



Defining the role of bempedoic acid in lowering low-density lipoprotein cholesterol

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ABSTRACT

There is an unmet medical need for patients who cannot achieve a sufficient reduction in low-density lipoprotein (LDL) cholesterol with the existing treatment options. Statin therapy remains the mainstay of treatment for both primary and secondary prevention. However, many patients cannot tolerate statin therapy because of statin-associated muscle symptoms. This underlines the importance of developing alternative cholesterol-lowering methods with good efficacy and tolerance in addition to statins. Bempedoic acid (ETC-1002) is one such novel cholesterol-lowering drug. It is an inhibitor of adenosine triphosphate citrate lyase, a cellular enzyme responsible for the production of precursors for the synthesis of fatty acids and cholesterol. Bempedoic acid reduces the synthesis of cholesterol in the liver cells and triggers the compensatory activation of the LDL receptor, as well as complementing other mechanisms targeted by current therapies, which leads to an additional decrease in LDL cholesterol. The current clinical trial's results suggest that bempedoic acid may represent a new therapeutic approach for lowering LDL cholesterol. The recent approval of bempedoic acid by the Food and Drug Administration (FDA) offers an additional option for lowering LDL cholesterol in patients with atherosclerotic cardiovascular disease or heterozygous familial hyperlipidemia. Additional data on the effects of bempedoic acid on long-term cardiovascular outcomes are currently being investigated in large cardiovascular outcome studies. In the present study, we discuss the history and development of bempedoic acid, the pharmacology, the relevant clinical trials, and the potential role of bempedoic acid as a lipid-lowering medication in the context of other currently available lipid-lowering therapies.

Introduction

Cardiovascular disease (CVD) is a major public health problem and the leading cause of mortality and morbidity worldwide (Arnett *et al.*, 2019). Changes in the metabolism of lipids and lipoproteins play an important role in the pathogenesis of CVD. Numerous epidemiological studies and randomized clinical trials have shown that elevated low-density lipoprotein (LDL) cholesterol is the main cause of atherosclerotic CVDs (Koskinas *et al.*, 2018; Navarese *et al.*, 2018).

Management of serum cholesterol is the main task in preventing atherosclerotic cardiovascular events (Brinton,

2015; Jacobson *et al.*, 2015; Khera *et al.*, 2016; Martin *et al.*, 2016). Currently, the standard treatment for patients with hypercholesterolemia is primarily statins, which can lower LDL cholesterol. Lowering LDL cholesterol with statins inhibits the progression of coronary atherosclerosis and reduces cardiovascular mortality and morbidity. However, some patients, especially patients with heterozygous familial hypercholesterolemia, coronary artery disease (CAD), risk equivalents of CAD, and other clinical manifestations of atherosclerotic CVD (Grundy *et al.*, 2019), require an additional reduction in LDL cholesterol in addition to what can be achieved with a maximum tolerated statin therapy.

In addition, there are patients who cannot tolerate statins due to adverse effects, such as muscle pain or an increase in blood glucose. This underlines the importance of developing alternative cholesterol-lowering methods with good efficacy and tolerance in addition to statins (Rosenson *et al.*, 2017).

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Managing LDL cholesterol can also be achieved by other mechanisms, such as inhibiting intestinal cholesterol absorption [i.e., ezetimibe (EZE)] or preventing degradation of LDL receptors (i.e., PCSK9 inhibitors) (Table 1). It is important to note that each of these mechanisms primarily reduces LDL cholesterol by upregulating the activity of LDL receptors, a mechanism that has been shown to reduce cardiovascular events (Bonaca *et al.*, 2018; O'Donoghue *et al.*, 2019). These strategies significantly influenced further expectations of lowering the cardiovascular risk in patients with concomitant high-risk diseases, which led to the combination of statins with other existing drugs that lower LDL cholesterol and to the need for new treatments with mechanisms that complement the effects of statins without increasing side effects in skeletal muscle (Newman *et al.*, 2019).

Bempedoic acid (BemA or ETC-1002) is one such novel cholesterol-lowering drug. It is an inhibitor of adenosine triphosphate (ATP) citrate lyase (ACLY), a cellular enzyme responsible for the production of precursors for the synthesis of fatty acids and cholesterol. ETC-1002 effectively reduces LDL and apolipoprotein (apo) B-containing lipoproteins (Bilen and Ballantyne, 2016; Pinkosky *et al.*, 2013).

ETC-1002 was first discovered at the original Esperion Therapeutics, which was acquired by Pfizer in 2004, and then stood out as Esperion Therapeutics in 2008 along with ETC-1002 and other assets. Esperion continues to develop ETC-1002, which is currently in phase III trials as an agent for lowering LDL cholesterol in patients with hypercholesterolemia.

Both phase 2 and phase 3 clinical trials showed that BemA as monotherapy or when added to background lipid-lowering therapy significantly lowered LDL-C, as well as other relevant lipids and biomarkers (Ruscica *et al.*, 2019).

The US Food and Drug Administration has approved BemA and the BemA and EZE-fixed dose combination tablet for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic CVD who require additional lowering of LDL cholesterol. The recommended dosage for the new drug, in combination with maximally tolerated statin therapy, is 180 mg administered orally once daily.

The applications to the European Medicines Agency for both preparations received positive opinions from the Committee for Medicinal Product for Human Use of the European Medicines Agency (EMA).

Table 1. Lipid modifying pharmaceuticals in development.

