



Effects of Xuezhikang in patients with dyslipidemia: A multicenter, randomized, placebo-controlled study

Patrick M. Moriarty, MD, Eli M. Roth, MD, Adam Karns, MD, Ping Ye, MD, PhD, Shui-Ping Zhao, MD, PhD, Yuhua Liao, MD, David M. Capuzzi, MD, Harold E. Bays, MD, Fumin Zhang, MD, Shaowen Liu, MD, Alan J. Reichman, MD, Osvaldo A. Brusco, MD, Guoping Lu, MD, Sam Lerman, MD, Zhenwen Duan, PhD, Shuren Guo, MD, Ping Lan Liu, MD, Junxian Zhao, MD, Yan Zhang, MD, Simon Li, MD, PhD*

Department of Medicine, University of Kansas, Kansas City, KS, USA (Dr Moriarty); Sterling Research Group, Ltd, Cincinnati, OH, USA (Dr Roth); Karns Medical Corporation, Los Angeles, CA, USA (Dr Karns); Chinese PLA General Hospital, Beijing, China (Dr Ye); The Second Xiangya Hospital of Central South University, Changsha, Hunan, China (Dr S.P. Zhao); Wuhan Union Hospital, Wuhan, Hubei, China (Dr Liao); Thomas Jefferson University, Haverford, PA, USA (Dr Capuzzi); L-MARC Research Center, Louisville, KY, USA (Dr Bays); Jiangsu Province Hospital, Nanjing, Jiangsu, China (Dr F. Zhang); Shanghai First People's Hospital, Shanghai, China (Dr S. Liu); Clinical Trial Network, Houston, TX, USA (Dr Reichman); Texas A&M School of Medicine, Corpus Christi, TX, USA (Dr Brusco); Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China (Dr Lu); Memorial Regional Hospital, Hollywood, FL, USA (Dr Lerman); Beijing Peking University WBL Biotech Co. Ltd. (WPU), Luye Pharma Group, Beijing, China (Drs Duan, Guo, P.L. Liu, J. Zhao, and Y. Zhang); and Luye America Pharmaceuticals, Ltd., Luye Pharma Group, Princeton, NJ, USA (Dr Li)

KEYWORDS:

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Cholesterol;
Lovastatin;
Red yeast rice;
Xuezhikang

BACKGROUND: Xuezhikang (XZK) is an extract of fermented red yeast rice that has lipid-lowering properties.

OBJECTIVE: To evaluate the effects of XZK on lipids in subjects with dyslipidemia but no coronary heart disease.

METHODS: A total of 116 adults with baseline non-high-density lipoprotein cholesterol (non-HDL-C) levels of approximately 208 mg/dL and low-density lipoprotein cholesterol (LDL-C) levels of approximately 175 mg/dL were randomized to either placebo or XZK 1200 or 2400 mg daily and treated for 12 weeks.

RESULTS: A majority of the patients were white (53.4%) or Asian (37.1%). Daily XZK 1200 mg and 2400 mg for 4 to 12 weeks resulted in statistically significant ($P < .001$) and clinically meaningful decreases in non-HDL-C (~24% reduction) and LDL-C (~27% reduction) compared with placebo. XZK treatment at either dose enabled approximately 50% of subjects to reduce their LDL-C levels by $\geq 30\%$. Doubling the XZK daily dose from 1200 to 2400 mg at treatment week 8 caused an additional 4.6% reduction in LDL-C. Significant benefits were also observed across secondary efficacy

* Corresponding author. Luye America Pharmaceuticals, Ltd., 502 Carnegie Center, Suite 104, Princeton, NJ 08540.

E-mail address: simonli@luye.cn

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variables, including total cholesterol (TC), apolipoprotein B (Apo B), triglycerides, HDL-C, the TC/HDL-C ratio, and the Apo B/Apo A-I ratio, at treatment week 8 or 12. XZK was safe and well tolerated. Safety and tolerability profiles were similar across treatment groups. Most adverse events were gastrointestinal. No subject experienced myopathy or markedly elevated liver transaminases or creatine kinase.

