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COMPARATIVE STUDY OF SAFETY AND EFFICACY OF ATORVASTATIN AND ROSUVASTATIN IN PATIENTS WITH HYPERLIPIDEMIA

Pharmacology

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ABSTRACT

Hyperlipidemia or dyslipidemia is the commonest cause of the blood vessel diseases and has been closely linked to the pathophysiology of cardiovascular disease. In India, there has been an alarming increase in the prevalence of CVD somuch so that it accounts for 24% of all deaths among adults aged 25–69 years. Statins are considered the first pharmacological line of treatment of dyslipidemia. Lowering of LDL-C is the main beneficial effect; although effects on HDL-C and other lipoproteins also play a role. The present study was planned to primarily evaluate and then to compare the efficacy and safety of newer emerging and promising statin rosuvastatin versus existing commonly used statin as atorvastatin. Ethical committee clearance and informed consent were obtained before the study. A total of 60 hyperlipidemic patients were enrolled and allocated into two groups of thirty each; Atorvastatin 10mg/kg (A group) and Rosuvastatin 10mg/kg (R group). Patients were followed up at the end of 12 and 24 weeks. Adverse events were recorded and treated accordingly. Mean percentage change of Total Cholesterol at 12 weeks was -25.2% and -30.2% and of LDL-C was -35.2% and -44.6% for group A and group R respectively. Mean percentage change of TC at 24 weeks was -32.5% and -40.4% and LDL-C was -40.5% and -48.7% for group A and group R respectively. The reduction of lipid parameters at the end of the study were significant within the group and between the groups; showed Rosuvastatin was better compared to Atorvastatin at improving the lipid parameters.

KEYWORDS

hyperlipidemia, dyslipidemia, statins, atorvastatin, rosuvastatin.

INTRODUCTION

Hyperlipidemia is the commonest cause of the blood vessel diseases and it leads to narrowing of lumen of arteries due to the sedimentation of lipid in their walls. Dyslipidemia occurs due to the disturbance in the range of Total Cholesterol(TC), Low density lipoprotein(LDL-C), Very low density lipoprotein (VLDL), Triglycerides (TGs) and High density lipoprotein(HDL-C). The incidence of this phenomenon is seen rising all over the world thereby increasing the morbidity and mortality due to cardiovascular diseases(CVDs). (Brunzell JD, 2007)

Dyslipidemia has been closely linked to the pathophysiology of CVD and is a key independent modifiable risk factor for cardiovascular disease. In India, there has been an alarming increase in the prevalence of CVD over the past two decades so much so that it accounts for 24% of all deaths among adults aged 25–69 years. Studies have shown that over three-fourth (79%) of the general adult population have abnormalities in at least one of the lipid parameters with no urban rural difference. Despite the increasing use of lipid lowering therapies (LLTs),many patients fail to achieve lipid goals recommended in the current guidelines. (Schwandt P, 2004) Although the effectiveness of LLTs increases with dose, doses are rarely titrated.

Statins are considered the first pharmacological line of treatment of dyslipidemia. (RR, 2001;19(3)) Lowering of LDL-C levels is thought to be the main beneficial effect of statin treatment ; although effects on HDL-C and other lipoproteins also play a role. There are currently seven approved statins & each has a different benefit-risk profile. To date, numerous randomized trials among various ethnicities have documented that rosuvastatin is the most effective statin at reducing LDL-C and triglycerides (TG) and at raising HDL-C levels. Atorvastatin, before the approval of rosuvastatin was documented to be the most potent statin at reducing LDL-C levels. Also, Rosuvastatin has been shown to be highly efficacious in modifying lipid levels. At an initial dose of 10 mg, it has been associated with a greater reduction in LDL-C levels compared with other statins at their respective starting doses and on a milligram-equivalent basis. (shepherd J, 2003;91) The muscular system ,hepatic function and renal function have been documented to be affected by statin therapy. (Vasudevan AR, 2005;72(11)) In general, large-scale randomized clinical trials have consistently demonstrated that statin therapy causes only a slightly increased risk of side effects compared with placebo. For instance, post marketing data suggest an overall adverse event frequency of less than 0.5% and a myotoxicity event rate of less than 0.1%.

