REVIEW

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New insights into the role of bempedoic acid and ezetimibe in the treatment of hypercholesterolemia

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Purpose of review
A number of new cholesterol-lowering drugs have been recently developed and approved, enriching the pharmacological armamentarium beyond and above statins. Ezetimibe, available since two decades, and bempedoic acid, a new drug inhibiting the same biosynthetic pathway targeted by statins but at an early step, represent valuable tools for the treatment of hypercholesterolemia, particularly in specific groups of patients.

Recent findings
Bempedoic acid, either alone or in combination with ezetimibe, appears to reduce significantly LDL-C levels, an effect that has been observed also in patients with statin intolerance. A Mendelian randomization study has anticipated a protective cardiovascular effect of bempedoic acid; a randomized clinical trial is currently assessing whether the pharmacological control of hypercholesterolemia with bempedoic acid translates into a clinical benefit. Bempedoic acid, as well as ezetimibe, does not appear to induce adverse events in muscles; moreover, whereas statins are associated with a modest, although significant, increased risk of new-onset diabetes, bempedoic acid does not, at least based on the available evidence.

Summary
On the basis of available data, and while awaiting the results of the outcome trial, bempedoic acid appears to represent a valuable approach for the treatment of hypercholesterolemia, either alone or in combination in ezetimibe.

Keywords
ATP citrate lyase, bempedoic acid, cholesterol biosynthesis, ezetimibe, hypercholesterolemia, lipid-lowering, low-density lipoprotein receptor

INTRODUCTION

Over the last few years, a number of cholesterol-lowering agents have been developed with the aim to enrich the lipid-lowering armamentarium beyond and above statins. We have witnessed the rapid development and approval of two monoclonal antibodies targeting PCSK9, one gene-silencing approach to inhibit PCSK9, and one nonstatin cholesterol synthesis inhibitor. The last, known as bempedoic acid, inhibits an early step in the cholesterol biosynthetic pathway by modulating the activity of ATP citrate lyase (ACL), an enzyme located upstream of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoAR, the target of statins), resulting in the upregulation of hepatic low-density lipoprotein receptor (LDLR) and the reduction of circulating LDL-C levels [1]. The observation that inherited variants in the gene encoding ACL (*ACLY*), mimicking the effect of bempedoic acid, reduce plasma LDL-C levels and the risk of cardiovascular disease similarly to variants in the gene encoding HMG-CoAR per unit decrease in LDL-C [2] has suggested that pharmacological inhibition of ACL might represent a valuable tool for the control of hypercholesterolemia and to reduce the risk of cardiovascular outcomes. Since then, phase

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KEY POINTS

- Several cholesterol-lowering agents have been recently developed, thus enriching the lipid-lowering armamentarium beyond and above statins.
- Muscle-related adverse events and increased risk of new-onset diabetes are two major perceived issues related to the use of statins.
- Bempedoic acid is a new cholesterol synthesis inhibitor that, based on the available data, does not induce muscular adverse symptoms or increase the risk of diabetes.
- Although waiting for the results of the outcome trial, bempedoic acid appears to represent a valuable tool for the control of hypercholesterolemia, either alone or in combination with ezetimibe.

1–3 clinical trials have shown that bempedoic acid reduces LDL-C levels by ~20%, with some variability related to the underground lipid-lowering therapy. It is worth mentioning that bempedoic acid increases also the activity of AMP-activated protein kinase (AMPK) [3], an enzyme involved in carbohydrate metabolism, but the possible clinical relevance of this effect in humans remains to be established. Bempedoic acid 180 mg has been approved for the treatment of adults with established atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) who require additional lowering of LDL-C.

Ezetimibe, on the other hand, reduces cholesterol absorption by inhibiting the Niemann-Pick C1 like 1 (NPC1L1) protein activity in the intestine, providing an alternative way for the control of LDL-C plasma levels with a very good safety profile [4]. Genetic variants in *NPC1L1* associated with lower levels of LDL-C, mimicking the effect of ezetimibe, protect against ischemic vascular disease [5,6]. The addition of ezetimibe 10 mg to a statin therapy is recommended by guidelines and represents the first step in the combination therapy aiming at reducing LDL-C plasma levels in patients who do not achieve the LDL-C goal or cannot tolerate a high-dose statin [7].

