Polymorphisms in CYP450 Genes and the Therapeutic Effect of Atorvastatin on Ischemic Stroke: A Retrospective Cohort Study in Chinese Population

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ABSTRACT

Purpose: Ischemic stroke (IS) is one of the most common neurologic diseases and is the main cause of death and disability in the Chinese population. This retrospective cohort study was performed to elucidate the relationship between single nucleotide polymorphisms (SNPs) in cytochrome P450 genes and the therapeutic effect of atorvastatin.

Methods: A total of 192 cases of IS were enrolled in the study. All patients were treated with atorvastatin, and their lipid levels and proportions were measured. Six SNPs in 4 cytochrome P450 genes (*CYP2C19*, *CYP2D6*, *CYP3A4*, and *CYP4F2*) related to drug metabolism were selected to be genotyped and analyzed.

Findings: Data were analyzed for 192 patients (sex, male/female, 122/70; mean age, 69.81 [9.35] years; Hypertension, 163[84.90%]; Cigarette smoking, 34 [17.71%]). Among the 192 patients with IS treated with atorvastatin, it was found that the G allele of rs1065852 (*CYP2D6*) had a better effect on lowering of ΔLDL ($P < 0.001$), ΔLDL/LDL ($P < 0.001$), Δ(LDL/HDL) ($P < 0.001$), and Δ(LDL/HDL)/(LDL/HDL) ($P < 0.001$). We also found that rs2242480 (*CYP3A4*) showed marginal association with ΔLDL ($P = 0.049$) under the dominant model. In addition, rs2242480 and rs1065852 exhibited cumulative effects on the lipid-lowering (ΔLDL, ΔLDL/LDL, and Δ[LDL/HDL]) efficacy of atorvastatin ($P < 0.001$).

Implications: The results suggest that *CYP2D6* and *CYP3A4* affect treatment with atorvastatin in patients with IS. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: atherosclerosis, atorvastatin, CYP450 genes, ischemic stroke, single nucleotide polymorphism.

INTRODUCTION

Stroke is considered a serious disease with high morbidity and high mortality.[1] More than 6 million deaths are reported each year worldwide, and the majority of the deaths are reported from developing countries such as India and China. In the Chinese population, the incidence of stroke is estimated to be >2 million people. There are huge economic and social burdens because of stroke in China.[2] Ischemic stroke (IS) is the most common type of stroke in China. According to epidemiologic studies, the incidence of IS in China is significantly higher than in developed countries.[1]

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Stroke is a multifactorial disease influenced by both genetic and environmental factors. There were >160 causes associated with stroke[3]; inflammation, atherosclerosis, and hyperlipidemia are the most common causes.[4] It has been reported that lowering the level of LDL can retard atherosclerosis while reducing the incidence and mortality of IS.[5,6] It is well known that atorvastatin is a statin used worldwide with safety and tolerance. It is used to reduce blood lipid levels.[7–9] However, some patients have a very poor response to atorvastatin therapy.[10] There is evidence that genetic factors contribute to the response to atorvastatin therapy.[11,12] The goal of the present study was to describe the association between the candidate single nucleotide polymorphisms (SNPs) and the efficacy of atorvastatin.

Cytochrome P450 (CYP450) is a group of structurally and functionally related superfamily genes widely found in organisms. It plays an important role in the metabolism of substances, including endogenous (eg, fatty acids, steroids, prostaglandins, bile acids) and exogenous (eg, drugs, environmental carcinogens, food additives) substances.[13] The human CYP450 gene has been basically defined, including 57 active genes and 58 pseudogenes. It was divided into 18 families and 44 subfamilies.[14] In addition, there is a large number of alleles in these genes. Among the genes, *CYP2C19, CYP2D6,* and *CYP3A4* are important subtypes of CYP450 genes involved in drug metabolism, which mediate 70% to 80% of the clinical drug metabolism in phase I metabolism and participate in exogenous chemical and endogenous substance metabolism.

In the present study, 4 genes (*CYP2C19, CYP2D6, CYP3A4,* and *CYP4F2*) related to blood lipid or drug metabolism from the CYP450 superfamily genes were selected. Six SNPs in 4 genes were enrolled by using the minor allele frequency >0.05 as the standard, including rs4244285 and rs4986893 in the gene *CYP2C19*; rs3892097 and rs1065852 in the gene *CYP2D6*; rs2242480 in the gene *CYP3A4*; and rs2108622 in the gene *CYP4F2*. They have been shown to be related to drug metabolism or blood lipid levels.[15] However, it is unclear whether SNPs influence the therapeutic effect of atorvastatin in patients with IS. We aimed to provide the correlation between the polymorphisms present in those genes and the therapeutic effect of atorvastatin on IS in the Chinese Han population.

PATIENTS AND METHODS

Study Patients

In this retrospective cohort study, a total of 192 Han Chinese patients (male:female = 122:70) with IS were recruited from Shanghai Eighth People's Hospital affiliated with Jiangsu University from November 2015 to March 2016. All patients were diagnosed as having IS with clinical manifestation and brain magnetic resonance imaging and/or head computed tomography imaging.

The inclusion criteria were as follows: (1) new onset <72 hours and no medical history of antiplatelet, anticoagulant, and thrombolytic treatment in the past 2 weeks; (2) subjects who had not taken 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors or any other lipid-lowering medication within 6 months before the study; (3) subjects were free of intracranial hemorrhage, subarachnoid hemorrhage, arteriovenous malformation, neoplasm, aneurysm, postoperation or posttrauma, infection diseases, autoimmune diseases, severe cardiac, and renal and hepatic diseases; and (4) they were stable residents for at least 20 years in the area.

Demographic data and established risk factors of stroke, such as age, sex, hypertension, and smoking habits, were also collected. Clinical data, such as HDL-C and LDL-C levels, were collected by the hospital information system; these levels were measured in the morning after the subjects had fasted overnight (12 hours). All 192 patients were receiving 20 mg of atorvastatin[†] daily for 3 months.

This study was performed according to the guidelines of the Declaration of Helsinki and was approved by the ethical committee of Shanghai Eighth People's Hospital. All patients provided written informed consent for the study.

DNA Extraction

Three- to five-milliliter venous blood samples were taken from patients and stored at −80°C for DNA extraction. DNA was extracted from the collected whole blood samples with the Lab-Aid nucleic acid (DNA) magnetic bead separation kit (Zeesan Biotech, Xiamen, China) according to the manufacturer's instructions. Agarose gel electrophoresis was used to evaluate the quality of genomic DNA.

[†]Trademark: Lipitor® (Pfizer Inc, New York, New York).