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Lipid-lowering effects of gefarnate in statin-treated patients with residual hypertriglyceridemia: a randomized controlled study

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ABSTRACT

BACKGROUND The prevention of coronary artery disease (CAD) faces dual challenges: the aspirin-induced gastrointestinal injury, and the residual cardiovascular risk after statin treatment. Geraniol acetate (Gefarnate) is an anti-ulcer drug. It was reported that geraniol might participate in lipid metabolism through a variety of pathways. The aim of this study was to assess the lipid-lowering effects of gefarnate in statin-treated CAD patients with residual hypertriglyceridemia.

METHODS In this prospective, open-label, randomized, controlled trial, 69 statin-treated CAD patients with residual hypertriglyceridemia were randomly assigned to gefarnate group and control group, received gefarnate (100 mg/3 times a day) combined with statin and statin alone, respectively. At baseline and after one-month treatment, the levels of plasma triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and total cholesterol were tested.

RESULTS After one-month gefarnate treatment, triglyceride level was significantly lowered from 2.64 mmol/L to 2.12 mmol/L (P = 0.0018), LDL-C level lowered from 2.7 mmol/L to 2.37 mmol/L (P = 0.0004), HDL-C level increased from 0.97 mmol/L to 1.17 mmol/L (P = 0.0228). Based on statin therapy, gefarnate could significantly reduce the plasma triglyceride level (P = 0.0148) and increase the plasma HDL-C level (P = 0.0307). Although the LDL-C and total cholesterol levels tended to decrease, there was no statistically significant difference.

CONCLUSIONS The addition of gefarnate to statin reduced triglyceride level and increased HDL-C level to a significant extent compared to statin alone in CAD patients with residual hypertriglyceridemia. This suggested that gefarnate might provide the dual benefits of preventing gastrointestinal injury and lipid lowering in CAD patients.

Statins remain the most effective medication to reduce the low-density lipoprotein cholesterol (LDL-C) level and further prevent cardiovascular disease.[1] However, the DYSlipidemia International Study confirmed that after standard statin treatment, there were still as many as 47.6% of patients with hypertriglyceridemia (HTG) and 35.9% of patients did not meet the non-high-density lipoprotein cholesterol standa-

rd.[2] HTG is the most common dyslipidemia type in China, is worthy of attention for its correlation with residual cardiovascular risk.[3] A meta-analysis showed that for every 1 mmol/L increase in triglyceride (TG), the risk of atherosclerosis cardiovascular disease (ASCVD) increased by 13%.[4] Currently, some drugs are available decrease TG, such as fibrates, but statins and some fibrates share similar drug metabolic pathways and pharmacokinetic characteristics.[5] Their combination poses safety concerns, such as rhabdomyolysis, myopathy and hepatic injury.

Geraniol, an acyclic monoterpene, is naturally found in the essential oil of many aromatic plants such as rose and citronella.[6] More and more animal experiments have found that geraniol can mediate the decrease in plasma lipids levels through a variety of signal pathways, including reduce the protein level and catalytic activity of HMGCR, elevated low-density lipoprotein receptor mRNA levels,[7] promote activation of lipoprotein lipase and increase the level of lecithin cholesterol acyltransferase,[8] our previous research also found geraniol can induce hepatocyte autophagy through SIRT1-AMPK-mTOR and accelerate the degradation of TG by hepatocytes.[9] In addition, geraniol could significantly reduce serum TG, total cholesterol (TC), free fatty acid and C-reactive protein levels, and inhibit liver sinus, it could also improve the thickening of arterial wall, fibrosis and lipid deposition disease.[10] The combination of simvastatin and geraniol synergistically inhibited cholesterol biosynthesis and proliferation of Hep G2 cell line.[11] Geraniol acetate (Gefarnate) is an anti-ulcer and gastritis treatment drug.[12] Studies have shown that in patients with ASCVD, 66.2% of patients taking the aspirin may suffer from gastrointestinal mucosal injury.[13] In addition, 93.2% of Chinese high-risk ASCVD patients have not reached the lipid-lowering target.[14] Considering the potential lipid-lowering effect of gefarnate, it may be a new choice with dual functions. Therefore, this trial is performed to investigate the protective lipid-lowering effects of gefarnate in coronary artery disease (CAD) patients on statin therapy with residual HTGand evaluate the safety of geraniol combined with statin.

