

EBM Tools for Practice:

A National Lipid Association Best Practices Guide: PCSK9 Inhibitors

Provided by: National Lipid Association's Therapeutics Committee



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COMMITTEE NOTE TO MEMBERS OF THE NATIONAL LIPID ASSOCIATION:

At the request of the NLA President, the NLA Board of Directors, the Science and Policy Council, the Practice Management Council and the Health Quality and Research Committee, it is with pleasure that the 2017-18 NLA Therapeutics Committee presents a Special Report on how to best incorporate PCSK9 Inhibitors into routine clinical lipid practice by integrating best available evidence into the

routine process of care. This report was generated independently from industry sponsorship to assist clinical lipidologists to ensure access to care for those patients who require additional LDL-C lowering in anticipation of lowering cardiovascular events. The Committee expects to provide future reports with additional updates as more clinical data becomes available.

Clinical Overview and Indications for PCSK9 Inhibitors

Alirocumab and evolocumab are both proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors that were approved in the United States in 2015 by the U.S. Food and Drug Administration (FDA). The alirocumab prescribing information (PI) most recently was updated in September 2017 and the evolocumab PI most recently was updated in December 2017.

REPATHA (evolocumab) now is indicated as follows:

- to reduce the risk of myocardial infarction, stroke and coronary revascularization in adults with established cardiovascular disease.¹
- as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C).¹
- as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.¹

PRALUENT (alirocumab) now is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C.

2017 Recommendations of the NLA Expert Panel on Treatment with PCSK9 inhibitors³

Atherosclerotic Cardiovascular Disease (ASCVD)

1. PCSK9 inhibitor therapy should be considered for ASCVD risk reduction in patients with stable atherosclerotic cardiovascular disease, particularly in those with additional ASCVD risk factors, on maximally tolerated statin therapy \pm ezetimibe, with on-treatment LDL-C ≥ 70 mg/dL or non-high-density lipoprotein cholesterol (HDL-C) ≥ 100 mg/dL. Strength A, Quality: High

2. PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients with progressive ASCVD on maximally tolerated statin therapy \pm ezetimibe, and on-treatment LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL. Strength B, Quality: Moderate

LDL-C ≥ 190 mg/dL (including polygenic hypercholesterolemia, HeFH, HoFH and the homozygous FH phenotype)

3a. PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients ages 40 to 79 years with pre-treatment LDL-C ≥ 190 mg/dL, no uncontrolled ASCVD risk factors, or other key additional high-risk markers, and on-treatment LDL-C ≥ 100 mg/dL or non-HDL-C ≥ 130 mg/dL on maximally tolerated statin therapy \pm ezetimibe. Strength B, Quality: Moderate

3b. PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients ages 40 to 79 years with pre-

treatment LDL-C ≥ 190 mg/dL, and the presence of either uncontrolled ASCVD risk factors, key additional high-risk markers, or genetic confirmation of FH, and on-treatment LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL on maximally tolerated statin \pm ezetimibe. Strength: B, Quality: Moderate

3c. PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients ages 18 to 39 years with pre-treatment LDL-C ≥ 190 mg/dL, and the presence of either uncontrolled ASCVD risk factors, key additional high-risk markers, or genetic confirmation of FH, and on-treatment LDL-C ≥ 100 mg/dL or non-HDL-C ≥ 130 mg/dL on maximally tolerated statin \pm ezetimibe. Strength: E, Quality: Low

3d. PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients with HoFH, either of unknown genotype or those known to be LDL receptor defective, on maximally tolerated statin therapy \pm ezetimibe with LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL. Strength B, Quality: Moderate

Very high risk/statin intolerance

4. PCSK9 inhibitor therapy may be considered to further reduce LDL-C in selected very-high-risk patients who meet the definition of statin intolerance (as previously defined by the NLA Statin Expert Panel) and who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid-lowering therapies. Strength C, Quality: Low

*Including history of uncontrolled high blood pressure, diabetes, current cigarette smoking or family history of premature ASCVD; or additional high-risk markers (coronary calcium ≥ 300 Agatston units [or ≥ 75 th percentile for the patient's

age, gender and ethnicity]; Lipoprotein(a) [Lp(a)] ≥ 50 mg/dL using an isoform-insensitive assay, high-sensitivity C-reactive protein [hs-CRP] ≥ 2 mg/L or chronic kidney disease [CKD] including albumin/creatinine ratio ≥ 30 mg/g).