CONCLUSION: Xuezhikang significantly reduced non-HDL-C and LDL-C, and was well tolerated. Further, longer-term studies in more diverse patient populations are needed to corroborate these findings.

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Some patients who are at elevated risk of cardiovascular disease and either do not tolerate 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) or prefer not to use them turn to alternative treatment options.¹ Natural lipid-lowering therapies include extracts of red yeast rice (RYR) fermented by *Monascus purpureus*. These products have served as dietary supplements and traditional medicines for centuries in China and many other countries.^{2,3}

Fermented RYR has lipid-lowering properties. However, the quality of RYR products varies significantly. Xuezhikang (XZK), a partially purified RYR under controlled pharmaceutical manufacturing conditions, contains a family of naturally occurring statins (monacolins)—most prominently monacolin K, which is identical to the lipid-lowering therapy lovastatin (Mevacor). Randomized placebo-controlled studies have proved the lipid-lowering efficacy of XZK in large patient populations.⁴

Objectives of this study were to assess the effects of XZK (vs placebo) on serum lipids and lipoproteins, as well as tolerability and safety profiles, among US and Chinese patients with dyslipidemia.

Methods

Study design

This phase 2 multicenter, double-blind, randomized, placebo-controlled, parallel-group trial was conducted at 15 sites in the United States (8 centers) and China (7 centers) between April 15, 2011 (first patient enrolled) and August 13, 2012 (final patient followed up). The study is registered at www.clinicaltrials.gov (identifier NCT01327014). Eligible subjects underwent a 4-week treatment-free run-in period, during which they followed a low-fat-modified diet.

Ethical conduct

The study was performed in conformity to ethical tenets originating in the Declaration of Helsinki, International Conference on Harmonization/Good Clinical Practice (ICH/GCP) guidelines, and applicable local regulatory

requirements and laws. All study candidates provided written informed consent before any study activity. The consent document, protocol, and all amendments were reviewed and approved by local institutional review boards in China and by a central institutional review board in the United States.

Subjects

Eligible subjects were aged ≥ 18 years with total cholesterol (TC) ≥ 240 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL (but ≤ 220 mg/dL), and triglycerides < 400 mg/dL. Other requirements included a body mass index < 36 kg/m².

Excluded were individuals with a history of cardiovascular disease (myocardial infarction, stroke, transient ischemic attack, cardiovascular surgery, or other major surgery) within 6 months before the screening visit and/or percutaneous coronary intervention within 3 months. Patients with peripheral arterial disease or aortic aneurysm were not excluded. Exclusion criteria also included a history of nephrotic syndrome, certain forms of renal and hepatic impairment, and/or elevations in liver transaminases to > 1.5 times the upper limit of normal (1.5XULN) or increases in creatine kinase (CK) to above the ULN.

Study drugs, blinding, and randomization

A centrally designed randomization code with a block of 6 was used to randomly allocate (in a 1:1:1 ratio) subjects to either placebo, XZK 1200 mg, or XZK 2400 mg daily. In each case, subjects were given 4 identically appearing capsules twice daily: 4 placebo capsules in the placebo group; 2 placebo and 2 300-mg capsules in the XZK 1200-mg group; and 4 300-mg capsules in the XZK 2400-mg group. Study medicines were prepared by WPU in Beijing (batch #LB20101001 for placebo and batch #LA20101001 for XZK).

Concomitant medications

Treatment with any lipid-lowering therapy (including XZK) and/or investigational agent within 4 weeks of the

run-in was prohibited. Also excluded were medications promoting weight loss (eg, orlistat) and agents that could affect lipid (or lovastatin/lovastatin acid) metabolism (other than XZK).