In this review, we will discuss the available evidence on the efficacy and safety of bempedoic acid, focusing on its potential use either alone or in combination with ezetimibe for the treatment of hypercholesterolemia.

STATIN-INTOLERANT PATIENTS: THE NEW TREATMENT OPTIONS

Despite the established and indisputable effectiveness of statins in reducing LDL-C levels and the incidence of cardiovascular events, there are some concerns about the use of this class of drugs that must be taken into consideration when managing hypercholesterolemia in specific groups of patients, and include both muscle-related adverse events and an increased risk of new-onset diabetes. The so-called statin-intolerance is the inability to tolerate an effective dose of statin because of the occurrence of statin-related adverse events, generally of muscular origin [8], which limits the effectiveness of treatment in clinical practice. Although the incidence of a true statin-intolerance appears to be much lower than reported, because of a 'nocebo effect' [9,10▪], many patients experiencing such adverse muscular outcomes are more likely to have a poor adherence to therapy or even discontinue medications. An alternative approach with a different drug may thus represent a valuable tool to control LDL-C levels and reduce the cardiovascular risk in patients unable to tolerate a statin therapy. Bempedoic acid is a pro-drug that is converted into its active form by the very-long-chain acyl-CoA synthetase-1 (ACSVL1), an enzyme highly expressed in hepatocyte, but not in skeletal muscle [1]. On the basis of this observation, bempedoic acid is not expected to cause muscle-related adverse events that are instead typically associated with the use of statins, thus fostering the interest on this drug as a promising option for the treatment of statin-intolerant patients.

Phase 2 studies

Phase 2 studies have reported significant reductions in LDL-C levels among patients treated with bempedoic acid alone, or as add-on to statin therapy or to ezetimibe. In patients having hypercholesterolemia and a history of statin intolerance, bempedoic acid was effective in reducing LDL-C levels either in monotherapy [11] or in combination with ezetimibe [12] (Table 1). Bempedoic acid alone reduced LDL-C levels by 32% from baseline to week 8, compared with a 3.3% reduction in the placebo group; among the patients who were not at LDL-C goal at baseline, 62% achieved their goal at week 8 [11]. The lipid profile was also improved, and high sensitivity C-reactive protein (CRP) levels were significantly reduced by 42% [11]. Rates of muscle-related adverse events were similar in bempedoic acid and placebo-treatment groups (27 and 32%, respectively) [11]. In another study, bempedoic acid 180 mg was given alone or in combination with ezetimibe, providing 30.1 and 47.7% reductions in LDL-C levels, respectively, compared with a 21.2% reduction observed with ezetimibe alone, with no differences between patients with and without statin intolerance [12].

Table 1. Effect of bempedoic acid on low-density lipoprotein cholesterol and CRP levels in phase 2 and phase 3 trials in statin intolerant patients

Study	Study design	Inclusion criteria	Primary outcomes	Treatment duration	Study groups	*N* patients	Percent change in LDL-C from baseline	Percent change in CRP from baseline
Thompson, 2015 Phase 2	Randomized double-blind placebo-controlled	Statin-intolerant LDL-C 100–220 mg/dl	Percent change in LDL-C	8 weeks	Increasing doses of BA Placebo	37 19	−32% −3.3%	−42% 0
Thompson, 2016 Phase 2b	Randomized Double-blind Placebo-controlled	18–80y LDL-C ≥ 130–220 mg/dl	Percent change in LDL-C	12 weeks	BA 120 mg BA 180 mg BA 120 mg + Eze 10 mg BA 180 mg + Eze 10 mg Eze 10 mg	99 97 22 24 98	−27.5% −30.1% −43.1% −47.7% −21.2%	−30.1% −40.2% −38.1% −25.6% −10.5%
Laufs, 2019 Phase 3	Randomized Double-blind Placebo-controlled Parallel group	Statin intolerant LDL-C at least 130 mg/dl (primary prevention) or LDL-C at least 100 mg/dl (secondary prevention or HeFH)	Percent change in LDL-C	24 weeks	BA 180 mg Placebo	234 111	−23.6% −1.3%	−25.4% +2.7%
Ballantyne, 2018 Phase 3	Randomized Double-blind Placebo-controlled Parallel group	Statin intolerant LDL-C at least 100 mg/dl	Percent change in LDL-C	4-week run-in with Eze 10 mg 12 weeks	BA 180 mg Placebo	181 88	−23.5% +5.0%	−32.5% +2.1%

BA, bempedoic acid; Eze: ezetimibe; CRP, high sensitivity C-reactive protein; LDL-C, low density lipoprotein cholesterol.

