Int J Clin Exp Med 2016;9(6):9533-9538
www.ijcem.com /ISSN:1940-5901/IJCEM0017547

Original Article

Clinical efficacy comparison of rosuvastatinwith atorvastatinin high-risk chinese dyslipidemic patients

Guoyu Wang[1], Fengzhi Wang[2], Yubo Wu[1], Jingru Cui[1], Kun Zhang[1]

[1]*Department of Pharmaceutical, The Forth Affiliated Hospital of Harbin Medical University, Harbin 150001, China;*
[2]*Department of Pharmacy, The First Affiliated Hospital of Jiamusi University, Jiamusi 154002, China*

Received October 9, 2015; Accepted December 30, 2015; Epub June 15, 2016; Published June 30, 2016

Abstract: Purpose: The study aimed to compare the cholesterol-lowering efficacy of Rosuvastatin with Atorvastatin in high risk Chinese dyslipidemicpatients. Methods: This randomized open-label study enrolled 90 high-risk dyslipidemic patients who were hospitalized in the fourth affiliated hospital of Harbin medical college from December 2013 to July 2014, and diagnosed according to the China Adult Dyslipidemia Prevention Guide criteria (2007 Edition). These patients were randomized into Atorvastatin and Rosuvastatin groups, which were medicated on Atorvastatin 20 mg/day and Rosuvastatin 20 mg/day for 8 weeks, respectively. The effects of Atorvastatin and Rosuvastatin on serum low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG) were evaluated between the two groups. Moreover, the goal attainment rates of LDL-C or TC in the two groups were assessed, respectively. Results: Rosuvastatin achieved a significantly better reduction of LDL-C (45.3% vs. 39.2%, $P<0.05$) and TC (35.2% vs. 29%, $P<0.05$) than Atorvastatin. Besides, Rosuvastatin group had a higher percentage of patients achieving the recommended goal of LDL-C and TC than the Atorvastatin group (55.1% vs. 40%, 51.2% vs. 36.2%). Conclusion: Rosuvastatin had stronger lipid-reducing efficacy than Atorvastatin in high risk hyperlipidemic patients in China.

Keywords: Rosuvastatin, atorvastatin, dyslipidemia, high-density lipoprotein, triglyceride

Introduction

Coronary heart disease (CHD) isregarded as number 1 killer of human being around the world [1]. Only in 2010, it causes over 7 million deaths globally [2]. It has been documented that CHD is associated with a number of risk factors, such as smoking, obesity and hyperlipidemia [3].

A rich body of evidence has demonstrated that the therapy to reduce cholesterol is beneficialfor individuals at high risk of CHD [4, 5]. Statins are a class of cholesterol-lowering drugs which could inhibit the HMG-CoA reductase and then impede cholesterol synthesis and treat CHD in early stages [6]. To date, a number of statins have been launched on the market andapplied in clinic, such as Atorvastatin, Rosuvastatin and Simvastatin. Rosuvastatin possesses a special sulfur structure and has less adverse effects compared with other statins. It has been reported that rosuvastatin could reduce the incidence of cardiovascular events [7].

A number of clinical trials have proved higher cholesterol-lowering efficacy of Rosuvastatin in comparison with other rivals of the statin class. It has been reported thatacross dose ranges (10-80 mg/day), administration of rosuvastatin exhibits significantly better effect to reduce total cholesterol than atorvastatin, pravastatin and simvastatin in American patients with hypercholesterolemia [8]. A clinical trial in North America shows that Rosuvastatin (10 mg) is more effective to attain European Atherosclerosis Society LDL cholesterol goals in hypercholesterolemic patients in comparison with Atorvastatin (10 mg) [9]. Another prospective multi-center trial in Japan has found that pitavastatinit (mg/day), rosuvastatin (2.5 mg/day) oratorvastatin (10 mg/day) appear to exert similar effect to lower LDL-C and have little difference in adverse drug reactions [10]. Similarly, the superiority of rosuvastatin over atorvastatin

(10 mg/day) has also been approved in patients at high risk of primary hypercholesterolemia and CHD by a clinical trial conducted in Finland, Iceland, and Ireland [11].

