Pharmacogenetics of Response to Statins: Where Do We Stand?

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Cardiovascular disease is one of the leading causes of death, especially in developed countries. Blood cholesterol lowering by way of statin therapy is a common risk-lowering therapy. The risk reduction for coronary artery disease for patients using statins is 27%. These reductions, however, are average effects for all patients included in the trials. There is notable interindividual variation in response to statins, and the origins of this variation are poorly understood. Pharmacogenetics seeks to determine the role of genetic factors in variation of drug response. In patients with primary hypercholesterolemia, 23 studies have examined the effects of genetic polymorphisms at 20 different loci on the lipid response to statin treatment, and 18 studies examined genetic polymorphisms involved in the benefits of statin therapy in the prevention of cardiovascular disease. Even though many studies have been performed, few results have been replicated. It is our contention that larger sample sizes and consideration of multiple genes are needed in the field of pharmacogenetics of statin response.

Introduction

Cardiovascular disease is one of the leading causes of death, especially in developed countries. Several modifiable risk factors for cardiovascular disease have now been well established, especially cigarette smoking, hypertension, and elevated plasma cholesterol. Pharmacotherapeutic interventions, such as the use of aspirin and other antithrombotic drugs, antihypertensive drugs, and cholesterol-lowering therapy, have contributed in part to the gradual decline in cardiovascular deaths over the past few decades [1,2]. Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, which inhibits cholesterol production in the hepatocyte, which in turn increases the synthesis of low-density lipoprotein (LDL) receptors and thereby lowers blood cholesterol levels. In recent years, at least eight landmark trials have been published that establish the efficacy of statin therapy in primary and secondary prevention [3–10]. Treatment with statins over a 5-year period was associated with a statistically significant reduction in mortality and in the number of patients experiencing a heart attack or a stroke, or undergoing a revascularization procedure. Overall, the risk reduction for coronary artery disease for subjects using statins was approximately 27% [11]. These reductions, however, are average effects for all patients included in the trials. There is notable interindividual variation in response to statins, and the origins of this variation are poorly understood.

Pharmacogenetics

Pharmacogenetics and pharmacogenomics are emerging disciplines that focus on genetic determinants of drug response at the levels of single genes or the entire human genome, respectively [12]. Although pharmacogenetics is not a new field, it has recently enjoyed a surge in activity as a result of the availability of better tools and a realization of potential benefit by both the pharmaceutical industry and government regulatory bodies. The applied objectives of pharmacogenetics include improving drug efficacy, avoiding harmful side effects, and improving the efficiency and timeliness of drug response.

Several reviews on the pharmacogenetics of statins have been published [13,14••,15,16]. Both the effects on cholesterol levels and on cardiovascular event response have been described. These effects might be different because statins have certain effects that are independent of cholesterol lowering, such as effects on blood pressure, coagulation, cell proliferation, immune function, and macrophage metabolism [17,18]. Importantly for statins, the effects on cholesterol levels alone may not accurately predict the effects on cardiovascular morbidity and mortality [19]. Although the initial focus of pharmacogenetics was on drug-metabolizing pathways (*ie*, pharmacokinetics), more recently the focus has shifted to the genetic basis of individual variation of drug efficacy (*ie*, pharmacodynamics). Although statins are highly metabolized by the liver and the cytochrome

Table I. Genetic association studies on statin response

Gene	SNP	Outcome	Study	Replicated*	Not replicated*
ApoE	E2/E3/E4	LDL cholesterol	Ordovas *et al.* [36]	[37–39]	[31,40–42]
		Death	Gerdes *et al.* [43]		[44]
LDLR	*Ava*II	LDL cholesterol	Salazar *et al.* [45]		[31]
	*Hin*cII				
	*Pvu*II				
APOB	Insertion / deletion	LDL cholesterol	Guzman *et al.* [46]		[31]
CETP	TaqIB	LDL cholesterol	van Venrooij *et al.* [47]		[31]
		Changes of MSD / clinical event	Kuivenhoven *et al.* [21]		[22,48,49]
HMGCR	33 SNPs	LDL cholesterol	Chasman *et al.* [31]		[50]
ACE	Insertion / deletion	Angiogram / clinical event	Marian *et al.* [51]		[23,24]

*Numbers refer to references in text.
LDL—low-density lipoprotein; MSD—mean segment diameter; SNP—single nucleotide polymorphism.

P450 enzyme system, the published literature on pharmacogenetics concerning statin response is dominated by pharmacodynamics. The results of several such studies are reviewed in the following text.

Results

In subjects with primary hypercholesterolemia, 23 studies have examined the effects of genetic polymorphisms (or their combinations) at 20 different loci on the lipid response to statin treatment, and 18 studies have examined genetic polymorphisms involved in the benefits of statin therapy in the prevention of atherosclerotic cardiovascular disease [14••]. Even though many studies have been performed, few results have been replicated. Hirschhorn *et al.* [20••] provide an insightful discussion on the possible reasons why genetic association results may not be replicated by other association studies.

