Canadian Journal of Cardiology 30 (2014) 1392–1395

Brief Rapid Report

The Effect of Infrequent Low-Dose Rosuvastatin on the Lipid Profile

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ABSTRACT

We retrospectively studied 21 patients who had difficulty tolerating daily or alternating-day statins. Patients received rosuvastatin at a mean frequency of 1.7 doses per week, and a mean dose of 11.7 mg per week. We assessed lipid profiles at baseline and after at least 3 months of therapy. We found that total and low-density lipoprotein cholesterol were reduced by 2.03 ± 2.04 and 1.31 ± 0.83 mmol/L (27.9% and 31.5%), respectively, from baseline (both $P < 0.001$). Thus, in patients with statin intolerance, infrequent low-dose rosuvastatin significantly improved low-density lipoprotein cholesterol and was well tolerated over the long term.

RÉSUMÉ

Nous avons étudié de façon rétrospective 21 patients qui toléraient mal la prise quotidienne de statines ou la prise en alternance un jour sur deux. Les patients ont reçu la rosuvastatine selon une fréquence moyenne de 1,7 dose par semaine et une dose moyenne de 11,7 mg par semaine. Nous avons évalué les bilans lipidiques initiaux et après au moins 3 mois de traitement. Nous avons observé que le cholestérol total et le cholestérol à lipoprotéines de faible densité avaient respectivement diminué de 2,03 ± 2,04 et 1,31 ± 0,83 mmol/l (27,9 % et 31,5 %) depuis le début ($P < 0,001$ pour les deux). Par conséquent, chez les patients intolérants aux statines, la prise occasionnelle de rosuvastatine à faible dose a significativement amélioré le cholestérol à lipoprotéines de faible densité et a bien été tolérée à long terme.

Increased plasma concentrations of low-density lipoprotein (LDL) cholesterol (C) increase cardiovascular disease (CVD) risk.[1] Thus, reducing LDL-C is a cornerstone of primary and secondary CVD prevention.[1] Statins might reduce LDL-C by as much as 55%.[1] The Cholesterol Treatment Trialists' Collaboration meta-analysis showed that a 1.0 mmol/L reduction in LDL-C decreases the risk of major CVD events by one-fifth.[1,2] A reduction of LDL-C by 2-3 mmol/L reduces CVD risk by up to 50%.[1,2] However, not everyone can tolerate statin therapy.

Statin intolerance encompasses a range of clinical features, including myopathy, myalgia, myositis, and rhabdomyolysis.[3] Mylagias are quite common and is sometimes accompanied by an increased serum creatine kinase.[3] These symptoms pose a major impediment to compliance, attenuating the potential life-saving benefits of statin therapy. Rosuvastatin has a longer half-life than the other statins (approximately18-20 hours),[4] and nondaily dosing of rosuvastatin in patients with statin intolerance has been recently evaluated.[5,6] Using rosuvastatin as infrequently as 3 times a week (approximately 30 mg/wk), helped achieve approximately a 34% reduction in LDL-C.[6] However, some patients cannot tolerate even this reduced dose, which prompted us to evaluate the efficacy and adverse effects of even less frequent, lower-dose regimens of rosuvastatin.

Methods

Study subjects

We retrospectively reviewed charts of patients who attended the Lipid Genetics Clinic, London Health Sciences Centre (London, Ontario, Canada). Inclusion criteria included patients who: (1) received nondaily rosuvastatin < 3 times per week (total dose < 20 mg/wk) for > 3 months; (2) had a history of statin intolerance, defined primarily by the presence of myalgia with or without increased level of creatine kinase, and inability to complete at least 2 previous trials of 2 different statins; and (3) were weight-stable over the time period of study, with a stable diet and stable doses of all other medications.

The primary outcomes were the absolute and relative changes in the lipid profile before and after initiation of infrequent, low-dose rosuvastatin therapy, and the percentage of patients who achieved their LDL-C target as per the 2012

Received for publication June 27, 2014. Accepted July 3, 2014.

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See page 1394 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2014.07.002

