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Effect of statins combined with PCSK9 inhibitors on the prognosis of patients with acute coronary syndromes after interventional therapy

Lu Shi, Zekang Ye, Qian Gu, Yong Li*

Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, China

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ABSTRACT

Acute coronary syndromes (ACS) are a leading cause of morbidity and mortality worldwide. It has been clinically confirmed percutaneous coronary intervention (PCI) can alleviate the symptoms of ACS, but there are still some patients with slow blood flow or no-reflow after surgery, which has adverse effects on the prognosis of patients. This study aimed to investigate the effect of statins combined with PCSK9 inhibitors on the prognosis of patients with ACS after interventional therapy. A total of 208 ACS patients treated in our hospital from January 2021 to December 2022 were separated into observation and control groups. Patients in the control group received oral rosuvastatin 20 mg/ day. Patients in the observation group received PCSK9 inhibitor elozumab (Repatha) 140 mg, subcutaneously injected twice a week. The levels of inflammatory factors, cardiac function indexes, clinical effectiveness rate, adverse events, and complications were compared before and after treatment. After 1 week of treatment and 4 weeks of follow-up, the levels of inflammatory indicators in the observation group declined relative to the control group ($P < 0.05$ and $P < 0.01$). After 4 weeks, LVEF in the observation group was elevated in comparison to the control group, while LVEDD in the observation group declined compared to the control group ($P < 0.05$). The incidence of adverse events after treatment in the observation group declined relative to the control group ($P < 0.05$). The incidence of complications in the observation group declined in contrast to the control group ($P < 0.05$). Statins combined with PCSK9 inhibitors significantly reduce LDL-C levels in ACS patients undergoing PCI without increasing cardiovascular events or major adverse clinical effects.

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Introduction

Acute coronary syndromes (ACS) is a kind of coronary artery disease in which plaque damage in the coronary arteries causes platelets to accumulate in the blood vessels and form blood clots. It has the features of high morbidity and mortality, which severely threatens to health of patients, affects the function of crucial organs such as heart, brain and kidneys, as well as causes complications such as stroke, myocardial ischemia, organ bleeding and stent thrombosis (1). ACS has a wide variety, of complex syndromes and different pathogenesis, and its worsening trend and prevalence are difficult to control, which has become a key issue to be solved urgently in modern medicine (2). It is common in elderly, male and postmenopausal women, smoking, hypertension, diabetes, hyperlipidemia, abdominal obesity and family history of premature coronary heart disease (3). The typical clinical manifestation of ACS is an episodic retrosternal dull pain, compression or pressure, and burning sensation, which can radiate to the left upper arm, jaw, neck, back, shoulder or left forearm ulnar side, showing intermittent or persistent, accompanied by sweating, nausea, dyspnea, asphyxia, and even syncope, lasting >10-20 minutes (4). ACS can be divided into acute ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTE-ACS) according to the presence or absence of st elevation in electrocardiogram (ECG) at the time of onset (5). It has been clinically confirmed percutaneous coronary intervention (PCI) can accelerate the opening of infarction in ACS disease and alleviate the symptoms of thrombosis, but there are still some patients with slow blood flow or no-reflow after surgery, and myocardial perfusion cannot be effectively improved, which has adverse effects on the prognosis of patients (6). Statins are the first choice of lipid-lowering drugs, which have lipid-regulating effects such as reducing plasma cholesterol and low-density lipoprotein cholesterol (LDL-C) concentration, anti-inflammatory, improving endothelial function, dilating coronary microvessels, and improving coronary blood flow (7, 8). Statins can decrease coronary plaque burden and lower the risk of cardiovascular death, recurrent myocardial infarction, stroke, as well as coronary revascularization in patients with ACS (9). Moreover, it has been reported that statin therapy is related to the restoration of gut microbiota homeostasis and improved prognosis in patients with ACS (10). Proprotein convertase subtilisin kexin 9 (PCSK9) has a key potential in regulating the circulating level of LDL-C. Loss of PCSK9 gene function can lead to low LDL-C levels and is associated with reduced cardiovascular risk, while increased PCSK9 function is positively linked to the incidence of hypercholesterolemia along with coronary heart disease (11). Therefore, the regulation of LDL-C can be achieved by reducing PCSK9 level, and the inhibition of PCSK9 can effectively decline the incidence of atherosclerotic cardiovascular disease. PCSK9 inhibitors are

* Corresponding author. Email: liyong_edu@outlook.com

a new class of drugs that can be used to treat lipid disorders in patients with cardiovascular diseases, including diabetes (12). Compared to statins, PCSK9 inhibitors can act through a different pathway and can provide additional clinical benefit to patients with cardiovascular disease who are treated alone or as adadjuvant statin therapy. To improve the prognosis of patients after PCI, long-term drug therapy is indispensable. The guideline recommends that patients take statins for a long time after surgery. However, there are few studies on the effects of PCSK9 inhibitors in China. This research investigated the influence of statins combined with PCSK9 inhibitors on the prognosis of patients with ACS after interventional therapy.

