Lipid lowering effects and safety of evolocumab in Chinese patients at very high cardiovascular risk: a single-center study

Meng Chai[1], Haitao Zhang[2], Lixia Yang[1], Jing Liang[1], Hongya Han[1], Xiaoli Liu[1], Xiaoteng Ma[1], Yan Liu[1], Dongmei Shi[1], Yingxin Zhao[1], Yuyang Liu[1], Yujie Zhou[1]

[1]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart Lung and Blood Vessel Disease, Beijing Key Laboratory of Precision Medicine of Coronary Atherosclerotic Disease, Clinical Center for Coronary Heart Disease, Capital Medical University, Beijing 100029, China;
[2]Department of Cardiology, Air Force Medical Center, Beijing 100142, China.

Low-density lipoprotein cholesterol (LDL-C) is an independent risk factor for atherosclerotic cardiovascular disease (ASCVD). Even after lipid-lowering therapy (LLT) with statins or statin–ezetimibe, a large proportion of patients at very high risk still do not reach the LDL-C targets (<1.4 mmol/L and ≥50% reduction).[1,2] Proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) is recommended for patients at high or very high cardiovascular risk in whom LDL-C reduction is not adequate with statin therapy or in those with statin intolerance. Limited data are available regarding the use of PCSK9i in China. Evolocumab, a PCSK9i, was approved as the first PCSK9i of its kind in China in 2019. However, there remains a paucity of real-world evidence for evolocumab use in the treatment of high-risk patients in China, exploring its efficacy and tolerance. This study aimed to report the results of evolocumab administered to very high-risk patients ($n = 63$) but did not achieve adequate LDL-C reductions with statins in a real-world setting at a single-center practice.

This study was approved by the Capital Medical University Clinical Research Ethics Committee (No. 2023049X), the written inform consent was obtained from all the participants. The patients from our hospital's Cardiology who received at least one prescription of evolocumab (140 mg) between March 2019 and January 2020 were considered for retrospective analysis. "Very high-risk" was defined according to the 2019 ESC/EAS dyslipidemia guidelines, including patients with documented ASCVD, diabetes with target organ damage, familial hypercholesterolemia with ASCVD or with another major risk factor, epidermal estimated glomerular filtration rate <30 mL·min^{-1}·1.73 m^{-2}, or calculated systematic coronary risk estimation >10%.[1] The inclusion criteria were very high-risk status and failure to achieve a goal LDL-C level of <1.4 mmol/L despite statin therapy for at least 4 weeks. Subjects without baseline values were excluded from the analysis.

Information regarding demographic characteristics, clinical comorbidities, ASCVD history, LLT use at baseline, pre- and post-treatment cholesterol levels, evolocumab-related side effects, and evolocumab compliance and adherence was obtained from the patients' medical records or telephone consultation. The statin therapy was divided into high-intensity (atorvastatin 40–80 mg or rosuvastatin 20 mg) and moderate-intensity (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, fluvastatin 80 mg, pravastatin 40 mg, or simvastatin 20–40 mg).

Patients initially received evolocumab at a dose of 140 mg every 2 weeks (140 mg Q2W). Follow-up was estimated as the period between the first prescription (baseline) and 6 months after the prescription. Treatment discontinuation was defined as the presence of a gap >30 days between the last prescription and the end of follow-up. The lipid profile along with transaminase and creatine kinase (CK) levels were recorded during follow-up visits at the outpatient clinic or examined and recorded in local hospitals. Baseline lipid profiles before therapy were compared with those obtained at 1, 3, and 6 months of treatment.

Data analyses were performed using R statistical software (version 3.6.3; R Foundation, Vienna, Austria). The normality of variable distributions was assessed using the Kolmogorov–Smirnov test. Continuous data are described as mean ± standard deviation or median (interquartile range) where appropriate, and categorical variables as numbers (percentages). Associations between continuous data were tested using Student's t-test or Mann–Whitney U test. The χ^2 test was used for categorical variables. Missing data were not imputed. Statistical significance was set at $P < 0.05$.

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Correspondence to: Yujie Zhou, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, No.2 Anzhen Road, ChaoYang District, Beijing 100029, China
E-Mail: azzyj12@163.com

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The median age of the patients was 58 years and 81.0% were men. At baseline, most patients received moderate-intensity statin therapy and 16 were prescribed statins plus ezetimibe [Supplementary Table 1, http://links.lww.com/CM9/B197]. The median baseline LDL-C level was 2.75 mmol/L [Supplementary Table 2, http://links.lww.com/CM9/B197].

LDL-C was reduced for the entire study group from baseline to 1, 3, and 6 months after evolocumab application by 62.50 ± 31.37%, 49.56 ± 36.83%, and 45.34 ± 30.25%, respectively [Figure 1A]. Significant reductions in non-HDL-C, triglyceride, and total cholesterol values were also observed from baseline to 6 months ($P < 0.05$). There was a major increase in HDL-C levels at 6 months of treatment ($P < 0.05$) [Supplementary Table 2, http://links.lww.com/CM9/B197]. Nevertheless, there was no apparent difference in Lp(a) levels before and after treatment. Furthermore, liver and muscle enzyme levels were similar before and after therapy.

