Effect of Alirocumab on Coronary Plaque in Patients With Coronary Artery Disease Assessed by Optical Coherence Tomography

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Research Article

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Effect of alirocumab on coronary plaque in patients with coronary artery disease assessed by optical coherence tomography

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Abstract

Background: Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors have been demonstrated with significant greater reduction of LDL cholesterol levels and cardiovascular events, compared with standard statin therapy. However, the evidence on the impact of PCSK9 inhibitors on coronary plaque composition and morphology are limited.

Methods: In this prospective, open-label, randomized study, eligible patients with intermediate coronary lesions and elevated LDL cholesterol values were randomized to either alirocumab 75 mg Q2W plus statin therapy (alirocumab arm) or statin therapy (standard care arm). Optical coherence tomography (OCT) assessment for target lesions were obtained at the baseline and at 36 weeks of follow-up.

Results: LDL cholesterol levels were significantly decreased in both alirocumab arm and standard care arm, whereas the absolute reduction of LDL cholesterol was significantly greater in patients with alirocumab (1.72±0.51 vs 0.96±0.59, P<0.0001). Compared with standard statin therapy, the addition of alirocumab to statins was associated with significant greater increase in minimum fibrous cap thickness (18.0 [10.8- 29.2]um vs 13.2 [7.4-18.6]um; P=0.029), minimum lumen area (0.20[0.10-0.33]mm^2 vs 0.13 [0.12-0.24]mm^2; P=0.006) and greater diminution in maximum lipid arc (15.1˚ [7.8 -24.5] vs. 8.4˚ [2.0 -10.5]; P=0.008).

Conclusions: The addition of alirocumab to statins can not only provide additional LDL cholesterol lowering effect but also have a potential role in promoting a more stable plaque phenotype.

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Keywords: coronary artery disease; PCSK9 inhibitors; statins; coronary plaque; optical coherence tomography

Introduction

Low-density lipoprotein (LDL) cholesterol lowering therapy with statins is the cornerstone for effective treatment of coronary artery disease [1, 2]. However, a substantial proportion of patients cannot achieve target LDL cholesterol levels or tolerate effective doses despite treated with statin therapy [3, 4]. In fact, markedly increased residual cardiac risks were observed in this population [1]. Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors in addition to statins have been demonstrated with significant greater reduction of LDL cholesterol levels as well as decreased incidence of adverse cardiovascular events, compared to statin therapy alone [5-7].

Recently, a series of intravascular ultrasound (IVUS) studies have demonstrated that adding PCSK9 inhibitors on top of statins achieved significantly greater percentage of atheroma volume regression [8-10]. Besides atheroma burden, fibrous-cap thickness is also an important indicator of plaque vulnerability [11,12]. However, due to the limited spatial resolution of IVUS, the influence of PCSK9 inhibition on fibrous-cap thickness cannot be assessed in these previous studies. Although the efficacy of LDL cholesterol lowering therapy on reducing coronary atheroma burden and increasing fibrous-cap thickness has been well established with statins [13,14], it remains unclear whether adding PCSK9 inhibitors to statins could further improve the thickness of fibrous-cap in coronary plaque. Optical coherence tomography (OCT) is currently the golden standard on evaluation of small changes in the fibrous-cap thickness [15,16]. Therefore, the aim of our study is to evaluate the impact of PCSK9 inhibitors plus statins on fibrous-cap thickness in patients with intermediate coronary lesions by OCT imaging.

Methods

The study is a prospective, open-label, single-center, randomized study involving patients with intermediate coronary lesions (50%-70% diameter stenosis) and who have elevated LDL cholesterol values despite stable statin therapy. From Mar 2019 to Jan 2020, all consecutive patients hospitalized for coronary angiogram and received OCT imaging measurement in An Zhen hospital (Beijing,

China), which is a teaching hospital performing over 15000 percutaneous coronary intervention procedures each year, were evaluated. Eligible patients included those who were (I) 18 – 80 years of age, (II) diagnosed as stable coronary artery disease or acute coronary syndrome on admission (III) undergoing clinically indicated coronary angiography and identified with at least one intermediate lesion (50%-70% diameter stenosis) on de novo coronary arteries, (IV) have an elevated LDL cholesterol values (LDL cholesterol ≥1.81 mmol/L [≥70 mg/dL] for patients with acute coronary syndrome [ACS] or ≥2.59 mmol/L [≥100 mg/dL] for non-ACS patients) despite taken rosuvastatin 10 mg/day or atorvastatin 20 mg/day for 2-4 weeks after initiation or with maximally tolerated statin therapy, (V) able to provide written, informed consent. Study exclusion criteria are listed in Table 1.

