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Lipid-lowering approaches to manage statin-intolerant patients

Massimiliano Ruscica[1,2], Alessandra Bertoletti[2], Cecilia Gobbi[2], Cesare R. Sirtori[1], Stefano Carugo[2,3], and Alberto Corsini[1]*

[1]*Department of Pharmacological and Biomolecular Sciences 'Rodolfo Paoletti', Università degli Studi di Milano, Milan;*
[2]*Department of Cardio-Thoracic-Vascular Diseases, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico ; and*
[3]*Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan*

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Statins have improved the potential to prevent cardiovascular disease events and to prolong the lives of patients. Statins, among the most widely used drugs worldwide, reduce the levels of low-density lipoprotein cholesterol (LDL-C) by an average of 30–50%. However, non-adherence to statin therapy, due to statin intolerance, might be as high as 60% after 24 months of treatment and is associated with a 70% increase in the risk of cardiovascular disease events. Statin intolerance can be classified as a complete inability to tolerate any dose of a statin or a partial intolerance with the inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective. Reasons for discontinuation are many, with statin-associated muscle symptoms being cited as the most frequent reason for stopping therapy and the incidence of muscle symptoms increasing with treatment intensity. Considering the causal effect of LDL-C in the atherosclerotic process, clinicians should consider that regardless of the lipid-lowering drugs patients are willing to take, any reduction in LDL-C they achieve will afford them some benefit in reducing cardiovascular risk. Besides statins, the current therapeutic armamentarium offers different strategies to reach LDL-C targets in statin-intolerant patients (i.e. a fixed combination between a lower dose of statin plus ezetimibe, bempedoic acid, or proprotein convertase subtilisin/kexin type 9 inhibition).

Introduction

It is estimated that by 2030, 22.2 million people will die each year from cardiovascular diseases (CVDs), an increase from the 19 million in 2019. Among the CVD spectrum, atherosclerotic CVDs (ASCVDs) are responsible for almost 2/3 of CVD cases and represent the leading cause of death worldwide despite excellent pharmacological approaches and revascularizations. As strongly supported by epidemiologic, interventional, and genetic studies, elevated levels of low-density lipoprotein cholesterol (LDL-C) are a major causal risk factor for ASCVD. Keeping LDL-C concentrations low to minimize the rate of progression of atherosclerotic plaques is a mandatory strategy to reduce the risk of events. The achieved lowering of LDL-C is directly associated with a reduced incidence of major ASCVD events. This benefit is maintained up to very low levels of LDL-C. In fact, a threshold level has not yet been identified.[1]

Statins, among the most widely used drugs worldwide, reduce LDL-C on average by 30–50% and they are recommended as the first choice for the management of hypercholesterolaemia and combined hyperlipidaemia. Although it is clearly proven a statin-driven ASCVD benefit, many patients to whom statins are prescribed do not adhere to therapy raising the risk of ASCVD.[2] This is reflected in the gap between clinical guidelines and clinical practice as reported in the DA VINCI (The EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care) and the SANTORINI (Treatment of high and very

*Corresponding author. Email: alberto.corsini@unimi.it

high riSk dyslipidemic pAtients for the preveNTion of cardiOvasculaR events in Europe—a multInatioNal observatIonal) studies showing that, among European patients at high and very high-risk for ASCVD, only 20–33% reach the LDL-C targets.

According to the most recent National Lipid Association scientific statement, statin intolerance is defined as one or more adverse effects associated with statin therapy that resolves or improves with dose reduction or discontinuation. Statin intolerance can be classified as a complete inability to tolerate any dose of a statin or a partial intolerance with the inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective. To classify a patient as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage.[3]

Within this spectrum, statin-associated adverse effects are sometimes sufficiently severe to lead to the discontinuation of treatment, with statin-associated muscle symptoms (SAMS) being cited as the most frequent reason for stopping therapy and the incidence of muscle symptoms increasing with treatment intensity. Although observational studies and registries indicate an incidence of SAMS between 17% and 30%, randomized clinical trials (RCTs) suggest a much lower rate (4.9%).[4] On this matter, the major expert panels present different definitions based on either symptoms and magnitude of creatine kinase (CK) elevation or evidence that takes into account the nature of the muscle symptoms, the elevation in CK levels, and their temporal association with statin initiation, discontinuation, and re-challenge.[5,6] However, in everyday clinical practice, statin discontinuation and re-challenge are the primary strategy for confirming the presence of statin intolerance pertaining to muscle. Indeed, there is no biochemical test or clinical syndrome features to determine whether muscle symptoms are directly attributable to statin use.[7]

