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Research article

# LDL-cholesterol lowering effect of a generic product of simvastatin compared to simvastatin (Zocor™) in Thai hypercholesterolemic subjects – a randomized crossover study, the first report from Thailand

Viroj Wiwanitkit MD*[1], Danai Wangsaturaka MD[2] and Oranee Tangphao MD[3]

Address: [1]Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand, [2]Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand and [3]Department of Medicine, Stanford University, School of Medicine, Palo Alto, California, USA

E-mail: Viroj Wiwanitkit* - wviroj@pioneer.netserv.chula.ac.th; Danai Wangsaturaka - wdanai@pioneer.netserv.chula.ac.th; Oranee Tangphao - oraneetd@hotmail.com

*Corresponding author

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## Abstract

**Background:** It is commonly agreed that people with a high blood LDL-cholesterol will have a higher risk of coronary artery disease (CAD) than people with low blood LDL-cholesterol. Due to the increasingly high costs of medication in Thailand, the government has set up several measures to combat the problem. One of such strategies is to promote the utilization of locally manufactured drug products, especially those contained in the National Drug List. Simvastatin, an HMG-CoA reductase inhibitor, is listed as an essential drug for the treatment of hypercholesterolemia. Here, we reported the study on the LDL-cholesterol-lowering effect of a generic simvastatin product in comparison with the Zocor©, in 43 healthy thai volunteers.

**Method:** The generic product tested was Eucor©, locally manufactured by Greater Pharma Ltd., Part, Thailand, and the reference product was Zocor© (Merck Sharp & Dohme, USA). The two products were administered as 10-mg single oral doses in a two-period crossover design. After drug administration, serial blood samples were collected every 4 weeks for 16 weeks. The major parameter monitored in this study was blood LDL-cholesterol.

**Result:** After taking the drugs for the first 8 weeks, no statistically significant difference was dedected in blood LDL-cholesterol between the first (Zocor©-treated) and the second (Eucor©-treated) groups. After crossover and taking drugs for further 8 weeks, a similar result was obtained, i.e., no significant difference in blood LDL-cholesterol between the first (Eucor©-treated) and the second (Zocor©-treated) groups was observed. Upon completion of the 16-week study, there was also no statisticaly significant difference in the changes of all tested blood parameters between the two products (randomized block ANOVA, N = 37). Only minor side effects, mainly dizziness and nausea, were observed in both products.

**Conclusion:** Our study demonstrated no significant differences in the therapeutic effect and safety between the generic and original simvastatin products.

## Introduction

It is commonly agreed that one with high blood LDL-cholesterol level will have higher risk of coronary artery disease (CAD) than one with low blood LDL-cholesterol level [1]. Decrease in the blood LDL-cholesterol can slow

down and reduce the incidence of CAD, and thus the mortality rate associated with the disease [2].

HMG-CoA reductase inhibitors are widely used in the treatment of hypercholesterolemia due to its high efficacy in reducing blood LDL-cholesterol [3,4]. One of them, simvastatin, has been included in Thailand's National Drug List since 1999. Presently, the majority of simvastatin products available in Thailand are imported from abroad either as the original product or imported generics. Only a few are locally manufactured in the country.

To help alleviate the rising cost of imported drugs, one strategy of the National Drug Policy is to promote the usage of locally made generic products [5]. Simvastatin is an essential drug of which the local production and utilization are strongly encouraged, provided that it can give equivalent safety and efficacy to the original product. Here, we report the outcome of the first randomized crossover study to be conducted in Thailand on the LDL-cholesterol lowering effect of a locally manufactured generic simvastatin product in comparison with the innovator's product Zocor©.

## Materials and methods

### *Protocol approval and setting of the study*

The study protocol was first sent to the Ethical Committee of the Faculty of Medicine, Chulalongkorn University, as well as to the Food and Drug Administration of Thailand for review. After protocol approval, the study was performed at King Chulalongkorn Memorial Hospital in Bangkok, which is the largest Thai Red Cross Society Hospital. All laboratory analyses were performed using automated clinical analyzers at the Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University. This laboratory is the first Thai laboratory accredited by ISO 9002: 1994 for the whole process [6].