Assessments

Efficacy

Fasting lipids and lipoproteins were measured at baseline and each monthly visit through treatment week 12 by an ICH/Good Laboratory Practice (GLP)-compliant central laboratory (certified by the Standardization Program of the Centers for Disease Control and Prevention, and the National Heart, Lung, and Blood Institute) using validated methods.

The primary efficacy endpoints were mean percentage changes from baseline to week 12 (or last observation carried forward) in serum non-high-density lipoprotein cholesterol (non-HDL-C) and LDL-C. Secondary endpoints included percent changes from baseline to week 12 in a range of other lipids and lipoproteins. We also determined proportions of patients whose LDL-C levels were reduced from baseline by $\geq 30\%$, at week 12, by treatment group.

Tolerability and safety

Adverse events were elicited via open-ended questioning at each study visit and coded as to system-organ class and

preferred term using Medical Dictionary for Regulatory Activities, version 14.0. Vital signs were measured at each visit. Physical examinations and 12-lead electrocardiograms (ECGs) were performed at the screening and 12-week (or early-termination) visits. Serum for clinical laboratory testing was obtained at each visit. Central laboratories were used for ECG (erT) and safety (Covance) assessments. Treatment compliance was assessed by pill count.

Sample size

Given published data on statins and a patient attrition rate of 10%, we required 20 patients in each group to have 90% power ($\beta = .90$) to detect a mean (standard deviation [SD]) difference of >20 (14) mg/dL in fasting serum LDL-C between actively treated and placebo groups at a 2-tailed $\alpha = .05$. A conservative enrollment approach targeted 40 patients for inclusion in each treatment group's intent-to-treat population (half each in the United States and China).

Statistical analysis

Changes from baseline to treatment week 12 (or last observation carried forward) within each treatment group were analyzed using an intragroup paired *t*-test. A 2-step process was used for hypothesis testing. A global null hypothesis that the average percentage changes in lipids/

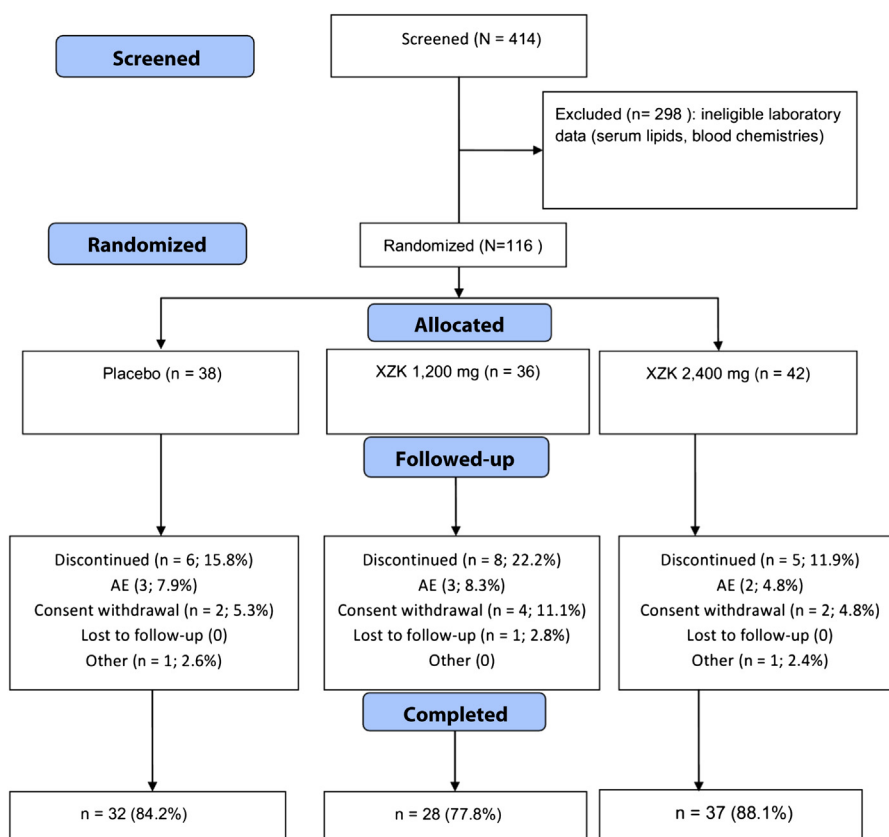


Figure 1 Consolidated Standards of Reporting Trials patient-disposition flow diagram. AE, adverse event; XZK, Xuezhikang.

