Myanmar Health Sciences Research Journal, Vol. 27, No. 3, 2015

Lipid Lowering and Antioxidant Effects of Atorvastatin and Rosuvastatin in Myanmar Hypercholesterolemic Subjects

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Hypercholesterolemia is a major risk factor for atherosclerosis. Atorvastatin is one of the routinely used statins and rosuvastatins, newest and efficacious statin, which is less frequently used in management of hypercholesterolemia in Myanmar. This study aimed to compare the lipid lowering effect and antioxidant effect {by measuring plasma malondialdehyde (MDA) level} of atorvastatin 10 mg with that of rosuvastatin 10 mg in Myanmar hypercholesterolemic subjects for 6 weeks therapy. Community-based, interventional study was done in North Okkalapa Township, in which forty-two hypercholesterolemic subjects screening blood total cholesterol (TC>200 mg/dl) were divided into two groups of equal number by randomized computerization. Serum TC, triglyceride (TG), high density lipoprotein (HDL) and MDA levels were measured. Low density lipoprotein (LDL) level was calculated. Lipid lowering and antioxidant effects of both drugs were not significantly different at baseline. After 6-week therapy, both atorvastatin and rosuvastatin significantly reduced TC (180.98±19.87 and 149.40±17.62 mg/dl, $p<0.001$), LDL (108.77±18.82 and 79.38± 15.49 mg/dl, $p<0.001$), TG (107.51±31.82 and 83.91±28.63 mg/dl, $p<0.05$), respectively and increased HDL (48.82±3.21 and 51.79±3.78 mg/dl, $p<0.05$), respectively. Although both drugs effectively reduced lipid profile, rosuvastatin significantly produced more reduction in lipid profile than atorvastatin. Both atorvastatin and rosuvastatin significantly reduced MDA (2.63±0.991 and 2.28±1.123 μmol/L, $p<0.05$) and rosuvastatin produced significantly greater reduction than atorvastatin ($p<0.05$). Therefore, this study suggested that rosuvastatin can also be used as a first-line agent in atherosclerosis because of more efficacious lipid lowering effect and antioxidant (MDA lowering) effect than that of atorvastatin.

Key words: Atorvastatin, Rosuvastatin, Lipid lowering effect, Antioxidant effect, Malondialdehyde

INTRODUCTION

Hypercholesterolemia is a major risk factor for the development and progression of atherosclerosis and continues to be leading cause of morbidity and mortality. Therefore, effective use of lipid modifying agents becomes essential to reduce elevated cholesterol concentration particularly LDL cholesterol.[1]

Among the various therapeutic agents for hypercholesterolemia, 3-hydroxy-3-methyl glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) are the treatment of choice because of their proven efficacy and safety profile. Although all statins share a common mechanism of action, they differ in terms of chemical structures, pharmacokinetic profiles and lipid modifying efficacy. Among the different statins, atorvastatin and rosuvastatin are more effective than the other statins in lowering LDL cholesterol because of their longer residence time in plasma than the others.[1]

Numerous studies showed that across the dose ranges, rosuvastatin was seen to be significantly more efficacious than atorva-

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statin in reducing LDL and improving other lipid parameters in patients with hypercholesterolemia.[2]

Furthermore, oxidized LDL is a major correlate of oxidative stress in hypercholesterolemic patients.[3] There is an increasing role of statins in managing cardiovascular risks in patients because of their beneficial pleiotropic effect addition to the cholesterol lowering effect. Atorvastatin possesses antioxidant effect and has been shown to prevent oxidative modification of LDL cholesterol. Rosuvastatin also has been shown to possess antioxidant properties more in comparison to other statins.[4]

Atorvastatin is one of the routinely used statins but the rosuvastatin, newest and efficacious one is less frequently used in management of hypercholesterolemia in Myanmar. Therefore, this study was aimed to compare the lipid lowering and antioxidant effects of rosuvastatin, at therapeutic dose (10 mg) with that of atorvastatin (10 mg) in Myanmar hypercholesterolemic patients.

