Current Choice for LDL-C Lowering in High-Risk CVD Patients Intolerant to Statins

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For more than 2 decades, statins have been the most commonly prescribed lipid lowering therapy (LLT); they remain a key component of current strategies to prevent events related to atherosclerotic cardiovascular disease (ASCVD) [1]. Robust evidence supports their use and they are recommended by all current guidelines; it is also well-established that the magnitude of low-density lipoprotein cholesterol (LDL-C) lowering by statins consistently predicts the reduction of ASCVD risk [2-4]. However, for many high and very-high risk patients even when the most potent statins at their highest tolerable doses are used, this is not sufficient to achieve evidence-based guideline recommended LDL-C goals [5]. In addition, drug intolerance, or its subjective equivalents, are an issue with adherence to treatment [6]. This problem is often complemented with hardly understood, and sometimes close to aggressive, anti-statin campaigns run by public media [7].

The issue of statin intolerance (SI) has been extensively discussed but a unified consensus definition is difficult to achieve [8,9]. Even in major randomized clinical trials (RCTs) different definitions are used and subsequently the results are not entirely comparable. In clinical practice, SI is usually defined as the inability to tolerate ≥2 statins at their lowest daily doses, due to adverse subjective symptoms, with or without supplementary objective parameters [8,10]. The most common adverse effect is muscle symptoms, followed by numerous, but more rarely reported, adverse events (e.g. gastrointestinal symptoms, fatigue, joint pains, skin rash, sexual dysfunction, hair loss, etc.) or laboratory abnormalities [e.g. elevated levels of activity of creatine kinase (CK) or liver enzymes (mainly alanine- and/or aspartate aminotransferase (ALT and/or AST)]) attributable to either the initiation of statin therapy or dose up-titration [10].

Overall, SI is overestimated and overdiagnosed [8, 9, 11]. Only a small minority of symptoms reported are genuinely due to the statins; the majority would occur just as frequently on placebo [12]. It is estimated that true SI occurs in only approximately 3-6% of statin users [6,12,13]. Statin-related myotoxicity is heterogeneous in presentation; phenotypes include the relatively more common myalgia, infrequent myopathies and rare rhabdomyolysis [14]. Statin associated muscle symptoms (SAMS) are the most common and represent a major barrier to maintaining long-term adherence. SAMS include an entire spectrum of symptoms like back pain, muscle spasm, tightness or weakness as well as musculoskeletal discomfort, pain and stiffness. Statin-induced necrotizing myositis caused by antibodies against HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase is rare (prevalence: 1 in 100,000) and may require immunosuppression to resolve [15]. Many factors (e.g. age, gender, genetic factors leading to a different metabolism, drug-drug interactions and psychological reasons) play a role in the manifestations of symptoms, and much less in the appearance of more objective clinical signs or laboratory abnormalities. Muscle symptoms are subjective and the real prevalence remains unclear in the absence of a definitive diagnostic test. The diagnosis of true statin-related myotoxicity can be challenging, particularly for mild cases that are frequently the consequence of alternative aetiologies and the nocebo effect. Consequently, early statin discontinuation is reported in >50% of patients. However, in a real-world setting only approximately 25% of patients referred to a specialized centre were confirmed as being completely statin intolerant following a thorough therapeutic effort [11].

Statins are likely to remain as a ‘conditio sine qua non’, and the backbone of contemporary ASCVD prevention. Clinicians should not prematurely discontinue statin therapy before considering other possible causes, including the nocebo effect. A more personalized, but comprehensive approach is needed rather than a ‘one size fits for all’ approach. Building trust and appropriate management of patient expectations can minimize the nocebo effect in statin-treated patients [16]. Not unrelated, additional refinement of our current approach to ASCVD risk assessment using modern and high-resolution imaging methods can reinforce the physician-patient relationship. After excluding other causes of muscle symptoms, the main principle of treatment is re-exposure to a very low dose of statin and slow up-titration until the maximally tolerated dose is established. Using this
approach, the large majority of patients can be treated with statins long-term [16,17]. As an adjunct, ezetimibe can be added [18]. Statin intolerance because of muscular issues associated with low serum vitamin D may be resolved by vitamin D supplementation in some cases [19]. Trials evaluating the efficacy of coenzyme Q10 (CoQ10) supplementation on SAMS failed to prove any effect on muscle pain or plasma CK activity. However, it is of interest that statins lower plasma CoQ10 levels [20]. CoQ10 intervention may still be useful in some patients, as a placebo effect [21,22].