Other biochemical parameters were beneficially affected by bempedoic acid treatment, including CRP [12].

Phase 3 studies

The effectiveness of adding bempedoic acid to ezetimibe in the treatment of statin-intolerant patients has been investigated also in two phase 3 trials included in the CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen) program of bempedoic acid (Table 1). The CLEAR Serenity trial [13] evaluated the effect of 180 mg bempedoic acid or placebo in hypercholesterolemic patients with a history of intolerance to at least two statins [13]. Most patients (∼58%) were not receiving any concomitant lipid-lowering therapy at baseline, and only 8.4% of patients had very low-dose statin as background therapy. LDL-C levels were significantly reduced by −23.6% from baseline to week 12 (vs. −1.3% with placebo); lipid profile was significantly improved and CRP was reduced in patients receiving bempedoic acid compared with those receiving placebo [13]. Muscle-related adverse events were similar between bempedoic acid and placebo group, also among patients receiving a very-low-dose statin background therapy [13]. In the CLEAR Tranquility trial [14], patients with a history of intolerance to statins and LDL-C greater than 100 mg/dl were treated with bempedoic acid or placebo added to ezetimibe. Concomitant lipid-modifying therapy (in addition to ezetimibe) was used by 44.8% of recruited patients, among which 31% were receiving concomitant statin therapy. The addition of bempedoic acid to a background ezetimibe therapy reduced LDL-C levels by 23.5%, compared with a 5% increase observed among placebo-treated patients [14]. Non-HDL-C, total cholesterol, apoB, and CRP were significantly reduced among patients receiving bempedoic acid [14]. Bempedoic acid had comparable LDL-C-lowering effects across subgroups, except when patients were analysed based on their background therapy: the effect of bempedoic acid was greater among patients receiving nonstatin or no background therapy (−34.7%) compared with those taking low or very low-dose statin (−20.5%) [14], an observation supported by the results of two additional studies included in the CLEAR program (CLEAR Harmony and CLEAR Wisdom). In these studies, patients treated with bempedoic acid added to the maximally tolerated dose of statin showed comparable reductions in LDL-C levels (−16.5 and −15.1%, respectively), compared with placebo (+1.6 and +2.4%, respectively) [15,16], that were lower than those observed when bempedoic acid was added to

ezetimibe. This finding, however, is unsurprising and can actually be anticipated by the mechanism of action of bempedoic acid, which inhibits the same pathway targeted by statins: in patients treated with the maximally tolerated dose of statin, the cholesterol biosynthetic pathway is already substantially inhibited, and the addition of bempedoic acid may just give a minor contribution.

A fixed-dose combination (FDC) of bempedoic acid and ezetimibe (180 and 10 mg, respectively) has been recently compared with bempedoic acid, ezetimibe, or placebo in high cardiovascular risk patients with residual hypercholesterolemia (LDL-C 149.8 mg/dl) despite receiving maximally tolerated statin therapy [17▪]. At week 12, the bempedoic acid-+ezetimibe FDC was more effective in reducing LDL-C levels than monotherapies, with a higher percentage of patients having reached LDL-C less than 70 mg/dl [17▪]. The combination reduced CRP by 35.1%, compared with a reduction of 8.2% in the ezetimibe group, whereas no difference was observed when compared with bempedoic acid alone (35.1 vs. 31.9% reductions, respectively) [17▪]. This combination also had a favourable safety profile when added to background statin therapy [17▪].

