



Short Communication

Bempedoic acid: A new player in lipid-lowering

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Abstract

Elevated LDL cholesterol remains one of the most important cardiovascular risk factors. For this reason, great scientific efforts have been made in recent decades to reduce elevated LDL cholesterol levels. After statins, ezetimibe, and PCSK9 inhibitors, bempedoic acid is a new promising option for the treatment of LDL-cholesterol.

Bempedoic acid is an inhibitor of adenosine triphosphate citrate lyase (ACL), an enzyme that converts citrate to acetyl-CoA in the cytosol. The active ingredient thus attacks the above HMG-CoA reductase, the target of statins, in the mevalonate/cholesterol biosynthesis pathway.

Bempedoic acid can be considered a prodrug that is converted intracellularly to ETC-1002-CoA by ACSVL1 (very long-chain acyl-CoA synthetase 1) via coenzyme A (CoA) activation. ACSVL1 is primarily expressed in the liver and not in skeletal muscle. Therefore, in contrast to statins, it is not associated with muscle pain, which is one of the great advantages of this drug.

High LDL-cholesterol values were shown to be among the most important cardiovascular risk factors in the INTERHEART study in 2004 [1]. However, the role of HDL-cholesterol as a protective risk factor in the mean time has been questioned. Recent large-scale cohort studies and Mendelian randomization trials have failed to confirm that higher HDL levels are associated with improved outcomes. Indeed, there are some reports of increased cardiovascular events and even increased mortality associated with very high levels of HDL. In addition, pharmaceutical intervention studies aimed at increasing HDL levels did not result in amelioration of cardiovascular outcomes [2-6].

LDL-cholesterol, on the other hand, is undoubtedly one of the most important risk factors, and several clinical studies and mendelian association studies have proven its causative role in cardiovascular disease. Accordingly, a lot of endeavor has been dedicated to efficient therapies for lowering LDL cholesterol. As of 1994, when the 4S Study [7] was published, lowering

LDL cholesterol proved to reduce myocardial infarction. Statins have been the cornerstone of lipid-lowering treatment for decades. With ezetimibe and its combination with statins, a new player proved its clinical efficacy in the IMPROVE-IT study [8]. Finally, a new, most efficacious treatment arrived with the discovery of the PCSK9 inhibitor [9-11].

Bempedoic acid is a new player on the ground. In a recent review, Drexel, et al. [12] described its mechanism and its clinical benefit based on the most recent data.

Bempedoic acid is certainly of great value, especially in patients who suffer from muscle pain, which is the most frequent adverse effect of statins. Among statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization), as was shown in the CLEAR Outcomes study [13]. However, monotherapy



with bempedoic acid might not be effective enough with LDL-lowering in the order of 20 to 30 percent. The combination of bempedoic acid with ezetimibe has been shown to lower LDL-cholesterol by about 50%, which is recommended by the ESC Guidelines on lipid lowering [14].

Unfortunately, bempedoic acid has a negative effect on HDL [15]. Bempedoic has a favorable safety profile; however, the studies showed that there was a significant increase in the risk of hyperuricemia [RR, 2.05 (95% CI: 1.81 to 2.33), $p < 0.001$] following bempedoic acid treatment [16]. A careful assessment of serum uric acid levels and the history of gout at baseline is therefore recommended.

Overall, it can be stated that bempedoic acid has advantages that make it a valuable new option for lipid-lowering therapy.

Conclusion

Bempedoic acid is a new option in the treatment of elevated LDL levels. It has a different mode of action compared to statins, although it also inhibits cholesterol synthesis. However, the effect is much smaller than with statins, which is why it is worth combining it with ezetimibe, which allows a reduction in LDL cholesterol of up to 50%. Bempedoic acid has a satisfactory safety profile except for an increased risk of gout.

Author contribution

WFR was responsible for the ideation, structure, and writing as well as the approval of this contribution.

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