### *Preparation of simvastatin*

Simvastatin tablets used in this study were from two sources. The first group was original product (Zocor©), 10 mg per tablet (lot no. W4010, Merck Sharp & Dohme, USA) whereas the second group was a locally manufactured generic product (Eucor©), 10 mg per tablet (lot no. RS 10202, Greater Pharma Ltd., Part, Thailand). Zocor© was directly purchased by the authors from the distributor. Eucor© was supplied by the local manufacturer.

All the simvastatin tablets from the original and locally-made sources were individually inserted by the third person into the similarly shaped capsules. The two products were respectively called drug A and drug B. Study design was double-blinded such that both the physicians in charge and the subjects did not know the true identity of the content inside the capsules.

Thirty capsules were put into a sachet and distributed to the individual subjects at each visit. They were instructed to take one capsule daily after an evening meal. The interval between each visit was 4 weeks. All subjects received physical examination and blood tests at each visit. They were also advised to practice diet control and regular exercise during the entire period of study.

### *Study design and protocol*

#### *Primary assumptions*

1. The population under study is representative of Thai population with hypercholesterolemia (blood LDL-cholesterol ≥ 160 mg/dL)

2. All drug capsules in this study had the same pharmaceutical properties, i.e., equal amount of active ingredient, similar *in vitro* release and dissolution profiles

#### *Screening visit*

After giving a written informed consent, each volunteer received physical examination and laboratory screening test (complete blood count, fasting blood sugar, glucose, BUN, creatinine, electrolyte, liver function test, CPK, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride).

The initial inclusion criteria of the subjects were 1) age between 30 and 70 years old, 2) fasting plasma LDL-cholesterol ≥ 160 mg/dL, 3) no previous history of using any antilipemic drugs, 4) no pregnancy (urine pregnancy test must be negative) and 5) voluntary participation by signing a consent form. The initial exclusion criteria were 1) history of allergy to HMG-CoA reductase inhibitors, 2) pregnancy or lactation, 3) perimenopause or menopause, 4) having personal illnesses such as diabetes mellitus, liver diseases, renal diseases, thyroid diseases, ischemic heart disease or epilepsy, 5) past and present use of cyclosporin, digoxin, erythromycin, gemfibrozil, niacin, vitamin $B_3$, warfarin, immunosuppressive agents or any other drugs with reported interaction with simvastatin, 6) heavy drinking habit of tea or coffee (≥ 1,000 ml/day), 7) heavy smoking (≥ 20 cigarettes/day), 8) serum aminotransferase more than three times normal, and 9) serum CPK more than three times normal.

During the first 4 weeks before taking the drugs (run-in period), all subjects were advised to practice diet control and regular exercise according to the Guideline for the Clinical Evaluation of Lipid Altering Agents in Adult and Children, September 1990 (USFDA), under the supervision of the Division of Nutrition and Endocrinology, King Chulalongkorn Memorial Hospital. They were also cautioned against any practice that may lead to the conditions of exclusion criteria.

