ORIGINAL ARTICLE

Efficacy of Generic Formation of Ezetimibe in Patients with High Cardiovascular Risk Receiving High-Potency Statin

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Background: Ezetimibe has been recommended to add on statin therapy when maximally tolerated statin cannot achieve low-density lipoprotein cholesterol (LDL-C) target. However, the safety and efficacy of generic formulation of ezetimibe has rarely been reported.

Objective: To examine efficacy of branded generic ezetimibe in patients with high cardiovascular risk receiving high-potency statin.

Materials and Methods: The present study was a prospective cohort study in adult patients with high cardiovascular risk receiving atorvastatin 40 mg/day, but the LDL-C level was still higher than 70 mg/dL. Branded generic ezetimibe 10 mg once daily (MiBEAZ™) was added on the high-potency statin therapy as a combination treatment. Lipid parameters were evaluated three months after ezetimibe treatment.

Results: Of the 61 patients, mean age was 62.4±11.5 years, and 33 (54.1%), were male. Coronary artery disease was reported in 58 patients or 95.1%. The median baseline of LDL-C was 95.0 mg/dL (IQR 79.5, 108.5). At 3-month follow-up, total cholesterol and LDL-C levels were significantly decreased by branded generic ezetimibe add-on therapy. The relative change of LDL-C reduction was 26.3% (IQR –38.8, –11.1, p<0.001). The LDL-C target under 70 mg/dL was attained in 60% of the patients. Triglyceride and high-density lipoprotein cholesterol levels remained unchanged. After ezetimibe medication, there were no differences in renal or hepatic function.

Conclusion: The authors demonstrated that branded generic ezetimibe significantly reduced levels of LDL-C in high cardiovascular risk patients with uncontrolled LDL-C level despite the high-potency statin treatment. There was no concern regarding safety issues with the branded generic ezetimibe add-on therapy.

Keywords: Low-density lipoprotein cholesterol; Generic ezetimibe; Lipid-lowering; Dyslipidemia

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Ezetimibe is a non-statin lipid-lowering medication that inhibits the absorption of dietary cholesterol by blocking the Niemann-Pick C1-Like 1 protein (NPC1L1). Due to enterohepatic circulation, its half-life is approximately 22 hours[1]. It is metabolized in the small intestine and the liver, not via the cytochrome P450 system, and excreted back in bile as means of elimination[2]. Ezetimibe lowers low-density lipoprotein cholesterol (LDL-C) by 15% to 20% when used alone as compared to 5% to 10% from doubling the dose of statin[3]. The most significant percentage reductions of 20% to 25% in LDL-C were reported with the addition of ezetimibe, according to a pooled analysis of double-blind trials of individuals already taking a statin[2,4]. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) has shown a benefit of ezetimibe on cardiovascular event reduction when added to a statin in post-acute coronary syndrome (ACS) patients[5,6].

The combination of statin and ezetimibe has been shown to improve LDL-C goal attainment and reduce major cardiovascular events[5]. Statins are recommended as the first-line lipid-lowering treatment in patients with atherosclerotic cardiovascular disease (ASCVD) by both European and American guidelines. Furthermore, individuals with uncontrolled LDL-C with statins or those who are intolerant to statins are advised to use ezetimibe in

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conjunction to proprotein convertase subtilsin/kexin type 9 (PCSK9) inhibitors[7,8]. The usage of generic medications, which are less expensive, has emerged as a substitute strategy during the current era of cost concerns in the healthcare public[9]. Nevertheless, the safety and efficacy of generic drugs should not be compromised when compared to the brand-name drug or proprietary drug. Therefore, the efficacy of generic ezetimibe merits the study. The present study aimed to study the efficacy and safety of generic version of ezetimibe in patients with high cardiovascular risk and uncontrolled LDL-C levels.

Materials and Methods

The present study was a prospective cohort study of patients presenting to the outpatient cardiology clinic at Maharaj Nakorn Chiang Mai Hospital between July 2021 and May 2022. The present study was approved by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University, Study Code MED-2564-08200, the investigations were carried out following the Declaration of Helsinki, including written informed consent from all participants. The inclusion criteria were 1) age of 18 years or older, 2) patients with high cardiovascular risk, including established ASCVD, diabetes with target organ damage, familial hypercholesterolemia with ASCVD, or another major risk factors, 3) have been receiving a stable dose of high-potency statin, such as atorvastatin 40 mg/day, and 4) LDL-C of 70 mg/dL or higher despite high-potency statin therapy.

