The clinical effect and tolerability of ezetimibe in high-risk patients managed in a specialty cardiovascular risk reduction clinic

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INTRODUCTION: Ezetimibe (EZ) is a selective cholesterol absorption inhibitor approved for use in Canada. The effect and tolerability of EZ among patients was evaluated in the clinical setting of a specialty cardiovascular risk reduction clinic at the University of Alberta Hospital, Edmonton, Alberta.

PATIENTS AND METHODS: All patients 18 years of age or older who were prescribed EZ were included, unless they failed to take EZ for a minimum of two weeks, did not have baseline and on-EZ low-density lipoprotein cholesterol (LDL-C) levels, or had concomitant lipid-lowering drugs or dosages changed within one month of starting EZ.

RESULTS: Eighty-four patients (mean age 57.9 years) were included. By Framingham risk calculation, 71.4% were found to be high-risk patients, 13.1% moderate-risk patients and 15.5% low-risk patients; 66.7% of patients had prior cardiovascular events. On EZ, the mean reductions were: total cholesterol level 1.11 mmol/L (16.5%); LDL-C level 1.01 mmol/L (22.3%); high-density lipoprotein cholesterol level 0.06 mmol/L (4.6%); and ratio of total cholesterol level to high-density lipoprotein cholesterol level 0.68 mmol/L (12.8%); all were statistically significant ($P < 0.001$). Results were similar when stratified by primary ($n = 28$) versus secondary ($n = 56$) prevention. Patients on EZ monotherapy ($n = 34$) had mean LDL-C reductions of 1.03 mmol/L (20.5%) compared with 1.19 mmol/L (30.1%) or 0.95 mmol/L (22.5%), where EZ was added to low-dose or high-dose statins ($P < 0.01$ for all). On EZ, 30 patients (35.7%) achieved previously unattainable target LDL-C levels. Four patients discontinued the drug due to side effects.

CONCLUSIONS: EZ is safe and effective in high-risk patients treated in the clinical setting of a cardiovascular risk reduction clinic. A mean LDL-C reduction of 1 mmol/L (20% to 30%) in all patient subgroups is consistent with previous clinical trial results. The significant reduction in LDL-C (mean 22.5%) observed in the EZ plus high-dose statin subgroup provides clinical evidence for use of this medication beyond published studies.

Key Words: Cholesterol; Ezetimibe; Hyperlipoproteinemia; Lipids; Risk factors

L'effet clinique et la tolérabilité de l'ézétimibe chez les patients très vulnérables pris en charge dans une clinique de réduction du risque cardiovasculaire

INTRODUCTION : L'ézétimibe (EZ) est un inhibiteur sélectif de l'absorption du cholestérol homologué au Canada. L'effet et la tolérabilité de l'EZ chez les patients ont été évalués dans un milieu clinique spécialisé de réduction du risque cardiovasculaire au *University of Alberta Hospital*.

MÉTHODOLOGIE : Tous les patients de 18 ans ou plus à qui on avait prescrit de l'EZ participaient à l'étude, à moins qu'ils n'aient pas suivi leur traitement à l'EZ depuis au moins deux semaines, qu'on ne connaisse pas leur taux de cholestérol à lipoprotéines de basse densité (C-LDL) ou que leurs hypocholestérolémiantes ou que leur dose aient été modifiés dans le mois précédant le début du traitement à l'EZ.

