Statin Intolerance and Suboptimal Statin Therapy

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Statin Intolerance

In any preventive guidelines on atherosclerotic cardiovascular diseases (ASCVD), statins are recommended as the first-choice medication to reduce the low-density lipoprotein (LDL) cholesterol levels, based on numerous randomized controlled trials. However, there is a certain number of individuals who exhibit “statin intolerance.” Although no diagnostic criteria exist at this point, statin intolerance is a well-recognized term, used to describe the situation where a patient needs to discontinue an effective dosage of statin, usually due to muscle symptoms. The first case of statin intolerance was described soon after the discovery of statin by Dr. Akira Endo. An extremely high dose of mevastatin was administered to a 17-year-old girl with homozygous familial hypercholesterolemia, and side effects, including muscular weakness at the proximal parts of the extremities with an elevated level of serum creatine phosphokinase, and glutamate-pyruvate transaminase and glutamate-oxaloacetate transaminase activities were documented. It is of vital importance to understand the prevalence of patients with such statin intolerance. In their article, Kajinami et al. used electrical medical records trying to estimate the frequency of statin intolerance as well as the attainment rate of guidelines among the patients with ASCVD using three different definitions. Despite the study limitations, patients covered by Definition 1 could be considered as having “highly likely statin intolerance,” patients covered by Definition 2 as having “potential statin intolerance,” and patients covered by Definition 3 as having “probable statin intolerance.” The authors found that the attainment rates of target LDL cholesterol/non high-density lipoprotein (HDL) cholesterol levels were significantly lower in patients suspected as having statin intolerance, regardless of definitions. It has also been shown that the attainment rate of the LDL cholesterol target level was lower in the higher risk group. This situation could be at least partially explained by the presence of statin intolerance, hence other emerging options, including cholesterol absorption inhibitors, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and a new fibrate could be considered.

Known Risk Factors of Statin Intolerance

Based on clinical trials and observational studies, several risk factors for statin intolerance have been detected: age, female sex, small body frame and frailty, multisystem disease, chronic kidney disease, hypothyroidism, alcoholism, grapefruit juice consumption, major surgery or perioperative period, excessive physical activity, history of myopathy while receiving another lipid-lowering therapy, history of creatine kinase elevation, unexplained cramps, family history of myopathy, family history of statin-induced myopathy, and antidepressant use. In addition to those clinical factors, a small study illustrated that a single nucleotide polymorphism encoding the organic anion-transporting polypeptide 1B1, which has been shown to regulate the hepatic uptake of statins was strongly associated with an increased risk of statin-induced myopathy. Some scoring systems using those factors may eventually be useful for risk prediction of statin intolerance.

Nocebo Effect of Statin Intolerance

In 2017, an interesting paper was published illus-
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Conflict of Interest
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References
1) Yamamoto A, Sudo H, Endo A. Therapeutic effects of ML-236B in primary hypercholesterolemia. Atherosclerosis, 1980; 35: 259-266
2) Kajinami K, Ozaki A, Tajima Y, Yamashita S, Arai H, Teramoto T. Real-world data to identify hypercholesterolemia patients on suboptimal statin therapy. J Atheroscler Thromb, 2019; 26: 408-431
3) Tada H, Kawashiri MA, Nohara A, Inazu A, Kobayashi J, Yasuda K, Mabuchi H, Yamagishi M, Hayashi K. Lipid Management in a Japanese Community: Attainment Rate of Target Set by the Japan Atherosclerosis Society Guide-
lines for the Prevention of Atherosclerotic Cardiovascular Diseases 2012. J Atheroscler Thromb, 2017; 24: 338-345

4) Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C; American College of Cardiology; American Heart Association; National Heart, Lung and Blood Institute. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. Circulation, 2002; 106: 1024-1028

5) SEARCH Collaborative Group, Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R. SLCO1B1 variants and statin-induced myopathy—a genomewide study. N Engl J Med, 2008; 359: 789-799

6) Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, Collins R, Sever P; ASCOT Investigators. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet, 2017; 389: 2473-2481

7) Banach M, Patti AM, Giglio RV, Cicero AFG, Atanasov AG, Bajraktari G, Bruckert E, Descamps O, Djuric DM, Ezhov M, Fras Z, von Haehling S, Katsiki N, Langlois M, Latkovskis G, Mancini GBJ, Mikhailidis DP, Mitchenko O, Moriarty PM, Muntner P, Nikolic D, Panagiotakos DB, Paragh G, Paulweber B, Pella D, Pitsavos C, Reiner Z, Rosano GMC, Rosenson RS, Rysz J, Sahebkar A, Serban MC, Vinereanu D, Vrablik M, Watts GF, Wong ND, Rizzo M; International Lipid Expert Panel (ILEP). The Role of Nutraceuticals in Statin Intolerant Patients. J Am Coll Cardiol, 2018; 72: 96-118

8) Mabuchi H, Nohara A, Kobayashi J, Kawashiri MA, Katsuda S, Inazu A, Koizumi J; Hokuriku Lipid Research Group. Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. Atherosclerosis, 2007; 195: e182-9

9) Qu H, Guo M, Chai H, Wang WT, Gao ZY, Shi AZ. Effects of Coenzyme Q10 on Statin-Induced Myopathy: An Updated Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc, 2018; 7: e009835