Journal of Community Hospital Internal Medicine Perspectives

Volume 14 | Issue 2 Article 6

2024

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Recommended Citation

Nisar, Sibtain; Sohail, Sidra; Fatima, Saman; Akhtar, Muhammad Talha; Ahmad, Muhammad; Hanif, Muhammad Waqar; Khan, Masood; Mehmoodi, Amin; and Malik, Jahanzeb (2024) "Efficacy and Safety of Bempedoic Acid in Patients with Hyperlipidemia and Non-Alcoholic Fatty Liver Disease," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 14: Iss. 2, Article 6.
DOI: 10.55729/2000-9666.1313
Available at: https://scholarlycommons.gbmc.org/jchimp/vol14/iss2/6

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REVIEW ARTICLE

Efficacy and Safety of Bempedoic Acid in Patients With Hyperlipidemia and Non-alcoholic Fatty Liver Disease

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Abstract

Hyperlipidemia and its association with cardiovascular diseases have been significant public health concerns for many decades. Statins have long been the primary therapeutic option for lowering cholesterol levels and reducing cardiovascular mortality. However, a substantial number of patients either do not achieve optimal lipid goals with maximally tolerated statin doses or experience statin intolerance. In recent years, there have been remarkable developments in the field of hyperlipidemia management, leading to the approval of novel hypolipidemic drugs in North America and Europe. This article reviews the clinical development of bempedoic acid, a promising new drug, alone and in combination with ezetimibe, as an alternative approach to managing hyperlipidemia. The Phase I trials established the safety and tolerability of bempedoic acid, paving the way for further investigation in Phase II and Phase III trials. Multiple phase II studies evaluated the lipid-lowering efficacy of bempedoic acid as monotherapy or in combination with other hypolipidemic agents, showing significant improvements in lipid levels and inflammatory markers. The recently approved fixed drug combination of bempedoic acid and ezetimibe presents a viable option for patients who need additional LDL-C lowering alongside dietary modifications and maximally tolerated statin therapy.

Keywords: Bempedoic acid, Ezetimibe, Hyperlipidemia, Cardiovascular diseases, LDL-C lowering

1. Introduction

Cardiovascular diseases (CVDs) are a major health concern in developed countries, causing significant disability and death.[1] One of the primary risk factors for CVDs is high levels of low-density lipoprotein cholesterol (LDL-C), commonly known as "bad cholesterol.[2]" Studies using Mendelian randomization have provided strong evidence that reducing LDL-C levels can substantially lower the risk of atherosclerotic CVD by over 50 %.[3] Bempedoic acid, a novel drug, offers a potential solution for reducing LDL-C levels and managing CVD risk.[4] It works by inhibiting ATP citrate lyase (ACLY), an enzyme that plays a crucial role in the synthesis of cholesterol and fatty acids.[5] By blocking ACLY, bempedoic acid increases the number of LDL receptors in the liver, which leads to enhanced uptake of LDL particles from the blood, effectively reducing LDL-C concentration.[6] The drug is administered orally once a day, and it is quickly absorbed in the small intestine. It acts as a prodrug, requiring activation by a liver-specific enzyme called very long-chain acyl-CoA synthetase 1.[7] Importantly, bempedoic acid's mechanism of action differs from statins, the most commonly used

Received 14 September 2023; revised 5 December 2023; accepted 2 January 2024.
Available online 4 March 2024

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https://doi.org/10.55729/2000-9666.1313