RÉSULTATS : Quatre-vingt-quatre patients (âge moyen de 57,9 ans) ont participé à l'étude. D'après le calcul du risque de Framingham, 71,4 % étaient des patients très vulnérables, 13,1 % des patients à la vulnérabilité modérée et 15,5 % des patients peu vulnérables. De ces patients, 66,7 % avaient déjà subi un événement cardiovasculaire. Lorsqu'ils prenaient de l'EZ, les taux de réduction moyens s'établissaient comme suit : taux de cholestérol total de 1,11 mmol/L (16,5 %), taux de C-LDL de 1,01 mmol/L (22,3 %), taux de cholestérol à lipoprotéines de haute densité 0,06 mmol/L (4,6 %) et ratio du cholestérol total et du cholestérol à lipoprotéines de haute densité de 0,68 mmol/L (12,8 %), ces taux étant tous statistiquement significatifs ($P < 0,001$). Les résultats étaient similaires lorsqu'ils étaient stratifiés par prévention primaire ($n = 28$) et secondaire ($n = 56$). Les patients sous monothérapie à l'EZ ($n = 34$) présentaient un taux de réduction du C-LDL de 1,03 mmol/L (20,5 %) par rapport à 1,19 mmol/L (30,1 %) ou 0,95 mmol/L (22,5 %) lorsque l'EZ était ajouté aux statines à faible dose ou à forte dose ($P < 0,01$ pour l'ensemble). En prenant de l'EZ, 30 patients (35,7 %) ont atteint les taux cibles de C-LDL, qu'ils étaient auparavant incapables d'obtenir. Quatre patients ont abandonné le traitement en raison des effets secondaires.

CONCLUSIONS : L'EZ est sécuritaire et efficace chez les patients très vulnérables traités dans un milieu clinique de réduction du risque cardiovasculaire. Une réduction moyenne du C-LDL de 1 mmol/L (20 % à 30 %) chez tous les sous-groupes de patients est conforme aux résultats des essais cliniques précédents. La diminution importante du taux de C-LDL (moyenne de 22,5 %) observée dans le sous-groupe de patients prenant de l'EZ associée à une forte dose de statines fournit des données cliniques d'utilisation de ce médicament qui dépassent les constatations des études publiées.

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Cardiovascular disease is the leading cause of death in Canada, accounting for 37% of total mortality (1,2). An elevated level of low-density lipoprotein cholesterol (LDL-C) is an important risk factor for the development of vascular disease and is recognized to be a major independent risk factor for coronary artery disease (CAD) (3-6). Clinical trials have conclusively demonstrated that the reduction of LDL-C levels successfully decreases the risk for developing CAD as well as cardiovascular mortality (7-21). On the basis of this cumulative evidence, expert groups have promulgated and regularly updated national guidelines to assist health care practitioners with the treatment of patients with dyslipidemias (22,23). Consequently, reducing LDL-C levels is a primary strategy for cardiovascular risk reduction.

The most commonly prescribed class of medications for the treatment of patients diagnosed with hypercholesterolemia is the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins. This class exerts its cholesterol-lowering effects by inhibiting cholesterol synthesis, and can also reduce LDL-C levels by 35% to 60% at maximum recommended doses. Despite the effectiveness of the statins in lowering LDL-C levels, numerous practice-pattern analyses have indicated that many hypercholesterolemic patients do not achieve their recommended target levels (24-27). For some patients, even the maximum suggested or tolerated dose of a statin is insufficient to lower their LDL-C levels to target levels. Consequently, additional and potentially complementary lipid-lowering agents have been the object of significant research and development.

Ezetimibe (EZ) represents the first agent in a new class of lipid-lowering medications (2-azetidinones), referred to as cholesterol absorption inhibitors. It has recently been confirmed that this novel agent inhibits the absorption of dietary and biliary cholesterol by inhibiting the critical sterol transporter Niemann-Pick C1-like 1 protein in the intestinal wall (28). Human studies have demonstrated that the usual clinical doses of EZ result in a greater than 50% reduction in total cholesterol (TC) absorption (29). In clinical trials, EZ 10 mg/day decreased LDL-C levels by 18% (30-33) and further enhanced the LDL-C-lowering effect of coadministered statins by an additional 21% to 22% (34-42). In addition, EZ modestly lowers triglyceride (TG) levels (by approximately 5%) and increases high-density lipoprotein cholesterol (HDL-C) levels (by approximately 3%); however, these results have been inconsistent in clinical trials, with a number of studies demonstrating that the effects of EZ on TG levels and/or HDL-C levels were not statistically significant (30-32,35,40-42).

In June 2003, EZ became the first cholesterol absorption inhibitor approved by the Health Protection Branch, Health Canada, for use in Canada. EZ has been indicated to treat primary hypercholesterolemia, either alone or concomitantly with a statin. It has also been approved for the treatment of homozygous familial hypercholesterolemia and homozygous familial sitosterolemia (phytosterolemia). The aim of the present study was to determine the clinical effect and tolerability of EZ in clinical practice among a group of patients managed in a specialty cardiovascular risk reduction clinic (CRRC).

