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Addressing elevated cardiovascular risk: The role of bempedoic acid in combination lipid-lowering therapy

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Nustendi®
Bempedoic acid and ezetimibe

Nilemdo®
Bempedoic acid

Concomitant use of Nilemdo (bempedoic acid) or Nustendi (bempedoic acid/ezetimibe) with simvastatin >40 mg daily is contraindicated.

Please refer to the relevant Summary of Product Characteristics for more information.

Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, accounting for over 18.5 million deaths in 2019.[1] Coronary heart disease, a largely preventable condition, is the primary contributor to CVD mortality, with elevated low-density lipoprotein cholesterol (LDL-C) being a major risk factor for CVD.[2] In the UK, 7.6 million people live with CVD, and it is responsible for 26% of all deaths, equating to approximately one death every three minutes.[3]

Randomised clinical trials have consistently demonstrated reducing LDL-C levels decreases the risk of cardiovascular (CV) events.[2] For every 1 mmol/L reduction in LDL-C there is a 22% proportional reduction in the risk of major adverse CV events (MACE) over a median follow-up of 5 years.[4] Guidelines from the European Society of Cardiology (ESC)[5] and the National Institute for Health and Care Excellence (NICE)[6] outline a risk-based approach to LDL-C management. However, despite these recommendations, LDL-C goal attainment in the UK falls below national targets. Notably, one in six people living in England with established CVD are not receiving any lipid-lowering therapy in 2024.[7]

Statins, the cornerstone of lipid-lowering therapy, are often underutilised.[8] Many patients who are prescribed statins do not adhere to or discontinue treatment with safety concerns—particularly regarding muscle-related side effects—being one of the most significant determinants of poor statin adherence.[8] In a meta-analysis of over 4 million patients, the prevalence of true statin intolerance however, was estimated at 9.1% (95% confidence interval [CI] 8-10%).[9] The Da Vinci European

observational study, showed that amongst very high-risk patients receiving statin monotherapy, the 2019 ESC/EAS risk based LDL-C goal attainment was 14% (95% CI 7–26), 16% (95% CI 13–18), and 22% (95% CI 19–25) in those receiving low-, moderate-, and high-intensity statins, respectively, suggesting that the use of combination lipid-lowering therapy, targeting multiple different biochemical pathways are required by many patients.[10] Thus, alternative or adjunctive therapies to statins, play a crucial role in LDL-C reduction, akin to combination treatment strategies for hypertension and diabetes.

Bempedoic acid in LDL-C reduction

Mechanism of action

Bempedoic acid is an orally taken prodrug, which requires activation by acyl-coenzyme A synthetase 1 (ASCVL1), an enzyme primarily expressed in the liver and likely absent in skeletal muscle. Once activated, bempedoic acid inhibits adenosine triphosphate-citrate lyase (ACL), an enzyme in the cholesterol biosynthesis pathway that is upstream of the enzyme targeted by statins (HMG-CoA reductase).[11] The lack of ASCVL1 in muscle cells provides a mechanistic basis for the reduced potential of myotoxicity with bempedoic acid in comparison with statins.[11]

Clinical trial evidence

Bempedoic acid has been extensively investigated in the large-scale Phase 3 CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen) clinical trial programme, and delivered a significant 17–28% LDL-C reduction versus placebo (placebo-corrected) from baseline at 12 weeks, depending on risk factors and concomitant medicine, in the Phase 3 primary hyperlipidaemia trial programme.[12,13] CLEAR Serenity[14] and CLEAR Tranquility[15] enrolled participants with hypercholesterolaemia and statin-intolerance. Given as monotherapy in CLEAR Serenity or as an add-on to ezetimibe in CLEAR Tranquility, bempedoic acid lowered LDL-C by 21.4% (95% CI, −25.1% to −17.7%; p<0.001) and 28.5% (95% CI: −34.4% to −22.5%; p<0.001), respectively after 12 weeks, compared with placebo (placebo-corrected).[14,15] CLEAR Wisdom[12] and CLEAR Harmony[13] enrolled participants with clinical atherosclerotic CVD and/or heterogenous familial hypercholesterolemia who were receiving statins at a maximally tolerated dose. Patients taking simvastatin at a daily dose of greater than 40 mg were excluded.