cholesterol-lowering drugs. This distinction is significant because it may address one of the key challenges with statin therapy, which is the occurrence of muscular adverse effects in some patients.[8] Statin intolerance, characterized by muscle-related symptoms, leads to poor adherence to therapy, limiting the number of patients who achieve their LDL-C targets.[9] Bempedoic acid offers a promising alternative for such individuals since it does not possess the same muscle-related side effects as statins, making it a potential solution for those who cannot tolerate statin treatment.[10] Clinical trials, including phase II and phase III randomized controlled trials, have shown encouraging results with bempedoic acid treatment.[11] It effectively lowers LDL-C levels, along with other atherogenic lipid markers such as triglycerides and apolipoprotein B.[12] Additionally, the drug exhibits a robust anti-inflammatory effect by reducing high-sensitivity C-reactive protein (hsCRP) levels, further contributing to its potential cardiovascular benefits.[13] Given the importance of achieving specific LDL-C targets to reduce cardiovascular risk effectively, the combination of multiple cholesterol-lowering therapies has been proposed. This includes high-intensity statin formulations (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) in combination with ezetimibe, which provides an additional LDL-C reduction.[14] Moreover, monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) have shown great promise in further reducing LDL-C levels when added to statin therapy.[15] However, despite the availability of various cholesterol-lowering treatments, a significant proportion of patients do not reach their LDL-C targets. Poor adherence to statin therapy is a primary reason for this, with statin-associated muscle symptoms (SAMS) being the leading cause of treatment discontinuation.[16] Nonetheless, recent research indicates that SAMS, characterized by myalgia without objective signs of muscle inflammation, is largely reversible, and statin re-challenge is often well-tolerated.[17] Apart from poor adherence, underestimation of cardiovascular risk by both healthcare professionals and patients contributes to the failure to achieve therapeutic targets.[18] To improve therapeutic adherence and outcomes, new cholesterol-lowering drugs with different administration methods have been developed. Inclisiran, for example, inhibits PCSK9 synthesis and requires biannual subcutaneous administration, offering a more convenient option for some patients.[19] Bempedoic acid, being an orally administered drug with a different mechanism of action and a good safety profile in terms of muscular side effects, represents another potentially valuable addition to the armamentarium of cholesterol-lowering drugs. Further studies and clinical evidence will be essential to better define its efficacy, safety, and long-term benefits for managing cardiovascular risk effectively.

2. Methods

In this narrative review, we aimed to evaluate the available clinical evidence on the efficacy and tolerability profile of bempedoic acid in the management of cardiovascular diseases (CVDs). The objective was to assess the impact of bempedoic acid on reducing low-density lipoprotein cholesterol (LDL-C) levels, its potential role as an alternative therapy for statin-intolerant patients, and its overall safety profile compared to existing cholesterol-lowering treatments. For the literature search, a comprehensive review of studies published up to the present date was conducted. Databases such as PubMed, Embase, and Cochrane Library were searched using appropriate keywords and Medical Subject Headings (MeSH) terms, including “bempedoic acid,” “LDL cholesterol,” “cholesterol-lowering drugs,” “cardiovascular disease,” and “statin intolerance.” Additionally, relevant conference proceedings, clinical trial registries, and reference lists of relevant articles were hand-searched to ensure the inclusion of all relevant studies. The inclusion criteria for studies comprised original research articles, including randomized controlled trials (RCTs), phase II, and phase III trials, and meta-analyses, evaluating the efficacy and tolerability of bempedoic acid in reducing LDL-C levels and its impact on cardiovascular outcomes. Only studies conducted on human subjects and published in English were eligible for inclusion. Studies that did not meet the inclusion criteria or contained insufficient data to address the review's objectives were excluded. Data extraction was conducted by two independent reviewers, and it included study characteristics (e.g., study design, sample size, duration), patient demographics, intervention details (e.g., dosage, administration), outcomes (e.g., LDL-C reduction, cardiovascular events), adverse events, and any relevant safety and tolerability data. The extracted data were then synthesized narratively to provide a comprehensive overview of the available evidence on bempedoic acid's efficacy and tolerability profile. The narrative review included a discussion of the findings from individual studies and an analysis of the

consistency and heterogeneity of the results across different trials.

