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Impact of 10 mg rosuvastatin daily or alternate-day on lipid profile and inflammatory markers

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ABSTRACT

Background: Statins are commonly administrated daily, while rosuvastatin can be given every other day due to its longer half-lives. We evaluated the potential efficacy of alternate-day dosing of 10 mg rosuvastatin compared with daily dosing of 10 mg rosuvastatin with regarding to lipid and inflammatory markers in patients with dyslipidemia.
Methods: Thirty-seven patients were randomly divided into the 2 groups: alternate-day group (rosuvastatin 10 mg every other day, n = 19) and once-daily group (rosuvastatin 10 mg every day, n = 18) for 6 weeks. The primary endpoints of the study were changes of the serum concentrations of low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP) and interleukin-6 (IL-6) following 6-week rosuvastatin therapy.
Results: Baseline characteristics of the 2 groups were well balanced. LDL-C decreased by 37.5% after the once-daily dosing period and by 36.9% after alternate-day dosing period ($p > 0.05$). Both dosing regimens provided similar improvement in high-density lipoprotein cholesterol and triglyceride. And also, both dosing regimens significantly decreased serum concentrations of CRP, which had an 18.3% reduction in once-daily dosing and a 16.7% reduction in alternate-day dosing of rosuvastatin ($p > 0.05$). Moreover, the pattern of plasma IL-6 concentrations was also similar between the two groups ($p > 0.05$).
Conclusions: Alternate-day dosing of rosuvastatin could be effective comparable with once-daily dosing of rosuvastatin in Chinese patients in improving not only lipid profile but also inflammatory markers, which may provide some cost savings and increase the compliance of patients.

1. Introduction

Increases in the concentration of low-density lipoprotein cholesterol (LDL-C), which has been closely linked to the pathophysiology of cardiovascular disease, is a key independent modifiable risk factor for cardiovascular disease [1,2]. Inflammation is an important feature of atherosclerotic disease, which is involved in all stages of atherosclerotic events [3,4]. It has been shown that effective reduction of LDL-C and inflammatory markers presents the two promising strategies in controlling the rate of morbidity and mortality of atherosclerotic diseases [5].

Statins have now become one of the more widely used therapeutic classes in clinical practice because the cardiovascular benefits of statins that reduce concentrations of LDL-C and inflammatory markers in primary and secondary prevention have already been confirmed in either several randomized studies or meta-analysis [6–8]. It has been demonstrated that statin-related cardiovascular benefits are not only through their effects on lipid profile but also through their anti-inflammatory effects, which are believed to play an important role as well [8].

The side effects and cost issue of statins are clinically major concerns in real world cardiovascular practice, which are associated with statin dosing used [9,10]. Generally, statins are remarkably well tolerated, but can produce myalgia, muscle cramps, and weakness in some patients [9]. Statins are also expensive for both the health care system and patients, especially for developing countries including China [10]. Therefore, statin treatment administrated every other day may result in a significant decrease in health expenses and reduce side effects. Previous studies have evaluated alternate-day dosing regimens with simvastatin, atorvastatin and rosuvastatin, and concluded that an alternate-day dosing strategy could provide comparable LDL-C reductions with that daily administration in patients with dyslipidemia [11–13]. However, whether the anti-inflammatory effects of alternate-day dosing of rosuvastatin are comparable with once-daily dosing of rosuvastatin is not investigated.

Rosuvastatin has been shown to reduce LDL-C in a dose-dependent fashion by 46% to 55%, and has a similar safety profile to other statins [14]. Compared with other statins, however, the terminal half-life of

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rosuvastatin is relatively long at approximately 18 to 20 h, its prolonged survival and hydroxy-methyl-glutaryl (HMG) CoA reductase inhibition allow rosuvastatin to be dosed every other day, but this possibility is unknown to many clinicians [15].

2. Methods

2.1. Study population

The study was conducted from October 2010 to May 2011 in our centers. The study protocol was approved by the institutional review board, and informed consent was signed by all participants. Patients were considered eligible if they were aged ≥ 18 y, and had LDL-C ≥ 160 mg/dl and/or triglycerides (TG) ≥ 200 mg/dl at baseline. Patients were excluded if they had abnormal concentrations of creatinine kinase (CK) and aminotransferase prior to or detected or other chronic hepatitis during the study. Previous intolerance or hypersensitivity to a statin, uncontrolled diabetes (glycated hemoglobin of 10% or higher), a history of excessive alcohol use, as well as patients with neoplasms chronic obstructive pulmonary disease, and hypothyroidism, and patients with previous heart disease such as heart failure or stroke or severe myocardial ischemia were also excluded.