Safety of PCSK9 Inhibitors

Alirocumab and evolocumab have been in general use in the United States since FDA approval in mid-2015. Their approval was based on clinical trials of safety and efficacy that involved several thousand patients, including studies of at least 1-year exposure.^{1,2}

Both agents are considered biologic therapies because they are injectable, fully human monoclonal antibodies. As with all injectable proteins, there is the potential for immunogenicity and a host response. Alirocumab and evolocumab represent fourth-generation Immunoglobulin G (IgG) monoclonal antibodies that are fully human, thus greatly reducing the potential for therapy-associated anti-drug antibodies (ADA) or neutralizing antibodies (NABs) developing in treated patients.⁴

Screening assays for ADAs and NABs are available and were used in the clinical pre-approval trials. These assays vary considerably in sensitivity and specificity and can be used to detect antibodies that bind to the paratope of the IgG therapies. Because of differences in handling, disease states, concomitant medications, and collection variables, etc., comparison of ADA occurrence rates between agents not studied together may be misleading.⁵

Across 10 placebo- and active- (ezetimibe) controlled trials with alirocumab of at least 24-week duration, ADAs were detected in 4.8% of patients on alirocumab compared to 0.6% on placebo. NABs were detected in 1.2% in patients on alirocumab vs. 0% in placebo; however, NABs with transient or continued loss of efficacy were only

noted in 0.3% of patients on alirocumab. ADA and NABs generally were transient in most patients, and about half of cases that developed antibodies did so after 12 weeks of therapy. Only low titers of these ADAs were detected in the trials and disappeared when the studies were concluded. The development of ADAs, however, was associated with a notably greater likelihood of injection-site reactions compared to the absence of ADAs (10.2% vs. 5.9%, respectively). Overall, clinically determined allergic reactions were reported in 8.6% of patients on alirocumab vs. 7.8% with placebo injections, including some cases deemed to be hypersensitivity reactions with pruritus, rash and/or urticarial, though few serious events – including vasculitis or hypersensitivity – requiring hospitalization were reported. Overall discontinuation because of allergic reaction occurred in only 0.6% of patients on alirocumab vs. 0.2% of placebo patients.¹

With evolocumab, screening immunoassays for ADAs found a 0.1% incidence, with no reported NABs identified among these patients. In clinical trials, overall allergic reactions were reported in 5.1% of patients on evolocumab vs. 4.7% of those on placebo. These included rash (1% in alirocumab vs. 0.5% in placebo), eczema (0.4% vs. 0.2% placebo), and urticarial (0.4% vs. 0.1% placebo).^{2,6}

The use of PCSK9 inhibitors is recommended in high- and very high-risk patients who are on maximally tolerated statin therapies because of the clinical benefits and safety of statins demonstrated in more than 30 years of outcome trials. Therefore, any issue of drug interactions with statins and PCSK9 inhibitors would be of utmost importance. PCSK9 inhibitors belong to the constantly growing class of biological drugs in which monoclonal antibodies are directed against different antigenic epitopes. In contrast to small-molecule drugs, which

can differ notably in their absorption, distribution, metabolism and excretion, all monoclonal antibodies share common pharmacokinetic and pharmacodynamic properties. They typically are removed by target-mediated clearance with PCSK9 or by non-saturable proteolytic pathways through the reticuloendothelial system. They are not thought to be glucuronidated or metabolized by the cytochrome P-450 system and do not interfere with drug transporters such as permeability glycoprotein (P-gp) or organic-anion-transport polypeptides (OATP). There is low likelihood that they alter statin blood levels pharmacokinetically. Thus, they do not seem to have important drug-drug interactions affecting statin safety with co-administration. However, PCSK9 inhibitor plasma mean half-life typically is shortened several days with simultaneous statin therapy, because statins lead to increased PCSK9 synthesis and greater target (PCSK9) abundance; this does not meaningfully affect PCSK9 therapy.⁷

