Efficacy of alternate day versus daily dosing of rosuvastatin

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BACKGROUND: Compared with other statins, rosuvastatin has a relatively long half-life, which may allow for the administration of this medication on an alternate day basis.

OBJECTIVE: To compare the efficacy of administering rosuvastatin on a daily basis versus on an alternate day basis for the treatment of dyslipidemia.

METHODS: In the present crossover study, 45 patients with documented hypercholesterolemia requiring pharmacotherapy were administered either 20 mg of rosuvastatin on alternate days or 10 mg of rosuvastatin daily for six weeks. After a four-week washout period, patients were then switched to the other regimen for another six weeks. The primary end point was the percentage reduction of low-density lipoprotein cholesterol (LDL-C).

RESULTS: LDL-C decreased by 48.5% versus 40.9% with daily and alternate day dosing, respectively. This represented an additional absolute reduction of LDL-C of 7.6% (95% CI 1.8% to 13.4%, $P=0.012$) with the daily dosing regimen. Both dosing regimens provided similar improvements in high-density lipoprotein cholesterol and triglycerides.

CONCLUSIONS: Compared with alternate day dosing, daily dosing of rosuvastatin provides a statistically significant advantage in LDL-C reduction. However, the alternate day regimen may be a viable option for those patients in whom cost is a limitation to compliance.

Key Words: Dyslipidemia; LDL cholesterol; Rosuvastatin

Efficacité de la rosuvastatine administrée quotidiennement plutôt que tous les deux jours

HISTORIQUE : Comparativement à d'autres statines, la rosuvastatine est dotée d'une demi-vie relativement longue, ce qui lui permet d'être administrée tous les deux jours.

OBJECTIF : Comparer l'efficacité de la rosuvastatine administrée quotidiennement ou un jour sur deux pour le traitement de la dyslipidémie.

MÉTHODE : Dans la présente étude avec permutation des groupes, 45 patients porteurs d'une hypercholestérolémie documentée et nécessitant un traitement pharmacologique ont reçu soit 20 mg de rosuvastatine un jour sur deux, soit 10 mg de rosuvastatine par jour pendant six semaines. Après une période d'élimination de quatre semaines, les patients passaient à l'autre schéma thérapeutique pendant six autres semaines. Le paramètre principal était le pourcentage de réduction du LDL-cholestérol (lipoprotéines de basse densité).

RÉSULTATS : Le LDL-C a diminué de 48,5 %, contre 40,9 %, lors de l'administration du médicament quotidiennement plutôt qu'un jour sur deux. Cela a représenté une réduction additionnelle absolue du LDL-C de 7,6 % (IC à 95 %, 1,8 % à 13,4 %, $p = 0,012$) avec le schéma posologique quotidien. Les deux schémas thérapeutiques ont procuré des améliorations similaires des taux de HDL-cholestérol et de triglycérides.

CONCLUSION : Comparativement à la posologie un jour sur deux, la posologie quotidienne de rosuvastatine confère un avantage statistiquement significatif sur le plan de la réduction du LDL-C. Toutefois, le schéma un jour sur deux peut être une option envisageable chez les patients pour qui le coût constitue un obstacle à l'observance thérapeutique.

The value of lowering low-density lipoprotein cholesterol (LDL-C) levels with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) for preventing major cardiovascular events and stroke has been well documented (1-4). As such, statins have become the keystone of therapy in the treatment of dyslipidemia for both the primary and secondary prevention of cardiovascular disease (5,6).

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 (7). Compared with other statins, however, the terminal half-life of rosuvastatin is relatively long at approximately 18 h to 20 h (8).

While many first-generation statins are recommended to be taken at bedtime because of their short half-lives and the fact that there is a diurnal variation in endogenous cholesterol synthesis, it is compelling to speculate that rosuvastatin could, in fact, be administered on an alternate day basis for the treatment of dyslipidemia (9,10). This concept is not without precedent; previous studies have evaluated alternate day dosing regimens with simvastatin and atorvastatin, and concluded that an alternate day dosing strategy could provide comparable LDL-C reductions with that of daily administration in patients with dyslipidemia, and provide some measure of cost

savings (11-13). Accordingly, the present trial was designed to compare the efficacy of administering rosuvastatin on a daily basis versus on an alternate day basis for the treatment of dyslipidemia.