2.2. Design and data collections

Before initiating the rosuvastatin administration, the data of all patients including height, weight, heart rate and blood pressure were collected, and patients who were previously on statin therapy were not enrolled. Blood sample was drawn after a 12 h fast, and aspartate aminotransferase, alanine aminotransferase, CK, electrolytes, creatinine and lipid parameters including total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), TG were measured. TC, HDL-C and TG were assessed enzymatically, while LDL-C was calculated from the Friedewald formula.

Patients were then randomly assigned to receive either a daily or alternate-day dose of rosuvastatin 10 mg for 6 weeks. All study subjects were given written and verbal instructions on dietary therapy. Safety and tolerability were evaluated throughout the study on the basis of adverse events reporting, laboratory studies, and physical findings. At the end of the study (6 weeks), data related to lipid profile, compliance and side effects were recorded. The medication cost of statins used was also evaluated.

2.3. CRP and IL-6 Determinations

EDTA-anticoagulated peripheral blood samples were taken from all enrolled patients after 12-hour overnight fast at baseline and at the end of follow-up period (6 weeks). The plasma was obtained after a centrifugation of 3000 rpm at 4°C for 15 min. The concentrations of CRP were determined using immunoturbidimetry (Beckman Array 360, Brea, CA) as our previously reported [16]. The median normal value for CRP was 0.8 mg/l, with 90% of normal values < 0.3 mg/l, with a lower detection limit of 0.2 mg/l. The inter-assay and intra-assay coefficients of variation were <5%, respectively. IL-6 was measured with a commercial assay kit in a duplicate manner (Quantikine human IL-6, R & D System, Minneapolis, MN), and both intra- and inter-assay CVs were <10%. The range of values detected by the assay for IL-6 was 3 to 5000 pg/ml as our previously reported [17].

2.4. Statistical analysis

Continuous variables were expressed as mean ± SD, and categorical variables were expressed as percentage. Comparison of categorical variables between the groups was performed using chi-square test. For comparison between pre- and posttreatments, the paired 2-tailed *t* test or the Wilcoxon signed rank test was used. Difference between groups or independent variables was compared by an unpaired *t* test for normally distributed variable or by the Mann–Whitney *U* test for variables with skewed distribution as our previously reported [6]. A $p<0.05$ was considered statistically significant. All statistical analysis was performed with SPSS ver 13 (SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline clinical characteristics

Baseline clinical characteristics of patients with dyslipidemia receiving alternate-day dosing of rosuvastatin (n = 19), or once-daily dosing of rosuvastatin (n = 18) were summarized in Table 1. There were no differences regarding clinical characteristics between the two groups including age, sex, body mass index, current smoker, history of coronary artery disease, hypertension, diabetes, and medications.

3.2. Changes of lipid profile

As shown in Table 2, there were no differences of baseline parameters of lipid profile between the groups. Changes of lipid profile in detail including TC, LDL-C, HDL-C and TG at 6-weeks follow-up periods from baseline were presented in Table 2, and the percentage changes were depicted in Fig. 1. At 6 weeks, the percentage changes in mean LDL-C was reduced by 37.5% in once-daily group and 36.9% in alternate-day group, respectively. Such changes were found to be no difference between the two groups ($p>0.05$) although it was significant compared with data at baseline in both groups. There were also similar trends in other lipid parameters including TC, HDL-C, and TG. The detailed changes of the lipid profile were shown in Table 2 and Fig. 1.

3.3. Decrease in CRP and IL-6 concentrations

As shown in Table 2 and Fig. 2, the plasma CRP concentrations were significantly decreased in both groups (18.3% reduction in once-daily group and a 16.7% reduction in alternate-day group, $p>0.05$). In addition, the effects of both treatments on plasma IL-6 concentrations were not significant between the two groups (26.4% vs 23.3%, $p>0.05$, Fig. 2).

4. Discussion

We demonstrated that alternate-day dosing of 10 mg rosuvastatin resulted in a significant lipid-lowering and anti-inflammatory impact comparable to that of once-daily administration. Apparently, our study confirmed and extended the previously published investigations,

Table 1
Baseline clinical characteristics (mean ± SD).

Variables	Alternate-day group (n = 19)	Once-daily group (n = 18)	p Value
Age (years)	48 ± 6	50 ± 8	NS
Male/Female	13/6	11/7	NS
Body mass index (kg/m^2)	23 ± 3	23 ± 4	NS
Current smoker, n (%)	5 (26)	3 (17)	NS
Family history of CAD, n (%)	3 (16)	2 (11)	NS
CAD	7 (37)	5 (28)	NS
Hypertension, n (%)	13 (68)	10 (56)	NS
Diabetes, n (%)	4 (21)	3 (17)	NS
Ejection fraction (%)	64 ± 8	63 ± 7	NS
Medications			
Aspirin (%)	13 (68)	10 (56)	NS
ACEI/ARB (%)	9 (47)	7 (39)	NS
β-blocker (%)	4 (21)	4 (22)	NS
CCB (%)	2 (11)	3 (17)	NS

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CCB = calcium-channel blocker.