Dose-Expanded Study in the Reinforcement of Efficacy of Simvastatin†

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Abstract

Two hundred and twenty two hyperlipidemic patients were recruited for a 12-week prospective, multicenter, open-label, titrate-to-goal study to evaluate the efficacy and safety of 20 to 40 mg per day of simvastatin in a Thai population. The efficacy on lipid lowering was evaluated at 4 weeks and 8 weeks after medication. Based on NCEP ATP II guideline and ADA position statement, subjects were categorized into three groups according to LDL-C goals; group I: patients without CHD and with <2 CHD risk factors, group II: patients without CHD and with ≥2 CHD risk factors and group III: CHD patients or diabetic patients with ≥1 risk factors. Significant changes of all lipid parameters from baselines were noted at 4 weeks after medication except for HDL-C levels. Reduction of serum LDL-C, TC and TG by 40 per cent, 29 per cent and 16 per cent respectively and increase of serum HDL-C by 5 per cent were observed at 8 weeks of therapy ($p<0.05$). At 4 weeks after taking simvastatin 20 mg/day, 78.9 per cent of patients in group I, 67.4 per cent in group II and 40.9 per cent in group III achieved LDL-C goals. Seventeen per cent of the patients who were evaluated at 8 weeks increased the simvastatin dosage to 40 mg per day in the second month of treatment. At 8 weeks of therapy with simvastatin 20-40 mg/day, 90.1 per cent of patients in group I, 77.4 per cent in group II and 66.7 per cent in group III achieved LDL-C goals. Adverse symptoms during therapy, mostly mild, developed in 6.3 per cent of the 222 patients.

Conclusion : Simvastatin 20-40 mg/day was effective and well tolerated in managing lipid parameters in Thai patients similar to other ethnic populations.

Key word : Simvastatin, HMG CoA Reductase Inhibitor, Lipid Lowering, Cholesterol, LDL-C, HDL-C, Triglyceride

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† Simvastatin = Zocor®, MSD

Simvastatin is a potent inhibitor of HMG-CoA reductase, the enzyme catalyzing the conversion of hydroxymethylglutarate to mevalonate, an early and rate-limiting step in the synthesis of cholesterol. In clinical studies, simvastatin was highly effective in reducing serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglycerides (TG) and very-low-density lipoprotein cholesterol (VLDL-C) concentrations and produced modest increases in high density lipoprotein (HDL-C)[1,2]. At dosage of 5-80 mg/day, simvastatin reduced LDL-C by 26-53 per cent and triglycerides by 14-36 per cent[3,4]. In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with simvastatin for a median of 5.4 years on mortality and morbidity was assessed in 4444 patients with coronary heart disease (CHD) and initial serum TC of 212-309 mg/dL (5.5-8.0 mmol/L). In this landmark study, simvastatin reduced the risk of death by 30 per cent ($p=0.003$), of coronary death by 42 per cent, of a major coronary event by 34 per cent ($p<0.00001$) and of hospital-verified non-fatal acute myocardial infarction by 37 per cent ($p<0.00001$). Furthermore, simvastatin reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37 per cent[5].

Most published studies on Western populations have used simvastatin 20 to 40 mg per day to treat hypercholesterolemia. Data for Thai patients particularly on a high dosage up to 40 mg per day are still lacking. Most patients in Thailand are usually given a daily dose of 5 to 10 mg in addition to nutritional therapy to control hypercholesterolemia. The concept of increasing the dosage to further enhance the drug efficacy and achieve a target goal is not well emphasized. Patients treated with simvastatin may gain benefits from lowering serum LDL-C levels down to the National Cholesterol Education Program (NCEP) recommended target[6,7].

This study aimed to evaluate the efficacy of simvastatin 20-40 mg/day on serum concentration of LDL-C, triglyceride, and HDL-C in Thai patients with hypercholesterolemia and also to study the drug safety and tolerability in this population over the period of 8 weeks.

