J Atheroscler Thromb, 2018; 25: 199-202.
http://doi.org/10.5551/jat.40204

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Statin Responses in Chinese Patients

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To the Editor

The recent review by Naito and colleagues provides an excellent summary of racial differences in statin responses and highlights the lower maximum doses of some statins approved in Japan compared with those in Western countries[1]. However, the doses of statins registered in China, Hong Kong, and Taiwan are generally similar to those in Western countries, and the highest doses may result in an increased risk of adverse effects in Chinese patients. The major dose-related toxicity of statins is severe myopathy, usually defined in clinical studies as elevation of creatine kinase (CK) levels at least ten times the upper limit of normal (ULN). This risk is generally related to the systemic exposure to the active form of the statin as determined by the plasma pharmacokinetics. The metabolism and tissue distribution of different statins varies according to their chemical structure (**Fig. 1**).

Differences in statin pharmacokinetics between East Asians and Caucasians are most obvious for rosuvastatin. The systemic exposure to rosuvastatin was on average twice as high in Chinese and Japanese subjects as that in Caucasians, and a study in Singapore showed that Indian and Malay subjects had intermediate levels between Chinese and Caucasians[2]. Rosuvastatin prescribing information contains the warning to start with lower doses and to consider the increased systemic exposure in treating Asian patients not adequately controlled on doses up to 20 mg/day. Considering that the 80-mg rosuvastatin dose was never developed because the risk of severe myopathy was too high in pre-approval studies in Western countries[3] and that based on the doubling of the systemic exposure to rosuvastatin in Chinese subjects compared to Caucasians[2] and that the systemic exposure to rosuvastatin is dose proportional over the dose range of 10 to 80-mg[4], the 40-mg dose in Chinese subjects would be expected to result in the same average systemic exposure as the 80-mg dose in Caucasians.. We therefore believe that the 40-mg dose of rosuvastatin should not be used in Chinese patients, although the advice in the prescribing information leaves this to the prescriber's discretion.

There is also evidence that systemic exposure to atorvastatin and to simvastatin acid, the active metabolite of simvastatin, is greater in healthy Chinese and Japanese subjects than in Caucasians in the United States[5]. Another analysis comparing single-dose pharmacokinetic studies with atorvastatin from different countries concluded that there were no differences in the systemic exposure to atorvastatin between Asian subjects from Japan, China, Singapore, and the United Kingdom and the Caucasian subjects[6]. The studies compared used different doses of atorvastatin and were likely to be different in other respects, and the systemic exposure to atorvastatin from the dose-normalized area under the concentration–time curve was actually 14% higher in the Asians than in the Caucasians before adjusting for body weight. Body weight usually has a small but significant effect on statin pharmacokinetics,[7] and this may contribute to the ethnic differences as East Asian patients typically have lower body weight than Caucasians.

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Received: February 14, 2017
Accepted for publication: June 2, 2017