Table 1. Baseline characteristics of patients

Characteristic	Overall	Male	Female
Age in years	66.4 (47-84)	66.5 (50-84)	66.3 (47-80)
n	21	10	11
Body mass index*	28.9 (21.4-38.3)	28.1 (23-38.3)	29.7 (21.4-38.3)
Type 2 diabetes	4 (19.1)	3 (30)	1 (9.1)
Smoking	8 (38.1)	4 (40)	4 (36.4)
Hypertension	9 (42.9)	4 (40)	5 (45.5)
History of coronary artery disease	5 (23.8)	2 (20)	3 (27.3)
Total cholesterol, mmol/L	7.31 ± 2.12	6.71 ± 0.93	7.84 ± 2.74
Triglyceride, mmol/L	2.54 ± 2.04	2.52 ± 2.76	2.57 ± 1.20
HDL-C, mmol/L	1.29 ± 0.40	1.25 ± 0.39	1.34 ± 0.41
LDL-C, mmol/L	4.47 ± 0.67	4.80 ± 0.71	4.18 ± 0.49
Apolipoprotein A1, g/L	1.34 ± 0.17	1.25 ± 0.23	1.43 ± 0.34
Apolipoprotein B, g/L	1.29 ± 0.40	1.34 ± 0.15	1.24 ± 0.19
Creatine kinase, U/L	144.7 ± 96.3	193.0 ± 146.6	114.7 ± 30.10
Aspartate transaminase, U/L	32.1 ± 14.0	26.0 ± 8.50	34.2 ± 15.50
Weekly rosuvastatin dose, mg	11.73 ± 5.90	12.4 ± 5.73	11.1 ± 6.26
Patients taking concomitant lipid-altering drugs (%)	10 (47.6)	5 (50)	5 (45.5)
Omega-3 fatty acid/fish oil	2 (9.5)	2 (20)	0 (0)
Ezetimibe	10 (47.6)	5 (50)	5 (45.5)
Niacin	3 (14.3)	2 (20)	1 (9.1)
Fibrate	1 (4.8)	1 (10)	0 (0)
Other supplements, n (%)	8 (38.1)	3 (30)	5 (45.5)

Except as otherwise noted, continuous variables are presented as mean (range) or ± SD, and discrete variables are presented as mean (%).
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
* Calculated as weight (kg)/height (m^2).

Canadian Cardiovascular Society guidelines for management of dyslipidemia.[7] Secondary outcomes included baseline demographic characteristics, assessment of baseline CVD risk, and the use of additional lipid-lowering therapies. Tolerability of the nondaily regimen was determined according to the absence of clinical symptoms at follow-up appointments, normal follow-up blood work, and persistence with therapy as prescribed.

Statistical analysis

Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC). Paired *t* tests were used to compare lipid levels before and after rosuvastatin therapy. Results were considered nominally significant for $P < 0.05$.

Results

Twenty-one patients who were taking infrequent, low-dose rosuvastatin met our study criteria for inclusion and analysis, and their baseline data are shown in Table 1. The mean dose of rosuvastatin was 11.7 mg/wk (range, 2.5-20 mg/wk): 6 patients took 10 mg twice weekly, 6 took 5 mg twice weekly, 3 took 10 mg once weekly, 2 took 5 mg once weekly, and 1 each took 5 mg once every 2 weeks, 2.5 mg thrice weekly, 2.5 mg thrice every 2 weeks, and 5 mg for 5 of every 14 days. Two patients who started the infrequent, low-dose rosuvastatin regimen stopped after 10 and 14 days, because of persistent myalgias, and were not included in the final analysis.

Table 2. Lipid profiles after treatment

	Overall	Male	Female
Weeks of statin therapy, mean (range)	89.2 (24-240)	86.6 (36-192)	91.6 (24-240)
Total cholesterol, mmol/L	5.27 ± 0.96	5.35 ± 0.90	5.20 ± 1.05
Triglyceride, mmol/L	1.99 ± 0.91	1.98 ± 0.99	2.01 ± 0.87
HDL-C, mmol/L	1.31 ± 0.42	1.24 ± 0.38	1.37 ± 0.47
LDL-C, mmol/L	3.06 ± 1.02	3.21 ± 1.00	2.91 ± 1.07
Patients at LDL-C target after treatment, n (%)	4 (19.1)	2 (20)	2 (18.1)

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Overall, the mean ± SD reduction of LDL-C was 1.43 ± 0.83 mmol/L or 31.5% ($P < 0.001$) (Table 2 and Fig. 1). Furthermore, total cholesterol was significantly reduced by 2.03 ± 2.04 mmol/L or 27.9% ($P = 0.0002$) (Table 2 and Fig. 1). Absolute changes in triglycerides and high density lipoprotein-C were 0.55 ± 1.49 and -0.02 ± 0.20 mmol/L, respectively (both not significant). The Pearson correlation coefficient between percentage of LDL-C reduction and total weekly rosuvastatin dose was 0.431 ($P = 0.066$). Thus, even at these low doses, the decrease in LDL-C tended to be correlated with total weekly rosuvastatin dose. Using this regimen, 4 patients (19%) attained the 2012 Canadian Cardiovascular Society Dyslipidemia Guidelines LDL-C target of < 2.0 mmol/L. Post hoc subgroup analyses found no difference in response to infrequent rosuvastatin therapy depending on sex or the use of concomitant medications (data not shown). Finally, there was no lower-dose threshold that provided a clear cutoff for no further statin efficacy.

Discussion

Statin intolerance is a commonly encountered clinical challenge.[8] In a small group of these patients, we found that an infrequent dosing regimen of rosuvastatin was associated with significant improvements in total cholesterol and LDL-C, which were reduced by 2.03 ± 2.04 and 1.31 ± 0.83 mmol/L (27.9% and 31.5%), respectively, from baseline (both $P < 0.001$). The total average weekly dose for patients in this study was 11.7 mg, with a mean of 1.7 tablets taken