MATERIALS AND METHODS

The community-based interventional study was conducted from June 2012 to May 2013. The estimated sample size was calculated by formula of Browener, *et al*.[5] Before the study, 200 subjects from Kagyi, Gagyi and Salane wards of North Okkalapa Township were recruited for screening of hypercholesterolemia. Among them, a total of 42 hypercholesterolemic subjects with screening serum TC>200 mg/dl were collected as study population according to inclusion and exclusion criteria. Collection of blood samples and determination serum lipid level and plasma MDA level were done at Department of Pharmacology and Department of Biochemistry, University of Medicine 2 (Yangon).

Both males and females with the age of 40-65 years, body mass index <30 kg/m^2 and screening blood TC>200 mg/dl were included in the study. The pregnant and lactating women, patients with significant renal or liver diseases, severely ill patients (e.g. unstable angina), smokers, alcoholics, patients with blood TG>400 mg/dl, patients who were taking drugs such as antioxidant vitamins: Vitamin C, Vitamin E; drugs that would affect the plasma lipid level (e.g. fibrate, cholestyramine niacin, diuretics, β blocker, calcium channel blocker); metabolic enzyme inducers (e.g. rifampicin, dexamethasone); metabolic enzyme inhibitors (e.g. erythromycin, cimetidine) were excluded from the study.

Drugs used in the study were atorvastatin tablet, 10 mg (Aztor, 10 mg tablet, SUN, India) and rosuvastatin tablet, 10 mg (Rozavel 10 mg tablet, SUN, India).

Study procedure

This protocol was approved by the Ethical Committee of University of Medicine 2 (Yangon) before commencement of the study. After thorough explanation about the study, informed consent was taken from each subject. Before the study, 3 ml of ten-hour fasting blood samples were taken from each subject for screening of hypercholesterolemia.

Selected subjects according to the inclusion criteria were inquired their personal data, medical history and drug history. Physical examination including measurement of body weight, height, and blood pressure and pulse rate was done according to the proforma and recorded. All the subjects were given dietary advice by giving pamphlets for nutritional guidelines and by explaining and encouraging to follow the nutrition guidelines published by Department of Medical Research.[6] They were also suggested to stop taking or not to use any traditional medicines during study period. They were asked to come back after one week to participate in clinical intervention.

After 1 week, 8 ml of ten-hour fasting venous blood samples were collected at 8:30 AM and analyzed immediately for TC, TG, HDL, and plasma MDA level for

baseline data from each subject. Serum LDL cholesterol was calculated as baseline data. All the subjects were divided into two groups with equal number by randomized computerized table. Atorvastatin (10 mg) was given to one group and rosuvastatin (10 mg), the other group, respectively and asked to take once daily after meal during evening for 6 weeks. During the intervention period, they were advised to follow dietary control. Follow-up was done every 2 weeks up to 6 weeks.

At the end of 6-week intervention, 8 ml of ten-hour fasting blood samples were collected and all the blood samples were analyzed immediately for TC, TG, HDL and plasma MDA. Serum LDL cholesterol was calculated and recorded.

Sample collection

Under aseptic condition, 8 ml of ten-hour fasting (from 10:00 PM to 8:00 AM) venous blood sample were withdrawn from antecubital vein of each subject and collected into two test tubes separately. Three milliliters of blood were placed into the tube containing ethylene diamine tetra-acetic acid for MDA assay. Five milliliters of blood were placed into another plain test tube for determination of serum lipid levels. The serum lipid levels and plasma MDA were determined immediately on the day of collection in the laboratory of Biochemistry Department, University of Medicine 2.

Methods used for measurements of biochemical parameters

Serum TC, HDL, TG, and plasma MDA levels were analyzed by a methods,[7] enzymatic colorimetric test, phosphotungstate magnesium, and thiobarbituric acid reaction test,[8] respectively. Serum LDL level was calculated by the formula of Fridewald.[9]

Data analysis

Data were collected and analyzed by means of the computer-based statistical package of statistical product and service solution (SPSS), version 16. Continuous data were analyzed by student and paired "t" test. Categorical variable was analyzed by X^2 test. Level of significant was set at $p<0.05$ (at 95% Confidence Interval).

RESULTS

In the present study, 42 hypercholesterolemic subjects were studied for changes of their serum lipid levels and plasma MDA level after 6-week period of statin; atorvastatin (10 mg) and rosuvastatin (10 mg) once daily for 6 weeks, each subjects were divided into two groups, twenty-one each atorvastatin and rosuvastatin.

