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Bempedoic acid – new agent in hyperlipidemia treatment – literature review

1. Aleksandra Makłowicz, MD
4. Military Clinical Hospital SP ZOZ, Rudolfa Weigla 5, 53-114 Wrocław, Poland,
https://orcid.org/0009-0007-7667-836X; ola.maklowicz@gmail.com

2. Agata Frańczuk, MD
4. Military Clinical Hospital SP ZOZ, Rudolfa Weigla 5, 53-114 Wrocław, Poland,
https://orcid.org/0009-0008-7840-5282; franczuk.agata@gmail.com

3. Agnieszka Głuszczyk, MD
4th Military Clinical Hospital, Rudolfa Weigla 5, 50-981 Wrocław, Poland,
https://orcid.org/0009-0003-5552-4186; gluszczyk.agnieszka@gmail.com

4. Jakub Plizga, MD
4th Military Clinical Hospital, Rudolfa Weigla 5, 50-981 Wrocław, Poland,
https://orcid.org/0009-0001-1172-9919; jakubplizga7@gmail.com

5. Katarzyna Słychan, MD
4. Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland,
https://orcid.org/0000-0003-3772-737X; kateslychan@gmail.com

6. Ewelina Kopczyńska, MD
Gromkowski Regional Specialist Hospital, Koszarowa 5, 51-149 Wrocław, Poland,
https://orcid.org/0009-0006-5665-6043; ewekop13@gmail.com

7. Angelika Szpulak, MD
Brzeg Medical Centrum, ul. Mossora 1, 49-300 Brzeg, Poland,
https://orcid.org/0009-0000-2660-7538; angelika@brzeg.net

8. Katarzyna Kuleta, MD
10. Military Clinical Hospital, Powstańców Warszawy 5, 85-681 Bydgoszcz, Poland,
https://orcid.org/0009-0007-3491-7721; kuletka8@gmail.com

9. Julia Głoskowska, MD
4. Military Clinical Hospital SP ZOZ, Rudolfa Weigla 5, 53-114 Wrocław, Poland,
https://orcid.org/0009-0004-2634-006X; juliagloskowska@icloud.com

10. Michalina Grzelka, MD
4. Military Clinical Hospital SP ZOZ, Rudolfa Weigla 5, 53-114 Wrocław, Poland,
https://orcid.org/0009-0000-1515-5564; michalinagrzelka1@gmail.com

Coresponding author: Aleksandra Makłowicz, MD; **ola.maklowicz@gmail.com**

Abstract:
Hyperlipidemia is becoming a more and more severe condition in modern society. High-fat diet, sedentary lifestyle, and lack of physical activity are the common factors leading to overweight, obesity, and problems with serum lipid control. Dyslipidemia is one of the most critical factors contributing to cardiovascular diseases and, therefore, lower quality of life, disability, and premature death. This forces the constant search for lipid-lowering drugs that can be successfully used in patients suffering from poor lipid control. Bempedoic acid (ETC-1020) is one of the newest, first-in-the-class medicines, first approved for use in the USA on 21st February 2020 in monotherapy and then on 26th February in combination with ezetimibe. It is a small synthetic prodrug molecule that is activated by acyl-CoA synthetase in the liver. Bempedoic acid competitively inhibits adenosine triphosphate citrate lyase (ACL) and, as a result, stops the further production of cholesterol and fatty acids. Research shows that ETC-1020 can reduce LDL-C cholesterol by up to 24%. It is also responsible for reducing total cholesterol, non-HDL-C, ApoB, and hs-CRP. Bempedoic acid is characterized by good pharmacokinetics and pharmacodynamics. ECT-1020 has a good drug-to-drug interaction profile. Many clinical trials have reported the efficacy and safety of its use with minimal side effects. Because its target point is located in the liver and kidney, it can be successfully used in patients with statin intolerance due to bypassing the decline of muscle cholesterol biosynthesis, which is the main cause of musculoskeletal adverse effects.

Objective: This article aims to provide basic information on a novel, lipid-lowering drug – bempedoic acid (ETC-1020) and to evaluate its efficacy and safety.