The present study was planned to primarily evaluate and then to compare the efficacy and safety of newer emerging and promising statin rosuvastatin 10mg/kg versus existing commonly used statin such as atorvastatin 10mg/kg for 24 weeks in patients with hypercholesterolemia. This is to guide the present treatment strategies in the management of hypercholesterolemia in South Indian population, in order to reduce the cardiovascular morbidity & thus the mortality associated with it. The doses chosen for the study are the generally recommended starting doses i.e. rosuvastatin- 10 mg and atorvastatin-10 mg.

METHODOLOGY: PATIENTS AND METHODS

This study was conducted in compliance with the protocol. The Institutional Ethics Committee (IEC) clearance was taken. Informed consent was obtained from all study participants and ICH/GCP guidelines were followed. The present study was carried out in the Department of Pharmacology, Government Medical College, Anantapuramu, in collaboration with the Department of Medicine and Biochemistry.

Nature of study

It's a randomized, open label, two arm, parallel group, comparative, prospective study.

Source of patient

The patients attending outpatient department (OPD) of Medicine were enrolled into the study after satisfying the inclusion and exclusion criteria.

Study population

Sixty hyperlipidemic patients were taken into study. The patients were allocated into two groups of thirty each using computer generated randomization table.

Source of drugs: The drugs used in the study were taken from the Pharmacy of the Hospital and the drugs are
Rosuvastatin : 10 mg/day
Atorvastatin 10 mg/day

Duration of study

The study was conducted for a period of 24 weeks for each patient

between June 2019 - Jan 2020. The patient was asked to come for follow up at the end of week-12 and week- 24.

INCLUSION CRITERIA:-
1. Males and females between 30 to 60 yrs
2. Patients with TG>200 mg/dl, TC>200 mg/dl, LDL>100 mg/dl, & HDL<40 mg/dl.
3. Patients willing to give written consent
4. Patients able to adhere to dose and visit schedule
EXCLUSION CRITERIA:-
1. Age < 30 or > 60 yrs
2. Pregnant women and lactating mothers
3. Patients with Kidney disease, Liver disease, Thyroid disease, and Gastro intestinal disease.
4. Patients on corticosteroids.
5. Endocrine diseases including diabetes
6. Patients on any other LLT.

PROCEDURE

In the present study, 84 patients were screened and after meeting the inclusion and exclusion criteria, a total of 60 patients were enrolled in the study. After enrollment, they were randomly allocated into two groups (R & A) of thirty each using computer generated randomization table.

Group R were to receive only Rosuvastatin (10mg) one tablet once a day after dinner for a period of 24 week
Group A were to receive Atorvastatin (I0 mg) one tablet once a day after dinner for a period of 24 week
During every visit, (at the end of week-12 and week-24), the reduction in the lipid parameters were evaluated in the central lab of our hospital.

Adverse event monitoring

Any adverse event that occurred was evaluated and recorded in case record form stating the onset, severity, duration, likely cause, action taken with reference to the study drugs and outcome. It was done at the end of 12 weeks and 24 weeks.

Rescue medication

If during the course of treatment, the patient experiences severe discomfort then they were at choice to take rescue medication as per physician's prescription . In case of no response to study medication, the case was evaluated and withdrawn from the study.

STATISTICAL ANALYSIS

The statistical analysis was carried out with IBM SPSS Version-20. Categorical data was presented as actual numbers and percentages. For normally distributed data, with-in group analysis was performed by using paired "t" test and between group analyses by unpaired "t" test. Non-normally distributed data were analysed by using non-parametric "Mann-Whitney U test". Categorical variables were analysed with "Fischer's exact test". All the efficacy parameters were presented as absolute change from baseline. A negative sign indicates decrease and vice versa. For statistical significance, a two tailed probability value of less than 0.05 was considered as significant.

OBSERVATIONS AND RESULTS

There was no statistically significant difference in demographic characteristics like age [45.9(7.7) vs. 45.2(4.8) Yrs, p=0.66], and body mass index [29.8(3.7) vs. 31.4(4.9) kg/cm2, p= 0.14] between A and R group respectively. In group A, 26.7% were current smokers, 16.6% were regular alcoholics, 43.3% were receiving antihypertensives and 20% were on anti-platelets. In group R, 23.3% were current smokers, 13.3% were regular alcoholics, 30.0% were receiving antihypertensives and 26.7% were on anti-platelet drugs.