METHODS

Men and women, 18 to 80 years of age, were recruited from the Southeastern Ontario Vascular Disease Prevention and Research Centre, located at Queen's University in Kingston, Ontario. Patients were eligible for the study if they had documented dyslipidemia, with an LDL-C of greater than 3.5 mmol/L. Patients were excluded if they had a history of hepatic disease (aspartate aminotransferase and alanine aminotransferase three times the upper limit of normal or greater), elevation of creatine kinase (CK; three times the upper limit of normal or greater), uncontrolled diabetes (glycated hemoglobin of 10% or higher), intolerance or hypersensitivity to statins, were pregnant or breastfeeding, had a history of excessive alcohol use, were enrolled in another study, or had an acute coronary syndrome or stroke within four weeks of enrollment. All patients provided written informed consent. Ethics approval was obtained from the Research Ethics Board at Queen's University.

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TABLE 1
Baseline demographics (n=39)

Age, years, mean $\pm$ SD	68.2 $\pm$ 12.3
Male sex, %	62.5
Coronary artery disease, %	
Angina	40
Previous myocardial infarction	35
Previous percutaneous coronary intervention	25
Previous coronary artery bypass graft	25
Cerebrovascular disease, %	40
Peripheral vascular disease, %	5
Lipid parameters, mmol/L, mean $\pm$ SD	
Total cholesterol (TC)	6.0 $\pm$ 0.9
Low-density lipoprotein	3.8 $\pm$ 0.8
High-density lipoprotein (HDL)	1.5 $\pm$ 0.9
Triglycerides	1.7 $\pm$ 0.9
TC:HDL ratio	4.3 $\pm$ 1.1
Smoking status, %	
Never smoked	15
Reformed smoker	55
Current smoker	7.5
Diabetes mellitus, %	22.5
Body mass index, kg/m ² , mean $\pm$ SD	30.4 $\pm$ 9.0
History of hypertension, %	67.5
Systolic blood pressure, mmHg, mean $\pm$ SD	126 $\pm$ 17
Diastolic blood pressure, mmHg, mean $\pm$ SD	74 $\pm$ 10
Antithrombotic therapy, %	95.6
Statin therapy, %	62.2
ACEI/ATII therapy, %	82.2

ACEI Angiotensin-converting enzyme inhibitor; ATII Angiotensin II receptor blocker

Patients who were previously on statin therapy underwent a four-week washout period before entering the study. Before random assignment, height, weight, heart rate and blood pressure were recorded. Bloodwork was drawn after a 14 h fast, and aspartate aminotransferase, alanine aminotransferase, CK, electrolytes, creatinine and lipid profile (total cholesterol [TC], LDL-C, high-density lipoprotein [HDL] cholesterol, triglycerides [TGs], TC:HDL ratio) were measured. TC and TG concentrations were measured enzymatically. All enzymatic lipid testing was performed on the Roche Modular (Roche Diagnostics Canada, Canada). LDL-C was calculated using the Friedewald formula applied to the values measured.

Patients were then sequentially assigned to receive either a daily dose of rosuvastatin 10 mg or an alternate day dose of rosuvastatin 20 mg for six weeks. Patients were not blinded to treatment allocation. When patients were on the alternate day dosing, they were provided with a pill box to assist with compliance. After completion of the first phase of the study, patients underwent a four-week washout period. The patients were then switched to the other regimen for another six weeks. At the end of each treatment regimen and washout period, patients returned to the clinic for repeat measurements and bloodwork. Patients who were completing the alternate day regimen were asked to come for their reassessment on the day that they were scheduled to take the rosuvastatin to ensure that the bloodwork was obtained during the trough drug levels. In addition, to determine the interday variability in lipid control on the alternate day regimen, fasting bloodwork was collected on consecutive days from 28 patients who were completing the alternate day dosing regimen. Changes in lipid values were analyzed. At each visit, data related to lipid profile, compliance and side effects were recorded. In total, patients came for four visits, unless they were previously on a statin, in which case they came for five visits.