Nonetheless, efficacy comparison between Rosuvastatin and other comparators in Chinese patients with high-risk dyslipidemia has not been fully elucidated. Considering the effect of individual variation on response to drugs, it is very necessary to conduct the comparison in Chinese patients with high-risk dyslipidemia. To address this issue, the study specifically targeted Chinese patients with high-risk dyslipidemia and compared Rosuvastatin and Atorvastatin for lipid-modifying effect on serum lipids including LDL-C, high-density lipoprotein cholesterol (HDL-C), TC, and triglyceride (TG). Besides, the percentages of patients attaining the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (NCEP) targets [12] for LDL-C or TC after 8 weeks of Rosuvastatin or Atorvastatin treatmenter were also evaluated, respectively. This study would lay a base for establishment of guidelines on efficacy and safety of Rosuvastatin and Atorvastatin.

Materials and methods

Patients

The prospective study enrolled 90 patients with high-risk dyslipidemia who admitted in the fourth affiliated hospital of Harbin medical college from December 2013 to July 2014. According to the China Adult Dyslipidemia Prevention Guide criteria (2007 Edition), these patients who met the following criteria were defined to be with high-risk dyslipidemia: TC, 5.18-6.19 mmol/L; LDL-C, 3.37-4.12 mmol/L; ≥1 of risk factors including age (male ≥ 45 years old, female ≥ 55 years old), smoking, HDL-C ≤ 1.04 mmol/L, obesity and family history of early-onset ischemic heart disease [13]. Patients with the following condition were excluded from the study: secondary hyperlipidemia, primary hypothyroidism, nephritic syndrome or renal impairment; type 1 or 2 diabetes without satisfactory glucose control; active liver disease, ALT and AST more than two times greater than the normal value; increase of creatine kinase (CK) to ≥ three times of the upper limit of the normal range or by unexplained reasons; being allergic or intolerant to the statin drug; long-term use of steroid hormones or thiazide diuretic agent in combination with statins, which could increase the risk of rhabdomyolysis; uncontrolled severe hypertension; taking other lipid-lowering drugs other than the statins used in the study. Prior to initiation of the trial, each enrolled patient provided signed informed consent.

Study design

This randomized open-label study was ratified by the ethnic committee of the fourth affiliated hospital of Harbin medical college. According to the China Adult Dyslipidemia Prevention Guide criteria (2007 Edition), 10 mg/day of Atorvastatin and 5-10 mg/day ofrosuvastatinare recommended as sufficient doseto decrease LDL-C by 30-40%. Based on clinical experience, 20 mg/day was chosen in the current study to achieve optimal efficacy without side effect. In the study, 90 patients were randomly divided into Atorvastatin and rosuvastatin groups, which received atorvastatin (Lipitor) 20 mg/day (Pfizer, USA) and rosuvastatin (Crestor) 20 mg/day (AstraZeneca, England) for 8 weeks, respectively. All the patients stopped administration of lipid-lowering drugs 4 weeks before onset of the study. Because it is considered that lipid-lower drugs have been metabolized after 5 half-lives in 4 weeks and would not affect the result of the study. Furthermore, none of enrolled patients was on the prescription of other medicines that might influence the effect of statins.

Finally, 71 patients finished the assigned treatment, including 30 patients involved in the Atorvastatin group and 41 patients involved in the Rosuvastatin group. The other 19 patients who failed to take medications or laboratories tests as required were excluded from the study. Prior to and after the treatment, venous blood sample was drawn from each patient after a 12-hour fast, respectively. TG, TC, LDL-C, and HDL-C were tested using Cobas 8000 automatic biochemical analyzer (Roche, Germany), respectively.

