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Comparative study of Azilsartan versus Olmesartan in treatment of hypertension with effect on Lipid Profile and C Reactive Protein

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Abstract

Azilsartan medoxomil (AZL-M) is an angiotensin receptor blocker (ARB) being developed for hypertension treatment. In this study, azilsartan 40-80mg was compared with olmesartan (OLM-M) 20-40mg. In a double blind randomized control study, 60 patients were followed up for 3 months. The primary endpoints were systolic blood pressure (SBP) and diastolic blood pressure (DBP), lipid profile (total cholesterol, triglycerides, HDL (High Density Lipoprotein) and LDL (Low Density Lipoprotein) and CRP (C Reactive Protein) levels. All 60 patients completed the study. The mean age of 60 patients was 53.85±10.56 years, 50% were male and 50% were female. Mean SBP reductions were 9.13±2.50 mm Hg in olmesartan group, 12.06±1.92 mmHg in azilsartan group. Dose dependent reductions in mean SBP and DBP occurred at the end of the study in both azilsartan and olmesartan groups. Reduction in mean SBP was greater with AZL–M 80 mg than OLM-M 40 mg by 2.93 mmHg ($p<0.001$). Mean DBP reductions were 6.26±1.87 mm Hg in olmesartan group, 10.13±1.81 mm Hg in azilsartan group. Reduction in mean DBP was greater with AZL–M 80 mg than OLM-M 40 mg by 3.87 mmHg ($p<0.001$). Reductions in lipid profile and CRP were not significant. The side effects were similar for both the groups. Azilsartan is well tolerated and more efficacious at its maximal dose than the highest dose of olmesartan.

Keywords: Azilsartan medoxomil, olmesartan medoxomil, systolic blood pressure, diastolic blood pressure, lipid profile, C Reactive Protein.

Introduction

Hypertension is a condition characterized by elevated blood pressure of more than or equal to 140/90 mmHg in the arteries. Hypertension affects more than 25% of the adult population worldwide.[1] In an analysis of worldwide data for the global burden of hypertension, 20.6% of Indian men and 20.9% of Indian women were suffering from hypertension in 2005.[2] According to the JNC 7th report on hypertension, a person is categorized as hypertensive if the systolic BP is 140 mmHg or more and diastolic BP is 90 mmHg or more at two different occasions.[3] It became evident in the early 1970s that only half of the hypertensive patients were aware of the condition and only about half of those aware of the problem were being treated and half of those treated were considered adequately treated.[4]Despite the availability of wide range of anti-hypertensive medications, ARBs are the most preferred drugs to treat hypertension because of their efficacy, tolerability and lowest side effect profile.[5]

The renin- angiotensin aldosterone system (RAAS) plays a central role in the pathophysiology of hypertension, cardiovascular and renal disease.[6,7] It contributes to the increase of blood volume, arterial pressure, alterations of endothelial function, vascular reactivity, fibrosis, tissue remodeling, oxidative stress and inflammation predisposing to the development of cardiovascular disease.[6-8] ACEI (Angiotensin Converting Enzyme Inhibitors) only partially inhibit the formation of angiotensin II (Ang II) because Angiotensin II can be produced by alternative pathways (chymases, caspases, elastases).[9,10] So ARBs provide a more rational tool to inhibit the RAAS activity.Angiotensin II exerts its effects through 2 different receptors: angiotensin type-1 (AT1R) and type-2 (AT2R) receptor. The AT1R is the predominant receptor in the cardiovascular system and mediates most of the deleterious effects of Angiotensin II such as vasoconstriction, endothelial damage, and cell growth.[11] The AT2R is now recognized as the counter-regulator of the AT1R, exerting mostly beneficial actions like vasodilatation, anti-proliferation, and tissue regeneration.[11] AT1R blockers (ARBs) are selective antagonists at the AT1R, thereby preventing the adverse Angiotensin II-mediated effects in the cardiovascular system. Furthermore, selective inhibition of the AT1R not only inhibits these effects but also leaves the AT2R open to stimulation by Angiotensin II, resulting in additional beneficial effects.[12]

C-reactive protein (CRP) is an annular (ring-shaped), pentameric protein found in blood plasma, whose levels rise in response to inflammation. It is an acute-phase protein. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via the C1Q complex.[13]CRP was so named because it was first identified as a substance in the serum of patients with acute inflammation that reacted with the 'C' carbohydrate antigen of the capsule of pneumococcus.[14] This acute phase response occurs as a result of a rise in the concentration of IL-6, which is prevalent in a wide range of conditions such as bacterial, viral, or fungal infections; rheumatic and other inflammatory diseases; malignancy; and tissue injury and necrosis.CRP rises within two hours of the onset of inflammation, up to a 50,000-fold, and peaks at 48 hours. Its half-life is 18 hours. CRP is a marker for inflammation that can be used to screen for inflammation.There are studies in mice stating ARBs decreased the CRP levels.