Baseline Lipid profile according to treatment group.

GROUP	Atorvastatin(A)		Rosuvastatin(R)		P value
	Mean	SD	Mean	SD	
TC(mg/dl)	268.8	33.2	282.4	26.4	0.08
TG(mg/dl)	235.6	30.9	249.7	41.8	0.14
LDL(mg/dl)	153.5	34.7	157.5	28.6	0.62
HDL(mg/dl)	41.6	5.4	42.9	5.6	0.35
VLDL(mg/dl)	45.8	5.6	46.9	7.3	0.21

Analysis of the baseline lipid profile parameters, did not significantly differ between the A and R groups.

Mean Change in lipid parameters at 12 weeks according to treatment group.

GROUP	Atorvastatin		Rosuvastatin		P value
	MEAN	SD	MEAN	SD	
TC(mg/dl)	-67.2	8.3	-84.7	7.9	<0.0001
TG(mg/dl)	-30.6	4.0	-49.9	8.4	<0.0001
LDL(mg/dl)	-53.7	12.1	-69.3	12.6	<0.0001
HDL(mg/dl)	2.9	0.4	7.7	1.0	<0.0001
VLDL(mg/dl)	-8.2	1.0	-10.0	1.5	<0.0001

Mean Change in lipid parameters at 24 weeks according to treatment group.

GROUP	Atorvastatin		Rosuvastatin		P value
	MEAN	SD	MEAN	SD	
TC(mg/dl)	-86.0	10.6	-112.9	10.6	<0.0001
TG(mg/dl)	-42.4	5.6	-69.9	11.7	<0.0001
LDL(mg/dl)	-61.4	13.9	-75.6	13.7	<0.0001
HDL(mg/dl)	5.0	0.7	10.3	1.3	<0.0001
VLDL(mg/dl)	-10.5	1.3	-14.0	2.1	<0.0001

When we evaluated the absolute change from baseline to 12 and 24 weeks in the lipid profile parameters between A and R groups, it became apparent that there was statistically significant difference between the two groups with p value of <0.0001.

Percentage mean change in lipid parameters after 12 and 24 weeks of treatment.

GROUP	Group A (12 weeks)	Group R (12 weeks)	Group A (24 weeks)	Group R (24 weeks)
TC(mg/dl)	-25.2%	-30.2%	-32.5%	-40.4%
TG(mg/dl)	-13.4%	-20.3%	-18.6%	-28.2%
LDL(mg/dl)	-35.2%	-44.6%	-40.5%	-48.7%
HDL(mg/dl)	+7.5%	+18.4%	+12.4%	+24.8%
VLDL(mg/dl)	-18.7%	-20.3%	-23.1%	-28.6%

When we evaluated the percentage mean change from baseline to 12 and 24 weeks in lipid profile parameters between A and R groups, it became apparent that there was significant difference between the two groups.

After 24 weeks of treatment, 56.6 % & 90% of patients achieved target LDL of <100 mg/dl in group A & group R respectively. Group R showed a significant target achievement rate compared to group A.

After 24 weeks of treatment, 83.3 % & 97.7% of patients achieved target HDL of >40 mg/dl in group A & group R respectively. However, there was no significant difference in target achievement rate between two groups.

Side effects reported during treatment.

Headache was reported in 10% and 6.6% of patients in Group A and Group R respectively. Backache was reported in 3.3% and 0% of patients, myalgia was reported in 13.3% and 6.6% of patients, constipation was reported in 6.6 % and 6.6% of patients and fatigue was reported in 16.7 % and 10 % of patients, dizziness was reported in 3.3% and 3.3% of patients, and muscle weakness was reported in 6.6% and 3.3% of patients in Group A and Group R respectively.

