European Heart Journal Supplements (2023) **25** (Supplement C), C109–C111
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad012

ESC
European Society
of Cardiology

Bempedoic acid: what prospective uses?

Ilaria Jacomelli[1]*, Luca Monzo[1,2], Germana Panattoni[1], Chiara Lanzillo[1], Marco Rebecchi[1], and Leonardo Calò[1]

[1]Department of Cardiology, Policlinico Casilino, Via Casilina 1049, 00169 Rome, Italy; and [2]Centre d'investigation Cliniques Plurithématique, Universitè de Lorraine INSERM, Nancy, France

KEYWORDS
Bempedoic acid;
Cardiovascular disease;
LDL-cholesterol;
Statin intolerance

There is still the need to lower LDL-c, although the use of statins, ezetimibe and proprotein convertase subtilisin/kexin type 9. Patients with atherosclerotic cardiovascular disease and/or familial hypercholesterolaemia are treated with statins at maximum tolerated dose, with or without further lipid-lowering drugs, but very often, we can't reach the goal, so bempedoic acid treatment lead to a significant reduction in low-density lipoprotein cholesterol, in different groups of patients, with a favourable safety profile.

General considerations

The powerful message of modern cardiology has been to promote and raise awareness among physicians and patients of the importance of LDL cholesterol reduction. This must be achieved according to prescribed therapeutic targets, based on the patient's risk class and, above all, must be maintained over time to reduce cardiovascular morbidity and mortality in primary prevention and lower residual risk in secondary prevention. For each 1-mmol/L (38.7-mg/dL) reduction in LDL-C, the risk of major cardiovascular events is reduced by 22%.[1] Recent data have highlighted how the real world is still so far from the ideal, in particular, early data from the SANTORINI study (Treatment of High and Very High riSk Dyslipidaemic pAtients for the PreveNTion of CardiOvasculaR Events in Europe) and previously from the START and DA VINCI registries.

SANTORINI is the first European observational study, since the 2019 guidelines, to assess whether the management of high- and very high-risk patients has improved. It is a multinational, prospective, observational, non-interventional study. The result is that only 20.7% of the patients achieved CV risk-based LDL-C goals. The majority of patients (53.0%) were receiving monotherapy, including 49.2% on statins, 1.7% ezetimibe, 1.6% a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i).[2] In the START registry, very high-risk patients were enrolled in a large cohort of established ASCVD managed by cardiologists, the lipid management and LDL-C targets attainment is largely suboptimal.[3] In the DA VINCI study gaps between clinical guidelines and clinical practice for lipid management across Europe persist, which will be exacerbated by the 2019 guidelines. Even with optimized statins, greater utilization of non-statin lipid loweing therapies is likely needed to reduce these gaps for patients at highest risk.[4]

Certainly, in this scenario there is a right position for bempedoic acid.

Bempedoic acid: identity card

Bempedoic acid is a prodrug that need to be actived in bempedoyl CoA, by the enzyme very long-chain acyl-CoA synthease-1 (ACSVL1).[5] It is the first orally administered drug in the class of the ACLY inhibitors. The ACSVL1 enzyme is expressed mainly in the liver and kidney, but not in the skeletal muscle or other tissues, this limits the risk of myalgia and myopathy. The lipid-lowering effects of bempedoyl-CoA are mediated through the inhibition of ACL in the liver, decreasing the activity of the lipid biosynthetic pathway of acetyl-CoA. ACL acts two steps upstream of 3-hydroxy-3-methylglutaryl-CoA reductase in this pathway. By inhibiting cholesterol synthesis in the liver, bempedoyl-CoA induces the upregulation of the LDL receptor and stimulates the uptake of LDL particles by the liver, which contributes to the reduction of LDL in the blood.[6]

*Corresponding author. Tel: +39 3381498051, Email: ilaria.jacomelli@gmail.com

Neither bempedoic acid, its active metabolite bempedoyl-CoA, nor the glucuronide forms are metabolized or interact with cytochrome P450 enzymes including CYP3A4 and CYP2C9.