Name	Company	Target	Support for Target	Mechanism of Action	Indication	Stage	Biochemical Effect	Current or Possible Use in 5 y
Lomitapide	Aegerion	MTP	RD/BCM/AM	Oral MTP inhibitor	HoFH	Approved	Reduces LDL-C and TG	HoFH; apheresis-eligible hypercholesterolemia
Mipomersen	IONIS/Genzyme	APOB	RD/BCM/AM/MR	Anti-APOB antisense	HoFH	Approved	Reduces LDL-C	HoFH; apheresis-eligible hypercholesterolemia
AAV8.TBG.hLDLR (RGX-501)	RegenXBio	LDLR	RD/BCM/AM/MR	LDLR gene therapy	HoFH	Phase 1	Reduces LDL-C	HoFH because of biallelic LDLR gene mutations
Bempedoic acid	Esperion	ACL	RD/BCM/AM/MR	Oral ACL inhibitor	Hypercholesterolemia	Phase 2-3	Reduces LDL-C	Adjunct to reduce LDL-C in ASCVD risk, FH, SI
Gemcabene	Gemphire	ND	BCM	Unknown; not PPAR	Hypercholesterolemia; hypertriglyceridemia	Phase 2-3	Reduces LDL-C and TG	Adjunct to reduce LDL-C in ASCVD risk, FH, SI
Inclisiran	Alynlyam	PCSK9	RD/BCM/AM/MR	Anti-PCSK9 ASO	HeFH	Phase 3	Reduces LDL-C	HeFH, high ASCVD not at LDL-C target
Alipogene tipavovec	uniQure	LPL	RD/BCM/AM/MR	LPL gene therapy	FCS	Approved	Reduces TG	FCS because of biallelic <i>LPL</i> gene mutations
Pradigastat	Novartis	DGAT ₁	RD/BCM	DGAT1 inhibitor	FCS; severe hypertriglyceridemia	No updates since 2017	Reduces TG	Uncertain future
Volanesorsen	IONIS/Akcea	APOC3	RD/BCM/AM/MR	Anti-APOC3 ASO	FCS	Not approved	Reduces TG	Uncertain future
Evinacumab	Regeneron	ANGPTL3	RD/BCM/AM/MR	Anti-ANGPTL3 antibody	Hypercholesterolemia; hypertriglyceridemia	Phase 2-3	Reduces TG, LDL-C, and HDL-C	FCS; HoFH; refractory severe hyperlipidemia
IONIS-APO(a)-L _{rx}	IONIS/Akcea	apo(a)	RD/BCM/AM/MR	Anti-apo(a) ASO	Elevated LP(a) levels	Phase 2-3	Reduces Lp(a)	Severe elevated Lp(a); ASCVD, CAVD risk
CSL-112	CSL Behring	APOA1	RD/BCM/AM/MR	APOA1 peptide infusion	Low HDL-C	Phase 3	Raises HDL-C	Severe depressed HDL-C; ASCVD risk
Sebelipase	Alexion	LIPA	RD/BCM/AM	LIPA replacement	LIPA deficiency	Approved	Reduces TG, LDL-C and liver lipids	LIPA deficiency or CESD only
ACP-501/MEDI6012	Medimmune	LCAT	RD/BCM/AM	Recombinant LCAT	LCAT deficiency	Phase 1	Raises HDL-C, redistributes HDL subfractions	LCAT deficiency and perhaps other HDL-C deficiencies

Thus, in the present study, we discuss the history and development of BemA, the pharmacology, the relevant clinical trials, and the potential role of BemA as a lipid-lowering medication in the context of other currently available lipid-lowering therapies.

Mechanism of action and pharmacology of bempedoic acid

BemA (8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid) is a new drug that reduces cholesterol synthesis by inhibiting ACLY (Figure 1). In animal models, BemA lowers LDL cholesterol and inhibits fatty acid synthesis, but in humans, it is mainly used to lower LDL cholesterol (Nikolic *et al.*, 2014). BemA significantly reduced LDL-C (up to 32%) in patients with normal or elevated triglycerides (TG). This effect of lowering lipid levels is better than currently approved nonstatin-based lipid-lowering drugs and is similar to the usual doses of many statins (Lemus and Mendivil, 2015). BemA also lowers levels of apoB, LDL cholesterol (non-HDL cholesterol), and highly sensitive C-reactive protein (hsCRP) (Zagelbaum *et al.*, 2019) and also has a beneficial effect on body weight and blood pressure (Nikolic *et al.*, 2014). Most importantly, BemA is well tolerated by patients without significant side effects.

ACLY is an important enzyme in the cholesterol biosynthesis pathway upstream of the 3-hydroxy-3-methylglutaryl

coenzyme A reductase [which is a target for statins (FERENCE *et al.*, 2019)]. ACLY produces acetyl-CoA (AcCoA) from mitochondrial citrate for the biosynthesis of cholesterol and fatty acids (Burke and Huff, 2017). ACLY forms homotetramers through the C-terminus (citrate synthase homeodomain) to facilitate the binding of ACLY to CoA and AcCoA production (Bazilevsky *et al.*, 2019). The Mendelian randomization of large human study cohorts has confirmed that ACLY can be used as a promising therapeutic target for lowering LDL cholesterol and protecting against atherosclerosis (Burke *et al.*, 2019).

ACLY catalyzes the conversion of citric acid to oxaloacetate and AcCoA (Verschuere *et al.*, 2019). AcCoA promotes key biochemical reactions, including the synthesis of fatty acids, cholesterol, and acetylcholine, as well as acetylation of protein substrates, including histones (Sivanand *et al.*, 2017; Wellen *et al.*, 2009). Typically, citrate is synthesized in mitochondria and transported to the cytosol via a mitochondrial citrate carrier protein (encoded by the SLC25A1 gene), which produces AcCoA and oxaloacetate by ACLY.