3. Mechanism of action

3.1. Inhibition of hepatic ATP-citrate lyase (ACLY)

Bempedoic acid, a pro-drug, is converted into its active form, bempedoyl-CoA, by the liver-specific enzyme very long-chain acyl-CoA synthetase-1 (ACSVL1).[20] The active form of bempedoic acid targets hepatic ATP-citrate lyase (ACLY), a key enzyme involved in the synthesis of lipids.[21] ACLY regulates the flow of extra-mitochondrial citrate, which is essential for the synthesis of lipids. Bempedoyl-CoA inhibits ACLY, resulting in the suppression of de novo sterol and fatty acid synthesis.[22] The direct inhibition of ACLY decreases gluconeogenesis and hepatic glucose production by reducing the availability of oxaloacetate. Furthermore, it interferes with the formation of malonyl-CoA, the precursor for fatty acid synthesis, and 3-hydroxy 3-methylglutaryl-CoA (HMG-CoA), the precursor for cholesterol synthesis mediated by HMG-CoA reductase (HMGR).[23] This mechanism of action leads to a decrease in cholesterol synthesis, similar to statins, but at a higher level in the metabolic synthesis pathway. One of the essential aspects of bempedoic acid's safety profile is its lack of activating enzyme ACSVL1 in skeletal muscle.[24] This prevents the drug from promoting toxicity associated with cholesterol synthesis inhibition in skeletal muscle, making it potentially suitable for statin-intolerant patients. Fig. 1 shows proteins and lipids involved in liver uptake.

3.2. Upregulation of AMP-activated protein kinase (AMPK)

In addition to inhibiting hepatic ACLY, bempedoic acid directly activates AMP-activated protein kinase (AMPK), a key regulator of whole-body glucose and energy homeostasis.[25] AMPK activation leads to the downregulation of key rate-limiting enzymes involved in gluconeogenesis, such as glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK).[26] Consequently, hepatic glucose production is reduced. Moreover, AMPK inhibits the rate-limiting enzymes of fatty acid and cholesterol synthesis pathways, acetyl-CoA carboxylase (ACC), and HMGR, respectively.[27] This dual action further contributes to the lowering of liver fatty acid and cholesterol synthesis, providing additional benefits to lipid metabolism.

3.3. Anti-inflammatory effects

Apart from its metabolic actions, bempedoic acid exhibits significant anti-inflammatory effects, particularly by reducing circulating high-sensitivity C-reactive protein (hsCRP), a marker of systemic inflammation.[28] Studies have demonstrated that bempedoic acid supplementation in LDLR−/− mice fed a high-fat diet resulted in reduced plasma and tissue lipid levels.[29] It also led to the attenuation of proinflammatory gene expression and suppressed cholesteryl ester accumulation in the aortic wall, effectively preventing the development of atherosclerotic plaques.[30] In vitro studies have further elucidated the anti-inflammatory mechanisms of bempedoic acid. It regulates the inflammatory response of activated monocytes by enhancing the anti-inflammatory AMPK pathway and inhibiting the pro-inflammatory mitogen-activated protein kinase (MAPK) pathway.[31] This leads to reduced release of proinflammatory cytokines and chemokines. Fig. 2 shows mechanism of action of bempedoic acid on liver and other organs.

4. Clinical targets

4.1. Dyslipidemia

Bempedoic acid has demonstrated its efficacy in reducing LDL-C levels in patients with hypercholesterolemia who are unable to tolerate statins.[32] Notably, the cholesterol-lowering effect tends to be more pronounced in patients with type 2 diabetes.[33] Combination therapy with bempedoic acid and ezetimibe, a cholesterol intestinal absorption inhibitor, has shown additive effects, resulting in a 45 % reduction in LDL-C.[34] Additionally, combining bempedoic acid with high-intensity statin therapy results in an increase of only about 15 % in LDL-C reduction compared to statin monotherapy.[35] For patients receiving PCSK9 inhibitor therapy, adding bempedoic acid further enhances LDL-C lowering effects, showing a synergistic action.

4.2. Liver steatosis

Non-alcoholic fatty liver disease (NAFLD) is closely associated with metabolic syndrome and can progress to more severe conditions like non-alcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma.[36] Studies on animal models have shown that inhibiting hepatic ATP-citrate lyase (ACLY), the target of bempedoic acid, can control hepatic de novo lipogenesis and reduce