Table 1 Baseline characteristics*

Characteristic	Placebo (N = 38)	XZK 1200 mg (N = 36)	XZK 2400 mg (N = 42)	Total (N = 116)
Mean (SD) age, year	56.0 (12.5)	57.8 (9.0)	56.3 (10.8)	56.7 (10.8)
Gender, no. (%) female	27 (71.1)	30 (83.3)	29 (69.0)	86 (74.1)
Race, no. (%)				
White	21 (55.3)	20 (55.6)	21 (50.0)	62 (53.4)
Asian	14 (36.8)	15 (41.7)	14 (33.3)	43 (37.1)
African	1 (2.6)	1 (2.8)	6 (14.3)	8 (6.9)
Native American or Alaska native	2 (5.3)	0	1 (2.4)	3 (2.6)
Ethnicity, no. (%)				
Hispanic/Latino	2 (5.3)	2 (5.6)	3 (7.1)	7 (6.0)
Mean (SD) body weight, kg	73.5 (16.9)	70.2 (15.1)	75.2 (14.9)	73.1 (15.7)
Mean (SD) height, cm	163.0 (10.2)	163.0 (7.5)	164.3 (9.0)	163.5 (8.9)
Mean (SD) BMI, kg/m ²	27.3 (3.8)	26.2 (4.3)	27.7 (3.9)	27.1 (4.0)
Smoker, no. (%)	3 (7.9)	5 (13.9)	4 (9.5)	12 (10.3)
History of lipid-lowering drug treatment, no. (%)	13 (34.2)	14 (38.9)	15 (35.7)	42 (36.2)
Comorbidities [†]				
Arthritis [‡]	14 (37.8)	12 (33.3)	9 (21.4)	35 (30.4)
Hypertension	13 (35.1)	11 (30.6)	10 (23.8)	34 (29.6)
GERD	6 (16.2)	6 (16.7)	7 (16.7)	19 (16.5)
Drug hypersensitivity	8 (21.6)	5 (13.9)	2 (4.8)	15 (13.0)
Insomnia	3 (8.1)	5 (13.9)	5 (11.9)	13 (11.3)
Depression	2 (5.4)	2 (5.6)	5 (11.9)	9 (7.8)
Anxiety	1 (2.7)	4 (11.1)	3 (7.1)	8 (7.0)
Hypothyroidism	4 (10.8)	3 (8.3)	0	7 (6.1)

BMI, body mass index; GERD, gastroesophageal reflux disease; SD, standard deviation; XZK, Xuezhikang.

*Analyses were by originally assigned groups (intent-to-treat population).

[†]The denominator for comorbidities was 115 (safety population), including 37 in the placebo group.

[‡]Includes osteoarthritis.

lipoproteins from baseline were the same in each treatment group was tested at a 2-tailed $\alpha = .05$. For the continuous efficacy endpoints, an analysis of covariance model was constructed with treatment group as a fixed factor, baseline value as a covariate, and study drugs as random effects. If this global null hypothesis was rejected, each XZK treatment group was compared individually with placebo at a 2-tailed $\alpha = .05$. In the event of a significant ($P < .15$) group-by-site interaction upon analysis-of-covariance modeling, we explored the nature of the interaction according to study site. Cochran-Mantel-Haenszel tests were performed to determine between-group differences in proportions of patients whose LDL-C levels were reduced by $\geq 30\%$.

