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SPECIAL ARTICLE

Bempedoic acid, when and how to use it?

Ácido bempedoico, ¿cuándo y cómo utilizarlo?

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Abstract

Bempedoic acid is an orally administered prodrug that, like statins, reduces cholesterol biosynthesis (by inhibiting ATP citrate lyase, a key enzyme in cholesterol synthesis prior to 3-hydroxy-3-methyl-glutaryl CoA reductase). Its lipid efficacy has been evaluated in several clinical trials, achieving a 17-28% reduction in LDL-c levels, and showing an anti-inflammatory effect. Unlike statins, their use is not associated with myotoxic effects. Recently, the cardiovascular benefit of bempedoic acid in patients intolerant to statins has been confirmed in the CLEAR OUTCOMES clinical trial. The use of bempedoic acid has been approved as an adjunct to diet and statins, alone or in combination with ezetimibe, in patients with hypercholesterolemia, mixed dyslipidemia, or statin intolerance. New recommendations also suggest their use as alternative drugs in individuals at high cardiovascular risk or with very high LDL-c levels who do not reach lipid targets with other lipid-lowering drugs. Likewise, it could be considered as a second- or third-line therapy in patients intolerant to statins.

Keywords: *Residual risk. Lipid-lowering therapy. Bempedoic acid.*

Resumen

El ácido bempedoico es un profármaco de administración oral que, al igual que las estatinas, reduce la biosíntesis del colesterol (inhibe la ATP-citrato liasa, una enzima clave en la síntesis de colesterol previa a la 3-hidroxi-3-metil-glutaril CoA reductasa). Su eficacia lipídica ha sido evaluada en varios ensayos clínicos y se ha observado una reducción en los niveles de colesterol LDL (c-LDL), de entre el 17 al 28%, además de un efecto antiinflamatorio. A diferencia de las estatinas, su uso no se asocia con efectos miotóxicos. Recientemente, el beneficio cardiovascular del ácido bempedoico en pacientes intolerantes a las estatinas se ha comprobado en el ensayo clínico CLEAR OUTCOMES. El uso de ácido bempedoico ha sido aprobado como complemento de la dieta y las estatinas, solo o en combinación con ezetimiba, en pacientes con hipercolesterolemia, dislipidemia mixta o intolerancia a las estatinas. Nuevas recomendaciones también sugieren su uso como droga alternativa en pacientes de alto riesgo cardiovascular o con un nivel de c-LDL muy elevado que no alcanzan los objetivos lipídicos con otros hipolipemiantes. Así mismo, podría considerarse como una terapia de segunda o tercera línea en pacientes intolerantes a las estatinas

Palabras clave: *Riesgo residual. Terapia hipolipemiante. Ácido bempedoico.*

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Introduction

Bempedoic acid (BA) is a prodrug which is rapidly converted by very long-chain acyl-CoA-synthetase 1 in the liver into coenzyme A, which is responsible for inhibiting ATP citrate lyase (ACL), a key enzyme in cholesterol synthesis prior to 3-hydroxy-3-methyl-glutaryl CoA (HMG CoA) reductase, leading to a greater expression of LDL receptors. Conversion to the active form only occurs in the liver, as very long-chain acyl-CoA-synthetase 1 is undetectable in muscle[1].

ACL lies at the intersection of nutrient catabolism and cholesterol and fatty acid biosynthesis, thus connecting glucose metabolism with lipogenesis. It is also an extra-mitochondrial enzyme which catalyzes the cleavage of mitochondrial citrate into cytosolic acetyl-CoA and oxaloacetate. Acetyl-CoA, a precursor in the mevalonate pathway for cholesterol biosynthesis, is the key element for de novo cholesterol and fatty acid synthesis[1].

This, in turn, reduces circulating LDL-c both in patients on moderate to high-intensity statins as well as in statin-intolerant patients on low or very low-intensity statins, or who do not take statins[2].

The results of Mendelian randomization analyses have shown that inhibiting ACL reduces the incidence of cardiovascular events proportionally to the LDL-c reduction[3].

Bempedoic acid is available in 180 mg doses, alone or combined with ezetimibe, for oral administration.

Materials and method

Informal consensus methods were used based on the scientific evidence and the judgement and clinical experience of a group of experts from different medical specialties. A literature search was conducted to find observational studies, clinical trials and systematic reviews or meta-analyses evaluating treatment with BA, published up to April 15, 2023, in the PubMed/Medline, EMBASE, SciELO, Google Scholar and Cochrane Clinical Trials electronic databases.

Content

Lipid efficacy

The lipid efficacy of BA has been tested in at least six clinical trials within a research program titled “Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR)”[4].