CLEAR Outcomes was a multinational, randomised, double-blind, placebo-controlled trial conducted to determine the effect of bempedoic acid on MACE among participants with hypercholesterolemia who were intolerant to or unwilling to take guideline-recommended doses of statins.[16] The primary end point was time to first event of four-component composite of MACE (MACE-4), defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularisation. A three-component composite of MACE (MACE-3; death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction) was a key secondary endpoint. The trial included participants at high risk for CV events (primary-prevention population; capped at 30%) as well as those who had already experienced CV events (secondary-prevention patients). In the primary prevention subgroup, participants were considered at high risk of CV events if they had a Reynolds Risk score >30%, or a SCORE risk >7.5% over 10-years, or were men over 60 years or women over 65 years with type 1 or 2 diabetes, or had coronary calcium score of >400 Agatston units.[17]

The CLEAR Outcomes trial enrolled 13,970 participants, with 6992 receiving bempedoic acid and 6978 receiving placebo. After 6 months, a 21.1% reduction in LDL-C level (placebo-corrected) was reported for bempedoic acid. Over a 40.6-month median follow-up, bempedoic acid significantly reduced the risk of a MACE-4 by 13% (hazard ratio [HR] 0.87 [95% CI 0.79 to 0.96]; P=0.004; 1.6% absolute risk reduction) and MACE-3 by 15% (HR 0.85 [96% CI 0.76 to 0.96]; P=0.006; 1.3% absolute risk reduction).[16]

The incidence of cholelithiasis was higher with bempedoic acid than with placebo, a finding that had not been observed in previous trials. Prespecified AEs of special interest were myalgia (occurring in 5.6% for the bempedoic acid group versus 6.8% for placebo), new-onset diabetes in patients either without diabetes at baseline (16.1% and 17.1%), prediabetes at baseline (19.5% and 20.4%) or normoglycaemia at baseline (5.5% and 6.3%), worsening hypoglycaemia (22.7% and 23.1%) or hypoglycaemia (4.3% and 3.8%). Elevations in the hepatic-enzyme levels were higher in the bempedoic acid group (4.5%) versus 3.0% in the placebo group, as were renal events (11.5% in the bempedoic acid group *vs.* 8.6% in the placebo group). The incidence of hyperuricaemia was higher in the bempedoic acid group than in the placebo group (10.9% *vs.* 5.6%), along with the incidences of gout (3.1% *vs.* 2.1%) and cholelithiasis (2.2% *vs.* 1.2%).[16]

In the primary prevention population subgroup of 4206 patients from the CLEAR Outcomes trial, bempedoic acid was associated with a reduction in risk of MACE-4 by 30% (HR 0.70 [95% CI 0.55 to 0.96]; P=0.002; 2.3% absolute risk reduction) and MACE-3 by 46% (HR 0.64 [95% CI 0.48 to 0.84]; P=<0.001; 2.4% absolute risk reduction) relative to placebo. To prevent one primary composite MACE-4 outcome, it is estimated that 43 patients needed to be treated.[17]

For full information on clinical trials, please refer to the relevant trial publications signposted under references.

Bempedoic acid is available as monotherapy (Nilemdo; bempedoic acid 180 mg)[18] and can be prescribed alone or in combination with statins and/or ezetimibe. When co-prescribing bempedoic acid with simvastatin, the simvastatin dose should be limited to 20 mg (or 40 mg in those at high risk of CVD) due to potential for drug-drug interactions.[18] Concomitant use with simvastatin at doses >40 mg daily is contraindicated.[18] Bempedoic acid is also available as a combination tablet with ezetimibe (Nustendi; bempedoic acid 180 mg/ezetimibe 10 mg).[19] In the CLEAR Combo study of patients receiving stable

maximally tolerated statin therapy (n=301), the post-hoc*, placebo-corrected decrease in LDL-C was 38%, 19% and 25% for Nustendi, bempedoic acid monotherapy and ezetimibe monotherapy respectively.[20] Significantly higher numbers of patients reached an LDL-C of less than 1.8 mmol/L with Nustendi vs placebo or either agent alone (31.3% for Nustendi versus 0% placebo [p<0.001] or 10% for ezetimibe [p≤0.002] or 6.1% for bempedoic acid [p≤0.003]).[20]

The most commonly reported adverse reactions (AR) for Nilemdo during pivotal trials were hyperuricaemia, pain in extremity, anaemia and gout†.[18] For Nustendi, the most commonly reported ARs were hyperuricaemia and constipation††.[19] This is not a full list of reported ARs; prescribers should consult the relevant Summary of Product Characteristics for a full list.