Methods: A literature review of articles published between 2018 and 2021 in Pubmed using the following words „bempedoic acid", „hypercholesterolemia", „cardiovascular disease", „dyslipidemia" and „lipid-lowering agent".

Keywords: bempedoic acid, ETC-1020, ATP-citrate lyase, hypercholesterolemia, low-density lipoprotein cholesterol, statin intolerance, cardiovascular drugs

Introduction and quick view on the drugs market:

Hypercholesterolemia is becoming more and more prevalent in modern society. Dyslipidemia is very likely to provoke various cardiovascular conditions such as stroke or heart disease, which may lead to disability and worsen the overall patient's quality of life. Research shows that nowadays, more than 92,000,000 citizens of the United States of America aged 20 and above deal with a total cholesterol level of over 200 mg/dL.[1] Low-density lipoprotein cholesterol (LDL-C) in high concentration in the plasma is an essential factor of atherosclerotic cardiovascular disease. [2] Cardiovascular disease (CVD) is one of the most common reasons of morbidity and untimely death spread worldwide. Research shows that approximately 92.1 million Americans live with kind of CVD. Statistics enclose that total cost, including direct and indirect loss, is estimated at 316 billion dollars per year as a result of lower efficiency and health expenses. [3] It is very important to treat and prevent CVD to improve the overall well-being of society in the whole world.

Lifestyle changes, such as regular physical activity, diet, and alcohol and cigarette restriction, can be useful in CVD interventions. Sometimes, it is not enough, and it is crucial to take pharmacological measurements to lower LDL-C. [4] There are several types of lipid-lowering drugs. However, statins are the most used thanks to their availability and proven action. They inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase, leading to the decline of cholesterol production. High-intensity therapy

including rosuvastatin in a dose of 20 to 40 mg or atorvastatin in a dose of 40 to 80 mg is proven in reduce LDL-C by 50% or even more starting from basal level. It is worth to noting that statins are also able to hold the level of hs-CRP (high-sensitivity C-reactive protein) at the point of <2 mg/L. Although there are plenty of advantages, sometimes usage of statin is limited by side effects ranging from mild, such as myalgia or myositis, up to potentially life-threatening rhabdomyolysis. This can limit the potential of treatment, and some of the patients cannot be administered sufficient doses of medicine. Moreover, side effects often lead to non-compliance with recommendations and self-loss of the cure by patients.

Even though statins and fibrates are world-spread medications used to treat dyslipidemia, sometimes it is really hard to achieve therapeutic goals. It forced me to search for new substances that can manage this issue. A few of non-statin agents added to basal statin therapy can visibly improve CVD treatment effects. Vytorin Efficacy International Trail showed the positive outcome of a combination cure using ezetimibe and simvastatin compared to a single simvastatin treatment, with the result of a 6% lowering CVD events. The protein convertase subtilisin/kexin type 9 (PCSK9)has recently been used as a promising non-

statin cure reducing LDL-C level
s.

Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects in Elevated Risk probe has proven a 15 % decline in CVD events when PCSK9 – evolocumab - was added to the statin therapy. [3] Usage of the antisense oligonucleotide to apoB100 - mipomersen and the inhibitor of a microsomal triglyceride transfer protein – lomitapide, drugs lowering the LDL-C level is strictly reserved for patients with homozygous familial hypercholesterolemia, so cannot be used in cure in the majority of cases. [5]

Ascending amounts of statin-intolerant patients have made it necessary to look for new alternative drugs that can improve compliance and minimize the potentiality of CVD events as much as possible. Bempedoic acid (ETC-1020) is one of the newest medications providing the lowering of cholesterol levels. This substance is an inhibitor to adenosine triphosphate (ATP) citrate lyase (ACL), an enzyme located in the cells that is responsible for manufacturing precursors for cholesterol and fatty acids.