In a group of people with cardiovascular disease or familial hypercholesterolemia on moderate or high-intensity statins, the CLEAR Wisdom and CLEAR Harmony studies evaluated changes in LDL-c at 12 weeks, and safety at 52 weeks, with a combined total of 3,000 patients[5,6]. The latter study had an open label extension for 1.5 years, CLEAR Harmony OLE, with more than 1,452 patients[7].

For patients with cardiovascular disease, familial hypercholesterolemia or in primary prevention with or without statins, at low intensity or low doses, or on ezetimibe, the CLEAR Serenity and CLEAR Tranquility studies gathered 614 people and evaluated LDL-c changes at 12 weeks and safety at 24 weeks[8,9]. The LDL-c changes at 12 weeks are presented in Table 1.

In statin-intolerant patients, the reduction was around 24%[4]. Beyond 12 weeks, data are only available from the open label extension (CLEAR Harmony OLE) in which, after 2.5 years of follow up, a sustained LDL-c reduction of -14.2 ± 0.9% was found[7].

Safety

Bempedoic acid was not associated in any study with muscle or liver adverse effects[10]. The most specific adverse effect (26% higher in patients with normal initial levels) is elevated uric acid (UA) due to the effects of the drug on the organic anion transporter OAT2. The mean UA elevation is 0.8 mg/dl (95% CI = 0.5-0.9 mg/dl), with a higher rate of gout attacks (OR = 3.2; 95% CI = 0.12-8.2) occurring within the first four weeks and persisting throughout treatment[10].

With a frequency of less than 2%, tendon rupture was reported as an adverse effect, including rupture of the biceps tendon, Achilles tendon and rotator cuff tendon. This was more common in those over the age of 60, those with previous tendon diseases, those on steroids or fluoroquinolones and patients with chronic kidney disease. Another effect with a small difference compared with the placebo (1.7 vs. 1.1%), and which was infrequent, was the incidence of atrial fibrillation[11].

Table 1. Percentage change in LDL-c at 12 weeks vs. placebo.

CLEAR Wisdom	-17.40%
CLEAR Harmony	-18.10%
CLEAR Serenity	-21.40%
CLEAR Tranquility	-28.50%

Compared with placebo, BA had 2.8 vs. 1.3% of cases of slightly elevated levels of transaminases and creatine kinase. A few patients have had mildly lowered hemoglobin levels in the first weeks which have persisted over time and normalize once treatment is stopped[10-11]. Other adverse effects are described in Table 2.

Table 2. Adverse effects higher than 2% vs. placebo.

Adverse effect	Bempedoic acid Statin + Others %	Placebo %
Upper respiratory tract symptoms	4.5	4.0
Muscle spasms	3.6	2.3
Back pain	3.3	2.2
Bronchitis	3.0	2.5
Anemia	2.8	1.9

Cardiovascular benefit

Before the results of the CLEAR OUTCOMES study were available, a meta-analysis including four randomized clinical trials (3,483 patients) analyzed the effect of BA (180 mg/day) on the primary endpoint of major cardiovascular events (myocardial infarction, stroke, cardiovascular mortality, hospitalization for unstable angina or coronary revascularization) compared with the placebo[12]. After an average of 35 weeks' follow up, no statistically significant reduction was found in the combined endpoint (RR = 0.83; 95% CI = 0.57-1.21; p = 0.34; I2 = 14%) with the lipid-lowering treatment. However, the authors reported a significant reduction of 59% in non-coronary revascularization procedures in the group assigned to BA, compared with the placebo (RR = 0.41; 95% CI = 0.18-0.96; p = 0.04; I2 = 0%). Likewise, another meta-analysis reported that the use of BA was associated with a significant reduction in the primary combined cardiovascular point (RR = 0.75; 95% CI = 0.56-0.99; I2 = 0%), although it only included two clinical trials in this evaluation[13]. Furthermore, this study reported neutral results when the cardiovascular events were evaluated individually.

On the other hand, a Mendelian randomization study showed that the genetic variants which "imitate" the effect of BA (lower ACL function) and statins (lower HMG CoA function) appear to reduce serum LDL-c levels through a similar mechanism of action, associated with similar effects on the risk of cardiovascular disease[14]. For every 10 mg/dl reduction in LDL-c associated with ACL, a 17.7% reduction in the risk of major cardiovascular events was found (OR = 0.82; 95% CI = 0.78-0.87), as well as a 19.4% reduction in the risk of myocardial infarction (OR = 0.81; 95% CI = 0.76-0.86).

In addition, a recently published simulation model (Markov model) showed that adding BA to ezetimibe, compared with ezetimibe as monotherapy, in patients with atherosclerotic cardiovascular disease who do not reach the LDL-c goal with the maximum statin dose, predicts an incremental reduction in major cardiovascular events[15]. As the patients' 10-year risk increases, largely driven by the baseline LDL-c, the incremental benefits grow in terms of major cardiovascular events.

