Bempedoic acid: LDL-C lowering without adverse reactions

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ABSTRACT

Low-density lipoprotein-cholesterol (LDL-C) causes atherosclerosis and increases patient risk for cardiovascular mortality. However, patients who cannot tolerate statins present a treatment challenge. Bempedoic acid, an oral once-daily drug that reduces cholesterol synthesis, may help close this treatment gap. A meta-analysis demonstrated that bempedoic acid provides a well-tolerated and effective therapeutic option for lipid lowering in patients with hyperlipidemia, both as monotherapy and in combination with various other lipid-lowering agents. Also, although bempedoic acid acts on the same pathway as statins, it does not cause the muscular adverse reactions associated with statins.

Keywords: bempedoic acid, cholesterol, statins, atherosclerotic cardiovascular disease, statin intolerance, LDL-C reduction

Bempedoic acid was approved by the FDA in February 2020 for use as an adjuvant therapy to lifestyle modifications and statin therapy for additional low-density lipoprotein cholesterol (LDL-C) lowering.[1] Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality for adults. The American Heart Association/American College of Cardiology (AHA/ACC's) 2018 guidelines for the management of cholesterol recommend an LDL-C reduction of greater than or equal to 50% of baseline LDL-C for patients with established ASCVD as well as for primary prevention of ASCVD in high-risk patients such as those with severe hypercholesterolemia (LDL-C greater than 190 mg/dL).[2] The backbone of therapy remains lifestyle modifications and high-intensity statins. Several trials, including IMPROVE-IT, have shown additional decreases in ASCVD events with the addition of alternative lipid-lowering therapy to statins.[2,3] Results of the IMPROVE-IT trial also suggest that improved outcomes from lipid lowering is not just an effect seen with statins, as previously thought.[3] However, patients may be limited in their use of higher-intensity statins due to myalgias and other muscle-related adverse reactions; for some patients, adverse reactions may prevent the use of this class entirely. For these patients and for those unable to reach their LDL-C-lowering goals, adjuvant therapies such as ezetimibe and PCSK9 inhibitors are included in this iteration of the guidelines. Ezetimibe's use is limited by its ability to reduce LDL-C (only 13% to 20%), and PCSK9 inhibitors by their cost-effectiveness.[2] Additional options are needed for patients who cannot tolerate statins or who are unable to meet their goals on combination therapy. Bempedoic acid may help to fill this gap.

Bempedoic acid is an oral prodrug given once daily. Once it is activated to the CoA form, the active metabolite inhibits adenosine triphosphate (ATP) citrate lyase, which plays an important role in the cholesterol biosynthesis pathway.[4,5] Furthermore, the enzyme that catalyzes the activation of the prodrug, acetyl-CoA synthetase long chain 1 (ACSVL1), is found in the liver but not in the skeletal muscle. Because bempedoic acid has no activity in skeletal muscle, patients are at minimal risk for the muscle-related adverse reactions that have been associated with statin use.[6]

Four randomized controlled studies showed efficacy and safety of bempedoic acid.[4,5,7,8] Two studies examined the effect in patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both.

- The CLEAR Harmony trial determined that adding bempedoic acid to maximally tolerated statins with or without ezetimibe reduced the mean LDL-C by 19.2 mg/dL (-16.5% from baseline) at 12 weeks.[4]
- CLEAR Wisdom expanded inclusion criteria to patients unable to tolerate any statin therapy and showed that addition of bempedoic acid reduced LDL-C significantly more than placebo at both week 12 and 24.[7]

The results from both studies indicated that bempedoic acid therapy was able to maintain LDL suppression up to 52 weeks.[4,7]

The remaining trials, CLEAR Tranquility and CLEAR Serenity, focused on patients with statin intolerance and LDL-C of 100 mg/dL or greater.[5]

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TABLE 1. Bempedoic acid trial comparisons

