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Research Paper

Comprehension of Bempedoic Acid in Patient with Hypercholestremia and Statin Intolerance

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ABSTRACT: *Bempedoic acid, a prodrug that is activated by a hepatic enzyme not present in skeletal muscle, inhibits ATP-citrate lyase, an enzyme upstream of b-hydroxy b-methylglutaryl-coenzyme Areductase in the cholesterol biosynthesis pathway. Short-term studies have shown that it reduces levels of low-density lipoprotein (LDL) cholesterol. Data are limited regarding the safety and efficacy of bempedoic acid treatment in long-term studies involving patients with hypercholesterolemia who are receiving guideline-recommended statin therapy. Inability to tolerate statins because of muscle symptoms contributes to uncontrolled cholesterol levels and insufficient cardiovascular risk reduction. This review gives an insight into the role of this inhibitor of ATP citrate lyase in patients with hypercholesrtremia and statin intolerance.*

KEY WORDS: *low-density lipoprotein (LDL) cholesterol, Hypercholesrtremia, Statin therapy*

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I. INTRODUCTION

Lipid-lowering therapies, primarily statins, have substantially reduced the burden of cardiovascular disease over the past three decades.[1] Registries and observational studies have reported statin intolerance prevalence rates of 7% to 29%, with the predominant symptoms being muscle-related side effects.[3] Statin-associated muscle symptoms account for >90% of side effects attributed to statins [4] and contribute to the high rate of nonadherence and discontinuation frequently observed with statin therapy.[3]As treatment with a statin, the cornerstone of lipid-lowering therapy, is not suitable at standard doses for individuals with intolerance, these patients are less likely to achieve adequate antiatherogenic lipid reduction and are, thus, at increased risk for adverse cardiovascular outcomes compared with statin-treated patients.[4,5] To reduce cardiovascular risk in these patients, additional pharmacologic lipid-lowering options are needed.[6] Bempedoic acid (Esperion Therapeutics Inc, Ann Arbor, MI)[7] is a first-in-class, small-molecule inhibitor of ATPcitratelyase, a component of the cholesterol biosynthesis pathway that works upstream of b-hydroxy b-methylglutaryl-coenzyme A.[8]Bempedoic acid is a prodrug that is activated by very-longchain acyl-CoA synthetase-1, an enzyme that is not present in skeletal muscle.[9] Therefore, although bempedoic acid acts on the same pathway as statins, lack of the activating enzyme in skeletal muscle may prevent the muscular adverse effects associated with statins.[10] In phase 2 and phase 3 clinical trials, bempedoic acid significantly reduced atherogenic lipoproteins and high-sensitivity C-reactive protein (hsCRP) levels, and was associated with a low risk for adverse events typically associated with statins such as muscle-related symptoms and new-onset diabetes mellitus.[11,12]Here, we report the results of CLEAR (Cholesterol Lowering via Bempedoic acid, an ACLInhibiting Regimen) Serenity, a phase 3 clinical trial designed to evaluate the efficacy, safety, and tolerability of bempedoic acid 180 mg daily versus placebo in statin-intolerant patients requiring lipid-lowering therapy for primary or secondary prevention of cardiovascular events.[13]Bempedoic acid (8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid) is a small molecule that has been shown to lower the LDL cholesterol level by inhibiting ATP citrate lyase, a key enzyme in the cholesterol biosynthesis pathway that acts upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the target for statins.[14,15,16] It is prodrug and requires activation by the enzyme very-long-chain acyl-CoA synthetase 1, which is present in the liver but absent in most peripheral tissues.[17] Therefore, an important feature differentiating bempedoic acid from statins is its liver-specific action. [18]

II. REVIEW OF LITERATURE

Clinical Perspectives and Implications:

The phase 3 CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen) Serenity clinical trial demonstrates the lipid-lowering efficacy of bempedoic acid, a first-in-class, prodrug, small-molecule inhibitor of ATPcitratelyase, among patients with established statin intolerance and elevated low-density lipoprotein cholesterol who were receiving stable background therapy.[19,20] Muscle-related symptoms contributed to the history of statin intolerance for almost all patients.[21]Although bempedoic acid acts on the same cholesterol biosynthesis pathway as statins, the muscle-related adverse event rate in CLEAR Serenity with bempedoic acid, which is not activated in skeletal muscle, did not differ from placebo, even among patients who had experienced muscle-related symptoms while on statin therapy.[22]