Materials and Methods

General data

A total of 208 ACS patients treated in our hospital from January 2021 to December 2022 were chosen as the observation objects and separated into the PCSK9 group (observation group) and rosuvastatin group (control group) using the random number table method, with 104 cases in every group. In the observation group, 58 males and 46 females were contained. The average age was (62.54±10.36) years old. There were 45 cases of left anterior descending artery, 27 cases of left circumferential artery and 32 cases of right coronary artery. There were 46 cases of hypertension, 31 cases of diabetes, as well as 20 cases of dyslipidemia. In the control group, 55 males and 49 females were contained. The age was (61.78±11.74) years old. There were 43 cases of left anterior descending artery, 31 cases of left circumferential artery and 30 cases of right coronary artery. There were 42 cases with hypertension, 29 cases with diabetes, and 19 cases with dyslipidemia. No difference was discovered in the general data of the two groups (P>0.05). Inclusion criteria: (i) The clinical diagnosis, experimental detection and imaging information met the diagnostic criteria of ACS disease, with complete clinical data; (ii) The participants were willing to participate in the study and cooperate with clinical examination; (iii) With angina pectoris, thrombosis, myocardial infarction and coronary artery stenosis and other symptoms; (iv) The signs were stable and there were no imaging contraindications. Exclusion criteria: (i) People with serious cardiopulmonary, liver and kidney dysfunction, together with patients with mental diseases; (ii) Clinical examination data are not complete; (iii) Pregnant patients, patients with bronchial asthma, patients with anemia, and patients with other serious cardiovascular diseases except ACS. This study was approved by the Ethics Committee of our hospital, and all patients signed informed consent.

Methods

Blood samples of patients were drawn within 24 h of admission. Total cholesterol (TC), triglyceride (TG), LDL-C and other biochemical indexes were detected in all patients by a biochemical analyzer (Hitachi, Tokyo, Japan). At the time of screening, patients were not currently receiving lipid-lowering therapy should undergo a 4-week lipid stabilization phase.

Patients in the control group were treated with oral rosuvastatin (MedChemExpress Company) 20 mg/ day, and patients in the observation group received PCSK9 inhibitor elozumab (Repatha, Amgen Manufacturing Limited) 140 mg, subcutaneously injection twice a week. In case of adverse reactions, the patient should report to the clinician within 24 hours. The patients in the two groups were followed up for 6 months. Blood routine, liver and kidney function as well as other indicators were regularly tested. Basic drugs such as hypoglycemic and hypotensive therapy were given reasonably according to individual conditions.

Observation indexes

The changes in serum inflammatory indexes in the two groups were observed 1 week after treatment and 4 weeks after follow-up. Serum inflammatory indicators: venous blood was collected and centrifuged at 1 week after treatment and 4 weeks after follow-up, and serum was collected for determination of serum interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), as well as other indicators. IL-6 concentration was measured using an ELISA kit (Thermo Scientific, USA). Hs-CRP concentration was determined by the ultrasensitive immunoturbidimetric assay DiaSys (Holzheim, Germany).

The cardiac function changes of the two groups were observed at different time points (1 week, 4 weeks) after treatment. The changes in left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD) were examined by echocardiography at 1 week and 4 weeks after treatment.

Clinical curative effect: diastolic blood pressure of patients was decreased > 10 mmHg, angina pectoris incidence was 0-25%, ST segment was decreased > 50%, hematological indicators were normal; the diastolic blood pressure was decreased by more than 10 mmHg, the incidence of angina pectoris was 25%-50%, the ST segment was decreased more than 50%, and the hematological indexes were basically normal. Ineffective: the blood pressure index was beyond the normal range, the incidence of angina pectoris was > 50%, the ST segment was < 50%, and the symptoms and hematological indicators were not improved. Effective rate = cure rate + obvious efficiency.

Comparison of adverse events and complications including stent thrombosis, myocardial infarction, respiratory disorders, and myocardial ischemia.