Substance information:

Bempedoic acid (ETC-1020) is a class of non-statin drug with antihyperlipidemic properties developed by Esperison Therapeutic, and it is used as a medicine for treating hyperlipidemia. ETC-1020 was approved in monotherapy in the USA on 21st February 2020 and 5 days later, so on 26th February, in one preparation with ezetimibe. The trade names of the drug are, respectively, in the USA – Nextetol, and Nilemdo in the EU in monotherapy. Nexlizet in the USA and Nustendil in the EU are the names of those mediations combined with ezetimibe. [6] Bempedoic acid in a daily oral dose of 180 mg has been registered in the USA and EU in use as an additional medication administered to patients with maximally tolerated therapy using statins to decline the level of LDL-C among the ones with heterozygous familial hypercholesterolemia and atherosclerotic cardiovascular disease.

Moreover, ETC-1020 has been approved in the European Union to manage hyperlipidemia in patients that cannot tolerate any dose of statins. [7] At this moment, there is no need to adjust the dose of bempedoic acid in the treatment based on the organ's function, age, or weight.[1] The research that ETC-1020 has undergone shows that this substance can significantly decline the level of LDL-C by about 15% up to 24%. [8]

Structure and mechanism of action:

Bempedoic acid (8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid, ETC-1020) is a small synthetic molecule showing in vivo improvement of lipid serum profiles and in vitro inhibiting the synthesis of the new lipid. [9] This substance is orally administered prodrug molecule, that is transformed into active (ETC-1020-CoA) in the liver by acyl-CoA synthetase. Activated ETC-1020-CoA inhibits competitively adenosine triphosphate citrate lyase (ACL), the enzyme linking the metabolism of carbohydrates to synthesis paths of cholesterol and fatty acids.

Surplus glucose in the hepatic cell activates the mitochondrial tricarboxylic acid (TCA) cycle to the production of acetyl Coenzyme-A (acetyl-CoA) and oxaloacetate by ACL form citrate molecules. Oxaloacetate and acetyl-CoA are essential substrates for the manufacture of cholesterol and fatty acids. Inhibition of ACL performed by bempedoic acid results in

reduction of biosynthesis of both – cholesterol and fatty acids. Due to the reduction of hepatic cholesterol production, the bempedoic acid leads to the upregulation of LDL-C receptors, increased reuptake of LDL-C in the liver, and decline in LDL-C level in the blood.
It is worth mentioning that the characteristic very-long-chain isoform of the enzyme acetyl-CoA synthetase-1 (ASCVL1) transforming the ETC-1020 to activated forms is present only in the cells of the liver and kidney. Myotoxicity connected with insufficient cholesterol biosynthesis in the skeletal muscles can be easily prevented.

Additionally after ACL modulation, bempedoic acid enhances the activity of adenosine monophosphate-activated protein kinase (AMPK) in rodents. This heterotrimeric complex inherent in the cytoplasm of all human flesh inhibits the process of phosphorylation of HMG-CoA reductase and acetyl-CoA carboxylase. It leads to the reduction of lipid and glucose biosynthesis, but ETC-1020 works through independent paths to decline LDL-C, triglycerides, and total cholesterol levels. [10]

Pharmacodynamics:

Multidose tolerance test, ETC-1020-02 was performed on 53 heathy patients, in which 39 was given bepedoic acid and the rest was treated with the placebo pill. This probe was divided into 4 cohorts depending on dose that was administered to the patients, appropriately 20,60,100 or 120 mg. The whole trial was performed for 2 or 4 weeks with the substance of ETC-1020 or for 14 days with placebo, in a 6:2 ratio. A bigger cohort living outside the clinical habitat at the time of treatment was given the therapy for 28 days (18 of them received a 120 mg dose of the drug, and 6 of them were taking a placebo pill). ETC-1020 was well-tolerated, no serious side effects were reported, and what is most important, up to 17% reduction of LDL-C level was achieved.