There is no significant renal clearance of PCSK9 inhibitors, thus no dosing adjustments are required in renal insufficiency. However, studies in severe renal insufficiency are lacking. As a general rule, demographics such as age, gender, race and body weight or creatinine clearance do not impose a need for dosage adjustment.⁷ Although evolocumab has been utilized in HoFH adolescent patients over age 12, both agents initially were approved only for use in adult patients.² Generally, adverse reactions to PCSK9 inhibitors reported in clinical trials to date have been low. The two available agents have not been studied together, so comparison of reported adverse event rates can be misleading, but they appear similar in most cases.⁷

The most commonly reported adverse effects seen with evolocumab at an incidence of 5% or greater, and greater

than placebo, include: nasopharyngitis, upper respiratory tract infection, influenza, back pain and injection-site reactions.² With alirocumab, similarly reported adverse events include: nasopharyngitis, injection-site reactions and influenza.¹

Muscle-related adverse events with evolocumab were reported in 6.4% of patients (vs. 6% in placebo) in pre-approval clinical trials and were comparable in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, with events reported in 5.0% of patients on evolocumab vs. 4.8% in placebo.² Myalgia was reported in 5.4% of patients on alirocumab (vs. 2.9% on placebo). In the safety analysis of 4,465 patients from the Open Label Study of Long Term Evaluation Against LDL-C (OSLER) trials⁸, creatine kinase (CK) elevations consecutively reported greater than five times upper limit normal were reported in 0.5% of patients on evolocumab (vs. 1.1% in placebo). In the Long-term Safety and Tolerability of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients with Hypercholesterolemia (ODYSSEY LONG TERM) study⁹ CK elevations greater than three times upper limit normal were reported in 3.7% of the 1,550 patients on alirocumab (vs. 4.9% on placebo). No excess risk of rhabdomyolysis because of PCSK9 inhibition has been reported in trial-enrolled patients in whom baseline moderate of high-intensity statin therapy typically also is used, frequently in addition to ezetimibe. Assessment of any accurate altered incidence of rhabdomyolysis would, however, require tens of thousands of subjects and likely will be defined in post-marketing analyses.

Given that statins generally also are used, a low background incidence of developing liver function abnormalities is expected and was observed. However, the appearance of transaminase elevations

greater than three times upper limit normal in the trials with both approved PCSK9 inhibitors was on the order of 1-2% and was seen in similar frequency to placebo or control arms.⁷ Nonetheless, elevated liver enzymes is the second most commonly reported adverse effect (next to allergic reactions), leading to discontinuation of alirocumab in placebo-controlled trials (0.3% in alirocumab vs. 0.1% in placebo).¹

Of late, neurocognitive events with statin therapies have been of considerable public and clinical interest. In the long-term studies to date, neurocognitive events reported with evolocumab are low, at 0.9% of patients (vs. 0.3% in placebo), and do not appear related to achieved LDL-cholesterol levels.⁸ A substudy of the FOURIER trial, Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS), examined cognitive function in 1,974 subjects using a validated cognitive instrument and did not find any significant difference in cognitive function between evolocumab and placebo after a mean of 19 months, regardless of the LDL-C level achieved (1.6% evolocumab vs. 1.5% placebo).¹⁰ A similar neurocognitive study for alirocumab nested within the ODYSSEY trials is under way, expected to be completed by 2020. Preliminary data show that similar rates for neurocognitive disorders using the custom Medical Dictionary for Regulatory Activities (MedDRA) query (including amnesia, memory impairment, confusional states) were noted in ODYSSEY with alirocumab at 1.2% (vs. 0.5% with placebo). However, total neurological events in this trial, including peripheral neuropathy and Guillain-Barré Syndrome, were slightly less frequent with alirocumab than placebo at just more than 4% each. Ophthalmologic issues, including broad conditions such as optic nerve, retinal or corneal disorders, were observed in 2.9% of patients

on alirocumab (vs. 1.9% on placebo [p=0.65]).⁹ In the FOURIER trial, there was no increased risk of cataracts, (1.7% of patients on evolocumab, vs. 1.8% on placebo), but data were not broken down by post-treatment LDL-C levels.⁶