PATIENTS AND METHOD

Patients population

The study population consisted of male and female patients aged 21 to 75 years old with elevated serum LDL-C levels according to NCEP-ATP II (at the time of recruitment and study, NCEP ATP-III has not been released) and ADA position statement [7,8]. The patients were categorized into 3 groups as follows. Group I: LDL-C ≥160 mg/dL (4.14 mmol/L) in patients without CHD and with <2 CHD risk factors (Table 1), Group II: LDL-C ≥130 mg/dL (3.4 mmol/L) in patients without CHD and with ≥2 CHD risk factors, Group III: LDL-C >100 mg/dL (2.6 mmol/L) in patients with CHD or in diabetic patients with ≥1 risk factor. Serum triglyceride levels were <400 mg/dl (4.5 mmol/L) in all groups.

CHD and diabetes mellitus were diagnosed in 10 per cent and 36 per cent of the patients. Other coronary risk factors including old age (according to the criteria), hypertension, smoking, familial history of premature CHD, low serum HDL-C and cerebrovascular diseases were found in 73 per cent, 53 per cent, 15 per cent, 9 per cent, 8 per cent and 2 per cent, respectively. A body mass index (BMI) of >25 kg/m^2 was recorded in 39 per cent of the subjects.

The following patients were excluded from the study: secondary hypercholesterolemia, homozygous familial types I, III, IV, or V hyperlipidemias, type 1 diabetes mellitus, type 2 diabetes with HbA1c >10 per cent, BMI >35 kg/m^2, alcohol consumption >10 drinks per week, serum creatinine >1.8 mg/dL, active liver disease or elevated liver transaminases >20 per cent above the upper limit of the normal range, acute coronary syndrome or percutaneous transluminal coronary angioplasty or coronary bypass surgery within the previous 3 months. Lipid lowering agents e.g. HMG CoA reductase inhibitors, bile acid sequestrants, fish oil and nicotinic acid must not be taken

Table 1. Risk factors.

CHD risk factors
Age (male ≥ 45; female ≥ 55 years)
Family history of premature CHD
Smoking
Hypertension
Low HDL-C, < 35 mg/dL (0.9 mmol/L)
Diabetes
Risk factors for diabetic patients
Family history of CVD
Smoking
Hypertension
Low HDL-C, < 35 mg/dL (0.9 mmol/L)
Microalbuminuria
Proteinuria

for at least 6 wks and fibrates for at least 8 wks. Immunosuppressive agents, corticosteroids, antifungal agents, anticoagulants and macrolide antibiotics were not permitted. Any other conditions or therapies which might pose a risk to the patients or confound the results of the study were excluded from the study.

All patients gave their verbal or written informed consent to participate in the study. The research was conducted in accordance with standards of good clinical practice and local regulations for the study of biomedical research in human subjects.

Method

This was a multicenter, open-label, titrate-to-goal study. Two hundred and twenty two patients were recruited from 31 collaborating centers located in the central, north, northeast and south of Thailand (see appendix). Patients who were receiving lipid-lowering agents were told to stop their medications as mentioned previously. A complete medical history, physical examinations including vital signs and BMI, and blood samples for serum lipids, creatinine, SGOT, SGPT and CPK concentrations were obtained at study entry. Eligible patients for the study were advised to follow the diet according to the American Heart Association step I or similar diet for 4 weeks.

Those who did not respond to dietary control were assigned to an 8-week active treatment period with simvastatin (Zocor®, MSD) The initial dose for every patient was a tablet of 20 mg simvastatin taken after evening meals or before going to bed. The dose of simvastatin was titrated up to 40 mg per day after 4 weeks of treatment in patients who did not reach the goal of NCEP and ADA guidelines. Each patient was given dietary advice at each visit by the investigator or his staff.

The percentage of patients achieving LDL-C goals specified in each group and changes in serum lipid levels compared to baselines were evaluated at 4-week and 8-week of drug therapy. Spontaneous reports of any adverse experiences or side effects were recorded in the case report forms. Safety evaluation was based on both the clinical and laboratory adverse experiences during and after drug therapy.

Blood chemistry and lipid analyses were performed by standard methods in each center. Compliance to drug treatment was ascertained by tablets counting at each visit. Data are expressed as mean$\pm$ SD. Statistical analysis was by Student's test. Differences were considered statistically significant at $p \leq 0.05$.

