Insights on the efficacy and safety of PCSK-9 inhibitor in Taiwanese patients

Harn-Shen Chen

Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC

Hypercholesterolemia is the major risk factor of cardiovascular diseases and statin is a cornerstone of cholesterol-lowering therapy. Statins are widely used, but some patients need additional cholesterol-lowering to improve their lipid control and require additive or alternative treatment.[1] Second-line for hyper- or dyslipidemias include niacin, ezetimibe, and fibrate, which can significantly improve lipid profiles, while not provide enough evidence of cardiovascular benefit similar to statins. The most investigated innovative drugs are Proprotein convertase subtilisn/kexin 9 (PCSK9) inhibitors. Low-density lipoprotein (LDL) receptors which expressed on hepatocytes bind LDL-cholesterol subsequently decrease LDL-cholesterol concentration in plasma. Then the LDL receptors are recycled and continue LDL-cholesterol uptake.[2] PCSK9 is a regulatory protease and can bind to LDL receptors, induce theirs degradation, prevent them from recycling, and further LDL-cholesterol uptake.[3] The monoclonal antibodies against PCSK9 prevent its binding to LDL receptors, which therefore can continue their uptake-recycle function.[4] As a result, LDL-cholesterol level could be decreased significantly in plasma.

The efficacy of PCSK9 inhibitors in reducing LDL-cholesterol was confirmed by the studies of Alirocumab and Evolocumab in 2015.[5,6] In patients with cardiovascular diseases and LDL-cholesterol higher than 70 mg/dL, Evolocumab on a background of statin therapy lowered LDL-cholesterol levels and reduced the risk of cardiovascular events.[7] Alirocumab therapy also showed the cardiovascular benefits among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy.[8] Therefore, PCSK9 inhibitors have revolutionized LDL-cholesterol-lowering treatment. These drugs are indicated in patients with familial hypercholesterolemia, in patients with cardiovascular disease whose LDL-cholesterol lowering is suboptimal despite maximal-tolerated first-line cholesterol-lowering therapy. In general, PCSK9 inhibitors seem to be safe and well tolerated. The most common side effects of available PCSK9 inhibitors (Evolocumab and Alirocumab) are flu-like myositis (10%), respiratory symptom or infection (8%), and injection-site reactions (6%).[9]

In the current issue of the journal, Chao et al report a subgroup analysis of Taiwanese patients from ODYSSEY KT, a multicenter, double-blind, parallel group, randomized controlled trial, carried out at 27 active sites across Taiwan and South Korea.[10] A total of 116 Taiwanese patients who had hypercholesterolemia at high cardiovascular risk and were receiving maximally tolerated statin were randomized to alirocumab (75 mg every 2 weeks with dose increased to 150 mg at week 12, if LDL-C ≥ 70 mg/dL at week 8) or placebo for 24 weeks. The primary endpoint of the ODYSSEY KT trial was the percent change in LDL-C from baseline to week 24. Safety profiles include treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events, laboratory data, and vital signs.

At week 24, the percent change in calculated LDL-C in the alirocumab group (n = 57) was decrease 51%, whereas that in the placebo group (n = 59) was increased 2.5%. By comparison the overall population, the incidence of TEAEs (alirocumab vs placebo, respectively: Taiwan, 68.4% vs 69.5%; overall, 58.8% vs 61.8%) and serious TEAEs (alirocumab vs placebo, respectively: Taiwan, 21.1% vs 8.5%; overall, 17.5% vs 9.8%) in Taiwanese population was higher in both groups. The incidence of TEAEs was similar between alirocumab and placebo, however, the rate of serious TEAEs was more frequent with alirocumab compared with placebo in Taiwan patients (alirocumab vs placebo, respectively: Taiwan, 21.1% vs 8.5%; overall, 17.5% vs 9.8%).

