Management of statin intolerance (SI) in patients at high risk for cardiovascular (CV) events: results of a Canadian study

PCV29

Dominic Mitchell,*[1] Mohdhar Habib,[2] Louisa Pericleous,[2] Robert J. Petrella[3]

*Presenter; [1]Research Center of the Centre hospitalier de l'Université de Montréal, Montréal, QC, Canada & Logimétrix Inc., Repentigny, QC, Canada; [2]Amgen Canada Inc., Mississauga, ON, Canada; [3]Individual Health Outcomes Inc. & Western University, London, ON, Canada

INTRODUCTION

- While the benefit of statins for reducing CV morbidity and mortality in patients with dyslipidaemia is well established, some patients develop SI due to adverse effects (AEs) including muscle aches and weakness, gastrointestinal (GI) symptoms, liver enzyme abnormalities, or other nonspecific complaints.[1]
- SI is reported in 5%–10% of subjects in randomized, placebo-controlled trials, and up to 20% in observational studies.[1]
- In patients with dyslipidaemia, SI can lead to statin discontinuation or dose reduction sufficient to prevent patients from reaching target low-density lipoprotein cholesterol (LDL-C) levels.[2] In patients experiencing SI who switch to different statins, symptoms of SI may recur.[2]
- Physician fear of myopathy and other statin-related AEs can also lead to unjustified termination of a statin or its use at insufficient doses, depriving patients at high risk for CV events of demonstrated clinical benefits.[3]
- In Canada, comprehensive guidelines on management of SI were published by the Canadian Working Group Consensus Conference in 2011,[4] and updated in 2013;[5] these recommend trying a different statin, or lower or intermittent statin dosing rather than discontinuation as the main method to manage SI.
- Currently, the management of SI in Canadian clinical practice is poorly understood.

Objective

- To describe the characteristics and management of SI in patients with dyslipidaemia treated in real-world clinical practice in Ontario, focusing on patients at highest risk for CV events.

METHODS

Study design

- This was a non-interventional, observational, retrospective, longitudinal, healthcare database study.

Data source

- Analyses were conducted using data from the proprietary Southwestern Ontario (SWO) Primary Care Practice Database (Individual Health Outcomes, Inc.), which contains longitudinal healthcare resource utilization and outcomes data for >330,000 adult patients, contributed by >100 participating physicians at >70 primary practices.
- All patient records in the SWO database are anonymized to conform to current confidentiality regulations.

Patient selection

- The study sample was an open cohort of adult patients diagnosed with hyperlipidaemia and initiating statin therapy (i.e., statin index date) between January 1, 2004 and December 31, 2012. Inclusion and exclusion criteria are listed in Table 1.
- Patients were stratified into three CV risk levels (Table 2).

Outcomes of interest

- This presentation focuses on the incidence and management of SI in the CV high-risk patient group.

Table 1. Eligibility criteria.

Inclusion criteria	Exclusion criteria
• Age ≥18 at statin index date*	• On statin without a hyperlipidaemia diagnosis†
• Diagnosis of hyperlipidaemia†	
• ≥1 statin prescription	
• ≥2 years of baseline data prior to statin index date* without any statin medication	

*Date of first statin prescription
†International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes E78.0, E78.2, E78.4, E78.5, or E78.9; ICD-9-CM 272.0, 272.2, 272.4, or 272.9

- SI was identified on the basis of ≥1 SI symptom accompanied by a change in the statin prescription within 1 month of the symptom(s):
  - Qualifying SI symptoms were myalgia, myositis, rhabdomyolysis, weakness/fatigue, elevated hepatic enzymes, GI complaints, pancreatitis, joint pain, rash/flushing, and neurologic symptoms. Symptoms were identified on the basis of International Classification of Diseases, 9th or 10th Revision, Clinical Modification (ICD-9-CM or ICD-10-CM) codes and laboratory values.
  - Change in statin prescription comprised interruption, dose decrease, switch from daily to alternate-day therapy, or the interruption of statin therapy.

Table 2. Cardiovascular risk levels.