RESULTS

Efficacy

A total of 222 patients (M/F=1/1.63) were recruited and given simvastatin. Their age and BMI (mean$\pm$SD) were 56.9$\pm$10.9 years and 25.2$\pm$3.6 kg/m^2 respectively. The baselines (mean$\pm$SD) of serum TC, LDL-C, TG and HDL-C are shown in Table 2.

While 222 patients could be assessed for drug safety, only 145 and 93 patients had complete data for efficacy evaluation at the end of 4th and 8th week respectively. Significant changes of all lipid parameters from baselines were found after a 4-week therapy with simvastin 20 mg/day except for serum HDL-C concentration. Serum TC, LDL-C and TG levels significantly decreased by 28.4 per cent, 37.4 per cent and 15.6 per cent respectively ($p<0.05$) while serum HDL-C levels increased by 2.2 per cent (n.s). At 8 weeks of therapy, all lipid parameters including serum HDL-C levels were significantly different from baselines ($p<0.05$) as shown in Table 3. TC level decreased by 29.4 per cent, LDL-C levels decreased by 39.5 per cent, TG levels decreased by 16.4 per cent and HDL-C levels increased by 5.1 per cent.

Table 2. Baseline serum lipid levels.

Lipid parameter	Total		Male		Female	
	mg/dL	SD	mg/dL	SD	mg/dL	SD
TC	285.0	46.0	283.1	45.0	286.5	47.0
LDL-C	200.1	39.4	198.3	36.6	201.3	41.2
TG	162.1	67.1	157.3	64.4	165.3	68.9
HDL-C	51.6	13.2	51.0	11.8	51.9	14.0

Table 3. Percentage of changes in serum lipid levels at 4 and 8 weeks after treatment with simvastatin.

Lipid parameter	Total %	Male %	Female %
At 4th week			
Total Cholesterol	-28.4	-27.6	-28.7
LDL-C	-37.4	-36.6	-37.8
Triglyceride	-15.6	-15.0	-16.0
HDL-C	+2.2	+6.5	+0.6
At 8th week			
Total Cholesterol	-29.4	-30.2	-29.0
LDL-C	-39.5	-40.5	-39.0
Triglyceride	-16.4	-10.7	-19.5
HDL-C	+5.1	+4.1	+5.9

Table 4. Percentage of achievement to goals.

Time/Simvastatin dosage	Group I	Group II	Group III
At 4th week (N=145)			
20 mg/day	78.9% (41/52)	67.4% (33/49)	40.9% (18/44)
At 8th week (N=93)			
20 mg/day	89.5% (34/38)	91.7% (22/24)	66.7% (10/15)
40 mg/day	100% (6/6)	28.6% (2/7)	66.7% (2/3)
20-40 mg/day	90.1% (40/44)	77.4% (24/31)	66.7% (12/18)

The mean absolute reduction of serum TC, LDL-C and TG at 8 weeks after simvastatin therapy were 84.5, 79.7 and 26.8 mg/dL, respectively; and the mean increase of serum HDL-C was 2.7 mg/dL Fig. 1-4 show the absolute changes of lipid levels in each gender.

Over the 4-week therapy period with simvastatin 20 mg per day, 78.9 per cent in group I, 67.4 per cent in group II, and 40.9 per cent in group III achieved target level of LDL-C specified in each group (Table 4). Further achievement was observed at the end of 8 weeks therapy with simvastatin 20-40 mg per day; 90.1 per cent in group I, 77.4 per cent in group II, and 66.7 per cent in group III.

Seventeen per cent of the patients had their drug dosage raised to 40 mg per day in the second month of treatment. However, the majority of patients (86.8%) were treated to goal after 8 weeks of therapy with simvastatin 20 mg per day.