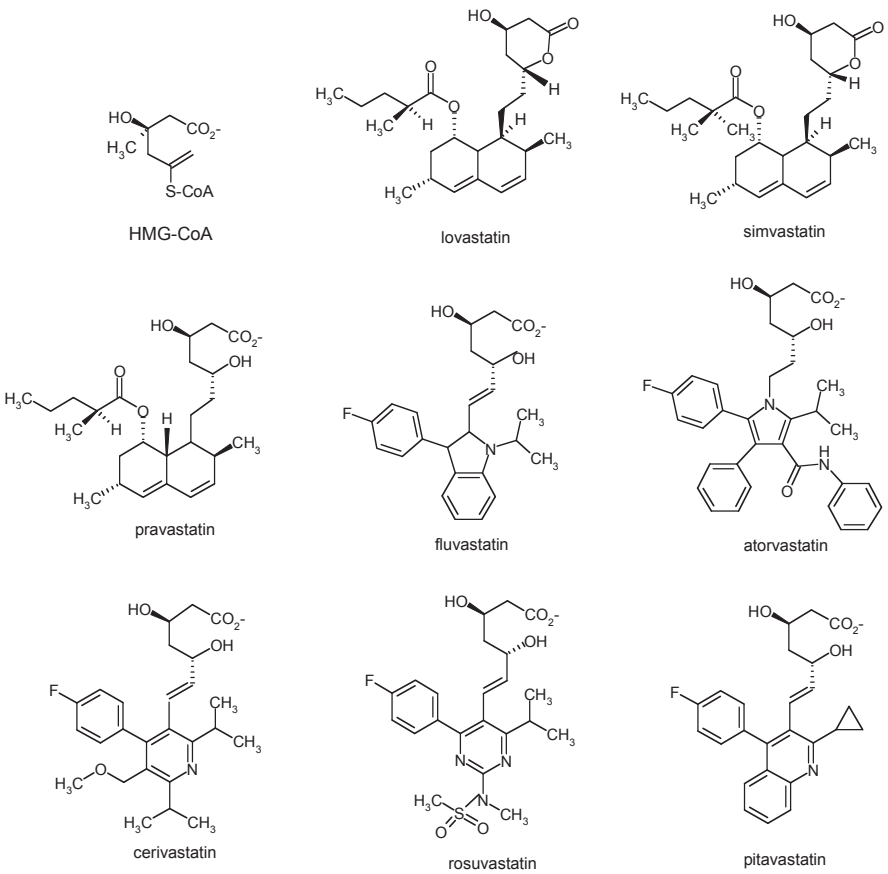

Fig. 1. Chemical structures of the statins and the natural substrate 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)

Lovastatin and simvastatin are administered in the inactive lactone forms and are hydrolyzed in the body to the active hydroxy acids. The other statins are administered in the active hydroxy acid forms. Cerivastatin was withdrawn from the market worldwide in 2001 because of the increased risk of rhabdomyolysis.

However, the major factor causing differences in stain responses between East Asians and Caucasians is probably pharmacogenetic. Statin pharmacokinetics and safety are strongly influenced by polymorphisms in the genes of the organic anion–transporting polypeptide 1B1 (OATP1B1, gene *SLCO1B1*) liver uptake transporter and the adenosine triphosphate (ATP)-binding cassette G2 (*ABCG2*) intestinal and liver efflux transporter[8, 9]. The genotypes or haplotypes of the ATP-binding cassette B1 (*ABCB1*) also have small effects on the pharmacokinetics of atorvastatin and simvastatin acid (**Table 1**)[8]. The nonsynonymous single-nucleotide polymorphism (SNP) c.521T>C (p. Val174Ala; rs4149056) in *SLCO1B1*, which results in the *SLCO1B1*5* haplotype when present alone or in the more common *SLCO1B1*15* and *SLCO1B1*17* haplotypes when combined with c.388A>G (p. Asn130Asp; rs2306283) or other SNPs, reduces the transporter activity of OATP1B1 and is the major genetic risk factor for severe myopathy with higher doses of simvastatin. It also increases the systemic exposure to pitavastatin, atorvastatin, rosuvastatin, and pravastatin but not fluvastatin[8]. However, the ethnic differences in rosuvastatin pharmacokinetics in the study in Singapore could not be explained on the basis of this SNP[2], probably because it has a similar allele frequency in East Asian and Caucasian subjects (**Table 2**).

The *SLCO1B1* c.388G variant resulting in the *SLCO1B1*1b* haplotype when present alone is the predominant allele in East Asians. This variant may result in increased liver uptake transporter activity for some substrates such as atorvastatin, and it was shown to be associated with lower plasma levels of atorvastatin, but not rosuvastatin, in a Canadian study mainly in Caucasians[10].

Table 1. Common polymorphisms in genes encoding drug transporters ATP-binding cassette B1 (*ABCB1*), ATP-binding cassette G2 (*ABCG2*) and organic anion–transporting polypeptide 1B1 (OATP1B1, gene *SLCO1B1*)[8, 9].

Polymorphism	Amino acid substitution	rs number	Effect on transporter activity for statins	Variant allele frequency in East Asians (%)
ABCB1				
1236C>T	Silent (Gly412Gly)	rs1128503	Minor effect	61-70
2677G>T/A	Ala893Ser/Thr	rs2032582	Minor effect	36-44/6-22
3435C>T	Silent (Ile1145Ile)	rs1045642	Minor effect	37-47
For the haplotypes, TTT/TTT genotype individuals have ~60% increased systemic exposure to atorvastatin and simvastatin acid compared with CGC/CGC individuals.				
ABCG2				
34G>A	Val12Met	rs2231137	Uncertain	15-36
421C>A	Gln141Lys	rs2231142	Reduced for most statins	28–35
SLCO1B1				
388A>G	Asn130Asp	rs2306283	Increased for some statins	60-90
521T>C	Val174Ala	rs4149056	Reduced for most statins	11-16

Table 2. Variant allele frequency (percentage) of polymorphisms having effects on statin pharmacokinetics in different ethnic groups

SNP	Chinese	Japanese	Caucasian	Indian[a]
SLCO1B1 521T>C	14.6-15.1	11.0	15.0	2.3
SLCO1B1 388A>G	81.7-83.7	65.1	40.3	55.7
ABCG2 421C>A	28.9-29.3	31.1-34.3	11.1-11.7	6.2

The *SLCO1B1* 521C allele results in the *SLCO1B1*5*, **15* and **17* haplotypes.
Data from HapMap. [a]Gujarati Indians in Houston, Texas.

