

# A Randomised, Parallel, Double-Blind Study Comparing the Lipid Lowering Effect of Xuezhikang (Lipascor) with Simvastatin in Asymptomatic Patients with Hyperlipidaemia

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## ABSTRACT

**INTRODUCTION:** Traditional Chinese Medicines have been used to treat several medical conditions. We aimed to compare the lipid lowering effect of Xuezhikang (Lipascor), a formulation used for cardiovascular disorders, with simvastatin.

**METHODS:** This is a randomised double-blind parallel trial conducted among patients without pre-existing vascular disease or other important comorbidities and hypercholesterolaemia. Following dietary intervention for 8 weeks, those with total or low-density lipoprotein (LDL) cholesterol levels >6.15 or 5.13 mmol/L, respectively, were eligible. Patients were randomly allocated to treatment with Xuezhikang (Lipascor) 1200 mg (n=17) or simvastatin 10 mg (n=13) daily for a period of 12 weeks.

**RESULTS:** The total cholesterol level was reduced from 7.24 to 5.97 mmol/L (relative

reduction (RR), 17.5%; p=0.001) and 6.87 to 4.99 mmol/L (RR, 27.4%; p=0.002) among patients treated with Xuezhikang (Lipascor) and simvastatin, respectively. However, the difference in the change of cholesterol level between the 2 agents did not meet the *a priori* hypothesis of non-inferiority. The fall in the level of LDL-cholesterol, triglycerides and apolipoprotein B was statistically significant for both groups. Correspondingly, high-density lipoprotein cholesterol and apolipoprotein A also rose significantly. There was no significant adverse effect in both groups.

**CONCLUSIONS:** Xuezhikang (Lipascor) and simvastatin improved the lipid profile in our group of patients. However, due to small sample size, the data were not able to support the non-inferiority of Xuezhikang (Lipascor) compared with simvastatin at the doses studied.

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## INTRODUCTION

Several epidemiological studies have shown the strong association between high serum cholesterol level and cardiovascular disorder (1-4). More recently, a number of clinical trials have established the beneficial effects of lipid lowering even among high-risk patients without established disease (5-8). While these findings are widely known, implementation by physicians is frequently met with resistance by patients for numerous reasons. Notably, asymptomatic Asian

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individuals with moderate hyperlipidaemia who are at risk for cardiovascular disease may not be keen to be treated with pharmacological agents.

Traditional Chinese Medicine has been practised for many years. Generally, such formulations are derived from a variety of food and herbal derivatives. As these are perceived to be natural, otherwise healthy individuals are generally more receptive to the administration of such products. One formulation, Xuezhikang (Lipascor) Jiaonang, has been used to treat patients with cardiovascular disorders. It is extracted from *Monascus purpureus* (special made red yeast rice or Hongqu) and contains rich amounts of lovastatin, unsaturated fatty acids, essential amino acids and other trace elements (9-10). In Singapore, this product is not classified as drug but registered under Control of Chinese Proprietary Medicines under the Medicine Act (1998 amendment). Pre-clinical studies have shown the ability of this formulation in preventing elevation of lipid levels in rabbits fed with a high fat diet (10). Although this agent has been studied in patients in China (11), we proposed to compare the efficacy of lipid lowering of Xuezhikang (Lipascor) with simvastatin among asymptomatic patients with moderate hyperlipidaemia.

## **MATERIALS AND METHOD**

### **Study Design and Patient Population**

This is a randomised, parallel, double-blind study comparing the safety and efficacy of simvastatin (Zocor<sup>®</sup>, Merck, Sharpe and Dohme, White House Station, NJ) with RY1 (Lipascor<sup>®</sup>, Wearnes Biotech and Medicals, Singapore) in lowering cholesterol level among asymptomatic patients without established vascular disease and hyperlipidaemia. Study period was from 2001 to 2004. The 2 sites participating in the study have received approval from their respective institutional review boards. Written informed consent is obtained from all participants. The study was designed independent of the Sponsors.

To be eligible, fasting total cholesterol and low-density lipoprotein (LDL) cholesterol should be at least 6.15 mmol/L (240 mg/dL) and 5.13 mmol/L (200 mg/dL) patients, respectively, after 8 weeks of dietary intervention. Premenopausal women, or patients with established vascular diseases, elevated liver transaminases, renal dysfunction (serum creatinine  $\geq 176 \mu\text{mol/L}$ ), secondary causes of hyperlipidaemia

(such as hypothyroidism), uncontrolled hypertension (systolic blood pressure  $\geq 200$  mmHg or diastolic blood pressure  $\geq 105$  mmHg), diabetes mellitus, high body mass index ( $>40 \text{ kg/m}^2$ ), history of malignancy or conditions limiting lifespan to less than 1 year, regular consumer of alcohol ( $>14$  drinks per week), known sensitivity to statin and active gall bladder disease were excluded. Those who are unlikely to be compliant with medications or taking prohibited medicines are also not included.

