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Bempedoic Acid for Lowering LDL Cholesterol

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Since the report of the first expert panel of the National Cholesterol Education Program in 1988, effectively the first contemporary professional cholesterol guidelines in the United States, lowering of low-density lipoprotein cholesterol (LDL-C) levels has been a cornerstone of atherosclerotic cardiovascular disease (ASCVD) prevention. Consistent with classical and genetic epidemiologic studies implying a causal relationship between LDL-C and ASCVD, multiple randomized clinical trials have consistently observed proportional relationships between LDL-C lowering and ASCVD risk reduction from statins. More recently, these findings have extended to nonstatin LDL-C–lowering medicines, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9)–inhibiting monoclonal antibodies.[1–3]

Given encouraging results from clinical trials, nonstatin LDL-C–lowering medicines are now guideline-recommended when the degree of LDL-Clowering attained by maximally tolerated statins is deemed insufficient.[4] Statins are generally well tolerated, with minimal differences compared with placebo for adverse symptoms in randomized clinical trials.[5] However, muscle symptoms are reported in 5% to 20% of patients prescribed statins in clinical practice and may lead to poor adherence.[6] Blinded studies of crossover statin

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rechallenge among patients with prior statin-associated muscle symptoms (SAMS) have shown an excess of muscle symptoms with statin rechallenge vs placebo.[7] Evaluating SAMS remains challenging clinically because diagnostic tests are imprecise, yet symptoms may sometimes be debilitating.[8]

Bempedoic acid, a first-in-class small molecule inhibitor of ATP-citrate lyase, may provide a suitable alternative for patients who are prescribed statins and experience SAMS. Bempedoic acid is an oral, once-daily prodrug metabolized in the liver to an active inhibitor of ATP-citrate lyase, blocking cholesterol synthesis upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and thereby increasing hepatic expression of the LDL receptor and decreasing circulating LDL-C levels.[9] In 2 separate clinical trials (CLEAR Tranquility and CLEAR Serenity), each with approximately 300 patients with hypercholesterolemia and SAMS, bempedoic acid, compared with placebo, lowered LDL-C levels by 21% to 29% without increasing risk of muscle symptoms compared with placebo within 6 months.[10,11] In the larger CLEAR Harmony clinical trial of 2230 patients with heterozygous familial hypercholesterolemia or ASCVD receiving maximally tolerated statins and with LDL-C levels of at least 70 mg/dL, LDL-C was reduced by 18% (absolute reduction of 19.2 mg/dL with bempedoic acid and increase of 0.1 mg/dL with placebo), and there was similarly no significant excess of muscle symptoms compared with placebo within 12 months.[12] While not designed to evaluate cardiovascular outcomes, CLEAR Harmony showed nonsignificantly fewer major adverse cardiovascular events with bempedoic acid (4.6%) vs placebo (5.7%) during this time frame.

In this context, Goldberg et al report in this issue of *JAMA* findings on the LDL-C–lowering efficacy and adverse effects of bempedoic acid (180 mg daily) in the similarly designed CLEAR Wisdom trial[13] that included 779 patients. Trial-eligible individuals had heterozygous familial hypercholesterolemia (5.5%) or ASCVD (94.5%), were taking maximally tolerated lipid lowering therapy, and had an LDL-C level of at least 100 mg/dL. Given differences in screening LDL-C cutoffs, mean baseline LDL-C value was 120.4 mg/dL in CLEAR Wisdom (compared with 103.2 mg/dL in CLEAR Harmony). At week 12, the reductions in LDL-C levels were significantly greater with bempedoic acid than with placebo (−15.1% vs +2.4%, respectively; least-squares mean difference, −17.4%). At week 12, mean LDL-C level was 97.6 mg/dL in the bempedoic acid group compared with 122.8 mg/dL in the placebo group.

While proportional LDL-C reduction was similar between the 2 trials, absolute LDL-C reduction was greater in CLEAR Wisdom given higher baseline LDL-C levels. CLEAR Wisdom was similarly not designed to evaluate cardiovascular outcomes, but these differences in absolute LDL-C-reduction were also consistent with the greater relative—albeit nonsignificant—major adverse cardiovascular events risk reduction from bempedoic acid (2.7% vs 4.7%) than was seen in CLEAR Harmony.

Similar to CLEAR Harmony and CLEAR Serenity but not CLEAR Tranquility, there was modest excess of study drug discontinuation with bempedoic acid vs placebo (10.9% vs 8.6%), but obvious reasons for differential discontinuation were not apparent. There was no excess of muscle-related symptoms. Consistent with prior trials of bempedoic acid,[10]

elevated uric acid concentration and gout were modestly more common in patients receiving bempedoic acid (4.2% with bempedoic acid vs 1.9% with placebo). Bempedoic acid is believed to contribute to elevated uric acid concentrations because of interference of a drug metabolite with renal uric acid excretion. Further analyses of this and prior trials indicate that preinitiation hyperuricemia or history of gout are strongly associated with acute gout risk among patients receiving bempedoic acid.

