Comparison of lipid profile improvements with low dose of rosuvastatin and simvastatin as lipid lowering drugs in high risk patients: A randomized clinical trial

Anjum Ilahi[1], Adnan Saleem Khan[2], Sadia Zainab[3], Mansur Ilahi[4]

ABSTRACT

Objective: To compare efficacy with percentage reduction in lipid profile of Rosuvastatin versus Simvastatin along with tolerability in patients of coronary artery disease.

Study Design: A randomized clinical trial

Setting: Cardiology Department of Medical Testing and Research Organization Islamabad from 1st October till 1st December 2016.

Methodology: A total of one hundred six patients with coronary artery disease were randomized into two equal groups to give Rosuvastatin 5mg to group I and Simvastatin 20mg to group II for eight weeks. As per guidelines of treatment of dyslipidemia the primary outcome was to lower LDLC< 100mg/dl. Secondary treatment outcomes were reduction of Total Cholesterol, elevation in HDL-Cholesterol and tolerability of both drugs.

Results: Rosuvastatin Group consisted of 62.3% males and 37.7% females while Simvastatin Group had 56.6% males and 43.4% females. Patients aged 55.20 ± 7.16 years in group I and 56.83 ± 6.30 years in group II. Primary treatment outcome was attained in patients of Rosuvastatin Group 75.5% as paralleled to Simvastatin 47.2%. Reduction in LDL-C from initial and terminal analyses showed significant results (Rosuvastatin 44.2% whereas Simvastatin group 39.4%). Data produced by Rosuvastatin group revealed clinically significant decrease in total Cholesterol 37.6% as compared to Simvastatin group 28.2% while more rise in HDL-C was determined in Rosuvastatin group 16.9% than Simvastatin group 7.1 %. No serious adverse effects were found in both treatments groups.

Conclusion: Rosuvastatin is more potent lipid modifying agent than Simvastatin and it has similarity to Simvastatin in tolerability.

Keywords: Rosuvastatin, Simvastatin, Dyslipidemia, Coronary artery disease, Cholesterol, LDL Cholesterol, HDL Cholesterol.

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INTRODUCTION

Dyslipidemia is one of the identifiable risk factors for the development of coronary artery disease (CAD) and cerebrovascular disorders. Treatment of hyperlipidemia has favorable outcomes in patients with CAD and stroke, and even more reduction of blood lipids is one of the main implementation in basic prevention of these diseases[1].

According to an estimate every other adult in the United States has deranged cholesterol values and every third person has high low-density lipoproteins cholesterol (LDL-C) levels[2].It has been determined to be a common cause of death in a great number of population of Pakistan. More than 180 million people in Pakistan have prevalence of coronary artery disease (CAD) with high risk factors especially in middle aged population[3].

Statins reduce cholesterol levels in patients with dyslipidemia in CAD and in those even in absence of risk to develop CAD by targeting the enzyme 3-hydroxymethylglutaryl-CoA reductase to inhibit cholesterol synthesis[4].Statins are the treatment of choice for treating deranged lipid levels, they markedly minimize cardiovascular and cerebrovascular events. Most of the effects are intervened by their antioxidant, anti-inflammatory and antithrombotic characteristics that contribute to their clinical effectiveness[5].Statins improve endothelial dysfunction and have an anti-plaque formation activity[6]. In such situations, the clinical benefits of other lipid lowering drugs are not clear and it needs further elucidation[7]. It has been well documented that available statins have slight differences in their lipid modifying actions and also in side effects profile[8]. Among all statins Simvastatin and

1. Associate Professor of Cardiology,
2. Registrar of Cardiology,
3. Assistant Professor of Physiology,

Al-Nafees Medical College & Hospital,
Isra University, Islamabad Campus, Islamabad

4. Consultant Physician and Geriatrician,
Medical Testing and Research Organization (MTRO)

Correspondence to:
Dr. Anjum Ilahi
Associate Professor of Cardiology,
Al-Nafees Medical College & Teaching Hospital Islamabad.
Email: ilahianjum@gmail.com

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Atorvastatin are most common in clinical practice[9]. Available Evidence from the Western studies has been determined that Rosuvastatin reasonably attains better declines in LDL-C with accomplishing high beneficial targets among all statins[10].

Less data is available from our country and an ample amount of evidence is available that Asians have different response than Europeans due to genetic differences, in drug absorption, disintegration in liver, receptors and transporters[11]. An increase in LDL-C carries increase risk for CAD[12]. Since stronger causal relationship exists between CAD and raised LDL-C, it remains the main target to develop strategies to focus at controlling LDL-C culminating to lessen morbidity and mortality[13]. Research has well determined that 42% decline in death rate by lowering LDL-C by 35%[14].

