Overcoming Statin Intolerance in Clinical Practice: An Enduring Effort

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Low-density lipoprotein cholesterol (LDL-C) reduction with statin therapy remains the cornerstone of lipid-lowering intervention to reduce the risk of atherosclerotic cardiovascular disease [1]. Even if statins are generally well tolerated by the vast majority of patients, 20–30% of the patients with a clinical indication for such a therapy may show some form of intolerance leading to treatment disruption [2]. As a matter of fact, owing to side effects or adverse reactions, the rate of statin therapy discontinuation only 1 year after initiation may reach 40–60% [2, 3].

In clinical practice, statin intolerance can be broadly defined as any adverse event and/or laboratory abnormality attributed to statin treatment and leading to its discontinuation [1–4]. In general, interruption of statin therapy due to laboratory abnormalities is less common, while most cases of intolerance are due to muscle complaints [1–4].

Pitavastatin is the most recent statin to receive regulatory approval with similar indications as to the other compounds of the same class [5]. Pitavastatin, as all other statins, inhibits HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A), thereby reducing LDL-C, Apo B, and triglycerides and slightly increasing high-density lipopro-

tein cholesterol [5, 6]. Differently from other statins, pitavastatin contains a cyclopropyl group that fits within the hydrophobic areas of the HMG-CoA reductase enzyme, partially explaining its potent inhibitory activities with a limited dosage (1–4 mg) [5, 6]. In fact, clinical studies have shown that pitavastatin has a three- to seven-fold greater potency than simvastatin and pravastatin [7].

Ezetimibe inhibits the absorption of cholesterol mediated by the sterol transporter Niemann-Pick C1-like-1 (NPC1L1) at the brush border of the small intestine [8]. The reduction in cholesterol absorption results in a decrease in LDL-C, with no significant effect on fat-soluble vitamins (vitamin A, D, and E) [8]. When used as monotherapy or in combination with statins, ezetimibe reduces LDL cholesterol by 15–22% [8, 9]. Consequently, in clinical practice, the association of ezetimibe with statins may represent a valuable option, allowing the achievement of significant reductions of LDL-C levels with a positive impact on cardiovascular outcomes [9]. In particular, the combination of pitavastatin and ezetimibe has proven both safe and effective in patients with a very high cardiovascular risk after an acute coronary syndrome [10].

Fig. 1. Simplified critical pathway in patients with statin intolerance. CK, creatine kinase; LDL-C, low-density lipoprotein cholesterol; ULN, upper limit of normal.

In this issue of *Cardiology*, Christou et al. [11] describe the interesting case of a high-risk patient suffering severe muscle disturbances while on several different statin agents. In the end, a significant 40% reduction of LDL-C was achieved by low-dose pitavastatin (1 mg) in combination with ezetimibe 10 mg, without any major muscle complaint.

Overall, the simple therapeutic strategy used in this case appears to be effective and appealing for practicing clinicians. A low dose of a highly effective statin in combination with ezetimibe may actually represent the standard of choice when facing persisting statin intolerance [2]. In fact, the synergic block of both hepatic cholesterol synthesis and intestinal absorption may contribute to a relevant LDL-C reduction [1]. In Figure 1, a specific algorithm of intervention is outlined, which

can be easily implemented in most cases of clinically relevant intolerance. In particular, the combination of low-dose pitavastatin (i.e., 1 mg) with ezetimibe may effectively reduce LDL-C by 35–50% [6, 7], thereby allowing a significant containment of cardiovascular risk.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Both authors have equally contributed to the manuscript.

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