Results

Patient disposition

Of 414 patients screened, 116 had eligible serum lipids/lipoproteins and blood chemistries and were randomized: 74 (63.8%) in the United States and 42 (36.2%) in China. Subjects were randomly allocated to the placebo ($n = 38$), XZK 1200 mg/day ($n = 36$), or XZK 2400 mg/day ($n = 42$) group (Fig. 1). The safety population, which

included all subjects who received ≥ 1 dose of study medication, was 115: a single patient randomized to placebo withdrew from the study before receiving study medication.

A total of 19 subjects discontinued the study prematurely, including 3 each with adverse events in the placebo (7.9%) and XZK 1200 mg/day (8.3%) groups as well as 2 subjects (4.8%) in the XZK 2400 mg/day group. Hence, 97 subjects (83.6%) completed the study (Fig. 1).

Treatment exposure and compliance

The mean (SD) treatment exposure was 10.9 (3.8) weeks. The overall mean (SD) medication compliance in the safety population was 81.8% (26.2%), including 79.9% (30.8%) in the placebo, 79.5% (27.3%) in the XZK 1200 mg/day, and 85.4% (20.3%) in the XZK 2400 mg/day arms.

Baseline characteristics

Patient characteristics were well balanced across treatment groups at baseline (Table 1). The mean (SD) age was 56.7 (10.8) years, and approximately three-quarters of subjects were women. More than 90% of subjects were white (62/116; 53.4%) or Asian (43/116; 37.1%).

Efficacy

Daily treatment with XZK 1200 or 2400 mg significantly reduced both non-HDL-C (by ~24%) and LDL-C (by 27%) from baseline to treatment week 12 (each $P < .001$ vs baseline and vs placebo; Fig. 2). There was no significant difference in percent non-HDL-C or LDL-C lowering between the 2 XZK treatments. Doubling the XZK daily dose from 1200 to 2400 mg at treatment week 8 resulted in an additional 4.6% reduction in the LDL-C level.

XZK enabled approximately 48% of subjects to reduce their LDL-C levels by $\geq 30\%$ compared with baseline (each $P < .001$ vs placebo; $P = .901$ for between-dose XZK comparisons). Significant changes were also observed across many secondary efficacy variables. In the XZK 1200 mg/day and 2400 mg/day groups, respectively, least-squares mean changes were significantly greater compared with placebo ($P < .001$) for TC and apolipoprotein (Apo) B (Table 2). Atherogenic ratios also decreased significantly from baseline to week 12 (by $>20\%$) with XZK at either dose (each $P < .001$ vs placebo). There was no difference between American and Chinese subjects in effects of XZK on lipid efficacy endpoints.

Tolerability and safety

Treatment with XZK was well tolerated, with similar tolerability profiles in the 3 treatment groups. Similar proportions of patients in the XZK and placebo groups reported adverse events (Table 3). Most adverse events were gastrointestinal (GI) and considered to be mild or moderate. A total of 3% to 5% of subjects experienced muscle spasms or myalgia with XZK, but none had evidence of myopathy (as specified in the protocol as muscle pain accompanied by an increase in CK to ≥ 10 XULN). Adverse events prompting study discontinuation that were related to study drugs were: (1) nausea along with other GI effects (diarrhea, abdominal pain) in 2 subjects, and cutaneous effects (flushing) in a third, within the placebo control group; (2) epigastric pain, jaw pain, and cutaneous effects (rash) in 1 subject each within the XZK 1200 mg/day group; and (3) insomnia and nausea/vomiting in 1 subject each within the 2400 mg/day group. Most of these events resolved after study drugs were withdrawn.

There were no clinically meaningful differences between treatment groups in laboratory tests, ECGs, vital signs, or physical examinations. No subject exhibited ≥ 2 -fold elevations in CK or liver transaminases. Three subjects experienced serious (non-drug-related) adverse events: (1) 1 American woman in the XZK 2400 mg/day group died of a pulmonary embolism after taking XZK for about 7 weeks; (2) another American woman in the same treatment group experienced a fractured leg, with study medication temporarily interrupted; and (3) a Chinese woman in the XZK 1200 mg/day group had thyroid cancer, with no change in her study medication.