Despite studies have reported that statins have more profound and efficacious effects on occurrence and progression of CAD by dropping LDL-C levels but morbidity and death rate is quiet high .The desired goals are not achieved, even though the treatment guidelines and provision of lipid controlling medicines[15]. Therefore, implementation of optimal treatment has considerable clinical and economical consequences for preventing cardiovascular events and for more cost effectiveness[16].

More recent research has pinpointed that cardiovascular targets to improve lipid profile more reduced with the development of more potent type of lipid lowering therapy[17]. Trials showed that Rosuvastatin is clinically more effective when corresponds to other statins[18,19]. However, data remains unavailable in our country hence we matched efficacy of pair combination of Rosuvastatin and Simvastatin in accomplishing National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) goal to control LDL-C level in patients with CAD. Furthermore lipid lowering effect of Rosuvastatin and Simvastatin with combination with other lipid lowering drugs like cholesterol absorption inhibitor and PCSK9 inhibitor has been well documented[20]. The current study was aimed to emphasize on comparison of effectiveness of Rosuvastatin and Simvastatin without combination with other lipid lowering drugs (ezetimibe and alirocumab).

METHODOLOGY

This randomized clinical trial was conducted in Cardiology Department of Medical Testing and Research Organization (MTRO) with duration of eight weeks (1st October till 1st December 2016) after taking approval from ethical review board. One hundred and six (N=106) patients with inclusion criteria included age group of 40-70 years with diagnosis of CAD who had elevated LDL-C >160mg/dl, selected for the study after taking informed consent. The sample was calculated by open epi calculator for clinical trials and study sampling was done by consecutive sampling. Patients with inclusion criteria were equally divided and allocated to two arms of the study to take either Rosuvastatin 5mg (n=53) or Simvastatin 20 mg (n=53). Patients had reported hypersensitivity to Statins, renal and liver dysfunctions, diabetes, hypertension, unstable angina, pregnancy, nursing mothers and oral contraceptive pills users were excluded from the study.

Demographic and biochemical parameters: Demographic parameters of project were documented on Performa. Patients involved in the study were advised to consume fat restricted diet whole period of the study. All aforementioned parameters of lipid profile along with Creatinine kinase (CK) and Alanine aminotransferase (ALT) were assessed in patients included in study at baseline and terminal stage of study.

The study was aimed to attain primarily the NCEP ATP III goal of LDL-C <100mg/dl in two groups. Secondary treatment outcomes were improvements in HDLC and TC from baseline to end between the two treatment groups. Drug tolerability of two drugs was determined by assessing side effects and raised ALT three folds and CK ten folds to normal.

Data Analysis: SPSS 20 was used to analyze data. Frequencies and percentages were presented of categorical parameters whereas continuous parameters stated as Mean ± SD. Results of relative analysis between the two groups were obtained by using Multivariate analysis of Variance (MANOVA) test. A statistical significance obtained by taking p value of <0.05.

RESULTS

A randomization of N=106 patients in total were allocated to two arms to get treatment with Rosuvastatin 5mg (group I) and with Simvastatin 20 mg (group II) for time period of eight weeks. Patients were equally (n=53) divided into two groups. 55.20 ± 7.16 years was mean age of patients in Rosuvastatin group and mean age of 56.83 ± 6.30 years in Simvastatin group. 33 (62.3%) males and 20 (37.7%) females were present in group I, while group II contained 30 (56.6%) males and 23 (43.4%) females. Diabetics were 20(37.7%) in group I and 25(47.2%) in group II. Hypertensive patients were 30 (56.6%) in group I and 30(56.6%) in group II. Smoking was present in 11(20.8%) patients of Rosuvastatin group and 13(24.5%) patients in Simvastatin group. Angina pectoris in Rosuvastatin and Simvastatin groups was 20 (37.7%), 17(32.1%) respectively. Myocardial infarction in Rosuvastatin and Simvastatin groups 15(28.3%), 16(30.2%) respectively. (Table-I)

Table-I: Clinical characteristics of patients with CAD* treated with Rosuvastatin versus Simvastatin (N=106)