PATIENTS AND METHODS

The present study was a retrospective cohort study among consecutive patients followed within the CRRC at the

University of Alberta Hospital, Edmonton, Alberta. The study was reviewed and approved by the Health Research Ethics Board of the University of Alberta.

The study group was composed of consecutive patients who were managed within the CRRC between June 2003 and February 2004. Patients were eligible for the study if they were 18 years of age or older, and were prescribed EZ during the study period and took the drug for a minimum of two weeks (the time it takes for EZ to produce its maximum LDL-C-lowering effects [30]). Patients were excluded from the study if they had their lipid-lowering medication regimen or doses changed within one month before EZ was prescribed, or if they did not have a fasting lipid profile (FLP) with a calculated or measured LDL-C level reflecting their pre-EZ treatment response to therapy, as well as a follow-up FLP reflecting their treatment response while on EZ.

The medical records of all eligible patients were reviewed and the following data were obtained: patient demographics (age and sex), complete FLPs at baseline and follow-up (levels of TC, LDL-C, HDL-C and TGs, and TC to HDL-C ratio [TC/HDL]). Cardiac risk factors, documented by a physician or pharmacotherapy practitioner, were recognized as the following: hypertension, smoking (current, past or never), family history of premature CAD and diabetes mellitus (type 1 or 2). In addition, novel cardiac risk factors such as elevated lipoprotein(a) (greater than 0.30 g/L) or elevated homocysteine (greater than 12.1 $\mu\text{mol/L}$) levels were identified. Documentation of the presence of any vascular disease was recorded, including myocardial infarction, angina pectoris, percutaneous coronary intervention, coronary artery bypass graft surgery, peripheral arterial disease (ie, aortofemoral bypass or symptoms suggestive of peripheral arterial disease), transient ischemic attack, stroke or endarterectomy.

The primary outcome measure in the present cohort study was the change in FLP between baseline (before EZ treatment was implemented) and after two to six weeks of EZ therapy. To evaluate potential differences in patient subgroups, assessment of the clinical effectiveness results with EZ treatment was stratified by primary versus secondary prevention, and EZ monotherapy versus EZ plus low-dose statin (20 mg/day or less of atorvastatin or its equivalent) versus EZ plus high-dose statin (more than 20 mg/day of atorvastatin or its equivalent). The secondary outcome of interest was the assessment of the percentage of patients able to achieve their LDL-C target levels in accordance with their calculated Framingham risk category and defined Canadian guidelines (23), with the addition of EZ therapy. Changes in HDL-C levels, TC/HDL ratio and TG levels were also determined. Patient tolerability of EZ was determined by reviewing patients' reports during clinical follow-up, and physician-, pharmacotherapy practitioner- and nurse-documented observations (physical examination findings), as well as results of specific laboratory tests and measurements (creatinine kinase levels, alanine aminotransferase levels and aspartate aminotransferase levels).

The descriptive demographic characteristics of all patients included in the study were summarized using means for continuous variables and proportions for categorical variables. All statistical analyses were performed using SAS statistical software (version 8.2, SAS Institute Inc, USA).

RESULTS

There were 91 patients who were prescribed EZ in the CRRC between June 2003 and February 2004. From this group, 84 patients fulfilled all of the study criteria and were included in the analysis. Five patients were excluded because of