Although a low incidence of worsening blood sugar levels or elevations of incident diabetes mellitus is noted with statin therapies, especially in high-intensity therapies, no worsening of diabetes in patients with a history of diabetes mellitus was reported in ODYSSEY, and the incidence of new-onset diabetes mellitus with alirocumab was 1.8% (vs. 2.0% with placebo).⁹ Likewise, there was no increased incidence of new-onset diabetes with evolocumab in FOURIER (8.1% on evolocumab vs. 7.7% placebo).⁶ Despite requiring subcutaneous injection, most patients given proper education adapt quickly to self-administration. There is little local discomfort typically, because the 27-gauge needles in the pen injectors are only 4mm long. Overall, injection-site reactions are reported in between 4% and 6% of patients with PCSK9 inhibitor injections, just slightly more than placebo. In FOURIER, injection-site reactions were lower, affecting 2.15% of patients on evolocumab and 1.6% of patients on placebo. However, local mild erythema is common – if episodic – at injection sites, and more so than occasional bruising, swelling or induration, which typically are transient; only infrequently will patients have to stop therapy for injection-site reactions, and the reported discontinuation rate for PCSK9 therapies often does not exceed placebo rates (i.e. 0.2% for alirocumab vs. 0.4% for placebo). Overall discontinuation of PCSK9 monoclonal antibody therapies because of any adverse events is reported at a low incidence for both agents and only slightly more frequently than for placebo injections (i.e. 5.3% for alirocumab in ODYSSEY patients vs. 5.1% in controls; 2.4% for

evolocumab in OSLER with placebo rate not reported).^{6,8,9}

PCSK9 inhibitor trials demonstrated the safety of achieving very low LDL-C. In the ODYSSEY LONG-TERM study⁹, 575 patients (37.1%) achieved LDL-C levels of less than 25mg/dL, and 288 patients (8.8%) achieved levels below 15mg/dL. No increased rates of adverse events were observed in those patients compared to patients with higher LDL-C levels. In OSLER, on-treatment LDL-C reductions were sustained at a median of 48 mg/dL, and adverse-event rates observed were similar in patients with LDL-C levels below 40 mg/dL or even below 25 mg/dL compared to those with higher LDL-C levels.⁸ In both cases, continuation of therapy generally occurred despite the low levels reached. Humans in utero in late gestation have LDL-C levels around 30 mg/dL, and patients with familial hypobetalipoproteinemia (HFBL) who have similarly low LDL-C levels, are characterized by longevity. Nevertheless, patients with abetalipoproteinemia have many medical issues associated with the absence of ApoB-containing lipoproteins. Some logistic regression analyses with limited data have suggested an inverse relationship between LDL-C levels and stroke risk, and death from non-coronary heart disease (CHD) causes in both genders. Excess hemorrhagic stroke also was noted with higher-intensity statin therapy in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, despite overall reduction in strokes.¹⁰ Cancer risks do not appear increased when very low LDL-C levels are attained with statins, and several studies suggest more-aggressive LDL-C lowering may further reduce residual cardiovascular risk.¹⁰ In FOURIER, at 48 weeks, LDL-C was reduced to at least 25 mg/dl in 42% of patients treated with evolocumab, as compared with <0.1% in the placebo group (p<0.001) with no new identified

safety concerns.¹¹

In a meta-analysis¹³ of 24 trials of PCSK9 inhibitor therapies, an overall clinical analysis by Navarese that suggests a reduction in all-cause mortality and no major increase in serious adverse events with the use of PCSK9 inhibitors is quite encouraging, but it must be considered preliminary. Long-term outcome trials (FOURIER and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab [ODYSSEY Outcomes]) with both available agents, as well as with bococizumab (Spire I, II), are completed – or discontinued, in the case of bococizumab – and may yield greater insight into this matter of safety.^{6,14-16}

PCSK9 Inhibitor Outcomes Studies

The first hint that PCSK9 inhibitors had a beneficial effect on cardiovascular outcomes came from the OSLER-1 and OSLER-2 trials using evolocumab.⁸ These were two open-label randomized trials that enrolled 4,465 patients who had completed one of 12 Phase II or Phase III studies of evolocumab on background statin (and other lipid-modifying) therapy. A pre-specified analysis included the adjudicated cardiovascular events of death, myocardial infarction, unstable angina, coronary revascularization, stroke, transient ischemic attack and heart failure. Data from the two trials were combined. Patients were followed for a median of 11.1 months and LDL-C levels were reduced from a median of 120 mg/dL to 48 mg/dL. The rate of cardiovascular events at one year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio in the evolocumab group was 0.47, $p=0.003$).

