department of Medicine in RVM Institute of Medical sciences and Research Centre.204 patients were randomized and divided into two groups. Group 1 received 40 to 80 mg of Azilsartan and Group 2 received 40 to 80mg of Telmisartan (figure 1).

In Telmisartan group, at baseline mean systolic blood pressure was 157.15±11.83, and at the end of the study mean systolic
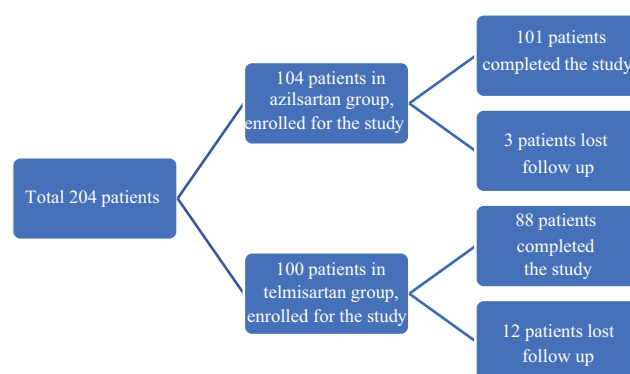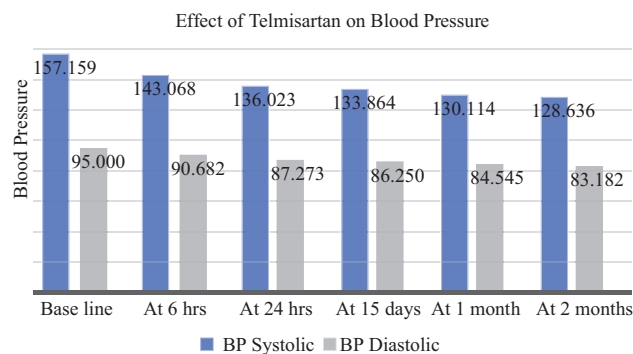

Figure-1: Number of patients in both groups

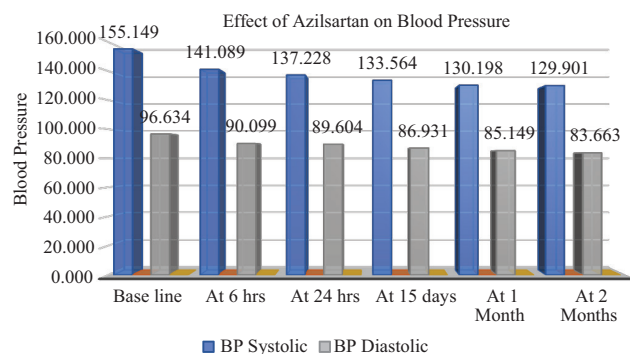**Figure-2:** Effect of Telmisartan on blood pressure

Figure-3: Effect of Azilsartan on blood pressure

Reddy, et al.   Efficacy and Safety of Azilsartan with Telmisartan in Hypertensive Patients

Section: Medicine

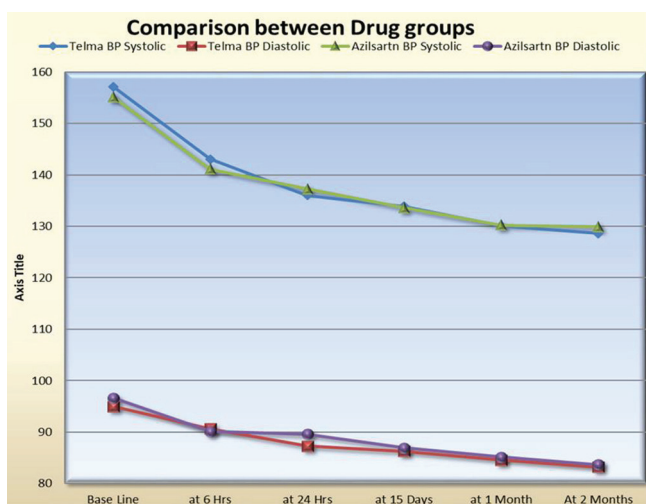**Figure-4:** Comparison between the two drugs

blood pressure was 128.63±8.33 (systolic blood pressure was reduced by 28.5±3.5mm of Hg). Mean diastolic blood pressure was decreased from 95.0 ± to 83.18(diastolic blood pressure was reduced by 11.11±2.058 mm of Hg). There was a significant reduction in both systolic and diastolic blood pressure (P value<0.001) (figure 2).

In Azilsartan group, mean systolic blood pressure at baseline was 155.14±10.73, and at the end of the study mean systolic blood pressure was 129.90±7.27(systolic blood pressure was decreased by 25.24±3.45 mm of Hg). Mean diastolic blood pressure at baseline was 96.63±8.63 and mean diastolic blood pressure at the end of the study was 83.66±5.42(diastolic blood pressure decreased by 3.208). There was a significant reduction in blood pressure.(P value<0.001) (figure-3).

