

Statin Intolerance—An Asian Perspective

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To the Editor

The recent article in this journal by Alonso and colleagues provides a helpful review of the diagnosis and management of statin intolerance¹. The authors listed the major risk factors for statin-associated muscle symptoms; however, they did not include Asian ethnicity in the list. Asian descent or ethnicity is included in the list of risk factors for statin-associated muscle symptoms by the European Atherosclerosis Society Consensus Panel Statement², which was adapted from the Canadian Working Group Consensus update 2013 (Table 1)³. It is also discussed in the recent scientific statement from the American Heart Association⁴ and the 2019 Taiwan Society of Lipids and Atherosclerosis expert consensus statement on statin intolerance⁵.

Increased risk of statin-associated adverse events in Asians is already taken into consideration in Japan as the maximum approved doses of all statins, except pitavastatin, are lower than those in other countries⁶. Similarly limited maximum doses have also been suggested in Chinese patients⁷.

Despite avoiding the higher doses of most statins in Japan, statin discontinuation and intolerance remain common. In a large retrospective survey of patients with atherosclerotic cardiovascular disease (ASCVD) and patients with diabetes mellitus initiating therapy with either a statin or ezetimibe, 32.9% of the patients with ASCVD discontinued therapy and 10% showed possible statin intolerance within 12 months after starting the treatment⁸; the figures were similar for the patients with diabetes.

The most obvious difference in statin pharmaco-

kinetics in East Asians is in terms of rosuvastatin, the systemic exposure of which was on an average twice as high in Chinese and Japanese subjects as that in Caucasians, as mentioned in the product label. This difference in plasma drug levels between East Asians and Caucasians for rosuvastatin, and to a lesser extent for atorvastatin and simvastatin acid, is partly pharmacogenetic. One of the major genetic determinants of rosuvastatin systemic exposure is the c.421C>A (p.Gln141Lys; rs2231142) single-nucleotide polymorphism (SNP) in the gene encoding the ATP-binding cassette G2 (*ABCG2*) intestinal and liver efflux transporter. The frequency of the c.421A minor allele associated with higher plasma rosuvastatin levels is almost three times greater in East Asians than in Caucasians (28%–35% vs, 11%), but it is less in South Asian Indians (6%)⁷.

The other major genetic factor influencing statin pharmacokinetics is the c.521T>C (p.Val174Ala; rs4149056) SNP in the gene encoding the organic anion-transporting polypeptide 1B1 (*OATP1B1*, gene *SLCO1B1*) liver uptake transporter. For this polymorphism, the frequency of the c.521C minor allele is similar between East Asians and Caucasians.

The maximum dose of simvastatin approved in Japan is 20 mg⁶. It was also suggested to be the maximum dose used in Chinese populations⁷. This dosing may have prevented a recently reported case of rhabdomyolysis⁹. This case involved a 69-year-old Chinese male who developed rhabdomyolysis following the use of simvastatin at 40 mg per day for 10 years. Genotyping revealed that he carried one copy of *SLCO1B1* c.521C and two copies of *ABCG2* c.421A. There was also a possible interaction with the herb *Stevia rebaud-*

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Table 1. Risk factors for statin-associated muscle symptoms

Anthropometric	Age >80 years (caution advised for age >75 years) Female gender Low body mass index (or low body weight) Asian descent
Concurrent conditions	Acute infection Hypothyroidism (uncontrolled) Impaired renal (CKD stage 3, 4, and 5) or hepatic function Biliary tree obstruction Organ transplant recipients Severe trauma Human immunodeficiency virus Diabetes mellitus Vitamin D deficiency
Surgery	Major non-cardiac surgery with high metabolic demands. Cardiac surgery - uncertain.
Muscle-related history	History of creatine kinase elevation, especially >10x the upper limit of the normal range and not related to exercise History of pre-existing/unexplained muscle/joint/tendon pain Inflammatory or inherited metabolic, neuromuscular/muscle defects (e.g. McArdle disease, etc.) Previous statin-induced myotoxicity History of myopathy while receiving another lipid-lowering therapy
Genetics	Genetic factors such as polymorphisms in genes encoding cytochrome P450 isoenzymes or drug transporters (mainly OATP1B1 and ABCG2)
Other risk factors	High level of physical activity Dietary effects (excessive grapefruit juice) Drug-drug and herb-drug interactions Excess alcohol Drug abuse (cocaine, amphetamines, heroin)

Adapted from references 2 and 3.

