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RESEARCH LETTER

Bempedoic acid: A nonstatin drug for the management of hypercholesterolemia

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1 | INTRODUCTION

Statins, or β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, are considered as the first-line treatment for the management of dyslipidemia in terms of reduction in the low-density lipoprotein cholesterol (LDL-C) level and impeding the cardiovascular events.[1] In many countries, statins are the most recommended medication; numerous clinical trials have consistently proven that statins could play a remarkable role in the reduction of cardiovascular events.[2] Statins are usually effective and well-tolerated, although they are not appropriate for all individuals.[3] Statins can induce rhabdomyolysis, hepatic dysfunction, renal failure, and other side effects. Statin intolerance has been reported in about 5% and 20% of individuals, which further lead to statin discontinuation.[4] To attain the significant changes in individuals with statin resistance, an alternative nonstatin should be practiced (bempedoic acid). This review discusses the overview of bempedoic acid.

1.1 | Overview of Bempedoic acid

Bempedoic acid (BA) was approved by the USFDA in the year 2020 as a nonstatin for hypercholesterolemia. It is an oral agent that inhibits adenosine triphosphate citrate lyase, which is an enzyme involved in cholesterol synthesis by catalyzing acetyl-CoA.[5] BA is activated by the enzyme acyl-CoA synthetase, which in humans is encoded by the gene *SLC27A2* and primarily expressed in the liver and kidney.[6] Molecular weight of BA was found to be 344.492; logP is 4.4699 with 14 rotatable bonds along with 3 acceptors and 3 donors. The water solubility of BA is −2.935 (log mol/L), $Caco_2$ permeability was 0.591 (log Papp in 10^{-6} cm/s), skin permeability is −2.735 (log kp), BA is not a substrate of P-glycoprotein, and BA is not a inhibitor of P-glycoprotein -I and II. While coming to distribution fraction unbound in human was 0.273 (Fu), blood–brain permeability was −1.205 (log BB), and central nervous system permeability was −3.14 (log PS). BA is not a substrate and inhibitor of CYP2D6, CYP3A4, CYP1A2, CYP2C19, CYP2D6, and CYP3A4 isoenzymes. The maximum tolerated dose in human is −0.498 (log mg/kg/d), Acute fathead minnow toxicity was −0.722 (log mM) and BA is not an inhibitor of hERG I and II inhibitors.[7]

The activated substance inhibits adenosine triphosphate citrate lyase, which is involved in the liver's biosynthesis of cholesterol upstream HMG-CoA reductase, the enzyme that is inhibited by statins. The half-life of BA is 15-24 hours, and the site of absorption is the small intestine. Bempedoic acid has been shown to provide a gradual decrease in LDL-C when used in fusion with both statins and ezetimibe at all doses.[8] Though bempedoic acid acts on the same cholesterol biosynthesis pathway as statins, the muscle-related adverse event rate in CLEAR Serenity with bempedoic acid was not activated in skeletal muscle and did not differ from placebo, even among patients who had experienced muscle-related symptoms while on statin therapy.[9]

1.2 | Clinical evidence of bempedoic acid

The initial dose of bempedoic acid is 180 mg/d. BA is a small molecule that is to be taken once daily orally that is absorbed through the small intestine. Once taken up by the liver, the half-life varies between 15 and 24 hours. Initial studies reported up to a 27% decrease in LDL-C with BA used as monotherapy, up to 24% additional decrease in LDL-C when used with statins, and up to 48% total decrease with

TABLE 1 Clinical evidences of bempedoic acid

S.no	Reference	Dose	Study design	Duration	Parameter	Outcome
1.	Arikeri and Punukula	BA-180 mg (n = 45) + ATV-80 mg (n = 23)	Open labeled, randomized	4 wk	LDL-C	Significant reduction in LDL-C levels.
2.	Ballantyne et al[16]	BA-180 mg (n = 110) + EZE-10 mg (n = 109)	Multicenter, double-blind study	12 wk	LDL-C	BA+EZE lowered LDL-C levels.
3.	Goldberg et al[17]	BA-180 mg (n = 522) Placebo (n = 257)	Randomized, double-blind, placebo-controlled clinical trial	12 wk	LDL-C	Addition of BA decreased LDL-C levels.

