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Original Research Article

Comparison of saftey and cost effectiveness of atorvastatin 40 mg daily, rosuvastatin 20 mg daily and rosuvastatin 20 mg alternate day in 300 patients with type 2 diabetes mellitus

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ABSTRACT

Background: Diabetes is recognized as a "coronary heart disease risk equivalent". This happens because high rates of dyslipidemia among diabetic patients which is thought to be one of the major factors leading to the high percentage of deaths among diabetics due to cardiovascular disease (CVD).
Methods: The study aims to compare the cost effectiveness and tolerance or safety profile of atorvastatin 40 mg daily and rosuvastatin 20 mg daily and on alternate day. This prospective observational study was conducted in 300, type-2 diabetes mellitus patients between November 2013 and 2014.
Results: The total CK level increased after 6 weeks among patients on atorvastatin 40 mg, rosuvastatin 20 mg, and rosuvastatin 20 mg alternate day was stastically significant although it was within accepted normal range. None of the patients reported to have muscle symptoms i.e. myalgia. SGOT, SGPT, bilirubin levels with atorvastatin 40 mg were statistically insignificant. Same was the case with rosuvastatin 20 mg daily. However the SGOT and bilrubin level increased with rosuvastatin 20 mg alternate day was statistically significant, but was within normal range, we attribute it to chance. The cost obviously has shown to half in rosuvastatin 20 mg on alternate day.
Conclusions: Atorvastatin 40 mg, rosuvastatin 20 mg and rosuvastatin 20 mg alternate day was statically significant ($p<.0010$). SGOT, SGPT, bilirubin with atorvastatin 40 mg were statistically insignificant. Same was case with rosuvastatin 20 mg daily. SGOT, bilirubin level increased with rosuvastatin 20 mg alternate day was statistically significant. Cost obviously shown to half in rosuvastatin 20 mg alternate day.

Keywords: Cost effectiveness, Creatine kinase, Dyslipidemia, Saftey profile

INTRODUCTION

In patients with diabetes the lipid abnormalities play an important role in development of atherogenesis**.** Diabetes is recognized as a "coronary heart disease risk equivalent"[1-4] This happens because high rates of dyslipidemia among diabetic patients which is thought to be one of the major factors leading to the high percentage of deaths among diabetics due to cardiovascular disease (CVD).[5] The differences in the lipid profile between diabetics (especially type 2 diabetics) and nondiabetics account for the increased CVD risk. Essentially, T2DM lipid profiles consist of elevations in triglyceride (TG) levels (>2 mmol/L) and reductions in high-density lipoprotein cholesterol (HDL-C). While low-density lipoproteins cholesterol (LDL-C) concentration levels are

normal, the particles are denser and smaller in size, which is believed to enhance their atherogenic potential. Statins are considered the first pharmacological line of treatment of dyslipidemia in diabetic patients[6]. 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.

Statins, like all other pharmacological treatments, inevitably have adverse side effects. The muscular system, hepatic function, and renal function have been documented to be affected by statin treatment.[7,8] In general, large-scale randomized clinical trials have consistently demonstrated that statin therapy causes only a slight increased risk of side effects compared with placebo.[9,10] For instance, postmarketing data report an overall adverse event frequency of less than 0.5% and a myotoxicity event rate of less than 0.1%.[11] In India there are no past studies or trials that have shown the safety and cost effectiveness of various statins prescribed to diabetic patients. The current study tries to build on the rising awareness against atherosclerosis, by examining the safety and cost effectiveness of commonly prescribed statin among Indian population.

METHODS

This prospective open labeled observational study was carried out on patients attending the Department of General Medicine, Dr. Ram Manohar Lohia Combined Hospital, Lucknow, Uttar Pradesh, India from November 2013 to November 2014.A Total of 300 adult subjects (both male and females) aged ≥ 18 years were included in this study. Study was done from November 2013 to November 2014.

The sample size was 300 patients estimated on the basis of a single proportion design. The target population from which we randomly selected our subjects was considered 20,000. We assumed the confidence interval of 10% and confidence level of 95%. The sample size actually obtained for this study was 96 patients for each group. We planned to include 300 patients (Group I- Control, Group II- Cases of 100 patients for each group) with 4% drop out rate.

