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Original Articles

Update on the use of PCSK9 inhibitors in adults: Recommendations from an Expert Panel of the National Lipid Association

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Abstract: An Expert Panel convened by the National Lipid Association was charged with updating the recommendations on the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody therapy that were provided by the 2015 National Lipid Association Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2. Recent studies have demonstrated the efficacy of these agents in reducing low-density lipoprotein cholesterol and non–high-density lipoprotein cholesterol and have confirmed their excellent safety profile. A cardiovascular outcomes study has shown that these agents reduce incident atherosclerotic cardiovascular disease (ASCVD) events in patents with stable ASCVD and concomitant risk factors. The current update provides the Expert Panel's evidence-based recommendations on the clinical utility of PCSK9 inhibitors in patients with stable ASCVD, progressive ASCVD, LDL-C ≥ 190 mg/dL (including polygenic hypercholesterolemia, heterozygous familial hypercholesterolemia and the homozygous familial hypercholesterolemia phenotype) and very-high-risk patients with statin intolerance.

Introduction

Subcutaneously administered human monoclonal proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody therapy reduces intrahepatic lysosomal degradation of internalized low-density lipoprotein (LDL) receptors, resulting in increased hepatic expression of LDL receptors (LDLRs) and a reduced concentration of circulating LDL cholesterol (LDL-C). The clinical use of these agents has

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been demonstrated to result in marked reduction in circulating LDL-C when given as monotherapy, or as additive therapy to statins, with or without concomitant ezetimibe therapy. Along with other evidence, 2 major PCSK9 inhibitor safety and efficacy studies published in 2015 were used to support the National Lipid Association's (NLA) Part 2 Recommendations on the use of PCSK9 inhibitors. Since that time, 1 study in 2016 evaluating percent atheroma volume and plaque regression by intravascular ultrasound and 1 cardiovascular disease outcomes study in 2017 demonstrated that currently available PCSK9 inhibitors are safe, efficacious in lowering LDL-C, reduce percent atheroma volume, induce plaque regression, and reduce the incidence of adverse cardiovascular outcomes. Additional studies have confirmed their safety and efficacy in lowering atherogenic lipoproteins in patients with LDL-C $\geq$ 190 mg/dL, a group with high or very high atherosclerotic cardiovascular disease (ASCVD) risk. Based on these results, the NLA now provides an update of our recommendations for the clinical use of these medications.

Methodology

A Writing Committee representing original authors of the NLA Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2 (C.E.O., T.A.J., J.L.R., and J.A.U.) and others in the leadership of the NLA was assembled with the objective to update the organization's position on the clinical use of PCSK9 inhibitors. The article was written with contributions from 3 authors (C.E.O., T.A.J., and J.J.S.) and a review for content and suggestions for revision was provided by 4 authors (A.S.B., A.M.G., J.L.R., and J.A.U.). The completed article was then submitted to the NLA Board of Directors, which approved the content of this update.

Grading of the strength of recommendations was made in accordance with the grading system used in the NLA Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2.[1]

The NLA 2015 recommendations for PCSK9 inhibitor therapy: The evidence base

In addition to available mechanistic data,[2,3] the NLA Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2 used 2 major safety and efficacy studies to inform our advice on the early clinical use of these agents. These studies are summarized below.

In 2015, a safety and efficacy trial of the PCSK9 inhibitor, alirocumab (ODYSSEY LONG TERM), enrolled 2341 adult subjects aged $\geq$18 years at high risk for cardiovascular events based on the presence of heterozygous FH (HeFH), established coronary heart disease (CHD), or coronary risk equivalent states.[4] A coronary risk equivalent state was defined as peripheral arterial disease, ischemic stroke, moderate chronic kidney disease (estimated glomerular filtration rate, 30 to <60 mL/min/1.73 m^2 or diabetes mellitus plus 2 or more additional risk factors [hypertension; ankle–brachial index of $\leq$0.90; microalbuminuria, macroalbuminuria, or a urinary dipstick result of >2+ protein; preproliferative or proliferative retinopathy or laser treatment for retinopathy, or a family history of premature CHD]). These subjects had LDL-C levels $\geq$70 mg/dL and were receiving statin therapies at the maximum-tolerated dose associated with an acceptable side effect profile, with or without additional lipid-lowering therapy. They were randomly allocated to receive alirocumab 150 mg subcutaneously or placebo every 2 weeks by subcutaneous injection for 78 weeks.

Subjects were a mean 60 years of age, 60% were male, and 93% were self-identified as "White." The mean body mass index was slightly >30 kg/m^2. Approximately, 18% had HeFH using World Health Organization-Simon Broome diagnostic criteria and or genotyping and 69% had CHD. Coronary risk equivalent states were identified in 41%, type II diabetes in 34%, and 21% were smokers. 99% were on statin therapy, 47% on 40 to 80 mg of atorvastatin, 20 to 40 mg of rosuvastatin, or 80 mg of simvastatin daily. Ezetimibe was taken by about 14%. The median baseline LDL-C was 122 mg/dL.

The primary efficacy endpoint was the change in calculated LDL-C at week 24. Alirocumab therapy was associated with a mean reduction in LDL-C from 122.8 $\pm$ 42.7 mg/dL to 48.3 $\pm$ 0.9 mg/dL, least squares mean percentage reduction from baseline -61.9 ± 1.3, (95% confidence interval [CI], -64.3 to -59.4, $P < .001$), compared with placebo. In the alirocumab group compared with placebo, there were more injection site reactions (5.9 vs 4.2%), myalgia (5.4 vs 2.9%), neurocognitive events (1.2% vs 0.5%), and ophthalmologic events (2.9% vs 1.9%). A post-hoc analysis at 78 weeks showed a lower incidence of major cardiovascular events (CHD death, nonfatal myocardial infarction (MI), fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization) 1.7% vs 3.3%, hazard ratio 0.52 (95% CI, 0.31–0.90; nominal $P = .02$).

A second safety and efficacy study simultaneously published in 2015 reported the results of 2 extension studies (OSLER-1 and OSLER-2) evaluating the PSCK9 inhibitor, evolocumab.[5] A total of 4465 subjects who had completed 1 of 12 phase 2 or 3 randomized trials were enrolled and were randomly assigned in a 2:1 ratio to receive either evolocumab, 140 mg every 2 weeks or 420 mg monthly plus standard therapy or standard therapy alone. These subjects were followed for a median of 11.1 months for lipid levels, safety and adjudicated cardiovascular events, including death, MI, unstable angina, coronary revascularization, stroke, transient ischemic attack, and heart failure. The data from the 2 trials were then combined and reported.

Subjects in this study had completed 1 of the parent studies and were further selected because they did not have an adverse event that led to discontinuation of the study drug