The ongoing CLEAR Outcomes study aims at establishing whether bempedoic acid treatment can reduce cardiovascular events in patients with statin intolerance, compared with placebo, over a 3.5-year follow-up period [18▪]. Recruited patients have a history of, or a high risk for, atherosclerotic cardiovascular disease on a clinical condition of a statin intolerance that started or increased during statin therapy and receded or ceased after stopping therapy [18▪]. The trial will assess the time from randomization to the first occurrence of a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization [18▪]. The estimated study completion date is December 2022.

THE RISK OF NEW-ONSET DIABETES IN PATIENTS TREATED WITH BEMPEDOIC ACID WITH OR WITHOUT EZETIMIBE

The effectiveness of statin therapy in reducing the cardiovascular risk in diabetic patients has been largely established [19], and statins are the gold standard treatment for CVD prevention also in these patients [7]. However, a link between statin therapy (and in particular, high-intensity statin dose) and an increased risk in new-onset diabetes became apparent from meta-analyses of either randomized clinical trials or observational studies [20–24], being still a matter of debate. This increased risk appears to be modest, especially when compared with the clinical benefit in terms of cardiovascular event risk reduction, and emerges mostly in patients having insulin resistance or prediabetes [25]. On the basis of the observation that bempedoic acid treatment not only attenuated diet-induced hypercholesterolemia but also reduced hyperglycaemia and improved glucose tolerance in an experimental model [26], and owing to the mechanism by which bempedoic acid inhibits cholesterol biosynthesis, it is conceivable that its effect on glucose homeostasis might differ from that of statins. Meta-analyses of available randomized clinical trials seem to suggest that this is the case, as bempedoic acid treatment was associated with a significant reduction in new-onset or worsening diabetes [27▪▪,28]. The results of a Mendelian randomization study using genetic scores composed of inherited variants in *ACLY* and *HMGCR* genes associated with lower LDL-C levels seem to support this finding: whereas *HMGCR* score (as well as other genetic scores) were associated with an increased risk of diabetes, the *ACLY* score was not [2]. Although acknowledging the limitations of the genetic analysis, especially the possibility that adaptation takes place to compensate for the effects of a genetic variant present since birth, which might impact on disease differently than drug inhibition, it appears that bempedoic acid could have an at least neutral effect on the risk of developing diabetes. Larger studies with a longer follow-up are, however, warranted to elucidate this aspect.

HOW BEMPEDOIC ACID WORKS IN DIABETIC PATIENTS

In an earlier phase 2 placebo-controlled trial, the LDL-C-lowering efficacy of bempedoic acid was evaluated in patients with type 2 diabetes and hypercholesterolemia (LDL-C at baseline: ~125 mg/dl) [29]. After 2 weeks with 80 mg bempedoic acid followed by 2 weeks with 120 mg, LDL-C was significantly reduced by 43% (vs. a 4% reduction with placebo); other lipids (non-HDL-C and total cholesterol) as well as CRP were significantly reduced in patients receiving bempedoic acid, without any worsening of glycaemic control [29].

More recently, a phase 2 randomized clinical trial has compared the efficacy of a bempedoic acid (180 mg) + ezetimibe fixed dose combination vs. ezetimibe or placebo in patients with type 2 diabetes and hypercholesterolemia (LDL-C at baseline: ~140 mg/dl) not receiving statins or other lipid-lowering therapies [30▪▪]. After 12 weeks, the combination therapy induced a 38.8% reduction in LDL-C, compared with a 19.2% reduction observed in ezetimibe-treated patients and a 0.9% increase with placebo [30▪▪]. Although none of the patients

treated with ezetimibe or placebo were able to achieve at least 50% reduction in LDL-C levels from baseline, the fixed-dose combination allowed 40.7% of treated patients to achieve at least 50% LDL-C reduction. Higher percentages of patients receiving the fixed-dose combination reached LDL-C levels less than 100 mg/dl (72.2% vs. 32.1% with ezetimibe and 8.8% with placebo) and less than 70 mg/dl (38.9% vs. 5.4% and 0%, respectively). The lipid/lipoprotein profile was largely improved with the combination therapy, with substantial reductions in apoB, non-HDL-C, and triglycerides; CRP decreased significantly in these patients (by 25.3%), but not in those receiving ezetimibe or placebo [30▪▪]. The only adverse event of special interest was blood glucose increase in three patients taking the combination therapy, among which only one was considered possibly related to the therapy.