The c.421C>A (p.Gln141Lys; rs2231142) SNP in *ABCG2* is probably the major genetic determinant of rosuvastatin systemic exposure, and it also influences the pharmacokinetics of simvastatin lactone and acid, atorvastatin and fluvastatin but not pitavastatin or pravastatin[8]. As the frequency of the c.421A minor allele is almost three times greater in East Asians than in Caucasians (**Table 2**), this is the most important SNP identified so far to account for the ethnic differences in rosuvastatin pharmacokinetics and probably simvastatin and atorvastatin pharmacokinetics as well[5]. This polymorphism and the *SLCO1B1* c.521T>C variant have been reported to be less common in some South Asian Indian groups than in other ethnic groups (**Table 2**), so the appropriate doses of statins for South Asians may be similar to those for Caucasians, but the data supporting this are limited.

There are no large studies directly comparing the incidence of myopathy with high doses of rosuvastatin or atorvastatin between Chinese and Caucasian patients, but in the Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events trial comparing the addition of placebo or extended-release niacin 2 g plus laropiprant 40 mg daily to simvastatin 40 mg with or without ezetimibe 10 mg, the combination of definite myopathy (unexplained muscle symptoms with CK >10× ULN) and incipient myopathy (alanine transaminase > 1.7× screening value and CK both >5× screening value and >3× ULN recorded within 7 days) was about 3 times higher among participants in China than among those in Europe (0.13%/year vs. 0.04%/year; $P<0.001$) in the placebo group and about 10 times higher among participants in China than among those in Europe (0.66%/year vs. 0.07%/year; $P<0.001$) in the niacin/laropiprant group[11]. These findings are compatible with increased systemic exposure to simvastatin in Chinese compared with that in Caucasian patients and an increased risk of a drug–drug interaction between simvastatin and niacin in Chinese subjects, which is likely to be pharmacokinetic. This led to a labeling revision for simvastatin by the U.S. food and drug administration in March 2010 to recommend caution when treating Chinese patients with simvastatin 40 mg or less in combination with cholesterol-modifying doses of niacin-containing products.

This polymorphism also influences the pharmacodynamics of rosuvastatin as shown by the reduction in low-density lipoprotein cholesterol (LDL-C) in Chinese patients[7]. This effect was also seen in the genome-wide association study of the LDL-C response to rosuvastatin in European subjects from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study, where non-functional SNPs in *ABCG2* in strong linkage with the c.421C>A SNP were associated with the greatest genome-wide effect on the reduction in LDL-C[12]. Reductions in LDL-C were 50.4%, 55.0%, and 62.3% with 0, 1, and 2 copies, respectively, of the A>G variant at rs1481012 in *ABCG2*, which is equivalent to doubling the dose of rosuvastatin for each copy of the variant.

The increased frequency of the *ABCG2* c.421C>A polymorphism in East Asians probably does not account entirely for the ethnic differences in rosuvastatin pharmacokinetics, and other genetic or phenotypic factors are likely to be involved. This could include factors mediating altered expression or activity of the ABCG2 transporter. Higher levels of plasma cholesterol or LDL-C were associated with increased ABCG2 expression and function[13]. Chinese and Japanese patients typically have lower baseline levels of LDL-C than Caucasians, and if the activity of ABCG2 is influenced by plasma LDL-C levels, this may contribute to decreased ABCG2 activity, which in turn would increase rosuvastatin plasma concentrations.

Overall, Chinese and Japanese patients appear to have similar pharmacokinetics with most statins, and we think that it is appropriate to avoid the highest available doses in Chinese patients, particularly those of rosuvastatin. Following the maximum doses approved in Japan would provide a safer option.

Conflicts of Interest

Brian Tomlinson has received grant/research funding from Amgen, AstraZeneca, Merk Serono, Merk Sharp & Dohme, Novartis, Pfizer, and Roche; he has also acted as a consultant/advisor to Amgen, AstraZeneca, Merck Serono, and Sanofi and been on speakers' bureau for Amgen, Merck Serono, and Sanofi. The other authors report no conflicts of interest.

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