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A Review Article: Bempedoic Acid as an Alternative for Statins in Reducing Cholesterol

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Abstract
Persons at high risk of cardiovascular disease can be effectively identified from a measurement of their serum cholesterol. Despite of effectiveness of statins in the treatment of lipid disorders like hyper cholesterolemia, hyperlipidaemia, atherosclerosis, Residual risk still exists, and some studies, additional drugs were added to statin therapy have been mainly negative or the outcomes were very modest. Bempedoic acid is a novel oral drug, which has been increasingly researched to play an important role in lowering LDL cholesterol. Some patients inability to tolerate statins because of muscle symptoms contributes to uncontrolled cholesterol levels, insufficient cardiovascular risk reduction, patients with familial hypercholesterolemia, fail to achieve LDL-C targets with statins alone, and others are either statin intolerant or tolerate only suboptimal low doses. The review covers the current state of knowledge on the mechanism of action of bempedoic acid (ETC-1002) and results from recent clinical studies.
Keywords: *Cardiovascular diseases, Hypercholesterolemia, Hyperlipidaemia, Atherosclerosis, Bempedoic acid.*

Introduction

The Registrar General of India reported that CHD led to 17% of total deaths and 26% of adult deaths in 2001-2003, which increased to 23% of total and 32% of adult deaths in 2010-2013.CVD death rates in India are estimated to have risen from 155.7 to 209.1 per 100,000 between 1990 and 2016, although this number seems to be almost entirely due to population aging. The prevalence of CVD in India has risen over the past 2 decades due to population growth, aging, and a stable age-adjusted CVD mortality rate. For more than three decades, pharmacological lipid lowering has helped reduce cardiovascular disease (CVD) risk in patients with hypercholesterolemia.[1] LDL-C, or the "bad" cholesterol, contributes to fatty build-up in the arteries. Decades of research has shown that high levels of LDL-C, the "bad" cholesterol, can increase one's risk for heart attack, stroke, and peripheral artery disease. Treating LDL-C IS a key reduce cardiovascular risk. Nonetheless, despite the development of effective therapeutic options, including statinssome patients require additional LDL-C reducxtion or patients who are statin intolerant. Bempedoic acid is novel non statin antihyperlipidaemic drug for lowering LDL cholesterol.

Why Statins Treatment is Stopped or Discontiued

Statins remain the primary drug treatment for lowering cholesterol, but since 2013, more studies

have shown the safety and efficacy of newer medications. Statins lower LDL-C by inhibiting hepatic 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway. This inhibition leads to reduced hepatic cholesterol levels, which triggers the upregulation of LDL receptors (LDLR) resulting in increased LDL particle clearance from the blood. Myalgia (muscle pain, cramping and/or weakness) constitutes the most common adverse effect associated with statin treatment and often results in dose limitations, poor compliance or even discontinuation.