Without a doubt, the greatest evidence to date of BA's cardiovascular benefit comes from a large clinical trial called CLEAR OUTCOMES (n = 13,970, median follow up: 40.6 months)[16]. This multicenter, randomized, double-blind, placebo-controlled trial included patients between 18 and 85 years old with a high cardiovascular risk (a history of cardiovascular disease or in primary prevention with a high cardiovascular risk), statin intolerance (two or more statins at any dose or one statin at any dose and unwilling to try a second statin). It is important to clarify that a small proportion of patients received minimal statin doses (23%) and that the proportion who received ezetimibe was conspicuously low (11-12%). The primary endpoint was a combination of four events: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and coronary revascularization. The average baseline level of LDL-c was 139 mg/dl in both groups. After six months, LDL-c reduction was greater with BA than with the placebo (difference: 29.2 mg/dl, 21.1%). The incidence of the primary endpoint was significantly lower in the BA group compared with the placebo group (11.7 vs. 13.3%; HR = 0.87; 95% CI = 0.79-0.96; p = 0.004). This benefit was also found when the incidence of fatal or nonfatal myocardial infarction (HR = 0.77; 95% CI = 0.66-0.91) and coronary revascularization (HR = 0.81; 95% CI = 0.72-0.92) was evaluated. Bempedoic acid had no significant effect on stroke, cardiovascular death and death from any cause.

In conclusion, this study showed that a moderate LDL-c reduction with BA in statin-intolerant patients reduced cardiovascular events. However, the population had a high baseline LDL-c compared with other studies. Consequently, it would be inappropriate to extrapolate these results to a population properly medicated with statins or with a lower LDL-c. This medication does not replace statins. Properly defining true "statin intolerance" will help avoid inappropriate treatment choices.

Recommended use

Bempedoic acid and the combination of a fixed dose with ezetimibe were approved by the United States Food and Drug Administration (FDA) in 2020 and are indicated as a complement to diet and statins for treating adults with heterozygous familial hypercholesterolemia or established cardiovascular disease who need additional LDL-c reduction[17]. Likewise, the European Medicines Agency (EMA) has recommended approval of BA, alone or combined with ezetimibe, for treating adults with primary hypercholesterolemia and mixed dyslpididemia[18].

A recent consensus document on the use of non-statin treatments produced by the American College of Cardiology (ACC) has provided recommendations for the use of BA in routine clinical practice[19]. It establishes that, for patients with established cardiovascular disease, the use of BA could be considered when the LDL-c goal is not reached despite correct statin treatment, and after evaluating other options like ezetimibe or PCSK9 inhibitors. This recommendation also applies for patients in primary prevention with a very high LDL-c level (> 190 mg/dl). On the other hand, the document recommends using BA as second-line treatment together with inclisiran (after the first-line treatment with ezetimibe or PCSK9 inhibitors) in statin-intolerant patients with cardiovascular disease or an LDL-c level > 190 mg/dl, or both. Finally, the authors recommend considering BA as third-line treatment (after the first-line treatment with ezetimibe or PCSK9 inhibitors and the second-line treatment with resins) in statin-intolerant patients with or without diabetes in primary prevention and with a moderately elevated LDL-c.

Conclusions

Bempedoic acid is an oral prodrug which, like the statins, acts by inhibiting cholesterol biosynthesis. Its lipid efficacy has been proven in a large number of clinical trials. The approximate reduction in LDL-c levels varies from 17 to 28%, with an anti-inflammatory effect also found. It is activated mainly in liver cells, and is not seen in muscle cells; consequently, unlike statins, its use is not associated with myotoxic effects. The cardiovascular benefits of BA, at least in patients with high cardiovascular risk and statin intolerance, have been proven in a recently published clinical trial. This treatment has been approved as a complement to diet and statins, alone or combined with ezetimibe, in patients with hypercholesterolemia, mixed dyslipidemia or statin intolerance. New recommendations also suggest its use as an alternative medication in individuals with high cardiovascular risk or a very high LDL-c level who do not reach the lipid goals with other lipid-lowering agents. Likewise, it could be considered as second or third-line treatment in statin-intolerant patients, when the LDL-c goals established by the current guidelines are not reached.

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Conflicts of interest

None.

Declaration of originality

The authors declare that the content of this article is original and has not been previously published, nor has it been sent or submitted for consideration to any other journal, as a whole or in part.

Ethical responsibilities

Human and animal protection. The authors declare that no experiments were conducted on animals or humans for this study.

Data confidentiality. The authors declare that no patient data are included in this article.

Right to privacy and informed consent. The authors declare that no patient data are included in this article.

Use of artificial intelligence to generate text. The authors delcare that they have not used any type of artificial intelligence generator to draft this manuscript or create the figures, graphs, tables or their respective captions or titles.

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