The FOURIER study⁶ was a randomized, double-blind, placebo-controlled trial involving 27,564 patients on statins with established cardiovascular disease and

an LDL-C level of 70 mg/dL or greater or non-HDL-C ≥ 100 mg/dL. Patients were randomly assigned to evolocumab versus a matching placebo given as a subcutaneous injection. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization. The median duration of follow-up was 2.2 years. At 48 months, LDL-C in the evolocumab group was reduced from a median of 92 mg/dL to 30 mg/dL. Compared to the placebo group, the evolocumab group reduced the risk of the primary endpoint from 11.3% to 9.8% (hazard ratio 0.85, $p<0.001$).⁶

A second major PCSK9 inhibitor/ cardiovascular outcome study has been completed, with topline preliminary results presented at the American College of Cardiology (ACC) meeting in March 2018; it is awaiting publication. The ODYSSEY Outcomes trial¹⁸ was a double-blind, placebo-controlled trial involving 18,536 patients within one year of an acute coronary syndrome and taking background statin (and other non-fibrate lipid modifying) therapy. Subjects were required to have baseline LDL-C greater than 69 mg/dl (or non-HDL-C greater than 99 mg/dl) or apoB ≥ 80 mg/dL and were randomized to injection with alirocumab or placebo. A target range for treatment LDL-C was established at 25-50 mg/dl, with acceptable levels down to 15 mg/dl. There were 730 patients blindly switched from alirocumab to placebo for consecutive LDL-C levels below 15 mg/dl. The primary endpoint was the time to first occurrence of coronary heart disease death, acute myocardial infarction, hospitalization for unstable angina, or ischemic stroke. On-treatment median LDL-C was 93 mg/dl with placebo and 38 mg/dl with alirocumab at 4 weeks. Compared to placebo, results presented at ACC revealed that alirocumab reduced the primary endpoint from 11.1% to 9.5%

(hazard ratio 0.85, log-rank $P=0.0003$). All-cause death was reduced from 4.1% to 3.5% (hazard ratio 0.85, log-rank $P=0.026$) with alirocumab, but this result was considered marginally significant because of the hierarchical secondary endpoint testing procedure. No statistically significant reductions were observed in CHD death or CVD death, which were tested before total mortality in the hierarchy, although both trended lower.

Keys to Successfully Prescribing PCSK9 Inhibitors

The preauthorization process

Because of the relatively high cost of PCSK9 inhibitors, getting approval for use of these drugs often is challenging and requires preauthorization from the patient's insurance company or health plan. The purpose of the preauthorization process is to determine if the patient has an appropriate diagnosis to prescribe a PCSK9 inhibitor, has been treated with guideline-based statin and adjuvant lipid-lowering therapy, and requires further LDL-cholesterol lowering to meet the patient's guideline-based LDL-cholesterol target. Healthcare providers sometimes have found the preauthorization process difficult to manage. A recent study found that, in patients with established ASCVD who had an LDL-cholesterol >100 mg/dL and in patients with FH who had an LDL-C >190 mg/dL despite appropriate statin-based lipid-lowering therapy, most prescriptions for PCSK9 inhibitors were denied.¹⁹ In the National Lipid Association (NLA) barriers to PCSK9 inhibitors prescriptions survey²⁰, denial rates of more than 75% were reported by more than one-third of respondents attempting to treat ASCVD patients and one-quarter of respondents attempting to treat FH patients.