The study population was drawn from consecutive diabetic patients who presented to Dr. Ram Manohar Lohia Combined Hospital with type 2 diabetes mellitus were prescribed the indicated statins are the study patients underwent fasting blood test of lipid profile and SGOT, SGPT, bilirubin and creatine kinase (total) before statin treatment initiation between from November 2013 to November 2014. Patients were divided into three groups (each group had 100 patients) according to type and dose of statins. The prescribed doses of statin in RMLH for diabetic patients with dyslipidemia were as follows:

Group A (N=100 patients): Atorvaststin 40mg daily.

Group B (N=100 patients): Rosuvastatin 20mg daily.

Group C (N=100 patients): Rosuvastatin 20 mg on alternative days.

Inclusion criteria

- Diabetic patients (fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L)
- Either sex
- Aged ≥18 years,
- Patients have a total cholesterol level of ≥154.68 mg/dl, LDL-C ≥96.6 mg/dl, HDL-C ≤ 138 mg/dl in men and ≤46.3 mg/dl in women,
- Fasting triglycerides ≥ 150.56 mg/dl, obtained within 1 week before the first use of statins which was then compared at first- and second-year intervals.

Exclusion criteria

- Pregnant women;
- Patients with genetic disorders
- Patients on other concurrent lipid lowering agents such as bile acid sequestrants (cholestyramine, colesevelam), niacin, ezetimibe, fenofibrate and/or omega 3 fatty acids
- Patients with previous history of angina, severe vascular disease, or other life threatening disease.
- Patients with nephropathy and/or hypothyroidism, active liver disease, bile duct problems, or ALT > 3 × ULN
- Patients with creatine kinase levels > 10 × ULN
- Patients taking concurrent corticosteroids, ciclosporin, and/or hormone replacement therapy
- Patients who were physically inactive
- Patients with a history of drug or alcohol abuse.

Predesigned proforma for data collection was prepared. After obtained written informed consent, a well-designed questionnaire was used to collect the data of the recruited patients. The questionnaire included socio-demographic characteristics such as age, gender, nationality, height, weight, and history of consanguineous marriage, physical activity and lifestyle habits like smoking and alcohol and statin prescribed for at least 2 years continuously and dose, type of DM, its duration, and clinical and biochemistry laboratory investigations such as fasting blood glucose, glycated hemoglobin (HbA1C), total cholesterol, HDL and LDL cholesterol levels, and TGs level. All lipid parameters were quantified on samples collected in the fasting state. Cholesterol and TG quantization was determined by enzymatic assay. LDL-C was calculated using the Friedewald equation for patients with TG ≤ 400 mg/dl and measured by b-quantification for those with TG > 400 mg/dl. Levels of non-HDL-C were calculated by subtraction of HDL-C from total cholesterol. Information about the type of statin (rosuvastatin, atorvastatin) was taken from the pharmacy

database. Baseline characteristics of the patients were collected from the database 1 week before the first use of statins. Again after using statins, biochemistry values were collected at 6weeks interval for comparison.

Height and weight were measured using standardized method. The body mass index (BMI) was calculated as the weight in kilograms (with 1 kg subtracted to allow for clothing) divide by height in meters squared. Blood pressure was recorded using an electronic instrument as the mean of two readings taken five minutes apart. The prescribed doses of statins for diabetic patients with dyslipidemia were as follows:

Group A- Atorvaststin 40mg;
Group B -Rosuvastatin 20mg; and
Group C - Rosuvastatin 20 mg at alternate days.

Cost-effectiveness

Cost-effectiveness which was measured in only the drug costs because this study focused on drug prices and the surrogate outcome (LDL-C level less than 100 mg/dL according to NCEP ATP III guidelines). It was assessed among statin types based on incremental cost effectiveness that outcome was measurement. The cost-effectiveness ratio (CER) usually referred to in pharmacoeconomics was the incremental cost-effectiveness ratio (ICER), which compares the costs and effects of one treatment (here, statin drug) with those of another (typically another statin drug). The ICER was defined as the difference in the cost of each statin type divided by the difference in their effectiveness. Thus, the ICER was calculated by:

Table 1: Method for calculation of cost effectiveness.

How to calculate on the ICER drug	Cost (USD)	Effect (% patients achieved the goal)	C/E (USD/% patients achieved the goal)	ΔC/ ΔE
Atorvastatin	A1	A2	A1/A2	(A1/A2)
Rosuvastatin 20mg	B1	B2	B1/B2	(B1-A1)/(B2-A2)
Rosuvastatin 20 mg alternate day	C1	C2	C1/C2	(C1-B1)/(C2-B2)

An economic value assessment was calculated based on provider perspective. Costs included only drug costs within a time horizon of 1 year. Drug costs are based on the retail price at Dr. Ram Manohar Lohia Combined Hospital in 2013-14. These prices were converted from Rupees unit to USD by using exchange rate as of average 2013-14. It was 66 Rs/USD.