Risk level	Framingham Risk Score[6]	CV high-risk features[7]
High	≥20%	Any of: • Clinical vascular disease • Abdominal aortic aneurysm • Diabetes and ≥1 of: – Age ≥40 years – >15 years duration + age ≥30 years – Microvascular disease • CKD • High-risk hypertension*
Intermediate	10%–19%	None
Low	<10%	None

CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; ECG: electrocardiogram; HDL-C: high-density lipoprotein cholesterol; HeFH: heterozygous familial hypercholesterolemia
*Hypertension plus ≥3 of the following characteristics: male, age ≥55 years, smoking, total cholesterol/HDL-C ratio >6, left ventricular hypertrophy, family history of premature CVD including HeFH, ECG abnormalities, microalbuminuria

- The SI index date was defined as the first date of SI symptom occurrence or change in statin prescription.

Statistical analysis

- Descriptive statistics are presented: mean, standard deviation (SD), confidence interval (CI), and percentage.

RESULTS

Patient characteristics

- A total of 41,733 patients who initiated statin therapy were included, of whom 14,607 (35%) were high-risk patients and 1294 (9% of high-risk patients) had SI.
- Patient characteristics at the SI index date are shown in Table 3. At baseline in the high-risk group, the mean (SD) age was 61 (8.9) years, 53% were male, and mean (SD) LDL-C was 2.8 (1.1) mmol/L.

Table 3. Patient characteristics at the statin intolerance index date*.

Characteristic	High-risk patients with SI (N=1294)
Age (y), mean (SD)	61 (8.9)
Gender, % male (n male)	53% (684)
LDL-C (mmol/L), mean (SD)	2.78 (1.1)
TC:HDL-C, mean (SD)	4.5 (1.0)
SBP, mean (SD)	138 (9)
DBP, mean (SD)	84 (6)
CV risk factors during prior 1-y period, % (n)	
Diabetes	14% (175)
Diabetes + age ≥40 years	8% (105)
Diabetes for >15 years + age ≥30 years	5% (65)
Diabetes + microvascular disease	<1% (5)
History of CVD	10% (128)
Current smokers	4% (49)
Smoking history	5% (65)
Male >45 years†	94% (646)
Female >55 years†	96% (585)
Family history of premature CVD	9% (114)
Family history of hyperlipidaemia	6% (78)
High-risk hypertension‡	25% (323)
CKD	5% (71)
Clinical evidence of atherosclerosis or abdominal aneurysm	5% (68)
Obesity (BMI >27 kg/m^2)	39% (502)

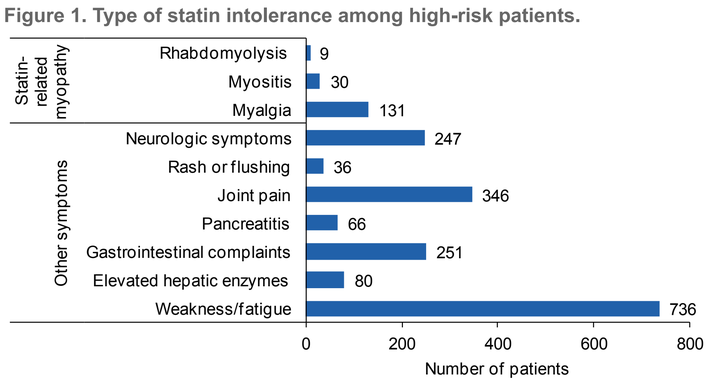
BMI: body mass index; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; DBP: diastolic blood pressure; ECG: electrocardiogram; HDL-C: high-density lipoprotein cholesterol; HeFH: heterozygous familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol
*Date when symptoms first occurred or when there was an observed change in statin prescription associated with a diagnosis of SI
†Gender-specific percentage
‡Hypertension plus ≥3 of the following characteristics: male, age ≥55 years, smoking, total cholesterol/HDL-C ratio >6, left ventricular hypertrophy, family history of premature CVD, ECG abnormalities, microalbuminuria

- In the high-risk group, the SI incidence rate (95% CI) was 125.23 (118.50, 132.24) per 10,000 person-years.
- At the SI index date 84% (n=1085) of patients had achieved the LDL-C target according to contemporaneous Canadian Cardiovascular Society guidelines, with the on-target proportion decreasing to 49% (n=638) 6 months post-SI.