Due to the limited number of patients included in these studies, and to the short duration of the trials, the results here described cannot be conclusive. This calls for larger trials with longer follow-up. The ongoing CLEAR Outcomes trial, which has an expected median duration of 3.5 years, includes ~43% of patients having diabetes at baseline; this may provide a more reliable indication on the effectiveness and safety of bempedoic acid in this specific population.

BEMPEDOIC ACID FOR FAMILIAL HYPERCHOLESTEROLEMIA

Patients having familial hypercholesterolemia, an inherited disorder caused by mutations in genes playing crucial roles in the metabolism of LDL (mostly in the *LDLR* gene), are characterized by a lifelong exposure to elevated cholesterol levels, and have an increased risk of cardiovascular events early in life. A substantial and timely LDL-C-lowering is essential to reduce the cardiovascular risk in these patients and typically requires the use of both conventional and newly developed drugs, possibly in combination to maximize the effect. In this context, patients with the heterozygous form of familial hypercholesterolemia (HeFH), carrying the pathological mutation only in one allele, might benefit from the addition of bempedoic acid to their current lipid-lowering therapy. A specific trial assessing the effect of bempedoic acid in HeFH is still lacking. However, an analysis of pooled data from phase 3 clinical trials showed that patients with HeFH, who had higher baseline LDL-C levels compared with non-HeFH patients, had a greater reduction in LDL-C levels when treated with bempedoic acid than non-HeFH patients (placebo-corrected reductions: 22.3 and 18.3%, respectively, $P < 0.001$), with significant reductions also in non-HDL-C, total cholesterol, apoB and CRP [31]. A recent report describes a 29-year-old HeFH man, who had a great response to the therapy with atorvastatin 80 mg, but unable to tolerate it; he was treated with bempedoic acid, showing a substantial reduction in LDL-C levels (from 215 to 51 mg/dl) [32]. Thus, it appears that bempedoic acid might represent a valuable tool for further reducing LDL-C levels in HeFH patients, even more in those who also present a statin-intolerance condition.

Familial hypercholesterolemia also includes the rarer but more severe homozygous form (HoFH), in which patients carry mutations in both alleles. The effectiveness of conventional drugs acting by upregulating LDLR (such as statins) is strictly related to the presence of a residual function of LDLR; thus, HoFH patients carrying null mutations, leading to an almost complete lack of LDLR, are not or minimally responsive to statin therapy, and instead require specific drugs, which may overcome the lack of LDLR. On the basis of available knowledge, and the known mechanism of action of bempedoic acid, HoFH patients are not expected to benefit from a bempedoic acid-based therapy.

CONCLUSION

To date, adverse events associated with bempedoic acid, either alone or in combination with ezetimibe, have been reported with an incidence comparable with that of placebo, including muscle-related effects; however, a modest increase in uric acid levels, fully reversible upon treatment discontinuation, has been reported among patients treated with bempedoic acid, likely related to the drug-mediated inhibition of a specific transporter (organic anion transporter 2) [33▪]. On the basis of findings reported in available phase 3 trials, and while awaiting the results of the outcome trial, where can bempedoic acid be located in the area of cholesterol-lowering agents? This drug, despite being less effective in reducing LDL-C levels compared with other cholesterol-lowering agents, including statins, may serve as an alternative approach to reduce hypercholesterolemia and, likely, cardiovascular risk in patients who cannot (or are not willing to) take statins, having experienced muscular adverse events, or in patients with altered glucose homeostasis. Its clinical benefit remains to be confirmed, and long-term adverse effects should be determined in studies specifically designed to address these aspects, with a special attention on patients having risk factors predisposing to diabetes or with a history of elevated uric acid or gout. However, its efficacy when combined with ezetimibe, even in the form of

fixed-dose combination, the potential beneficial effect on inflammation (as suggested by the relevant reduction in CRP), together with a lower cost when compared with other recent cholesterol-lowering therapies, make bempedoic acid a relevant player in the fight against CVD.

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Conflicts of interest

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