Recently, the crystal structures of bacteria and ACLY have been resolved with high resolution, in which conformational plasticity, substrate binding, and ACLY catalytic processes have

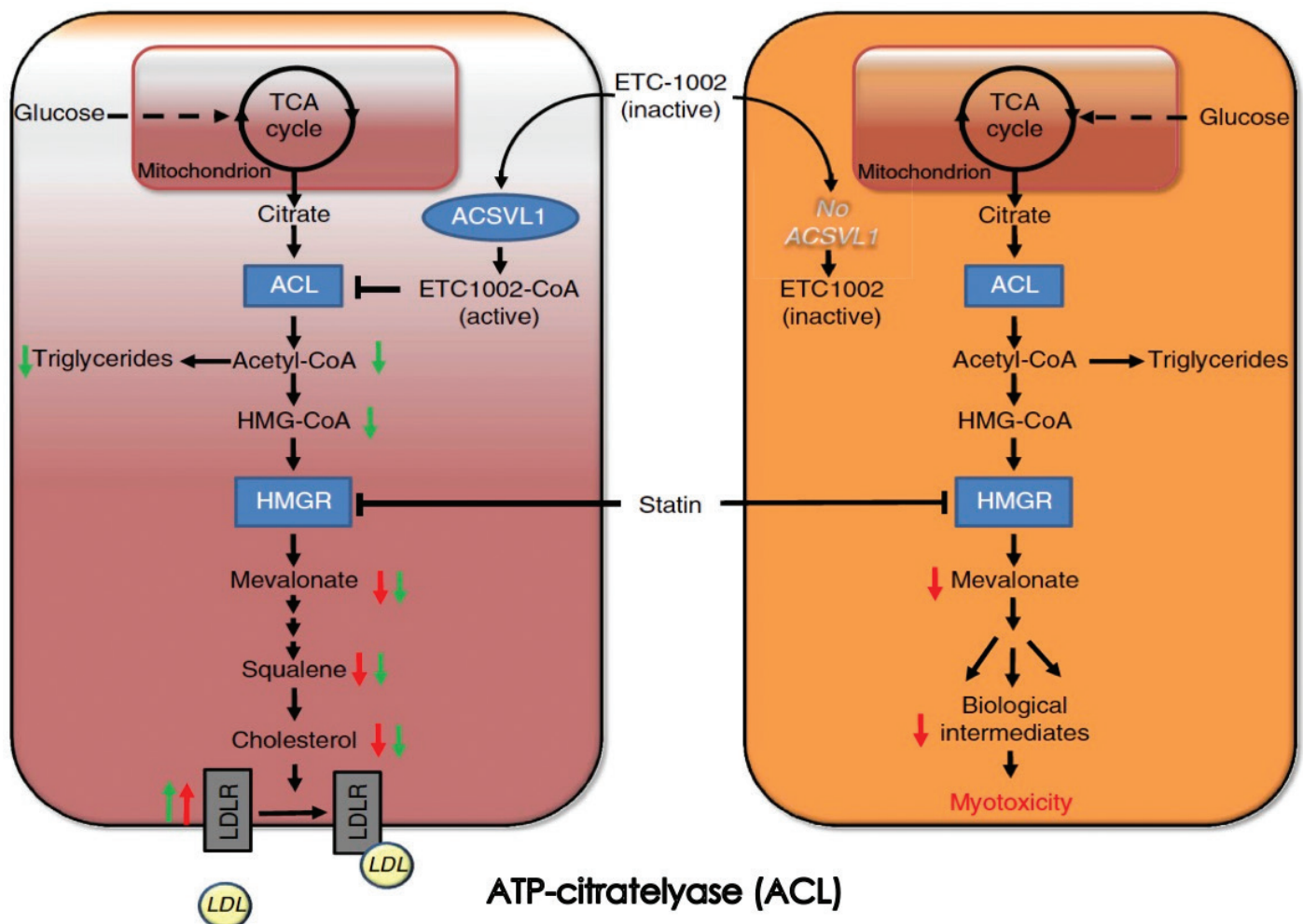


Figure 1. Major metabolic pathways affected by bempedoic acid (ETC 1002) in humans. Author's figure. No permission is required.

been characterized. These results will provide important clues for the development of new ACLY inhibitors and highlight the therapeutic potential of ACLY inhibitors in hyperlipidemia and various types of cancer (Verschuere *et al.*, 2019; Wei *et al.*, 2019).

ACLY is a key enzyme in the production of AcCoA, which is necessary for the synthesis of fatty acids and cholesterol and thus represents an important molecular target for lowering lipids (Hatzivassiliou *et al.*, 2005; Xie *et al.*, 2015). ACLY is abnormally expressed in many cancers, CVDs, and metabolic disorders (Bazilevsky *et al.*, 2019). A previous study showed that ACLY expression in macrophages increased during treatment with proinflammatory stimuli, lipopolysaccharide (LPS), tumor necrosis factor α (TNF α), and Interferon gamma (IFN γ) (Infantino *et al.*, 2013). Interestingly, the pharmacological inhibition of ACLY by SB-204990 attenuated the inflammatory response and oxidative stress in activated macrophages obtained from mouse bone marrow (Infantino *et al.*, 2013).