Statistical analysis

SPSS 22.0 statistical software was utilized for analysis. Data conforming to normal distribution were indicated as ($x \pm s$). Two independent sample t-test was adopted for comparison of the two groups. Enumeration data were unveiled as (%) and X^2 test. $P < 0.05$ was significant.

Results

Comparison of serum inflammatory indexes between the two groups 1 week after treatment and 4 weeks after follow-up

One week after treatment and four weeks of follow-up, the levels of inflammatory indicators in the observation group were reduced compared to the control group ($P < 0.05$ and $P < 0.01$, Figure 1).

Comparison of the recovery of cardiac function between the two groups 1 week after treatment and 4 weeks after follow-up

As unveiled in Figure 2, no difference was found in

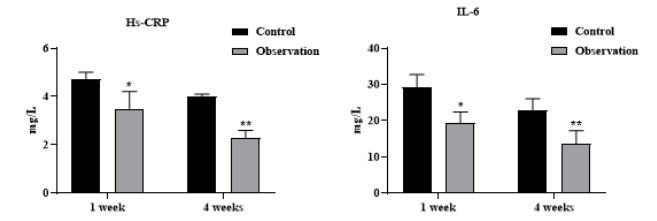

Figure 1. Changes of serum inflammatory indicators in the two groups at 1 week after treatment and 4 weeks of follow-up. *P < 0.05, **P < 0.01, relative to the control group.

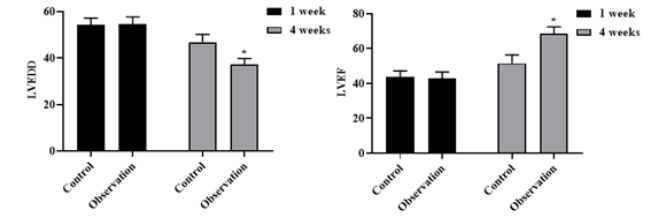

Figure 2. Cardiac function recovery of the two groups 1 week after treatment and 4 weeks after follow-up. *P < 0.05, relative to the control group.

LVEF together with LVEDD between the two groups 1 week after treatment (P > 0.05). Meanwhile, LVEF in the observation group was increased relative to the control group, while LVEDD was decreased compared to the control group 4 weeks after follow-up (P < 0.05).

Comparison of adverse events

The total incidence of adverse events including malignant arrhythmia, recurrent myocardial infarction, acute heart failure, and sudden cardiac death in the observation group was 2.88%, which was reduced compared to the control group of 9.60% (P < 0.05, Table 1).

Comparison of complications

The total incidence of complications including stent thrombosis, hemorrhage, respiratory disturbance, and myocardial ischemia in the observation group was 7.68%, which was declined relative to the control group of 17.28% (P < 0.05, Table 2).

Comparison of clinical efficacy between the two groups

The total effective rate of the observation group was 91.35%, which was increased compared to the control group of 83.65%, but the difference was not significant (P > 0.05, Table 3).

Comparison of LDL-C compliance rate between two groups 1 week after treatment and 4 weeks after follow-up

The patients in the two groups were followed up at 1 week and 4 weeks, respectively, and the LDL-C compliance rate was compared between the two groups at 1 week and 4 weeks (reaching the standard: LDL-C<1.4 mmol/L). The results demonstrated that at the first week of treatment, the LDL-C compliance rate in the observation group was 81.73%, but that in the control group was 20.19%. At the fourth week of treatment, the LDL-C compliance rate in the observation group was 91.35%, and that in the control group was only 28.83%, as shown in Figure 3. It could be seen that the LDL-C compliance rates in the observation group were all higher than those in the control group 1 week after treatment and 4 weeks after follow-up (P < 0.05).

Table 1. Occurrence of adverse events in the two groups (n, %).

Group	Malignant arrhythmia (Number)	Recurrent myocardial infarction (Number)	Acute heart failure (Number)	Sudden cardiac death (Number)	Total incidence (%)
Observation group	2 (1.92)	1 (0.96)	0 (0)	0 (0)	2.88
Control group	6 (5.76)	2 (1.92)	1 (0.96)	1 (0.96)	9.60
X^2	2.115				
P value	<0.05				

Table 2. Complications in the two groups (n, %).

Group	Stent thrombosis	Hemorrhage	Respiratory disturbance	Myocardial ischemia	Total incidence (%)
Observation group	2 (1.92)	1 (0.96)	1 (0.96)	4 (3.84)	7.68
Control group	4 (3.84)	3 (2.88)	3 (2.88)	8 (7.68)	17.28
X^2	4.062				
P value	<0.05				

Table 3. Clinical efficacy of the two groups (n, %).

