Bempedoic acid: An equally efficacious alternative to statins?

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Bempedoic acid [1] is a substance that was recently approved for the treatment of dyslipidemia (familial or not) in patients in need of pharmacological treatment, where the optimal statin therapy is contraindicated or not tolerated or as adjuvant treatment to conventional antilipidemic therapy in patients where target low-density lipoprotein cholesterol (LDL-C) is not achieved. It is mostly excreted via renal route (up to ~30% in stool). Bempedoic acid, not currently marketed in Greece, is a prodrug which after activation in its sulfate ester formation from the coenzyme A inhibits the ATP citrate lyase (ACL). ATP citrate lyase is a major participant in cellular metabolism, mainly due to the fact that it is the primary source of acetyl-Coenzyme A, which by itself is a precursor for cholesterol and fatty acid synthesis, as well as, protein acetylation. It is apparent then, that APT citrate lyase inhibition agents are a probable effective way in reducing lipid-related pathologies.

The need for hypolipidemic therapy in patients with evidenced cardiovascular disease, for secondary prevention, is well established, as well as the need for primary prevention in individuals at high risk with comorbidities, either due to metabolic syndrome or familial hypercholesterolemia. In 2019, the European Society of Cardiology presented, during their annual symposium, the new guidelines for the treatment of dyslipidemia, as well as the goals for different patient groups, mainly aiming for a >50% decrease in the LDL-C baseline setting a <55 mg/dl target for the very high risk group, a <70 mg/dl for the high risk group, a <100 mg/dl for the intermediate risk group and a <116 mg/dl LDL-C target for the low risk group, respectively. Dietary adjustments, weight loss and smoking cessation, irrespective of pharmacotherapy, remain the cornerstone of the dyslipidemia treatment.

The use of statin or rather Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors for the treatment of dyslipidemia dates back to the 80's, with lovastatin being the first statin approved for marketing in 1987. A well-established necessity for an effective lipid-lowering drug in order to alleviate the cardiovascular risk burden was previously poorly fulfilled, while the available treatments (cholestyramine, fibrates, mainly clofibrate and nicotine acid), as well as the usual dietary adjustments, were far from potent. During the 90's various statins were synthesized (pravastatin being the first followed by simvastatin, atorvastatin, fluvastatin, pitavastatin and rosuvastatin) presenting different strengths in various dosages. In the 00's, ezetimibe, another lipid-lower agent, was added to the standard pharmacotherapy as adjuvant treatment in patients not achieving their LDL-C goals or as monotherapy in patients not able to receive statin therapy. As with the vast majority of drugs, statins are not shy of side effects, with the most common being liver/pancreatic enzymes elevation, myopathy and rhabdomyolysis and neuropathy, while drug-drug interaction is mostly presented in cyclosporin, protease inhibitor, gemfibrozil and warfarin coadministration. A diabetes mellitus predisposition is also noted in statin use, mainly rosuvastatin.

A novel drug group, the PCSK9 inhibitors (PCSK9i) [2], was approved for the treatment of dyslipidemia

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in 2015 following research beginning in 2003. PCSK9 inhibitors are part of the monoclonal antibodies drug group effectively targeting the PCSK9 enzyme and reducing the LDL-C serum levels. The primary indication for PCSK9 inhibitors, in their advent, was the secondary prevention in patients presenting with familial hypercholesterolemia not adequately controlled on conventional therapy or in patients who could not tolerate statins and were poorly controlled while on ezetimibe. As of 2021, PCSK9i received indication for primary prevention in patients with homozygous familial hypercholesterolemia not achieving their LDL-C goals while on conventional therapy.

As of 2020, bempedoic acid [3] was added in the pharmacotherapy arsenal against dyslipidemia [4]. In April 2023, the CLEAR Outcomes, a drug vs placebo double-blind study, was published, in which bempedoic was compared to placebo comparing efficacy in MACE (Major Adverse Cardiovascular Events). CLEAR Harmony was another study that was concluded in 2019, in which patients with known atherosclerosis and/or heterozygous familial hypercholesterolemia [5], who received the maximally tolerated statins, were provided with bempedoic acid and were compared to patients that received placebo concerning MACE, again during the 52-week trial bempedoic did not lead to a higher incidence of adverse effects and led to significantly lower LDL-C levels. The result in CLEAR Outcomes was the predominance of bempedoic vs placebo suggesting that bempedoic is a safe alternative to statin treatment or primary option in patients unable to receive them.

In international literature, even before CLEAR Outcomes [6] was published, bempedoic was used on patients presenting with homozygous familial hypercholesterolemia that were unable to treat with or could not tolerate statins, who were already on PCSK9i and did not achieve their LDL-C goal. Consequently, subsequent published studies [7] examined the concomitant use of bempedoic acid, ezetimibe, and the maximal tolerated statin dose vs a control group and confirmed the superiority of the triple-therapy group on the grounds of effectiveness of lipid-lowering strategy and cardiovascular risk control.

A recent study [8] indicates the efficacy of standard dose bempedoic regimen administration, in LDL-C reduction, up to 30%, while the addition of ezetimibe would result in a 45% decrease. Adjunctive administration of bempedoic to high intensity statin therapy, however, did not present an adequate reduction in LDL-C, maintaining a 15% lowering effect compared to statin monotherapy, while a near 30% reduction was observed in the combination of PCSK9i-bempedoic. An increased risk of new-onset diabetes is well established, reaching approximately 12%, when statin therapy is prescribed as lipid-lowering therapy, possibly by affecting the pancreatic beta-cell function by promoting insulin resistance and having a deleterious effect on GLP-1 (glucagon-like peptide 1) [9]. Bempedoic presented no such interference concerning glucose metabolism and insulin resistance, which was observed in most studies, thus making it a preferable therapeutic regimen to statins, when indicated.

During the period between 2020 and 2022 a series of studies were published [10,11], examining the safety profile and bempedoic pharmacodynamics, the first of them being CLEAR Wisdom [12]. All of them coalesced in assuring that bempedoic acid is a safe, alternative, option for statin therapy. Bempedoic acid, as aforementioned, is a prodrug that inhibits ACL by intervening in the ketogenesis pathway having as a final result the increase of LDL receptors and the clearance of low-density lipoproteins in the serum. The prodrug activation is mostly induced in the intracellular environment, chiefly in liver cells and in lesser extent in renal cells, whereas no activity is observed in adipose or muscle tissue, the latter possibly being the reason of miniscule risk of rhabdomyolysis.

In conclusion, bempedoic constitutes a safe and efficacious choice [13] of hypolipidemic drug therapy that could be prescribed as adjunctive medication to the standard of care or as monotherapy [14], even as an alternative to PCSK9i possibly on the basis of potential reduced cost, in patients either not achieving the LDL-C target values under maximal tolerated statin therapy and/or ezetimibe, or presenting inability to receive statin therapy [15]. It should also be noted that bempedoic would be a possible alternative to primary initiation of statin therapy in patients at high risk of developing new-onset diabetes, due to its neutral effect on pancreatic beta-cells, and further investigation of the role of bempedoic ought to be made, concerning its possible effect in liver steatosis and non-alcoholic fatty disease.

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