Safety and adverse drug experiences

Fourteen of the 222 patients (6.3%) developed clinical adverse experiences (A/E) after drug treatment. Most were mild and common symptoms included abdominal discomfort (1.4%), nausea (0.9%), and dizziness (0.9%). Two cases had symptoms defined as serious A/E and discontinued from the study. One was hospitalized because of palpitation and dizziness after taking simvastatin 20 mg in the evening. An anti-hypertensive drug was also taken and symptoms improved without specific treatment. Another patient developed calf pain without serum CPK elevation, but serum SGPT rose to 217 IU/L. Nine patients (5.1% of subjects with laboratory data) reported significant laboratory A/E with increased serum enzymes to more than 2 times upper normal limits, 3 cases with elevated serum CPK, 6 cases with elevated serum SGPT and 1 case with elevated serum SGOT. All cases were defined as non-serious A/E and continued the medication until the study was completed.

DISCUSSION

This study demonstrated that simvastatin, at doses of 20-40 mg/day, enabled the majority of Thai patients with hyperlipidemia to achieve the goal of LDL-C levels suggested by NCEP and ADA position statement guidelines. Most patients, 90.1 per cent in group I, 77.4 per cent in group II and 66.7 per cent in group III achieved target serum LDL-C levels of <160 mg/dL, <130 mg/dL and ≤100 mg/dL, respectively.

Significant changes from baseline in all lipid parameters were seen at 8 weeks after therapy. Serum LDL-C, TC and TG reduction of 40 per cent, 29 per cent and 16 per cent, respectively; and increased serum HDL-C of 5 per cent were observed after 20 to 40 mg per day of simvastatin. The result was quite similar to the 4S study using a similar dosage of drug in a larger European population. In the 4S, mean changes from baseline of serum LDL-C, TC, TG and HDL-C were -35 per cent, -25 per cent, -10 per cent and +8 per cent. The minor different result could be related to the lower mean baseline serum lipid levels in the 4S, serum LDL-C, TC, TG and HDL-C levels of 259, 187, 130 and 45

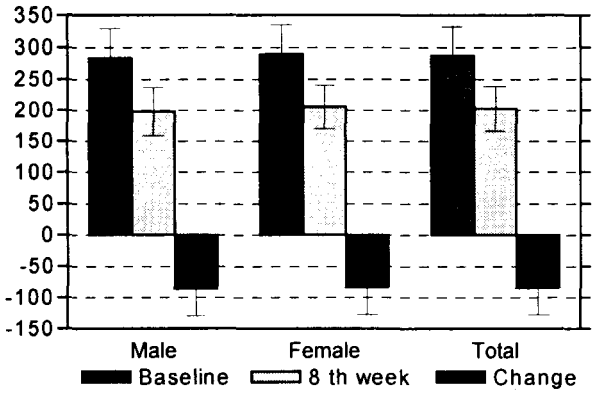

Fig. 1. Mean change of serum TC levels at the end of 8th week (mg/dL).

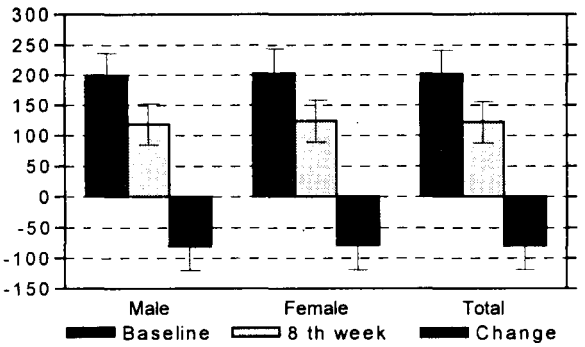

Fig. 2. Mean change of serum LDL-C levels at the end of the 8th week (mg/dL).

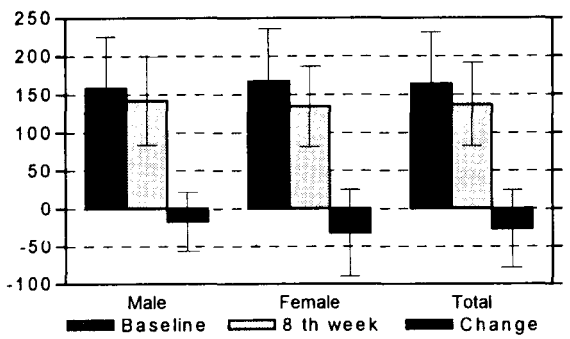

Fig. 3. Mean change of serumTG levels at the end of the 8th week (mg/dL)