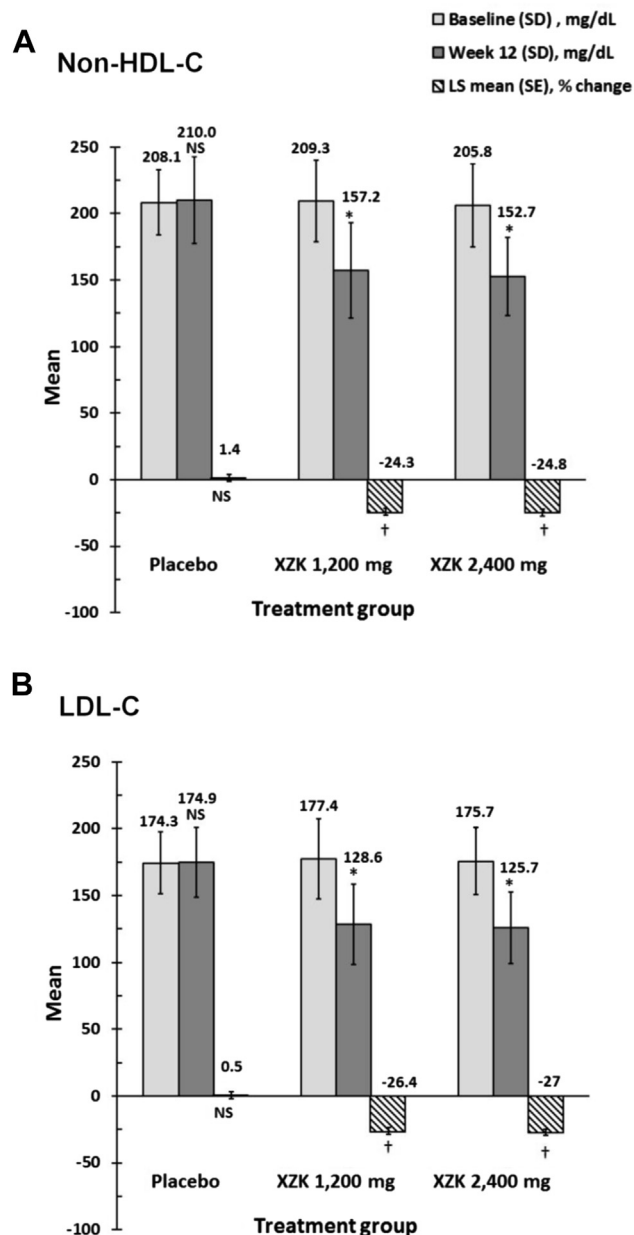


Figure 2 (A) Mean (SD; error bars) non-high-density lipoprotein cholesterol (non-HDL-C); (B) and low-density lipoprotein cholesterol (LDL-C); levels at baseline and treatment week 12 (or last observation carried forward), by treatment group, with least-squares (LS) mean (SE) percent changes. * $P < .001$ for treatment week 12 compared with baseline; † $P < .001$ for active treatment compared with placebo. There were no significant differences between XZK doses for either parameter. NS, not statistically significant; SD, standard deviation; SE, standard error; XZK, Xuezhikang.

