

Novel therapies in clinical use for the management of hyperlipidaemia

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Abstract

Optimal control of low-density lipoprotein cholesterol (LDLc) is identified as a major target in reducing cardiovascular disease burden globally. However, existing lipid-lowering therapies have not been able to achieve LDLc targets even in developed countries. Therefore, novel therapies for the management of hyperlipidaemia are being trialled. Currently, there are three main groups of newer medicines; bempedoic acid, PCSK9 inhibitors and inclisiran, in addition to statins and ezetimibe in use for the management of hyperlipidaemia. This article aims to introduce these newer medicines and their clinical use in the treatment of hyperlipidaemia.

Key words: Novel therapies, hyperlipidaemia, LDL, bempedoic acid, PCSK9 inhibitors, inclisiran, siMRNA

Introduction

Controlling hypercholesterolaemia is a major target in the reduction of cardiovascular disease (CVD) burden in the world.(1-3) Statin was a landmark invention in this regard and has been the first line in the management of hyperlipidaemia since 1976.(4) Even though statins are able to reduce low-density lipoprotein cholesterol (LDLc) by more than 50%, there is still a huge unmet need for cholesterol control in the world attributed to statin intolerance, poor compliance, and tolerance to statin.(5-7) This led to the development of newer medications to assist statins in the control of LDLc.

Several newer medications are being trialled currently. There are three main groups of newer medicines in the current practice, especially in developed countries in addition to statins and ezetimibe which are already in use in most countries. This article is aimed to introduce the newer medicines and their clinical use in the treatment of hyperlipidaemia.

(1) Bempedoic acid

Bempedoic acid is an adenosine triphosphate citrate lyase inhibitor. It inhibits the cholesterol biosynthesis pathway in the liver as the statins but inhibits at a different step upstream of HMG-CoA reductase (Figure 1).(8) Unlike statins, bempedoic acid is a pro-drug which gets activated only in the liver and not muscles and hence is unlikely to give rise to muscle-related side effects of statins. Therefore, bempedoic acid is FDA approved in the USA as an adjunct to maximally tolerated statin therapy for the treatment of hyperlipidaemia and cardiovascular outcome and is especially indicated in patients with statin intolerance as a monotherapy or in combination with ezetimibe. Bempedoic acid was first licensed in 2016. It is recommended for both primary and secondary prevention of CVDs. It is reported to reduce LDLc up to 27% when used as monotherapy and by further 28% when combined with ezetimibe (9) and up to 18-24%.(10,11) Among statin intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events.(9)

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The main adverse effects of bempedoic acid is that it can predispose to gout attacks.(9) However, there are no serious drug interactions reported.

(2) PCSK9 inhibitors

These are serine proteases, mainly expressed in the liver, that target LDL-R. It leads the receptors to lysosome-mediated degradation, thus diminishing their recycling and decreasing the removal rate of circulating LDL particles in the liver.

Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors are the first injectable medicines licensed for the treatment of hyperlipidaemia which came into the market in 2015. These are monoclonal antibodies against the PCSK9 protein. PCSK9 protein impairs LDLc scavenging by the liver by leading to lysosome-mediated degradation of LDL receptors and reducing LDL receptor recycling.(13) PCSK9 inhibitors bind PCSK9 protein and inhibit its binding with LDL receptors thus preventing LDL receptor degradation. This allows the liver to clear LDLc in the blood.

Evolocumab or alirocumab are two PCSK9 inhibitors used in practice. PCSK9 inhibitors have efficacy in reducing LDLc by 60% and are a valuable add-on therapy to statins.(14) It is recommended for subcutaneous, self-injection, twice a month and therefore is good to improve drug compliance. It has been shown to reduce the rate of major cardiovascular events and deaths by 15% over an average follow-up period of 2.2 years in clinical trials. (15-17) It is also shown that the higher the patients' risk –the higher the benefit they gain. Its adverse effects include flu-like symptoms with injections and nasopharyngitis. There was no increase in liver or muscle-related complaints nor clinically significant drug interactions. The main limitation of PCSK9 inhibitors is their high cost. Therefore, it is recommended mainly for secondary prevention of CVD in high-risk patients who have an LDLc of more than 130 mg/dL in 2023 National Institute for Health and Care Excellence (NICE) guidelines. (18) It has a limited recommendation to be used for primary prevention of CVD in patients with primary heterozygous-familial hypercholesterolaemia.