Variables	Rosuvastatin Group n=53	Simvastatin Group n=53	Pearson Chi square asymp significance
Age(years) Mean	55.20 ±7.1	56.83 ± 6.3	> 0.05
Male	33 (62.3%)	30 (56.6%)	> 0.05
Female	20 (37.7%)	23 (43.4%)	> 0.05
Diabetes	20 (37.7%)	25 (47.2%)	> 0.05
Hypertension	30 (56.6%)	30 (56.6%)	> 0.05
Smoking	11 (20.8%)	13 (24.5%)	> 0.05
Angina	20 (37.7%)	17 (32.1%)	> 0.05
MI	15 (28.3%)	16 (30.2%)	> 0.05

CAD* Coronary artery disease

Rosuvastatin group revealed statistically significant results reflected by better drop in LDL-C 44.2% (ranged 173.7±1.2 mg/dl - 96.9±1.1 mg/dl) with respect to Simvastatin group 39.4% (from 174.1±1.3 mg/dl to 105.4±4.7 mg/dl) p=0.001denoted in Table-II. Less than 100mg/dl of LDL-C was obtained in both groups but greater number of the patients in group I 40 (76.3%) as contrasted to group II 27(50.9%) p = 0.001 after eight weeks of statins treatment. Data resulted from Total Cholesterol displayed the similar trend of improvement as we had for LDL-C levels.

Table-II: Comparison of Mean±SD of parameters of lipid profile of patients with CAD treated with Rosuvastatin versus Simvastatin by Multivariate Tests (N=106)

Parameters	Rosuvastatin Group n=53	Simvastatin Group n=53	p-value
LDL-C initial	173.7±1.2	174.1±1.3	>0.05
LDL-C terminal	96.9±1.1	105.4±4.7	<0.001
Total Cholesterol initial	246.8±4.9	249.7±5.2	<0.001
Total Cholesterol terminal	154.0±1.1	179.2±4.6	<0.001
HDL-C initial	34.7±2.2	33.8±2.2	<0.01
HDL-C terminal	40.6±2.0	36.2±3.4	<0.001

* p value ≤ 0.05 was considered as significant
** p value ≤ 0.01 was considered as highly significant
*** p value ≤ 0.001 was considered as highly significant

Table-III: Frequency of patients of CAD* with Side effects treated with Rosuvastatin versus Simvastatin (N=106)

Adverse Effects	Rosuvastatin Group n=53	Simvastatin Group n= 53
Myalgia	3(5.7%)	2(3.8%)
Abdominal pain	2(3.8%)	2(3.8%)
ALT 1-2 times normal	1(1.9%)	1(1.9%)
CK1-2 times normal	2(3.8%)	1(1.9%)

ALT alanine aminotransferase
CK Creatinine kinase
CAD* Coronary artery disease

Normality of the data was checked through SPSS 20.0. Therefore, parametric tests were applied in which Multivariate analysis of Variance (MANOVA) used to find out significant difference between two groups on multiple dependent numerical variables (LDL,TC,HDL).Categorical variables were tested by Pearson Chi square test.

Group I 37.6% (from 246.8±4.9 mg/dl to 154.0±1.1 mg/dl) as paralleled to group II 28.2% (from 249.7±5.2 mg/ dl to 179.2±4.6 mg/dl) p=0.001. Drastic elevation in HDL-C was noticed in Rosuvastatin group 16.9% (from 34.7±2.2 mg/dl to 40.6±2.0 mg/dl) relative to Simvastatin group 7.1% (from 33.8±2.2 mg/dl to 36.2±3.4 mg/dl) p=0.001. Treatments were well tolerated in both groups and exhibited similarity in adverse effects. Myalgia was the most common found as a side effect in both the groups. 1.9% of patients from two groups developed a rise in ALT within 1-2 times normal while CK was raised to 1- 2 times normal in 2(3.8%) patients in group I and 1(1.9%) in group II. Table-III depicts none of the patients developed serious side effects in all patients of both groups.

DISCUSSION

In Rosuvastatin group mean value of LDL-C showed the decline of 44.2% in the current study with duration of eight weeks. Contrariwise mean value of 39.4% LDL-C was obtained in the group received Simvastatin therapy. The current study has been in agreement with the results produced by James W et al, they reported 40.6% reduction of LDL-C in the group treated by Rosuvastatin as compare to 35.7% decrease in the group received Simvastatin[21]. In this study primary target was to reduce LDL-C according to the guideline by (NCEP ATP III) to reduce the risk for CAD development and atorvastatin treatment group had been denoted as control group. Atorvastatin group as a control because it was considered more potent lipid modifying drug previously. In order to produce the small reductions in LDL C double dose of statins (atorvastatin, simvastatin and pravastatin) is required as compare to the comparator the Rosuvastatin.