The study included a 36-week open-label treatment period (including post-treatment OCT imaging), starting within 4 weeks of baseline coronary angiogram (Figure. 1). During the open-label treatment period, patients were randomized 1:1 to either alirocumab arm or standard care arm. Patients in the alirocumab arm received alirocumab 75 mg Q2W on top of statin therapy (atorvastatin 20 mg/day or rosuvastatin 10mg/day). The last dose of alirocumab were given at week 34. Patients in the standard care arm continued to receive atorvastatin 20 mg/day or rosuvastatin 10 mg/day. Statin dose escalation or adding other concomitant non-statin lipid-lowering therapy could be considered by their responsible physician to achieve target LDL cholesterol levels. Antithrombotic therapy and other concomitant medications were exclusively decided by the responsible physicians. Follow-up coronary angiograms and OCT imaging analyses of the same vessels were carried out at the end of treatment period (at week 36 ± 2 weeks, depending on patient availability) in both study arms. Regular medical examination and laboratory tests were conducted at weeks 4, 12 and 36. All enrolled patients were monitored and evaluated for safety and any other adverse events during the study period. The study was approved by the local medical ethics committee, and informed consent was obtained from each patient.

Optical coherence tomography

OCT images were obtained at the baseline and at week 36 ± 2 weeks follow-up. Optical frequency domain imaging systems (Ilumien or Optis Imaging System™, Abbott Vascular, USA) were used.

The imaging catheter was advanced 10mm distal to the target lesions. Contrast injection was previously tested to ensure a complete wash-out of the vessel lumen. All imaging analysis was performed by an independent investigator who was blinded to the study protocol. The baseline and follow-up OCT images were reviewed to match the target lesions based on the distance from landmarks (e.g. branching sites and calcifications). Calibration was applied before OCT image analysis. Values of minimal lumen area, minimal fibrous cap thickness, and maximal lipid arc were measured. The target plaque was characterized using previously validated criteria [17]. The minimum lumen area in each target lesion was calculated by an automated measurement algorithm and manual corrections. Minimum fibrous cap thickness was determined as the smallest fibrous cap thickness in the three candidate frames selected by manual screening. Maximum lipid arc was determined as the largest lipid arc from the center of the lumen in the three candidate frames selected by manual screening. The entire length of the target lesions and adjacent segments (5 mm proximal and distal) were evaluated at 1 mm intervals.

Study endpoints

The primary endpoint of the study was the OCT derived changes in minimum fibrous-cap thickness between the baseline and follow-up. Secondary endpoints included the changes in minimum lumen area between the baseline and follow-up, as well as the absolute changes in maximum lipid arc. In addition, the incidence of cardiac death, myocardial infarction (defined according to the fourth universal definition of myocardial infarction) [18], ischemia-driven target-lesion revascularization, major adverse cardiac events (defined as the composite outcome of death, myocardial infarction, and ischemia-driven target-lesion revascularization), and treatment related adverse reactions during the follow- up period were recorded as well.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are reported as counts and percentages. Distribution was assessed for each variable with the Kolmogorov-Smirnov test. Comparison of continuous variables between the two groups were performed using the Mann–Whitney U test or the unpaired Student t test depending on their distributions. Continuous variables between the baseline and follow-up were

compared by 1-sample Student t tests or the Wilcoxon signed rank test accordingly. Categorical variables were compared by chi-squared or Fisher's exact test. A two-tailed p-value < 0.05 was regarded as statistically significant. The IBM SPSS Statistics 25.0 package was used.