Efficacy endpoints

Primary endpoints of the present study were the percentages of patients attaining the treatment goal of LDL-C or TC in each group after 8 weeks of treatment according to the NCEP ATP III. Secondary endpoints consisted of the changes between before and after the 8 week

Table 1. Demographic characteristic of the patients in Rosuvastatin and Atorvastatin groups

Characteristic	Rosuvastatin group (n=41)	Atorvastatin group (n=30)	Total (n=71)	t-value/X^2	*P*-value
Age (years)	60.5±9.7	60±9.0	60.3±9.2	0.221	0.83
Male/Female [n (%)]	23 (56.1)/18 (43.9)	18 (60.0)/12 (40.0)	41 (57.1)	0.108	0.74
Body weight index (kg/m^2)	24.9±3.2	24.9±3.0	24.9±3.1	<0.001	1
Hypertension [n (%)]	12 (29.3)	8 (26.7)	20 (28.2)	0.058	0.81
Diabetes [n (%)]	4 (9.76)	3 (10.0)	7 (9.86)	<0.001	1
Smoking [n (%)]	17 (41.3)	12 (40.0)	29 (40.8)	0.015	0.9

Age and Body weight index were expressed as mean ± standard deviation.

Table 2. Serum lipid changes of Rosuvastatin and Atorvastatin groups

Parameters	Rosuvastatin group (n=41)			Atorvastatin group (n=30)			*P*-value
	0 week	8 week	Change	0 week	8 week	Change	
TC (mmol/L)	6.52±0.78	4.22±0.86	↓35.2	6.56±0.71	4.66±0.65	↓29.0	<0.05
LDL-C (mmol/L)	3.99±0.61	2.18±0.79	↓45.3	3. 93±0.49	2.40±0.79	↓39.2	<0.05
HDL-C (mmol/L)	1.40±0.54	1.49±0.43	↑5.7	1.37±0.57	1.43±0.45	↑4.4	>0.05
TG (mmol/L)	2.23±0.69	1.79±0.72	↓19.7	2.30±0.61	1.90±0.79	↓17.4	>0.05

Table 3. Goal attainment rates of Rosuvastatin and Atorvastatin groups

Parameters	Rosuvastatin group (n=41)	Atorvastatin group (n=30)	X^2	*P*-value
LDL-C	23(56.1%)	12(40%)	1.796	0.180
TC	21(51.2%)	11(36.7%)	1.482	0.223

treatment in LDL-C, TC and HDL-C and TG levels.

Safety

Safety events were closely monitored and assessed throughout the study, including abnormal laboratory variables.

Statistical analysis

Quantitative data was expressed as median ± standard deviation (SD). Student'st test was used to compare the differences of quantitative data. Chi-square test was applied for qualitative data comparison. SPSS 15.0 software was employed to perform statistical analysis in the present study. Difference with *p*-value<0.05 was defined to be significant.

Result

Demographics of patients

Demographic data of the 71 patients in Atorvastatin and Rosuvastatin groups was displayed in **Table 1**. The two groups had insignificant discrepancy in age, sex, body-weight index, hypertension, diabetes and smoking (P>0.05).

Efficacy analysis

As shown in **Table 2**, insignificant difference was observed in TG, TC, LDL-C and HDL-C between the Atorvastatin and Rosuvastatin groups (P>0.05) before the treatment. At 8 weeks after the treatment, LDL-C in Rosuvastatin and Atorvastatin groups decreased by 45.3% and 39.2%, respectively. The magnitude of decrease in LDL-C was significantly different between the two groups (P<0.05). Similarly, TC in Rosuvastatin group also decreased significantly greater than that in Atorvastatin group (35.2% vs. 29%, P<0.05). Besides, both groups had decreased TG and increased HDL-C at 8 weeks after the treatment in comparison with those before the treatment. Nonetheless, no significant difference was observed in magnitude of decrease of TG or increase of HDL-C between the two groups (P>0.05).