TABLE 1
Patient demographics

Parameter	n=84
Mean age in years (range)	57.9 (26–81)
Sex, n (%)	
Male	43 (51.2)
Female	41 (48.8)
Documented vascular disease*, n (%)	
CAD (MI, PCI, CABG or angina)	50 (59.5)
Cerebrovascular disease (TIA or stroke)	8 (9.5)
Peripheral arterial disease	1 (1.2)
Diabetes mellitus, n (%)	
Type 1 or type 2	13 (15.4)
Distribution of risk factors, n (%)	
Hypertension	32 (38.1)
Smoking history	
Current smoker	18 (21.4)
Past smoker	36 (42.8)
Never	30 (35.7)
Positive family history of premature CAD in a first-degree relative	59 (70.2)
Elevated lipoprotein(a) levels	19 (22.6)
Hyperhomocysteinemia	9 (10.7)
Primary versus secondary prevention, n (%)	
Primary prevention	28 (33.3)
Secondary prevention	56 (66.7)
Risk categories, n (%)	
High-risk patients (history of vascular disease or DM, or Framingham 10-year CAD risk 20% or greater)	60 (71.4)
Moderate-risk patients (Framingham 10-year CAD risk 11% to 19%)	11 (13.1)
Low-risk patients (Framingham 10-year CAD risk 10% or lower)	13 (15.5)

*Not mutually exclusive because each patient may have had more than one documented event. CABG Coronary artery bypass graft surgery; CAD Coronary artery disease; DM Diabetes mellitus; MI Myocardial infarction; PCI Percutaneous coronary intervention; TIA Transient ischemic attack

adjustments made in the doses of their other lipid-lowering treatments concurrent with the addition of EZ. Two patients developed side effects thought to be related to EZ (myalgias in one patient; headaches, nausea, vomiting and dizziness in another patient) and discontinued the drug before obtaining an FLP to reflect their response to therapy. Therefore, the study group consisted of 43 men and 41 women with a mean age of 57.9 years. By Framingham risk calculations, 71.4% were found to be high-risk patients, 13.1% moderate-risk patients and 15.5% low-risk patients. Fifty-six (66.7%) patients were secondary prevention patients, based on the documentation of prior CAD or vascular events (Table 1). Based on each patient's absolute lipid values, it was concluded that 57 of 84 (67.9%) patients had a genetic dyslipidemia.

Mean baseline levels were: TC 6.71 mmol/L, LDL-C 4.52 mmol/L, HDL-C 1.30 mmol/L, TGs 2.05 mmol/L and TC/HDL ratio 5.33. While patients were on EZ, the mean reductions in levels were: TC 1.11 mmol/L (16.5%), LDL-C 1.01 mmol/L (22.3%), HDL-C 0.06 mmol/L (4.6%) and TC/HDL ratio 0.68 (12.8%); all of these findings were statistically significant ($P<0.001$) (Table 2). Results were

TABLE 2
Total population summary (n=84)

Lipid parameter	Baseline, mean	On ezetimibe, mean	Absolute change, mean (%)	P
TC, mmol/L	6.71	5.60	-1.11 (-16.5)	<0.001
LDL-C, mmol/L	4.52	3.50	-1.01 (-22.3)	<0.001
HDL-C, mmol/L	1.30	1.24	-0.06 (-4.6)	<0.001
Triglycerides, mmol/L	2.05	2.09	+0.04 (+1.9)	0.60
TC/HDL-C ratio	5.33	4.65	-0.68 (-12.8)	<0.001

HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol; TC Total cholesterol

similar when stratified by primary (n=28) versus secondary (n=56) prevention (Table 3). Among the primary prevention group, only the TC levels, LDL-C levels and TC/HDL ratio reductions were statistically significant. In the secondary prevention group, the reductions in TC levels, LDL-C levels, HDL-C levels and TC/HDL ratio all achieved statistical significance. Patients on EZ monotherapy (n=34) had a mean level reduction in LDL-C of 1.03 mmol/L (20.5%), compared with 1.19 mmol/L (30.1%) or 0.95 mmol/L (22.5%) in patients in whom the medication was added to a low-dose (n=12) or a high-dose (n=38) statin ($P<0.01$ for all), respectively. The impact of EZ on other lipid parameters, stratified by these treatment strategies, is summarized in Table 4. The addition of EZ produced a significantly greater reduction in LDL-C levels among patients considered to have a genetic dyslipidemia, compared with patients with a nongenetic dyslipidemia (mean LDL-C level reduction of 1.17 mmol/L versus 0.71 mmol/L, respectively; $P=0.02$). Four patients in total (two of 84 patients included in the effectiveness assessment) discontinued EZ for side effects thought to be related to the drug (Table 5). On EZ, 30 patients (35.7%) achieved previously unattainable target LDL-C levels (seven of 34 [20.6%] in EZ monotherapy group, five of 12 [41.6%] in the EZ plus low-dose statin group and 18 of 38 [47.4%] in the EZ plus high-dose statin group).