Results

A total of 61 eligible patients (31 patients in the standard care arm and 30 patients in the alirocumab arm) with complete clinical and OCT imaging follow-up were analyzed. Nearly half of the patients (15/31) in the standard care arm received ezetimibe and statin combination therapy. The clinical characteristics were listed in Table 2. Of note, patients were predominantly male and had a high prevalence of cardiovascular risk factors. Both groups demonstrated a high rate of prescription of guidelines recommended medical therapies. All the participants were prescribed with antiplatelet therapy, and approximately 90% of them were treated with beta blockers. The baseline and procedural characteristics were not statistically significantly different between the two groups.

Biochemical measures throughout the study were summarized in Table 3. At baseline, no significant differences were observed between the standard care arm and the alirocumab arm. At 36 weeks, LDL cholesterol levels were significantly decreased in both groups compared with baseline, from 3.18 mmol/L to 2.22 mmol/L (P<0.0001) in standard care arm, and from 3.04 mmol/L to 1.32 mmol/L in alirocumab arm (P<0.0001), respectively. However, the absolute changes of LDL cholesterol levels were significantly higher in patients with alirocumab (1.72±0.51 vs 0.96±0.59, P<0.0001). In addition, patients in alirocumab arm demonstrated favorable changes in triglycerides levels, but it did not attain statistical significance. C-reactive protein (CRP) levels decreased in both groups, but no significant difference was observed between the groups.

OCT-derived baseline parameters did not significantly differ between the two groups (Table 4). However, at 36 weeks follow-up, a significant greater increase in the changes of minimum fibrous cap thickness (18.0 [10.8- 29.2]um vs 13.2 [7.4-18.6]um; P=0.029) and the changes of minimum lumen area (0.20[0.10-0.33]mm^2 vs 0.13 [0.12-0.24]mm^2; P=0.006) were observed in the alirocumab group compared to the standard care group. Similarly, the absolute changes of maximum

lipid arc were also significantly greater in the alirocumab group compared to the standard care group (15.1° [7.8 -24.5] vs. 8.4° [2.0 -10.5]; P=0.008). Additionally, patients in alirocumab arm demonstrated a numerically greater but not statistically significant reduction in the percentage of TACF compared to those in standard care arm (3.3% vs 16.1%; P=0.09).

No death or myocardial infarction event was found in either alirocumab or standard care arm (Table 5). However, there was 1 ischemia driven target lesion revascularization occurred in the standard care arm, but not in the alirocumab arm. Treatment-related adverse reactions were reported at generally similar frequencies in both groups. Nasopharyngitis (SoC: 1 patient; alirocumab: 2 patients) was the most common reaction. In total, 2 (6.7%) patients in the alirocumab group experienced local injection-site reaction. All the treatment-related adverse reactions found in this study were classified as mild in intensity, and all the participants were tolerated to continue to receive study treatment.

Discussion

The results of our study indicated that the addition of alirocumab to statins was associated with significant greater reduction of LDL cholesterol levels, greater increase in fibrous cap thickness, and greater diminution in maximum lipid arc, compared with standard statin therapy.

The effect of lipid lowering therapy on the atheroma plaque morphology was initially established in statin trials [19]. Coronary plaque regression can be achieved when the decrease in LDL cholesterol level exceeded 50% due to the treatment of statins [20]. However, our previous epidemiology study indicated large numbers of patients cannot achieve enough LDL cholesterol reductions despite treated with statin therapy [3]. PCSK9 inhibitors are novel pharmacologic agents, and it has been shown that the addition of a PCSK9 inhibitor to statins can further reduce LDL cholesterol levels by 43 to 64% [21]. However, the evidence on the impact of PCSK9 inhibitors on atheroma plaque composition and morphology was limited. The ODYSSEY J-IVUS trials showed that the addition of alirocumab to statins resulted in a trend of greater reduction in total atheroma volume, but it did not attain statistical significance due to limited sample size and treatment duration