Monotherapy with azilsartan 40mg, to 80mg daily has been compared with telmisartan 40mg to 80mg daily. There was no significant difference between the two drugs in both mean systolic and diastolic blood pressure at 6hrs, 15 days, 1 month and 3 months. Mean diastolic blood pressure at 24 hrs was reduced more with telmisartan compared to azilsartan (P value=0.011) which was statistically significant (figure-4).

The most common adverse effects occurring in 3% of the patients in the Azilsartan group were rashes, and in 3% were hypotension related events (dizziness, dizziness postural, syncope, vertigo and vertigo positional), whereas in telmisartan group dizziness, postural syncope and vertigo were observed in nearly 8%.

DISCUSSION

Azilsartan a newer angiotensin receptor blocker has shown cardiovascular benefits of lowering blood pressure in preclinical as well as clinical trials. These benefits are due to its property of high affinity to and slow dissociation from AT1R. 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%[15].

Azilsartan in clinically approved doses as azilsartan medoxomil has demonstrated 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[16-18].

In the present study we observed that Monotherapy with azilsartan is equally efficacious to telmisartan given once daily in reducing mean blood pressure, by using mean systolic BP and mean diastolic BP monitoring at 8 weeks as primary efficacy end point. Telmisartan has shown slightly greater reduction in diastolic blood pressure at 24 hours.

Other studies have demonstrated superior efficacy and safety of azilsartan over routinely used ARBs but we observed patients who complained of rashes(3%) required discontinuation of azilsartan.

There were no remarkable findings of clinical concern in laboratory test results, vital signs, body weight and 12-lead electrocardiogram findings

CONCLUSION

Azilsartan, a newer angiotensin receptor blocker is an effective and safe blood pressure lowering drug. Its efficacy is comparable to that of telmisartan with additional benefit of lesser side effects and hence can be safely used in all the patients.

REFERENCES

1. Whalen Karen, Richard Finkel, and Thomas A. Panavelil. Lippincots illustrated reviews: Pharmacology. Sixth edition. Philadelphia: Wolters Kluwer, 2015 pg. no:225.
2. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet. 2001;358:1305–1315.
3. Turnbull F, for the Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively designed overviews of randomized trials. Lancet. 2003;362:1527–1535.
4. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, for the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High BP. Hypertension. 2003; 42:1206–1252.
5. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertension. 2003; 21:1011–1054.
6. Schmidt-Ott K. M., Kagiyama S., Phillips M. I. The multiple actions of angiotensin II in atherosclerosis. Regul. Pept. 2000;93, 65–77.
7. Olivares-Reyes J. A., Arellano-Plancarte A., Castillo-Hernandez J. R. Angiotensin II and the development of insulin resistance: implications for diabetes. Mol. Cell. Endocrinol. 2009;302:128–139.
8. Bertram G Katzung, Anthony J Trevor Katzung, Basic and Clinical Pharmacology 13th Edition, 2015, page

International Journal of Contemporary Medical Research
ISSN (Online): 2393-915X; (Print): 2454-7379 | ICV: 77.83 | Volume 5 | Issue 5 | May 2018

E53

Section: Medicine

no:185.

9. Takeda Pharmaceuticals North America. Edarbi prescribing information. 2011.

10. Kohara Y, Imamiya E, Kubo K, Wada T, Inada Y, Naka T. A new class of angiotensin II receptor antagonists with a novel acidic bioisostere. Bioorganic Medicinal Chemistry Letters. 1995;5:1903-8.

11. Kohara Y, Kubo K, Imamiya E, Wada T, Inada Y, Naka T. Synthesis and angiotensin II receptor antagonistic activities of benzimidazole derivatives bearing acidic heterocycles as novel tetrazole bioisosteres. J Med Chem. 1996;39:5228-35.

12. Rakugi H, Enya K, Sugiura K, Ikeda Y. Comparison of the efficacy and safety of azilsartan with that of candesartan cilexetil in Japanese patients with grade III essential hypertension: a randomized, double-blind clinical study. Hypertens Res.; 2012.

13. Naka T, Kubo K. A new class of diacidic nonpeptide angiotensin II receptor antagonists: candesartan cilexetil. Curr Pharm Des. 1999;5:453-72.

14. Baker WL, White WB. Azilsartan medoxomil: A new angiotensin II receptor antagonist for treatment of hypertension. Ann Pharmacother. 2011;45:150615.

15. Neal B, MacMahon S, Chapman N. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ace inhibitors, calcium antagonists, and other bloodpressure-lowering drugs: Results of prospectively designed overviews of randomised trials. Blood pressure lowering treatment trialists' collaboration. Lancet. 2000;356:1955-64.

16. Zannad F, Fay R. Blood pressure-lowering efficacy of olmesartan relative to other angiotensin II receptor antagonists: an overview of randomized controlled studies. Fundam Clin Pharmacol. 2007;21:181-90.

17. Sica D, White WB, Weber MA, Bakris GL, Perez A, Cao C, et al. Comparison of the novel angiotensin II receptor blocker azilsartan medoxomil vs valsartan by ambulatory blood pressure monitoring. The Journal of Clinical Hypertension. 2011;13:467-72.

18. White WB, Weber MA, Sica D, Bakris GL, Perez A, Cao C, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. Hypertension. 2011;57:413-20.