The overall percentages of patients who achieved an LDL-C goal of <1.8 mmol/L or ≥50% reduction at 1, 3, and 6 months after evolocumab therapy were 85.5% (47/55), 67.4% (29/43), and 60.0% (24/40), respectively. Moreover, 72.7% (40/55) of the patients at 1 month, 53.5% (23/43) at 3 months, and 40.0% (16/40) at 6 months of treatment attained the goal of LDL-C <1.4 mmol/L and 50% reduction [Supplementary Table 3, http://links.lww.com/CM9/B197].

One patient received evolocumab as monotherapy and lowered LDL-C levels by 40% at 3 months of treatment (baseline LDL-C value, 1.85 mmol/L; at 3 months, 1.11 mmol/L). The remaining 62 patients received evolocumab in combination with other LLT therapy and an obvious LDL-C reduction was found at 1 month (1.02 ± 0.79 mmol/L), 3 months (1.42 ± 0.84 mmol/L), and 6 months (1.65 ± 0.88 mmol/L) compared with baseline LDL-C value (2.96 ± 1.09 mmol/L) [Figure 1B].

Of the 63 patients, 9 (14.3%) were maintained 140 mg Q2W throughout the 6-month follow-up. In this subgroup, the evolocumab treatment led to a mean decrease in LDL-C from 2.77 ± 0.84 mmol/L to 1.29 ± 0.77 mmol/L at 1 month, 1.35 ± 0.63 mmol/L at 3 months, and 1.04 ± 0.35 mmol/L at 6 months of treatment [Figure 1C]. Based on the physicians' clinical judgment, the original dosing frequency of 140 mg Q2W was switched to 140 mg Q3W in eight (12.7%) patients during a 6-month follow-up. Switching dosing schedules to Q3W led to a marked elevation of LDL-C levels in the majority of these eight patients [Figure 1D].

Five patients were lost to follow-up. The mean duration of evolocumab use was 4 months in these 63 patients. Twenty-seven patients (42.9%) discontinued evolocumab over the 6 months: 19 patients because of high cost, four patients due to LDL-C being too low as per the physicians' judgment, one because of surgery, one because of low blood pressure, one because of lack of efficacy, and one