The most important pharmacological interactions involving bempedoic acid are those between bempedoic acid and simvastatin and pravastatin. Co-administration of simvastatin 20 mg with bempedoic acid 240 mg, or simvastatin 40 mg with bempedoic acid 180 mg, in healthy participants resulted in an approximately two-fold and 1.5-fold increase in simvastatin AUC and Cmax, respectively. A similar two-fold increase in AUC and Cmax was seen when pravastatin 40 mg was dosed with steady-state bempedoic acid 240 mg in healthy participants. These interactions are important, given that many patients taking bempedoic acid also take statins concomitantly, including patients who are intolerant of higher-intensity statin therapy; therefore, doses of simvastatin >20 mg and pravastatin >40 mg should be avoided. The interaction of bempedoic acid with pravastatin may be due to the effects of bempedoic acid on the OATP2 transporter, which transports pravastatin.[7]

After oral intake, steady state is reached after seven days, and food has no effect on the oral bioavailability. The elimination of bempedoic acid occurs primarily in the kidneys, with 70% recovered in urine and 30% in faeces.

Bempedoic acid administered as a 180-mg once-daily dose is approved in the USA and in Europe as an adjuvant to maximally tolerated statin therapy to lower LDL-C for patients with ASCVD and for patients with heterozygous familial hypercholesterolaemia (HeFH). In addition, bempedoic acid is approved in the European Union to treat patients who are unable to take any dose of a statin (statin intolerant) or for whom a statin is contraindicated. Bempedoic acid is also available as a fixed-dose combination drug product that consists of 180 mg of bempedoic acid and 10 mg of ezetimibe.

Bempedoic acid increases the incidence of elevated uric acid, which, sometimes, can lead to hyperuricaemia or gout. The mechanism of this increase of uric acid might be due to competition between uric acid and the bempedoic acid glucuronide metabolite for the same renal OAT2 transporter. Uric acid levels should be assessed periodically as clinically indicated, patients should be monitored for signs and symptoms of hyperuricaemia, and urate-lowering drugs should be initiated as appropriate.

Tendon rupture or injury (including tendon rupture, rotator cuff syndrome, biceps tendon injury, and Achilles tendon injury) occurred in 0.5% patients treated with bempedoic acid. Bempedoic acid should be discontinued if tendon rupture occurs. Patients with known risk factor, such as concomitant statin use, fluoroquinolone or systemic corticosteroid use, diabetes, gout, rheumatoid arthritis, renal failure, age > 60 years, should be monitored closely as rupture may occur more frequently.

Study evidence: what about efficacy

The efficacy and safety of bempedoic acid, including the occurrence of muscle-related adverse events, have been addressed by Phase 2 and Phase 3 clinical trials. Phase 3 clinical trials, CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity, and CLEAR Tranquility, demonstrated that in patients with atherosclerotic cardiovascular disease and/or familial HeFH, the use of bempedoic acid leads to a significant reduction in low-density lipoprotein paying a small price of side effects. An ongoing Phase 3 study is currently evaluating the effect of longer-term (median duration of 3–4 years) treatment with bempedoic acid on the incidence of cardiovascular events.

Clear Harmony[8]: randomized double-blind parallel-group vs. placebo study designed to evaluate efficacy and safety of bempedoic acid in a group of patients with established cardiovascular disease already on maximal statin therapy. The trial enrolled 2229 patients randomized 2:1 to bempedoic acid 180 mg as a single daily administration ($n = 1488$) vs. placebo for 52 weeks. The target population consisted of patients with established cardiovascular disease (97.6%), heterozygous familial HeFH (3.5%), or both; all patients had to be already on statin treatment at the maximum tolerated dose for at least 4 weeks and with C-LDL levels >70 mg/dL. Regarding baseline statin treatment, 148 patients (6.6%) were treated with low-intensity statins, 970 patients (43.5%) with moderate-intensity statins and 1112 patients (49.9%) with high-intensity statins; only 7.7% of patients were on ezetimibe therapy; no patients on PCSK9i.