Considering that the decision on which drug to use in statin-intolerant patients is often based on patients' preference, tolerability of self-administered injections, and affordability, the aim of the present narrative review is to discuss the most suitable lipid-lowering approaches to manage hypercholesterolaemia in statin-intolerant patients. *Figure 1* shows the expected theoretical LDL-lowering efficacy of different lipid-lowering therapies.[8]

Statin re-challenge and combination with ezetimibe

Most patients with statin intolerance are able to tolerate some statin therapy. According to the PALM (Patient and Provider Assessment of Lipid Management) registry, a significant proportion of statin users (59%) can restart therapy following the discontinuation without any serious adverse effect.[9] Finding a dose regimen that is acceptable may require switching agents, dosages, or dosing on alternate days. Indeed, continued statin prescriptions after an adverse reaction were associated with a lower incidence of death and cardiovascular events. To improve adherence, if symptoms/CK abnormalities resolve after discontinuation of a statin, re-challenge with the same statin at a lower dose or switching to an alternative statin should be considered.[5] Furthermore, alternate-day or twice-weekly dosing strategies can reduce LDL-C by 12–38%, a strategy tolerated by ~70% of previously intolerant patients. However, this strategy may expose the patients to blood levels inadequate to achieve the pleiotropic effects of statins. Overall, lower doses of a high-intensity statin with a long half-life (e.g. atorvastatin and rosuvastatin) are more appropriate.

An alternative strategy to reduce the required dose of statins is the addition of ezetimibe to a lower-intensity statin. In partial statin intolerant, a 50–60% reduction of LDL-C can be achieved by using the combination of a 10 mg daily dose of ezetimibe and atorvastatin 20 mg (achieving the same expected reduction in LDL-C as 80 mg atorvastatin, but with a smaller likelihood of adverse effects). The superiority of ezetimibe in combination with a statin to reduce ASCVD events was demonstrated in the IMPROVE-IT (The Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study. Compared with simvastatin (40 mg) as

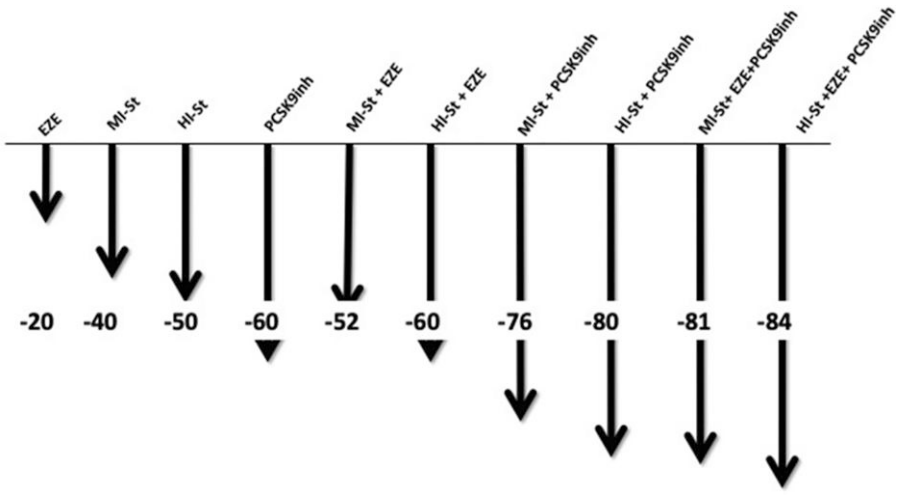

Figure 1 Recommended lipid lowering therapy combinations and their efficacy. Eze, ezetimibe; HI-St, high-intensity statin; MI-St, moderate intensity statin; PCSK9inh, PCSK9 inhibitors. Reproduced by permission of Springer Nature.[8]

monotherapy, the combination simvastatin/ezetimibe (40 mg/10 mg) incrementally lowered LDL-C and improved [hazard ratio (HR) = 0.936; 95% confidence interval (CI) 0.89–0.99) cardiovascular outcomes at 7 years (composite of cardiovascular death, non-fatal myocardial infarction, and unstable angina requiring rehospitalization). Discontinuation was higher in patients given simvastatin compared with those given the combination simvastatin/ezetimibe (Kaplan–Meier rate 52.0% vs. 49.8%).[10]