DISCUSSION

National guidelines in both Canada and the United States have defined LDL-C target levels for patients with dyslipidemia to optimally reduce the risk of CAD events (22,23). Despite these widespread efforts, evidence consistently demonstrates the undertreatment of patients with dyslipidemia and the failure to attain target goals for optimal risk reduction (24-27). While the statins are a potent and efficacious class of lipid-lowering agents, these drugs alone at the maximum recommended doses do not adequately lower LDL-C levels in some patients, often due to the presence of genetic hypercholesterolemia. In other patients, the statins are inadequate to achieve their target LDL-C concentrations because the patients are unable to tolerate the maximum dose titration necessary. Consequently, combination therapy that is effective and tolerable is needed for many patients.

EZ represents a new class of cholesterol-lowering agents with a novel mechanism of action that involves the selective inhibition of dietary and biliary cholesterol absorption from the intestine. Clinical trials (30-33) demonstrate that EZ produces modest reductions (approximately 18%) in LDL-C levels when used as monotherapy. The mechanism of action of EZ complements that of statin therapy and when coadministered with statins, it produces an additive

TABLE 3
Mean results stratified by primary versus secondary prevention

Lipid parameter	Primary prevention (n=28)				Secondary prevention (n=56)			
	Baseline	On ezetimibe	Absolute change (%)	P	Baseline	On ezetimibe	Absolute change (%)	P
TC, mmol/L	7.49	6.32	-1.17 (-15.6)	<0.001	6.33	5.25	-1.08 (-17.1)	<0.001
LDL-C, mmol/L	5.25	4.10	-1.15 (-21.9)	<0.001	4.16	3.22	-0.94 (-22.6)	<0.001
HDL-C, mmol/L	1.44	1.39	-0.04 (-2.8)	0.06	1.23	1.17	-0.06 (-4.9)	<0.001
Triglycerides, mmol/L	1.84	1.92	+0.07 (+3.8)	0.50	2.15	2.18	+0.03 (+1.4)	0.81
TC/HDL-C ratio	5.34	4.72	-0.62 (-11.6)	<0.001	5.33	4.62	-0.71 (-13.3)	<0.001

HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol; TC Total cholesterol

TABLE 4
Mean results stratified by ezetimibe (EZ) treatment strategy

Lipid parameter	EZ monotherapy (n=34)				EZ + low-dose statin (n=12)				EZ + high-dose statin (n=38)			
	Baseline	On EZ	Absolute change (%)	P	Baseline	On EZ	Absolute change (%)	P	Baseline	On EZ	Absolute change (%)	P
TC, mmol/L	7.29	6.29	-1.00 (-13.7)	<0.001	6.31	4.78	-1.53 (-24.2)	0.0016	6.30	5.22	-1.08 (-17.1)	<0.001
LDL-C, mmol/L	5.03	4.01	-1.03 (-20.5)	<0.001	3.96	2.78	-1.19 (-30.1)	0.0017	4.22	3.26	-0.95 (-22.5)	<0.001
HDL-C, mmol/L	1.37	1.33	-0.04 (-2.9)	0.0454	1.39	1.30	-0.09 (-6.5)	0.0261	1.21	1.14	-0.06 (-5.0)	0.0017
TGs, mmol/L	2.10	2.36	+0.26 (+12.4)	0.0357	2.10	1.54	-0.56 (-26.7)	0.0255	1.99	2.03	+0.03 (+1.5)	0.7753
TC/HDL-C ratio	5.45	4.92	-0.53 (-9.7)	<0.001	5.06	3.79	-1.28 (-25.3)	0.0180	5.33	4.68	-0.63 (-11.8)	<0.001

HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol; TC Total cholesterol; TGs Triglycerides

TABLE 5
Patients intolerant to ezetimibe (n=4)