METHODS

Study Population

Participants were all recruited from the First Affiliated Hospital, Harbin Medical University, Harbin, China between December 2018 and February 2021. The inclusion criteria were as follows: (1) patients were aged 18–75 years with stable CAD who was treated with antiplatelet drug; (2) treated with maximum tolerated dose of statin for more than one month; and (3) plasma TG level ≥ 1.7 mmol/L. The exclusion criteria were as follows: (1) individuals with active hepatopathy or unexplained elevated blood aminotransferase; (2) prostatic hypertrophy or contraindications to prostaglandin drugs such as glaucoma patients; (3) creatinine clearance rate < 30 mL/min; (4) those who are allergic to any component of gefarnate; and (5) individuals who use the cholesterol absorption inhibitors ezetimibe and PCSK9 inhibitors.

Study Design

This study (ClinicalTrials.gov identifier: NCT0361-0321) was an open-label, randomized, prospective clinical trial in CAD patients complicated with HTG conducted at a single center. The study was approved by the Ethics Committees of the First Affiliated Hospital (No.20 1867), Harbin Medical University, Harbin, China. A written informed consent was required before study screening. Of 84 screened patients, five subjects refused to participate in this trial and three individuals did not meet inclusion criteria. Seventy-six subjects were assigned by random number table to two groups. The gefarnate group was given gefarnate (100 mg/3 times a day) on the basis of statin treatment, while the control group maintained the original statin treatment regimen for one month. At baseline and after the one-month treatment period, the levels of plasma lipids [TG, high-density lipoprotein cholesterol (HDL-C), LDL-C and TC], myocardial enzyme, liver and kidney function were detected. Adverse events were recorded and monitored throughout the study. CAD, defined as stable angina pectoris and objective evidence of CAD, a previous myocardial infarction, or previous revascularization with percutaneous coronary intervention or coronary artery bypass grafting.

Study Outcomes

The primary endpoint was the mean change of TG after treatment. The major secondary endpoints included the mean change of LDL-C, HDL-C and TC after treatment.

Adverse Event Assessments

Adverse events were recorded and monitored throughout the study, including continuous increase of blood

transaminase, myositis, myalgia, rhabdomyolysis, palpitation, headache, rash, dizziness, blurred vision, taste disorder, impotence, insomnia, hepatitis, pancreatitis, dry mouth, nausea, vomiting and constipation. The safety and tolerability variables comprised of vital signs, physical examination.

Power Analysis

To estimate the group size in the study, we conducted a pilot study for measuring the levels of plasma TG at one month in 30 patients who received gefarnate (100 mg/3 times a day) combined with statin or statin alone. The results suggested that the gefarnate group showed lower levels of TG (2.12 ± 0.81 mmol/L) than the control group (2.77 ± 1.07 mmol/L). With $\alpha = 0.05$, $\beta = 0.20$, we needed 34 patients per group. Considering a compliance rate of 90%, we needed 76 patients to participate in this study.

Statistical Analysis

Categorical data were presented with counts (percentages). Continuous variables were described as mean ± SD or median (interquartile range). The Kolmogorov-Smirnov test was performed to determine whether the data were normally distributed. The Student's *t*-test, Pearson's chi-squared test or Fisher's exact test was used to compare the demographic characteristics between two groups. The paired *t* test or sign test was performed to compare the blood lipid level between pretreatment and posttreatment. The significant level was set at 0.05 and two-tailed *P*-value < 0.05 were considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Baseline Clinical Characteristics

The disposition of patients and reasons for trial discontinuation were shown in Figure 1. Nearly 91% (69/76) of the participants completed the present study. Demographics and baseline clinical characteristics were summarized in Table 1. Including gender, age, past medical history, medication, biochemical parameters, etc. The distributions of the demographic and clinical characteristics among the gefarnate group and the control group were well balanced and homogeneous.