In addition, the IL-4 M2 polarizing agent increases ACLY phosphorylation and AcCoA production in M2 macrophages via the Akt-dependent pathway (Covarrubias *et al.*, 2016). However, studies conducted on macrophages originating from human monocytes suggest that ACLY was not necessary for IL-4-induced M2 polarization using human macrophages in which ACLY was reduced or knocked out (Namgaladze *et al.*, 2018). These conflicting results can be caused by the different types of cells used and the inappropriate effects of ACLY inhibitors. These recent studies have shown that the exact role of ACLY in macrophage activation and polarization remains to be confirmed *in vitro* and *in vivo*. There is currently no information on whether ACLY deletion or pharmacological inhibition affects the biosynthesis of TG and cholesterol in macrophages.

Moreover, liver-specific ACLY deletion prevents liver steatosis, while fat-specific ACLY deficiency does not have a phenotype (Zhao *et al.*, 2016). A possible reason may be that ACLY breaks down citrate to form AcCoA outside mitochondria for *de novo* glucose-dependent lipogenesis, and ACLY expression is strongly regulated by the presence of nutrients in adipocytes, and its expression is induced by carbohydrates and suppressed by dietary fiber. Thus, the presence or absence of ACLY in adipocytes should not have any significant effect on lipid metabolism, unless the mice are on a high carbohydrate diet. It has recently been reported that the sexual dimorphic function of ACLY derived from adipocytes supports systemic metabolic homeostasis by activating the nutrient-dependent carbohydrate response element-binding protein (Fernandez *et al.*, 2019). These data indicate that the presence of the phenotype in the absence of ACLY in adipose tissue depends on gender and diet, thus adding complexity to the functions of ACLY in the regulation of cardiometabolic disorders.

The sterol transporter ATP-binding cassette transporter G5/8 (ABCG5/8) regulates the final stage of reverse cholesterol transport, which promotes hepatobiliary transport of cholesterol. ACLY inhibition has an antiatherosclerotic effect due to increased expression of ABCG5/8 (Molusky *et al.*, 2018). The depletion of AcCoA levels induces an autophagic flow, while increased levels of cytosolic AcCoA effectively inhibit autophagy. Dimethyl α -ketoglutarate (DMKG) increases intracellular levels of α -ketoglutarate, which is converted to AcCoA by isocitrate dehydrogenase (IDH1 or IDH2) and ACLY. Repeated treatment

with DMKG inhibits myocardial autophagy in mice undergoing thoracic aortic narrowing, while eliminating pathological heart remodeling (Marino *et al.*, 2014). In addition, carboxylesterase 1 (CES1) is an important enzyme that hydrolyzes TG and cholesterol esters. Knockdown of CES1 in mouse liver significantly increases blood glucose levels after meals. ACLY can also regulate histone acetylation, while ACLY knockout inhibits glucose-induced histone acetylation of CES1 and CES1 expression in the liver (Xu *et al.*, 2014).

BemA is a new drug that treats dyslipidemia and other CVDs. It has been identified from a number of long hydrocarbon chains that inhibit the synthesis of cholesterol and fatty acids *in vitro* and *in vivo* (Oniciu *et al.*, 2006; Pinkosky *et al.*, 2013). BemA rapidly forms BemA-CoA in the liver (thus, functioning as a direct and potent competitive ACLY inhibitor), which reduces the levels of non-HDL cholesterol, and TG and insulin and also increases the plasma β -hydroxybutyrate level in obese Zucker (fa/fa) rat (Pinkosky *et al.*, 2013).

Mounting studies have shown that BemA has pharmacological effects, especially in the liver (Pinkosky *et al.*, 2013, 2016). A very long chain acyl-CoA synthetase-1 (ACSVL1) is required to convert BemA into its active coenzyme A derivative. ACSVL1 is an enzyme specifically expressed in the liver that provides the theoretical basis for preventing potential muscle side effects. In addition to ACLY inhibition, BemA can also activate the fuel sensor AMP-activated protein kinase (AMPK) in rodents, although the effect of AMPK activation is not observed in humans. In particular, BemA selectively activates AMPK β 1 in mice instead of β 2 (Pinkosky *et al.*, 2016).

Effect of bempedoic acid on lipid metabolism

BemA has a mechanism of action similar to that of statins, which inhibits ACLY-dependent cholesterol biosynthesis, a step prior to β -Hydroxy β -methylglutaryl-CoA (HMG-CoA) reductase. Since BemA is a prodrug that is activated only in the liver, therefore, BemA has minimal myotoxicity (unlike statins) (Katwan *et al.*, 2019). In patients with statin intolerance who need to achieve a significant reduction in the risk of CVD, the high tolerance of BemA makes it a useful alternative, either alone or in combination with EZE. BemA treatment is also associated with a significant reduction in the biomarker of systemic inflammation, such as hsCRP (Goldberg *et al.*, 2019).

In five randomized controlled trials (RCTs) that were systematically evaluated, BemA was better than placebo in lowering serum levels of LDL cholesterol, non-HDL cholesterol, and apoB. Compared to EZE, BemA is superior in lowering LDL cholesterol. From a safety point of view, the frequency of all adverse events (including headache, joint pain, and myalgia) did not statistically differ between the BemA groups and placebo, suggesting that BemA seems to be an appropriate drug in patients with statin intolerance (Wang *et al.*, 2019).