ABCG2=ATP-binding cassette G2; CKD=chronic kidney disease; OATP1B1=organic anion-transporting polypeptide 1B1.

diana or linagliptin, which had both been started recently and may have had a mild inhibitory effect on simvastatin metabolism. According to the Clinical Pharmacogenomics Implementation Consortium guideline, he should not have been administered simvastatin (40 mg) considering his *SLCO1B1* genotype; however, genotyping is rarely performed prospectively. This case also illustrates the fallacy of the notion that if a patient has been receiving a high dose of simvastatin for over 1 year, it will be indefinitely safe. Increase in age and gradual decline in renal function, typically seen in patients with diabetes, along with weak interactions with other drugs or herbs, could easily tip the balance at any time, and the seemingly safe drug dose might result in potentially lethal rhabdomyolysis.

Another area of controversy mentioned by Alonso *et al.* is the role of vitamin D deficiency and

vitamin D replacement in patients with statin-associated muscle symptoms. Surprisingly, in some of the subtropical areas of East Asia, vitamin D deficiency is quite common. A study measuring serum 25-hydroxyvitamin D in healthy adolescents in Hong Kong found that 11.4% of the subjects showed deficient (<25 nmol/L) and 64% showed insufficient (≥ 25 and ≤ 50 nmol/L) serum 25-hydroxyvitamin D levels¹⁰. Similarly, a study of community-dwelling older adults in Taiwan found that 33.6% showed deficient (<20 ng/mL or 50 nmol/L) and 50.5% showed insufficient (20–30 or 50–75 nmol/L)¹¹ serum 25-hydroxyvitamin D levels. We have encountered cases of statin-associated muscle symptoms with severe vitamin D deficiency whose symptoms resolved with vitamin D replacement such that they were able to continue statin therapy. Although clinical trials have not shown a significant benefit of vitamin D supple-

ments in patients with statin-associated muscle symptoms, we recommend measuring serum vitamin D levels and providing adequate doses of vitamin D replacement in such patients.

We have also encountered patients whose statin-associated muscle symptoms appeared to respond to supplements of coenzyme Q10, some of which were self-initiated. We agree with Alonso *et al.*¹⁾ that the current evidence from a meta-analysis of randomized controlled trials does not support the use of coenzyme Q10 for statin-related symptoms, and anecdotal case reports do not provide high-quality supportive evidence. Nevertheless, we would suggest that it is worth conducting a trial of coenzyme Q10 in some patients with apparent statin intolerance as it is essential for patients to continue statin therapy when it is truly indicated. Perhaps, in some cases, a placebo effect of coenzyme Q10 may overcome the nocebo effect of statin treatment!

For patients who appear to be intolerant of effective doses of statins, alternative treatments are available. Ezetimibe has been available in most countries for many years and is generally well tolerated; however, the reduction in low-density lipoprotein cholesterol (LDL-C) with ezetimibe alone is only ~18%¹²⁾. The proprotein convertase subtilisin/kexin 9 inhibitors, alirocumab and evolocumab, are available in Japan and some other Asian countries and are more effective than ezetimibe. They can reduce LDL-C by 50%–60%. These drugs were generally well tolerated in patients with statin intolerance in the Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects (GAUSS) series of studies with evolocumab¹³⁻¹⁵⁾ and the ODYSSEY ALTERNATIVE trial with alirocumab¹⁶⁾, although skeletal–muscular adverse events were still reported with these agents in some patients. Bempedoic acid, a novel inhibitor of ATP-citrate lyase, is currently undergoing regulatory review. It was safe and well tolerated in statin-intolerant patients, and muscle-related adverse events were less common with active treatment than with placebo. Therefore, in the future, bempedoic acid may provide another option for these patients to reduce LDL-C by ~21%¹⁷⁾.

Conflicts of Interest

Brian Tomlinson has received grant/research funding from Amgen Inc, Merck Sharp and Dohme, Pfizer Inc and Roche and has acted as consultant, advisor and/or speaker fees for Amgen Inc, Dr. Reddy's Laboratories Ltd, Merck Serono and Sanofi for which he has received honoraria. The other authors report no conflicts of interest.

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