Patients who refused to participate in the study were excluded. Patients who met the inclusion criteria and gave informed consent were enrolled in the present study. Baseline characteristics including age, gender, body mass index, comorbidities, socio-economic status, and concomitant medications, and laboratory data including lipid profile, renal function, and liver function were collected. The enrolled patients had been receiving MiBEAZ™, a branded generic ezetimibe, manufactured by Siam Pharmaceutical, Bangkok, Thailand, 10 mg once daily for three months. The formulation of MiBEAZ™ contains the active pharmaceutical ingredient ezetimibe, and diluent, binder, solubilizer, disintegrant, and lubricant. The pharmacokinetic study was performed and concluded to be bioequivalent to innovator product. The plasma concentration at predetermined time intervals was previously evaluated. The branded generic ezetimibe (MiBEAZ™) has been approved by the Food and Drug Administration of Thailand (FDA) since December 2018.

The change of statin dose was discouraged during the study period. At a three-month follow-up, the lipid profile, renal function, and liver function were measured. The adverse events during the three months were also collected. Methods of measuring medication adherence included the use of pill counts.

Statistical analysis

The authors calculated the sample size by comparing a mean to a known value (pair t-test). A previous study demonstrated that the mean level of LDL-C after high-potency statin was 100 mg/dL and ezetimibe on top of high-potency statin could reduce LDL-C level by 20%[10]. The standard deviation of the sampled population was estimated at 35 mg/dL[11]. The estimated sample size was 54 patients. The authors anticipated that 10% of the patients may have been lost to follow-up or had a drug compliance issue. Therefore, a sample size of 60 patients was required in the study.

Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) and the categorical variables were reported as counts with percentages. Descriptive statistics were presented for baseline demographic and clinical information. The numerical variables were compared within groups with paired t-test or Wilcoxon matched paired sign-rank test. Statistical software package IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA, https://www.ibm.com/products/spss-statistics) was used for analysis.

Results

Sixty-one patients who received a 40 mg dose of atorvastatin, once daily, to control LDL-C levels for at least three months and still had LDL-C higher than 70 mg/dL were included in this study. The branded generic ezetimibe (MiBEAZ™) 10 mg oral once daily was added on top of the atorvastatin as a combination treatment for the next three months. The baseline characteristic of dyslipidemia patients is shown in Table 1. The mean age was 62.6±11.5 years, minimum of 35 years old and the maximum age was 87 years old with 33 patients (54.1%) being male, and the mean body mass index was 24.4±3.9 kg/m².

The three most common co-morbidities included coronary artery disease in 58 patients (95.1%), hypertension 36 patients (59.0%), and diabetes mellitus 24 patients (39.3%). One patient had the diagnosis of familial hypercholesterolemia. Antiplatelet medications were used by 60 patients

Table 1. Baseline clinical characteristics of dyslipidemia patients before receiving branded generic ezetimibe

Characteristics	n=61 patients
Age (years); mean±SD	62.4±11.5
Male; n (%)	33 (54.1)
Body mass index (kg/m^2); mean±SD	24.5±3.9
Health care payment scheme; n (%)	
Civisl Servant Medical Benefit Scheme	6 (9.8)
Universal health-care coverage scheme	41 (67.2)
Social security	14 (22.9)
Comorbid diseases; n (%)	
Diabetes mellitus	24 (39.3)
Chronic kidney disease	17 (27.9)
Hypertension	36 (59.0)
Coronary artery disease	58 (95.1)
Cerebrovascular disease	4 (6.5)
Familial hypercholesterolemia	1 (1.6)
Current medications; n (%)	
Antiplatelet	60 (98.4)
Betablocker	54 (88.5)
ACEI/ARB/ARNI	53 (86.9)
Anti-diabetic drug	21 (34.4)
Proton pump inhibitor	24 (39.3)
Fibrate	2 (3.3)

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor neprilysin inhibitor; SD=standard deviation

(98.4% of the patients) and beta-blockers by 54 patients (88.5% of the patients). Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or angiotensin receptor neprilysin inhibitors were used by 53 patients (86.9% of the patients)

Two patients used fibrate in addition to statin to control LDL-C. However, no bile acid sequestrants, niacin, or PCSK9-inhibiting drugs were used in the present study population. There were no reports of myalgia, transaminitis, or rhabdomyolysis in patients who received branded generic ezetimibe.

The lipid profile, renal function, and liver function are shown in Table 2. At baseline, total cholesterol was 163.5 mg/dL (IQR 149.5, 183.2), HDL-C was 44.5 mg/dL (IQR 39.0, 57.2), LDL-C was 95.0 mg/dL (IQR 79.5, 108.5), and triglyceride was 141.5 mg/dL (IQR 93,2, 175.2). At three months after generic ezetimibe 10 mg once daily was added as a combination treatment, triglyceride was 117.0 mg/dL (IQR 92.0, 163.5), total cholesterol was 134.0 mg/dL (IQR 114.5, 164.5), HDL-C was 44.0 mg/dL (IQR 37.0, 57.0), and LDL was 63.0 mg/dL (IQR 56.0, 91.0). Total cholesterol and LDL-C were significantly decreased by ezetimibe add-on therapy. The median absolute change of the lipid parameters is shown in Table 2. The median absolute change of total cholesterol level was –27.0 mg/dL (IQR –50.7, –16.0), p<0.001. The median relative change of total cholesterol level was –17.4% (IQR –29.3, –8.0), p<0.001.