Discussion

Daily treatment with XZK 1200 or 2400 mg resulted in statistically and clinically significant (~24% to 27%) reductions from baseline to week 12 in non-HDL-C and LDL-C. XZK also significantly reduced other atherogenic lipids and lipoproteins, and enabled approximately 50% of

Table 2 Efficacy of XZK on secondary endpoints

Parameter, mean \pm SD	Treatment group					
	Placebo			XZK 1200 mg		
	Baseline	Week 12	LS mean Δ , %	Baseline	Week 12	LS mean Δ , %
Total cholesterol, mg/dL	265.0 \pm 26.4	266.2 \pm 32.3	+0.4	269.8 \pm 30.7	219.7 \pm 33.2	-17.8*
Triglycerides, mg/dL	169.1 \pm 64.8	190.8 \pm 172.9	+12.0	160.2 \pm 60.2	142.9 \pm 62.1	-8.0
HDL-C, mg/dL	57.0 \pm 11.9	56.2 \pm 14.9	-2.2	60.5 \pm 12.8	62.5 \pm 13.7	+4.3
TC/HDL-C ratio	4.8 \pm 0.9	5.0 \pm 1.4	+5.0	4.6 \pm 1.0	3.7 \pm 0.9	-20.2*
Apo B, mg/dL	131.8 \pm 17.7	134.9 \pm 16.7	+2.9	133.7 \pm 15.7	108.4 \pm 23.6	-19.0*
Apo A-I, mg/dL	155.7 \pm 20.5	155.6 \pm 24.0	0	159.6 \pm 21.3	168.0 \pm 24.7	+5.8*
Apo B/Apo A-I ratio	0.9 \pm 0.2	0.9 \pm 0.2	+3.9	0.9 \pm 0.2	0.7 \pm 0.2	-22.9*

Apo A-I, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LS, least-squares; SD, standard deviation; TC, total cholesterol; XZK, XuezhiKang.

* $P < .001$ vs placebo.

subjects to achieve $\geq 30\%$ reductions in LDL-C from baseline. Efficacy findings were similar in American and Chinese study participants.

Our efficacy data are largely consistent with results from previous studies. The decreases of approximately 27% in LDL-C and 18% in TC with XZK 1200 or 2400 mg daily in our study fall within ranges established by previous Chinese trials involving similar XZK dosages: LDL-C decreased by approximately 17% to 34% and TC by 10% to 44% in prior studies of XZK 1200 to 2400 mg daily.³⁻¹⁴ In a European study of white patients, treatment with RYR (HypoCol) for 16 weeks decreased LDL-C by 23.0% and TC by 15.5% (each $P < .001$ vs placebo).⁷

These percent declines are similar to data for lovastatin at daily doses of 10 to 40 mg in US populations.¹⁵⁻¹⁷ In the US Air Force/Texas Coronary Atherosclerosis Prevention Study, daily treatment with lovastatin 20 to 40 mg/day for 1 year reduced LDL-C by 25.0% and TC by 18.4% in subjects with average cholesterol levels.¹⁸ In a study of low-dose lipid-lowering therapy, daily treatment with lovastatin 10 mg decreased LDL-C by 22% and TC by 15%.¹⁵

Our study revealed slightly more marked decreases in LDL-C ($\sim 27\%$) and TC ($\sim 18\%$) with XZK at a nearly equivalent lovastatin dosage (1200 mg = 12 mg lovastatin). There are at least 2 plausible explanations for potentially higher mg:mg LDL-C- and TC-lowering capacities of XZK compared with corresponding, equipotent doses of lovastatin. First, the oral bioavailability of lovastatin in RYR products may be superior to lovastatin administered alone because of enhanced dissolution and decreased crystallinity of monacolin K within XZK.¹⁹ Second, the presence of other potential lipid-lowering constituents in XZK, including other monacolins²⁰ and phytosterols, may lead to more effective cholesterol lowering (vs lovastatin alone).

Similar frequencies of adverse events (chiefly GI effects) were observed in the XZK and placebo groups. Although 3% to 5% of subjects receiving XZK experienced muscle symptoms, none had myopathy. In previous trials, RYR derivatives proved to be safe and well tolerated in patients with preexisting abnormal liver function tests⁵ or statin-associated myalgia.^{21,22} In our study, frequencies of adverse events were highest in American subjects randomly assigned to placebo. This trend might suggest cultural issues, including apprehensions about using RYR among US (vs Chinese) residents.