Clear Wisdom[9]: randomized, double-blind, parallel-group vs. placebo study to evaluate efficacy and safety of bempedoic acid (180 mg as a single daily administration) in patients with high cardiovascular risk already on maximal statin therapy. Specifically, patients had to have established cardiovascular disease, defined as ischaemic heart disease or equivalent (atherosclerotic cerebrovascular disease or peripheral arterial disease, however, patients with only diabetes mellitus were excluded), had to have C-LDL levels >100 mg/dL, and be on maximal hypolipidaemic therapy. In total, the study enrolled 779 patients, randomized to bempedoic acid ($n = 522$) 180 mg vs. placebo.

CLEAR Serenity[10] confirms the tolerability of bempedoic acid in a population, such as statin-intolerant patients, where hypolipidaemic therapeutic options are limited and where new molecules are needed rapidly to reach guideline-recommended C-LDL targets.

The latest published Phase 3 study of the CLEAR project is the CLEAR Tranquility study,[11] which enrolled 269 hypercholesterolaemic people with statin intolerance and on ezetimibe 10 mg therapy, randomized 2:1 to bempedoic acid 180 mg (n = 181) as a single administration vs. placebo. In the CLEAR Tranquility study, patients, to be defined as intolerant, had to report that they started statin therapy and were unable to tolerate it because of adverse events that arose or worsened during treatment, events that later resolved or improved with discontinuation or dose reduction. This definition based on what the patient reported, although not strict, is adherent to routinary clinical practice. Patients had to have a history of established and stable cardiovascular disease, or history of cardiovascular risk factors such as hypertension and diabetes, and C-LDL levels >100 mg/dL.

Baseline LDL-C levels across these four trials ranged from 103.2 to 157.6 mg/dL. Despite the different patient populations enrolled, bempedoic acid was consistently associated with significant decreases in LDL-C at week 12, compared with essentially no change in the placebo arm. In the two trials of bempedoic acid added to stable maximally tolerated lipid-lowering therapy (ASCVD and/or HeFH on statins pool), the placebo-corrected change in

LDL-C from baseline at Week 12 was a decrease of 17.4–18.1%. Patients with HeFH made up only a minority of patients in these trials. Analysing, patients with HeFH had a greater placebo-corrected change in LDL-C of −22.3% ($n = 112$) compared with −18.3% among those patients without a diagnosis of HeFH ($n = 2897$) [37]. In the two trials conducted in patients taking low dose or no statin (statin-intolerant pool), the placebo-corrected change in LDL-C from baseline was a decrease at week 12 of 21.4% to 28.5%. These improvements in LDL-C were sustained through 24–52 weeks of follow-up. Similar patterns were observed for changes in other lipid parameters, including non-high-density lipoprotein cholesterol, total cholesterol, and apolipoprotein B). These data demonstrate that bempedoic acid is an effective treatment option to lower atherosclerotic LDL-C either in combination with maximally tolerated lipid-lowering therapy in patients with ASCVD and/or HeFH or as monotherapy in patients who are unable to take statin therapy.

Finally, essential message about the bempedoic acid fixed dose with ezetimibe in patients at high risk of cardiovascular disease due to atherosclerotic vascular disease or multiple risk factor or HeFH. The study included four treatment arms: bempedoic acid and ezetimibe fixed-dose combination, bempedoic acid alone, ezetimibe alone, and placebo. Overall, 46.5% of patients in this trial had diabetes, and 85.4% had hypertension. The bempedoic acid and ezetimibe fixed-dose combination decreased LDL-C by 36.2% at week 12, as compared with a 23.2% decrease with ezetimibe alone, 17.2% with bempedoic acid alone, and a 1.8% increase with placebo. Ezetimibe used alone in this study had only a small effect on hsCRP (8.2% decrease) at 12 weeks, compared with a 31.9% decrease in hsCRP with bempedoic acid alone. A 35.1% decrease in hsCRP was observed at 12 weeks with the bempedoic acid and ezetimibe fixed-dose combination; patients in the placebo arm had a 21.6% increase in hsCRP. In conclusion, the bempedoic acid and ezetimibe fixed-dose combination significantly lowered low-density lipoprotein cholesterol versus placebo or other oral monotherapies and had a favourable safety profile when added to maximally tolerated statin therapy in patients with HeFH and high cardiovascular disease risk.[12]