For patients with true SI and/or persisting SAMS that are not at LDL-C goal with their maximally tolerated dose of statin, combination therapy with ezetimibe and/or proprotein convertase subtilisin/kexin-9 inhibitors (PCSK9i) are available options. In accordance with the current guidelines, ezetimibe is usually the first additional step [3]. Ezetimibe has an excellent safety and tolerability profile, however, used as monotherapy, it only decreases LDL-C levels by approximately 20% [23-25]. In contrast, monoclonal antibodies against PCSK9 (evolocumab, alirocumab), used as monotherapy or as add on to statins, can reduce LDL-C levels by approximately 55-60% on average, with a well-established safety and tolerability record [25-29].

In this issue of the journal, Benhuri et al. [30] report the results of a meta-analysis of 8 RCTs with 1,602 enrolled patients comparing the 2 most commonly available pharmacological approaches which can be applied in patients not on statins: ezetimibe and/or the currently available PCSK9i (alirocumab or evolocumab). In statin intolerant patients, PCSK9i lowered LDL-C levels significantly more than ezetimibe (by -36.1%, p<0.00001) [30]. In several smaller scale and short-term individual trials, it was demonstrated that the use of PCSK9i monotherapy compared with ezetimibe resulted in up to 43% greater plasma LDL-C reduction [31,32]. Treatment with PCSK9i resulted in a significant reduction of the number of major ACSVD-related events in longer-term RCTs, though being used as an add-on to ongoing statin therapy [33,34]. All this, combined with favourable tolerability, suggests that the currently available PCSK9i are a more promising monotherapy option than ezetimibe for addressing the largely unmet clinical needs of statin intolerant patients at (very) high ASCVD risk with LDL-C not at the recommended goal [30]. Long-term cardiovascular outcome RCTs involving these alternative drug choices used as monotherapy are lacking, so we need to rely on the prediction of their effects proven in studies where they were used as an add-on to statins.

Premature discontinuation and/or low persistence on LLT profoundly influence the overall effectiveness of these drugs. The Benhuri et al. meta-analysis [30] in statin-intolerant patients reported an odds ratio 0.65 comparing the discontinuation rates for PCSK9i and ezetimibe (range of discontinuation was 5.6-23.8% for PCSK9i, and 2.2-33.6% for ezetimibe). Individually, discontinuation rates on PCSK9i were low in the majority of the included RCTs, but again, as for statin trials, much lower than we actually experience in everyday clinical practice; so, we cannot exclude the effect of RCTs (e.g. more intensive follow-up and patient selection) which can improve adherence. It is worth mentioning that the highest treatment discontinuation rates in the analysis were from the ODYSSEY ALTERNATIVE trial, where statin-intolerant patients were randomised for the first 24-weeks double-blind phase of the trial, into 1 of 3 arms, to receive alirocumab, ezetimibe or atorvastatin (in a 2:2:1 proportion) [35]. The rest of the trial was an open label treatment period of 3 years, where all patients received alirocumab. The overall rates of the adverse events leading to treatment discontinuation in the first phase were 18.3, 25.0, and 25.4%, for the alirocumab, ezetimibe, and atorvastatin groups, respectively [35]. In the open-label treatment period skeletal muscle events were reported altogether by 38.4% of patients, with the similar safety outcomes as for the alirocumab group in the double-blind period. The exception was a much lower discontinuation rate due to skeletal muscle events observed with alirocumab (3.2 vs 15.9% in the double-blind period) [35].

