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Long Term Efficacy of Generic Atorvastatin by a University Hospital Database

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Abstract

BACKGROUND: There is limited long-term data of generic atorvastatin in terms of clinical efficacy and safety.

AIM: This study aimed to evaluate the efficacy and safety of generic atorvastatin in a 12-month period.

METHODS: This was a pre-test-post-test/quasi experimental study and conducted at Khon Kaen University Hospital, Khon Kaen, Thailand. The inclusion criteria were adult patients who received the original atorvastatin for at least 3 months and then switched to the generic atorvastatin for 12 months. Those who had taken other lipid lowering medications or medications affect lipid level, had no follow-up data on lipid profiles, or had different dose of atorvastatin during treatment period were excluded. Eligible patients were retrieved from the hospital database. Therapeutic lipid profiles and safety profiles were evaluated after 12 months of switching therapy.

RESULTS: During the study period, there were 297 patients that met the study criteria. The mean (SD) age of the patients was 61.05 (11.51) years. Male: female ratio was 0.87: 1 (139 male and 158 female patients). For lipid outcomes, only high-density lipoprotein cholesterol (HDL-c) was significantly increased by 2.05 mg/dL ($p = 0.001$). Low-density lipoprotein cholesterol (LDL-c) was slightly decreased by 3.26 mg/dL ($p = 0.560$). Serum creatinine was increasing by 0.07 mg/dL, while estimated glomerular filtration rate was decreasing by 2.55 ml/min/1.73 m^2. Other laboratory outcomes were not significantly changed after 1 year including ALT, AST, and CK.

CONCLUSION: Generic atorvastatin had comparable effect on LDL-c reduction and significant increasing of HDL-c compared with baseline after treatment with original atorvastatin for 3 months. Renal deterioration was found in this study population with generic atorvastatin. Physicians should be aware of declining of renal function in long-term use of generic atorvastatin.

Background

Cardiovascular diseases, namely, myocardial infarction, atrial fibrillation, peripheral arterial disease, stroke, heart failure, or hypertension, are prevalent. A report from UK found that 21.3% of 1,275,174 adult patients had one of the cardiovascular diseases [1]. Dyslipidemia is one of the major risk factors for cardiovascular diseases as well as other risk factors such as hypertension or sleep apnea [2], [3], [4], [5]. The previous reports and guidelines recommended lowering low-density lipoprotein cholesterol (LDL-c) in both primary and secondary prevention [6], [7]. For primary prevention, reduction of LDL-c by 1-mmol/L may reduce vascular events by 23% ($p < 0.001$) [6]. While, statin therapy reduces mortality in patients with myocardial infarction by 25% [7].

Even though statin therapy is beneficial in cardiovascular disease, it may be high cost with original statin particularly in resource limited setting or patients without health insurance [8]. Atorvastatin is a potent statin with several supportive data [9], [10], [11]. A study from Korea found that generic atorvastatin was comparable with original atorvastatin in term of efficacy [12]. Difference of LDL-c reduction between both drugs was 1.38% ($p = 0.49$). However, the Korean study was conducted for 8 weeks. Therefore, there is lack of a long-term clinical efficacy and safety data of generic atorvastatin treatment. This study aimed to evaluate the efficacy and safety of generic atorvastatin in a longer period of 1 year in a real-world setting.

Methods

This was a pre-test-post-test/quasi experimental study and conducted at Srinagarind Hospital, a University

Hospital of Khon Kaen University, Khon Kaen, Thailand. This hospital has a capacity of 1000 beds. The inclusion criteria were adult patients who received the original atorvastatin for at least 3 months and then switched to the generic atorvastatin for 1 year. Those who had taken other lipid lowering medications or medications affect lipid level, had no follow-up data on lipid profiles, or had different dose of atorvastatin during treatment period were excluded from the study. The other lipid lowering medications were gemfibrozil, fenofibrate, ezetimibe, cholestyramine, prednisolone, dexamethasone, hydrocortisone, or fludrocortisone. The original atorvastatin is Xarator (Pfizer Phamaceuticals, Peurto Rico), while the generic atorvastatin is Atorvastatin Sandoz (Lek Pharmaceuticals, Slovenia). The study period was between October 2016 and March 2018. The study protocol was approved by the ethic committee in human research, Khon Kaen University, Khon Kaen, Thailand (HE611147).