BemA requires activation by the specific enzyme ACSVL1, which is largely limited to the liver. Therefore, it is believed that unlike statins, myotoxicity is unlikely to occur with BemA, since it does not inhibit ACSVL1 in these cells (Pinkosky *et al.*, 2016). The BemA effect is additive rather than redundant compared to statins, because the BemA target (ACLY) is an excellent regulatory reference point for cholesterol biosynthesis

than HMG-CoA reductase, the main target of statins. Failure to tolerate statins due to muscle symptoms contributes to uncontrolled cholesterol levels and an insufficient reduction in cardiovascular risk. The mechanism of action of BemA is similar to the mechanism of action of statins, but since it does not inhibit the pathway of cholesterol biosynthesis in skeletal muscle, thereby providing a mechanistic basis for reducing the potential for side effects associated with muscle (Filippov *et al.*, 2013).

Animal experiments and clinical trials in humans have shown that ACLY inhibitors can significantly improve dyslipidemia (especially lowering LDL cholesterol) and inhibit atherosclerotic lesions (Burke *et al.*, 2017; Ruscica *et al.*, 2019). These inhibitors have a comparable effect with statins and have some potential advantage over other nonstatin hypolipidemic drugs (in lowering the level of LDL cholesterol). Among these inhibitors, BemA is the only liver-specific ACLY inhibitor that has been approved for clinical trials, and it is a prodrug that has a lipid-lowering effect by ACLY inhibition, which requires activation by ACSVL1. Therefore, BemA can serve as a good alternative and additional medicine for patients who cannot use high doses of statins due to side effects.

In people with dyslipidemia, BemA not only lowered LDL cholesterol in the blood but also significantly reduced the level of hsCRP, a clinical biomarker of systemic inflammation. BemA also inhibits inflammatory responses in primary macrophages derived from human monocytes and in mice. Fundamental mechanisms include the signaling pathways of hepatic kinase B1 serine-threonine kinase 11 (LKB1)/AMPK, mitogen-activated protein kinase, and c-Jun N-terminal kinase (Filippov *et al.*, 2013).

Individual differences in drug effects have always been an important part of clinical pharmaceutical research and precision medicine (Ahmad *et al.*, 2011; Guo *et al.*, 2018). However, there is still no clear study of the relationship between the genetic variants of ACSVL1 and its enzymatic activity. In addition, BemA targets are upstream of statins, while ApoE-E4-carrying patients undergoing statin therapy are less effective (Thompson *et al.*, 2009). Therefore, the ApoE genotype can also influence the effectiveness of BemA.

In addition, during remodeling of the heart caused by acute myocardial infarction, ACLY expression was significantly increased (Guo *et al.*, 2018), suggesting that ACLY may play an important role in heart hypertrophy and heart failure. All these data confirm the prospect of ACLY inhibition for reducing CVDs and other metabolic disorders (Pinkosky *et al.*, 2017). However, further studies are needed in the future to clarify the exact role of ACLY in heart disease and to evaluate the side effects of BemA, not associated with myopathy, in large-scale, randomized clinical trials in patients with CAD.

Effect of bempedoic acid on atherosclerosis in preclinical models

Studies in LDLR^{-/-} minipigs and mice, and ApoE^{-/-} mice have shown that BemA lowers LDL cholesterol and inhibits atherosclerosis. In LDLR^{+/-} and LDLR^{-/-} pigs fed a high fat diet, BemA was administered to pigs for 160 days. In LDLR^{+/-} pig aorta, BemA reduced total cholesterol and LDL cholesterol by 40% and 61%, respectively. At the same time, BemA significantly reduced the *en face* area (-58%) and the lesion area in the left

anterior descending coronary artery (-40%). In LDLR^{-/-} pigs, BemA reduced plasma cholesterol and LDL cholesterol by 27% and 29%, respectively. Moreover, BemA reduced the area of aortic lesion (-47%) and the left-sided lesion of the descending coronary artery (-48%) (Burke *et al.*, 2019). In LDLR^{-/-} mice fed a diet high in fat and cholesterol, treatment with BemA for 12 weeks (at doses of 3, 10, and 30 mg/kg/day) leads to a decrease in lipid accumulation in plasma, liver, and aorta, since as well as weakened aortic inflammation (attenuates the proinflammatory expression of the M1 gene). BemA dose-dependently reduces hypertriglyceridemia, hyperinsulinemia, hypercholesterolemia, hyperglycemia, aortic sclerosing lesions, and obesity (Samsouandar *et al.*, 2017).

In ApoE^{-/-} and double-knockout (DKO) (ApoE^{-/-} and Ampk β 1^{-/-}) mice, BemA (30 mg/kg/day, 12 weeks) significantly inhibited atherosclerotic lesions of the aorta. In addition, BemA treatment reduced TG and LDL cholesterol levels in both genotype mice, while plasma amyloid A serum amyloid A (SAA) levels also decreased significantly (Pinkosky *et al.*, 2016). These results show that the antiatherosclerotic effect of BemA mainly regulates lipid metabolism in the liver and reduces LDL cholesterol levels and inflammation, regardless of AMPK activation. The results of the above-mentioned animal experiments convincingly demonstrate the protective effect of BemA in atherosclerosis, and this mechanism mainly involves the regulation of lipid metabolism and the inhibition of inflammation.

Clinical efficacy of bempedoic acid

BemA has wide clinical efficacy in patients with CVD diseases as monotherapy or combination therapy with other lipid modulating drugs.