Besides the association with simvastatin/ezetimibe, the results of the RACING (RAndomized Comparison of Efficacy and Safety of Lipid-lowerING With Statin Monotherapy Versus Statin/Ezetimibe Combination for High-risk Cardiovascular Diseases) trial demonstrated that the combination therapy rosuvastatin/ezetimibe (10 mg/10 mg) was non-inferior to high-intensity statin monotherapy (rosuvastatin 20 mg) to reduce ASCVD events. Combination therapy allowed a higher proportion of patients to achieve LDL-C concentrations ≤ 70 mg/dL and a lower rate of intolerance-related drug discontinuation or dose reduction owing to adverse events or intolerance. It occurred in 4.8% of patients given the combination therapy and in 8.2% of those given rosuvastatin.[11]

Bempedoic acid

In view of the general preference of patients for the use of oral agents to achieve better LDL-C lowering, bempedoic acid has raised interest after the results of the CLEAR-Outcomes [Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid (ETC-1002) or Placebo] study. Bempedoic acid is a small-molecule first-in-class inhibitor of ATP citrate lyase. It is a pro-drug, rapidly converted in the liver by the very long-chain acyl-CoA synthetase 1 to a coenzyme A, which is responsible for the inhibition of ATP citrate lyase, a cytosolic enzyme two steps upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Conversion to the active form happens only in the liver, since in muscle, the very long-chain acyl-CoA synthetase 1 is undetectable. On the basis of this observation, bempedoic acid was not expected to cause muscle-related adverse events, thus fostering the interest in this drug as an option for the treatment of statin-intolerant patients.[12]

The CLEAR-Outcomes study demonstrated that among patients in primary or secondary prevention of ASCVD but who were unable or unwilling to take guideline-recommended doses of statins, the risk of a primary endpoint event (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularization) was 13% lower (HR = 0.87; 95% CI 0.79–0.96) with bempedoic acid than with placebo after a median of 40.6 months of follow-up. When death from cardiovascular causes, non-fatal stroke, or non-fatal myocardial infarction (the first secondary endpoint) was considered, HR was 0.85 (95% CI 0.76–0.96).

In a subgroup of high-risk primary prevention patients, risk reduction for the composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularization was 30% (adjusted HR = 0.70; 95% CI 0.55–0.89). Furthermore, the levels of high sensitivity C-reactive protein (hsCRP) were reduced by 21% at 6 months (95% CI −23.7 to −19.6) in favour of bempedoic acid. Treatment with bempedoic acid led to few adverse events, and the incidences of discontinuation for any reason, including adverse musculoskeletal effects, were similar to those with placebo.[13]

Bempedoic acid is currently available as 180 mg tablets to be taken once daily as a monotherapy (European brand name NILEMDO) or in fixed combination with ezetimibe 10 mg (brand name NUSTENDI). It is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or with mixed dyslipidaemia, as an adjunct to diet (i) in combination with a statin in patients unable to reach LDL-C goals although at the maximally tolerated dose of a statin in addition to ezetimibe, (ii) alone in patients who are either statin intolerant or for whom a statin is contraindicated and are unable to reach LDL-C goals with ezetimibe alone, and (iii) in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.

Another aspect that is worth considering relates to its efficacy when combined with ezetimibe, in a fixed-dose combination. In patients with type 2 diabetes and hypercholesterolaemia not treated with statins, the fixed combination bempedoic acid/ezetimibe (180 mg/10 mg) reduced mean LDL-C by 38.8% (at 12 weeks), an effect that was superior compared with ezetimibe alone (19.2%) allowing 38.9% of patients to achieve LDL-C levels < 70 mg/dL compared with 5.4% of patients at ezetimibe. Median hsCRP levels were reduced by 25.3% with fixed-dose combination and by 2.1% with ezetimibe monotherapy. A similar benefit was achieved in adult patients at high risk of CVD due to ASCVD, heterozygous familial hypercholesterolemia, or multiple CVD risk factors.[12]

Lipid-lowering biotechnological approaches: proprotein convertase subtilisin/kexin type 9 inhibition