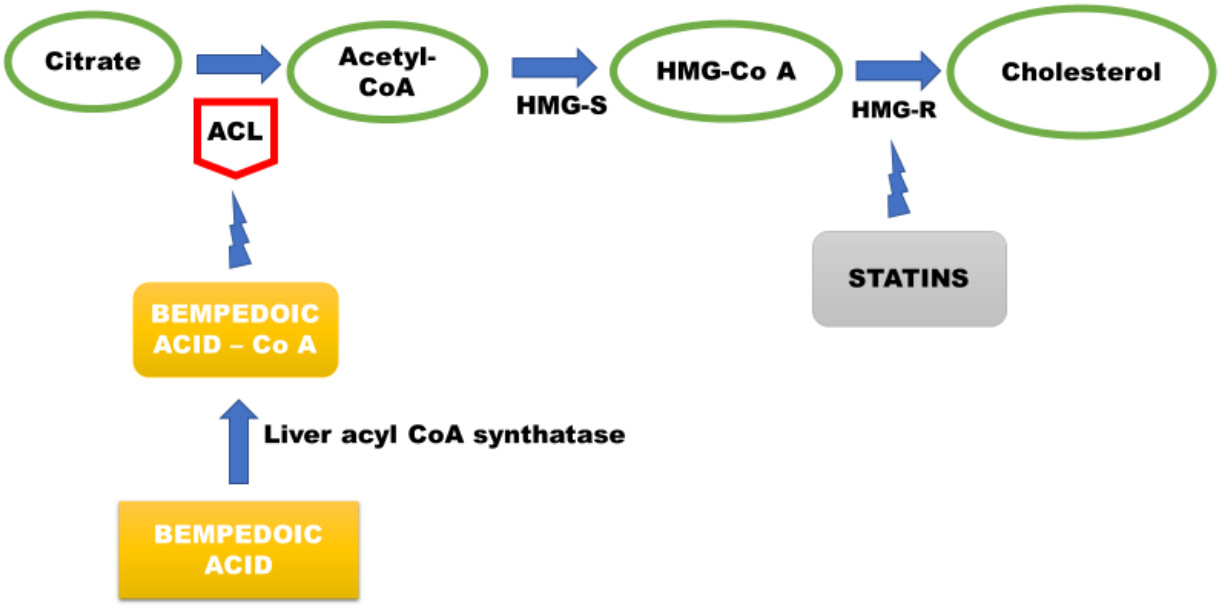
An estimated 2–7 million patients in the United States have stopped statin treatment due to muscle complaints despite being at risk for cardiovascular diseases. One of the major reasons for the lack of adherence to high- or moderate-dose statin therapy as recommended in the guidelines is the concern of both patients and physicians about adverse events with high-efficacy statins. The most common adverse events of statins are muscle-related adverse events, which range from myalgia to rare, but life-threatening, rhabdomyolysis, followed by asymptomatic elevation in hepatic transaminases. Furthermore, recent evidence suggests that high-dose statins may increase the risk of developing type 2 diabetes. Although such side effects are rare, they reduce patient compliance and medication adherence. Although the underlying pathophysiology of statin-induced myalgia is not completely understood, significant evidence supports that it is linked to HMG-CoA reductase inhibition in skeletal muscle resulting in reduced production of one or more biological intermediates important to maintain normal muscle cell function. This insight has attracted interest in identifying novel treatment strategies capable of complementing the LDL-C-lowering effects of statins without blocking the biosynthesis of key products required for normal skeletal muscle function.

Why Bempedoic Acid Over Statins

In clinical practice, a large proportion of patients with hypercholesterolemia do not achieve an adequate decrease in LDL-C levels, even with maximally tolerated statin treatment, and others experience statin intolerance. Additional LLT options are needed to decrease the risk of adverse cardiovascular outcomes in such patients. Bempedoic acid (Esperion Therapeutics Inc) is an oral, once-daily, first-in-class, small molecule that decreases LDL-C level as a consequence of competitive inhibition of adenosine triphosphate–citrate lyase, a key enzyme in the cholesterol biosynthesis pathway upstream of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Inhibition of cholesterol synthesis with bempedoic acid, similar to statins, upregulates hepatic LDL receptor expression, thus decreasing LDL-C blood levels by increasing clearance of circulating LDL-C. Bempedoic acid, a prodrug, requires activation by very long-chain acyl-coenzyme A synthetase-1, an enzyme that is present mainly in the liver but not in skeletal muscle. The lack of skeletal muscle activity of this enzyme is postulated to decrease risk of muscle-related adverse effects with bempedoic acid compared with statin therapy.

Bempedoic Acid Mechanism of action

Bempedoic acid (ETC-1002), a novel therapeutic approach the excellent tolerability of it makes it a useful alternative for low-density lipoprotein cholesterol (LDL-C) lowering, inhibits ATP citrate lyase (ACL), an enzyme involved in fatty acid and cholesterol synthesis.



