Laboratory Medicine in the Clinical Decision Support for Treatment of Hypercholesterolemia

Pharmacogenetics of Statins

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KEYWORDS

• Statins • Myopathy • Coenzyme Q_{10} • Pharmacogenetics • Physiogenomics • Myalgia • Lipid metabolism • PCSK9 inhibitors

KEY POINTS

- Genotype–phenotype associations in large cohorts have confirmed loci at APOB, APOE-APOC1-APOC4-APOC2, LDLR, HMGCR, and proprotein convertase subtilisin/kexin 9 (PCSK9) that are associated with low-density lipoprotein cholesterol (LDLC) in patients with elevated cholesterol.
- Variants in the gene that encodes cholesteryl ester transport protein, though not associated with total LDLC, have been linked to LDLC subfractions.
- Research has linked polymorphisms in the SLCO1B1 gene to elevated serum creatine kinase activity (myalgia) in patients receiving simvastatin therapy.

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Supported in part by the NIGMS NIH Small Business Innovation Research Grant R44 GM-085201 *System for DNA-Guided Optimization and Personalization of Statin Therapy.* The ClinicalTrials.gov identifier for the SINM study is NCT00767130. Dr G. Ruaño is Principal Investigator of the study and President and Founder of Genomas Inc. The views presented in this article are strictly those of the authors, and do not represent the opinions of the companies Genomas Inc, Sanofi, or Cyclica that employ, respectively, Dr G. Ruaño, Dr R. Seip, and Dr A. Windemuth. Dr A.B.H. Wu and Dr P.D. Thompson report no conflicts.

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Clin Lab Med 36 (2016) 473–491
http://dx.doi.org/10.1016/j.cll.2016.05.010 **labmed.theclinics.com**
0272-2712/16/$ – see front matter

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- COQ2, ATP2B1, and DMPK, representing pathways involved in myocellular energy transfer, calcium homeostasis, and myotonic dystonia, respectively, have been validated as markers for the common myalgia observed in patients receiving statin therapy, and integrated into a physiogenomic predictive model for myalgia diagnosis and prognosis in clinical therapeutics.
- Statin pharmacogenetics is expected to play a significant role in the selection and confirmation of patients for PCSK9 inhibitors.

PERSONALIZED MEDICINE OF STATINS

One of the promises of the Human Genome Project is individualization of patient care based on highly heterogeneous innate metabolic factors determined by DNA typing of gene polymorphisms. Translation of such gene polymorphisms into clinical decision support for personalized health care is the basis for DNA-guided medicine. Statin responsiveness is an area of high research interest given the success of the drug class in the treatment of hypercholesterolemia, and in primary and secondary prevention of cardiovascular disease (CVD). Interrogation of the patient's genetic status for variants will eventually guide hyperlipidemic intervention.

Statins selectively and competitively inhibit the intracellular enzyme hydroxymethylglutaryl coenzyme A (HMGCoA) reductase that is expressed to different degrees in various tissues. HMGCoA reductase is the rate-limiting enzyme in cholesterol biosynthesis.

In addition to the inhibition of cholesterol synthesis, the inhibition of HMGCoA activity reduces synthesis of geranyl and farnesyl products, leading to decreased isoprenylation of proteins and possible impairment of many varied cellular functions. Statin entry into cells can be gated, and metabolic pathways for the drugs of this class are varied and drug-dependent.

Statins are the most prescribed drugs in the United States[1] and the world.[2] Atorvastatin, simvastatin, and rosuvastatin make up 85% of the prescriptions written in the United States.[1] The success of this drug class in primary and secondary prevention of CVD[3] has fostered increasingly aggressive use and dosing.

STATIN EFFICACY

Administered at maximum dosages, the most common statins (ie, atorvastatin, simvastatin, rosuvastatin, and pravastatin) lower low-density lipoprotein (LDL) cholesterol (LDLC) by 37% to 57% in patients with primary hypercholesterolemia.[4–7] The magnitude of the LDLC response differs according to phenotypic, demographic, and as yet unexplained characteristics.[8]

Although approximately 50% of the variability in plasma LDLC is estimated to be due to inheritance,[9] only a small number of common and multiple rare gene variants that contribute to the phenotype are known.[9–11] Pharmacogenetic studies of LDLC-lowering associated with statin therapy have focused mainly on genes in cholesterol synthetic, lipoprotein lipid transport, and pharmacokinetic pathways, showing that single nucleotide polymorphisms (SNPs) in genes of cholesterol metabolism, such as *HMGCR*,[12–15] and lipoprotein transport, such as *APOE*[15–24] and *LIPC*,[25] can influence the statins' ability to lower LDLC levels. Variants in pharmacokinetic genes, such as *SLCO1B1* that encodes the organic ion transporter protein 1B1, and *CYP7A1* that