Group	Cure	Remarkable effect	No effect	Effective rate (%)	
Observation group	52 (50.00)	43 (41.35)	9 (8.65)	91.35	
Control group	41 (39.42)	46 (44.23)	24 (16.35)	83.65	
X^2					1.325
P value					>0.05

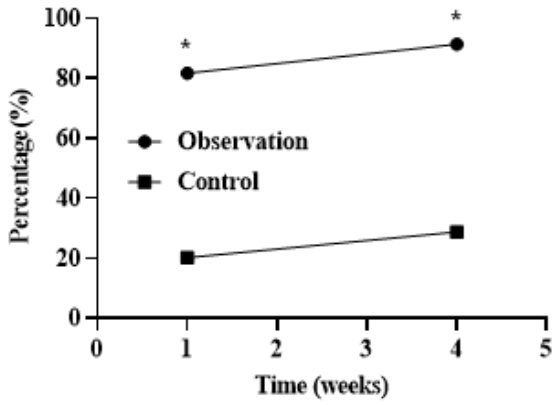

Figure 3. LDL-C compliance rate in the two groups 1 week after treatment and 4 weeks after follow-up. *P < 0.05, compared with the control group.

Discussion

LDL-C elevation is a main risk factor for unstable plaque rupture in ACS. Only when LDL-C is reduced to a very low level can it be possible to reverse plaque and thus reduce cardiovascular events (13). Statin therapy for coronary heart disease is effective in reducing LDL-C, but many patients do not achieve the expected reduction in LDL-C. In addition, high-dose statins significantly increase adverse reactions such as myolysis, myalgia, and elevated liver enzymes (14, 15). The poor reduction in LDL-C and the high residual risk suggest the need for treatment other than statins to provide the most effective cardiovascular prevention.

In general, low-density lipoprotein receptor (LDLR) on the surface of hepatocytes is involved in the uptake of LDL-C, and PCSK9 can destroy LDLR in lysosomes and increase LDL-C level. Literatures have shown that PCSK9 inhibitors can decline circulating LDL-C levels and improve other lipid parameters (16). Regulation of hepatic LDLR expression by PCSK9 provides a potential LDL-C reduction target to address residual cardiovascular risk in patients treated with statins. It has been demonstrated in some cases that LDL-C levels are not effectively controlled even with the highest dose of statins, whereas PCSK9 inhibitors can reduce the LDL-C level in these patients (17). In the GLAGOV study, which included nearly a thousand patients with coronary artery disease, nearly all of whom were treated with statins before entering the study, intravascular ultrasound (IVUS) was used to evaluate the effect of the PCSK9 inhibitor elloyumab on coronary plaque. The outcomes showed that the addition of PCSK9 inhibitor could significantly decline LDL-C and atherosclerotic plaque volume (18). ACS patients undergoing PCI have a high cardiovascular risk. As an innovative strategy for lowering blood lipids, PCSK9 inhibitors have potential applications in the field of PCI (19, 20).

Relevant studies have pointed out that the application of all antiplatelet drugs can inhibit platelets and protect cardiomyocytes and cardiac function in the process of inhibiting the damage of vascular endothelium and cardiomyocytes caused by platelets (21). The findings of this research demonstrated there was no difference in the improvement degree of cardiac function at 1 week after treatment of the two groups (P > 0.05). However, the cardiac function of the two groups was significantly improved during the 4-week follow-up, and the improvement degree in the observation group was the most significant (P < 0.05), which was in line with the results of literature (22). Reviewing two groups of ultrasound, we found that LVEF in the observation group was increased relative to the control group, while LVEDD was decreased compared to the control group (P < 0.05), mirroring the earlier elozumab is used, on the one hand, it can obtain a stronger effect of inhibiting platelet aggregation, on the other hand, it can effectively protect the intima of blood vessels and cardiomyocytes, and repair the injured cardiomyocytes as soon as possible. With one accord, it has been reported that PCSK9 is inversely correlated with LVEF in patients with STEMI (23).