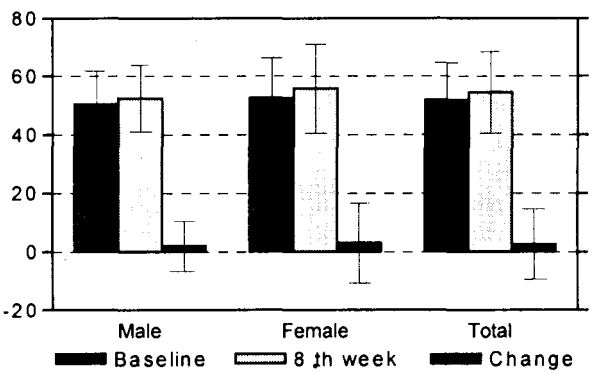

Fig. 4. Mean change of serum HDL-C levels at the end of the 8th week (mg/dL).

mg/dL, respectively. Another important aspect was the proportion of patients taking 40 mg of drug per day, it was 37 per cent in the 4S compared with 17 per cent in the present study. Since less than 30 per cent of the patients in the 4S achieved the goal of serum LDL-C levels of <100 mg/dL[9], much less than 66.7 per cent in the present study, it seemed that Thai patients with hypercholesterolemia were relatively more sensitive to simvastatin. In other Asian population with hypercholesterolemia e.g. the Japanese, lower doses of simvastatin (5-10 mg per day) were given with satisfactory results[10].

A previous report on simvastatin treatment in Thai patients involved only 59 patients and the maximal dosage used was 20 mg/day[11]. They reported quite a similar result on serum lipid levels except for serum TG which was reduced by 10 per cent.

Recent studies have focused on a higher dosage of simvastatin up to 80-160 mg/day to maximize the reduction of serum LDL-C[12,13]. The studies were limited to a short period of 4-6 weeks. In the multi-national Asian population study of 133 subjects with CHD[13], increasing the dose of drug

from 40 to 80 mg/day for 4 weeks was able to raise the cumulative percentage of patients to achieve the LDL-C goal from 90.1 per cent to 100 per cent.

More aggressive lipid-lowering therapy will bring a greater reduction of serum LDL-C. Both the final serum LDL-C levels and the percentage reduction of LDL-C were related to the coronary events and degree of atherosclerosis[9].

Since CHD is the most common cause of death in type 2 diabetic patients and elevated serum LDL-C concentration is the most important coronary risk factor[14], it was appropriated that this study included 36 per cent of patients with diabetes mellitus, a much larger proportion than other lipid lowering studies. Diabetic patients without a history of CHD had a mortality rate not less than nondiabetic patients with CHD[15], and the recent NCEP-ATP III report[7] had ranked diabetes mellitus as CHD risk equivalent, it is thus mandatory to aggressively treat dyslipidemia in diabetic patients.

In the present study, 6.3 per cent of the patients developed clinical A/E and only 0.9 per cent (2 cases) had to discontinue the medication due to severe A/E. This result is comparable to another Asian study using drug doses of 20-80 mg/day which gave the corresponding figures of 10.5 per cent and 2.3 per cent respectively[13]. In the 4S, 6 per cent of patients in both the treatment and placebo groups discontinued the study because of drug events.

The authors concluded that simvastatin dosage of 20 to 40 mg per day was effective, well tolerated and safe in Thai patients. It is justified to start simvastatin with a moderate dose of 20 mg per day in patients with CHD or CHD risk equivalent with significantly elevated serum LDL-C concentration in order to reduce the risk of coronary events. More aggressive reduction of serum LDL-C may be required with the dose up to 80 mg/day to achieve the LDL-C target goal according to the third National Cholesterol Education Program (NCEP) report. Restriction of cholesterol and saturated fat in the diet has to be continued during drug therapy. In addition, it's necessary to treat and correct other modifiable coronary risk factors.

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APPENDIX
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Rayong Hospital:	Songpon Wannasatit.
Prapokklao Hospital:	Vithayut Namsiripongpun.
Sunpracharuk Hospital:	Chatchavan Huntrakoon.

