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REVIEW ARTICLE

Pharmacogenetics of Statin Therapy: Genetic Determinants of Response and Non-response with Emphasis on Drug-metabolizing Enzymes and Transporter Genes

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ABSTRACT

Statins are one of the most widely prescribed drugs globally. The group of medicines is meant to reduce high levels of serum cholesterol and prevent the occurrence of cardiovascular events in future. However, they have the potential to bring LDL cholesterol to normal levels and, therefore, diminish the menace of heart attack or stroke, patients individually show significantly different responses. Hence, in some patients (responders), statin treatment may result in very obvious good effects. Those who are on the same medication as these patients, however, may experience little or no change in their conditions at all (non-responders). This difference was increasingly blamed on genetics, which not only influence the effectiveness but also the safety of statin therapy. Pharmacogenomics has made several strides and discovered that many genetic polymorphisms exist in the genes for drug-metabolizing enzymes and protein membrane transporters that regulate statin pharmacokinetics and pharmacodynamics. The different cytochrome P450 enzymes, like CYP3A4, CYP3A5, CYP2C9, and CYP2C19, determine the metabolism of statins, while the gene variations coding for hepatic acceptance and efflux transporters, e. g., SLCO1B1, ABCB1, and ABCG2, influence the absorption, distribution, and elimination of statins. These genetic variants result in changes in plasma drug concentrations, drug therapeutic effectiveness, and drug-related side effects, specifically, statin-induced myopathy. This review consolidates recent evidence regarding pharmacogenetic factors that lead to the identification of responder and non-responder phenotypes, mainly dealing with essential metabolizing enzymes and transport proteins. These genetic influences clarify a great deal of the variability between individuals in their response to statins and point to the potential of statin dosage personalization to be one of the main tools of precision medicine in the prevention of cardiovascular diseases.

KEYWORDS: Cytochrome P450, Genetic, Pharmacogenetics, Statin, Transporter Genes.

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INTRODUCTION

Hypercholesterolemia represents a major public health problem worldwide. It has a sizable proportion of the global population impacted directly or indirectly, and is one of the leading causes of cardiovascular morbidities and mortalities at the global level.[1] On the other hand, it has been demonstrated that raised levels of low-density lipoprotein cholesterol (LDL-C) are the principal cause of atherosclerotic cardiovascular disease (ASCVD), which includes peripheral artery disease, myocardial infarction, and stroke. The World Health Organization (WHO) has ranked dyslipidemia among the top most critical modifiable risk factors leading to premature death due to cardiovascular causes. This highlights the absolute necessity of using lipid-dropping drugs for both principal and subordinate anticipation of cardiovascular disease.[2] Statins a group of 3, hydroxy, 3, methylglutaryl, coenzyme A (HMG, CoA) reductase inhibitors, relieve the lipid burden by the selective and competitive inhibition of HMG, CoA reductase, which is the rate-limiting enzyme in the body's cholesterol biosynthesis. Liver cholesterol deficiency results in a compensatory mechanism where an increased number of low-density lipoprotein receptors are expressed on hepatocytes, leading to the enhanced hepatic uptake and clearance of circulating LDL particles as well as very-low-density lipoprotein (VLDL) remnants.[3] The end result of this process is a marked decrease in plasma LDL-C levels. On top of their cholesterol-lowering capability, statins can also have certain pleiotropic effects such as upgrading the function of endothelial, stabilization of atherosclerotic plaques, anti-inflammation,