As an effective treatment for patients with acute ACS, the use of PCI therapy can increase the rate of open blocked blood vessels, and improve myocardial reperfusion, but the operation is easy to cause platelet activation, and ischemia-reperfusion injury can induce platelet activation, and compound body/local inflammatory response (24). Once a sustained severe inflammatory reaction occurs, it will promote the necrosis of cardiomyocytes and cardiac remodeling, and then cause a series of adverse cardiovascular events, delay the prognosis of patients, increase the cost of treatment, and increase the psychological and economic burden of patients. Hs-CRP, an acute relative protein, is synthesized in hepatocytes. Its level increases within a few hours after the onset of inflammation reaches a peak within 45 hours, and gradually returns to a normal level as the lesion resolves. At present, the detection of hs-CRP has been applied more and more widely in clinical practice, such as diagnosing acute infectious diseases, monitoring postoperative infection, observing the efficacy of antibiotics, and judging the prognosis (25). At the same time, it has also become an independent risk factor for assessing the prognosis of cardiovascular diseases, especially acute coronary syndrome, myocardial infarction, stroke, stable coronary artery disease, and other diseases, which is a powerful and predictive risk factor. IL-6 is a kind of interleukin, produced in a variety of cells, such as epithelial cells, keratinocytes, monocyte/macrophage, T lymphocytes, and B lymphocytes (26). It stimulates and participates in the immune response of cell proliferation, and differentiation, and can elevate enhanced immune function. At the same time, it also can facilitate the production of inflammatory cytokines along with inducing an inflammatory cascade reaction (27). Some studies have pointed out that IL-6 has a good predictive role in PCI in patients with acute ACS, which is convenient for doctors to detect and manage adverse cardiovascular events in time (28). In our study, it was found that the levels of hs-CRP, IL-6 along with other indicators in the observation group declined compared to those in the control group one week after treatment and four weeks after follow-up (P < 0.05 and P < 0.01), indicating that PCSK9 inhibitor elozumab had a higher effect on reducing the level of inflammatory indicators than rosuvastatin, namely reducing inflammatory reaction, improving symptoms and reducing adverse cardiovascular events, which was consistent with former studies (29). Likewise, PCSK9 inhibitors have been proven to exert anti-inflammation function in cardiovascular diseases (30).

This study probed the clinical efficacy of PCSK9 inhi-

bitors in ACS patients after PCI. The results showed that on the basis of statin treatment, the differences in serum lipid indexes in the observation group were statistically significant compared with the control group. In the first week of treatment, the LDL-C compliance rate of the observation group was 81.73%, whereas that of the control group was 20.19%. In the fourth week of treatment, the LDL-C compliance rate of the observation group was 91.35%, while that of the control group was only 28.83%. There was a significance in the LDL-C compliance rate between the two groups, but at the first and fourth weeks, no difference was found in the LDL-C compliance rate of the observation group. These results demonstrated the use of statins combined with PCSK9 inhibitors could achieve LDL-C target rapidly and stably, which was more beneficial to improve the prognosis of patients. Consistently, previous literatures have also indicated that the LDL-C compliance rate was significantly increased in the statins combined with PCSK9 inhibitors group compared with the control group (31). Additionally, the total effective rate of the observation group was 91.35%, which was increased compared to the control group of 83.65%, but the difference was not significant. This may be due to the small sample size and short duration of medication in this study, and the experimental results may be biased. At the same time, no difference was observed in the incidence of cardiovascular events of the two groups. No increase was discovered in major clinical adverse reactions in the two groups. All these data suggested that the combination of statins and PCSK9 inhibitors in the treatment of ACS patients undergoing PCI could play a synergistic role, with significant therapeutic effect, and will not increase the risk of cardiovascular events in patients, with fewer adverse reactions and higher safety. Consistently, it has been documented that the addition of PCSK9 inhibitors can enhance lipid-lowering, increase the patient's LDL-C compliance rate in the short term, and improve cardiovascular prognosis but will not increase adverse reactions in patients with extremely high-risk ACS (32).

There are some deficiencies and limitations in this study. Currently, the number of cases studied is only 208, and the follow-up time is only half a year. It is necessary to increase the number of cases studied in the next trial study, prolong the follow-up time, as well as continue to improve the detection of relevant indicators.

In summary, statins combined with PCSK9 inhibitors significantly reduced LDL-C levels in ACS patients undergoing PCI without increasing cardiovascular events or major adverse clinical effects. As a novel lipid-lowering target, PCSK9 will attract more and more attention, which can provide an updated perspective for lipid-lowering therapy and is a treatment method worthy of promotion.

Informed Consent
The authors report no conflict of interest.

Availability of data and material
We declared that we embedded all data in the manuscript.

Authors' contributions
SL conducted the experiments and wrote the paper; YZ and GQ analyzed and organized the data; LY conceived, designed the study and revised the manuscript.

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