Dyslipidemia is a recognized cardiovascular risk factor and is a potent predictor of cardiovascular morbidity and mortality with the addition of hypertension, based on evidence from epidemiology, basic science, and clinical trials. This evidence has led to the development of management guidelines for control of comorbid conditions and clinical suggestions regarding patient adherence to therapy.[3,15,16] The simultaneous treatment of hypertension and dyslipidemia is an important strategy to decrease cardiovascular risk, considering the significant contribution of comorbid conditions in patients with and without documented cardiovascular disease.[17]Coronary Artery Disease (CAD) is due to atherosclerosis of large and medium sized arteries and dyslipidemia has been found to be one of the most important contributing factor.[18]In addition to direct end-organ protection, some ARBs have been suggested to improve abnormalities of glucose and lipid metabolisms, resulting in an anti-atherosclerotic effect in patients with hypertension.Based on the pleiotropic effects on lipid metabolism, we can envision that ARBs would provide the promising outcome for hypertensive patients aggregating metabolic risk factors, including dyslipidemia.[19]
Azilsartan medoxomil (AZL-M) is an investigational ARB in development for the treatment of hypertension. It is a prodrug that is rapidly hydrolyzed to its active moiety, azilsartan. This paper presents data on the efficacy and safety of different azilsartan doses compared with an established ARB, olmesartan (OLM-M).

Methods

This study was a randomized controlled double-blind trial to evaluate the efficacy and safety of AZL-M in patients with primary hypertension and its pleiotropic effect on lipid profile and CRP. Efficacy was assessed with both SBP and DBP obtained in the clinic. The planned sample size was 60 participants. Patients were randomized to receive either azilsartan 40-80 mg or olmesartan 20-40 mg and were followed up for a period of 3 months.

Patient eligibility:

60 patients of essential hypertension of either sex, between 30 to 80 years of age attending outdoor patient department or admitted in Guru Nanak Dev Hospital attached to Govt. Medical College Amritsar were included in the study

Patients were excluded for the following: Age < 30 years and >80 years, pregnancy with hypertension, patients of Chronic Renal Failure, patients of Chronic liver disease, hypothyroidism, collagen vascular disease, chronic heavy alcohol drinkers, patients on steroidal, non-steroidal anti-inflammatory drugs, immune suppressants or oral contraceptives, patients of uncontrolled heart failure, patients of neurological defects or deformities.

End points:

The primary end point was change in SBP and DBP, lipid profile and CRP at 3 months. Safety end points included adverse events, safety laboratory tests (LFT and RFT), electrocardiographic findings, and vital signs.

Procedure:

SBP and DBP were measured by mercury sphygmomanometer using auscultatory method (Korotkoff sounds). Patient was rested adequately for 10 minutes and BP was checked in both arms and the arm with highest BP was taken as the BP of the patient. Estimation of total cholesterol in serum was done by enzymatic– Cholesterol oxidase/peroxidase method, serum triglycerides was done by enzymatic-glycerolphoshpate / peroxidase method HDL Cholesterol was done by direct detergent method and LDL Cholesterol was calculated by Friedewald's equation. CRP was quantified by TURBILYTE CRP kit which is based on the principle of agglutination reaction. SBP and DBP were repeated every month, lipid and CRP levels were repeated at the end of 3 months. At each visit, the investigator assessed whether the patient had experienced any adverse events, and the patient could report events spontaneously throughout the study. Each event was categorized as nonserious or serious and whether it resulted in discontinuation of treatment. Safety laboratory tests were analyzed at the end of 3 months.

Statistics:

Sample size: 60 patients attending the outdoor or indoor department in Guru Nanak Dev Hospital, Amritsar.

Analysis of End points:

The primary end points were evaluated using student t test and x^2 were applied to the results. Comparisons were made between azilsartan and olmesartan groups. After all results were tabulated and compared as per standard statistical protocols, the difference between the groups was considered to be statistically significant if the p value was found to be < 0.05.

Results

A summary of the patients recruited and the number who completed the trial is summarized in Figure 1 and 2. All the patients completed the study. There was no withdrawal.