The key to the ultimate success of obtaining preauthorization is to meet the requirements of the patient's specific

health plan and to submit all requested information in as clear and concise a manner as possible. Submitting individual visit entries or an entire medical record printed from the electronic health record (EHR) without context may overwhelm the initial reviewer, who may not be well-versed in cardiovascular or lipid disorders. A systematic approach using a checklist is the best way to garner success. General support in obtaining authorization is available through the field access specialists for each PCSK9 inhibitor manufacturer, and prescribers should be encouraged to take advantage of this opportunity.

The process for obtaining approval begins with submission of a PCSK9 inhibitor prescription and with the patient's medical history. This can be done through hub services set up by the manufacturers or by specialty pharmacies that either are freestanding or within a particular health system. Most prescribers have found that specialty pharmacies are easier to use and reduce the paperwork that an individual health care provider needs to complete. It is important for both the health care provider and staff to be informed as to what documentation is needed for preauthorization. In the NLA survey, practice staff completed preauthorization documentation for 52% of prescriptions, while physicians completed the paperwork for only 29% of prescriptions. Therefore, it is equally important to train the practice staff in what is needed for appropriate documentation in the preauthorization process. Identifying a specific person or group of staff to handle preauthorization in a practice is a useful strategy to improve success in getting approval for PCSK9 inhibitors, because experience improves the approval process.

The survey also provided insights into what barriers exist to providing greater success in getting approval for a PCSK9 inhibitor

and the keys to overcoming those barriers. The NLA has published a checklist that prescribers can use when seeking approval for a PCSK9 inhibitor. The checklist includes the following items that must be submitted along with the prescription as part of the preauthorization process because barriers to prescribing a PCSK9 inhibitor can be overcome with an efficient process coupled with good documentation.

1. Indication and documentation of medical conditions

The FDA has approved the use of PCSK9 inhibitors in addition to diet and maximally tolerated statin therapy in adult patients with clinical ASCVD or FH who require additional LDL-C lowering. Alirocumab has been approved for heterozygous FH while evolocumab has been approved for both heterozygous and homozygous FH. The 2013 ACC/American Heart Association (AHA) cholesterol guidelines defined clinical ASCVD as a history of an acute coronary syndrome or myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease presumed to be of atherosclerotic origin.²¹ The International Atherosclerosis Society has provided a similar definition but also includes a history of coronary heart disease, carotid disease and other forms of atherosclerotic vascular disease.²² In the NLA survey, inadequate documentation of FH was a common reason for denial of a PCSK9 inhibitor. When prescribing a PCSK9 inhibitor for a patient with presumed FH, the following must be documented clearly: a history of an LDL-C level > 190 mg/dL and a family history of a first-degree relative with premature ASCVD or elevated LDL-C.²³ If available, include the pre-treatment LDL-C level. The presence of tendon xanthomas, corneal arcus in a person <45 years of age, a history of premature ASCVD (men age <50 years or women age <60 years), or positive genetic testing for a mutation

in the genes coding for the LDL receptor, ApoB or PCSK9 will strengthen the FH diagnosis and should be documented and submitted along with the preauthorization paperwork to improve the likelihood of approval.

2. A recent lipid panel (<30 days old)

Lack of current laboratory values was another reason for denial cited by the respondents in the NLA survey. The prescriber should not submit a preauthorization form for a PCSK9 inhibitor without a current lipid panel.

3. Statin history

Current guidelines recommend a high-intensity statin, either atorvastatin 40 mg or 80 mg daily or rosuvastatin 20 mg or 40 mg daily for patients with clinical ASCVD or FH.²¹⁻²⁴ However, many high-risk patients are unable to tolerate a high-intensity statin because of statin intolerance.²⁵ In the NLA survey, lack of documentation as to why the patient was not on a high-intensity statin or a maximally tolerated statin dose was the third most common reason reported for denial in ASCVD patients and the second most common reason reported for denial in FH patients. The phrase "maximally tolerated statin" includes any statin at any dose, as well as patients on no statin therapy because of intolerance.