According to the ATP III of NCEP [12], 55.1% of patients achieved the LDL-C goal of <100 mg/dL in the Rosuvastatin group, while 40% achieved the LDL-C goal in the Atorvastatin group. The goal attainment rate of LDL-C in the Rosuvastatin group was higher than that in the Atorvastatin group. Similarly, Rosuvastatin

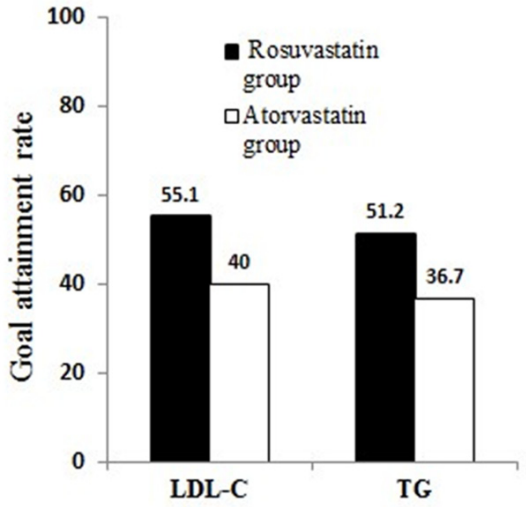

Figure 1. Goal attainment rates of LDL-C and TG in Rosuvastatin and Atorvastatin groups. Rosuvastatin achieved higher attainments rates of LDL-C and TG than Atorvastatin. The ordinate axis stands for goal attainment rate; the abscissa axis stands for serum lipid parameters.

group had a larger proportion of patients attaining the recommended TC goal than the Atorvastatin group (51.2% vs. 36.2%, P>0.05) (**Table 3** and **Figure 1**). However, the discrepancies in the attainment rates of LDL-C and TC were insignificant (P>0.05).

Safety

Insignificant difference between the two groups was observed in liver enzymes, creatinine, CK and glucosewhen comparing before to after 8-week treatment (P>0.05). In Rosuvastatin group, there were one patient experiencing increase of aspartate aminotransferase (AST) up to 63 U/L and one patient experiencing increase of ASTup to 63 U/L and increase of Alanine aminotransferase (ALT) up to 45 U/L. These abnormal increases went back to normal in two weeks, without disturbing the medications of the study. Additionally, in the Atorvastatin group, only one patient had increased AST up to 45 U/L which was then decreased to normal with the assigned medication of Atorvastatin. The two drugs exhibited similar drug tolerability and safety during the study.

Discussion

Rosuvastatin is a member of statins which are a class of HMG-CoA reductase inhibitors. It is characterized by high efficacy of cholesterol-lowering effect. To extend the understanding of the efficacy and safety of Rosuvastatin and Atorvastatin, this study focused on comparison of the lipid-lowering effect between Rosuvastatin and Atorvastatin in Chinese patients with high-risk hyperlipidemia. The study unveiled that 20 mg/day of Rosuvastatin for 8 weeks achieved a better LDL-C reduction than the same dose of Atorvastatin. The findings would add more weight to the evidences in supportive of the superiority of Rosuvastatin over Atorvastatin in hyperlipidemic patients.

The benefits of the therapy targeted at reducing LDL-C have been confirmed in patients at high-risk hyperlipidemia, resulting in decreased incidence of cardiovascular diseases and improved life quality of patients [12]. Based on the convincing findings from a number of randomized controlled clinical trials with large sample size, the ATP III of NCEP issuesa series of guidelines on blood cholesterol management in 2004. The recommendations from ATP III have been widely accepted in clinical trials and researches on cholesterol management [14, 15]. Therefore, they were also adopted in the present study. However, other opinion also exists,arguing that elevations of LDL-C should not be regarded as a main goal of the cholesterol-lowering therapy in ATP III, due to deficiency of solid clinical evidences [16].