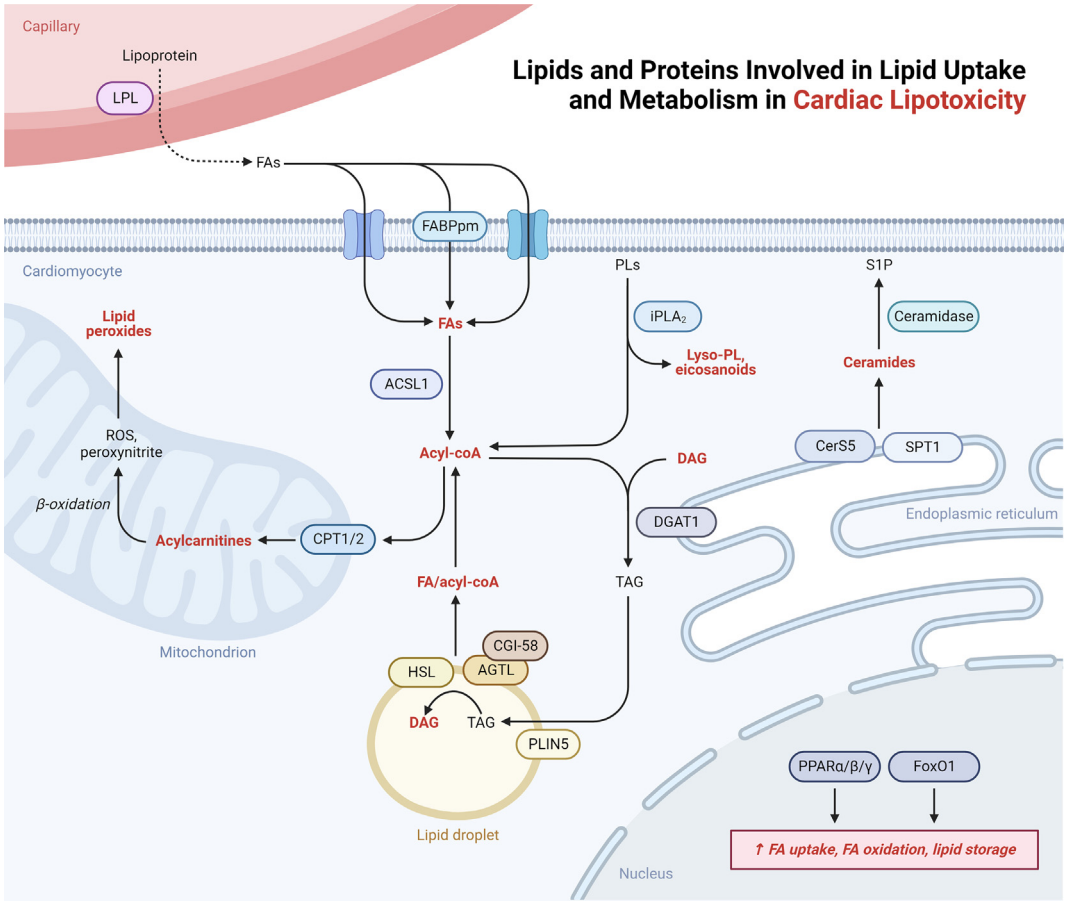

Fig. 1. Mechanism of lipid and protein uptake in liver.

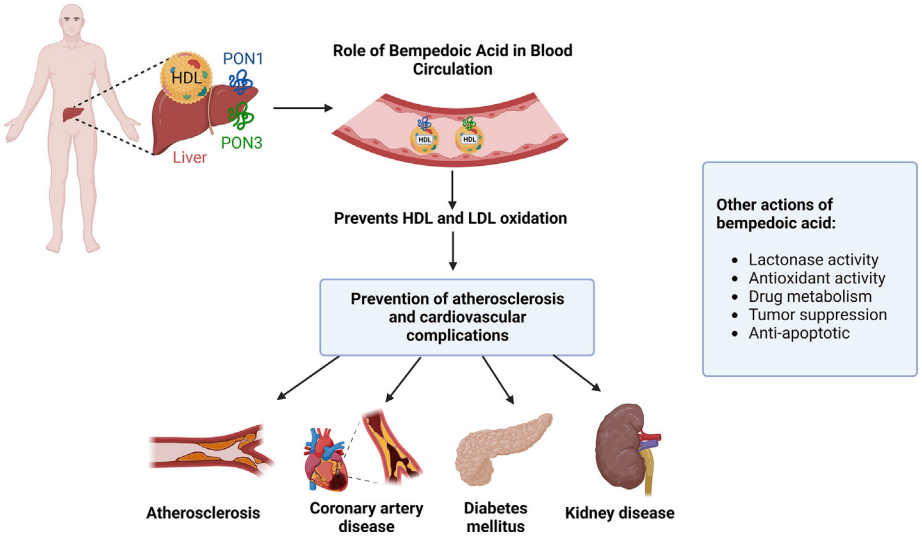

Fig. 2. Mechanism of bempedoic acid.