**Table 1: Characteristics of the subjects in both groups at initial visit (before taking drugs)**

| Parameters | mean ± standard deviation (90 % confidence interval) | | P-value |
|---|---|---|---|
| | 1st group (N = 22) | 2nd group (N = 21) | |
| Age (years) | 48.90 ± 10.83 (45.01–52.79) | 48.45 ± 9.36 (45.17–51.73) | NS |
| Total cholesterol (mg/dL) | 259.30 ± 31.83 (247.87–270.73) | 254.40 ± 33.47 (242.66–266.14) | NS |
| HDL (mg/dL) | 45.50 ± 12.27 (41.10–49.90) | 44.80 ± 10.04 (41.28–43.32) | NS |
| Triglyceride (mg/dL) | 160.00 ± 90.71 (127.44–192.56) | 168.40 ± 89.23 (137.11–199.69) | NS |
| LDL (mg/dL) | 181.90 ± 25.33 (172.81–190.99) | 175.90 ± 30.71 (165.13–186.67) | NS |
| Sgot (U/L) | 26.40 ± 10.33 (22.69–30.11) | 24.50 ± 8.38 (21.56–27.44) | NS |
| Sgpt (U/L) | 30.00 ± 15.26 (24.52–35.48) | 31.30 ± 20.95 (23.95–38.65) | NS |
| CPK (U/L) | 123.80 ± 68.94 (99.05–148.55) | 125.70 ± 73.54 (99.91–151.49) | NS |

*Study visit*

After a 4-week run-in period, 43 subjects who had passed the screening laboratory tests and met all other inclusion criteria were included in the study. They were randomly allocated into 2 groups for participation in a randomized crossover study without washout period [7,8]. The first group received drug A for 8 weeks, then switched to drug B for another 8 weeks. Vice versa, the second group took drug B for the first 8 weeks followed by drug A for another 8 weeks.

During the 16 weeks of drug intake, the individual subjects were followed up at a 4-week interval, thereby making a total of 4 study visits. At each visit, they were interviewed and physically examined for any possible side effects. They were also tested for plasma lipid profiles (triglyceride, total cholesterol, HDL- and LDL-cholesterol) and other blood chemistry parameters such as serum aminotransferase and CPK. They were dropped out from the study if the latter two parameters exceeded three times the normal values. Additional exclusion of subjects was set in cases of 1) development of serious side effects, and 2) poor subject compliance (taking 20% less capsules than normal or refusal to continue drug intake). The primary outcome to be focused in this study was blood LDL-cholesterol.

***Statistical analysis***

The study was designed with the sufficient number of subjects to ensure that it had the power to detect 10% difference in the effect, if such difference existed. Appropriate statistical analyses were employed in this study [7–9]. In brief, we selected ANCOVA analysis, using the initial measure of LDL-cholesterol and other biochemical parameters previously mentioned as covariates, and afterwards, testing the period, sequence, treatment and subject effects as in the classical model of MANOVA crossover design. Unpaired t-test comparisons were also done in the middle of the study. All statistical analyses were performed at 5% significance level.

## Results

After run-in period, 43 subjects passed the inclusion criteria to participate in the core study. 22 subjects were randomly allocated into the first group and 21 in the second group. There were no significant differences in the age and all the blood chemistry parameters between the two groups in this pre-medication period (Unpaired t-test, $P > 0.05$) (Table 1). ANCOVA also revealed that there was no significant effect of other covariates on LDL-cholesterol.

After taking drugs for the first 8-week period, 2 subjects in the second group were excluded from the study due to minor drug side effect (dizziness and nausea). Data in Table 2 show that all the blood chemistry parameters, including

**Table 2: Characteristics of the subjects in both groups after taking drugs for 8 weeks**

| Parameters | mean ± standard deviation (90 % confidence interval) | | P-value |
|---|---|---|---|
| | 1st group (N = 22) | 2nd group (N = 19) | |
| Total cholesterol (mg/dL) | 191.80 ± 37.41 (178.37–205.23) | 198.90 ± 31.48 (187.02–210.78) | NS |
| HDL (mg/dL) | 45.50 ± 8.38 (42.49–48.51) | 50.80 ± 10.49 (46.84–54.76) | NS |
| Triglyceride (mg/dL) | 140.90 ± 69.49 (115.96–165.84) | 129.20 ± 78.59 (99.54–158.86) | NS |
| LDL (mg/dL) | 118.20 ± 30.92 (107.10–129.30) | 122.30 ± 22.43 (113.84–130.76) | NS |
| SGOT (U/L) | 28.60 ± 12.71 (24.04–33.16) | 28.50 ± 15.35 (22.71–34.29) | NS |
| SGPT (U/L) | 35.80 ± 27.02 (26.10–45.50) | 34.80 ± 26.71 (24.72–44.88) | NS |
| CPK (U/L) | 125.80 ± 55.61 (105.84–145.76) | 119.60 ± 57.17 (98.02–141.76) | NS |

the LDL-cholesterol, were similar between the two groups at the end of the first 8 weeks (Unpaired t-test, $P > 0.05$).