Clinical implications Bempedoic acid may offer a novel treatment option to reach low-density lipoprotein cholesterol goals for the large number of patients who have difficulty tolerating statin treatment due to muscle-related side effects.[23]Consistent lipid lowering across patient subgroups and when administered as monotherapy or when added to stable background lipid-lowering therapy indicate the potential for bempedoic acid to provide an effective, oral therapeutic alternative that is complementary to statins and other non-statin therapies.[24]

Efficay of Bempedoic Acid in LDL-C lowering:

The efficacy of bempedoic acid, an oral agent, was initially reported in several phase 2 trials. Ballantyne et al. demonstrated a dose-dependent LDL-lowering effect of bempedoic acid monotherapy in patients with hypercholesterolemia.[25,26] In this phase 2 trial, participants were randomized to three incremental doses of bempedoic acid (40 mg, 80 mg and 120 mg daily) or placebo. Bempedoic acid 120 mg lowered LDL-C by 23% compared to 2.3% in the placebo group.[27] Additional phase 2 trials have assessed the combination of bempedoic acid with other lipid-lowering medications, in particular statins and ezetimibe.[28] When compared to ezetimibe monotherapy, Thompson et al. reported that bempedoic acid monotherapy at a dose of 180 mg daily reduced LDL-C by 30% at 12 weeks compared to 21% LDL-C reduction for ezetimibe alone.[29,30] A combination of bempedoic acid and ezetimibe resulted in 48% LDL-C reduction at 12 weeks.[31]

Phase 3 trials as part of the ongoing CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-inhibiting Regimen) trial series have investigated the efficacy of bempedoic acid.[32] The CLEAR Tranquility trial studied the efficacy and safety of bempedoic acid added to a background lipid-lowering therapy that included ezetimibe in statin-intolerant patients with LDL-C ≥100 mg/dl.[33] Bempedoic acid led to a 28.5% reduction in LDL-C compared to placebo at 12 weeks. Similarly, the CLEAR Serenity trial by Laufs et al. also assessed the efficacy and safety of bempedoic acid in statin-intolerant patients with hypercholesterolemia over a period of 24 weeks.[34] In this trial, approximately 8.4% of the participants continued their tolerated low-dose statin therapy. At 12 weeks, bempedoic acid yielded a 21.4% reduction in LDL-C level compared to placebo.

The CLEAR Wisdom and CLEAR Harmony trials both assessed the safety and efficacy of bempedoic acid in high risk cardiovascular patients with ASCVD, heterozygous familial hypercholesterolemia (HeFH) or both. In the CLEAR Wisdom trial, Goldberg et al. randomized 779 high risk cardiovascular patients with LDL-C ≥70 mg/dL on maximally tolerated statin therapy to bempedoic acid (180 mg) or placebo.[35,36] The addition of bempedoic acid resulted in a 13.9% to 17.4% reduction in LDL-C at 12 weeks.

The CLEAR Harmony included high risk patients on maximally tolerated statin therapy with or without additional lipid-lowering therapy.[37] Approximately 8% of participants were on ezetimibe and 4% were on a fibrate in addition to statins. Participants randomized to bempedoic acid attained an additional 18% LDL-C reduction compared to placebo.