The median absolute change of LDL-C level was –25.0 mg/dL (IQR –38.5, –10.5). The median relative change of LDL-C level was –26.2% (IQR –39.6, –10.9), p<0.001. The LDL-C target below 70 mg/dL was achieved in 37 patients (60.6%) after ezetimibe treatment. Triglyceride and high-density lipoprotein cholesterol levels remained unchanged. There were no statistically significant differences in terms of renal and liver function before and after taking the ezetimibe.

Table 2. Biochemical parameters before and after adding branded generic ezetimibe

Biochemical parameters	At baseline median (IQR)	At 3 months median (IQR)	Absolute change median (IQR)	Relative change (%) median (IQR)	p-value
Total cholesterol (mg/dL)	163.5 (149.5, 183.2)	134.0 (114.5, 164.5)	–27.0 (–50.8, –16.0)	–17.4 (–29.2, –8.5)	<0.001
HDL-C (mg/dL)	44.5 (39.0, 57.2)	44.0 (37.0, 57.0)	–1.0 (–6.0, 3.5)	–2.1 (–11.5, 9.4)	0.319
LDL-C (mg/dL)	95.0 (79.5, 108.5)	63.0 (56.0, 91.0)	–25.0 (–38.5, –10.5)	–26.3 (–38.8, –11.1)	<0.001
Triglyceride (mg/dL)	141.5 (93.2, 175.2)	117.0 (92.0, 163.5)	–9.0 (–54.8, 18.5)	–5.5 (–30.3, 19.0)	0.074
BUN (mg/dL)	17.0 (13.0, 20.5)	15.5 (13.0, 21.5)	–1.0 (–3.0, 3.0)	–7.3 (–17.7, 21.4)	0.609
Creatinine (mg/dL)	1.1 (0.8, 1.2)	1.0 (0.8, 1.2)	0.0 (–0.1, 0.1)	0.0 (–9.1, 7.7)	0.927
AST (U/L)	25.0 (20.0, 32.0)	25.5 (20.0, 36.0)	–1.0 (–5.0, 7.0)	–4.0 (–17.5, 21.2)	0.926
ALT (U/L)	23.0 (18.0, 35.0)	29.5 (22.0, 38.0)	2.0 (–4.0, 12.0)	10.0 (–17.4, 60.0)	0.053
ALP (U/L)	95.0 (67.0, 109.0)	85.5 (68.0, 106.0)	–3.0 (–15.0, 7.0)	–2.9 (–15.8, 8.5)	0.376
Total bilirubin (mg/dL)	0.5 (0.4, 0.8)	0.6 (0.4, 0.8)	0.1 (–0.1, 0.1)	6.8 (–12.8, 37.5)	0.133
Direct bilirubin (mg/dL)	0.2 (0.2, 0.3)	0.2 (0.2, 0.3)	0.0 (–0.0, 0.1)	5.3 (–10.8, 42.9)	0.114

ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; HDL=high-density lipoprotein; IQR=interquatile range; LDL=low-density lipoprotein

Medication adherence included the use of pill counts reported in 100% among 57 patients, 90% in one patient, 87% in one patient, 76% in one patient, and 61% in one patient. No patients were lost to follow-up. No serious adverse effect was reported in all of the patients during treatment time (LDL-C goal attainment in patients with less than 90% adherence).

Discussion

When a maximally tolerated statin cannot reach the target LDL-C, ezetimibe has been recommended as an addition to statin therapy[12]. However, the CORE-Thailand registry, which offers data on Thai patients with several risk factors or established atherosclerotic disease, revealed suboptimal LDL-C control[13]. Despite the fact that the majority of patients received statin therapy, individuals with high cardiovascular risk had an average LDL-C of 99 mg/dL, which is higher than the recommended target of 70 mg/dL. Ezetimibe add-on therapy was only given to 4% of Thai patients in this registry[13].

Patients taking ezetimibe experienced fewer recurrent cardiovascular events, with the number needed to treat that was 30, according to a cost-effectiveness analysis of non-statin lipid-modifying agents for secondary cardiovascular disease prevention among statin-treated patients in Thailand[14]. However, from the societal perspective and based on current acquisition costs in 2018, incremental cost-effectiveness ratios (ICERs) of ezetimibe were $US 27,361 per quality-adjusted life-years (QALYs) gained. Ezetimibe's costs must be cut by 85% to be cost-effective[14].

