LETTER

Cost effectiveness is important, but the clinical effectiveness and safety still needed to be validated

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We agree that currently available human proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (Alirocumab (Praluent) and Evolocumab (Repatha)) are extremely overpriced. Cost effectiveness is important to provide affordable medicines for patients. However, the clinical effectiveness, itself, although recently reported to reduce deaths from cardiovascular disease and show comparable safety compared to placebo via phase III randomized controlled trials, needs to be further validated.

The data of Alirocumab¹ reported that it reduces low-density lipoprotein cholesterol (LDL-C) levels by 62% compared to placebo. In their subgroup analysis, the rate of the LDL-C lowering effect was stratified by increasing baseline LDL-C levels (baseline LDL-C < 100 mg/dL, 100 to <130, 130 to <160, ≥160; LDL-C lowering effect 74.9%, 62.5%, 54.6%, 41.3%; respectively).¹ Various mechanisms regulate statin-resistant hypercholesterolemia, including genetic HMG-CoA reductase polymorphisms, PCSK9 mutations, and accelerated cholesterol absorption in the intestines.² Polymorphisms in NPC1L1 and/or HMGCR, the target sites of ezetimibe and statins, respectively, have approximately the same per unit effect on lowering LDL-C and the risk of coronary heart disease (CHD).³ Additionally, the recent IMPROVE-IT trial showed that ezetimibe combined with statins had beneficial effects on CHD by inhibiting cholesterol absorption.⁴ These data suggest that concurrent usage of ezetimibe, combined with genetic susceptibility, could be a potential confounder.
Although the authors concluded that there are clinical benefits, the data regarding ezetimibe is limited, especially for higher refractory to statin therapy.

In addition, although the clinical results from Evolocumab\(^4\) showed that comparable safety profiles, the higher incidence of neurocognitive disorder during 1 year follow-up periods compared to placebo (Evolocumab 0.9% vs 0.3%\(^4\) and Alirocumab\(^1\) 1.2% vs 0.5%; respectively) should be recognizable with increased vigilance. There are three possible explanations. First, blood brain barrier (BBB) may be damaged under hyperlipidemic condition by oxidized low-density lipoprotein.\(^5\) Diabetes and hypercholesterolemia-associated vascular inflammation may contribute to early breakdown of the brain homeostasis.\(^6\) Increased permeability to lipoproteins and monoclonal antibodies can inhibit neuronal anti-apoptotic effect through \(\beta\)-site APP-cleaving enzyme 1 (BACE1)/amyloid precursor protein (APP)/amyloid \(\beta\) peptide (A\(\beta\)) metabolic pathway.\(^7\) Secondly, apolipoprotein E (ApoE) is expressed in various tissues, with the highest expression in the liver followed by the brain. ApoE interacts with both brain A\(\beta\) oligomer production and A\(\beta\) plaque deposition in an isoform-dependent manner (ApoE4 > ApoE3 > ApoE2).\(^8\) Since ApoE is mainly cleared via LDL receptor, changes in LDL receptor activity induced by PCSK9 inhibitor can contribute to intraneuronal toxicity via various mechanisms including inflammatory and immune modulation.\(^9\) Thirdly, intracellular cholesterol levels are also regulated by cholesterol biosynthesis and the efflux/influx of lipoprotein-bound cholesterol in brain neuronal cells.\(^10\) The excess intracellular cholesterol accumulation by PCSK9 blockade can lead to intracellular lipid accumulation, inflammatory responses, and apoptosis.\(^10\) Therefore, the early manifestations of neurocognitive safety warning signs should not be underestimated.
REFERENCES