What is the clinical implications of this study? It is well established that the efficacy of alirocumab in reducing LDL cholesterol was confirmed.[5,6] In the ODYSSEY LONG TERM Trial, the addition of alirocumab (150 mg subcutaneous injection every 2 weeks) to statin therapy resulted in an LDL cholesterol level was 62% lower than the placebo group at week 24.[5] There is also emerged evidence that PCSK9 inhibitor not only decrease LDL cholesterol level, but also might improve cardiovascular outcome in some conditions.[8] In the ODYSSEY OUTCOMES trial, the use of alirocumab to target an LDL cholesterol level of 25 to 50 mg/dL after an acute coronary syndrome resulted in a lower risk of major adverse cardiac events than placebo.[8] Although the high cost of PCSK9 inhibitors, the use of this medication may increase gradually in the few years. The most common TEAEs should be understood in clinical practice. The most common TEAEs in Taiwanese patients observed in this study were nasopharyngitis, upper respiratory infection, headache, diarrhea, dizziness, cough, and injection-site reactions.[10]

Address correspondence: Dr. Harn-Shen Chen, Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: chenhs@vghtpe.gov.tw (H.-S. Chen).

Conflicts of interest: The author declares that he has no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2019) 82: 809-810.

Received August 18, 2019; accepted August 19, 2019.

doi: 10.1097/JCMA.0000000000000183.

From a pharmacoeconomic point of view, PCSK9 inhibitors are currently expensive due to the development of innovative drugs and the needed to investigate the effects on the cardiovascular outcomes. Another concern of PCSK9 inhibitors is the putative negative effect on cognition function. As cholesterol is a component of the central nervous system, some concerns have been raised about the potential neurological side effects of intensive cholesterol-lowering treatment. Moreover, several observation suggested that PCSK9 might play a role in neurogenesis, neuronal migration, and apoptosis. It was postulated that PCSK9 takes part in neurogenesis, post-ischemic recovery of the brain, neuronal migration, and apoptosis.[11] The neurocognitive deterioration after PCSK9 inhibitor treatment may be due to very low cholesterol influence or direct medication effects.

In conclusion, PCSK-9 inhibitors represent a promising option in control of dyslipidemia in high risk of statin-intolerant people. Most of these medication are effective, safe, and well tolerated and we can expect that they will be widely used in the future. Since the longevity of human is prolonged significantly, the preserve the cognitive function will be more and more important. Therefore, I suggest that further studies for PCSK-9 inhibitors should let the cognition in the prescribe end points.

REFERENCES

1. Banach M, Mikhailidis DP. Statin intolerance: some practical hints. *Cardiol Clin* 2018;**36**:225–31.
2. Banach M, Penson PE. What have we learned about lipids and cardiovascular risk from PCSK9 inhibitor outcome trials: ODYSSEY and FOURIER? *Cardiovasc Res* 2019;**115**:e26–31.
3. Chao TH, Hsiao PJ, Liu ME, Wu CJ, Chiang FT, Chen ZC, et al. A subanalysis of Taiwanese patients from ODYSSEY South Korea and Taiwan study evaluating the efficacy and safety of alirocumab. *J Chin Med Assoc* 2019;**82**:265–71.
4. Kasichayanula S, Grover A, Emery MG, Gibbs MA, Somaratne R, Wasserman SM, et al. Clinical pharmacokinetics and pharmacodynamics of evolocumab, a PCSK9 inhibitor. *Clin Pharmacokinet* 2018;**57**:769–79.
5. Mannarino MR, Sahebkar A, Biankoni V, Serban MC, Banach M, Pirro M. PCSK9 and neurocognitive function: should it be still an issue after FOURIER and EBBINGHAUS results? *J Clin Lipidol* 2018;**12**:1123–32.
6. Maxwell KN, Breslow JL. Adenoviral-mediated expression of pcsk9 in mice results in a low-density lipoprotein receptor knockout phenotype. *Proc Natl Acad Sci USA* 2004;**101**:7100–5.
7. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al.; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;**372**:1489–99.
8. Rudenko G, Henry L, Henderson K, Ichtchenko K, Brown MS, Goldstein JL, et al. Structure of the LDL receptor extracellular domain at endosomal pH. *Science* 2002;**298**:2353–8.
9. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al.; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–22.
10. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al.; Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;**372**:1500–9.
11. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al.; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;**379**:2097–107.
12. Shah P, Glueck CJ, Goldenberg N, Min S, Mahida C, Schlam I, et al. Efficacy, safety, low density lipoprotein cholesterol lowering, and calculated 10-year cardiovascular risk reduction of alirocumab and evolocumab in addition to maximal tolerated cholesterol lowering therapy: a post-commercialization study. *Lipids Health Dis* 2017;**16**:19.