Tolerance or saftey profile

All the patients included in the study underwent the the measurement of SGOT, SGPT, serum bilirubin, total C.K levels before the start of treatment and after 6 weeks.

Statistical analysis

Data was analyzed using SPSS version 20 (SPSS Inc., Chicago, IL). Student's *t*-test was used to ascertain the significance of differences between mean values of two continuous variables and confirmed by nonparametric Mann-Whitney test. In addition, paired *t*-test was used to determine the difference between baseline and 2 years after regarding biochemistry parameters, and this was confirmed by the Wilcoxon test which was a nonparametric test that compares two paired groups. Chi-square and Fisher exact tests were performed to test for differences in proportions of categorical variables between two or more groups. The level P <0.05 was considered as the cutoff value or significance.

RESULT

On administration of a regular dose of Atorvastatin 40mg, the cost works out to be 40.97(USD) for each patient. The cost of treatment per head was 35.79(USD) with a regular dose of Rosuvastatin 20mg, whereas it was 704.21 (USD) per head while treating with an alternate dose of Rosuvastatin 20 mg (Table 2).

Table 2: Comparisons of cost-effectiveness in achievement of LDL-C goal according to NCEP ATP III guidelines among statin therapy.

Drug	Cost (USD)	Effect (% patients achieved the goal)	C/E (USD/% patients achieved the goal)	ΔC/ ΔE
Atorvastatin 40mg	1515.79	37	1515.79/37 = 40.97	40.97
Rosuvastatin 20mg	1408.42	40	1408.42/40 = 35.21	35.79
Rosuvastatin 20 mg alternate days	704.21	39	704.21/39 = 18.06	704.21

Table 3: Incremental cost-effectiveness ratios (ICER).

Drug	Effectiveness % attain LDL-C goal	Mean annualized cost (USD)	Incremental cost (ΔC)	Incremental effect (ΔE)	ICER
Atorvastatin 40mg	37	15.16	15.16	37	0.41
Rosuvastatin 20mg	40	14.08	1.08	3	0.36
Rosuvastatin 20mg alternate days	39	7.04	8.12	1	8.12

Incremental cost-effectiveness ratio (ICER), which is calculated as the difference in the expected cost of two interventions, divided by the difference in the expected QALYs produced by the two interventions (Table 3). The incremental cost-effectiveness ratio (ICER) is a method used in cost-effectiveness analysis to summarise the cost-effectiveness of a health care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect (Table 4).

Table 4: The incremental cost-effectiveness ratio (ICER).

Statin therapy	Effectiveness % attain LDL-C goal	Annualized cost (Rs.)	Annualized cost (USD)*	Mean annualized cost (USD)**	CER (mean annualized cost/effectiveness)	ICER
Atorvastatin 40mg	37	100800	1515.79	15.16	0.41	0.41
Rosuvastatin 20mg	40	93660	1408.42	14.08	0.35	2.78
Rosuvastatin 20mg alternate	39	46830	704.21	7.040	0.19	5.54

Table 5: National cholesterol education program NCEP ATP III goal.

Number of patients (%) achieving NCEP ATP III goal		
Statin therapy	Achieved (%)	Total
Atorvastatin 40mg	37 (37)	100
Rosuvastatin 20mg	40 (40)	100
Rosuvastatin 20mg alternate days	39 (39)	100
Total	116 (38.66)	300

NCEP ATP III goal was achieved by 40 (40%) patient treated with a regular dose of Rosuvastatin 20mg, 39 (39%) patient could achieve the goal with an alternate dose of Rosuvastatin 20mg. As for treatment with Atorvastatin 40mgwas concerned only 37 (37%) patient achieved the goal as stipulated by National Cholesterol Education Program NCEP ATP III goal (Table 5).

Table 6: Comparison of enzymes and bilirubin levels of studied patients among groups.