Trial and patient demographics	Treatment arms	Conclusions
CLEAR Harmony[4] 2,230 patients with ASCVD, heterozygous familial hypercholesterolemia, or both	Bempedoic acid (n = 1,488) or placebo (n = 742) added to maximally tolerated statins with or without additional lipid-lowering therapy	Bempedoic acid added to maximally tolerated statin therapy did not lead to a higher incidence of overall adverse reactions than placebo and led to significantly lower LDL-C levels.
CLEAR Wisdom[7] 779 patients with ASCVD, heterozygous familial hypercholesterolemia, or both	Bempedoic acid (n = 522) or placebo (n = 257) added to maximally tolerated statins, or no statin, with or without additional lipid-lowering therapy	Compared with placebo, bempedoic acid provided additional LDL-C lowering in patients who did not achieve an adequate response to lipid-lowering therapy.
CLEAR Tranquility[5] 269 patients with a history of statin intolerance; primary or secondary prevention	Ezetimibe plus either bempedoic acid (n = 181) or placebo (n = 88) to current background therapy	Bempedoic acid may provide an oral therapeutic option complementary to ezetimibe in statin-intolerant patients who require additional LDL-C lowering
CLEAR Serenity[8] 345 patients with a history of statin intolerance; primary or secondary prevention	Bempedoic acid (n = 234) or placebo (n = 111)	Bempedoic acid offers a safe and effective oral therapeutic option for lipid lowering in patients who cannot tolerate statins.

• CLEAR Serenity compared the addition of bempedoic acid therapy or placebo with current therapy (either low-dose statin, no statin, or other lipid-lowering therapy) in primary and secondary prevention patients.[8] At 12 weeks, the treatment group's LDL-C decreased by 21.4%, which again was maintained throughout the 24-week study.[8]
• CLEAR Tranquility compared the addition of bempedoic acid or placebo with maximally tolerated statin therapy and found a 28.5% greater reduction in LDL-C at 12 weeks with the addition of bempedoic acid compared with placebo.[5] Of note, the percentage reduction of LDL-C was greater in this population of statin-intolerant patients than in the CLEAR Harmony or CLEAR Wisdom trials.[5,7]

Decreases in other markers for ASCVD (non-HDL cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein) also were observed in all four trials over their duration.[4,5,7,8] In addition to these four trials, a 10-study meta-analysis demonstrated overall safety as well as greater LDL-C reductions with bempedoic acid compared with placebo (mean difference -23.16%, 95% CI -26.92% to -19.04%).[9]

Aside from increases in hyperuricemia and gout, adverse reactions were similar with addition of bempedoic acid or placebo across the trials.[4,5,7] Increases in uric acid levels may be due to inhibition of renal tubular organic anion transporter 2 (OAT2) or by competition between a metabolite of bempedoic acid and uric acid at the same renal transport.[1,8] This effect was seen in all the studies, but at low rates and predominantly in patients with elevated uric acid levels at baseline.[4,5,7,8] Of particular interest, myalgias and other muscle-related adverse reactions, a limiting factor in the use of statins, were similar between treatment and placebo arms in all four studies.[4,5,7,8] Decreased kidney function was noted at initiation, with subsequent improvement over the trial durations.[4,5,7] Elevations in creatinine kinase and aminotransferase levels occurred in less than 2.1% and 4%, respectively, of patients in the treatment arm.[4,5,7] In addition, the CLEAR Harmony and CLEAR Wisdom trials found no increase in patients' A1C with the addition of bempedoic acid.[4,7]

CONCLUSION

LDL-C reductions lead to decreased risk for adverse cardiovascular outcomes. Current guidelines focus on treatment with statins with a few options for secondary augmentation with other medications. Patients who are unable to tolerate statins or reach treatment goals with these therapies are in need of additional options for treatment. In four studies, bempedoic acid has proven to be a safe and effective therapy for LDL-C lowering with and without statins, with some caution for those with preexisting gout or hyperuricemia. The combination of bempedoic acid and ezetimibe, especially when added to a statin, will be very helpful in clinical practice as patients with ASCVD try to reach the ever-lower LDL-C treatment goals. Cardiovascular outcomes data are pending from the ongoing CLEAR Outcomes trial.[5] Although bempedoic acid has not been included in the AHA/ACC Guideline on the Management of Blood Cholesterol, it appears to be a useful tool for clinicians to add to their LDL-C-lowering tool box. **JAAPA**

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