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INVITED EDITORIAL

Bempedoic acid: Everything with a place and purpose

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Based on an abundance of cohort studies, Mendelian randomization studies and randomised double blind placebo controlled trials, it has been proven beyond reasonable doubt that a lower level of low-density lipoprotein cholesterol (LDL-c) has a causal relation with a reduction in cardiovascular disease. The three most commonly used types of LDL-c lowering medication (HMG-CoA reductase (HMGCR) inhibitors (statins), inhibitor of the Niemann-Pick C1-like protein (NPC1L1) and antibodies to proprotein convertase subtilisin/kexin type 6 (anti-PCSK9) all work via an increase in the expression of the LDL-receptor on the liver, leading to lower plasma LDL-c levels. The benefits from these three types of medication are furthermore directly linked to their absolute LDL-c lowering effect and no pleotropic effects of any one of these classes seem likely at this moment.[1] Despite multiple therapeutic options being available, there remains a clear need for new therapeutic LDL-c lowering options. Guidelines suggest ever lower LDL-c goals, not all currently available treatment options are deemed cost-effective in all patients, the mode of use is sometimes not in line with the patients preferences (e.g. subcutaneous injections) and perceived side effects may preclude use.

ATP-citrate lyase (ACLY) inhibition

Bempedoic acid provides us with the first orally administered drug in the class of the ACLY inhibitors. Inhibition of ACLY reduces the conversion of citrate to acetyl-CoA which is the substrate for both cholesterol and fatty acid synthesis. The eventual decreased hepatic cholesterol production leads to upregulation of the hepatic LDL-c receptors and increased clearance of LDL-c from the circulation, similar to how statins, ezetimibe and anti-PCSK9 reduce LDL-c. A recent Mendelian randomization study supports the causality of ACLY in relation to lower plasma LDL-c levels and a lower chance of cardiovascular events.[2] One of the presumed benefits of bempedoic acid is that it is a pro-drug and needs activation by very long-chain acyl-CoA synthetase-1 (ACSVL1). As ACSVL1 is highly expressed in the liver and not in skeletal muscle, it is thought that bempedoic acid has a lower chance of inducing muscle symptoms compared to statins. In a well-executed meta-analysis of randomised controlled trials published in this edition of the journal, Dai *et al.* report on both the efficacy and safety of bempedoic acid.[3]

Efficacy

In the short term (< 12 weeks), bempedoic acid lowers plasma LDL-c (as calculated with the Friedewald formula) by 23% (mean difference –23.16% (95% confidence interval (CI) –26.92 to –19.40) when compared to placebo. In the three included studies with the longest duration, LDL-c lowering was comparable reaching a mean difference of –18.58% (95% CI –21.74 to –15.41). There was however considerable heterogeneity in the analyses, with the largest reduction in LDL-c in a trial with patients with type 2 diabetes.[4] This begs the question whether part of the calculated LDL-c lowering is due to lowering of smaller very low-density lipoprotein cholesterol (VLDL-c) and intermediate-density lipoprotein cholesterol (IDL-c) which are more abundant in patients with type 2 diabetes and maybe 'misclassified' as LDL-c when using the Friedewald formula. As bempedoic acid in the meta-analysis by Dai *et al.* did not show an effect on plasma triglycerides at all when all populations were taken together and in contrast to what we know from statins, studies on more detailed lipid profiles after treatment are welcome. The currently available trials included in the meta-analysis are all of relatively short duration and the results of cardiovascular outcomes study investigating bempedoic acid (CLEAR-Outcomes) are eagerly awaited. The inclusion criteria of CLEAR-Outcomes are similar to those in CLEAR-Serenity (statin intolerance), apart from the baseline risk which is higher in CLEAR-Outcomes.[5] With a baseline plasma LDL-c of ~4.0 mmol/l in CLEAR-Serenity and with an expected ~20% decrease in LDL-c based on the current meta-analysis, an absolute LDL-c decrease of around ~0.8 mmol/l would be expected. Based on the expected hazard ratio of 0.79 for the occurrence of cardiovascular events per 1.0 mmol/l decrease in LDL-c based on meta-analyses of statin trials, the results from the Clear-Outcomes study will probably give us a

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hazard ratio (HR) of around ~0.85. An important caveat however is whether the investigators can keep the drop-out rate in CLEAR-Outcome low, which might be difficult in light of the ~20% dropout rate in both arms in the only 24 weeks duration CLEAR-Serenity study which also included statin intolerant patients.