Parameters	Baseline value			After 6 week treatment		
	Atorvastatin 40mg	Rosuvastatin 20mg	Rosuvastatin 20mg alternate	Atorvastatin 40mg	Rosuvastatin20mg	Rosuvastatin20 mgalternate
SGOT (U/L)	22.24±3.5	20.11±3.4	20.25±3.6	23.01±2.7	21.14±3.5	22.15±3.18
SGPT(U/L)	46.49±4.6	46.32±4.7	47.34±4.5	46.66±4.8	48.34±5.1	49.77±5.5
Bilirubin(mg/dl)	1.11±0.4	0.67±0.2	0.89±0.5	1.17±0.3	1.12±0.4	1.20±0.3
CK (IU/L)	80.45±41.5	111.6±33.7	125.4±55.3	133.1±92.2	141.85±55.3	172.05±43.7

Bilirubin level had gone up to a highest level in patient group treated under a regular dose of Rosuvastatin 20mg.The maximum increase in the CK (IU/L) enzymes level had been observed in the patient treated under regular dose of Atorvastatin 40mg. Also levels of SGOT (U/L) and SGPT (U/L) enzymes were highest for patient

group treated by an alternate dose of Rosuvastatin 20mg. An increase in the levels of Bilirubin (mg/dl) and enzymes are SGOT (U/L), SGPT (U/L) and CK (IU/L) from baseline values had been recorded in the patients treated with a regular dose of Atorvastatin 40 mg. The variation in the level of CK (IU/L) among the patients after 6-week treatment was highly statistically significant as P<0.001 (Table 6).

An increase in the levels of bilirubin (mg/dl) and enzymes SGOT (U/L), SGPT (U/L) and CK (IU/L) from baseline values had been recorded in the patients treated with a regular dose of Rosuvastatin 20 mg. The variation in the level of CK (IU/L) and Bilirubin (mg/dl) among the patients after 6-week treatment was statistically highly significant as P<0.001 (Table 7). An increase in the levels of bilirubin (mg/dl) and enzymes SGOT (U/L), SGPT (U/L) and CK (IU/L) from baseline values had been recorded in the patients treated by Rosuvastatin 20 mg on alternate days. The variation in the level of CK (IU/L), SGOT (U/L) and Bilirubin (mg/dl) among the patients after 6 week treatment was statistically highly significant as P<0.001 (Table 8),

Table 7: Post treatment effect of bilirubin and enzymes by atorvastatin 40 mg.

Parameters	Baseline value	After 6 week treatment	p-Value
SGOT (U/L)	22.24±3.5	23.01±2.7	0.083
SGPT (U/L)	46.49±4.6	46.66±4.8	0.798
Bilirubin (mg/dl)	1.11±0.4	1.17±0.3	0.232
CK (IU/L)	80.45±41.5	133.1±92.2	<0.001

Table 8: Post treatment effect of bilirubin and enzymes by rosuvastatin 20 mg.

Parameters	Baseline value	After 6 week treatment	p-Value
SGOT (U/L)	20.11±3.4	21.14±3.5	0.036
SGPT (U/L)	46.32±4.7	48.34±5.1	0.004
Bilirubin (mg/dl)	0.67±0.2	1.12±0.4	<0.001
CK (IU/L)	111.6±33.7	141.85±55.3	<0.001

Table 9: Post treatment effect of bilirubin and enzymes by rosuvastatin 20 mg alternative days.

Parameters	Baseline value	After 6 week treatment	p-Value
SGOT (U/L)	20.25±3.6	22.15±3.18	<0.001
SGPT (U/L)	47.34±4.5	49.77±5.5	0.008
Bilirubin (mg/dl)	0.89±0.5	1.20±0.3	<0.001
CK (IU/L)	125.4±55.3	172.05±43.7	<0.001

DISCUSSION

Dyslipidemia in patients with diabetes plays a key role in development of atherogenesis. Statins are the standard of treatment for dyslipidemia. For the treatment of dyslipidemia, the most commonly used statins are atorvastatin and rosuvastatin.

Safety data from several large-scale clinical and pharmacoepidemiologic studies has shown that the safety of rosuvastatin 10-40 mg was like that observed for the other statins studied and that rosuvastatin demonstrated a favourable benefit-risk profile across this dose range.[13-15] Results from a recent study by the national lipid association (NLA) also support these findings.[16]

As if now no Indian study is available for treating diabetic patients with dyslipidemia or dyslipidemia alone with statin on alternate day and no previous study has documented, safety and cost effectiveness of various statins prescribed to diabetic patients. Thus the current study aims at examining cost effectiveness and safety of the two most commonly prescribed statins in India.