Jones PH et al had determined that Rosuvastatin at the dose of 10 mg reduced LDL-C 12% -18% more than that of Simvastatin at dose of 20 mg with duration of six weeks trial[22]. The difference in percentage reduction could be due to double dose of Rosuvastatin as compared to the current study in which low dose 5 mg has been used. A meta-analysis has been done by Law and colleagues presented 38% drop in LDL-C in group I as paralleled to 32% in comparator the group II which is comparable to our results[23]. This study reports the compiled results from 164 randomized placebo controlled trials in which Rosuvastatin had been found the most potent lipid modifying agent. Another study by DISCOVERY-Beta exhibited the similar trend as unveiled by current study, depicted a decline of 38.79% in LDL-C with Rosuvastatin at dose of 10 mg as distinguished to 32.03% with Simvastatin at dose of 20 mg with difference in study duration and distribution of numbers of the participants in each group and found Rosuvastatin stronger lipid lowering agent[24].

Lowering LDL-C levels in high risk patients of CAD remained a main focus in optimizing treatment[17]. The considerably drastic diminution in LDL-C with Rosuvastatin as contrasted to Simvastatin in our study renders more patients in group I to accomplish NCEP ATP III target. The results had determined LDL-C 40 (76.3%) in the group received Rosuvastatin against 27(50.9%) in the group taken Simvastatin (p=0.000).

The current study revealed the results which are in consistent with other studies. A MERCURY II trial study showed that LDL-C was attained in 82% patients with Rosuvastatin and 33% with Simvastatin[25]. Another study done by MERCURY I stated 80% patients in Rosuvastatin group achieved the target of LDL-C as per guidelines of dyslipidemia treatment when paralleled to 54% in group received Simvastatin[26]. Optimum control LDL-C level has been clearly linked with betterment in treatment outcomes of cardiovascular disorders. Rosuvastatin therapy may show relatively more valuable results in control of not only LDL-C level but other parameters of lipid profile in both type of patients which include with and without high risk patients of CAD[20].

Statistically significant results attained in our study regarding decrement in TC levels induced by Rosuvastatin therapy which showed 37.6% while 28.2% in Simvastatin therapy within 8 weeks. This fall in TC is in line with other clinical trials. A clinical trial showed 37% decrease in TC with Rosuvastatin depicted as stronger anti-hyperlipidemic statin than Simvastatin which decreased TC levels up to 24.1%[25]. A meta-analysis by Edwards and Moore described 30% fall in TC in Rosuvastatin therapy and 21% by Simvastatin[27]. James W et al found the results which have been in agreement with the results of current study, documented 28% lessening in TC in Rosuvastatin and 23% in Simvastatin treatments groups with time span of 12 weeks[21].

A time frame of eight weeks which was the duration of present study by statin therapy, revealed a rise in HDL-C levels 16.9% in group I as contradistinction to group II 7.1%.This increase indicated comparable trend of statin therapy determined by other researches. Edwards and Moore estimated 9% rise in HDL with Rosuvastatin as associated with 8% by Simvastatin[27]. A review by Mc Taggart and Jones appraised 8.5% elevation in HDL-C in Rosuvastatin contrasted 6.4% in Simvastatin treatment[28]. A DISCOVERY-Beta study found somehow analogous trend in results with raised levels of beneficial cholesterol both with Rosuvastatin (0.66%) and Simvastatin (2.26%)[24]. This uncertain improvement of HDL-C in DISCOVERY study can be due to less difference in plasma levels of HDL-C at initial and terminal stage of study. It has been reported that simvastatin increase the HDL-C further than the atorvastatin but not more than the comparator Rosuvastatin[21].

The present study determined that Rosuvastatin treatment has been associated with adverse effects which showed analogy to greater extent to those produced by Simvastatin treatment. The findings are in consistent with the outcomes appraised by other clinical trials[26,29,30]. More recent data report that Rosuvastatin has been determined more efficacious than the other statins in different pair combinations on modifying LDL-C, TC and HDL-C[31]. The current study, denoted that Rosuvastatin with low dose of 5mg exhibited stronger effectiveness on modifying lipid profile and showed similarity to Simvastatin 20mg pertaining to development of side effects.

CONCLUSION

Rosuvastatin is more potent statin than Simvastatin as it has profound effects on improvements of all components of lipid profile but showed indifferent results related in drug tolerability to Simvastatin.

CONTRIBUTION OF AUTHORS

Ilahi A: Conceived idea, Designed research methodology, Data analysis, Manuscript writing
Khan SA: Manuscript writing, Data analysis.
Zainab S: Data collection, Literature review
Ilahi M: Manuscript writing

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