Figure 1 Comparison of the effects of alternate day (q2day) versus once-daily (od) dosing of rosuvastatin on low-density lipoprotein cholesterol (LDL-C) level over time

Statistical methods

The primary outcome was the percentage change in LDL-C from the baseline to the six-week assessment. Due to the crossover design, the statistical comparison was based on the within-patient difference in this outcome between the daily and alternate day dosing periods. A mixed effects model was used to pool results across periods and to estimate the mean difference in outcomes between the alternate day and daily dosing schedules after adjusting for period effects. The mixed model permitted incorporation of data from subjects with only one period (dosing schedule), but it provided estimates identical to the classical analysis of the AB/BA crossover study described by Fleiss (14) and others (15,16) when all subjects have complete data. Although efficient and unbiased in the presence of a period (or nondifferential carryover) effect, the model assumes that no differential carryover effect is present. All subjects with available data for at least one period were analyzed as randomly assigned, according to the intention-to-treat principle. The proportions of patients who reached target LDL-C levels after each dosing schedule were compared using the Mainland-Gart test. A paired *t* test was used to compare the lipid values between one and two days after the last dose of the alternating schedule. All tests are two-sided. Analyses were performed using SAS (SAS Institute Inc, USA) version 8.2 (17).

RESULTS

Between July 6, 2004, and January 25, 2005, 45 patients were enrolled in the study. Thirty-nine patients completed the entire crossover study. Four patients dropped out of the study in the initial washout period and were excluded from all analyses; one of these patients experienced a transient ischemic attack two days into the first washout period. A fifth patient dropped out after completing the first period of the study, while a sixth patient dropped out during the second period of the study. One patient with asymptomatic elevation of CK without previous statin therapy was inadvertently included in the study and, after review by the research ethics board, the patient was permitted to continue participating in the study. No adverse events occurred in this patient during the study. The baseline demographic and laboratory characteristics are listed in Table 1.

During the six weeks of treatment, LDL-C decreased by 48.5% with the daily dosing regimen, compared with 40.9% with the alternate day dosing regimen (Figure 1). This represented an additional reduction in LDL-C of 7.6% (95% CI 1.8% to 13.4%, *P*=0.012) with the daily dosing regimen compared with the alternate day dosing regimen (Table 2). A similar trend was seen with TC and TC:HDL ratio, in which the daily dosing arm provided an additional 7.0% (95% CI 2.3% to 11.6%,

TABLE 2

Baseline and changes from baseline in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides and TC:HDL ratio after six weeks of alternate day and daily dosing of rosuvastatin

	Rosuvastatin (10 mg daily)				Rosuvastatin (20 mg q2day)				% difference		P
	Baseline	6 weeks	% change	P	Baseline	6 weeks	% change	P			
TC, mmol/L	6.0	4.0	-32.7	<0.001	5.8	4.3	-25.7	<0.001	7.0		0.004
LDL-C, mmol/L	3.8	1.9	-48.5	<0.001	3.7	2.1	-40.9	<0.001	7.6		0.012
HDL-C, mmol/L	1.4	1.5	4.9	0.008	1.4	1.5	6.1	0.002	1.1		0.63
Triglycerides, mmol/L	1.7	1.2	-16.8	0.001	1.5	1.3	-12.2	0.016	4.6		0.48
TC:HDL ratio	4.3	2.8	-35.3	<0.001	4.3	3.0	-29.1	<0.001	6.2		0.026

q2day Alternate day dosing

P=0.004) and 6.2% (95% CI 0.8% to 11.7%, P=0.026) absolute reduction, respectively. Both dosing regimens provided similar improvement in HDL cholesterol and TGs (Table 2).

Before initiating therapy, only one patient was below the LDL-C target of 2.5 mmol/L, which had been the LDL-C target previously recommended in the 2003 update of the recommendations for the management of dyslipidemia and prevention of cardiovascular disease; the study was completed before the latest guideline target of 2.0 mmol/L (6). After treatment, 92.5% versus 75.0% of patients reached target levels below 2.5 mmol/L in the daily dosing and alternate day dosing regimens, respectively (P=0.048). Using the new target of an LDL-C below 2.0 mmol/L, 47.5% of the patients on a daily dosing regimen of rosuvastatin compared with 37.5% of the patients taking rosuvastatin on an alternate day dosing regimen were able to achieve this goal (P=0.52). However, neither of these differences were statistically significant.