If a patient is not on a high-intensity statin and there is no history of statin intolerance, the patient should be placed on a high-intensity regimen (atorvastatin 40 mg or 80 mg daily or rosuvastatin 20 mg or 40 mg daily) before prescribing a PCSK9 inhibitor. For patients not on high-intensity statin or on no statin because of intolerance, the prescriber must clearly document what statins, at what doses, and when those statins previously were prescribed. If the patient has not been tried on at least two statins, one at the normal starting dose and another at any

dose, the patient should be re-challenged with a statin before prescribing a PCSK9 inhibitor. Studies have shown that patients with a history of statin intolerance can successfully be re-challenged with another statin.²⁶ In the NLA survey, more than 75% of respondents routinely tried three or more statin medications before considering a high-risk patient to be statin intolerant.

4. LDL-cholesterol goal

Both the ACC and the NLA have published pathways and recommendations defining specific LDL-C levels at which a PCSK9 inhibitor should be considered.^{3,27} The prescriber must document the individual patient's LDL-C and comment that, despite maximally tolerated statin therapy, their patient is not at their goal. The thresholds for additional pharmacotherapy are LDL-C >70 mg/dL for patients with ASCVD and >100 mg/dL for patients with FH and no clinical evidence for ASCVD. Alternatively, the prescriber may choose a goal of >50% reduction in the patient's baseline LDL-C level. In the NLA survey, most respondents (84%) said they prescribed lipid-lowering therapy to achieve a specific LDL-C, while the remainder treated to a specific high-dose statin.

5. Adjuvant therapy

Current guidelines recommend PCSK9 inhibitors or ezetimibe as additional therapy to lower LDL-C after statins have been initiated in high-risk patients.^{3,27} In the NLA survey, most respondents (85%) would add non-statin adjuvant therapy such as ezetimibe for high-risk patients who are unable to achieve adequate LDL-C reduction on a maximally tolerated statin dose and then add a PCSK9 inhibitor, if needed. Many health plans require that other agents, such as ezetimibe or bile acid sequestrants, be added to a statin prior to considering PCSK9 inhibitors; if there is >25% reduction needed in LDL-C, ezetimibe may be bypassed. Individual health plans' requirements

should be evaluated carefully to determine what should be tried and failed prior to considering PCSK9 inhibitors. The prescriber must document the use of adjuvant non-statin LDL-C-lowering medications and also document in their office note that the patient has been counseled on intensive lifestyle changes.

The NLA survey highlighted the importance of accurate and current documentation in the PCSK9 inhibitor approval process. Using a checklist of all required information and documents that need to be submitted to support an approval and training of the prescriber's office staff are recommended. However, despite appropriate indications and documentation, denials may still occur. Patients should be informed during the initial discussion regarding PCSK9 inhibitor usage that they may receive an initial denial of the medication.

The appeal process

Should a PCSK9 inhibitor prescription be denied, both the patient and the prescriber will receive a copy of the denial letter with the reason for the denial. The appeal process will be delineated within the letter. The prescriber should correct any deficiencies outlined in the denial letter and resubmit for approval. The specialty pharmacy can help in this process. If an appropriate patient is denied a PCSK9 inhibitor prescription, the prescriber often may be able to appeal the decision. This can be done in letter form or as a peer-to-peer discussion. Maintenance of a sample appeal letter can be helpful when composing an individual appeal; however, a peer-to-peer review is recommended and more likely to lead to approval. A peer-to-peer review usually is a brief telephone conversation with a physician – often one of the medical directors for the insurance company – during which an opportunity is provided for the prescriber to make a case for PCSK9 inhibitor therapy. It is important

to have all the supporting documentation and medical records available at the time of the phone call. In the NLA survey, almost all respondents (96%) took some further action after a denial and persisted in their attempts for seeking approval. After the initial denial, many respondents eventually were successful in obtaining approval for a PCSK9 inhibitor.

Should the initial medical appeal be denied, an external review or a secondary appeal can be requested. For patients enrolled in Medicare Part D, there are several levels of appeal, from appealing to the Part D plan sponsor to, finally, requesting a review by a federal district court. For patients with commercial insurance, the provider first should appeal to the patient's insurance company and, if the request for the medication continues to be denied, patients and/or their provider could contact their state's insurance commission board to file a formal complaint. All patients who have been inappropriately denied coverage should be encouraged to file a complaint. Information on how to file a complaint can be found online or by contacting the patient's state insurance department. For patients with self-funded commercial insurance through their employer, the patient first should contact his or her company's Human Resources or benefits department. As a final resort, patients may contact the Patient Advocate Foundation at www.patientadvocate.org. Navigating the appeal process can be confusing and difficult for both patients and providers. Field access specialists from each PCSK9 inhibitor manufacturer also can be particularly helpful in aiding both the patient and physician through the process.