The present study was an open label prospective comparative study done in Department of General Medicine, at Dr. Ram Manohar Lohia Combined Hospital hospital, Lucknow, Uttar Pradesh in the time interval of November 2013 to November 2014.

Tolerance or safety profile

One of the most common complaints related to statin use is related to the effect of statins on muscular function. Muscle symptoms range from myalgia, which includes muscle pain without creatine kinase (CK) elevations, to myositis which is muscle symptoms with CK elevations.[18] In general, elevations of CK of more than

ten times the upper limit of normal are regarded as significant elevations justifying the discontinuation of statin treatment. Although there was a significant increase in total CK levels in all the 3 treatment groups, but was within the accepted normal range. We did not observe muscle related abnormalities in any of the patients. In other words, all statins, irrespective of dose, were regarded as safe in terms of myositis and in the current study also we found the similar results as previous studies. However, since the follow up in the present study was short, it is difficult to comment on what may be the results in long run.

Hepatic function is also known to be affected by statin use.[18] This is mainly measured by asymptomatic elevations of the liver enzymes ALT and AST, otherwise known as transaminitis.

Surprisingly a rise in SGOT level was found to be significantly higher in rosuvastatin in 20 mg alternate day group, though it was within acceptable normal limits. This was not seen in patients on atorvastatin 40 mg daily and rosuvastatin 20 mg daily. We believe it was a chance finding.[17] This is not surprising, as clinical trials have reported a 0.5-3.0% occurrence of elevations in aminotransferases among patients receiving statins and very rare episodes of severe liver injury. In general, the incidence of hepatic failure in patients taking statins appears to be in different from that in the general population.[17]

Cost analysis

The comparisons carried out in the present study indicate that rosuvastatin 20 mg daily or rosuvastatin 20 mg alternative is likely to be cost-effective over generic atorvastatin 40 mg in terms of reducing cardiovascular mortality and morbidity among patients at moderate to high cardiovascular risk over a patient's lifetime. The simulations modeled indicated overall ICERs (cost/QALY) associated with the use of rosuvastatin versus the other statins ranging from SEK 88,113 (versus simvastatin 40 mg at $30% 10-year risk) to SEK497,542 (versus atorvastatin 40 mg at $20% 10-year risk). The time horizon for this analysis extends beyond the anticipated market entry of generic rosuvastatin, and the current analysis therefore accounts for this as in previous work based on the JUPITER trial[18]. Accounting for future generic drug costs is recognized as increasing the reliability of estimates of the true cost-effectiveness of a medical intervention.[19-21]

The World Health Organization has suggested international cost-effectiveness threshold values of three times the gross domestic product per capital and thresholds up to US$100,000 have been suggested.[22,23] In Sweden, values equivalent to around US$100,000 (about €70,000) have been indicated on the basis of willingness to pay for prevention of road deaths.[24] Based on the average exchange rate for USD to SEK in 2013/14 (avg Rs. 61) this indicates equivalence to approximately INR 3628 which would encompass all the quality-adjusted lifetime horizon estimates generated by the comparisons carried out here.

It is worth noting that a pharmacoeconomic analysis of the primary MERCURY results showed that treatment with rosuvastatin 20 mg was more cost-effective, compared to equivalent or higher doses of atorvastatin and rosuvastatin alternative and that switching patients from a comparator statin to rosuvastatin improved LDL-C goal attainment at relatively little additional cost, with equivalent (or lower) associated drug costs.[12,17] Thus, rosuvastatin 20 mg may have pharmacoeconomic advantages, compared to atorvastatin 40 mg, while providing comparable efficacy.

The major limitation of the study were that although the study showed biochemical benefits, but since follow up was short so the hard end points could not be studied. Concluding the total CK level increased after 6 weeks among patients on atorvastatin 40 mg, rosuvastatin 20 mg and rosuvastatin 20 mg alternate day was statistically significant although it was within accepted normal range. None of the patients reported to have muscle symptoms i.e myalgia.

SGOT, SGPT, bilirubin levels with atorvastatin 40 mg were statistically insignificant. Same was the case with rosuvastatin 20 mg daily. However the SGOT and bilrubin level increased with rosuvastatin 20mg alternate day was statically significant, but was within normal range, we attribute it to chance. The cost obviously have shown to half in rosuvastatin 20 mg on alternate day.

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