At the end of the first period, all the subjects in the first group switched brands from A to B and the second group from B to A. The medication was then continued for further 8 weeks. At the end of this period (16th week), one subject in the first group and 3 subjects in the second group dropped out due to failure to comply with the administration protocol (not due to drug-related side effects), thus leaving a total of 37 subjects to complete the study. All subjects were found to have good drug tolerance regardless of the brand taken. Similarly, data in Table 3 also reveal that there were no significant differences in the lipid and other blood chemistry parameters between the two groups (Unpaired t-test, $P > 0.05$).

Randomized block ANOVA also showed no significant differences in the LDL-cholesterol level and other blood chemistry parameters between product A and product B over the entire 16 weeks ($N = 37$, $P > 0.05$). The 90% confidence interval for the difference in the LDL-cholesterol between A and B was 0–12.96 mg/dL.

## Discussion

To cope with the problems of increasing demand for medicines and to help reduce the costs of imported finished pharmaceutical products, a number of developing countries including Thailand have set up several strategies, one of which is to promote the local manufacture and usage of quality generic drugs. For any generic products to be approved by the regulatory authority, scientific evidence about the product safety and efficacy must be demonstrated [10]. In this article, we reported the outcome of the first randomized crossover study in Thailand, which compared the clinical efficacy of a locally manufactured generic 10 mg simvastatin tablets with that of original, imported product (10 mg Zocor© tablets) in 43 healthy Thai volunteers with hypercholesterolemia.

In general, study to establish bioequivalence between the original and the generic products involves measurements of the drug level or active metabolite(s) in the blood, which is based on a pharmacokinetic approach. However, measurements of plasma simvastatin concentration proved to be more difficult because the drug is in an inactive lactone form which is preferentially taken up by the liver, the target site of action. Simvastatin has a high liver uptake after gastrointestinal absorption, with hepatic extraction ratio greater than 90%. Less than 5% of the simvastatin dose was reported to reach the systemic circulation in healthy human volunteers [11]. Thus, most of the drug will accumulate in the liver, where it is metabolized to several active compounds, the major one of which is simvastatin acid. The active metabolites will act by inhibiting hepatic enzyme HMG-CoA reductase, thereby interfering with the synthesis of endogenous cholesterol in the liver. Apparently, accurate determination of extremely low concentrations of simvastatin metabolite(s) in the blood could be very difficult to achieve. And even if it is possible, it may not represent the actual amount of drug accumulating in the target organ and thus, it may not provide good correlation to the drug therapeutic result.

**Table 3: Characteristics of the subjects in both groups after crossover and continuation of drug for further 8 weeks**

| Parameters | mean ± standard deviation (90 % confidence interval) | | P-value |
|---|---|---|---|
| | 1st group (N = 21) | 2nd group (N = 16) | |
| Total cholesterol (mg/dL) | 200.30 ± 36.86 (187.07–213.53) | 182.40 ± 17.24 (175.31–189.49) | NS |
| HDL (mg/dL) | 47.40 ± 9.64 (43.94–50.86) | 49.40 ± 10.38 (45.13–53.67) | NS |
| Triglyceride (mg/dL) | 142.40 ± 62.54 (119.95–164.85) | 127.40 ± 58.40 (103.38–151.42) | NS |
| LDL (mg/dL) | 124.40 ± 31.70 (113.02–135.78) | 107.50 ± 14.65 (101.48–113.52) | NS |
| SGOT (U/L) | 25.10 ± 7.96 (22.24–27.96) | 23.90 ± 9.50 (19.99–27.81) | NS |
| SGPT (U/L) | 37.60 ± 22.32 (29.59–45.61) | 30.60 ± 21.79 (21.64–39.56) | NS |
| CPK (U/L) | 106.20 ± 42.49 (90.95–121.45) | 118.40 ± 42.35 (100.98–135.82) | NS |

