Nutrition, Metabolism & Cardiovascular Diseases (2022) **32**, 17–20

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

VIEWPOINT

Clinical evaluation of bempedoic acid for the treatment of hyperlipidaemia

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Received 5 July 2021; received in revised form 21 September 2021; accepted 24 September 2021
Handling Editor: A. Siani
Available online 7 October 2021

KEYWORDS
Bempedoic acid;
ATP citrate lyase;
LDL-cholesterol;
Lipid-lowering treatment;
Novel LDL-C treatment

Abstract Bempedoic acid (BA) is a novel first-in-class oral lipid-lowering therapy. BA has been approved by the European Medicinal Agency and Food and Drug Administration and has been commercialised throughout Europe since the end of 2020 as an add-on therapy in patients at high/very-high cardiovascular risk that are not at LDL-C goals with current lipid-lowering treatments. Recently, Italian lipid management experts gathered to discuss several open questions on BA characteristics and BArelated practical clinical issues. The panel permitted collection of its opinions in a ten Q&A format.
Aim: The aim of this viewpoint is to discuss and answer several open questions on BA characteristics and BA-related practical clinical issues.
Data synthesis: The data includes main phase III studies, subanalysis and meta-analysis on BA.
Conclusions: The panel permitted collection of its opinions in a ten Q&A format.

Bempedoic acid (BA) is an oral, once-daily, small molecule, first-in-class ACL (adenosine triphosphate-citrate lyase) inhibitor, an enzyme integral to the cholesterol synthesis pathway that acts upstream of HMGCR (hydroxy-methyl-glutaryl coenzyme A reductase). BA is a pro-drug converted to the active form by the very-long-chain acyl-CoA synthetase-1 (ACSVL1), expressed in the liver but not in the skeletal muscle [1]. The lack of skeletal muscle activity of this enzyme is postulated to decrease risk of muscle-related adverse effects with BA compared with statin therapy [2]. BA also activates AMPK (AMP-activated protein kinase) and it thought to exert its glucose-lowering effect through the suppression of hepatic glucose production [3].

BA's efficacy and safety profiles have been defined in the CLEAR program encompassing 3623 patients [4–7]. LDL-C percentage reduction was 17.8% (placebo corrected) among patients with atherosclerotic cardiovascular disease (ASCVD) and/or HeFH receiving a maximally tolerated statin and 24.5% (placebo corrected) among individuals with statin intolerance [2]. In a fixed-dose combination with ezetimibe (FDC trial), BA reduced LDL-C by 38.0%

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https://doi.org/10.1016/j.numecd.2021.09.023

(placebo corrected), irrespective of statin utilization and intensity. The extent of lipid-lowering suggests an additive effect of bempedoic acid and ezetimibe due to the known differences in their action mechanisms. Interestingly, 33.7% of patients experienced an LDL-C reduction from baseline of 50% or greater [8]. BA-induced LDL-C decrease is sustained during long-term follow-up [9]. In addition to LDL-C lowering, bempedoic acid improved other parameters such as total cholesterol, non-HDL-C, apoB, and hs-CRP consistently across different trials [2].

The most common adverse events did not differ compared to placebo. Rates of other adverse events of special interest were low and differed in frequency by less than 2% between treatment groups. BA may be responsible for minor elevations in serum creatinine and uric acid by inhibiting organic anion transporter OAT2, which plays a role in uric acid and creatinine uptake from blood to proximal tubular cells. These effects are stable and completely reversible after BA discontinuation [10]. Further pooled analyses have shown that the gout incidence was higher in subjects with a history of gout and particularly in those with raised uric acid levels at baseline (above upper limit of normal) [11] The incidence of new-onset or worsening diabetes was significantly lower in patients treated with BA [2,12].

Practical open questions

1. When to use BA alone, and when a fixed-dose combination with ezetimibe?

BA will be available alone or in an FDC with ezetimibe 10 mg. The experts agree the FDC will improve adherence and compliance in patients receiving statins and ezetimibe alone or other lipid-lowering therapies. Moreover, in patients already receiving combinations of statin plus ezetimibe, switching to FDC, containing drugs at a fixed dosage, may help clinicians modulate statins types and dosages in some particular cases.

2. Poly-pharmacotherapy: can BA be used in poly-treated patients?

The experts agree on the favourable safety and tolerability profile of BA. Considering BA is an add-on therapy experts agree on the benefit of associating it with any intensity and any dose statin as no clinically significant interactions were demonstrated, except for a high dose of simvastatin ($\geq$40 mg) that is not commonly used in high/very-high risk patients. Since BA is not metabolized by and does not inhibit or induce cytochrome P450 enzymes, experts suggest preferring BA in high-risk comorbid poly-treated patients to avoid the risk of interactions.

3. Can BA be an option for elderly patients?

The strict control of lipid levels in patients aged 80 and older remains controversial [13,14]. These patients are underrepresented in the major trials that established the cardiovascular benefits of lipid-lowering therapy. Experts agree that BA may be a strategic tool in such individuals who cannot reach the recommended target with currently available treatments. The panel recognizes that BA could represent a valid novel therapeutical option since the CLEAR program enrolled a sub-fraction (although small) of patients with age >80. Moreover, BA's selectivity makes the molecule very suitable for the elderly in terms of tolerability and general safety.

4. Are there concerns about BA in patients with hyperuricemia or gout?

Experts agree that the modest increase in uric acid levels associated with BA treatment is not a concern since the clinical benefits of BA treatment would outweigh the potential risk of gout. Experts acknowledge that the complete reversibility of the acid uric elevation after discontinuation of BA treatment is reassuring. Experts also recognize that patients with asymptomatic hyperuricemia (serum urate >6.8 mg/dL with no prior gout flares or subcutaneous tophi) do not require urate-lowering therapy as recommended by the current guidelines [15].