The study showed that significantly better reduction of LDL-C and TC was achieved with daily dose of 20 mg of Rosuvastatin for 8 weeks in comparison with the same dose of Atorvastatin. Moreover, the medication of Rosuvastatin resulted in higher percentage of patients attaining the recommended goal of LDL-C and TC than medication of Atorvastatin. Our study reflected that Chinese patients with high-risk dyslipidemia were also more sensitive to Rosuvastatin than Atorvastatin.

These findings were in concordance with a previous study reporting that more patients with Rosuvastatin (10 to 40 mg) have achieved LDL-C levels <100 mg/dl than those with atorvastatin [17]. Similarly, another randomized and open-label trial has found that rosuvastatin treatment at 10 mg is capable to lead to more patients at high risk of CHD reaching the NCEP ATP III LDL-C goal compared with atorvastatin at 10 mg/day and simvastatin at 20 mg/day

[18]. There is evidence that Rosuvastatin (10 mg and 20 mg) facilitates 63.95% of patients with dyslipidaemia to achieve the total cholesterol target of ATP IIIin Indian [19]. Similarly, 20 mg of Atorvastatin or of Rosuvastatin was adopted in the present study based on clinical experience, because Atorvastatin (10 mg) and Rosuvastatin (5-10 mg) are sufficient to reduce LDL-C by 30-40% according to the China Adult Dyslipidemia Prevention Guide criteria (2007 Edition). It suggested Rosuvastatin at 20mg might be suitable for Asian patients with dyslipidemia.

It should be noted that approximately 44.9% of patients failed to achieve the target goal of LDL-C even with Rosuvastatin, suggesting the need of improvements of the lipid-lowering medications. A recent study in USA has demonstrated that medication of ezetimibetogether with Rosuvastatin could achieve a better reduction of LDL-C compared to Rosuvastatin alone [20]. A randomized trial has shown that combination of Atorvastatin and SAR236553, an antibody against serum proprotein convertase subtilisin/kexin 9 (PCSK9) exhibits a better lipid-lowering effect than the same dose of Atorvastatin [21]. It delivers a clue that addition of SAR236553 might also strengthen the lipid-lowering effect of Rosuvastatin. More efforts should be made to further improve or optimize the efficacy of Rosuvastatin. In the current study, the two drugs showed similar safety, and few adverse events were observed during the 8 weeks.

The study has limitations. First, its samples size is relatively small. Large scale studies should be conducted to confirm and extend the finding of the study. Second, it should be mentioned that there is an imbalance in the number of withdrawals between Atorvastatin and Rosuvastatin groups, which might potentially be a source of bias, although there is insignificant difference in demographic and baseline characteristics between the two groups.

Conclusion

Generally, medication of Rosuvastatin could reach a better lipid-reducing effect and yield a higher attainment rate of LDL-C and TC than Atorvastatin in same dose in high risk hyperlipidemic Chinese patients. The study afforded additional evidence supporting superior therapeutic efficacy of Rosuvastatin over Atorvastatin.

Acknowledgements

This study was supported by Clinical efficacy and safety studies of Rosuvastatin (No. 2013RFQYJ156).

Disclosure of conflict of interest

None.

Address correspondence to: Jingru Cui, Department of Pharmaceutical, The Forth Affiliated Hospital of Harbin Medical University, No. 37 Yiyuan Street, Nangang District, Harbin 150001, China. Tel: 86-0451-85939577; Fax: 86-0451-85939577; E-mail: cjinriin@163.com

References

[1] Finegold JA, Asaria P and Francis DP. Mortality from ischaemic heart disease by country, region, and age: Statistics from World Health Organisation and United Nations. Int J Cardiol 2013; 168: 934-945.

[2] Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R and Ahn SY. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2013; 380: 2095-2128.

[3] Kivimäki M, Nyberg ST, Batty GD, Fransson EI, Heikkilä K, Alfredsson L, Bjorner JB, Borritz M, Burr H and Casini A. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. Lancet 2012; 380: 1491-1497.