Phase 1 studies

A first-in-human, phase 1a single-dose clinical trial, ETC-1002-001 (Esperion Therapeutics, 2015) evaluated safety, tolerability, and pharmacokinetics of ETC-1002 in 18 healthy subjects. Similarly, ETC-1002-002 (ClinicalTrials.gov) was a staged phase 1b multiple-dose tolerance clinical trial over 2 and 4 weeks in 53 patients, 39 of whom received ETC-1002 and 23 received placebo. Subjects were divided into four different cohorts of six subjects, each of whom received 20, 60, 100, or 120 mg of ETC-1002 or placebo once a day for 14 days. This was followed by the study of a larger cohort, which was treated for 28 days, during which the subjects lived outside the clinical site for the entire treatment period. ETC-1002 was safe, well tolerated, and associated with no dose-limiting side effects.

Finally, ETC-1002-004 (ClinicalTrials.gov) was a 2-week, phase 1b, clinical trial of multiple-dose tolerance in 24 subjects, 18 of which received ETC-1002. This clinical trial was designed to evaluate the safety and tolerability of increasing multiple oral doses of ETC-1002 above 120 mg/day. Subjects in this clinical trial received 140, 180, or 220 mg of ETC-1002 or placebo once a day for 14 days. LDL cholesterol levels were reduced by an average of 36% for subjects receiving 220 mg/day of ETC-1002, compared with an increase of 4% for subjects receiving placebo ($p < 0.0001$). Subjects receiving ETC-1002 showed no serious side effects. ETC-1002 was safe, well tolerated, and associated with no dose-limiting side effects.

Phases 2 and 3 studies

Bempedoic acid monotherapy

In a phase 2 clinical trial, 60 patients with hyperlipidemia and type 2 diabetes mellitus who discontinued antidiabetic and lipid modulating drugs were randomly assigned to the BemA group (80 mg of ETC-1002 once daily for 2 weeks, followed by 120 mg of ETC-1002 once daily for 2 additional weeks) and placebo (Gutierrez *et al.*, 2014). LDL cholesterol levels after 4 weeks of treatment with ETC-1002, which was the primary endpoint, were reduced by an average of 43% in patients receiving the 120 mg ETC-1002 dose, compared with an average of 4% in patients receiving placebo ($p < 0.0001$). Approximately, 80% of the patients were not at their National Cholesterol Education Program Adult Treatment Panel III LDL-C goal of less than 100 mg/dl at the beginning of the study. Of these, 88% of patients receiving ETC-1002 achieved their goal by the end of the study compared to 4% of patients receiving placebo ($p < 0.0001$). HsCRP levels were reduced by 41% at the dose of ETC-1002 of 120 mg compared to 11% with placebo ($p = 0.001$). Non-HDL cholesterol decreased by 32% in patients receiving ETC-1002, compared with a 1% increase in patients receiving placebo ($p < 0.0001$). A 24-hour continuous glucose assessment showed a slight improvement in glycemic control in the treatment of ETC-1002. Overall, 24-hour ambulatory blood pressure monitoring did not show differences between treatment groups in mean changes from baseline to day 28.

In another phase II clinical trial, 177 patients with elevated LDL cholesterol were randomized to receive BemA (40, 80, or 120 mg once daily for 12 weeks) or placebo (Ballantyne *et al.*, 2013). This clinical study was designed to evaluate the efficacy and safety of LDL lowering with ETC-1002 compared with placebo in patients with hypercholesterolemia (LDL from 130 to 220 mg/dl) and normal TG (less than 150 mg/dl) or elevated TG (150–400 mg/dl). The four groups were placebo and 40, 80, and 120 mg doses of ETC-1002 once daily. LDL cholesterol levels were reduced on average by 18%, 25%, and 27% for patients receiving ETC-1002, 40, 80, and 120 mg, respectively, compared with an average of 2% for patients receiving placebo ($p < 0.0001$). ETC-1002's lowering of LDL-C levels was maintained across a range of baseline triglyceride levels. ETC-1002 also reduced levels of atherogenic biomarkers apo B, non-HDL cholesterol, and LDL particle number ($p < 0.0001$) in a dose-dependent manner. Patients treated with ETC-1002 showed a tendency to decrease hsCRP from 20% to 26% compared with 2% in patients treated with placebo. In the subgroup of patients with increased hsCRP, patients receiving ETC-1002 showed a tendency to decrease hsCRP from 43% to 64% compared with a decrease of 7% in patients receiving placebo.

In a 6-week, multicenter, randomized, double-blind, placebo-controlled study in a parallel group phase 2, the safety and efficacy of ETC-1002 were compared with placebo in 143 patients with both hypercholesterolemia and hypertension (ClinicalTrials.gov). After washout of any lipid-modifying therapy and blood pressure therapy, 71 patients received 180 mg ETC-1002 and 72 patients received placebo. Patients treated with ETC-1002 achieved

a 21% reduction in LDL cholesterol after 6 weeks compared with a 3% increase in LDL cholesterol in the placebo group ($p < 0.0001$). The decrease occurred during the first 2 weeks after the start of therapy and continued throughout the treatment period. HsCRP levels were reduced by 25% with ETC-1002, compared with a 20% increase in the placebo group ($p < 0.0001$). ETC-1002 had a neutral effect on blood pressure and was safe and well tolerated. Despite the effective reduction in LDL cholesterol using ETC-1002, HDL cholesterol and triglyceride levels were unchanged in all treatment groups in these studies. In patients receiving ETC-1002, no serious side effects were observed. ETC-1002 was safe, well tolerated, and associated with no dose-limiting side effects.

