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Statins Treatment under the Umbrella of Pharmacogenetics

Kolovou Vana[1,2] and Kolovou Genovefa[1]

1 Cardiology Department, Onassis Cardiac Surgery Center Athens, Greece
2 Molecular Immunology Laboratory, Onassis Cardiac Surgery Center Athens, Greece

Abstract

Pharmacogenetics explores heritable genetic polymorphisms that can effect responses to drug therapy. Many studies have focused on several genetic polymorphisms, which are involved in cholesterol metabolism, trying to define their contribution to a potential genotype-guided treatment against dyslipidemia.

Keywords: Statins; Pharmacogenetics; Gene polymorphism

Correspondence: Genovefa Kolovou, MD, PhD, FESC, SFASA, Director

genovefa@kolovou.com

Cardiology Department, Head of Outpatient Clinics and Preventive Cardiology, Head of LDL Apheresis Service, Onassis Cardiac Surgery Center, 356 Sygrou Ave, 17674 Athens, Greece

Tel: +302109493520. **Fax:** +302109493336

Introduction

The 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors [statins (lovastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin and pitavastatin)] are the first-line drugs for treating hypercholesterolemia and reducing cardiovascular events [1]. The considerable variability in total cholesterol (TC), low and high density lipoprotein cholesterol (LDL-C and HDL-C, respectively) and triglycerides (TGs) response to statin treatment is attributed to genetic factors, also [2]. Numerous genes involved in lipid metabolism have been already evaluated. Also, genome-wide association (GWA) studies examine many common genetic variants in large cohorts according to various nations, gender and diseases [3]. From the most frequently studied gene concerning effectiveness of statin treatment is that one, which encodes the CETP (Cholesteryl ester transfer protein; facilitates the transport of cholesteryl esters and TGs between the lipoproteins) and particularly Taq1B polymorphism. It was found that individuals with B1B1 genotype treated with statin showed slower progression of coronary heart disease compared with with B2B2 genotype carriers [4]. However, Boekholdt et al., [5] in a meta-analysis of 13,677 subjects showed no significant interaction between the Taq1B gene polymorphism and treatment with pravastatin. Data from REGRESS (Regression Growth Evaluation Statin Study) study showed significantly higher 10-year mortality rate among male patients who were receiving pravastatin and were carriers of the B2 allele compared with the B1 allele [6]. Our group has found that the *CETP* I405V polymorphism modifies the effect of simvastatin treatment on TG reduction and HDL-C elevation [7]. Moreover, *CETP* I405V polymorphism seems to modify the response to atorvastatin treatment concerning the decrease of LDL-C levels in patients with HDL-C ≥ 1 mmol/l (40 mg/dl) [8]. Another widely studied gene is *APOE* gene that encodes apolipoprotein E (involved directly in the uptake and distribution of plasma lipids). Our group has reported a negative association of the ε2 allele with myocardial infarction among Greek patients with coronary heart disease [9]. Many studies showed a correlation between carriers of the ε2 allele of APOE gene and an augmented response to statins, proven by lower lipid levels and less coronary events. However, in other studies such correlation was not proven [10]. Recently, Mushi [11] has reported that the individuals with the HindIII (-/-) genotype of the *LPL* (lipoprotein lipase; hydrolyzes TGs in the lipoproteins) gene would benefit more from atorvastatin therapy. Lately, ATP-binding cassette transporter family (ABC; mediates the transport of cholesterol and phospholipids from cells to lipid-poor apolipoproteins) is being evaluated. Hoenig et al., [12] found that atorvastatin efficacy is influenced by *ABCB1* polymorphism. Wei et al., [13] in their study found that *CYP7A1*-204A and *ABCG8* 1199A alleles interact with lipid-lowering response to atorvastatin. Voora et al., [14] reported that polymorphism in *ABCA1* and the *APOE* ε3 allele are associated with reduced LDL-C lowering by statins and identify individuals who may be resistant to maximal LDL-C lowering by statins. The cytochrome (CYP) P450 proteins, which

catalyze reactions involved in drug metabolism plays a significant role in lowering statin efficacy and exaggerating the risk of adverse effects. Concerning the impact of *CYP* gene polymorphism on the effectiveness of statin treatment, the results are still unclear. Li et al., [15] compared the lipid lowering efficacy of simvastatin or atorvastatin according to CYP3AP1*3 (non-expressors) variant allele in Chinese hyperlipidemic patients. They reported that in women treated with simvastatin, the % reduction of LDL-C level was greater in the CYP3AP1*3/*3 compared with the