Eligible patients were retrieved from an electronic database of the hospital. Clinical and demographic data were reviewed and recorded including age, sex, body mass index, lipid profiles (total cholesterol, triglyceride, high-density lipoprotein cholesterol [HDL-c], and LDL-c), serum blood urea nitrogen, serum creatinine, estimated glomerular filtration rate (eGFR), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and serum creatinine kinase (CK). The laboratory tests were recorded at baseline or before the treatment of generic atorvastatin and 12 months after the treatment by generic atorvastatin. The baseline laboratory values were compared with the laboratory values at 12 months after treatment. A paired T test was used to compute differences between both time points if data were normally-distributed, while Wilcoxon Sign-Rank test was used if data were not normally-distributed. Data were presented as mean (SD), and mean difference between baseline and at 6 months with their 95% confidence interval (CI). A significant difference was defined by $p < 0.05$. Statistical analyses were performed by STATA software, College Station, Texas, USA.

Results

During the study period, there were 297 patients met the study criteria. The mean (SD) age of the patients was 61.05 (11.51) years. Male: female ratio was 0.87: 1 (139 male and 158 female patients). Co-morbid diseases were found as follows: Hypertension (170 patients; 57.24%); diabetes (147 patients; 49.49%); chronic kidney disease (32 patients; 10.77%); coronary artery disease (29 patients; 9.76%); stroke (12 patients; 4.04%); atrial fibrillation (8 patients; 2.69%), and heart failure (8 patients; 2.69%).

The most common dose of generic atorvastatin was 40 mg/d (159 patients; 53.54%), followed by 20 mg/d (132 patients; 44.44%). The other dosages were 10 mg/d (2 patients; 0.67%), 60 mg/d (3 patients; 1.01%), and 80 mg/d (1 patient; 0.34%). For lipid outcomes, only HDL-c was significantly increased by 2.05 mg/dL ($p = 0.001$) as shown in Table 1. LDL-c was slightly decreased by 3.26 mg/dL ($p = 0.560$). Serum creatinine and eGFR were significantly different after 1 year of switching therapy. Serum creatinine was increased by 0.07 mg/dL, while eGFR was decreased by 2.55 ml/min/1.73 m^2. Other laboratory outcomes were not significantly changed after 1 year including ALT, AST, and CK (Table 1).

Table 1: Clinical parameters of dyslipidemia patients who switched treatment from original atorvastatin to generic atorvastatin before and 12-month after switching therapy

Factors	Baseline	12th month	Mean differences	95% CI	p value*
BMI	26.76 (5.73)	26.74 (5.46)	−0.02	−0.29, 0.26	0.664
LDL	111.16 (44.54)	107.90 (39.17)	−3.26	−8.26, 1.74	0.560
HDL	51.28 (12.99)	53.33 (14.55)	2.05	0.80, 3.31	0.005
Tg	142.38 (61.56)	148.28 (72.41)	5.90	−2.62, 14.40	0.292
Chol	174.55 (47.65)	169.27 (42.14)	−5.28	−11.16, 0.60	0.084
BUN	18.15 (10.59)	18.41 (9.72)	0.26	−0.89, 1.41	0.679
Cr	1.20 (1.04)	1.27 (1.29)	0.07	0.02, 0.11	<0.001
eGFR	73.89 (26.50)	71.34 (26.58)	−2.55	−3.78, −1.32	<0.001
AST	29.12 (12.03)	31.85 (28.79)	2.73	−3.75, 9.21	0.785
ALT	34.14 (19.44)	38.96 (36.69)	4.82	−3.61, 13.25	0.361
CK	205.10 (115.27)	178.00 (112.85)	−27.10	−85.40, 31.20	0.723