Frequency of statin intolerance symptoms

- Among the 1294 patients identified with SI, 170 (13%) experienced myopathy and 1124 (87%) had other SI-related symptoms (Figure 1).

Figure 1. Type of statin intolerance among high-risk patients.



Note: subcategories of myopathy are mutually exclusive; other symptoms are not mutually exclusive

- There were nine rhabdomyolysis cases, two resulting in hospitalization and seven treated in outpatient clinics.
- Weakness and fatigue were over twice as common as the next-most-frequent symptom, joint pain.

Management of statin intolerance

- Of the 1294 high-risk patients with SI, 412 (32%) discontinued statin therapy and 677 (52%) had a dose decrease (Table 4).
- Maintaining the same statin dose after the first SI event was more common in patients on LDL-C target vs. those not on LDL-C target 6 months after the first SI event: 28% vs 7%, respectively (Table 4).
- Among the 636 patients not on LDL-C target at 6 months post-SI, 279 (44%) were switched to a non-statin therapy (primarily fibrates); in contrast, no patients on LDL-C target at 6 months post-SI switched to a non-statin.

Table 4. Management of statin intolerance among high-risk patients.

Variable, % (n)	High-risk patients with SI (N=1294)
Patients on an intensive statin dose at the SI index date*	36% (462)
Patients with discontinued statin therapy	32% (412)
Patients with decreased statin dosage	52% (677)
Patients who were switched from an intensive dose statin to an intermediate dose statin	24% (308)
Patients with change in therapy frequency (alternate day)	<1% (5)
Patients who were on LDL-C target at the SI index date*	84% (1085)
Patients on LDL-C target 6 months after the SI index date*	49% (638)
Decrease dose	30% (191)
Stop and switch	17% (107)
Stop and not switch	25% (162)
Maintained same dose	28% (178)
Patients not on LDL-C target 6 months after the SI index date*	49% (636)
Decrease dose	21% (131)
Stop and switch to another statin	20% (126)
Stop and not switch	8% (54)
Maintained same dose	7% (46)
Switch to a non-statin drug	44% (279)
Resins (bile acid sequestrans)	3% (8)
Fibrates	62% (174)
Nicotinic acid	30% (84)
Cholesterol absorption inhibitor	5% (13)

LDL-C: low-density lipoprotein cholesterol; SI: statin intolerance
*Date when symptoms first occurred or when there was an observed change in statin prescription associated with a diagnosis of SI

CONCLUSIONS

- SI affects the optimal treatment of dyslipidaemia in this high-risk population, with half of patients with SI not achieving their LDL-C target.

References
1. Mampuya WM, et al. Treatment strategies in patients with statin intolerance: The Cleveland Clinic experience. *Am Heart J* 2013;166:597-603
2. Arca M, Pigna G. Treating statin-intolerant patients. *Diabetes Metab Syndr Obes* 2011;4:155-66
3. Rallidis LS, Fountoulaki K, Anastasiou-Nana M. Managing the underestimated risk of statin-associated myopathy. *Int J Cardiol* 2012;159:169-76
4. Mancini GB, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: proceedings of a Canadian Working Group Consensus Conference. *Can J Cardiol* 2011;27:635-62
5. Mancini GB, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Working Group Consensus update. *Can J Cardiol* 2013;29:1553-68
6. D'Agostino RB, Sr., et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743-53
7. Anderson TJ, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* 2013;29:151-67

Acknowledgements: This study was sponsored by Amgen Canada Inc., Mississauga, ON, Canada. D Mitchell has received a research grant from Genome Québec and Genome Canada funds, and consulting fees from Amgen, Baxter, Dymaxium, Jamp, Leo Pharm, Medicus Economics LLC, Montreal Heart Institute, Pfizer, Pharmascience, and Triton. L Pericleous and M Habib are employees of Amgen and hold ownership interest in Amgen. RJ Petrella has received research grants from Am PI Fourier, Amgen, Novartis, and Sanofi, and consulting fees from Amgen and Sanofi. Amgen Canada Inc. provided funding to W. Mark Roberts, Montreal, QC, Canada, for writing and editorial assistance, and graphics support.

AMGEN®

© 2015 Amgen Canada Inc.

Poster presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 18th Annual European Congress, 7–11 November 2015, Milan, Italy.