A major therapeutic boost in the field of lipidology came from the approval of two fully human monoclonal antibodies [alirocumab (IgG1) and evolocumab (IgG2)] and, more recently, by a gene-silencing agent (inclisiran) against proprotein convertase subtilisin/kexin type 9 (PCSK9). Proprotein convertase subtilisin/kexin type 9 inhibitors have allowed to reach unprecedented low levels of LDL-C (i.e. <30 mg/dL). This evidence prompted a change in the LDL-C goals in guidelines such as those from European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS), now recommending more stringent goals for high and very high-risk patients (e.g. <55 mg/dL) and those from American College of Cardiology (ACC)/American Heart Association (AHA) with LDL-C target of <70 mg/dL in patients with high-risk ASCVD. Thus, according to the topic of the present review, evolocumab and alirocumab can be prescribed to patients with hypercholesterolaemia and mixed dyslipidaemia and to those with established ASCVD who are statin intolerant or for whom a statin is contraindicated.

A meta-analysis of 28 RCTs comprising 89 115 participants found that compared with placebo, PCSK9 monoclonal antibodies significantly reduced the risk of major adverse cardiovascular events (MACE) by 17% [relative risk (RR) = 0.83, 95% CI 0.79–0.88]. Specifically, PCSK9 monoclonal antibodies were superior to placebo to reduce the

incidence of stroke (RR = 0.75, 95% CI 0.66–0.86) and myocardial infarction (RR = 0.81, 95% CI 0.76–0.87), but not the risk of cardiovascular death (RR = 0.96, 95% CI 0.86–1.07). Specifically related to statin intolerance, the open-label study ODYSSEY ALTERNATIVE [Study of Alirocumab (REGN727/SAR236553) in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular (CV) Risk, Who Are Intolerant to Statins] concluded that in statin-intolerant patients with very high baseline LDL-C, alirocumab was well tolerated and produced durable LDL-C reductions over 3 years. The incidence of skeletal muscle symptoms was 46.0% for patients treated with atorvastatin in the double-blind design compared with 39.0% for the same group of patients in the open-label design. The lower incidence of skeletal muscle symptoms was potentially related to these patients not being on a statin in the open-label design (only five patients in the atorvastatin group in the double-blind design were on a statin in the open-label design).[14]

Besides monoclonal antibodies, a new RNA-based approach to lower PCSK9 levels is now available. The positive results of the first phase 3 clinical trials testing the safety and efficacy of inclisiran have led the Food and Drug Administration (FDA) and European Medicine Agency (EMA) to approve the use of inclisiran as a lipid-lowering agent in patients with ASCVD and heterozygous familial hypercholesterolemia. In early 2023, the FDA expanded indications to treat adults with high LDL-C and who are at increased risk of heart disease.

Awaiting for the results of ORION-4 (A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease) and VICTORION-2 PREVENT [Study of Inclisiran to Prevent Cardiovascular (CV) Events in Participants With Established Cardiovascular Disease] studies that are testing the hypothesis that inclisiran reduces MACE in patients with clinical ASCVD or high ASCVD risk, a pooled analysis of ORION-9, ORION-10, and ORION-11 trials reported that inclisiran has the potential to reduce MACE by 26% [odds ratio (OR) = 0.74; 95% CI 0.58–0.94], but not fatal and non-fatal myocardial infarction (OR = 0.80; 95% CI 0.50–1.27) or fatal and non-fatal stroke (OR = 0.86; 95% CI 0.41–1.81). Furthermore, twice-yearly inclisiran provided sustained reductions in LDL-C and PCSK9 concentrations and was well tolerated over 4 years in the extension study.[15]

Overall, ongoing studies of PCSK9i in patients at lower risk and with acute myocardial infarction have shown the potential to broaden their indication.

Conclusions

Statin intolerance occurs when side effects attributable to statin therapy lead to discontinuation or suboptimal use of these drugs. The problem of statin intolerance is unlikely to be solved within a reasonable time; thus, careful selection and motivation of patients will allow clinicians to better handle this frequent clinical problem. Individualized and patient-centric care is essential in the effective management of statin intolerance to enable patients to initiate a therapy that they are willing to take and that will allow them to reach LDL-C targets for ASCVD reduction. All in all, it is recommended to provide patients with clear information about the rationale for statin therapy, to direct patients to trusted websites with accurate information about statins, and to engage patients during follow-up visits (e.g. offer direct inquiry into adherence and adverse effects with non-judgmental questioning).[7]

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