5. Can BA be safely used in patients with renal or hepatic impairment?

Experts agree that the slight increase in creatinine level and the modest reduction in eGFR are not clinically meaningful. Indeed, the slight decrease in eGFR is stable over time, and the elevation in creatinine levels is reversible after BA discontinuation.

BA's pharmacokinetics have been studied in subjects with normal hepatic function or mild or moderate hepatic impairment (Child-Pugh A or B), and no dose adjustment is needed [10]. BA has not been investigated in patients with severe hepatic impairment (Child-Pugh C). Experts recognize that BA can be used in subjects with mild or moderate hepatic impairment based on the observation that aminotransferase elevations are asymptomatic and reversible regardless of continuation or discontinuation of BA treatment.

6. Can BA be safely used in patients with alteration in glucose metabolism?

Experts agree that BA does not alter glucose metabolism but conversely appears to be protective against hyperglycemia and this effect may be clinically relevant in individuals with overt diabetes and at risk of developing diabetes (pre-diabetes). BA may help reach the LDL-C goal levels in diabetic patients since deterioration in glucose control may be one reason for poor adherence to statins, and hence, for suboptimal treatment in diabetic patients at high cardiovascular risk. Moreover, experts agree that a randomized controlled trial aimed to determine the clinical relevance of BA's effects on the risk of developing diabetes in individuals at high cardiovascular risk having impaired fasting glucose levels, impaired glucose

tolerance, or both would help support further the benefits of BA in these subjects.

7. Can BA be suitable for patients with Heterozygous Familial Hypercholesterolemia (HeHF)?

Experts agree that HeHF patients represent a difficult-to-treat population, having LDL-C ranging from about 160 mg/dL to over 300 mg/dL. According to the guidelines [16], HeFH patients belong to high/very high-risk categories: about half of them require a reduction of 50%–90% to achieve the LDL-C objectives, demanding almost always PCSK9 inhibition as an add-on therapy. However, experts agree that BA may represent an additional choice to further optimize the treatment, especially in HeFH patients who are statin-intolerant or unable to reach the LDL-C goal with currently available therapies.

8. How could BA be used in relation to PCSK9i?

Experts agree that using BA in some cases could be cost-effective compared to more expensive therapies and can be considered as a very attractive third line therapy before PCSK9i in high or very high-risk patients who are not far from the individual LDL-C goal after prescription of high intensity statins plus ezetimibe. For example, BA could be added before PCSK9i in statin-intolerant patients receiving ezetimibe who require about 35% LDL-C reduction [4]. Furthermore, according to preliminary data that demonstrated an additional 30% reduction of LDL-C with BA added to evolocumab [17], experts agree that the two therapies could be intertwined according to the therapeutic goal and reimbursability criteria.

9. Can BA have a protective effect on the prevention of cardiovascular events?

The effect of BA on cardiovascular morbidity and mortality has not been determined yet. An ongoing cardiovascular outcomes trial, the CLEAR-outcomes trial [18], evaluates the efficacy of BA compared to placebo on the first occurrence of MACEs, in statin-intolerant patients with ASCVD or at high risk of developing ASCVD. Experts agree that the currently available evidence suggests that BA might exert clinical cardiovascular benefit along with its LDL-C lowering effect. The results of the CLEAR-outcomes trial will help to establish the cardiovascular benefits of BA treatment.

10. Can BA be used in patients with ASCVD who experience a second vascular event within two years and have already reached LDL-C of 55 mg/dL?

Within the pool of very high-risk patients, particular subgroups benefit the most by lowering LDL-C far below the recommended threshold of 55 mg/dL and possibly below 40 mg/dL, according to the 2019 ESC/EAS Guidelines for the management of dyslipidaemias [16]. In such patients, adding BA to standard therapy might be reasonable, even when the 55 mg/dL LDL-C target has been achieved with statins and ezetimibe to reduce further LDL-C levels maximize the MACE reduction. Therefore, the panel suggests considering, in a framework of personalized medicine, a more aggressive therapeutical strategy in the "extremely high risk" individuals, such as post–MI patients with diabetes and metabolic syndrome or with multiple ischemic episodes or with multivessel coronary disease or cerebrovascular or peripheral arterial disease. Furthermore, experts agree that for any high/very-high risk category with LDL-C $<$100 mg/dL, BA is a practical, tolerable and cost-effective therapeutical option to reduce LDL-C and the resulting cardiovascular risk further.

Declaration of competing interest

This manuscript is a result of a meeting unconditionally supported by Daiichi Sankyo. The authors do not declare other conflicts of interest with regard to this manuscript.

Acknowledgements

Participants of the The Italian Clinical Network on Bempedoic Acid are Daniele Andreini, Maurizio Averna, Claudio Bilato, Enzo Bonora, Gianluca Campo, Roberto Catalini, Matteo Marco Ciccone, Salvatore De Rosa, Carlo Di Mario, Claudio Ferri, Nicola Ferri, Liliana Grigore, Antonio Lanzilli, Giuseppe Mandraffino, Tiziana Montalcini, Federico Nardi, Matteo Pirro, Roberto Pontremoli, Francesco Prati, Francesco Purrello, Vincenzo Russo, Tiziana Sampietro, Riccardo Sarzani, Marino Scherillo, Roberto Scicali, Giorgio Sesti, Patrizia Suppressa, Pierluigi Temporelli, Pierfranco Terrosu, Maurizio Tespili, Roberto Trevisan.

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