Patient	Duration of ezetimibe	Fasting lipids on ezetimibe (study inclusion)	Symptoms	Other lipid-lowering drug intolerances (reported symptoms)
1	10 days	No	Myalgias	Niacin, pravastatin, atorvastatin, simvastatin rosuvastatin (myalgias)
2	20 days	No	Headaches, nausea, vomiting and dizziness	Gemfibrozil and cerivastatin (rhabdomyolysis), fenofibrate and colestipol (nausea and vomiting), pravastatin (headache)
3	Approximately 6 weeks	Yes	Depression and emotional lability	Atorvastatin and simvastatin (fatigue and depression), colestipol (nausea)
4	Approximately 6 weeks	Yes	Progressive leg weakness	Atorvastatin and fenofibrate (leg weakness)

LDL-C-lowering effect. Clinical trials (34-42) have demonstrated that the coadministration of EZ 10 mg/day with low-dose statins produces LDL-C-lowering effects (an additional 21% to 22%) comparable with or greater than those of the highest dose of the statin alone.

The present study evaluated the effect and tolerability of EZ among high-risk patients in the clinical setting of a specialty CRRC. The retrospective cohort design was intended to evaluate whether the clinical use of EZ, outside of the controlled setting of a clinical trial, would yield similar results. By design, clinical trials are limited to a highly selected and homogeneous group of patients who are carefully monitored by study personnel. Consequently, the benefits of EZ in our usual clinical practice, which involves many high-risk and/or genetically hyperlipidemic patients who are not able to achieve their target cholesterol goals because of multiple drug intolerances or a lack of an adequate response to the usual maximum doses of available medications, are unknown. In addition, because there is a limited amount of

published data investigating the efficacy of EZ in combination with high-dose statins, we sought to evaluate this clinical application of EZ.

The LDL-C-lowering effect of EZ observed for the entire group of patients in the present study was comparable with those seen in clinical trials – an absolute LDL-C level reduction of 1.0 mmol/L, or a 22.3% decrease ($P<0.001$). We also observed that the addition of EZ produced an absolute TC/HDL ratio reduction of 0.68, or a 12.8% decrease, which was statistically significant ($P<0.001$). The minor changes in TG and HDL-C levels observed in our study were in the opposite direction of those published for some clinical trials (33,34,36-39), with an absolute decrease in HDL-C levels by 0.06 mmol/L or 4.6% ($P<0.001$), and an absolute increase in TG level by 0.04 mmol/L, or 1.9% ($P = \text{not significant}$). This difference in the observed change in HDL-C and TG levels between the present study and previously published trials might be due to the smaller sample size in our study. However, changes produced by EZ on both HDL-C and TG levels have

been inconsistent in clinical trials and reported to be not statistically significant in a number of clinical trials (30-32,35,40-42).

In our study, we prespecified that we would analyze the results with patients stratified by both primary versus secondary prevention and the specific EZ treatment strategy used. The LDL-C-lowering effect of EZ was consistent across all of these subgroups. The observed decrease in LDL-C level was 1.15 mmol/L, or 21.9%, in primary prevention patients, compared with 0.94 mmol/L, or 22.6%, in secondary prevention patients. More interesting was the consistent LDL-C level reduction observed in the three prespecified EZ treatment strata: 1.03 mmol/L, or 20.5%, for EZ monotherapy versus 1.19 mmol/L, or 30.1%, for EZ plus low-dose statin (20 mg/day or less of atorvastatin or its equivalent) versus 0.95 mmol/L, or 22.5%, for EZ plus high-dose statin (20 mg/day or greater of atorvastatin or equivalent). Previously published results (34-42) have demonstrated that the addition of EZ to a low-dose statin produces a comparable LDL-C-lowering effect that is similar to that of the highest dose of the statin alone. However, there are limited data regarding the additive LDL-C-lowering effect of the combination of EZ with high-dose statins, and we speculated that this combination may not produce as significant of a LDL-C reduction due to a diminished potential; that is, because the LDL-C may not be as high in patients on a high-dose statin, the additive LDL-C reduction achieved with EZ may be lower. This speculation did not hold true, because we found that the LDL-C benefit of combining EZ with a high-dose statin was just as significant.