CI: Confidence interval, BMI: Body mass index (kg/m^2), Chol: Cholesterol (mg/dL), Tg: Triglyceride (mg/dL), HDL: High density lipoprotein-cholesterol (mg/dL), LDL: Low density lipoprotein-cholesterol (mg/dL), BUN: Blood urea nitrogen (mg/dL), Cr: Creatinine (mg/dL); eGFR: Estimated glomerular filtration rate (ml/min/1.73 m^2), ALT: Alanine aminotransferase (U/L), AST: Aspartate aminotransferase (U/L), CK: Creatinine kinase (U/L), *p values were calculated by Wilcoxon Singed Rank test.

Discussion

This study showed that generic atorvastatin had comparable efficacy in LDL-c reduction compared with baseline after treatment with original atorvastatin for 3 months.

The Korean study found that generic and original atorvastatin reduced LDL-c level to 85.5 and 79.8 mg/dL, respectively [12]. The differences between both drugs ranged from −2.32 to 5.24 mg/dL. These data were similar to our study (Table 1) which had 95% CI of mean differences from −8.26 to 1.74. The results may imply that generic atorvastatin had persistent LDL-c reduction effect for at least 1 year. As recommended by the guideline to follow up lipid profiles every 12 months if good adherence [13]. Our results may imply that using generic atorvastatin may be justified to check LDL-c level every 1 year if the patients have good adherence and the LDL-c already met the goal. Surprisingly, the generic atorvastatin had significantly increased of HDL-c level than the baseline. The previous report showed that atorvastatin may increase HDL-c level by 6–7% [14]. These HDL-c differences may be due to different atorvastatin.

Regarding safety profiles, renal function was declined evidenced by increased serum creatinine by 0.07 mg/dL and decreased eGFR by 2.55 ml/min/1.73 m^2 after 1 year of treatment (Table 1). Even though statin

therapy may be beneficial in terms of cardiovascular disease prevention in chronic kidney disease patients [15], data on renal safety by statin are still matter of debate. A study from France found that atorvastatin had increased risk of acute kidney injury regardless of sex [16]. The odds ratios (95% CI) for men and women to develop acute kidney injury were 1.53 (1.21, 1.93) and 1.38 (1.02, 1.88). While, a post hoc analysis on six randomized controlled trials found that higher dose of atorvastatin group (80 mg) had lower proportion of renal decline than lower doses of atorvastatin group (10 mg) at 2.0% versus 2.5% [17]. Statin induced rhabdomyolysis may be one possible mechanism of acute kidney injury in statin treated patients [18]. Another study also found that patients treated with statin may have 34% increasing risk of acute kidney injury [19]. Possible explanations include inhibition of coenzyme Q10, antioxidant enzyme, by statin [19], [20], [21]. Further studies are required to evaluate this issue.

There are some limitations in this study. There was no specific dose for the generic atorvastatin in this study. The results may imply the efficacy of generic atorvastatin regardless of dose. We hypothesized that the patients in this study had good adherence and similar life style modifications throughout the study period. However, these statements may not be 100% confident. Moreover, some factors associated with atherosclerotic cardiovascular diseases and their treatments were not studied such as obstructive sleep apnea, and albuminuria [22], [23], [24], [25], [26].

Conclusion

Generic atorvastatin had comparable effect on LDL-c reduction compared with baseline after treatment with original atorvastatin for 3 months. Renal deterioration was found with increasing HDL-c level in this study population with generic atorvastatin. Physicians should be aware of declining of renal function in long-term use of generic atorvastatin.

Data Availability Statement

All data relevant to the study are included in the article.

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