Efficacy Outcomes

Primary outcomes

After one-month gefarnate treatment, the level of TG was significantly lowered from 2.64 ± 0.84 mmol/L to 2.12 ± 0.95 mmol/L ($P = 0.0018$). The mean value of TG in

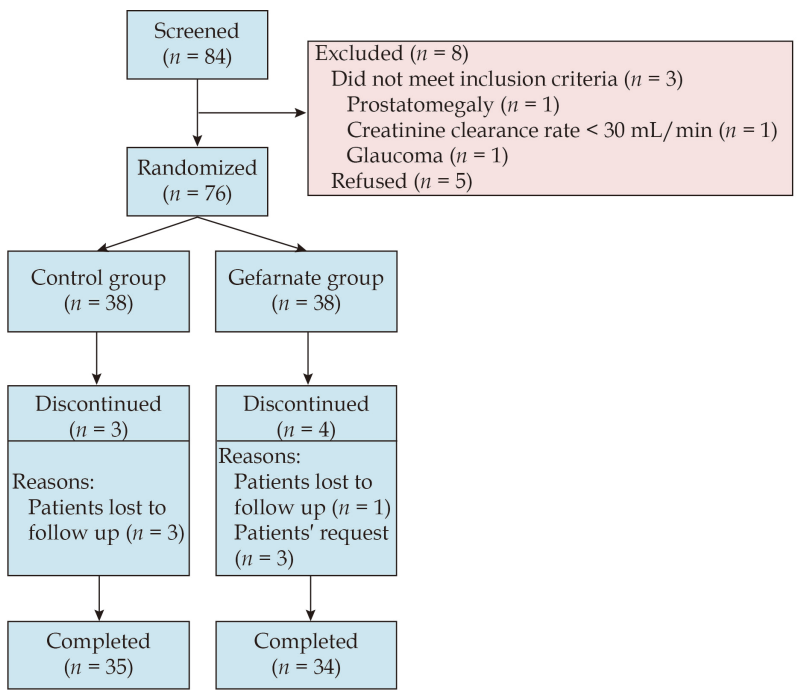

Figure 1 Disposition of patients.

Table 1 Demographics and baseline clinical characteristics of patients.