Finally, a phase 3 trial of a fixed-dose combination of bempedoic acid 180 mg and ezetimibe 10 mg in high-risk patients with ASCVD, HeFH, or multiple cardiovascular risk factors and hypercholesterolemia on maximally tolerated statin therapy was performed.[38] In this trial, 301 participants were randomized to either a fixed-dose combination therapy or 180 mg bempedoic acid or 10 mg ezetimibe or placebo. At 12 weeks, the fixed-dose combination led to a 38% LDL-C lowering compared to placebo.[38]

Bempedoic acid and Glycemic control:

A recent pooled analysis of 3,621 participants from four phase 3 trials examined blood glucose and hemoglobin A1C (HbA1c) levels at 12 weeks compared to baseline. In participants randomized to bempedoic acid versus placebo on top of maximally tolerated statin therapy, bempedoic acid was not associated with increased incidence of new-onset diabetes or worsening glycemic control among patients with known diabetes.[17]

Bempedoic acid and cardiovascular outcomes:

The effect of bempedoic acid on cardiovascular morbidity and mortality has yet to be determined. The CLEAR Outcomes trial is an ongoing phase 3 trial that is seeking to bridge this knowledge gap by assessing the effect of bempedoic acid on major cardiovascular events in patients with or at high risk for cardiovascular disease and who have statin intolerance.[1] This double-blind, placebo-controlled trial began enrollment in December 2016 and is estimated to enroll 14,032 participants. The primary composite endpoint includes time from randomization to the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or coronary revascularization. Trial completion is anticipated in March 2022.[33]

Safety and side effects of bempedoic acid:

As anticipated, in light of its lack of active metabolites in skeletal muscles, bempedoic acid added to maximally tolerated statin therapy was not associated with an increased incidence of muscular disorders or serious adverse events compared to placebo in the CLEAR Harmony trial.[38] However, bempedoic acid was associated with hyperuricemia and gout symptoms especially in patients with history of gout.

Of note, bempedoic acid was associated with a slightly increased risk of tendon rupture, involving the biceps tendon, rotator cuff, or Achilles tendon. This risk may be increased in patients over 60 years of age, patients taking corticosteroid or fluoroquinolone drugs, patients with renal failure, and patients with previous tendon disorders. Other more commonly reported adverse events in clinical trials were upper respiratory tract infection, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes.[23]

Given the above evidence demonstrating efficacy and safety, once-daily, oral bempedoic acid (branded as NEXLETOL™) at a dose of 180 mg was approved by the US Food and Drug Administration (FDA) in February 2020 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or established ASCVD who require additional lowering of LDL-C.[40] Considering the LDL-C lowering of about 40% seen in trials of bempedoic acid in combination with ezetimibe, the FDA also approved a fixed-dose combination of bempedoic acid and ezetimibe (branded as NEXLIZET™) for the same indications.

Bempedoic acid demonstrated efficacy in lowering LDL-C either as monotherapy or in combination with ezetimibe. A fixed-dose bempedoic acid and ezetimibe reduces LDL-C by approximately 40%. This amount of LDL-C lowering achieved with the combination drug is two-thirds the amount of LDL-C lowering typically achieved with PCSK9 inhibitors. Bempedoic acid offers an important opportunity for further LDL-C lowering in statin-intolerant patients or in those requiring further LDL-C reduction despite maximally tolerated statin therapy and who are unable to afford a PCSK9 inhibitor. Given that the 2018 ACC/AHA/MS Cholesterol guideline was assembled and published prior to data from phase 3 trials on the efficacy of bempedoic acid in LDL-C lowering, bempedoic acid was not officially included as a nonstatin option in the cholesterol guidelines in America.

Across the Atlantic, the 2019 European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) guideline for the management of dyslipidemias have included bempedoic acid as a potential novel therapy for LDL-C lowering.[15] We eagerly await data on the impact of bempedoic acid on cardiovascular outcomes. Considering the well-established association of LDL-C with ASCVD, and experience thus far with bempedoic acid, a significant reduction is fully anticipated in the primary endpoint in the ongoing CLEAR Outcomes trial. Currently, bempedoic acid is FDA approved for ASCVD secondary prevention or primary prevention in patients with HeFH as an adjunct to diet and maximally tolerated statin therapy.

III. CONCLUSION

Bempedoic acid is a novel class of nonstatin therapy that targets hepatic cholesterol synthesis and has demonstrated significant LDL-C lowering ability as monotherapy and especially in combination with ezetimibe. If data on long-term safety and cardiovascular outcomes in ongoing trials are favorable, bempedoic acid will improve cardiovascular risk prevention in statin-intolerant patients and in resource limited settings.

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