DISCUSSION

Cholesterol along with some other types of fats cannot be dissolved in the blood. Moreover, in order to be transported to and from cells, they have to be specially carried by certain molecules called lipoproteins, which consist of an outer layer of protein with an inner core of cholesterol and triglycerides. The lipids can be classified as TC, triglycerides, LDL, HDL and VLDL cholesterol. In adults, LDL is strongly associated with a higher risk, and HDL is associated with a lower risk of coronary heart disease (CHD). Hyperlipidemia refers to elevated levels of lipids and cholesterol in the blood, and is also identified as dyslipidemia, to describe the manifestations of different disorders of lipoprotein metabolism.

A variety of risk factors have been found to be associated with hyperlipidemia like cholesterol rich food, overweight, alcohol abuse,

diabetes and stress. (Crawford AG, 2010;13) (Lipman TH, 2000;49). Saturated fat and cholesterol in the food has been noted to increase cholesterol levels in the body. .

Lowering lipids through dietary or pharmacological therapy has been shown to decrease the incidence of atherosclerotic events. Presently, medications from five major classes of drugs are being used to treat people with detrimental lipid levels. They include statins, nicotinic acid derivatives, fibric acid derivatives, bile acid binding resins and cholesterol absorption inhibitors. Several clinical trials have demonstrated that statins induce regression of vascular atherosclerosis and decrease in CAD mortality and morbidity in patients with and without CAD.

Statins are inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA), the enzyme which catalyzes an early, rate limiting step in cholesterol biosynthesis. Statins posses a side group that is structurally similar to HMGCoA. As a result of their structural similarity to HMG-CoA, statins are reversible competitive inhibitors of the enzymes natural substrate HMG-CoA.

Niacin has diverse actions affecting cholesterol formation. The chief effect of niacin and its derivatives involves the decreased production of triglycerides in the body and increase HDL cholesterol levels. (Guyton JR, 2008 Apr 22;51(16)). The common side effects of niacin drugs include flushing, hot flashes, itching and headache.

Fibric acid derivatives reduce the formation and increase the breakdown of cholesterol and triglycerides in the body. (McCullough PA, 2011;12). Common side effects of this class of drugs are heartburn and stomach pain. The potent members of fibrates are clofibrate, fenofibrate and gemfibrozil.

Bile acid sequestering resins, regarded as the medications that bind with bile acids and preventing the intestine from recycling them. The common side effect of this drug is constipation. The potent members of the class include cholestyramine, colestipol and colesevelam. (Hou R, 2009;38).

Ezetimibe, by blocking absorption of cholesterol in the small intestine reduces hyperlipidemia.

Statins effectively lower blood cholesterol levels and reduce the risk of cardiovascular events in many patients, and are therefore recommended as first-line agents for lowering LDL-C levels. According to NCEP III recommendations' amendments, the aggressive treatment should lower the LDL-C levels below 1.81 mmol/L (70 mg/dL), benefiting patients with high-risk coronary artery disease. (Paolo Rubba, 2009;5). Use of one of the more potent statins can serve the purpose, especially rosuvastatin or atorvastatin. The range of 40 - 60 mg/dL is designated as optimum HDL–C as per ATP III guidelines. Rosuvastatin produces favorable effects on HDL cholesterol, which is an independent marker of cardiovascular risk. In the present study, 67.06% of the total patient population achieved the HDL-C range of 40-60 mg/dL after 24 weeks of Rosuvastatin treatment.

Statins show similar chemical structures as they all show a similar analogy to the radical beta-hydroxyl-beta methyl glutaryl (HMG). Rosuvastatin, however, has a methyl-sulfonamide group which allows more interaction with some amino acid residues of the HMG CoA reductase, and a high affinity for the active site of the enzyme. Additionally, rosuvastatin hepatic selectivity shall be taken into account as it is relatively hydrophilic (the same as pravastatin), compared to other statins. In fact, classic head-to-head randomized controlled clinical trials (RCT) such as STELLAR (Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin), have shown rosuvastatin to be the inhibitor of HMGCoA reductase significantly achieving greater reduction/decrease of LDL-C. (Jones PH D. M., 2003;92).

