Application of proprotein convertase subtilisin/kexin type 9 inhibitor, evolocumab, in patients with severe hypertriglyceridemia

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To the Editor: The proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitor, evolocumab, can bind with PCSK9 in plasma and reduce the degradation of the PCSK9-low density lipoprotein (LDL) receptor complex, thereby reducing LDL levels.[1] In clinical practice, PCSK9 inhibitors can reduce low-density lipoprotein cholesterol (LDL-c) significantly and reduce triglycerides (TG) by about 8% to 17%.[2] We used PCSK9 inhibitors to lower blood lipids in three patients with severe hypertriglyceridemia (HTG) and performed whole-exome sequencing (WES) to analyze the genes that may contribute to hyperlipidemia in detail. We have obtained patients' consent forms. We found that PCSK9 inhibitors significantly reduced blood lipid levels, regardless of the presence of HTG mutations. These results provide new evidence for the use of PCSK9 inhibitors in the treatment of patients with severe HTG.

Patient 1: A 38-year-old man with a body mass index (BMI) of 30.1 kg/m^2 was admitted to the hospital on June 1, 2020, due to acute coronary syndrome, complicated with hypertension two and type 2 diabetes, and his highest TG level was 29.94 mmol/L. During hospitalization, he was administered fenofibrate and atorvastatin for lipid-lowering. Because of little effect, evolocumab 140 mg biweekly was administered since June 4, 2020. WES revealed two heterozygous mutation sites in the *LPL* gene (rs3735959 and rs316).

Patient 2: A 61-year-old woman with a BMI of 20.7 kg/m^2 was admitted to the hospital repeatedly for acute pancreatitis and HTG since 2003, and her highest TG level was 52.96 mmol/L. She started consuming fenofibrate in 2004 and added atorvastatin in 2017, with poor results. She was additionally treated with evolocumab 140 mg biweekly since May 20, 2019. WES found that its *APOA5* gene has a homozygous mutation site (rs2075291), and the TG-related *LMF1* gene contains multiple mutation sites.

Patient 3: A 40-year-old man with a BMI of 23.9 kg/m^2 was found to have HTG during physical examination in 2015. He was diagnosed with high triglyceride acute pancreatitis (HTG-AP) in 2016 and 2018. He was treated with fenofibrate and simvastatin, to which we added evolocumab 140 mg biweekly administration on December 6, 2019. However, the patient TG levels fluctuated significantly in relation to diet. WES indicated the presence of LMF1 (rs181731943) and *ANGPTL8* (rs192460764) heterozygous mutations.

None of the three patients had evolocumab-related side effects during treatment. The changes in blood lipid levels of the three patients are shown in [Supplementary Figure 1, http://links.lww.com/CM9/A851]. In addition, both patients two and three showed the presence of GPIHBP1 (rs11538388) and APOA5 (rs2266788). All three samples revealed the rs2278426 mutation site of *ANGPTL8*.

According to the new classification criteria for HTG and chylomicronemia,[3] all three cases were considered polygenic chylomicronemia (World Health Organization type 5). In patient one, TG increased mainly due to *LPL* (heterozygous large effector gene) and *ANGPTL8* (small effector gene) mutations, and the addition of evolocumab significantly reduced TG, with a stable decrease of about 70%. Both patients two and three had elevated TG levels due to APOA5, GPIHBP1, and LMF1 (large effector genes) and ANGPTL8 (small effector genes), and the addition of evolocumab significantly reduced TG. In patient two, the therapeutic effect of evolocumab was relatively stable, with a decrease of 41.41% to 71.46%. In patient three, TG was controlled at a low level when the patient had a light diet, and the decrease was approximately 84%. From these three cases, it can be inferred that evolocumab can significantly reduce TG levels even with TG-related gene mutations.

Based on the study of these three cases, we found that in patients with severe HTG, PCSK9 inhibitors had a significant TG-lowering effect, which was different from

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001896

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Chinese Medical Journal 2022;135(6)

Received: 23-04-2021; **Online:** 15-12-2021 **Edited by:** Lishao Guo

the data (8–17%) in the general population (TG <5.65 mmol/L), possibly because of the effect of PCSK9 inhibitors on TG which was related to baseline.[3]

Currently, the common TG-lowering drugs are of three types: statins, *n*–3 fatty acids, and fibrates. However, statins are mainly used to reduce LDL-c, and TG is decreased by 5% to 15%[4]; the cardiovascular benefitof *n*–3 fatty acids is only found in icosapent ethyl, where TG is decreased by 20%[5]; fibrates are not effective for chylomicronemia with genetic mutations; other new TG-lowering drugs are in clinical trials, and no additional benefit beyond TG-lowering has been demonstrated.[4] Therefore, if the PCSK9 inhibitors, which have the effect of lowering LDL-c, can be proven to lower TG, it may broaden its indications for lowering lipids; however, the mechanism of PCSK9 inhibitors in reducing TG and the safety of its application in patients with severe HTG needs to be further studied, and the higher cost may also limit their clinical use.

Conflicts of interest

None.

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How to cite this article: Peng Y, Guo D, Jiang S, Zheng H. Application of proprotein convertase subtilisin/kexin type 9 inhibitor, evolocumab, in patients with severe hypertriglyceridemia. Chin Med J 2022;135:730–731. doi: 10.1097/CM9.0000000000001896