Table 1. Demographic data of the study population (n=42)

Parameter	Atorvastatin group	Rosuvastatin group	p value
Male (No.)	11	10	
Female (No.)	10	11	
Age (year)	51.05±5.74*	50.76±6.09*	0.894
BMI (kg/m^2)	23.01±2.10*	22.11±1.94*	0.099

*=Mean±SD

Table 2. Comparison of baseline serum lipid levels and plasma MDA level between two groups (n=42)

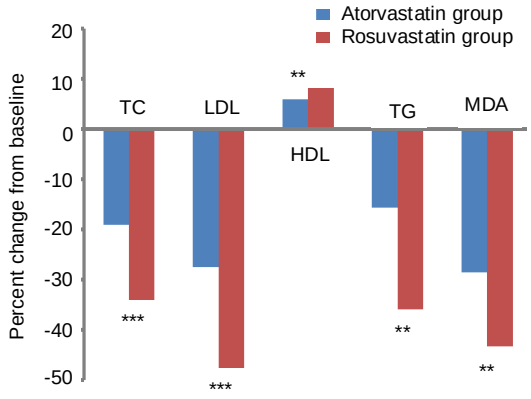
Parameters	Atorvastatin Mean±SD	Rosuvastatin Mean±SD	p value
TC (mg/dl)	223.76±21.30	227.17±19.47	0.391
LDL (mg/dl)	149.95±19.98	151.41±18.87	0.767
HDL (mg/dl)	46.10±3.86	47.31±3.59	0.333
TG (mg/dl)	127.51±32.94	130.84±31.09	0.735
MDA (mmol/L)	3.69±0.292	4.02±1.01	0.195

Table 3. Comparison of mean values of serum lipid levels before and after 6-week period of atorvastatin and rosuvastatin therapy (n=21)

Parameters	Atorvastatin Mean±SD		p value	Atorvastatin Mean±SD		p value
	Before	After		Before	After	
TC (mg/dl)	223.76 ±21.30	180.98 ±19.87	<0.001	227.17 ±19.47	149.40 ±17.62	<0.001
LDL (mg/dl)	149.95 ±19.98	108.77 ±18.82	<0.001	151.41 ±18.87	79.38 ±5.49	<0.001
HDL (mg/dl)	46.10 ±3.86	48.82 ±3.21	<0.001	47.31 ±3.59	51.79 ±3.78	<0.001
TG (mg/dl)	127.51 ±32.94	107.51 ±31.82	<0.001	130.84 ±31.09	83.91 ±28.63	<0.001
MDA (μmol/L)	3.69 ±0.929	2.63 ±0.991	<0.001	4.02 ±1.010	2.28 ±1.123	<0.001

All subjects were non-smokers and had no history of alcohol drinking (Table 1). Regarding the biochemical data, the fasting blood glucose, serum creatinine, and alanine aminotransferase levels of all 42 subjects were found to be within normal range. Therefore, baseline physical and biochemical data of two groups were comparable in this study.

As shown in Table 2, the comparison of baseline serum lipid levels (TC, LDL, HDL and TG) and plasma MDA level between two groups was not statistically significant ($p>0.05$). As shown in Table 3, both atorvastatin (10 mg) and rosuvastatin (10 mg) once daily, significantly decreased the mean serum TC, LDL, TG and plasma MDA levels ($p<0.001$) and also significantly increased serum HDL level after 6-week therapy in hypercholesterolemic subjects ($p<0.001$).



TC =Total cholesterol
LDL=Low density lipoprotein
HDI=High density lipoprotein
TG =Triglyceride

*** =$p<0.001$
** =$p<0.05$

Fig. 1. Comparison of percent changes of lipid profile and plasma MDA level between atorvastatin and rosuvastatin groups

Comparison of the serum lipid levels (TC, LDL, HDL and TG) and plasma MDA level between two groups after 6-week therapy showed that (Fig. 1), rosuvastatin significantly decreased serum TC, LDL, TG and plasma MDA levels than atorvastatin and significantly increased serum HDL level than atorvastatin ($p<0.05$) (Fig. 1).