Alternative multidose tolerance test – ETC-1020-04 was performed to evaluate tolerability of the drug at a daily dose exceeding 120 mg. 24 subjects were included in the research, 18 of which were randomized to bempedoic acid at one of the doses of 140,180 or 220 mg for 14 days. The rest of the subjects were taking placebo pills. The level of LDL-C was declined in average of 36% in the patients taking ETC-1020. Probands taking placebo pill were reported with 4% elevation of LDL-C level. No side effects or necessity of dose reduction were reported. [11]

The murine model in vivo shows that bempedoic acid reduces the level of LDL-C to the same range (38 % and 44%) in APOE-deficient mice, and the ones with APOE-deficient crossed with those with a lack of AMPK β1. [6]

Pharmacokinetics:

The dose range between 60 mg up to 200 mg of bempedoic acid is characterized by linear pharmacokinetics. After 7 days of persistent administration of ETC-1020 in dose of 180 mg per day, the steady-state was reached by treated patients. 3.5 hours was the median time to achieve the maximal concentration, 20 μg/mL was the steady-state of maximal concentration, 289.0 μg·h/mL was the area under the curve.

The distribution of bempedoic acid was 18L, the clearance was in the level of 11.2 mL/min, average half-life was 21 hours and the binding of plasma protein was 99,3%. ETC-1020 is mostly decomposed by acyl glucuronide, however it can be also metabolized by

aldehyde-ketone reductase. After oral intake of 240 mg dose 70% is excreted in urine and the rest of 30% is eliminated with feces. The concentration of bempedoic acid that was unchanged was less than 5%.

Research shows that there were no clinically important differences among the population pharmacokinetics basing on patient's race, age, gender, weight and mild to moderate hepatic or renal impairment. There were no conducted studies in the group of patients with severe renal and hepatic impairment. [4]

Concurrent food does not have any impact on oral intake of bempedoic acid, however food can slow down the absorption of ETC-1020 with a persistent level of 0.32 per hour. [12]

Drug-to-drug interaction

Bempedoic acid, active form-bempedoyl-CoA or glucuronide forms are not metabolized and do not interact with CYP3A4 and CYP2C9, the enzymes of cytochrome P450. It results in no interaction between ETC-1020 and the medicines metabolized by this path, including warfarin.

In vitro experiment indicated that glucuronide of bempedoic acid is a substratum for the organic anion transporter 3 (OAT3) transporting lower hydrophilic organic anions. ETC-1020 has ability to inhibit OAT3 at the concentration much above the clinically essential stage. Application of bempedoic acid with probenecid, which is OAT inhibitor causes the increase of maximal concentration and AUC of bempedoic acid and bempedoyl-CoA.

Relatively the most important is the interaction between bempedoic acid and pravastatin and simvastatin. Simultaneous use of 40 mg simvastatin and 180 mg of bempedoic acid or 20 mg of simvastatin and 240 mg of bempedoic acid results in around 1.5-fold and 2.0-fold increase in maximum concentration and AUC in simvastatin. A similar outcome was reported when 40 mg of pravastatin was combined with the dose of 240 mg of bempedoic acid with the result of 2.0-field increase in AUC and maximum concentration. The reaction between ETC-1020 and pravastatin can be a result of specific impact on OATP2 transporter transferring pravastatin. The correlation between simvastatin and bempedoic acid is still not so clear, but it is believed that the whole process is performed out of the cytochrome P450. Simultaneous use of ETC-1020 and pravastatin or simvastatin may enhance the possibility of myopathy. [4] There were observation of 1.7-fold growth in AUC after intake of rozuvastatin, atorvastatin or their active metabolites with bempedoic acid. Moreover high dose of atorvastatin (80 mg) administered with ETC-1020 caused less than 30% change in maximum concentration and AUC of atorvastatin and its active particle, which is ortho-hydroxy atorvastatin.

Single dose of ezetimibe added to steady-state of bempedoic acid resulted in less than 20% increase of maximum concentration and AUC. Including glucuronide form of ezetimibe there were noticed growth in AUC and maximal concentration in the range between 1.6-fold up to 1.8-fold. In a trial conducted by Ballantyne and colleagues, where 301 patients at high risk of ASCVD taking statin on a regular basis with a maximal tolerated dose, who did not meet the therapeutic point and suffered from maintained hypercholesterolemia (average LDL-C level of 3.87 mmol/L). Probands were randomized into four groups and were taking combination of bempedoic acid 180 mg and ezetimibe 10 mg, ezetimibe 10 mg, bempedoic acid 180 mg or placebo respectively. Results show that after 12 weeks of oral intake

combination of ETC-1020 and ezetimibe reduced the level of LDL-C in about 36.2% comparing to ezetimibe – 23.2% and bempedoic acid – 17.2%. Placebo users were observed with the delicate increase in LDL-C level (1.8%). This research clearly indicate advantage of bempedoic acid and ezetimibe in common usage. [13]