Variables	Gefarnate group	Control group	Total	*P*-value
Demographics				
Men	21 (61.76%)	21 (60%)	42 (60.87%)	0.8806
Age, yrs	56.5 ± 10.12	59.91 ± 8.93	58.23 ± 9.62	0.1416
Body mass index, kg/m^2				0.8193
< 24	7 (20.59%)	8 (22.86%)	15 (21.74%)	
≥ 24	27 (79.41%)	27 (77.14%)	54 (78.26%)	
Medical history				
Hypertension	26 (76.47%)	21 (60%)	47 (68.12%)	0.1422
Type 2 diabetes mellitus	11 (32.35%)	15 (42.86%)	26 (37.68%)	0.368
Prior myocardial infarction	6 (17.65%)	13 (37.14%)	19 (27.54%)	0.0699
Prior stroke	2 (5.88%)	6 (17.14%)	8 (11.59%)	0.2595
Heart failure	2 (5.88%)	5 (14.29%)	7 (10.14%)	0.4283
Smoke	12 (35.29%)	8 (22.86%)	20 (28.99%)	0.2549
Renal insufficiency	1 (2.94%)	1 (2.86%)	2 (2.9%)	1
Hyperuricemia	0	4 (11.43%)	4 (5.8%)	0.1142
Treatment				
Aspirin	34 (49.28%)	35 (50.72%)	69 (100%)	1
Clopidogrel/Ticagrelor	31 (91.18%)	32 (91.43%)	63 (91.3%)	1
Beta-blockers	20 (58.82%)	24 (68.57%)	44 (63.77%)	0.4584
Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers	11 (32.35%)	14 (40%)	25 (36.23%)	0.5088
Spironolactone	3 (8.8%)	3 (8.57%)	6 (8.7%)	1
Diuretic	1 (2.94%)	3 (8.57%)	4 (5.8%)	0.6139
Calcium channel blocker	20 (58.82%)	8 (22.86%)	28 (40.58%)	0.0024
Statins				0.3879
Atorvastatin 20 mg, once a day	22 (64.71%)	28 (80%)	50 (72.46%)	
Pitavastatin 2 mg, once a day	3 (8.82%)	1 (2.86%)	4 (5.8%)	
Pravastatin 40 mg, once a day	1 (2.94%)	0	1 (1.45%)	
Rosuvastatin 10 mg, once a day	8 (23.53%)	6 (17.14%)	14 (20.29%)	
Biochemical parameters				
Systolic blood pressure	143.85 ± 18.69	134.43 ± 15.86	139.07 ± 17.83	0.0270
Diastolic blood pressure	88.47 ± 14.67	80.77 ± 12.6	84.57 ± 14.11	0.0223
Low-density lipoprotein cholesterol/High-density lipoprotein cholesterol	2.67 (2.2–3.41)*	2.73 (2.21–3.05)*	2.67 (2.21–3.08)*	0.4567
Glucose	5.92 (5.26–7.09)*	5.81 (5–8.08)*	5.9 (5.1–7.57)*	0.8149
Uric acid	337.4 ± 76.81	344.9 ± 106.37	341.2 ± 92.38	0.7388
Creatinine	68 (62.1–78.1)*	75 (65.5–82)*	71.8 (62.7–80)*	0.1498
Blood urea nitrogen	5.1 (4.55–5.5)*	5.95 (4.37–6.83)*	5.39 (4.55–6.31)*	0.1145
Alanine aminotransferase	24.45 (15.3–34.1)*	29.2 (18.5–40.5)*	25.3 (16.5–35.8)*	0.1532
Aspartate transaminase	19.65 (15.6–25.7)*	23.8 (17.5–31.1)*	21.3 (16.1–28.5)*	0.0336

Data are presented as means ± SD or *n* (%). *Presented as median (interquartile range).

the control group before and after treatment were 2.67 ± 1.36 mmol/L *vs.* 2.77 ± 2.13 mmol/L with no statistical difference (P = 0.5046). Compared with the statin treatment alone, gefarnate combined with statin can significantly reduce the plasma TG level (P = 0.0148) (Table 2).

Secondary outcomes

After one-month gefarnate treatment, HDL-C level increased from 0.97 ± 0.2 mmol/L to 1.17 ± 0.41 mmol/L (P = 0.0004). The mean value of HDL-C in the control group before and after treatment were 1.01 ± 0.21 mmol/L *vs.* 1.04 ± 0.27 mmol/L with no statistical difference (P = 0.3111). Compared with the statin treatment alone, gefarnate combined with statin can significantly increase the plasma HDL-C level (P = 0.0307) (Table 2).

After one-month gefarnate treatment, LDL-C level lowered from 2.7 ± 0.76 mmol/L to 2.37 ± 0.8 mmol/L (P = 0.0004). The mean value of LDL-C in the control group before and after treatment were 2.54 ± 0.65 mmol/L *vs.* 2.36 ± 0.57 mmol/L, also with no statistical difference (P = 0.1876). In the gefarnate group, the changes in the reduction in LDL-C were significantly greater than that in the control group, but there was no significant difference between the two groups (P = 0.4783) (Table 2).