Patients who have been previously treated with lipid lowering therapy may participate in the study after a washout period of at least 4 weeks. Investigators identified potential participants.

### ***Treatment Regimens***

After obtaining informed consent, all patients participated in an 8-week lifestyle modification phase. At the end of this period of dietary and lifestyle modification, if the cholesterol levels met the selection criteria, each patient is randomly allocated to either Lipascor 1200 mg or simvastatin 10 mg every night for a period of 12 weeks. Compliance with treatment is assessed by counting of capsules returned at each follow-up visit.

### ***Randomisation Procedures***

Patients and investigators were blinded to treatment assignment. Randomisation is conducted through the Clinical Trials, Epidemiology and Research Unit by means of telephone call or website. Patients were entered into the trial based on a 1:1 treatment allocation of Lipascor<sup>®</sup> and Zocor<sup>®</sup>, once eligibility had been confirmed and informed consent had been given. The treatment allocation was generated using a computer program.

### ***Study Medicines***

The study medicine, Lipascor<sup>®</sup> consists of 600 mg of Xuezhikang powder encapsulated in size O gelatin capsule with a dark green body and light green cap. Simvastatin 5 mg is mixed with excipient provided by Wearnes Biotech Laboratory – Beijing University Biotech Company to make up a weight of 600 mg, encapsulated to ensure identical appearance as Lipascor<sup>®</sup> capsule. The excipient used was of the same colour and texture as the Xuezhikang (Lipascor) powder. Both medicines are packed into opaque high-density

polyethylene bottles. Each patient should take 2 capsules every night after meal.

Labeling and sealing of medicines were performed by the manufacturer under the supervision of the staff from the Clinical Trials, Epidemiology and Research Unit. Each container was labeled with a tear-off duplicate that was to be attached to the Case Report Form when the medicine was dispensed.

### Outcomes

The primary endpoint of the study was the amount of reduction of LDL-cholesterol levels at 12 weeks compared with baseline between the 2 groups of patients. Secondary endpoints included change in the levels of total and high-density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein A-1, apolipoprotein B-100 and lipoprotein (a) at 12 weeks compared with baseline between the 2 groups. Safety parameters including myalgia and various biochemical markers of liver and muscle dysfunction were also monitored.

### Data Management and Statistical Analysis

The primary endpoint of this trial was to show that Lipascor<sup>®</sup> was non-inferior to Zocor<sup>®</sup> in the reduction of LDL cholesterol level over 12 weeks. The standard deviation for the difference in LDL cholesterol level reduction was anticipated to be approximately 0.8. With a power of 80% and a 1-sided test of 5%, a total of 100 subjects were anticipated to be recruited to accept a 0.4 mmol/L difference between Lipascor<sup>®</sup> and Zocor<sup>®</sup> as non-inferior (12).

Continuous variables are expressed as mean with standard deviation and categorical variables are expressed as proportion. The data were to be analysed based on intention-to-treat. The non-inferiority of Lipascor<sup>®</sup> was assessed on the 90% confidence interval (CI) of the difference between the treatments in the reduction of LDL-cholesterol level at 12 weeks compared with baseline. To investigate whether there were any differences between the LDL-cholesterol level at baseline and 12 weeks, Wilcoxon Signed Rank test was performed. As for other secondary endpoints (total cholesterol, HDL cholesterol, triglyceride, apolipoprotein A-I, apolipoprotein B and lipoprotein (a)), paired t-test was carried out to evaluate the differences between the levels at baseline and 12 weeks if normality assumption was met. Otherwise, Wilcoxon

Signed Rank test was performed. The relationships between each of the lipoprotein parameters and change in weight at 12 weeks compared with baseline were assessed using Pearson's correlation coefficient if normality assumption was met; otherwise, Spearman's rho was carried out. Multiple regression analyses on response variables were performed, adjusting for relevant co-variates.

