Review Article

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Role of Pharmacogenomics in Statin Responsiveness; A Review

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Abstract

Statins have been used for decades as a successful cholesterol-lowering class of medicines. Statins are widely prescribed for the primary and secondary prevention of coronary artery disease. They reduce cardiovascular risk and improve health outcomes in people with cardiovascular disease. Although statins are considered as a safe medicine and are well tolerated by patients, prediction of an individual patient's response to statin therapy remains unclear. Variation to statin therapy has been attributed to both environmental and genetic factors. In this review, a number of candidate genes that affect statin pharmacokinetics and pharmacodynamics are discussed. Moreover, the association of demographic factors with statin response in related studies is described. In this article we have reviewed the literature concerning pharmacogenetic studies on statin response. Thirty seven English-language clinical trials, prospective or retrospective human investigations, case series, case reports, published between 1998 to 2015, were evaluated. Based on these data, there are some candidate genes that have been established as affecting genes on statin efficacy and suggest that drug therapy, based on individuals' genetic makeup, may result in a clinically important reduction in variation of statin response.

Keywords: Cardiovascular, Pharmacodynamics, Pharmacogenetic, Statins.

1. Introduction

Coronary heart disease (CHD) is one of the leading causes of death in most of the industrialized countries of the world. It is still the most common cause of death in North America and Europe. Like other countries, cardiovascular disease is the most important cause of mortality in Iran(1). Dyslipidemia has been established as the primary risk factor for cardiovascular disease (CVD)(2). Statins, 3-hydroxy-3-methylglutaryl-CoA reductase (known as HMG-CoA reductase, a key enzyme in the intracellular synthesis of cholesterol) inhibitors, , in large clinical trials, have shown to reduce the risk of cardiovascular events and are considered to be first-line therapy in conjunction with life-style modification in the management of dyslipidemia (3). They reduce the risk of myocardial infarction and cerebrovascular accidents by approximately 20% for every 1 mmol/L reduction in the serum level of low-density lipoprotein (LDL-C)(4).

Although statins are considered to be safe and are well-tolerated by patients, some patients may develop adverse drug reactions (ADRs) or may not reach the desired pharmacological effect. In fact, there is considerable variation among individuals in the effectiveness of statin therapy (5). Variation in response to statin treatment has been attributed to both environmental and genetic factors. Environmental predictors include age, sex and body mass index (BMI)(6,7). Genetic factors like variants in known regulators of cholesterol metabolism might be associated with statin response (8). However, the total variability due to genetic variants is still unknown. In this sense,

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pharmacogenetic studies have shown that genetic polymorphisms of enzymes, transport proteins, and receptors are involved in both statin and lipid metabolism and they also have important effects on common clinical lipid parameters, total cholesterol (TC), LDL-C, HDL-cholesterol (HDL-C), and triglycerides (TG)(9). Current studies provide evidence that genetic factors, such as polymorphisms in the Apo lipoprotein E (APOE), solute carrier organic anion trans¬porter (SLCO1B1), cytochrome P4503A4 (CYP3A4), Kinesin Family Member 6(KIF6), Cholesteryl ester transfer protein (CETP), HMGCoA-reductase, and ATP-binding cassette subfamily B member 1(ABCB1) genes, can contribute to interindividual variations in response to lipid-lowering statin therapy and toxicity of statins(9). An economic review of the benefits of genetic screening to guide cardiovascular therapy by Sorichet, declared that it might be more cost benefit to avoid statin types and doses of which may lead to serious side effects than to implement routine screenings (10).

Pharmacogenetics is the study and evaluation of the inherited differences (genetic variations) that affect drug metabolism and an individual's response to medications. Today, the role of genetic in the incidence of disease diagnosis, outcome and prognosis, and drug response is established (11-13). Inter-individual variation in drug response is a central feature of all drug therapies which contribute generously to variable efficacy and toxicity in patients (12-14). The present review describes progress in understanding genomic variability in response to statin and how this knowledge may be used in clinical care. Pharmacogenetic study results are discussed in order to clarify pharmacokinetic and pharmacodynamic variants regarding to statin responsiveness. Moreover, the association of demographic factors with statin response in related studies is described.