Table 1 showing sex wise distribution in both the groups

Sex	Group A (Olmesartan)		Group B (Azilsartan)		Total	
	No of cases	%age	No of cases	%age	No of cases	%age
Male	15	50%	15	50%	30	50%
Female	15	50%	15	50%	30	50%
Total	30	100%	30	100%	60	100%

Table 2 showing age wise distribution in both the groups

Age (years)	Group A (Olmesartan)	Group B (Azilsartan)
< 40	3	6
40 – 60	17	17
> 60	10	7
Mean±S.D.	54.47±10.60	53.23±10.53

There were dose dependent changes in the SBP and DBP in both the groups.But the decrease in SBP in azilsartan group was 2.93 mm Hg more than that of olmesartan group and it was statistically significant (p<0.001). The decrease in DBP in azilsartan group was 3.87 mm Hg more than that of olmesartan group and it was stastically significant (p<0.001). There was no significant decrease in total cholesterol, triglycerides, HDL, LDL levels (p>0.05). The change in CRP levels were also not significant (p>0.05) during the period of study.

Figure 3 showing mean ±S.D of comparing parameters in olmesartan group

Investigations	0 weeks		12 weeks	
	Mean	S.D	Mean	S.D
SBP	159.26	12.26	150.13	11.41
DBP	100.60	6.8	94.33	5.94
Total Cholesterol	181.93	23.84	179.66	22.96
Triglycerides	106.93	20.70	105.60	19.02
HDL	42.10	7.03	41.56	6.59
LDL	118.44	22.35	116.98	21.81
CRP	2.49	0.96	2.45	0.91

Graph showing Mean ± S.D of comparable parameters in Olmesartan group

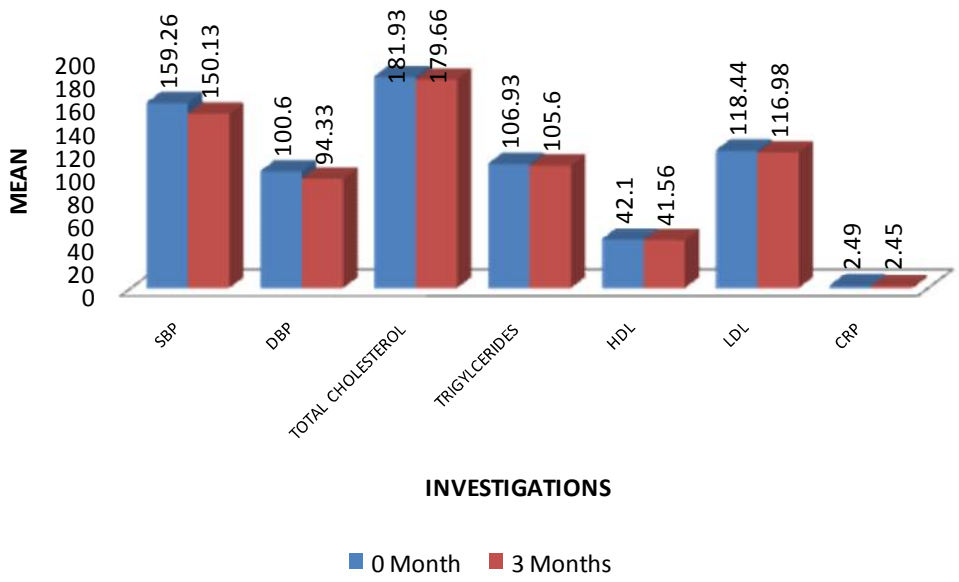
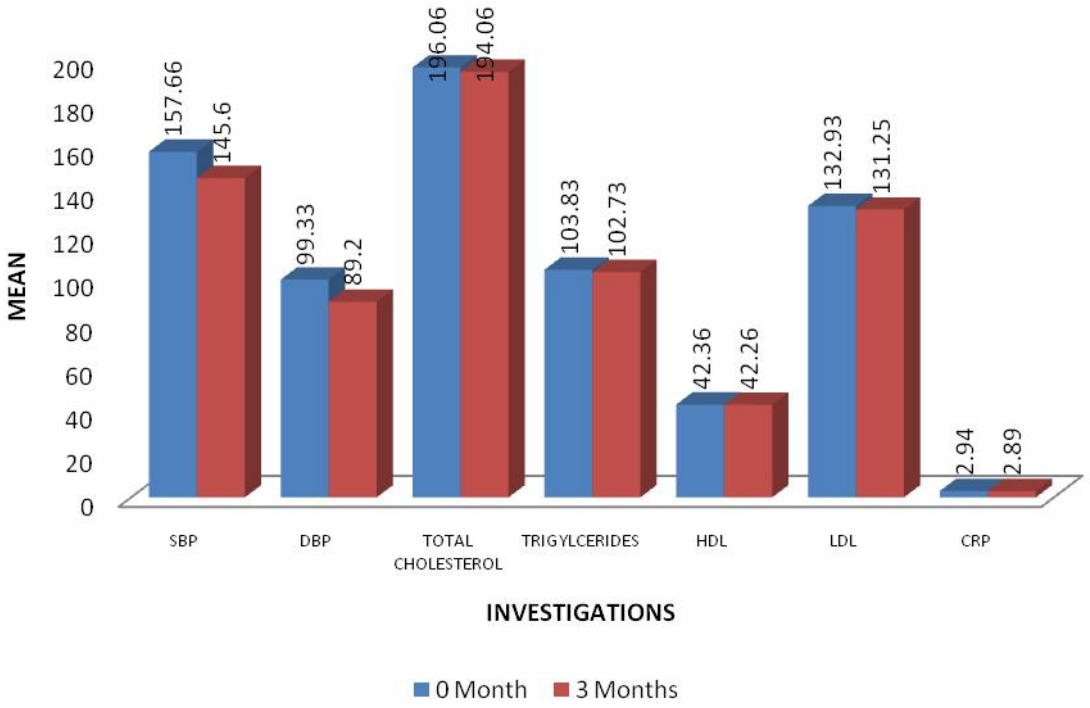