hepatic steatosis.[37] Inhibition of ACLY by bempedoic acid has also shown promise in reducing fibrosis and preventing the progression of NAFLD to NASH in mice.[38] Clinical studies in humans are needed to confirm the efficacy of bempedoic acid on hepatic steatosis, as the rates of hepatic de novo synthesis of fatty acids are relatively low in normal human subjects.

4.3. Diabetes mellitus

Statins have been associated with an increased risk of new-onset diabetes, while PCSK9 inhibitors have shown no such effect.[1] In contrast, bempedoic acid exhibits potential positive effects on glucose metabolism and insulin sensitivity via the activation of AMP-activated protein kinase (AMPK), which inhibits hepatic glucose production through the downregulation of gluconeogenesis.[39] Phase III RCTs on bempedoic acid have included type 2 diabetic patients, and the results have shown a decrease in hemoglobin A1c (HbA1c) levels. Meta-analyses have also demonstrated lower rates of new-onset or worsening of type 2 diabetes mellitus with bempedoic acid.[40]

4.4. Inflammation

Statins have been known to have anti-inflammatory effects, with reductions in high-sensitivity C-reactive protein (hsCRP) levels.[41] This anti-inflammatory action is believed to contribute to their reduction in cardiovascular risk independently of LDL-C lowering. Bempedoic acid administration has also been associated with a significant decrease in hsCRP levels, indicating a similar anti-inflammatory action comparable to statins.[42] The anti-inflammatory effect of bempedoic acid is primarily achieved through the activation of AMPK and the inhibition of the MAPK pathway in immune cells, suggesting potential benefits in reducing cardiovascular events.[26]

4.5. Pharmacokinetics of bempedoic acid

Bempedoic acid is typically administered at a recommended daily dose of 180 mg orally with meals or between meals.[4] It undergoes elimination through renal excretion (70 %) and conjugation with glucuronic acid.[43] Approximately 30 % of bempedoic acid clearance occurs through liver elimination.[2] No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh class A and B)
[44]. However, patients with severe liver disease (Child-Pugh class C) should not receive bempedoic acid. Patients with mild or moderate renal impairment generally tolerate bempedoic acid therapy well, and no dose adjustments are currently required.[45] There is limited data on the use of bempedoic acid in severe renal impairment (eGFR <30 ml/min/1.73 m^2) or in patients with end-stage renal disease on dialysis.

4.6. Management of patients on bempedoic acid therapy

Bempedoic acid has received approval for use in adults with HeFH and/or established ASCVD.[6] It can be administered as monotherapy or in combination with other LDL-C lowering drugs such as ezetimibe, statins, or PCSK9 inhibitors to achieve target LDL-C levels. It is essential to avoid administering bempedoic acid in combination with high-dose simvastatin (>20 mg/day) or pravastatin (>40 mg/day) to reduce the risk of myotoxicity. Bempedoic acid has shown no significant association with myalgia or muscle weakness, even in patients with statin intolerance.[46] Patients with an increased risk of hyperuricemia and gout should have their uric acid levels assessed regularly. Additionally, those at risk of tendon injury (e.g., age >60, taking corticosteroids or fluoroquinolones, having renal failure or arthritis) should be advised to rest at the first sign of tendon inflammation or rupture.[47] Table 1 shows treatment recommendations of bempedoic acid in hyperlipidemia.

5. Expert opinion

5.1. Clinical trials assessing bempedoic acid for clinical safety and outcomes

5.1.1. Phase I trials

The initial phase of clinical trials focused on evaluating the safety and tolerability of bempedoic

Table 1. Recommendations on the use of bempedoic acid.