Additional drug-to-drug interaction tests showed no essential impact on pharmacokinetics of metformin also contraceptive pill consisting of 0.035 ethinyl estradiol and 1 mg norethindrone. [7]

Clinical Efficacy and safety of use:

In Phase I of clinical trial there were conducted tests on tolerability and safety of single and multiply doses of ETC-1020 in group of healthy patients and those with mild dyslipidemia. Obtained reduction of LDL-C was counted on between 17% up to 36%. Any side effects were reported in Phase I trial basing on dose.

Phase II clinical trial focused on investigating efficacy and safety of bempedoic acid in bigger cohorts. All of the patients included in phase II trial suffered from hypercholesterolemia. Additionally probands with specific states such as statin intolerance, diabetes mellitus type 2, hypertension, those treated with low- or high-dose statin, ezetimibe or using evolocumab.

56 patients with statin-intolerance were enrolled into phase II, double-blind, multicenter, 8 weeks trial with dose of 60 mg of bempedoic acid at the beginning or placebo pill. The amount was elevated every 2 weeks of 60 mg up to 240 mg. The level of LDL-C was declined 18%, 28.5% and 30% respectively after 2-,4- and 8-weeks trial. There were no significant myopathy in patients treated with ETC-1020 comparing to probands given placebo pill.

Trial in phase II was also conducted on patients on high-intensity statin treatment. 68 probands were enrolled into placebo-controlled, double-blind probe. Probands were taking 80 mg atorvastatin for 4 weeks, and then where randomized into two groups given additional treatment of 180 mg bempedoic acid or placebo pill for the next 4 weeks. Combined therapy of atorvastatin and ETC-1020 resulted in crucial reduction of LDL-C, non-HDL-C, total cholesterol, hs-CRP and ApoB.

The effect of bempedoic acid was checked on patients suffering from diabetes mellitus type 2 and increased LDL-C level in double-blind, single-center, placebo-controlled trial. Probands were randomized into group receiving bempedoic acid in dose of 80 mg for 2 weeks, and then elevated on 120 mg for next 2 weeks or placebo pill. Significant efficacy was noticed in the group of bempedoic acid users with the result of 43% reduction in LDL-C level comparing to 4% reduction in users of placebo pill. Glycemic control was not worsen in the group of ETC-1020 users.

Phase II did not reveal any essential, neither dose-limiting adverse effects. Headache (20%) and constipation (7%) were the most reported side effects. They were solved after the end of trial.

Plenty of Phase III trials were conducted to assume the safety and efficacy of bempedoic acid treatment alone or in accompany of statin or ezetimibe. Phase III trials enrolled patients with statin intolerance, familial hypercholesterolemia and ASCVD.

CLEAR Harmony probe enrolled in total 2230 patients with the level of LDL-

C >70mg/dL using the maximally tolerated dose of statins. Probands were also suffering from familial hypercholesterolemia or ASCVD. Participants were randomized into 2:1 ratio receiving bempedoic acid (n = 1487) or placebo pill (n = 742). Patients were taking prescribed medication for 52 weeks. The aim of the trial was to establish LDL-C ending point and safety. At week 12 ETC-1020 demonstrated a 16.5% decline of LDL-C level to the baseline and 18.5% decline comparing with placebo.

Side effects were observed in 1167 probands (78.5%) treated with bempedoic acid versus 584 probands taking placebo (78,7%). Myalgia, nasopharyngitis, urinary tract infections, upper respiratory infections, muscle spasms, dizziness, arthralgia and diarrhea were the most common adverse effects of therapy. 13 of the patient using ETC-1020 and 2 treated with placebo were reported dead. All of the passed away participants underwent autopsies. No relation was indicted between mortality and bempedoic acid use.