Abbreviations: BA, bempedoic acid; LDL-C, low-density lipoprotein cholesterol.

ezetimibe.[10,11] Existing reports say that use of bempedoic acid may increases the uric acid and creatinine.[12]

1.3 | Increase uric acid leads to

1. Endothelial dysfunction: Uric acid nurtures hypertension due to increased systemic vascular resistance also by reducing the bio-availability of nitric oxide.
2. Inhibiting insulin pathway: Uric acid inhibits the trigger of an insulin signaling pathway.
3. Thrombus platelet aggression.
4. Uric acid contributes activation of RAAS by increasing juxtaglomerular renin. In diabetes, RAAS can cause, vascular dysfunction and inflammation leading to renal AND cardiovascular complications.[13,14]

2 | DISCUSSION

This review includes patients with a high risk of cardiovascular diseases, patients already on statin therapy, patients who take ezetimibe. Many studies proved BA as an essential drug of choice for patients who are intolerant to statins (Table 1). Some systematic reviews conclude about the effects of BA. Ray et al concluded that the use of BA increases uric acid and GOUT but also said that it is reversible after discontinuation.[18-20] Arikeri and Punukula concludes that BA might be safe in combination with statins as well as ezetimibe and appears to be effectively lower LDLC and has the potential to reduce the risk of muscle-related adverse events.[15] Ballantyne et al concludes that BA +EZE provides a potent therapy that is complementary to existing lipid-modifying regimens.[16] Goldberg et al concludes that patients at higher risk for CVD receiving maximally tolerated statins, along with BA compared with placebo resulted in a significant lowering of LDL-C level over 12 weeks.[17] There were no new oral nonstatin options for LDL-C lowering in nearly 20 years, and Nexletol (BA) is an anticipated solution for the appropriate patients that have not been able to reach their LDL-C goals and could benefit from Nexletol immediately. The drug's approval by the US Food and Drug Administration comes after studies showed an 18% to 28% fall in LDL cholesterol, compared with placebo, in patients who were also on statin. BA cost is approximately 374 USD for 30 tablets. Even though BA might have effects in increasing UA and creatinine, but it is highly reversible and is safe using BA as monotherapy or in combination with atorvastatin or ezetimibe. Using BA in combination especially with atorvastatin helps decrease LDL-C faster and also avoid other muscle-related adverse events.

3 | CONCLUSION

Statin is a golden standard drug, for the management of hyperlipidemia, which has a dual role in the reduction of bad cholesterol and increase in HDL. However, 50% of patients are intolerant to statins because of their frequently reported ADR's in a higher ratio. The long-term safety and efficacy of BA, including effects on cardiovascular outcomes, are currently being assessed in phase 3 clinical trials. This outcome study will be important for determining the function of BA as a suitable alternative for statin intolerance.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial, or otherwise.

AUTHOR CONTRIBUTIONS

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All authors have read and approved the final version of the manuscript.

TRANSPARENCY STATEMENT

The corresponding author confirms that the manuscript is an honest, accurate, and transparent account of the study being reported.