Once the prescription is approved

Both the patient and the prescriber will be notified that the PCSK9 inhibitor prescription was approved. Once approved, the patient must connect with the

specialty pharmacy to ensure delivery. A representative from the specialty pharmacy will advise the patient about any monthly co-pay and verify the delivery address. A delivery time frame is agreed on, because the medication is sent via overnight express mail and is packaged to ensure the drug is received at the appropriate temperature of between 2 and 8 degrees C (36-46 degrees F) and is placed in the refrigerator as soon as possible to maintain its stability. There have been reports that, despite approval, patients do not hear from the specialty pharmacy and, therefore, many patients find that receipt of the drug is unduly delayed. Thus, it is beneficial for the patient to be contacted by the prescriber's office informing them that the drug has been approved and advising them to contact the specialty pharmacy. The prescriber's office will need to provide the patient with the specialty pharmacy's phone number.

Financial assistance

Many patients find the co-pay to be cost prohibitive, regardless of insurance approval, but they should be reassured that there is a great deal of available financial assistance. Information on financial assistance can be provided by the specialty pharmacy, by the manufacturer's field access specialists, and found online at the manufacturers' websites *MyPraluent* (Sanofi Regeneron) or *Repatha Ready* (Amgen) and provided by the manufacturer's field access specialists. Copay cards are available from both Sanofi Regeneron and Amgen for people with commercial insurance. They apply to their deductible, coinsurance and copay. Some insurance companies recently have not allowed the use of copay cards, and people with federal, state or government-funded health care plans may not be eligible for copay cards. Having a point person within the office to help with the procurement of financial assistance can be helpful and reassuring to patients. Field access

specialists can provide the patient and the office staff with other programs that may help cover the cost of the PCSK9 inhibitor. Patients with Medicare Part D without supplemental insurance often have a very high copay that may make the medicine unaffordable. Patients should be informed of this when being considered for a PCSK9 inhibitor prescription.

Resources also are available for individuals who are not insured or are under-insured. Representatives from *MyPraluent* and *Repatha Ready* can help patients by identifying and finding potential assistance from charitable organizations and foundations. The Patient Access Network (PAN) Foundation is an independent, national 501(c)(3) organization that is dedicated to helping federally and commercially insured people living with chronic, life-threatening and rare diseases cover out-of-pocket costs for their prescribed medications. Both Sanofi-Regeneron and Amgen provide patient assistance programs based on financial need for uninsured or underinsured patients to help cover the cost of a PCSK9 inhibitor. Information on subsidies for low-income individuals is available by contacting the Centers for Medicare and Medicaid Services.

In addition to financial assistance, other support services are available through *MyPraluent* and *Repatha Ready* and include one-on-one nurse support, medication reminders, helpful emails, free needle disposal kits, and alcohol swabs. All patients should be encouraged to sign up for these support services.

Medication adherence is key, and many patients require a great deal of support to remain compliant. Clinical pharmacists within the specialty pharmacy networks often will provide programs that improve adherence rates. They can and will call patients to see if they are having any

difficulties taking the medications and will provide additional education regarding the medication or assistance with injection administration. The nurses from Sanofi-Regeneron and Amgen will go to patients' homes or the physician office to teach or administer an injection. Videos are available online at both manufacturers' websites that provide self-injection training.

Conclusions

Navigating the health care system continues to become more and more complex and our patients are relying on us – their health care providers – to advocate for them in all areas, including obtaining preauthorization, financial assistance and additional clinical support. Providers at all levels serve as patient advocates, helping them to achieve the best possible health. The road to navigating approval for a PCSK9 inhibitor is sometimes tortuous, yet an efficient process, perseverance and experience will make the road easier to travel. ■

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