While the specific levels of LDL-C optimal for maximizing CAD risk reduction are not definitively known, recent clinical trials (19-21) have demonstrated both the safety and efficacy of achieving lower LDL-C target levels than are currently recommended. In a recent publication (43), the coordinating committee of the National Cholesterol Education Program (Adult Treatment Panel III) recommended that an intensified LDL-C goal of less than 1.8 mmol/L should be a 'therapeutic option' for clinicians with patients at very high risk of coronary events and high-risk patients with a baseline LDL-C level of less than 2.6 mmol/L. Because it is likely that future updates of the Canadian guidelines will recommend more intensive LDL-C-lowering for high-risk patients, more potent therapeutic approaches will be required. Evidence from our current study supports the safety and efficacy of combining EZ with a high-dose statin, which would be a logical approach to achieving lower LDL-C targets in appropriate patients.

We were able to achieve the recommended LDL-C target levels for 35.7% of the patients with the addition of EZ. This is a clinically significant observation considering the high prevalence of patients with genetic dyslipidemias included in our cohort. The patients in the present study had significantly elevated mean baseline LDL-C levels (LDL-C 5.03 mmol/L in monotherapy group) without treatment or persistently elevated LDL-C levels, despite maximum tolerated statin therapy (mean LDL-C 4.22 mmol/L in the high-dose statin group and LDL-C 3.96 mmol/L in the low-dose statin group). While one previous study (39) had demonstrated that addition of EZ to ongoing statin therapy facilitated attainment of LDL-C goals for more than 75% of patients, these results were achieved in patients with a baseline LDL-C level that was only moderately elevated relative to the target goal (mean LDL-C 3.57 mmol/L). In addition, the eligibility criteria for this

previous study permitted enrolment of a large number of patients (18% of the entire study population), who were technically at target levels at the time of random assignment. The same study also demonstrated that 27.3% of the statin plus placebo-treated patients achieved the target LDL-C levels after eight weeks in the study.

Published clinical evidence suggests that EZ is well tolerated by patients both as monotherapy and in combination with a statin. Neither symptomatic liver nor significant skeletal muscle dysfunction (myalgias and/or elevated creatine kinase) has been reported in the published clinical trials with EZ alone or in combination. However, recent adverse drug reaction reports received by Health Canada (44) have prompted the revision of the Canadian product monograph to reflect the risks of both myalgias and rhabdomyolysis, as well as other adverse events (hepatitis, acute pancreatitis and thrombocytopenia) in patients taking EZ alone or in combination with a statin.

Consistent with previous reports on the tolerability of EZ, in our clinical experience there have been no laboratory abnormalities associated with the use of this agent. Two patients included in the present study discontinued EZ due to side effects associated with the drug; one patient experienced depression and emotional lability, while the second patient reported progressive leg weakness. There were two additional clinic patients who experienced side effects and discontinued EZ; however, these patients were not included in the effect analysis because they stopped the medication before obtaining an FLP that reflected their on-EZ treatment response. Interestingly, in all four cases, EZ was discontinued due to a side effect that each of the patients had previously experienced while receiving other lipid-lowering medications used as monotherapy or in combination with other treatment strategies.

CONCLUSIONS

The results of the present study demonstrate that EZ is safe and effective in high-risk patients treated in the clinical setting of a CRRC. Unlike the highly selected group of patients included in the clinical trials, the patients in our retrospective cohort consisted of mainly high-risk dyslipidemic patients who were not at their target cholesterol goals because of multiple drug intolerances or lack of an adequate response to the usual maximum doses of available medications. In this group of patients, we observed a mean LDL-C level reduction of 0.94 mmol/L to 1.19 mmol/L (20% to 30%) in all patient subgroups, which was consistent with or slightly superior to published clinical trial results (30-42). Similarly, the mean reduction in TC/HDL ratio from 0.53 to 1.28 (10% to 25%) observed across all patient subgroups was comparable with the results of previous clinical trials (37,38,40). In addition, the significant reduction in LDL-C levels (mean 0.95 mmol/L [22.5%]) that was observed in the EZ plus high-dose statin subgroup provided clinical evidence for EZ use beyond published studies.

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