In this case, indirect study by measurements of its pharmacodynamic or therapeutic effect can provide a good resolution [12]. A study design based on a clinical approach was utilized here to compare the safety and efficacy of a generic simvastatin with that of the original product. Similar to the general bioequivalence study based on plasma drug concentration measurements, studies employing a clinical/pharmacodynamic approach can provide useful information on the quality of the locally made products so as to assure both the physicians and the patients that the products can produce equivalent therapeutic outcome.

However, there are a number of variables to be concerned in this type of study. Differences in the individual subjects' physiology, age, sex, lifestyle, diet and exercise control, as well as compliance, can lead to great variation in the therapeutic response. Control of these factors is very important. Thus, strict inclusion and exclusion criteria have been observed throughout this study. Closed monitoring of the patient compliance was also carried out by direct interview of the individual subjects as well as by checking the amount of the capsules remaining after each visit. To further control the variation, the number of subjects was carefully calculated to account for the increased variability associated with the dynamic nature of the study [13–15]. A conventional bioequivalence study using a crossover design with plasma drug concentration measurement will usually requires 12–24 subjects. In our study, however, the number of subjects was calculated to have sufficient power to detect at least 10% difference in the primary outcome (blood LDL-cholesterol level). By using the above condition and the standard deviation from the previous clinical trial [16], the value of 17 subjects was obtained. The total number of subjects in this study was 43, which was acceptable for statistical analysis (even in the case of several dropouts) based on the hypothesis that both drugs provided no difference in the primary therapeutic outcome [16,17].

According to the result of this study conducted in Thai hypercholesterolemic subjects without other related diseases (DM, CAD, etc.), there was no statistical significant difference between the two products with regards to changes in blood LDL-cholesterol either at 8 weeks or 16 weeks ($P > 0.05$). The result indicated that the two products were equivalent in terms of efficacy. Also, other blood chemistry parameters were found to be similar such as the triglyceride level and hepatic enzyme activities.

Apart from direct evaluation of the therapeutic result, another advantage of the clinical study over the conventional bioequivalence test is the ability to compare the drug unwanted side effects. The side effects reported here (dizziness and nausea) may or may not relate to the drug. Some reported drug side effects in clinical trials may also originate from the placebo known as the placebo effects. However, it is also possible that the side effects may be due to the presence of impurities or the inclusion of inappropriate " inert" excipients in the drug formula. In this study, the incidence of the side effect was mild. Only two subjects in the second group reported symptoms of dizziness and/or nausea and voluntarily withdrew from the study. A few other subjects in both groups reported the

same symptoms but remained in the study until completion. In general, the subjects appeared to have good tolerance for both products and the frequency of side effect was similar. The rest of the dropouts were due to non-compliance (failure to adhere to the administration routine).

## Conclusion

The result from this comparative study showed that the 10-mg generic simvastatin tablet produced in Thailand (Lot no. RS 10202, Greater Pharma) showed no statistical significant difference in the change in blood LDL-cholesterol, either at 8 weeks or 16 weeks (after crossover), from the original 10-mg Zocor© tablet (Lot no. W4010; Merck, Sharp and Dohme). No difference in the side effects was also detected between the two products based on symptom observation and hepatic enzyme activity measurements. Both products were well tolerated by the subjects without any serious side effects.

## Competing interests

This study was supported by Greater Pharma Limited, Partnership, Bangkok, Thailand, for the laboratory costs and study materials including simvastatin capsules.

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