2. Methods

2.1. Literature search

A literature search was performed in the following databases: Scopus, Medline, Google scholar, Cochrane Central Register of Controlled Trials, and Cochrane Database Systematic Reviews. The key words used were as follows: "statin", "polymorphism", "demographic factor", "genetic variation, "therapy". The time frame of the review was from 1998 to 2015. All published English-language clinical trials, prospective or retrospective human investigations, case series, and case reports were included. Moreover, we applied outcome measures for our selection criteria: studies that measure the effect of genetic polymorphism or demographic factors on statin response among patients or healthy participants (both positive and negative response/association), were considered eligible for inclusion. Non-English language articles in vitro and experimental studies were excluded. Finally, 37 articles were recruited in this review. Candidate genes for this review can be classified into the following two groups: 1) genes encoding for drug metabolizing enzymes and transporters that influence pharmacokinetic; 2) genes that influence pharmacodynamics.

3. Results

3.1. Pharmacokinetics variants and lipid response to statin

The following section discusses a number of candidate genes that have contributed to considerable variation in pharmacokinetic properties such as systemic exposure, area under the curve (AUC) and half-life for which substantial experimental evidence exists, supporting their role in affecting statin pharmacokinetics.

3.1.1. Cytochrome P450 system variants

CYP3A4 enzyme is involved in the metabolism of lovastatin, atorvastatin, and simvastatin and CYP2C9 is responsible for fluvastatin metabolism (15). CYP3A4 is the main CYP isoform in human liver and intestine and is involved in the metabolism of many drugs. CYP3A4 genetic polymorphisms can lead to modulation of enzymatic activity and drug efficacy (16) . There are inconsistent results among pharmacogenetic studies of this gene; A recent study among 273 Chinese patients, revealed no significant association between CYP3A4*1G, CYP3A4*22, CYP3A5*3 as well as rs4823613 A>G polymorphisms and the lipid-lowering responses after 6 weeks of treatment with 40 mg/day simvastatin (17). Kajinami *et al* studied 340 subjects who re-

ceived atorvastatin for 52 weeks. They declared that a promoter variant was associated with higher post-treatment LDL-C levels, whereas a missense variant (M445T) was associated with lower LDL-C levels before and after treatment (18).

CYP2C9 also has a major role in the hepatic clearance of medications (19). Genetic polymorphisms in the CYP2C9 gene have been associated with significant changes in fluvastatin pharmacokinetics (20). In Kirchheiner's clinical study, 24 healthy German volunteers received 40 mg/day fluvastatin for 14 days. It showed that carriers of the CYP2C9*3/*3(rs1057910) genotype achieved a 3-fold higher AUC of the active enantiomer of fluvastatin when compared to those carrying the CYP2C9*1/*1 wild-type, but differences in plasma concentrations were not reflected in cholesterol lowering effects of fluvastatin (21). A more recent study in the Czech population among 87 patients with hypercholesterolemia treated by fluvastatin 80 mg daily identified that patients who carried heterozygous CYP2C9*1/*3 had a greater reduction in plasma LDL-C levels than wild-type subjects (22).