Recommendation	Class	Level of Evidence
In patients with ASCVD who have not achieved the LDL-C target at their maximum tolerated statin and ezetimibe dose, combination therapy with bempedoic acid may be considered.	IIb	B
In FH patients at very high risk not achieving the LDL-C target with the maximum tolerated statin and ezetimibe, consider combination therapy with bempedoic acid.	IIb	B
If a statin-based regimen is not tolerated at any dose (even after rechallenge), bempedoic acid or the combination of ezetimibe and bempedoic acid may be considered.	IIb	B

acid.[48] Phase 1a study included 53 subjects with mild dyslipidemia, and they were treated with increasing doses of bempedoic acid up to 120 mg daily. A 17 % reduction in LDL-C level was observed with an average dose of 100 mg daily. The phase 1b study enrolled 24 healthy subjects who received bempedoic acid in dose increments of 140, 180, and 220 mg daily, resulting in a significant 36 % reduction in LDL-C levels compared to placebo.[49] The ETC-1002-011 study assessed the absorption, metabolism, and excretion of a single dose of bempedoic acid in urine and feces in 6 healthy male subjects. No major adverse events were noted in phase I studies, despite renal impairment.

5.1.2. Phase II trials

Multiple phase 2 studies evaluated the lipid-lowering efficacy of bempedoic acid as monotherapy or in combination with other agents.[50] The study population included hyperlipidemic patients with other cardiovascular risk factors, such as diabetes mellitus, hypertension, or statin intolerance. Bempedoic acid as a single agent or in combination with other hypolipidemic agents led to significant improvements in lipid levels and inflammatory markers. For instance, one phase-II trial (NCT02659397) investigated the addition of bempedoic acid to stable high-intensity atorvastatin therapy in patients with hypercholesterolemia, resulting in a 22 % reduction in mean LDL level compared to baseline.[51]

5.1.3. Phase III trials

The Phase III trials, collectively known as the CLEAR trial series, focused on evaluating the efficacy of bempedoic acid.[52] The initial four trials (CLEAR Tranquillity, CLEAR Serenity, CLEAR Wisdom, and CLEAR Harmony) aimed to assess the LDL-C lowering efficacy of the drug, while the ongoing CLEAR OUTCOME trial is focused on evaluating cardiovascular outcomes with bempedoic acid.[53-56] In the CLEAR Tranquillity trial, bempedoic acid 180 mg daily as an add-on therapy to ezetimibe 10 mg daily resulted in an additional 28.5 % LDL-C lowering compared to placebo, along with improvements in other lipid and lipoprotein parameters. The CLEAR Harmony trial, a longer 24-week study, showed a reduction of 18.1 % in LDL cholesterol level with bempedoic acid compared to placebo, with a lower incidence of diabetes and disease worsening. The CLEAR Serenity trial demonstrated a significant reduction in LDL-C levels in patients intolerant to at least two statins. The CLEAR Wisdom trial, though underpowered, revealed a 15.4 % reduction in LDL-C with bempedoic acid. Combination Therapy: One Phase-III trial investigated the safety and efficacy of the fixed-dose combination (FDC) of bempedoic acid 180 mg with ezetimibe 10 mg in high-risk patients on maximum tolerated statin therapy. The FDC showed a significant reduction in LDL level compared to bempedoic acid as a single agent, ezetimibe alone, or placebo. In a subgroup analysis, FDC also reduced LDL-C in patients not receiving statin due to intolerance and those on high-intensity statin. These findings support the use of bempedoic acid and ezetimibe combination in lowering LDL, even in patients not on statins. Additional Potential of Bempedoic Acid: Systematic analyses have indicated a lower incidence of new-onset and worsening diabetes mellitus with bempedoic acid, potentially expanding its use in diabetes dyslipidemia. Bempedoic acid has also been shown to reduce hsCRP levels. The ongoing CLEAR Outcomes trial, involving a large population of high cardiovascular disease risk statin-intolerant patients, is aimed at studying the cardiovascular outcomes with bempedoic acid. The CLEAR trials, consisting of four Phase III randomized controlled trials (RCTs), have been conducted to evaluate the safety and efficacy of bempedoic acid in reducing LDL-C levels. The trials included patients with atherosclerotic cardiovascular disease (ASCVD), heterozygous familial hypercholesterolemia (HeFH), and statin intolerance. The primary objective of these trials was to assess the safety of the treatment, while the secondary objective was to evaluate the reduction effects on LDL-C.