### RESULTS

A total of 30 patients were enrolled for the study. There were difficulties in obtaining the required sample size because of the epidemic of Severe Respiratory Syndrome (SARS) and the issue of Slim-10<sup>®</sup> during the period of study. During the SARS period, access to Medical Centres was restricted and the case of Slim-10<sup>®</sup> causing liver dysfunction has generated much adverse publicity. Baseline characteristics were comparable between patients receiving simvastatin and Lipascor<sup>®</sup> (Table 1). The study population was made of predominantly middle-age Chinese men. There was one patient with a congenital ventricular septal defect, one patient has hypertrophic cardiomyopathy and one patient has mitral valve prolapse in the Lipascor<sup>®</sup> group. None of the patient suffered from hypertension.

**Table 1. Baseline characteristics**

Characteristics	Lipascor <sup>®</sup> (n=17)	Simvastatin (n=13)
Age, years	54.9 ± 10.2	55.2 ± 10.6
Male gender	11 (64.7)	7 (53.8)
Ethnic Chinese	14 (82.4)	13 (100)
Weight, kg	68.7 ± 15.2	63.3 ± 9.7
Body mass index, kg/m <sup>2</sup>	26.1 ± 3.9	23.3 ± 2.7
Systolic BP, mmHg	120.9 ± 14.8	124.6 ± 8.8
Diastolic BP, mmHg	74.4 ± 7.0	76.9 ± 4.8
Heart rate, beats/min	66.8 ± 7.4	67.7 ± 7.9
Current smoker	5 (29.4)	1 (7.7)

BP, blood pressure

Compared with baseline, 12 weeks of treatment with either Lipascor<sup>®</sup> or simvastatin lowered the levels of fasting triglycerides, total and LDL cholesterol were significantly (Fig. 1). Correspondingly, the level of apolipoprotein B was also reduced by both agents (Table 2). Importantly, the levels of HDL-cholesterol and apolipoprotein A were increased in both groups. The absolute amount of reduction of LDL-cholesterol

**Table 2 Other Lipoprotein and Biochemical Markers**

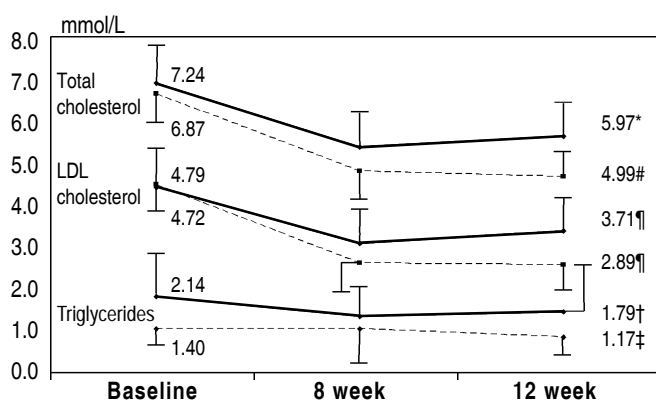
Markers	Lipascor®			Simvastatin		
	Baseline	8 weeks	12 weeks	Baseline	8 weeks	12 weeks
HDL-C mmol/L	1.52±0.38	1.54±0.36	1.63±0.39*	1.53±0.30	1.57±0.33	1.57±0.34#
Apo A, g/L	1.49±0.33	-	1.73±0.32¶	1.53±0.25	-	1.66±0.31†
Apo B, g/L	1.43±0.23	-	1.18±0.17‡	1.31±0.20	-	0.98±0.21§
Lp (a), mg/dL	23.6±22.8	-	22.0±18.4	27.6±23.0	-	32.0±36.8
ALT, U/L	22.2±10.2	17.6±5.3	22.2±10.2	20.3±8.4	22.2±11.3	24.1±10.6
AST, U/L	21.3±5.3	18.1±1.5	21.0±4.5	19.2±4.6	21.8±6.0	22.6±9.1
Bilirubin, µmol/L	13.9±4.4	15.8±4.9	13.5±4.2	14.7±6.7	14.6±4.5	15.8±6.5
Creatine kinase,U/L	160±77	109±28	152±116	122±51	123±38	204±248

HDL-C, high-density lipoprotein cholesterol; Apo A, apolipoprotein A; Apo B, apolipoprotein B; Lp (a), Lipoprotein (a); ALT, Alanine aminotransferase; AST, Aspartate aminotransferase

P-values are for the comparison at 12-week and baseline within each group \*p=0.036; #p=0.031; ¶p=0.022; †p=0.045; ‡p=0.001; §p=0.004

## LEGEND

Fig. 1



The effect of Lipascor® 1200 mg daily (continuous line) and simvastatin 10 mg daily (broken line) on fasting total cholesterol, low-density lipoprotein cholesterol and triglycerides.