[10]. The GLAGOV trial, on the other hand, reported a significant reduction on atheroma volume by lowering LDL cholesterol to the level of 36 mg/dL with 76 weeks treatment of evolocumab plus statins [8]. However, the GLAGOV trial showed that the addition of evolocumab did not produce differential changes in plaque composition compared with statin monotherapy by IVUS assessment. While in these two studies the addition of PCSK9 inhibitors have been shown to reduce plaque burden, there is a gap of evidence regarding the impact of PCSK9 inhibition on changes of other presumed vulnerable plaque features, for instance, fibrous cap thickness. OCT imaging analysis, which provides a detailed image of ten times greater resolution than that achieved with IVUS, is the ideal imaging modality to assess the fibrous cap thickness of coronary plaque [16,22]. In a recent retrospective, observational OCT study revealed that compared to statin monotherapy, statin plus evolocumab provided a greater increase in fibrous-cap thickness of coronary plaques in patients with recent acute coronary syndrome [23]. The results of our study were consistent with the previous findings and we demonstrated a significant greater increase in minimum lumen area in the alirocumab arm assessed by OCT imaging. Notably, the addition of alirocumab to statins was associated with significant greater increase in fibrous cap thickness, and greater reduction in maximum lipid arc, compared with standard statin therapy. The current results indicated that the addition of alirocumab to statins can not only provide additional LDL cholesterol lowering effect but also have a potential role in promoting a more stable plaque phenotype.

Interestingly, our study observed no incremental reduction in CRP with treatment of alirocumab. These findings provide additional evidence suggesting that the effects of PCSK9 inhibition are exclusively due to favorable effects on lipids. Although statins have demonstrated with pleiotropic effects and CRP lowering associated with benefits on plaque regression [24,25] and cardiovascular events risks [26], PCSK9 inhibitors have not yet been reported with a similar effect.

There are potential limitations to our study. The first major limitation of our study is the relatively small number of patients and the short treatment duration for follow-up OCT. Another important limitation is that there is no compelling evidence demonstrating a direct relationship between the increase of fibrous-cap thickness by OCT and the improvements on adverse cardiovascular events. However, there is a series of pathological research demonstrate that the thickness of the fibrous cap

is a major determinant of plaque vulnerability [11,27]. Furthermore, it is well acknowledged that OCT-based thin-cap fibroatheroma is associated with the presence of high-risk features evaluated by other imaging modalities such as virtual histology intravascular ultrasound [28], all of which have a strong link to future adverse clinical events [22,29]. Therefore, to date the thickening of the fibrous cap has been considered as the representation of coronary plaque stabilization [30-33]. Further studies are needed to clarify the clinical implications of the changes in fibrous cap thickness measured by OCT.

Abbreviations

LDL: Low-density lipoprotein; PCSK9: proprotein convertase subtilisin kexin type 9; IVUS: intravascular ultrasound; OCT: optical coherence tomography; ACS: acute coronary syndrome; CRP: C-reactive protein

Declarations

Ethics approval and consent to participate

The study protocol was approved by Ethics Committee of Beijing Anzhen Hospital, Capital university and all participants provided written informed consent. The study was performed in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None.

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Authors' contributions

F Gao and Y J Zhou were in charge of the study design and management. H Shen were responsible for the data resources and integrity. Z J Wang and X T Ma conducted the OCT Imaging analysis. L X Yang helped with data management and statistical analysis. F Gao analyzed the data and drafted the manuscript. The authors read and approved the final manuscript.

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Table legend

Table 1. Exclusion criteria
Table 2. Baseline characteristics
Table 3. Biochemical parameters
Table 4. OCT -derived study endpoints
Table 5. Clinical events

Table 1. Exclusion criteria

Exclusion criteria
Known hypersensitivity or contraindications to alirocumab and/or statin therapy
Received balloon angioplasty or stent implantation for target lesion
Unable to conduct OCT imaging analysis
Prior usage of PCSK9 inhibitors
Severe renal dysfunction (creatinine clearance <30 mL/min)
Severe hepatic dysfunction
Baseline triglyceride > 400 mg/dl
History of hemorrhagic stroke
Pregnant or breast-feeding women
Life expectancy < 1 year
Inappropriate for the study for any reason based on the investigators' judgement