3.1.2 Drug transporter variants

ABCB1, an efflux pump expressed by intestinal epithelial cells, hepatocytes, and renal tubular cells, is involved in the cell membrane transport of drugs which leads to variation in drug disposition and response (23). Two more common polymorphisms at the ABCB1 gene (C3435T and G2677T/A/C) have been linked to the differences in gene expression and statin response (24-26). In the Alzoubi et al. study, both the TT genotype of G2677T (ABCB1) and the TT genotype of the C3435T (ABCB1) polymorphisms were associated with lower levels of LDL-C after atorvastatin treatment in Jordanian hypercholesterolemic patients (27). A report by Hoenig et al. in Australian patients treated with 80mg/day of atorvastatin, revealed that the CC genotype at the C3435T polymorphism in ABCB1, is associated with reduced atorvastatin efficacy, independent of cholesterol metabolism, following a 6-week course of atorvastatin therapy (28). A large cohort study by Thrombolysis in Myocardial Infarction (TIMI) Study Group, investigated the response to pravastatin (40 mg/day) and atorvastatin (80 mg/day) in Boston and found a significant effect of non-synonymous SNPG2677T/A/C variant on pravastatin but not on atorvastatin response. GG carriers revealed more reduction in plasma level of LDL-C after pravastatin treatment than T/A homozygotes (29). Thompson et al. also reported a different reduction in plasma levels of LDL-C between homozygote carriers of G2677T/A/, but only for low dose atorvastatin (10mg/day) treatment in the Caucasian group (30).

3.1.3 Others

SLCO1B encodes the organic anion transporting polypeptide 1B1 (OATP1B1) which is expressed exclusively in the liver and mediates absorption of various drugs including statins by hepatocytes, and its polymorphisms (rs2306283 and rs4149056), influence the clearance of statins from the circulation. Pravastatin is a substrate of OATP1B1. Two more common variants (rs4149056 and rs2306283) have been studied extensively. One of these variants, the 521T>C (rs4149056, Val174Ala), has been associated with pravastatin pharmacokinetics (31). A study by Niemi and colleagues was done on 32 subjects from Finland receiving 40 mg pravastatin once daily. According to this report, the AUC of pravastatin blood levels were significantly greater for those subjects carrying the less common genotype (CC) versus the wild type (TT) genotype (31). Hedman and colleagues have reported that SLCO1B1 521T>C genotype significantly affects pravastatin metabolism and has also proven to affect LDL-C lowering response in 20 children with familial hypercholesterolemia and 12 cardiac transplant recipients from Finland after 2 months of treatment with pravastatin (32). Another non-synonymous single nucleotide polymorphism (SNPs) identified in the SLCO1B1 gene that has been linked to statins in some studies, is rs2306283 or 388A>G (33). A recent meta-analysis study by Rong Dai resulted from 13 studies with 7079 participants, declared no significant association between 521 T>C as well as 388A>G polymorphism of SLCO1B1 gene and the effectiveness of statins (34). To recap, it is obvious that genetic variants in transporters and CYP-enzymes can substantially affect statin pharmacokinetics. SLCO1B1 521T>C and ABCB1 transporters have been consistently linked

to statin efficacy, making them as potential candidates for screening. In terms of CYP2C9 and CYP3A4 gene variants, the present findings suggest that differences may exist, but larger trials are required before any conclusive recommendation is given

3.2. Genetic markers affecting the pharmacodynamics of statins

APOE is secreted by the liver and has a role in the hepatic receptor-mediated uptake of lipoproteins(35). The primary role of APOE in plasma lipid metabolism is to mediate the interaction of chylomicron remnants and intermediate density lipoprotein particles with lipoprotein receptors.ε2, ε3, and ε4 are three isoforms of APOE which are expressed in the general population. The effect of APOE polymorphisms on the outcome of statin therapy have been studied extensively (36, 37). In the case of APOE, two variants (rs7412 and rs429358) are involved in the expression of APOE isoform. Patients with the ε2 allele especially benefit from statin and has been shown to be associated with significantly higher reduction in plasma level of LDL-C after pravastatin and atorvastatin treatment compared to ε4 (29, 38). Therefore, statins may be less effective in reducing cholesterol levels in carriers of ε4 isoform (39, 40). In a meta-analysis of genome-wide association study (GWAS) including almost 40,000 subjects, nine SNPs in the APOE gene were investigated. The minor allele of the lead SNP rs445925, which is a proxy for the ε2 isoform, was associated with a larger LDL-C-lowering response to statins compared with carriers of the major allele(41).