After one-month gefarnate treatment, TC level lowered from 4.25 ± 0.92 mmol/L to 4.08 ± 0.94 mmol/L, with no statistical difference (P = 0.3165). The mean values of TC in the control group before and after treatment were 4.26 ± 0.76 mmol/L *vs.* 3.95 ± 0.71 mmol/L, with statistical difference (P = 0.0228). There was no significant difference in the mean change of TC between the two groups (P = 0.4825) (Table 2).

Adverse events

As summarized in Table 3, one patient in the gefarnate group had mild diarrhea, one patient had increased creatine kinase with myalgia and four patients had increased transaminase. In the control group, one patient had myalgia and increased creatine kinase and two patients had increased transaminase.

Table 2 Change from baseline in plasma TC, TG, HDL-C, LDL-C and non-HDL-C at the one-month timepoint.

Variables	Gefarnate group		P^a	Control group		P^b	P^c
	Before	After		Before	After		
TC, mmol/L	4.25 ± 0.92	4.08 ± 0.94	0.3165	4.26 ± 0.76	3.95 ± 0.71	0.0228	0.4825
TG, mmol/L	2.64 ± 0.84	2.12 ± 0.95	0.0018	2.67 ± 1.36	2.77 ± 2.13	0.5046	0.0148
HDL-C, mmol/L	0.97 ± 0.2	1.17 ± 0.41	0.0004	1.01 ± 0.21	1.04 ± 0.27	0.3111	0.0307
LDL-C, mmol/L	2.70 ± 0.76	2.37 ± 0.87	0.0426	2.54 ± 0.65	2.36 ± 0.57	0.1876	0.4783
Non-HDL-C, mmol/L	3.27 ± 0.83	2.91 ± 0.87	0.0321	3.25 ± 0.69	2.91 ± 0.67	0.0068	0.9149

Data are presented as means ± SD. P^a refers to comparison of mean chance of five blood lipid indexes before and after treatment in the gefarnate group. P^b refers to comparison of mean chance of five blood lipid indexes before and after treatment in the control group. P^c refers to mean change of five blood lipid indexes between the two groups. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride.

Table 3 Adverse events in the gefarnate group and the control group of patients.

Adverse events	Gefarnate group (n = 34)	Control group (n = 35)
Aminotransferase increase	4	2
Myositis	0	0
Myalgia	1	1
Skin rash	0	0
Pancreatitis	0	0
Rhabdomyolysis	0	0
Nausea and vomiting	0	0
Diarrhea	1	0
Dry mouth	0	0
Constipation	0	0

DISCUSSION

The present data demonstrated that after one-month gefarnate treatment, TG level was significantly lowered from 2.64 ± 0.84 mmol/L to 2.12 ± 0.95 mmol/L, HDL-C level increased from 0.97 ± 0.2 mmol/L to 1.17 ± 0.41 mmol/L, LDL-C level lowered from 2.7 ± 0.76 mmol/L to 2.37 ± 0.8 mmol/L. Compared with the control group, gefarnate could further reduce TG and increase HDL-C based on statin treatment. In summary, this is the first study to show that gefarnate is able to reduce TG level and increased HDL-C level to a significant extent compared to statin alone in CAD subjects with residual HTG.

HTG is associated with an increased risk of cardiovascular disease. TG is a major component of TG-rich lipoproteins which includes chylomicron emulsion and very LDL-C.[15] Varbo, *et al*.[16] suggested that TG is also an independent risk factor for ischemic heart disease. In addition, some of the lipids are retained in adipose tissue which may have direct effects on cardiac diseases.[17] Due to the high prevalence of HTG and subsequent independent risk for cardiovascular event, TG should be considered in the treatment of dyslipidemia. Moreover, TG-rich lipoproteins have atherogenic effects by inducing macrophage dysfunction, endothelial cell inflammation, and coagulation abnormality.[18]