ACL is an important enzyme with significant effects on fatty acid and cholesterol metabolism. It is a cytosolic enzyme highly expressed in lipogenic tissues such as the liver and white adipose tissue and is positioned upstream from HMG-CoA reductase in the mammalian cholesterol biosynthesis pathway. It links energy metabolism from carbohydrates to the production of fatty acids through catalyzing acetyl CoA synthesis, the fundamental substrate for the biosynthesis of both fatty acids and cholesterol. Its crucial role in lipid biosynthesis makes ACL a potential target for lipid-lowering intervention. Historically, several compounds have proven capable of inhibiting ACL in vitro, including, difluorocitrate, several benzonesulfonamides, and the naturally occurring compound hydroxy citrate. Nevertheless, their development as pharmacologic agents have been limited due to poor ability to cross cell membranes, poor affinity for ACL, and poor specificity leading to undesirable inhibition of other essential enzymes in vivo. Among several ACL inhibitors that were tested, ETC-1002 (8-hydroxy-2,2,14,14-tetramethylpentadecaned–ioic acid; bempedoic acid) is in the most advanced stage of clinical development and has improved bioavailability and specificity compared with earlier compounds.

Early Clinical Studies

In animal models, BA also influences fatty acid synthesis, but in humans, its role is limited primarily to lowering low-density lipoprotein cholesterol (LDL-C). In early clinical trials, BA was well tolerated and without major side effects. Alone or in various combinations with atorvastatin and/or ezetimibe, LDL-C lowering ranged from 17% to 64%. In addition, BA lowers levels of non–high-density lipoprotein cholesterol, C-reactive protein, and apolipoprotein B. Statins are first-line agents for primary and secondary prevention of cardiovascular disease.

Combination Therapy: Bempedoic Acid in with High Dose Atrovastatin

The Phase 2 study was conducted to assess the low-density lipoprotein cholesterol (LDL-C)–lowering efficacy of bempedoic acid added to stable high-intensity atorvastatin background therapy and multiple-dose plasma pharmacokinetics of atorvastatin alone and combined with steady-state bempedoic acid in patients with hypercholesterolemia (NCT02659397). Patients received once-daily open-label atorvastatin 80 mg for 4 weeks then were randomized 2:1 at baseline to receive double-blind bempedoic acid 180 mg (n = 45) or placebo (n = 23) plus open-label atorvastatin

80 mg for 4 weeks. Efficacy was assessed 4 weeks after randomization. The results shown in study were the 4-week stabilization phase with 80 mg atorvastatin resulted in approximately 40% lowering of LDL-C values from screening. The placebo-adjusted least squares mean lowering of LDL-C from baseline to Day 29 with bempedoic acid was 22% (P = .003). Placebo-adjusted reductions from baseline with bempedoic acid also were significant for total cholesterol (−10%; P = .014), non–high-density lipoprotein cholesterol (−13%; P = .015), apolipoprotein B (−15%; P = .004), and high-sensitivity C-reactive protein (−44%; P = .002). Point estimates of bempedoic acid effects on steady-state atorvastatin and ortho-hydroxy atorvastatin area under the curve were <30% and not clinically meaningful. The study concluded that Bempedoic acid 180 mg added to stable high-dose atorvastatin therapy effectively lowers LDL-C in patients with hypercholesterolemia without causing clinically important increases in atorvastatin exposure.The combination of bempedoic acid and high-dose atorvastatin is well tolerated.

In Phase 3 trials and one outcomes study are currently under way to better define this agent's potential clinical role. Bempedoic acid seems to have unfavourable effects on Serum uric acid, creatinine level and the incidence of gout. The ongoing Cardiovascular Outcomes Trial (CVOT) will explore the longer-term safety of treatment with bempedoic acid and clarified that its effect on cardiovascular events and mortality. Adverse effects of current lipid-lowering agents can be dose-limiting, and combination approaches to lipid-lowering may often be utilized for optimal CV risk reduction. Because of this, new lipid-modulating drugs are urgently required. Bempedoic acid (ETC-1002) has a unique mechanism of action (adenosine triphosphate-citrate lyase inhibition). It has been shown to be safe in combination with statins as well as ezetimibe, and appears to effectively lower LDL-C and has the potential to reduce the risk of muscle-related adverse events, which can limit the utilization and effectiveness of statin therapy.

Conclusion

Bempedoic acid acts on same cholesterol biosynthesis pathway as statins, but it is a novel option for statin intolerant patients who experience muscle related symptoms. Lipid- lowering efficacy of bempedoic acid, a first- in- class, prodrug, small- molecule inhibitor of ATP- citrate lyase it offers safe and effective oral therapeutic option for lipid lowering in patients who cannot tolerate statins

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