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REFERENCES

1. Schaiff RAB, Moe RM, Krichbaum DW. An overview of cholesterol management. *Am Health Drug Benefits*. 2008;1(9):39-48.
2. Liu Y, Lv X, Xie N, et al. Time trends analysis of statin prescription prevalence, therapy initiation, dose intensity, and utilization from the hospital information system of Jinshan Hospital, Shanghai (2012-2018). *BMC Cardiovasc Disord*. 2020;20(1):201.
3. Toth PP, Patti AM, Giglio RV, et al. Management of statin intolerance in 2018: still more questions than answers. *Am J Cardiovasc Drugs: Drugs Devices Other Interventions*. 2018;18(3):157-173.
4. Stulc T, Ceška R, Gotto AM Jr. Statin intolerance: the clinician's perspective. *Curr Atheroscler Rep*. 2015;17(12):69.
5. Brandts J, Ray KK. Bempedoic acid, an inhibitor of ATP citrate lyase for the treatment of hypercholesterolemia: early indications and potential. *Expert Opin Investig Drugs*. 2020;29(8):763-770.
6. Feng X, Zhang L, Xu S, Shen AZ. ATP-citrate lyase (ACLY) in lipid metabolism and atherosclerosis: an updated review. *Prog Lipid Res*. 2020;77:101006.
7. Cicero AFG, Fogacci F, Cincione I. Evaluating pharmacokinetics of bempedoic acid in the treatment of hypercholesterolemia. *Expert Opin Drug Metab Toxicol*. 2021;17(9):1031-1038.
8. Srivastava RA, Pinkosky SL, Filippov S, Hanselman JC, Cramer CT, Newton RS. AMP-activated protein kinase: an emerging drug target to regulate imbalances in lipid and carbohydrate metabolism to treat cardio-metabolic diseases. *J Lipid Res*. 2012;53(12):2490-2514.
9. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol*. 2012;6(3):208-215.
10. Ballantyne CM, McKenney JM, MacDougall DE, et al. Effect of ETC-1002 on serum low-density lipoprotein cholesterol in hypercholesterolemic patients receiving statin therapy. *Am J Cardiol*. 2016;117(12):1928-1933.
11. Pinkosky SL, Filippov S, Srivastava RA, et al. AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC-1002, a novel small molecule regulator of lipid and carbohydrate metabolism. *J Lipid Res*. 2013;54(1):134-151.
12. Cicero AFG, Pontremoli R, Fogacci F, Viazzi F, Borghi C. Effect of bempedoic acid on serum uric acid and related outcomes: a systematic review and meta-analysis of the available phase 2 and phase 3 clinical studies. *Drug Saf*. 2020;43(8):727-736.
13. Zagelbaum NK, Yandrapalli S, Nabors C, Frishman WH. Bempedoic acid (ETC-1002): ATP citrate lyase inhibitor: review of a first-in-class medication with potential benefit in statin-refractory cases. *Cardiol Rev*. 2019;27(1):49-56.
14. Filippov S, Pinkosky SL, Newton RS. LDL-cholesterol reduction in patients with hypercholesterolemia by modulation of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase. *Curr Opin Lipidol*. 2014;25(4):309-315.
15. Arikeri S, Punukula H. A review article: bempedoic acid as an alternative for statins in reducing cholesterol. *J Med Sci Clin Res*. 2020;08(10):116-121. https://jmscr.igmpublication.org/home/index.php/archive/181-volume-08-issue-10-october-2020/9646-a-review-article-bempedoic-acid-as-an-alternative-for-statins-in-reducing-cholesterol
16. Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol*. 2019;27(6):593-603.
17. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR wisdom randomized clinical trial. *JAMA*. 2019;322(18):1780-1788.
18. Cicero AFG, Fogacci F, Hernandez AV, Banach M, Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group and the International Lipid Expert Panel (ILEP). Efficacy and safety of bempedoic acid for the treatment of hypercholesterolemia: a systematic review and meta-analysis. *PLoS Med*. 2020;17(7):e1003121.
19. Dai L, Zuo Y, You Q, Zeng H, Cao S. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia: a systematic review and meta-analysis of randomized controlled trials. *Eur J Prev Cardiol*. 2020;28(8):825-833. https://doi.org/10.1177/2047487320930585
20. Ray KK, Bays HE, Catapano AL, et al; CLEAR Harmony Trial. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med*. 2019;380(11):1022-1032.

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