Considering that other nonstatin LDL-C–lowering medicines are available and have been incorporated into professional guidelines, the clinical role for bempedoic acid remains to be defined. The CLEAR Outcomes trial (NCT02993406), designed to assess the efficacy of bempedoic acid for reducing cardiovascular risk in 12 600 patients, is anticipated to report in 2022. Nevertheless, LDL-C reduction is a long-standing surrogate recognized by the US Food and Drug Administration (FDA) and has been the basis of approval for statins, ezetimibe, alirocumab, and evolocumab. Given the results from all 4 CLEAR trials for LDL-C–lowering efficacy and safety, should bempedoic acid similarly be used in clinical practice before results from CLEAR Outcomes are reported? If so, with the availability of several LDL-C–lowering agents, when should patients and their physicians consider bempedoic acid?

A major driver for the use of bempedoic acid may be the effort toward increasingly stringent LDL-C reduction. The 2013 iteration of the American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines endorsed high-potency statin therapy for secondary ASCVD prevention with the goal of lowering LDL-C level more than 50% from baseline.[14] Without an obvious “floor” of efficacy or safety,[15] the 2018 ACC/AHA guidelines extended prior recommendations by establishing an LDL-C goal of less than 70 mg/dL for secondary prevention for individuals at “very high-risk” of future ASCVD events.[4] The 2018 guidelines now support the use of nonstatin LDL-C–lowering medicines, specifically ezetimibe, alirocumab, and evolocumab, to further reduce LDL-C levels as necessary among such very high-risk individuals. Contemporary analyses indicate a large fraction of patients with very high-risk ASCVD still have inadequate LDL-C concentrations.[16] Recent European Society of Cardiology guidelines now further recommend LDL-C targets less than 55 mg/dL for patients with very high-risk ASCVD and less than 40 mg/dL in those with recurrent events within 2 years.[17] The addition of bempedoic acid is likely necessary in many patients to achieve such newly proposed LDL-C targets.

Prior to the availability of cardiovascular outcomes data for bempedoic acid, it may have a potential role in the primary prevention setting as well, in which PCSK9 inhibitors are only narrowly recommended for familial hypercholesterolemia because of cost considerations. In the setting of statin in tolerance and intermediate to high 10-year ASCVD risk, ezetimibe monotherapy may be insufficient to attain suitable LDL-C lowering. Bempedoic acid could be an option in this scenario. For patients with statin intolerance in both primary and secondary prevention, a fixed-dose combination of ezetimibe with bempedoic acid could be an efficient oral strategy to achieve the LDL-C–lowering efficacy of a moderate potency (ie, 30%–50% lowering) statin regimen.[18]

In practice, patient and payer preferences are likely to determine the order of nonstatin LDL-C–lowering medicine prescriptions. Current nonstatin medicine options are balanced by oral route of administration vs decreased-interval dosing frequency with subcutaneous administration; various concerns and goals may influence patient preferences of one vs the other. The 2018 guidelines now further emphasize the payer perspective by introducing cost-effectiveness into the guidelines. Using prices preceding those guidelines, the authors deemed PCSK9 monoclonal antibodies not cost-effective. As a result, the guidelines supported the use of ezetimibe, which is currently only FDA-approved for LDL-C lowering, prior to the use of PCSK9 monoclonal antibodies, which are currently FDA-approved for both LDL-C lowering and ASCVD risk reduction. Pricing of bempedoic acid may influence where it falls within this hierarchy, and before incorporation into guidelines, this may be most strongly influenced by payers.

Current iterations of guidelines for management and prevention of ASCVD should evolve into more dynamic entities to accommodate the dynamic nature of biomedical scientific evidence. For example, the same day the 2018 guidelines were unveiled, a large cardiovascular outcomes trial of icosapent ethyl was presented, with potential practice-changing implications.[19] Before incorporation in 2018 guidelines, PCSK9 monoclonal antibody prescription “success” was often determined by payers and out-of-pocket costs. While cost containment remains an important goal of the health care system, professional societies would ideally lead the charge through adaptive practice guidelines.

Elevated LDL-C level remains an important modifiable risk factor for first and recurrent ASCVD events. The next few years will see results from trials of additional nonstatin LDL-C–reducing agents. After focusing the last 3 decades exclusively on statins, the increasingly diverse options to attain maximally tolerated LDL-C reduction are welcome additions for management of high-risk patients.

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