Bempedoic acid add-on to statin therapy

In a phase 2 clinical trial, 134 patients with hyperlipidemia undergoing statin treatment were randomized to receive additional treatment with BemA 120, 180 mg, or placebo for 12 weeks. It was observed that 120 or 180 mg of BemA dose-dependently reduced the level of LDL cholesterol, apoB, non-HDL cholesterol, total cholesterol, and LDL particles compared to placebo. The incidence of muscle side effects and treatment interruption was the same in both groups (Ballantyne *et al.*, 2016).

In an 8-week, phase 2a clinical trial in 58 patients, of which 42 were treated with ETC-1002, the primary endpoint was the number of patients with side effects, clinical laboratory abnormalities, and other safety data (ClinicalTrials.gov). ETC-1002 as a supplement to 10 mg of atorvastatin was well tolerated and did not lead to any serious side effects. Although the study was not designed to evaluate the decrease in LDL cholesterol using ETC-1002, it was measured as a secondary endpoint to determine if a decrease in LDL-C would be observed with the addition of ETC-1002 during statin therapy. In patients treated with atorvastatin, ETC-1002 lowered LDL-C levels by an average of 22% compared with a 0% change in placebo ($p < 0.0001$).

The following ETC-1002 study (Ballantyne *et al.*, 2015) was a double-blind, placebo-controlled, multicenter, parallel-group study that evaluated 134 patients with baseline LDL cholesterol levels of 115–220 mg/l, while taking atorvastatin \leq 20 mg, simvastatin \leq 20 mg, rosuvastatin \leq 10 mg or pravastatin \leq 40 mg randomized to receive 120 mg of ETC-1002, 180 mg of ETC-1002, or placebo once a day for 12 weeks. ETC-1002 lowered LDL levels by up to 24% ($p < 0.0001$), significantly more than placebo, in addition to statin therapy. ETC-1002 also lowered ($p < 0.05$) levels of apo B and non-HDL cholesterol, as well as total cholesterol and LDL particle number by more than placebo. A slight decrease in hsCRP was observed with ETC-1002, 120 mg (22%, $p = 0.26$), and 180 mg (30%, $p = 0.08$) compared to 0% with placebo. No significant changes in HDL cholesterol or TG levels were observed in any study. Adverse event associated with muscle events, discontinuation of treatment due to adverse events, and clinical safety laboratory levels were generally similar compared to placebo.

In addition, 68 patients with hypercholesterolemia who received atorvastatin 80 mg for 4 weeks were randomly divided into an experimental group (BemA 180 mg + atorvastatin 80 mg) and a control group (placebo + atorvastatin 80 mg) in a 2:1

ratio (phase 2). After 4 weeks, the level of LDL cholesterol, total cholesterol, apoB, and hsCRP in the experimental group was significantly lower than that in the control group. In addition, by determining the level of atorvastatin and its metabolites, it was found that BemA 180 mg does not increase the clinical exposure of atorvastatin (Lalwani *et al.*, 2019). These studies show that BemA can further improve blood lipids in hyperlipidemic patients taking large doses of statins (Table 2).

In addition, a recently published randomized controlled clinical trial involved 2,230 patients (with CVD, with/without heterozygous familial hypercholesterolemia) who received the most tolerated dose of statin therapy. Of these patients, 1,488 were prescribed for BemA (180 mg once daily, 52 weeks) and 742 were prescribed for placebo. The results showed that the level of LDL cholesterol in the BemA group was significantly lower, with no apparent difference in the frequency of adverse events between the two groups (Ray *et al.*, 2019).

Bempedoic acid in statin-intolerant patients

Fifty-six patients with statin intolerance were randomized to receive BemA or placebo in a 2:1 ratio (phase 2). The initial dose of BemA was 60 mg per day, which was increased to 120, 180, and 240 mg at 2-week intervals for a total of 8 weeks. The results showed that BemA treatment reduced LDL-C by 28.7% compared with placebo. Moreover, BemA significantly reduced levels of non-HDL cholesterol, apoB, total cholesterol, and hsCRP. However, in the BemA group, there were no significant differences in the levels of TG and HDL cholesterol. The frequency of side effects associated with muscle was the same in both groups (Thompson *et al.*, 2015).

In a phase 2 clinical trial, 349 hypercholesterolemic patients with or without statin intolerance were randomly administered BemA 120, 180 mg, EZE, BemA 120 mg + EZE, or BemA 180 mg + EZE for 12 weeks. With a decrease in LDL cholesterol, EZE, BemA (120 and 180 mg), and BemA (120 mg + EZE and 180 mg + EZE) were reduced by 21%, 27%, 30%, 43%, and 48%, respectively. Compared to EZE alone, using BemA alone or in combination with EZE also reduces non-HDL cholesterol, total cholesterol, apoB, LDL, and hsCRP particles. BemA was safe, effective, and well tolerated, and the incidence of muscle side effects was the same in all treatment groups (Thompson *et al.*, 2016).

In phase 3 of the clinical trial, 345 patients with hypercholesterolemia not tolerating at least two statins (one of the statins was intolerant at the lowest available dose) were randomly administered to the BemA group (180 mg, one time per day) or placebo group at 2:1. The results showed that BemA treatment significantly reduced LDL cholesterol (-21.4%), non-HDL cholesterol (-17.9%), total cholesterol (-14.8%), apoB (-15, 0%), and hsCRP (-24.3%). The incidence of muscle side effects in the BemA and placebo groups was 4.7% and 7.2%, respectively. These results indicate that, in patients with statin intolerance, BemA provides a safe and effective lipid-lowering effect (Laufs *et al.*, 2019).