Table 2. Baseline characteristics

	Standard of care (N=31)	Alirocumab (N=30)	P Value
Age, yrs	61.3±9.9	61.3±8.9	0.97
Male	74.2 (23)	66.7 (20)	0.52
Diabetes	25.8 (8)	23.3 (7)	0.82
Current smoker	25.8 (8)	30 (9)	0.72
Hypertension	61.3 (19)	56.7 (17)	0.71
Prior MI	9.7 (3)	13.3 (4)	0.65
Prior stroke	3.2 (1)	10.0 (3)	0.28
ACS	41.9 (13)	36.7 (11)	0.67
Antiplatelet	100 (31)	100 (30)	-
Beta-blocker	90.3 (28)	93.3 (28)	0.67
ACEI/ARB	64.5 (20)	60.0 (18)	0.72
Chronic statin before enrollment	32.3 (10)	26.7 (8)	0.63
Imaged artery			
Left anterior desending	41.9 (13)	43.3 (13)	0.91
Left circumflex	22.6 (7)	26.7 (8)	0.71
Right coronary	32.2 (10)	30.0 (9)	0.85
Others	3.2 (1)	0	0.32

Table 3. Biochemical parameters

	Standard of care (N=31)	Alirocumab (N=30)	P Value
LDL cholesterol, mg/dl			
Baseline	3.18±0.97	3.04±0.78	0.54
After 36 weeks treatment	2.22±0.69	1.32±0.39	<0.0001
Changes from baseline	-0.96±0.59	-1.72±0.51	<0.0001
HDL cholesterol, mg/dl			
Baseline	1.30±0.41	1.41±0.61	0.42
After 36 weeks treatment	1.38±0.43	1.48±0.47	0.34
Changes from baseline	0.08±0.36	0.07±0.38	0.86
Triglycerides, mg/dl			
Baseline	1.56 (1.19 to 2.38)	1.84 (1.19 to 2.56)	0.66
After 36 weeks treatment	1.53 (1.09 to 2.26)	1.54 (1.00 to 2.09)	0.68
Changes from baseline	-0.05 (0.64 to 1.42)	-0.29 (-0.96 to 0.35)	0.077
CRP, mg/l			
Baseline	1.62 (0.90 to 3.00)	1.69 (0.75 to 3.37)	0.80
After 36 weeks treatment	1.10 (0.89 to 2.50)	1.59 (0.92 to 2.61)	0.64
Changes from baseline	0.54 (-0.46 to 1.34)	0.12 (-0.74 to 1.08)	0.50

Table 4. OCT -derived study endpoints

	Standard of care (N=31)	Alirocumab (N=30)	P Value
Minimum fibrous cap thickness, um			
Baseline	116.4 (90.1 to 136.2)	126.0 (87.5 to 145.5)	0.44
After 36 weeks treatment	124.2 (98.2 to 144.3)	144.0 (111.5 to 151.8)	0.049
Changes from baseline	13.2 (7.4 to 18.6)	18.0 (10.8 to 29.2)	0.029
Maximum lipid arc, degree			
Baseline	110.9 (90.2 to 132.4)	109.6 (89.8 to 130.0)	0.53
After 36 weeks treatment	102.2 (87.0 to 123.1)	93.5 (77.5 to 108.1)	0.19
Changes from baseline	-8.4 (-2.0 to -10.5)	-15.1 (-7.8 to -24.5)	0.008
Minimum lumen area, mm^2			
Baseline	2.47 (2.20 to 2.74)	2.32 (2.07 to 2.63)	0.22
After 36 weeks treatment	2.60 (2.19 to 2.90)	2.57 (2.27 to 2.90)	0.77
Changes from baseline	0.13 (0.12 to 0.24)	0.20 (0.10 to 0.33)	0.006
TACF, %(n)			
Baseline	25.8 (8)	20.0 (6)	0.59
After 36 weeks treatment	16.1 (5)	3.3 (1)	0.09

Table 5. Clinical events

	Standard of care (N=31)	Alirocumab (N=30)
Adverse cardiac events		
Cardiac death	0	0
Myocardial infarction	0	0
Ischemia driven target lesion revascularization,	1	0
Treatment-related adverse events		
Nasopharyngitis	1	2
Injection-site reaction	0	2
Back pain	0	1
Transaminase elevation	1	1