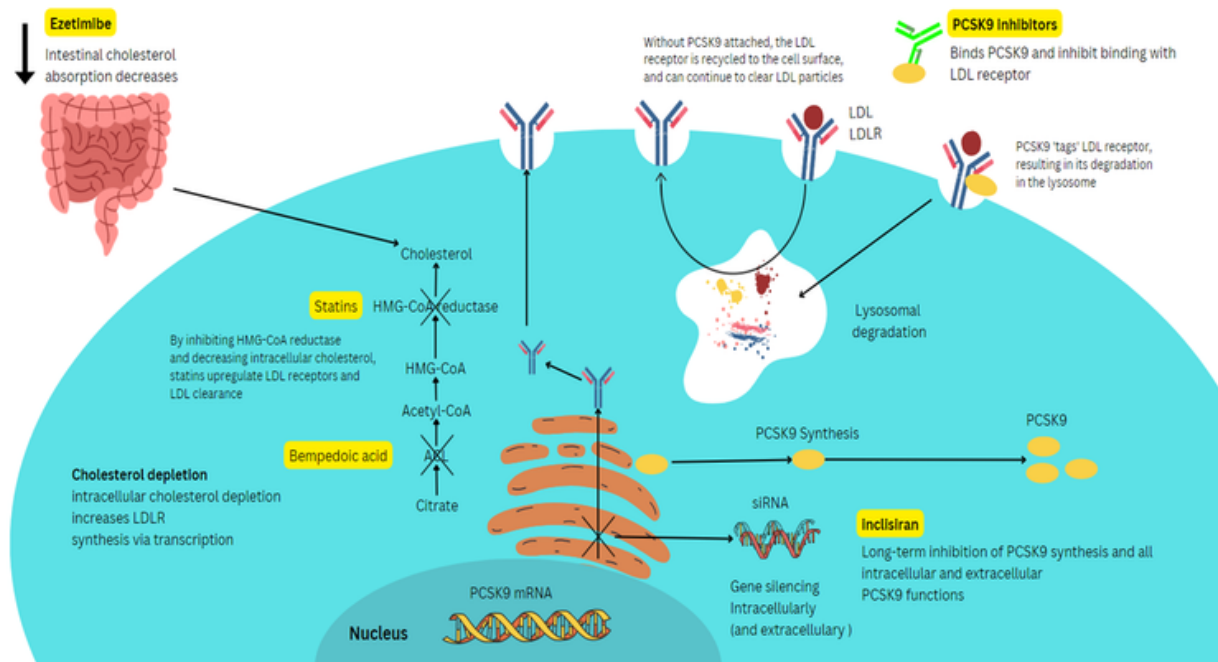


Figure 1 - Therapeutic approaches to reducing LDLc

Adapted from Nordestgaard BG et al. Nat Rev Cardiol. 2018 (12)

ACL – ATP-citrate lyase; CoA – coenzyme A; HMG – 3-hydroxy-3-methylglutaryl; LDL – low-density lipoprotein; LDLc – low-density lipoprotein cholesterol; LDLR – low-density lipoprotein receptor; mRNA – messenger ribonucleic acid; PCSK9 – proprotein convertase subtilisin/kexin type 9; siRNA – small interfering ribonucleic acid

(3) Inclisiran

Inclisiran works by stopping PCSK9 production by acting on the nucleus of liver cells by silencing the mRNA responsible for the PCSK9 protein production. It acts through small interfering RNA (siRNA) technology. This was first licensed in 2021 and is used as an add-on therapy for statins. Inclisiran reduces LDL cholesterol levels by 50% and has sustained efficacy for a long time therefore it needs to be given twice a year starting from 3 months after the 1st injection.(19) This is even better than PCSK9 inhibitors in terms of compliance. Since it is not involved in the Cytochrome P450 enzyme, it does not cause drug interactions. The main adverse drug reaction reported is a minor reaction at the injection site. It does not need dose reductions in the elderly, mild to moderate liver impairment or renal impairment.(20) Continuous production of PCSK9 protein at the same time statins reduce LDLc is thought to be the reason for statin tolerance. Since inclisiran blocks the final common pathway of PCSK protein production, it is effective in overcoming statin tolerance which is an added advantage of this drug. High cost is a limiting factor but is subsidised in the National Health Service, England considering its benefits to the patient. Therefore, it is recommended as an add-on therapy in both primary and secondary prevention of CVDs in patients with an LDLc >100 mg/dL despite being on statin.(18) However, there is no confirmed trial evidence on CVD outcomes of inclisiran which is being tested in the ORION4 trial conducted by the University of Oxford and the early results are expected at the end of 2024.

Conclusion

Statin remains the cornerstone in the management of hyperlipidaemia at present and the novel bempedoic acid, PCSK9 inhibitors and inclisiran are useful add-on therapies or alternatives in statin intolerance. There are some other newer medications currently being trialled in addition to the above, that are yet to come to clinical practice.

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