การศึกษาประสิทธิภาพของยาซิมวาสเตตินขนาดสูงในคนไทย

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คณะผู้วิจัยได้ทำการศึกษาเพื่อประเมินประสิทธิภาพและความปลอดภัยของยาซิมวาสเตติน (Zocor®, MSD) ในผู้ป่วยไทยที่มีระดับไขมันในเลือดสูงจำนวน 222 คน โดยแบ่งผู้ป่วยเป็น 3 กลุ่ม กลุ่มแรกเป็นผู้ป่วยที่ไม่มีโรคหัวใจและหลอดเลือดและมีปัจจัยเสี่ยงน้อยกว่าสองอย่าง กลุ่มที่ 2 เป็นผู้ป่วยที่ไม่มีโรคหัวใจและหลอดเลือดแต่มีปัจจัยเสี่ยงเท่ากับหรือมากกว่า 2 อย่าง และ กลุ่มที่ 3 เป็นผู้ป่วยที่มีโรคหัวใจและหลอดเลือด (CHD) หรือเป็นโรคเบาหวานและมีปัจจัยเสี่ยงมากกว่า 1 อย่าง ผู้ป่วยจำนวน 145 คน และ 93 คน ได้รับการประเมินประสิทธิภาพของยาที่สัปดาห์ที่ 4 และสัปดาห์ที่ 8 หลังจากที่ได้รับยา simvastatin ขนาด 20 มิลลิกรัม และ 20 ถึง 40 มิลลิกรัมต่อวัน ตามลำดับ พบว่าที่สัปดาห์ที่ 4 ระดับไขมันทุกตัวมีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติจาก baseline ยกเว้น HDL-C และที่สัปดาห์ที่ 8 ระดับ serum LDL-C ลดลง 40% ระดับโคเลสเตอรอลในเลือดลดลง 29% ระดับไตรกรีเซอร์ไรด์ ลดลง 16% และระดับ HDL-C เพิ่มขึ้นร้อยละ 5 ซึ่งเป็นการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติจาก baseline ทุกตัว พบว่าผู้ป่วยในกลุ่มที่ 1 จำนวนร้อยละ 78.9 กลุ่มที่ 2 จำนวนร้อยละ 67.4 และกลุ่มที่ 3 จำนวนร้อยละ 40.9 สามารถบรรลุระดับ LDL-C เป้าหมาย (NCEP goal) ได้หลังจากใช้ยาไป 4 สัปดาห์ ร้อยละ 17 ของผู้ป่วยที่มาประเมินผลหลังจากได้รับยาไปแล้ว 8 สัปดาห์เป็นคนไข้ที่ได้รับยา simvastatin ขนาด 40 มิลลิกรัมต่อวันในเดือนที่สองของการรักษา ผลของการรักษาด้วยยา simvastatin เป็นเวลา 8 สัปดาห์ในขนาด 20 ถึง 40 มิลลิกรัมต่อวัน พบว่า คนไข้ในกลุ่มที่ 1 จำนวนร้อยละ 90.1 กลุ่มที่ 2 จำนวนร้อยละ 77.4 และคนไข้กลุ่มที่ 3 จำนวนร้อยละ 66.7 สามารถบรรลุ ระดับ LDL-C เป้าหมาย (NCEP goal) ได้ การประเมินผลทางด้านความปลอดภัย พบว่า ร้อยละ 6.3 เกิดอาการข้างเคียงซึ่งเป็นอย่างไม่รุนแรง

สรุป : ผลการใช้ยา simvastatin (Zocor®, MSD) ขนาด 20 ถึง 40 มิลลิกรัมต่อวันในคนไทย มีประสิทธิภาพในการควบคุมระดับไขมันได้ดี และผู้ป่วยสามารถทนต่อยาได้ดี ไม่แตกต่างจากผลการรักษาในคนชนชาติอื่น

คำสำคัญ : ยาซิมวาสเตติน, ระดับไขมันในเลือดสูง, ระดับโคเลสเตอรอล, ระดับไตรกรีเซอร์ไรด์

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