Table 4 showing mean ±S.D of comparing parameters in azilsartan group

Investigations	0 weeks		12 weeks	
	Mean	S.D	Mean	S.D
SBP	157.66	8.86	145.60	8.04
DBP	99.33	5.56	89.20	4.94
Total Cholesterol	196.06	18.61	194.06	17.81
Triglycerides	103.83	12.44	102.73	12.31
HDL	42.36	5.93	42.26	5.03
LDL	132.93	17.86	131.25	16.89
CRP	2.94	1.34	2.89	1.26

Graph showing Mean ± S.D of comparable parameters in Azilsartan group



Discussion

In this randomized control study, 60 patients with hypertension having BP>140/90 were included. They were divided into 2 groups of 30 each, group A and group B. Patients in group A were given olmesartan 20 or 40 mg, patients in group B were given azilsartan 40 or 80 mg. Lipid profile and CRP levels were done at the start of the study and at 12 weeks. Blood pressure was measured at every 4 weeks intervals for 3 months. After 3 months of study, results were compared among both groups.

The average age of patients in our study was 54.46±10.60 in group A and 53.23±10.53 in group B. In group A males comprised 50% and females 50% and in group B, males comprised 50% and females 50%.

At the start of the study the patients in groups A and B were having SBP (159.26±12.26, 157.66±8.86 respectively), DBP (100.60±6.8, 99.33±5.56 respectively), total cholesterol (181.93±23.84, 196.06±18.61 respectively), TGL (106.93±20.70, 103.83±12.44 respectively), HDL (42.10±7.03, 42.36±5.93 respectively), LDL (118.44±22.35, 132.93±17.86 respectively), CRP (2.49±0.96, 2.94±1.34 respectively).

After 12 weeks there was a highly significant fall in SBP from baseline in both the groups, but group B had greater decrease of 12.06±1.92 compared to 9.13±2.50 in group A which was found to be statistically significant ($p<0.001$). There was a highly significant fall in DBP from baseline in both the groups, but group B had greater decrease of 10.13±1.81 compared to 6.26±1.87 in group A which was found to be statistically significant ($p<0.001$). As seen in this study, the decrease in SBP and DBP in group B i.e. group receiving azilsartan was significantly more than group A i.e. group receiving olmesartan suggesting a significant anti-hypertensive role for azilsartan.

The results of this trial indicate that AZL-M is an efficacious and well-tolerated ARB that has BP-lowering effects greater than OLM-M when the highest doses of both were compared. Moreover, this greater efficacy is not associated with a worse adverse effect profile, as all the patients in azilsartan group completed the study.

As seen in the data, the change in total cholesterol, triglyceride, HDL, LDL, CRP levels were all found to be statistically non-significant ($p>0.05$) suggesting both azilsartan and olmesartan have no role in decreasing the cholesterol or CRP levels.

Differences between groups in office SBP of 2 mmHg to 3 mmHg or more in both epidemiologic analyses and interventional trials is associated with greater cardiovascular risk reduction.[20] In this trial, we note a 2.93 mmHg difference in SBP and a 3.87 mmHg difference in DBP which may be clinically relevant based on previous meta-analyses demonstrating reduced cardiovascular risk with this magnitude of change. The greater SBP reduction conferred by AZL-M is unlikely to be due to inadequate dosing of OLM-M.

Conclusion

From the study it is concluded that azilsartan is a much effective anti-hypertensive drug than olmesartan in terms of systolic and diastolic blood pressure. There were no significant improvements in the lipid profile and C reactive protein of the patients in either group.

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Conflict of interest: None declared

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