Research shows negative affect on uric acid level in blood stream and frequent gout occurrence. Serum creatinine can be minimally increased at the beginning of the treatment with bempedoic acid. It is thought to be connected with interaction with renal-transporters.

CLEAR Serenity was the next, double-blind, placebo-controlled Phase III trial involving 345 patients suffering from hypercholesterolemia during stable lipid-lowering treatment who also had two statin intolerance record. Probands were randomized into two groups in ratio 2:1 receiving 180 mg bempedoic acid and placebo pill for 24 weeks. At week 12^{th} it was noticed that use of bempedoic acid significantly decreased the level of LDL-C for about 23.6% to the baseline and 21.4% compared to placebo. Decline of hs-CRP was also reported. Side effects were mainly connected with connective tissue and musculoskeletal and were noted in 64.1% of patients using bempedoic acid comparing to 56.8% with those on placebo pill. Severe cardiovascular events were reported in 9 patients in bempedoic acid treatment and were not occurred in placebo group. All of those patients had previous cardiovascular history.

CLEAR Tranquility was double-blind, randomized, placebo-controlled, multi-center study involving 269 probands with intolerance of statin and the LDL-C >100 mg/dL. The aim of this trial was to judge efficacy and safety of addition of the ETC-1020 to regular treatment. Enrolled patients were taking 10 mg ezetimibe for 4 weeks and were randomized in ratio 2:1 to the group given 180 mg of bempedoic acid and placebo pill respectively for 12 weeks. LDL-C has been reduced by 23.5% in the ETC-1020 group and 5% increase were noted in the group of placebo. Declines were also reported in total cholesterol (18%), non-HDL-C (23.6%), hs-CRP (31.0%) and ApoB (19.3%). Adverse effects were seen in 48.6% in bempedoic acid users and in 44.8% in placebo users. Treatment was frown away by 6.1% of ETC-1020 users comparing to 5.7% in placebo pill takers. Muscle disturbance was reported in both groups of patients with similar percentage (3.4% vs 3.3%). 14 testers given bempedoic acid and 2 placebo users were reported with asymptomatic uric acid elevation. Worsening or new-onset gout were not noted.

CLEAR Wisdom is randomized trial enrolling 779 probands with ASCVD history with or without heterozygous familial hypercholesterolemia and the level of LDL-C >=70 mg/dL. Patients were planned for 52 weeks to take 180 mg of bempedoic acid. After 12 weeks there were reported decline of 15.1% in LDL-C level to the baseline (17.4% vs placebo). Depletion was also indicated in total cholesterol (9.9%), hs-CRP (18.7%) and ApoB (9.3%).

Hyperuricemia, nasopharyngitis and urinary tract infections were the most popular side events.

Trials on Phase III confirmed efficacy and safety of ETC-1020 among various patients' characteristics such as statin intolerance, familial hypercholesterolemia and previous ASCVD history. [14]

Conclusion:

Bempedoic acid is first in the class, new, promising ACL inhibitor that can be successfully used in the patients suffering from hyperlipidemia. Clinical trials visibly reported ETC-1020 to be able of reduction of LDL-C, total cholesterol, non-HDL-C, ApoB and hs-CRP. For now it is the only alternative to the statins oral intake drug, that directly block intracellular cholesterol synthesis. This fact proves that it can be used in the treatment of statin-intolerant patients. Its efficacy and safety were confirmed in plenty of clinical trials. Moreover research shows its potentially upregulation abilities when combined with other lipid-lowering medicine, such as ezetimibe. Tests indicate safety and good tolerance of drug use with time-to-time mild to moderate side effects, that are gone soon after bempedoic acid withdrawal.

Disclosures

Author's contribution:

Conceptualization Methodology: AG, JP, MG; Software: not applicable; Check: AM, AF, KS, EK, MG; Formal analysis: AM, AS, KK, JG; Investigation: AG, JP, KS Resources: not applicable; Data curation: Writing - rough preparation: JG, AG, KK, MG Writing - review and editing: AM, AF, EK, JP ; Visualization: EK, KK, JG, AS; Supervision: AM, AF, AS, KS; Project administration: AM

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