Currently, some components are available to decrease TG, for example, fibrates, omega-3 fatty acids, and nicotinic acid. The combination of statin and some fibrates has potential safety hazards. Previous studies have found that gemfibrozil interacts with glucuronidase homologues of statins metabolism, and the combination of the two resulted in severe reactions.[5] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found that over a mean of 4.7 years of follow-up, the combination of simvastatin and fenofibrate resulted in a decrease of TG and a numerically small but significant increase in HDL-C.[19] Although no severe liver injury or rhabdomyolysis occurred in this study, caution should be exercised regarding the use of fibrates with statins. As observed in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study,[20] over a mean of 2-year of follow-up, niacin therapy had significantly increased the median HDL-C level, lowered the TG level and LDL-C level. But the trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy. And they also found that the use of nicotinic acids could affect plasma glucose and increase the risk of diabetes and stroke risk. The Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) study[21] demonstrated that omega-3 CA could increase the median level of HDL-C and decrease the median level of TG. However, high-purity omega-3 fatty acids product is expensive.

Geraniol is one of the important isoprenoids and main ingredient of oil of rose and palmosora also present as an active constituent in essential oil of lemon, ginger, rose, orange, etc.[22] Recent researches have demonstrated that geraniol can decrease the plasma lipids levels.[7] Jayachandran, *et al*.[10] demonstrated that geraniol could significantly reduce serum TG, TC and free fatty acid. Geraniol acetate is an anti-ulcer and gastritis treatment drug.[12] Recent study had shown that 66.2% of patients with ASCVD taking aspirin may suffer from gastrointestinal mucosal injury.[13]

Animal studies have shown that gefarnate can mediate the reduction of plasma lipid levels through a variety of signaling pathways as follows[7–9,23]: it could inhibit the translation of cholesterol synthesis rate-limiting enzyme HMGCR mRNA, leading to a decrease of protein activity and expression level, reducing cholesterol production; it could increase very low density lipoprotein and LDL receptor protein mRNA levels, which lead to degradation of above lipoproteins; reduce free fatty acids to inhibit TG synthesis; hepatocyte autophagy was induced via SIRT1-AMPK-mTOR pathway to accelerate the degradation of TG; it could promote PPAR-γ, thereby inhibiting the lipid metabolism disorder induced by chronic inflammatory response which caused by activation of tumor necrosis factor α; it could also promote activation of lipoprotein lipase, resulted in decrease of TG and increase the level of lecithin cholesterol acyltransferase which can increase plasma HDL-C.

Gastrointestinal injury is a common complication in CAD patients treated with antiplatelet agents.[24] Compared with the other HTG treatment drugs mentioned above, gefarnate can not only increase the prostaglandin level and hexamine concentration of the gastric mucosa, but also decrease the plasma TG and increase the plasma HDL-C, may be a new option for lipid-lowering therapy in patient with CAD.

LIMITATIONS

There were several limitations in our study. Firstly, th-

is study is an open-label study, with a small sample size, short follow-up time and the randomized subjects from a single center were the major limitation. Secondly, this study only evaluated the lipid-modulating efficacy and safety of gefarnate treatment for one month, while the efficacy of the drug needs to be tested for a longer time. Last but not least, HTG is closely related to residual cardiovascular risk, and the present study only evaluated the effect of gefarnate on TG-lowering performance, but the effect among patients who have achieved statin therapy on residual cardiovascular risk is not available here. Therefore, the effects of gefarnate on long-term clinical endpoint in patients with CAD requires further investigation.

CONCLUSIONS

We performed a carefully randomized controlled study to investigate the protective lipid-lowering effects of gefarnate in CAD patients on statin therapy with residual HTG and observe its safety. Our results showed that gefarnate could effectively reduce the plasma TG and increase the plasma HDL-C. We expect the current study to provide valuable insights into the role of gefarnate as dyslipidemia treatment drugs or reduce the cardiovascular residual risk.

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