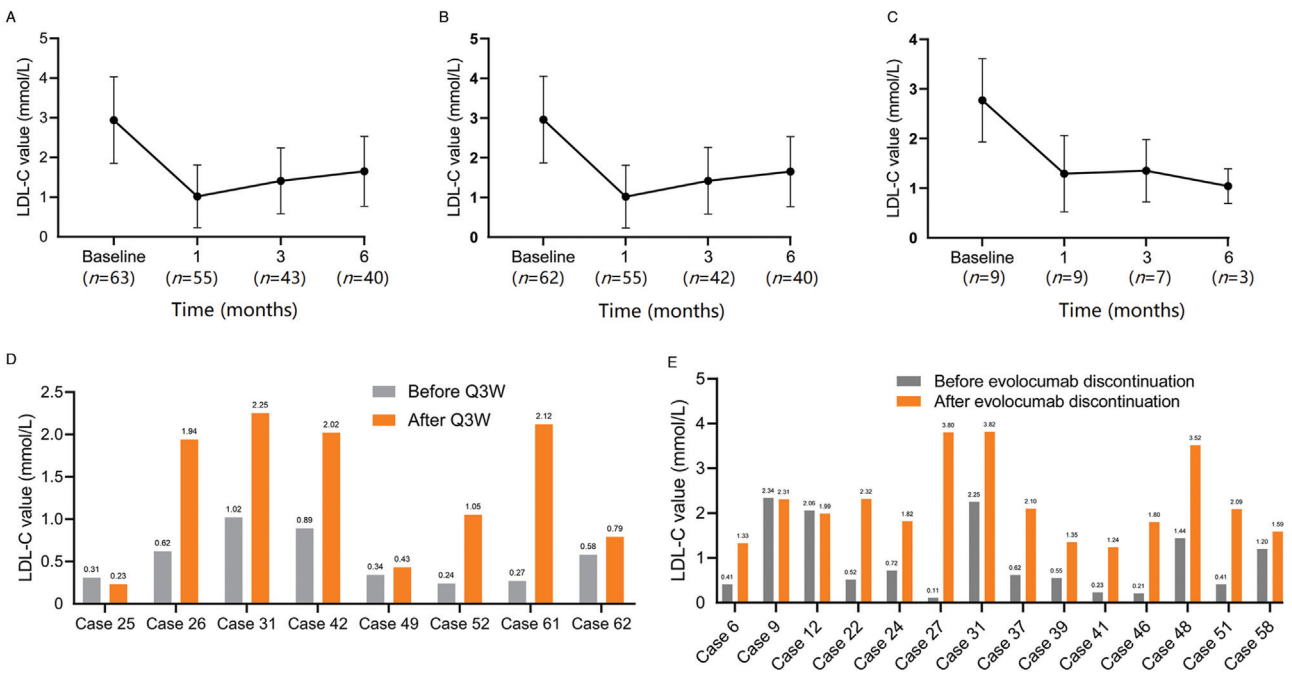

Figure 1: Effect of evolocumab on LDL-C profile. (A) LDL-C changes for 63 patients from baseline to 1, 3, and 6 months after evolocumab application. (B) LDL-C changes in 62 patients who received evolocumab in combination with other LLT therapy. (C) LDL-C changes in nine patients maintained on Q2W dose regimen. Plot is based on observed data, and missing data were not imputed. (D) LDL-C changes in eight patients switching dose schedules to Q3W from Q2W. The two LDL-C values of each patient were respectively taken from the latest available one before (median: 3 days before evolocumab prescribed as Q3W) and after (median: 41 days after evolocumab prescribed as Q3W) Q3W adjustment during the 6-month follow-up period. (E) LDL-C changes of several representative cases before and after evolocumab discontinuation. The two LDL-C values of each patient were respectively taken from the latest available one before (median: 21 days before the last injection of evolocumab) and after (median: 73 days after the last injection of evolocumab) evolocumab discontinuation during the 6-month follow-up period. It is important to note that case 9 received evolocumab 140 mg every month against the doctor's advice; case 31 switched dose schedules to Q3W and then discontinued evolocumab therapy. LDL-C: Low-density lipoprotein cholesterol; LLT: Lipid-lowering therapy.

because of inconvenience or difficulty in accessing the medication. Eight (12.7%) patients received only one or two injections of evolocumab. A marked increase in LDL-C levels after evolocumab discontinuation was observed in most patients [Figure 1E].

Injection-site reactions were reported in two patients, including erythema (one patient) and muscle pain (one patient), but led to short discontinuation of evolocumab therapy in only one patient. There were no significant changes in transaminase and CK levels compared with pretreatment levels in these two patients (data not shown). No other side effects were observed in the study cohort.

Our study cohort included 63 very high-risk patients who failed to achieve the LDL-C goal of 1.4 mmol/L despite statin therapy for at least 4 weeks, illustrating the difficulties clinicians face in reaching their therapeutic goals. Under evolocumab treatment, a notable proportion of patients fulfilled the strict 2019 ESC/EAS LDL-C treatment goal of LDL-C <1.4 mmol/L and ≥50% reduction even though they may need to intensify their lipid-lowering therapies, illustrating the effectiveness of evolocumab in very high-risk Chinese patients. These results should be validated by long-term duration and further follow-up. Notably, the observed data revealed a 52% reduction in LDL-C level at 3 months after evolocumab therapy in combination with conventional LLTs, which was higher than that of evolocumab monotherapy (40%). These results suggest the synergistic effects of evolocumab and conventional LLTs on circulating lipid levels.

In clinical practice, evolocumab was generally well tolerated. The dosing schedule of eight patients was switched to 140 mg Q3W at the discretion of the treating physician mainly because of financial considerations and safety concerns about very low levels of LDL-C lower than the guide-recommended targets of 1.4 mmol/L or lower than 1.0 mmol/L. Further evaluation with longer study periods is important to examine whether extremely low LDL-C levels *per se* may provoke adverse effects.[3] Surprisingly, switching to Q3W led to a marked elevation in LDL-C levels in five of these eight patients, which may be affected by the irregular LDL-C measurement time. A previous study has shown the possible benefits of extending the dosing interval to a 3-week interval to further individualize treatment.[4] Thus, whether a longer dosing interval of evolocumab maintains LDL cholesterol-lowering efficacy warrants further investigation.

Approximately 43% of the patients discontinued evolocumab treatment, due mainly to the high cost and low affordability, making medication persistence challenging.[5] This situation is very similar to the early days when evolocumab was first approved by authorities in North America and Europe before the substantial price reduction.[6] Another common justification for this discontinuation decision included adequate lipid-lowering to achieve LDL-C targets. Clinicians should closely monitor and assess medication adherence and interfere with adequate patient education about medications.

This observational and non-comparative study has some limitations: its retrospective and single-institution nature, loss of precision due mainly to missing of some measured lipid data. The COVID-19 pandemic had a major impact on data collection and patient recruitment. The short duration of the 6-month follow-up may have led to an underestimation of adverse event incidence. The small sample size may not be representative of the results of evolocumab treatment in Chinese patients. Large, multicenter, real-world studies with longer follow-up periods are required.

In conclusion, we describe here our clinical experience with evolocumab prescription in very high-risk Chinese patients and showed similar lipid-lowering effects and safety profiles compared with previous clinical trials. However, a high discontinuation rate primarily due to the high cost and low affordability of evolocumab was reported. Fortunately, evolocumab has been recently included in the 2021 National Reimbursement Drug List, which could improve patients' affordability and access to evolocumab, increasing persistence and adherence. More real-world studies in the future may aid in the treatment of a wider population.

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Conflicts of interest

None.

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