Because of its expensive price and limited generalizability, ezetimibe was only very infrequently used among several countries. In addition, pharmacists and physicians often have negative opinions of generic medications, which could be a barrier to their usage[15,16]. Due to all of these aspects, the generic ezetimibe must have a comparable safety and efficacy profile to the brand-name drug to expand its use.

The majority of the participants in the present study had established coronary artery disease, reflecting a group with a high cardiovascular risk. The present study findings demonstrated the clear efficacy of branded generic ezetimibe in combination with high-potency statins to lower LDL-C levels. The median relative reduction of LDL-C level after three months of branded generic ezetimibe medication was 26%, which was comparable to the outcomes from the brand-name ezetimibe studies[6,10,11].

A meta-analysis found that adding brand-name ezetimibe to a statin did not increase the risk of transminitis, myopathy, rhabdomyolysis, and treatment discontinuation due to adverse effects[17,18]. Similar to the present study results, there were no adverse side effects of branded generic ezetimibe reported during the three months study period.

Finally, the authors demonstrated the branded generic ezetimibe (MiBEAZ™) 10 mg once daily added on high-potency statin therapy enhanced the attainment of LDL-C target below 70 mg/dL in the majority of the patients. Due to the lower cost than the brand-name counterpart, the proven efficacy and safety of branded generic ezetimibe would potentially increase the generalizability of ezetimibe therapy. As a result, the generic version of ezetimibe has the potential to improve dyslipidemia management leading to better long-term cardiovascular outcomes.

Limitation

First, the present study was a non-randomized, non-blinded clinical study. The authors compared LDL-C levels before and after adding generic ezetimibe in the same patient without a control group. The authors also did not perform the clinical equivalence study compared to the original form of ezetimibe. Nevertheless, the present study demonstrated that generic ezetimibe reduced LDL-C level by 26%, which was comparable to the effect that original ezetimibe reported in the previous studies. Due to the lack of control group, the effect of generic ezetimibe in LDL-C lowering in the present study could be biased from the Hawthorne effect (attention bias). The patients enrolled in the present study may have changed their behavior as a result of being observed that might have affected the LDL-C level. However, the effect of life-style modification such as reduced dietary saturated fat and exercise has been shown to reduce LDL-C level only 5% to 10%[7]. As a result, the possible confounders may have had only minor effect on LDL-C level in the present study. Second, most of the patients enrolled in this study had established cardiovascular diseases. The present study results might not be reflected in lower risk population. However, the efficacy of LDL-C reduction should be similar in various risk groups. Third, the follow-up period in the present study was short. Beyond three months, it is unclear whether branded generic ezetimibe would effectively sustain LDL-C levels. Fourth, the cost-utility analysis was not performed. As a result, the cost-effectiveness of branded generic ezetimibe has yet to be proven. To support the present study findings, additional trials

with cost-utility analysis and longer-term follow-up are required.

Conclusion

The addition of branded generic ezetimibe therapy to high-potency statin therapy has been demonstrated to significantly lower LDL-C and total cholesterol levels in patients with high cardiovascular risk and uncontrolled LDL-C levels. There was no concern regarding safety issues with the branded generic ezetimibe add-on therapy. These findings could increase the patient and physician confidence in generic ezetimibe therapy to manage dyslipidemia efficiently in patients with high cardiovascular risk.

What is already known on this topic?

Ezetimibe has been recommended as an add-on to statin therapy when maximally tolerated statin cannot achieve LDL-C target. However, the safety and efficacy of the generic formulation of ezetimibe has rarely been reported.

What this study adds?

This study has demonstrated that the branded generic ezetimibe (MiBEAZ™) 10 mg once daily added on high-potency statin therapy enhanced the attainment of LDL-C target without being concerned about safety issues.

Due to the lower cost of generic ezetimibe compared to original form, it might lead to an increased use of generic ezetimibe leading to the higher rate of LDL-C target achievement in Thai patients with high cardiovascular risk.

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Authors' contributions

NP performed statistical analysis, wrote the manuscript and tables. AP performed statistical analysis, data analysis, and data interpretation. SG collected and re-checked the data prior to the analysis. WW designed the cohort, conception of the data analysis, data interpretation, and critically revised the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Availability of data

The data that support the findings of the present study are available from the corresponding author upon reasonable request.

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Conflicts of interest

The branded generic ezetimibe (MiBEAZ™) used in this study was provided by Siam Pharmaceutical, Bangkok, Thailand. The investigators independently designed and conducted the study. The data was analyzed, and the manuscript was written by the investigators.

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