In this review, we do not provide an exhaustive summary of genetic association studies for response to statins. Rather, we restrict our analysis to genes that have been studied in at least two different study populations (Table 1). The genes that are studied more than once are apolipoprotein E (ApoE) (the ε2/ε3/ε4 polymorphism), the LDL receptor (*Ava*II, *Hin*cII, and *Pvu*II polymorphisms), APOB (insertion/deletion polymorphism), cholesteryl ester transfer protein (CETP; the TaqIB polymorphism), hydroxy-methylglutaryl coenzyme A reductase (HMGCR; different single nucleotide polymorphisms [SNPs]), and the angiotensin-converting enzyme (ACE; insertion/deletion polymorphism). Only the interaction between the ApoE gene and the cholesterol-lowering effect of statins was found in more than one study. Even for this well-studied gene, four out of eight studies were not able to show a significant interaction between the gene variation and statin treatment on the study outcome. This is the case for both LDL cholesterol response and risk reduction. In the cases of ACE and CETP, not only could the interaction not be replicated, but opposite effects were found. Kuivenhoven *et al.* [21] found that subjects with the B2B2 genotype had no beneficial effect from statins on reducing mean segment diameter, whereas Carlquist *et al.* [22] concluded that subjects with the B1B2 and B2B2 genotype had the most beneficial effect from statins on reducing the amount of clinical events. In the study by Bray *et al.* [23], ACE D carriers had a larger risk reduction than ACE II subjects, whereas in the observational study by Maitland-van der Zee *et al.* [24], men with the ACE II genotype had the best risk-reducing effect of statins.

In the pharmacogenetics of statins as in other pharmacogenetic studies, there are multiple reasons why different association studies can report different results, and these reasons may be acting simultaneously when comparing any two studies.

First, the results of an association study depend on the outcome being analyzed, and different outcomes have been used by different studies (*eg*, cholesterol-lowering effect, effect on mean segment diameter, effect on reducing frequency of clinical events). Second, the results may depend on the population sampled and the study design. Populations differ in allele frequencies at most genes, and there may be differences in the role of other (not studies) genetic, environmental, and social influences. Also, pharmacogenetic studies may or may not include a placebo arm, and the comparison groups are often complex [25]. Third, different results may be found because of differences in the statin that was used. The various statin drugs are known to have different effects [26], and there are possibly different responses across the different statins. Lastly, the sample sizes of many pharmacogenetic studies may not be sufficiently large in light of the likely small effects expected of common genetic variation. There is an unsupported expectation in both the scientific community and the public-at-large that single nucleotide variation

will have a large effect on health and disease. In contrast, although the role of genetic effects in total may be large, the effects of individual genes and gene variations are only small to moderate in size. There have been few pharmacogenetic studies that have attempted to examine a large number of genes in combination [27•], and none of these genomic studies have examined response to statins.

Clinical Trials versus Observational Studies

Nearly all studies on the pharmacogenetics of statins have been performed in a clinical trial setting. Although trials are considered the best setting to study the efficacy of drugs, many trials were carried out in the distant past and did not save DNA, did not obtain appropriate informed consent, or the sponsors of the trial viewed pharmacogenetics as a confounding factor to their business plan. Repeating such trials only for the purpose of pharmacogenetic studies would be prohibitively expensive and difficult to justify.

Large observational studies might be a good addition to clinical trials for pharmacogenetics. Most large-scale observational studies today collect and code quality drug information [28]. The main difficulty in assessing intended effects in observational studies is confounding by indication, because physicians decide which patient will be treated and with which drug [29,30]. Although determining effectiveness in observational studies is complicated and not always accurate, there is no reason to assume that confounding will be different among participants with different genotypes. Therefore, observational studies might be very useful in the study of pharmacogenetic interactions. Large studies are necessary to study the small effects of genetic differences. Important for pharmacogenetic research in cohort studies is that drug use is repeatedly assessed and well documented. For outcomes consisting of clinical events, the duration of the study has to be long enough (at least 10 to 15 years depending on the age of the cohort) that a sufficient number of cases have accumulated. In cross-sectional studies, the concept of "control" (*eg*, cholesterol levels are at goal values) may be used for pharmacogenetic studies by comparing the frequencies of control among genotypes, but such studies may be plagued by numerous sources of confounding and misclassification.

Conclusions

Although many proteins and many genes may influence the reduction of cardiovascular events by statins, most published studies have evaluated only one SNP at a time. The study by Chasman *et al.* [31] considered 148 SNPs across 10 candidate genes, but all genes were analyzed separately. Statins act on a particular biosynthetic and metabolic pathway, and statin response is the result of complex interactions among numerous biologic pathways related to lipid metabolism, inflammation, and atherosclerosis. Therefore, it is appropriate to examine sets of SNPs in different genes and analyze these SNPs jointly rather than testing each SNP in isolation. When multiple SNPs are analyzed, the sample size and study design become even more important. One can envision both testing the effects of variation in known candidate genes as well as scanning the entire genome to identify loci that influence response to statin therapy. The number of genotypes produced by comprehensive candidate gene approaches will be on the order of a few thousand SNPs. Genome-wide association studies can include genotypes on hundreds of thousands of SNPs. It remains an impressive challenge to identify the particular SNP and combination of SNPs that contribute to differences in response to statin therapy. The combination of conditional logistic regression with the false discovery rate method [32] and the set-association approach by Hoh *et al.* [33•] can be used for this purpose. In addition, newer methods, such as random forests [34•] and Bayesian networks [35•], are emerging from the field of computer science and migrating to the field of human genetics. However, it remains the case in pharmacogenetics, in general, that developments in the laboratory for SNP collection have advanced far greater than advances in data analysis and interpretation. At present, no SNP or combination of SNPs has been identified that renders statin treatment ineffective based on clinical outcomes. Most studies lack sufficient power to detect gene-drug interactions. Therefore, results from large trials combined with large population-based studies that consider variation in multiple genes are needed. Finding the genetic profile that will predict response to statins is going to be a major challenge.

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