Frequencies of statin adverse events, particularly myotoxicity, are dose related. That 1200 mg of XZK contains 12 mg of lovastatin, which is below US therapeutic dosages, might be consistent with an overall favorable safety/tolerability profile for XZK. Taken together with the potentially higher mg:mg lipid-lowering potency of XZK compared with equidose lovastatin, this finding suggests a potentially advantageous benefit:risk ratio for XZK in patients with modest LDL-C elevations.

Table 3 Adverse events*

Treatment-emergent signs or symptoms	No. (%) of patients			
	Placebo (N = 37)	XZK 1200 mg (N = 36)	XZK 2400 mg (N = 42)	Total (N = 115)
All†	19 (51.4)	17 (47.2)	22 (52.4)	58 (50.4)
Gastrointestinal†	10 (27.0)	5 (13.9)	10 (23.8)	25 (21.7)
Discolored feces	5 (13.5)	0	5 (11.9)	10 (8.7)
Dyspepsia	1 (2.7)	3 (8.3)	1 (2.4)	5 (4.3)
Nausea	2 (5.4)	0	2 (4.8)	4 (3.5)
Diarrhea	1 (2.7)	2 (5.6)	0	3 (2.6)
Abdominal discomfort	2 (5.4)	0	0	2 (1.7)
Investigations/laboratory abnormalities†	5 (13.5)	2 (5.6)	1 (2.4)	8 (7.0)
Increased ALT	2 (5.4)	0	0	2 (1.7)
Increased AST	2 (5.4)	0	0	2 (1.7)
Increased blood CK	2 (5.4)	0	0	2 (1.7)
Increased leukocyte count	0	2 (5.6)	0	2 (1.7)
Infections	4 (10.8)	4 (11.1)	5 (11.9)	13 (11.3)
Upper-respiratory-tract infection	3 (8.1)	0	2 (4.8)	5 (4.3)
Nervous system disorder	3 (8.1)	1 (2.8)	3 (7.1)	7 (6.1)
Headache	2 (5.4)	1 (2.8)	2 (4.8)	5 (4.3)
Musculoskeletal and connective-tissue disorders	1 (2.7)	4 (11.1)	5 (11.9)	10 (8.7)
Muscle spasm	0	0	2 (4.8)	2 (1.7)
Myalgia	0	1 (2.8)	2 (4.8)	3 (2.6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; TESS, treatment-emergent signs or symptoms; XZK, Xuezhikang.

*TESS reported by ≥ 2 subjects in any treatment group within the safety population (N = 115), irrespective of relationship to study medications.

†Individual frequencies do not add to totals because some subjects had >1 TESS.

Potential study limitations

The eligibility criteria applied in our study may not allow us to generalize our findings to patients with more complicated medical histories and/or drug regimens. Women were overrepresented in the study population. Our findings are most generalizable to patients who have moderately elevated LDL-C but no history of coronary heart disease or stroke (ie, primary prevention). The maximum duration of our double-blind treatment period (12 weeks) may have been insufficient to discriminate between treatment groups in terms of infrequent adverse events such as statin-associated myopathy, manifestations of which often take ≥ 6 months to emerge.²³ Our study excluded patients with histories of markedly elevated CK and liver transaminase levels. The study protocol was developed, and the trial conducted, before the American College of Cardiology and American Heart Association had issued its new consensus guidelines on cholesterol management to limit atherosclerosis.²⁴

Conclusions

Treatment with XZK 1200 or 2400 mg daily for 12 weeks significantly reduced non-HDL-C, LDL-C, and other atherogenic lipids and lipoproteins, and was safe and well tolerated in American and Chinese subjects with moderately elevated LDL-C. Further prospective randomized controlled trials are warranted to evaluate the efficacy, safety, and tolerability of XZK in larger, more clinically heterogeneous patient populations followed for longer intervals.

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