DISCUSSION

Hypercholesterolemia plays a crucial role in the initiation and progression of atherosclerotic lesions. Moreover, oxidative stress is an important event in the pathogenesis of atherosclerosis.[10] Statins have been recommended as the first-line therapy for hypercholesterolemia and exert beneficial cardiovascular effects not only by improving the lipid profile but also because of pleiotropic effects such as antioxidant effect.[11]

Atorvastatin is well-established member of the statin class that has demonstrated efficacy and safety in the treatment of hypercholesterolemia across its dose ranges.[12] In the present study, the reduction of the TC, LDL, TG levels and elevation of HDL level were statistically significant after 6-week therapy of atorvastatin (10 mg) ($p<0.001$) (Table 3).

Rosuvastatin, the latest statins introduced in clinical practice, was found to be highly efficacious in reducing plasma LDL levels and favorably modifying the other lipid parameters in hypercholesterolemic patients in both short-term and long-term clinical trials.[13] In the present study, the reduction of the TC, LDL, TG levels and elevation of HDL level were statistically significant after 6-week therapy of rosuvastatin (10 mg) ($p<0.001$) (Table 3).

The recommendations for initiation and goals of therapy are based primarily upon LDL cholesterol.[14] Despite the proven benefits of LDL reduction, lipid management is suboptimal and many patients fail to achieve recommended LDL cholesterol goals. In high-risk patients with elevated LDL cholesterol, goal attainment is particularly poor since treatment with higher doses of statins is often necessary to achieve their target LDL cholesterol levels. The most effective statin at the lowest dose would represent a simple, effective treatment strategy, enabling more patients to achieve goals without the need for dose titration.[15]

In this study, rosuvastatin seemed to have a significantly greater TC, LDL, TG reducing effect and greater HDL raising effect than atorvastatin at equal effective dose (10 mg). It has been consistently found that rosuvastatin (10 mg) significantly reduced LDL, TC and increased HDL cholesterol as compared to atorvastatin (10 mg) at 12 weeks, 47% *vs.* 35%, 33% *vs.* 26% and 7% *vs.* 2.7%, respectively ($p<0.001$) in a study.[16] But, effects of the 2 drugs on TG were similar (19% *vs*. 17%, $p>0.05$).

In another comparative study[17] significantly greater reductions in LDL cholesterol and TC were seen with rosuvastatin than equal dose of atorvastatin ($p<0.017$) in hypercholesterolemic patients after 6-week trial. Rosuvastatin (10 mg) also increased HDL and decreased TG more than atorvastatin but the differences were not statistically significant.[17]

Oxidative stress also plays an important role in the pathogenesis of atheroslcerosis. In the present study, antioxidant effect of atorvastatin and rosuvastatin was represented by measuring plasma MDA level since MDA is one the oxidative stress markers.[18] Comparison of the baseline MDA levels of two groups in the study before intervention therapy showed no statistically significant difference ($p>0.05$) (Table 2). After 6-week therapy, both drugs significantly reduced plasma MDA level and rosuvastatin produced greater reduction in MDA level than atorvastatin ($p<0.05$) (Fig. 1). Therefore, rosuvastatin had more MDA lowering effect which reflects the antioxidant action than atorvastatin in addition to its lipid lowering effects that produces beneficial effect in management of cardiovascular events.

Statins are widely-used and effective treatments for the prevention of cardiovascular disease.[19] The review of the literature on statin therapy showed that statin monotherapy is generally well-tolerated, with a low frequency of adverse effects.[20] In this study, both study treatment regimens were extremely well-tolerated. Mild and transient adverse drug reactions such as constipation, diarrhoea, anorexia and headache were seen in both groups which did not need reduction of the dose or withdrawal of the drugs.

According to the present study, rosuvastatin (10 mg) was more efficacious than atorvastatin (10 mg) in lipid lowering and antioxidant (MDA lowering) effects in management of hypercholesterolemic patients. Both drugs are equally safe and well-tolerated over 6 weeks.

Conclusion

Statins are the therapy of choice in the management of hypercholesterolemia and atherosclerotic diseases due to their proven clinical efficacy and safety profile. In the present study, among the two statins, rosuvastatin was found to be highly efficacious in reducing plasma LDL cholesterol, TC and TG, MDA level and elevating HDL cholesterol than atorvastatin at the same dose (10 mg). According to this study, rosuvastatin can also be used as the first-line agent in prevention and treatment of atherosclerosis because of more efficacious lipid lowering and antioxidant (MDA lowering) effect than those of atorvastatin.

ACKNOWLEDGEMENT

We would like to express sincere thanks to all subjects participated for their keen participation in this study.

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