The efficacy, safety and tolerability of evolocumab vs ezetimibe in statin intolerant patients were studied in series of 3 shorter-term (12-24 weeks), GAUSS (Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects) trials [36-38]. The most recent (GAUSS-3) followed an interesting two-phase design [38]. During phase A, patients intolerant to ≥2 statins were followed during a 24-week double-blind, placebo-controlled cross-over procedure with atorvastatin or placebo to identify patients having symptoms only with atorvastatin. After 2 weeks wash-out 218 patients entered 24-weeks phase B in which they were randomized to either ezetimibe (10 mg/day) or evolocumab (420 mg every 4 weeks). During this phase, any muscle-related adverse event occurred less frequently with PCSK9i (in 28.8% of ezetimibe- and 20.7% evolocumab-treated patients, log-rank p=0.17) [38]. As an additional indicator of better tolerability, the time to patient-reported muscle symptoms was longer in patients treated with evolocumab vs ezetimibe, with a hazard ratio (HR) of 0.68 (95% CI 0.39 - 1.19; p=0.17). Both ezetimibe and evolocumab were well tolerated during the trial, with 6.8% ezetimibe- and 0.7% evolocumab-treated patients discontinuing active treatment because of muscle-related adverse events [38].

A recent report on real-world single-centre experience with the use of both of the currently available PCSK9i (n=635, 68 weeks follow-up) demonstrated 8.5% discontinuation, while overall 47.1% of patients reported adverse events [myalgia (12.6%), rhinitis (11.6%), and fatigue (10.3%) being the most common] [39]. Comparatively low short- and longer-term discontinuation rates can certainly help in making a choice to use PCSK9i easier for statin-intolerant patients. In addition, Benhuri et al. reported almost no difference of efficacy between every 2 vs every 4 weeks evolocumab dosages providing an additional opportunity to overcome limited compliance [30].

Since all statin regimens and ezetimibe are mostly generically available we can conclude that for secondary prevention of ASCVD, adding low-cost ezetimibe to high-intensity statin therapy further reduces LDL-C and ASCVD risk cost-effectively [40]. With this in mind, the authors of the present meta-analysis also discussed the important and obvious constraints in adopting PCSK9i as monotherapy due to the high price of these drugs [30]. From this viewpoint, despite less efficacious LDL-C lowering, ezetimibe, with its almost entirely generic availability, may offer an alternative monotherapy to statins for patients suffering from SI.
Choosing the adjunct or alternative to statins, besides ezetimibe and PCSK9i, there are some ‘new players’ quickly approaching the stage of clinical practice [41]. Bempedoic acid is a first-in-class among the drugs lowering LDL-C by inhibiting ATP citrate lyase, a key enzyme in the cholesterol biosynthesis pathway upstream from HMG-CoA reductase [41]. Bempedoic acid was recently approved drug by both the U.S. Food and Drug Administration (FDA) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211616s000lbl.pdf) and European Medicines Agency (EMA) (https://www.ema.europa.eu/en/medicines/human/EPAR/nilemdo) [42]. This drug has an acceptable safety profile and lowers LDL-C levels by 15-25% as monotherapy; in addition, it exerts favourable effects on the entire lipid profile, as well as high-sensitivity C-reactive protein levels [41-45]. However, the cardiovascular outcome study with this drug has not yet been completed. Seemingly an even more attractive option is a reduction of circulating PCSK9 by silencing PCSK9 messenger RNA (mRNA) [46]. Inclisiran is at an advanced stage of development; this is a small interfering RNA (siRNA) that specifically prevents the translation of PCSK9 mRNA, leading to decreased concentrations of the protein and significant lower LDL-C levels (by approximately 50%) in conjunction with an advantageous administration of a single subcutaneous injection every 6 months [46-49]. Within the ORION (Inclisiran for Subjects With ACSVD or ACSVD-Risk Equivalents and Elevated Low-Density Lipoprotein Cholesterol) [47,48] clinical development programme the safety and efficacy of inclisiran as well as its ability to reduce ASCVD outcomes were demonstrated. But again, it is not only the efficacy and safety of these new available LLT options which will define their fate, but also their cost-effectiveness [49].

In summary, the Benhuri et al. [30] meta-analysis clearly demonstrated that the use of PCSK9i is a better choice over ezetimibe, in terms of LDL-C lowering, in statin intolerant patients. Cost remains a major issue. However, taking time with our patients and cautious, more individualized care is needed to address these symptoms because they greatly impair drug adherence. Fortunately our armamentarium of available pharmacologic interventions for truly statin intolerant patients is expanding. However, further well-designed studies are needed to assess the clinical effectiveness and long-term safety of any new pharmacological option.

CONFLICT OF INTEREST
ZF reports grants, has given talks, acted as a consultant for Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Krka Pharma, Novo Nordisk, Pfizer, Sanofi and Servier.

REFERENCES


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