P-values are comparing the values at 12-week and baseline

\*p=0.001; #p=0.002; ¶p=0.003; †p=0.0035; ‡p=0.009

at 12 weeks between Lipascor® and simvastatin was 0.71 mmol/L (90% CI, 0.22 to 1.27). However, the non-inferiority margin for this difference was <0.40 mmol/L. After adjusting for age, gender, body mass index, systolic blood pressure and baseline levels of triglycerides, apolipoprotein A-I, apolipoprotein B and lipoprotein (a), the difference was 0.26 mmol/L (90% CI, -0.44 to 0.96) The absolute amount of reduction of total cholesterol at 12 weeks between Lipascor® and simvastatin was 0.63 mmol/L (90% CI, 0.15 to 1.10). When each of the lipoprotein parameters was correlated with change in weight, the relationship was statistically

significant for triglycerides in the Lipascor® group. The Pearson's correlation was 0.71 (p=0.014) for absolute change and 0.75 (p=0.005) for relative change. In the simvastatin group, the correlation (r=0.83) was significant with HDL-cholesterol level (p=0.005).

There was no difference in the temporal trend of liver transaminases and creatine kinase in both groups of patients (Table 2). There was one patient in the simvastatin group who slipped and fell. She suffered from large haematomata on both thighs and the level of creatine kinase was raised to 975 U/L. The level normalised and the haematomata resolved spontaneously.

## DISCUSSION

Although we found that both Lipascor® and simvastatin reduced the levels of total and LDL cholesterol, triglycerides, apolipoprotein B after 12 weeks of treatment, the non-inferiority of Lipascor® could not be concluded. This finding is likely to be attributed to the small sample size. After adjusting for baseline characteristics, the amount difference in the efficacy of lipid lowering became smaller. Importantly, we also found that HDL-cholesterol and apolipoprotein A increased with treatment with either agent. Our findings corroborated with the results of a similar study conducted in China (11). It compared the effects of lipid lowering between Xuezhikang (Lipascor) and simvastatin in 28 patients. Importantly, those treated with the traditional formulation showed a 21% (p<0.001) and 28% (p<0.01) relative reduction in total

and LDL-cholesterol. This result was comparable to those receiving simvastatin. Xuezhikang (Lipascor) also lowered the level of triglycerides. Unlike the results of our study, the level of lipoprotein (a) was decreased by 31% and 28% with Xuezhikang (Lipascor) (Lipascor) and simvastatin, respectively.

An earlier study conducted in China randomly assigned 84 patients with hyperlipidaemia, including 56 of them with atherosclerosis, to Xuezhikang (Lipascor) 1200 mg twice daily and another 32 patients to 3 Jiaogulan tablets (Shanxi, Ankang) twice daily (13). At entry, total serum cholesterol was greater than 5.90 mmol/L (230 mg/dL), triglyceride level was more than 1.80 mmol/L (200 mg/dL) and HDL-cholesterol <1.03 mmol/L (40 mg/dL) for men and 1.15 mmol/L (45 mg/dL) for women. At 8 weeks, total cholesterol was reduced by 21%, triglycerides by 32% and HDL-cholesterol was increased by 27%. In contrast, there was little change in these lipid fractions in the control group. Notably, there was no significant side effect reported. There was also no significant change in serum transaminase, urea, creatinine, glucose, uric acid and blood counts. However, there were 3 patients (3.6%) with elevated creatine kinase level in the treated group. The level normalised following withdrawal of formulation.

In another clinical trial involving 446 patients with hyperlipidaemia, 324 of them received Xuezhikang (Lipascor) and another 122 were treated with Jiaogulan (14). The levels of triglycerides, total and LDL-cholesterol were lowered by 23%, 31% and 34%, respectively, among those treated with Xuezhikang (Lipascor). On the other hand, the reduction in the levels of triglycerides, total and LDL-cholesterol was relatively modest among patients treated with Jiaogulan (7%, 8% and 13%, respectively). The level of HDL-cholesterol was increased by 20% in the Xuezhikang (Lipascor) and 8% in the Jiaogulan groups.

There are several limitations in our study. Importantly, the small sample size because of the intrinsic difficulties in recruiting patients particularly during a challenging period prevented us from obtaining the required number of subjects. Nonetheless, our study showed that the traditional Chinese formulation, Lipascor®, improves lipid profile without significant adverse effects. However, its efficacy of lowering the levels of total and LDL-

cholesterol cannot be concluded as non-inferior to simvastatin at the doses studied.

## TRIAL ADMINISTRATION

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