Figures

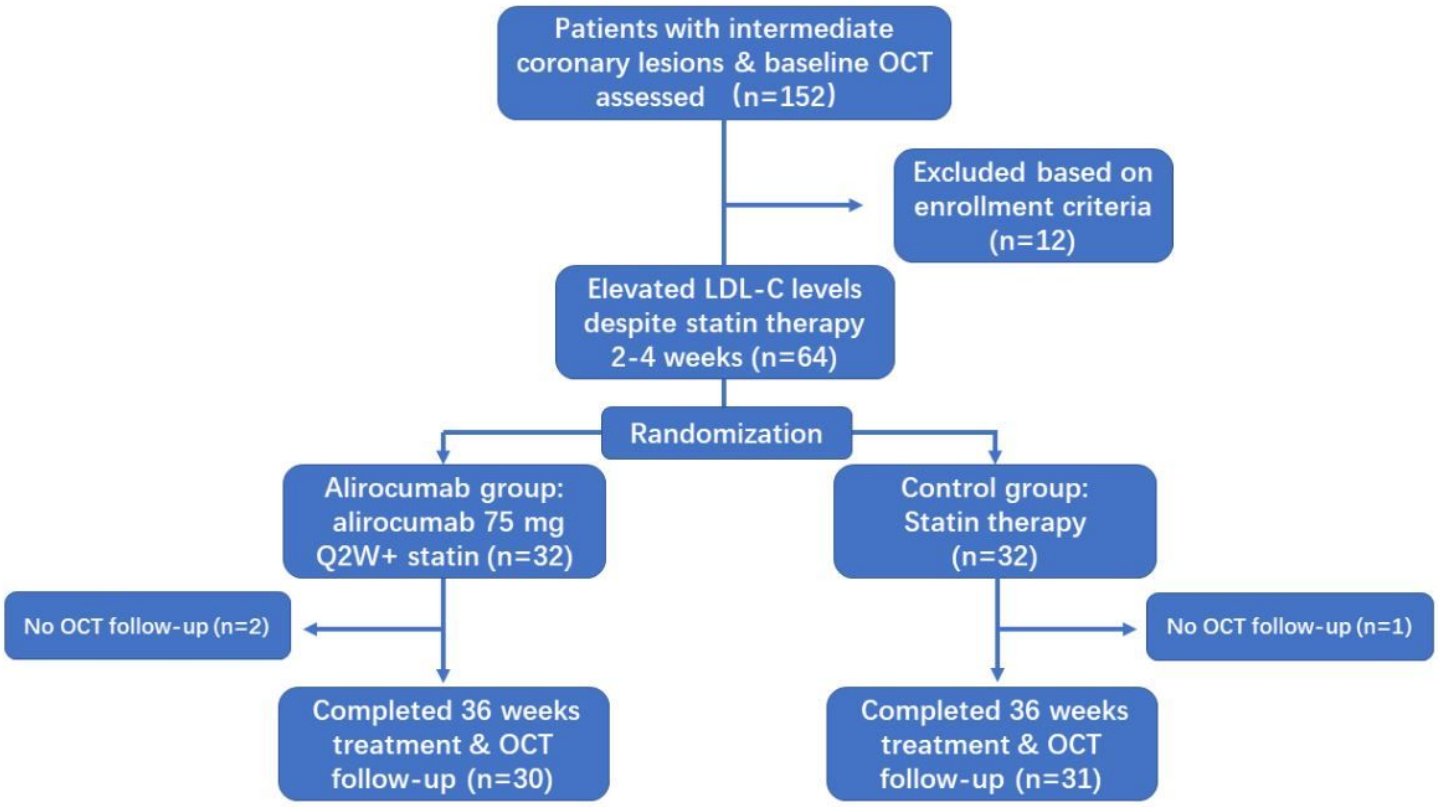

Figure 1

The study included a 36-week open-label treatment period (including post-treatment OCT imaging), starting within 4 weeks of baseline coronary angiogram (Figure. 1)