5.2. Safety profile of bempedoic acid

A meta-analysis of the pooled results from the CLEAR trials involving 3623 patients demonstrated that common adverse events occurred at similar rates between bempedoic acid and placebo groups, indicating a high degree of safety.[57] However, bempedoic acid was associated with modest and reversible increases in blood uric acid levels, leading to a higher incidence of gout. Patients with previous episodes of gout were at a higher risk of developing acute gout during bempedoic acid therapy. The drug also led to mild and reversible increases in blood creatinine levels, as well as small decreases in estimated glomerular filtration rate (eGFR), which were secondary to the drug-induced reduction in tubular secretion of creatinine. Tendon Disorders and Myalgia: Bempedoic acid therapy was associated with a tendency for tendon disorders, primarily affecting the Achilles tendon, rotator cuff, and biceps tendon.[58] These tendon injuries occurred in patients taking moderate or high-dose statins and

were not observed in statin-intolerant patients treated with bempedoic acid. Risk factors for tendon injury included the use of moderate or high-dose statins, fluoroquinolone or corticosteroid therapy, gout, diabetes, rheumatoid arthritis, renal failure, aging, and male sex. Importantly, bempedoic acid therapy did not result in myalgia and muscle weakness, and no cases of rhabdomyolysis were observed in patients with statin intolerance.

6. Conclusion and future directions

For many years, statins were the primary drugs used for lowering cholesterol levels and reducing cardiovascular mortality. However, some patients either couldn't achieve their target lipid levels with maximum statin doses or experienced intolerance to statins. In the last five years, there have been significant developments in the field of hyperlipidemia and cardiovascular diseases, leading to the approval of several new drugs in North America and Europe. As a result, updated guidelines from organizations like ACC/AHA and ESA/ESC have been introduced to keep up with these advancements. The continuous development of new classes of drugs has also been accompanied by clinical trials demonstrating improved cardiovascular outcomes with additional reduction in LDL-C levels. Consequently, the target LDL-C goals for primary and secondary prevention in very high-risk and high-risk ASCVD patients have become progressively lower over time. Among the new drugs available, ezetimibe, PCSK9 inhibitors, and bempedoic acid offer clinicians options to target these LDL-C goals and create optimized combinations with maximum cost-effectiveness for their patients. The recently approved combination of bempedoic acid and ezetimibe is particularly noteworthy as a treatment option. It can be considered before attempting PCSK9 inhibitors, which have certain limitations like injectable administration and higher costs. Clinical trials have shown that the fixed drug combination of bempedoic acid and ezetimibe can achieve LDL-C reduction comparable to PCSK9 inhibitors. In February 2020, the US FDA approved oral bempedoic acid as a once-daily medication for use in patients with heterozygous hypercholesterolemia or established ASCVD who require additional LDL-C lowering alongside dietary modifications and maximally tolerated statin therapy. The once-daily oral regimen and the favorable adverse effect profile make bempedoic acid an attractive alternative. However, a major limitation of bempedoic acid use is the lack of cardiovascular outcome data, which is expected to be addressed in future clinical trials. Additional barriers to its widespread use in real-world clinical practice include insurance approvals and cost considerations, which also need to be addressed to promote its adoption. In summary, the last few years have witnessed significant advancements in the field of hyperlipidemia and cardiovascular diseases, leading to the approval of novel therapies. Bempedoic acid, in combination with ezetimibe, provides a promising alternative for patients who cannot achieve their LDL-C goals with statins alone or are intolerant to statins. As research continues, future clinical trials will provide more comprehensive data on the cardiovascular outcomes of bempedoic acid and further enhance its role in dyslipidemia management.

Funding

The authors received no specific funding for this manuscript.

Conflicts of interest

The authors declare no conflict of interests.

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