Another phase 3 clinical study included 269 patients with statin intolerance. After 4 weeks of EZE treatment (10

mg/day), the patients were randomly assigned (2:1 ratio) to the BemA 180 mg + EZE 10 mg group and the EZE 10 mg + placebo group for 12 weeks. The results showed that, compared with placebo, BemA lowered LDL cholesterol by 28.5%, total cholesterol by 18.0%, non-HDL cholesterol by 23.6%, apoB by 19.3%, and hsCRP by 31.0% [76]. In addition, the incidence of muscle-related adverse events and interruptions was the same in both groups. These results suggest that BemA may be an additional treatment option for patients with statin intolerance, but requires a significant reduction in LDL cholesterol (Ballantyne *et al.*, 2018).

Phase 3 program CLEAR (cholesterol lowering via bempedoic acid, an ACLY-inhibiting regimen)

The phase 3 CLEAR Serenity clinical trial demonstrated the lipid-lowering efficacy of BemA among patients with established statin intolerance and elevated LDL cholesterol who received stable background therapy. Although BemA acts on the same cholesterol biosynthesis pathway as statins, the incidence of muscle-related side effects in CLEAR Serenity with BemA is no different from placebo, even among patients who have symptoms, associated with the muscles, while being on statin therapy (Banach *et al.*, 2019; Ray *et al.*, 2019).

In the CLEAR Harmony study (Evaluation of Long-Term Safety and Tolerability of ETC-1002 in High-Risk Patients with Hyperlipidemia and High Cardiovascular Risk), patients who received maximally tolerated therapy with statins treated with BemA had significantly lower LDL cholesterol than which received a placebo (mean difference, 18%), without an increase in serious side effects (Ray *et al.*, 2019).

The efficacy and safety of BemA will be further defined in a larger study of cardiovascular outcomes, CLEAR Outcome [Evaluation of Major Cardiovascular Events in Patients with, or at High Risk for, CVD Who Are Statin Intolerant Treated with Bempedoic Acid (ETC-1002) or Placebo], which includes 12,600 patients with high cardiovascular risk who have side effects in response to statins and have LDL cholesterol level of 100 mg per deciliter or higher (Banach *et al.*, 2019).

In the published systematic review with meta-analysis of RCTs to assess safety and efficacy of 180 mg BemA in patients with hypercholesterolemia, it has been shown that a more significant reduction in LDL cholesterol (MD, -17.5%; 95% CI, -22.9% to -12.0%), total cholesterol (MD, -10.9%; 95% CI, -13.3% to -8.5%), non-HDL cholesterol (MD, -12.3%; 95% CI, -15.3% to -9.20%), apo B (MD, -10.6%; 95% CI, -13.2% to -8.02%), and hsCRP (MD, -13.2%; 95% CI, -16.7% to -9.79%) in BA-treated patients compared with controls. Results were confirmed when separately analyzing studies on patients with high cardiovascular risk, studies on statin-intolerant patients, and studies on patients with hypercholesterolemia on maximally tolerated lipid-lowering therapy. BemA-treated subjects reported a higher rate of treatment discontinuation caused by adverse effects, of gout flare, and of increase in uric acid compared with controls. On the other hand, BA-treated patients showed a lower incidence of new-onset diabetes mellitus than controls (Di Minno *et al.*, 2020).

Table 2. Bempedoic acid.

- * Bempedoic acid (2,2,14,14-tetramethyl-8-hydroxypentadecanedioic acid, ETC-1002) is a first in-class oral small molecule inhibitor of adenosine triphosphate citrate lyase, a key enzyme in the cholesterol synthesis pathway.
- * Bempedoic acid lowers LDL-C and other atherogenic lipoprotein fractions (eg, non-high-density lipoprotein cholesterol [non-HDL-C], apolipoprotein B [apo B], total cholesterol [TC]) as well as the inflammatory marker high sensitivity C-reactive protein (hsCRP), alone and in combination with other lipid-modifying therapies including statins, ezetimibe, or PCSK9i
- * It leads to upregulation of low-density lipoprotein receptors similar to statins
- * Bempedoic acid is inactive in skeletal muscle cells.
- * Avoids adverse/toxic effects observed with statins in skeletal muscle
- * In randomized controlled Phase 3 clinical trials a lower (-0.2%) HbA1c was observed in patients with hyperlipidemia and diabetes
- * Reduces LDL-C by 20% as monotherapy
- * Reduces LDL-C by an additional 20% when paired with ezetimibe

Conclusion

The current clinical trial results suggest that BemA (ETC-1002) may represent a new therapeutic approach for lowering LDL cholesterol. BemA is a prodrug specifically activated in the liver, where it inhibits ACLY, a regulatory checkpoint within the cholesterol biosynthesis pathway. By inhibiting ACLY, BemA reduces the synthesis of cholesterol in the liver cells and triggers the compensatory activation of the LDL receptor, as well as complementing other mechanisms targeted by current therapies, which leads to an additional decrease in LDL cholesterol, without leading to increases in adverse events.

BemA for lowering lipid levels is showing promising results in early clinical trials and is awaiting confirmation of benefit and safety in large cardiovascular outcome studies. The Food and Drug Administration (FDA) has approved BemA for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic CVD who require additional lowering of LDL cholesterol. The 2019 European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidemias recommend BemA as a potential novel therapy for lowering LDL cholesterol.

The potential value for cardiovascular risk reduction will depend on the results of the pending cardiovascular outcomes trial. Long-term safety data and effect on cardiovascular outcomes are needed. The results of these studies may change future lipid management practices.

CONFLICT OF INTEREST

All the authors declare that they have no conflicts of interest for this work.

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