[4] Treasure CB, Klein JL, Weintraub WS, Talley JD, Stillabower ME, Kosinski AS, Zhang J, Boccuzzi SJ, Cedarholm JC and Alexander RW. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. N Engl J Med 1995; 332: 481-487.

[5] Unit ES. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005; 366: 1267-1278.

[6] Taylor F, Huffman MD, Macedo AF, Moore T, Burke M, Davey Smith G, Ward K and Ebrahim S. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; 1: CD004816.

[7] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P,

Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359: 2195-207.

[8] Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, Cain VA, Blasetto JW; STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol 2003; 92: 152-160.

[9] Davidson M, Ma P, Stein Ea, Gotto Am, Raza A, Chitra R and Hutchinson H. Comparison of effects on low-density lipoprotein Cholesterol and high-density lipoprotein cholesterol with Rosuvastatin versus Atorvastatin in patients with type IIa or IIb hypercholesterolemia. Am J Cardiol 2002; 89: 268-275.

[10] Saku K, Zhang B and Noda K. Randomized head-to-head comparison of pitavastatin, atorvastatin, and rosuvastatin for safety and efficacy (quantity and quality of LDL)-The PATROL trial. Circulat J 2011; 75: 1493-1505.

[11] Strandberg TE, Feely J and Sigurdsson EL. Twelve-week, multicenter, randomized, open-label comparisonof the effects of rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: a DISCOVERY study. Clin Therapeut 2004; 26: 1821-1833.

[12] Grundy SM, Cleeman JI, Merz CNB, Brewer HB, Clark LT, Hunninghake DB, Pasternak RC, Smith SC and Stone NJ. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. J Am Coll Cardiol 2004; 44: 720-732.

[13] Committee CADP. China adult dyslipidemia prevention guide. Beijing, China: People's Health Publishing House; 2007.

[14] Kavousi M, Leening MJ, Nanchen D, Greenland P, Graham IM, Steyerberg EW, Ikram MA, Stricker BH, Hofman A and Franco OH. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. JAMA 2014; 311: 1416-1423.

[15] Virani SS, Woodard LD, Landrum CR, Pietz K, Wang D, Ballantyne CM and Petersen LA. Institutional, provider, and patient correlates of low-density lipoprotein and non–high-density lipoprotein cholesterol goal attainment according to the Adult Treatment Panel III guidelines. Am Heart J 2011; 161: 1140-1146.

[16] Hayward RA, Krumholz HM. Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. Circ Cardiovasc Qual Outcomes 2012; 5: 2-5.

[17] McKenney JM, Jones PH, Adamczyk MA, Cain VA, Bryzinski BS and Blasetto JW. Comparison of the efficacy of rosuvastatin versus atorvastatin, simvastatin, and pravastatin in achieving lipid goals: results from the STELLAR trial. Curr Med Res Opin 2003; 19: 689-698.

[18] Insull W Jr, Ghali JK, Hassman DR, Y As JW, Gandhi SK, Miller E; SOLAR Study Group. Achieving low-density lipoprotein cholesterol goals in high-risk patients in managed care: comparison of rosuvastatin, atorvastatin, and simvastatin in the SOLAR trial. Mayo Clin Proc 2007; 82: 543-50.

[19] Shah S and Arneja J. Efficacy of rosuvastatin in achieving target HDL, LDL, triglycerides and total cholesterol levels in type 2 diabetes mellitus (T2DM) with newly diagnosed dyslipidaemia: an open label, nonrandomised, non-interventional and observational study in India. J Assoc Physicians India 2013; 61: 721-726, 732.

[20] Foody JM, Toth PP, Tomassini JE, Sajjan S, Ramey DR, Neff D, Tershakovec AM, Hu H and Tunceli K. Changes in ldl-c levels and goal attainment associated with addition of ezetimibe to simvastatin, atorvastatin, or rosuvastatin compared with titrating statin monotherapy. Vasc Health Risk Manag 2013; 9: 719.

[21] Roth EM, McKenney JM, Hanotin C, Asset G and Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med 2012; 367: 1891-1900.