Future prospective

Introduction of a new hypolipidaemic drug invites us to rethink all the therapeutic options for most complex patients. Identification of the c-LDL target is the first step, followed by in-depth examination of patient's clinical characteristics.

Starting from the 'the lower-the better' principle, it is possible to choose for each patient a dual or triple hypolipidaemic therapy, aimed at achieving the LDL-c target with the least possible side effects, to be even more incisive in reducing cardiovascular morbidity and mortality.

With this in mind, bempedoic acid can be added to maximum tolerated statin therapy or used alone or in combination with ezetimibe in statin-intolerant patients.

The impact on outcomes remains to be clarified, although data from the Clear Harmony Open-Label Extension Study highlighted that bempedoic acid was generally well tolerated and demonstrated sustained efficacy with up to 2.5 years of continuous treatment.[13]

Funding

None declared

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

References

1. Cholesterol Treatment Trialists Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C *et al*. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670–1681.
2. Catapano1 AL, Manu MC, Burden A, Ray KK, The SANTORINI Investigators. LDL-C goal achievement and lipid-lowering therapy in patients by atherosclerotic cardiovascular disease subtype: the SANTORINI study. *Eur Heart J* 2022;**43**:ehac544–2373.
3. De Luca L, Arca M, Temporelli PL, Meessen J, Riccio C, Bonomo P *et al*. Current lipid lowering treatment and attainment of LDL targets recommended by ESC/EAS guidelines in very high-risk patients with established atherosclerotic cardiovascular disease: Insights from the START registry. *Int J Cardiol* 2020;**316**:229–235.
4. Ray KK, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G *et al*. EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study. *Eur J Prev Cardiol* 2021;**28**:1279–1289.
5. Pinkosky SL, Newton RS, Day EA, Ford RJ, Lhotak S, Austin RC *et al*. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun* 2016;**7**:13457.
6. Burke AC, Telford DE, Huff MW. Bempedoic acid: effects on lipoprotein metabolism and atherosclerosis. *Curr Opin Lipidol* 2019;**30**:1–9.
7. Ballantyne CM, Bays H, Catapano AL, Goldberg A, Ray KK, Saseen JJ. Role of bempedoic acid in clinical practice. *Cardiovasc Drugs Ther* 2021;**35**:853–864.
8. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR *et al*. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med* 2019;**380**:1022–1032.
9. Goldberg AC, Leiter LA, Stroes ESG, Baum SJ, Hanselman JC, Bloedon LT *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**:1780–1788.
10. Laufs U, Banach M, Mancini GBJ, Gaudet D, Bloedon LT, Sterling LR *et al*. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. *J Am Heart Assoc* 2019;**8**:e011662.
11. Ballantyne CM, Banach M, Mancini GB, Lepor NE, Hanselman JC, Zhao X *et al*. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. *Atherosclerosis* 2018;**277**:195–203.
12. Ballantyne CM, Laufs U, Ray KK, Leiter LA, Bays HE, Goldberg AC *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 Prevent Cardiol* 2020;**27**:593–603.
13. Ballantyne CM, Banach M, Bays HE, Catapano AL, Laufs U, Stroes ESG *et al*. Long-term safety and efficacy of bempedoic acid in patients with atherosclerotic cardiovascular disease and/or heterozygous familial hypercholesterolemia (from the CLEAR Harmony Open-Label Extension Study). *Am J Cardiol* 2022;**174**:1.