*Study 053 was a Phase 3, randomised, double-blind, multicentre study in patients (N=382) with ASCVD, HeFH or multiple CVD risk factors, taking maximally-tolerated statin therapy (which could be no statin). Patients were randomised to Nustendi (180 mg/10 mg), bempedoic acid (180 mg), ezetimibe (10 mg) or placebo for 12 weeks. The post-hoc efficacy population included 301 patients (Nustendi n=86, bempedoic acid n=88, ezetimibe n=86, placebo n=41) due to the exclusion of 81 patients from 3 study sites because of data integrity concerns. Reduction in LDL-C of 38.0% (p<0.001) for Nustendi (n=86) vs placebo (n=41). Reduction in LDL-C of 13.1%, p<0.001 (36.2% vs 23.2%) for Nustendi (n=86) vs. ezetimibe (n=86).20

†Hyperuricaemia (3.8%), pain in extremity (3.1%), anaemia (2.5%), and gout (1.4%).

††Hyperuricaemia (4.7%) and constipation (4.7%).

Practical use of bempedoic acid: Adult case example

Patient 1 has established CVD and had an LDL-C of 3.0 mmol/L. She has true statin intolerance. Her GP commences ezetimibe 10 mg once daily bringing the LDL-C to 2.4 mmol/L, above both the NICE target of 2.0 mmol/L[6] and the ESC target of 1.4 mmol/L.[5] Nustendi (bempedoic acid/ ezetimibe) combination is then offered to replace ezetimibe alone, reducing the LDL-C to 1.86 mmol/L over a 3-month period.

Key: CVD = cardiovascular disease; ESC = European Society of Cardiology; GP = general practitioner; LDL-C = low-density lipoprotein cholesterol; NICE = National Institute for Health and Care Excellence

Special warnings and precautions for use

Treatment with Nilemdo/Nustendi should be discontinued if hyperuricaemia accompanied with symptoms of gout appear.[18,19] Liver function tests should be performed at initiation of Nilemdo/ Nustendi therapy and treatment should be discontinued if an increase in transaminases >3x upper limit of normal persists.[18,19] Evidence for the use of Nustendi in patients at high risk of CVD is only available for the lipid-lowering effect in absence of any CV risk reduction estimation for ezetimibe in primary prevention patients.[19] For patients taking concomitant bile acid sequestrants, dosing of Nustendi should occur either at least 2 hours before or at least 4 hours after administration of the bile acid sequestrant.[19]

Conclusions

Lowering LDL-C is vital for enhancing both individual and population health by reducing the burden of cardiovascular disease. Lipid-lowering combination therapy is an effective strategy, targeting multiple pathways in lipid metabolism to achieve greater LDL-C reduction. Bempedoic acid, an ATP-citrate lyase inhibitor, can be an important component of this combination approach. It provides an additional mechanism for lowering LDL-C, of particular consideration for patients who are statin-intolerant or require further LDL-C reduction. Bempedoic acid's role in combination therapy supports improved CVD risk management.

Abbreviations

ACL: adenosine triphosphate-citrate lyase; AE, adverse event; AR: adverse reactions; ASCVL1: acyl-coenzyme A synthetase 1; CI: confidence interval; CLEAR: Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen; CV: cardiovascular; CVD: cardiovascular disease; ESC European Society of Cardiology; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; NICE; National Institute for Health and Care Excellence; SmPC; Summary of Product Characteristics

Conflicts of interest

Professor Derek Connolly and Professor Raj Thakkar have received an honorarium to support the development of this advertorial.
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