Safety

The meta-analysis by Dai *et al.* shows that the overall rate of adverse events is not different between the bempedoic acid and placebo arms in the included studies (odds ratio (OR)=1.02 95% CI 0.88–1.18). As one of the advantages of bempedoic acid over statins is the purported lower incidence of muscle-related adverse events, the absence of a difference between the bempedoic acid and placebo treatment arms in muscle-related adverse events is at least reassuring (OR=1.21 95% CI 0.97–1.51). Although Dai *et al.* do not mention this in the introduction or discussion of their article, in the randomised double-blind placebo-controlled trials with statins there is in reality a < 1% five-year risk of muscle symptoms caused by statin use, and the high incidence of side effects seen in clinical practice is more likely caused by misattribution and nocebo effects.[6] In fact, the high drop-out rate in CLEAR-Serenity which included patients with known statin intolerance in both the bempedoic acid and placebo arms somewhat supports this. Bempedoic acid is relatively well-tolerated, including in patients with perceived statin intolerance, but the real benefit in terms of a lower chance of muscle-related side effects when compared to statins is still to be determined. Bempedoic acid does have a particular side effect which is attributable to the drug itself. As seen in the current meta-analysis the higher incidence of gout might hamper the use of bempedoic acid (OR=2.70 95% CI 1.08–6.75) in some patients (particular in those with poor renal function) although the overall incidence of gout is low (CLEAR-Harmony 1.2% vs 0.3%).[7] These results have been corroborated by a recent meta-analysis which showed an increase in uric acid and a similar increase in the incidence of gout with the use of bempedoic acid.[8] Also discussed in the current meta-analysis is type 2 diabetes as a possible side effect. From meta-analysis of trials and Mendelian randomization studies, it is clear that genetic variants or inhibitors (statins) of HMG-CoA reductase are associated with in increased risk of development of type 2 diabetes.[6] The meta-analysis by Dai *et al.* suggests that bempedoic acid, at least in the short-term, is not associated with an increased risk of type 2 diabetes. The results from the Mendelian randomization study on ACLY support the absence of this side effect, making ACLY stand out from the crowd of HMGCR, NPC1L1 and PCSK9[2] and might be a bonus associated with the use of bempedoic acid.

Place and purpose

While we await the results from the CLEAR-Outcomes study and in light of the recent FDA and EMEA approval of bempedoic acid, the place and purpose of bempedoic acid in the lipid-lowering repertoire should be discussed. Patients with FH will probably benefit most as combination therapy of bempedoic acid with ezetimibe (and a statin) is very effective in reducing plasma LDL-c levels (–28.5% versus placebo when added to ezetimibe, –38% for the fixed bempedoic acid and ezetimibe combination when added to maximum-tolerated statin therapy and –60.5% in combination with ezetimibe and atorvastatin versus placebo).[9–11] This combination of 2–3 orally administered drugs will give younger patients with FH an easier to use and cheaper option to reduce their plasma LDL-c levels and, subsequently, their cardiovascular risk. Again, the combination of bempedoic acid and ezetimibe, especially when added to a statin, will be very helpful in clinical practice when we try to reach the ever lower LDL-c treatment goals in patients with ASCVD. Although more research into how we should reduce the misattribution and nocebo effects when it comes to perceived muscle symptoms with the very low-cost and safe class of drugs with which we have decades of experience (statins) is most welcome, the combination of bempedoic acid and ezetimibe also provides us with a new option when treating patients with perceived statin intolerance.

Until the results from CLEAR-Outcomes study are reported we can take comfort in the results from the meta-analysis by Dai *et al.* which underlines that bempedoic is an efficacious (especially in combination with ezetimibe and/or a statin) LDL-c lowering therapeutic option with, for now, an acceptable safety profile.

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