Lipid profiles were collected on two consecutive days for 28 patients when they completed the alternate day dosing regimen. The LDL-C values were not significantly different, with a mean difference of -0.1 mmol/L (range -4.8 mmol/L to 4.5 mmol/L, P=0.95) between the two days.

No major complications occurred during the study. One patient experienced myalgias without a rise in CK, which resolved with time. Gastrointestinal upset was the most common complaint.

DISCUSSION

The present study has shown that daily dosing of rosuvastatin provides a statistically significant advantage in LDL-C reduction compared with alternate day dosing of rosuvastatin, both in terms of absolute LDL-C reduction as well as in the percentage of patients able to reach both the new and old LDL-C targets, as set forth by the Canadian guidelines. The daily dosing regimen was able to provide an additional 7.6% reduction in LDL-C lowering, which is comparable with the amount of reduction expected from doubling the daily dose of rosuvastatin from 10 mg to 20 mg daily (18). Based on this, one could speculate that increasing the alternate day dosing of rosuvastatin to 40 mg would provide equivalency to 10 mg of rosuvastatin administered on a daily basis; however, further study would be needed to confirm this postulate. A previous study was able to achieve comparable LDL-C reductions with alternate day dosing and daily dosing regimens using a titration strategy, whereby atorvastatin was titrated as necessary to achieve target LDL-C reductions (12).

Whether a 7.6% reduction in LDL-C represents a clinically meaningful difference, however, is less clear. Based on the data from the meta-analysis by the Cholesterol Treatment Trialists' (CTC) Collaborators, a reduction of 1.6 mmol/L that was achieved with alternate day dosing would result in a reduction in major coronary events and major vascular events by more than 37% (19). This would compare with a reduction in major coronary events by 44% in association with a reduction in LDL-C by 1.9 mmol/L, as seen in the daily dosing regimen.

However, despite the fact that the alternate day dosing regimen was less effective than the daily dosing regimen, the alternate day dosing regimen still provided an LDL-C reduction of 40.9%, which would be

comparable with 20 mg of atorvastatin or 80 mg of simvastatin administered on a daily basis, and LDL-C reductions of this magnitude would not be achievable with less potent statins such as fluvastatin, lovastatin and pravastatin (7). The fact that 75% of patients treated with the alternate day dosing regimen were able to achieve a target LDL-C of 2.5 mmol/L would suggest that alternate day dosing has a potential role in clinical practice.

The cost of medications can be prohibitive for patients without a drug plan, and can contribute to cost-related medication nonadherence by patients, which, in turn, may result in adverse clinical events (20-23). A simpler approach to cost conservation would be to administer rosuvastatin on alternate days, at double the strength. Alternate day dosing would result in reducing costs significantly. In the present study, the six-week cost of daily dosing of 10 mg rosuvastatin was \$57.12, whereas the cost of alternate day dosing of 20 mg rosuvastatin was \$35.70, reducing the cost by 37.5% (24). Another potential option would be to prescribe a 20 mg tablet of rosuvastatin and advise the patient to split the tablets in half (25). Although this would also result in a cost savings of 50%, this practice can be technically difficult due to the design of some tablets. Of course, both strategies could be combined; cutting a 40 mg tablet in half and administering it on an alternate day regimen could reduce the six-week cost of the medication to \$20.90. This is 63.4% less expensive than the cost of the daily regimen. Although not as efficacious as daily dosing, alternate day dosing may be a practical solution for those patients with limited financial resources without compromising the clinical benefits of lipid lowering.

Limitations

The patients in the present study were not blinded. Although blinding would have provided a more valid assessment of the efficacy of an alternate day dosing regimen, we believe that an open label design allowed us to more accurately determine the effectiveness of the strategy because a potential concern with an alternate day dosing strategy is noncompliance. In the present study, patients were given pill boxes to facilitate the organization and administration of their medication.

The present study was not powered to detect differences in clinical outcomes between the two treatment groups. Accordingly, the consequences of long-term use of alternate day dosing are not known and require the completion of larger randomized and blinded studies.

CONCLUSIONS

Daily dosing of rosuvastatin provides a statistically significant advantage in LDL-C reduction, and may allow a greater percentage of patients to reach the target LDL-C. While daily dosing is modestly better than an alternate day dosing regimen, the alternate day regimen may be an option for patients in whom cost is a limitation to compliance.

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