Statins are potent inhibitors of HMG CoA-reductase and competitively inhibit the rate-limiting step in cholesterol synthesis (42). Several studies investigated some common SNPs in the HMG CoA-reductase gene that can affect lipid lowering response by statins (43, 44). In the Chung study, one of the HMG CoA-reductase gene variants (rs3846662) in 24 healthy Korean participants who received 20 mg atorvastatin daily for 14 days was evaluated. The GG genotype was quantitatively associated with statin responsiveness (43). However, this result was not confirmed by Thompson study in the Netherlands (38). Another large survey involving 707 renal transplant patients from northern Europe and Canada, examined the association between 42 polymorphisms in 18 candidate genes and the lipid response to 40mg/day fluvastatin. In that study, there was no significant association between HMG CoA-reductase gene polymorphisms and LDL-C reduction by fluvastatin treatment (16, 45).

The LDL receptor (LDLR) gene has also been associated with improved outcomes and response to statin therapy. In a recent study, 944 healthy adult volunteers (African-American, N=335 and European-American, N=609) were treated by 40 mg/day simvastatin for 6 weeks. The authors suggested that polymorphism in the 3UTR of LDLR can be associated with attenuated lipid-lowering response to simvastatin treatment (46).

3.3. Demographic factors and lipid response to statin

A number of demographic factors would have to be considered in statin therapy. For example; obesity is a major health hazard and can affect a patient's response to statins. BMI is a simple method of estimating adiposity. Toplak et al. showed that statin response increases with the extent of obesity. This might be due to the fact that free fatty acid (FFA) levels stimulate HMG-CoA-reductase, resulting in more pronounced hyperlipidemia (47). on the other hand, the results of the multiple regression analysis of a placebo-controlled clinical trial research among 63 French Canadian heterozygous familial hypercholesterolemia patients revealed that BMI was inversely correlated with greater LDL cholesterol response to simvastatin (48).

A recent study by Smiderle and his colleagues among 495 patients who used simvastatin/atorvastatin lipid-lowering therapy, revealed that women had higher mean levels of TC and LDL-C compared to men (7). The majority of studied women were post-menopausal and hormone-deficient. This condition may lead to a worse lipid profile due to a decrease in estrogen production. Analysis of statin therapy revealed that the decrease in plasma TC and LDL-C levels was greater in females than males (7). Another meta-analysis study by Kostis et al. was performed to evaluate the effectiveness of statins in decreasing cardiovascular events in men and women. They assessed 18 randomized clinical trials of statins involving 141,235 partici-

pants in order to analyze sex-specific differences. They observed that the benefits of statins were similar in males and females, regardless of the type of control (49). Likewise, Lahoza and his colleagues studied 440 Spanish subjects with hypercholesterolemia receiving 20 mg/day of pravastatin for 16 weeks. According to univariate analysis, they found that age, BMI, sex, alcohol consumption, weight change, smoking habit, and the presence of hypertension did not significantly influence the response of the LDL-C to pravastatin treatment(50).

4. Conclusion

In this narrative review, we have summarized the results of pharmacogenetic studies related to statin therapy. However, the results of published studies are equivocal. These discordant results may be justified by different types of population, ethnicity, concomitant diseases, small sample size (affects the power to detect a good effect size) and use of different and often not comparable statistical analysis and methodologies to assess the response rates. Gene's regulating pharmacokinetic and pharmacodynamic properties of statins are the most promising targets in this regards. It might be more difficult to determine the genetic variability responsible for common chronic diseases such as coronary artery disease than the genetic variability responsible for variations in drug response. Based on these data, there are some candidate genes that have been established as affecting genes on statin efficacy; however, this does not seem possible to put in routine practice for statins in the immediate future as similar to CYP2C19 polymorphism for clopidogrel and CYP2C9 or VKORC1 polymorphism for warfarin according to current guidelines (11, 51). As a basis, prospective, rather than retrospective, multicenter trials with large patient numbers should be considered in order to achieve enough statistical power and to gain estimates of predictive values of polymorphisms.

Conflict of Interest

None declared.

6. References

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