CYP3AP1*1 genotype. Also, Kivisto et al., [16] evaluated the association between the expression of CYP3A5 and an impaired lipid-lowering response to statins and found that lovastatin, simvastatin and atorvastatin were significantly less effective in CYP3A5 carriers than in non-carriers. Shin et al., [17] evaluated the efficacy of atorvastatin and found that the CYP3A5 genotype has insignificant effects on the pharmacokinetic parameters of atorvastatin and its interaction with clarithromycin. Willrich et al., [18] reported that CYP3A5*3A allele leaded to a reduced cholesterol-lowering response to atorvastatin. Moreover, Wang et al., [19] studied the CYP3A4 polymorphism in individuals treated with atorvastatin or simvastatin or lovastatin and found that T carriers required lower statin doses than non-T carriers. Our group also studied the influence of CYP gene polymorphisms on response to statin treatment [20,21]. In a head to head comparison of the efficacy of the same dose of simvastatin versus atorvastatin in individuals with the same CYP3A5 genotype, we found an advantage for atorvastatin, although equivalent doses of atorvastatin versus simvastatin showed no difference in the % change in any of the lipid parameters [22]. Barber et al., [23] have shown that carriers with two copies of the minor allele of rs8014194 polymorphism of the calmine (CLMN; unknown function, but the protein sequence contains a calponin-like binding domain that is expected to have actin-binding activity) gene treated with statins had 3.0% less reduction of TC levels compared with non-carriers. Rosales et al., studied the effect of 4 polymorphisms of CYP3A4, CYP3A5 and ABCB1 genes and response to atorvastatin subjects with hypercholesterolemia. They observed that G allele of CYP3A4-290A>G polymorphism presents a better response to atorvastatin [24]. Rodrigues et al., investigated the relationship between *SLCO1B1* [Solute carrier organic anion transporter family member 1B1; mediates the Na(+)-independent uptake of organic anions such as pravastatin, methotrexate and others] and *SLCO2B1* gene polymorphisms and lipid-lowering response to atorvastatin among hyperlipidemic individuals and found that *SLCO1B1* c.388A>G polymorphism causes higher response to atorvastatin treatment. Hu et al analyzed 125 polymorphisms in 61 candidate genes in patients treated with rosuvastatin 10 mg daily. The polymorphisms which mainly associated with the LDL-C response were 421C>A in the *ABCG2* gene, 18281G>A (V257M) in the *FMO3* gene, 1421C>G in the LPL gene and rs4420638 in the Apo E/C-I/C-IV/C-II gene cluster [25]. Chien et al., [26] observed a strong correlation with sequence variants of HMGCoA reductase (*HMGCR*), Sterol Regulatory Element-Binding Factor 1 (*SREBF1*) and *ABCG8* genes with the reduction of LDL-C after statin treatment.

In the Genetic Effects On STATins (GEOSTAT-1) Study, [27] which was a genetic substudy of Secondary Prevention of Acute Coronary Events-Reduction of Cholesterol to Key European

Targets (SPACE ROCKET) (a randomized, controlled trial comparing 40 mg of simvastatin and 10 mg of rosuvastatin) that recruited 601 patients after myocardial infarction, were genotyped for the following functional SNP in the genes coding for the CYP450 metabolic enzymes, CYP2C9*2 (430C>T), CYP2C9*3 (1075A>C), CYP2C19*2 (681G>A), CYP3A5*1 (6986A>G), and hepatic influx and efflux transporters SLCO1B1 (521T>C) and breast cancer resistance protein (BCRP; 421C>A). LDL-C levels and the number of patients reaching the current LDL-C target of <70 mg/dL (<1.8 mmol/L) were assessed after 3 months. A greater response to rosuvastatin was found for patients with variant genotypes of either *CYP3A5* or *BCRP*. Furthermore, multivariate logistic-regression analysis showed that patients with at least 1 variant CYP3A5 and/or BCRP allele were more likely to achieve the LDL-C target (rosuvastatin 54% vs simvastatin 34%) [27]. Hubacek et al., [28] studied the association between *APOA5* SNPs (c.-1131T>C, c.56C>G and c.457G>A) and efficacy during 3 months of statin treatment. They observed that carriers of the *APOA5* genotype TT-1131 showed greater benefit from statin treatment when compared with the C-1131 allele carriers.

Thus it seems that gene polymorphisms involved in lipid metabolism alter the effect of statin treatment. The genotype evaluation may help to identify individuals with better response to therapy. Thus, the identification of individuals who have a various response to statins, may improve the risk-to-benefit ratio of statin therapy. However, the evaluations of gene polymorphisms are still expensive and more studies should be performed to drown final conclusions.

Declaration of interest

The authors declared no potential conflicts of interest with respect to the publication of this article.

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