Rosuvastatin ensures HMG CoA reductase sustained inhibition as it has more extended half-life (20 hrs) among statins. (F, 2003;4). This characteristic makes it a more valuable therapeutic option in the context of intolerance where up to 72.5% of patients with intolerance resolve their symptoms by taking rosuvastatin once every other day. Such dosing (5.6mg mean) reduces LDL cholesterol by 34.5%. In fact, two controlled clinical studies assessed rosuvastatin 10 or 20 mg once every other day versus rosuvastatin 10mg/daily during six weeks, resulting in LDL-C reduction up to 48.5%for daily dose and up to 40.9% for 20 mg once every other day(p=0.012). (Li JJ, 2012;413) (Dulay D, 2009;25). Pharmacokinetics of rosuvastatin have exhibited a prolonged effect on hepatic cholesterol synthesis in a rat model when compared with five other statins. At 7 hours after dosing, rosuvastatin showed 62% inhibition compared with 7% for atorvastatin, 31% for cerivastatin, and 13% for simvastatin. (Alberton M, 2012;105) Both in vitro and in vivo data indicate that rosuvastatin is not extensively metabolized. It is not metabolized in vivo by microsomes and is only slowly metabolized by hepatocytes, primarily via the CYP2C9. Ninety percent of a single oral dose undergoes biliary excretion and is recovered in the faeces; 92% is recovered as the parent drug. Ten percent of an oral dose is recovered in the urine and 50% metabolized. Neither age nor gender appears to affect the pharmacokinetics of rosuvastatin. Likewise, the drug's pharmacokinetics did not differ significantly between healthy subjects and those with mild to moderate hepatic impairment. LDL-C reductions were still clinically significant in the population with mild to moderate hepatic impairment, although activity appeared to be reduced in patients with more severe hepatic disease. Like pravastatin, rosuvastatin is relatively hydrophilic and exhibits a greater affinity for hepatocytes than the more hydrophobic statins. (Pasternak RC, 2002;33) It exhibits a higher rate of active uptake into hepatocytes than both pravastatin and simvastatin.

At the end of this study, rosuvastatin was found to be the most effective statin at reducing LDL-C when compared with atorvastatin.(-48.7 % vs. 40.5% respectively , p=0.0001). The present study revealed and confirmed that rosuvastatin is the most effective statin at reducing LDL-C, TGs, and total cholesterol, at the lowest dose (10 mg) at 12 and 24 weeks. Moreover, it increased HDL-C in comparison to atorvastatin by 24%.

In 2015, Aydin MU et al. conducted study in one hundred and twenty patients with STEMI showed that rosuvastatin was more effective in terms of ability to increase HDL-C level. (Aydin MU, 2015) In 2014 Khan MA et al.suggested that rosuvastatin (10mg) was more efficacious than atorvastatin (10mg) in lipid lowering effect and HDL-C raising effect but should be used with great caution and care in patients with uncontrolled hyperglycaemia and in those with compromised hepatic status. (Khan MA, 2014). Lolwa et al. concluded in his retrospective study that the most effective statin at reducing LDL-C was rosuvastatin 10 mg. and atorvastatin was the safest statin in relation to renal function. (Lolwa B, 2013)

Our present study revealed and confirmed that rosuvastatin is the most effective statin at reducing LDL-C, TGs, and total cholesterol, at the lowest dose (10 mg) at 12 and 24 weeks. Moreover, it increased HDL-C in comparison to atorvastatin by 24%.

As a class, statins are generally very safe medications. The most concerning adverse event associated with the class is rhabdomyolysis. In our study, there was no statistically significant difference in incidence of adverse effects between the groups.

Study Limitations:

We must admit that this research has some limitations. First of all the study duration is relatively short i.e. only 24 weeks, because of which we could not study any cardiovascular events, since it generally requires at least 52 weeks of follow up from baseline.

Secondly, subjects were recommended to undergo only lipid tests, since these are not routinely recommended in Indian clinical setting. Given the large number of patients, it was economically not viable to support additional laboratory tests which are not a part of routine tests in India. However, we would like to consider these points and conduct follow up studies to supplement the current findings.

CONCLUSION

In conclusion, it is possible to assert that rosuvastatin is more advantageous than atorvastatin with regard to its pharmacokinetics, LDL-C reduction, HDL elevation and percentage of patients reaching a goal, with a similar safety profile. By taking into account these assertions together with the quality of evidence found in the studies aforementioned; rosuvastatin could be considered as the first-choice over atorvastatin in patients of dyslipidemia.

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