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and the increase of vascular compliance.[3] Despite statins being effective according to evidence, in medical practice, a significant variation of patients' response to the therapy is usually observed. Around 10-15% of the patients, even after being given maximum tolerated statin doses, fail to achieve LDL-C targets acclaimed by guidelines, while some patients obtain dramatic lipid reductions with only small doses. The inconsistency also extends to the drugs to be tolerated as some people may experience statin-associated muscle symptoms (SAMS) at a regular dose, whereas others may carry out high intensity statin therapy without any adverse effect. The variation in both efficacy and safety causes a clinical problem and points to the necessity for more personalized treatment strategies. Given that statins are widely used, the enormous economic burden of cardiovascular disease, and the global public health implications, it is worthwhile to look for biomarkers predicting statin response.[4] Pharmacogenetic markers, especially genetic variants in genes coding drug metabolizing enzymes and membrane transporters have become a major source of interindividual differences in statin pharmacokinetics and therapeutic consequences. The incorporation of these genetic factors in clinical practice can be a way of statin selection and optimized dosing, enhancing therapeutic efficacy, minimizing adverse effects, and improving patient adherence. These precision medicine approaches imply a move from standard population-based treatment strategies to more personalized biology-driven cardiovascular care.[5]

AN OVERVIEW OF STATIN PHARMACOGENETICS

The study of genetic variants is known as pharmacogenetics, which affect drug behaviour of different individuals. It involves pharmacokinetic processes, such as pharmacodynamic effects drug targets and subsequent biological reactions, as well as absorption, dissemination, metabolism, and elimination. The larger field of pharmacogenomics covers both common genetic variants, for instance, single-nucleotide polymorphisms, and rare mutations that together account for the variability in drug response.[6] Pharmacogenetics of statin treatment is the first step in discovering genetic differences in genes encoding enzymes, transporters, and molecular targets that regulate statin disposition and action. These genetic factors explain why some people may get a lot of lipid-lowering benefits from statins, while others may have poor efficacy or even develop treatment-limiting adverse effects.[7]

Impact of Genetic Variations' Effect on Drug Response

The differences between individuals in drug response are due to the interaction of their genetic makeup, environmental factors, disease states, medications taken together, and lifestyle factors. The most common genetic variations are found in the genes that code for transport proteins, metabolizing enzymes, and drugs significant of single factor to account for the fluctuation of therapeutic outcomes among different individuals. Such polymorphisms may change the protein structure, protein expression, or functional capacity of the corresponding proteins, resulting in decreased, normal, or increased enzymatic activity and transporter function. These changes impact numerous pharmacokinetic processes that determine how the drug is absorbed, for example, statin absorption, hepatic uptake, metabolism, and elimination; thus, penetration of the circulating drug in the body, therapeutic efficacy, and the chance of adverse effects will be affected.[8]

Responder and Non-Responder Phenotypes

Clinical Relevance Identification of statin therapy response patients as either responders or non-responders has major effects on the clinical practice of the optimization of the treatment and reducing cardiovascular risk. Usually, responders are considered those who accomplish a 40 to 50% or higher decrease in LDL, C levels or those who attain lipid targets recommended by guidelines with the use of standard or high-intensity statin regimens, additionally, they keep good tolerability. On the other hand, non, responders are defined as those who have a minimal reduction in LDL, C (usually <10%) even after being treated with the maximum statin dose that can be tolerated or those who discontinue the therapy at an early stage because of adverse effects, e.g., statin-associated muscle symptoms or other types of intolerance. A very important point is that non responders should be separated from those who are truly biologically or genetically resistant and those who apparently do not respond but are poorly adherent have drug interactions or are inadequately dosed. Pharmacogenetic testing can be a great method to distinguish between these cases and to help doctors make more appropriate, and personalized therapy decisions.[9]

GENETIC DETERMINANTS INFLUENCING STATIN METABOLISM

Statin metabolism is highly dependent on genetic variations that impact the production among drug-metabolizing enzymes, especially the enzymes of cytochrome P450 (CYP450) superfamily (Table 1). These Genetic variables are in charge of time, related variances in statin plasma levels, therapeutic response, as well as the possibility of adverse effects like statin-associated muscle symptoms (SAMS).[10]

Cytochrome P450 Enzymes: Role of the CYP450 System

The CYP450 system is a set of heme-containing monooxygenases that are primarily found in the liver as well as the intestine. For many statins, these enzymes are in charge of Phase I oxidative metabolism, thus making their biotransformation and excretion possible.

Variations in activity of CYP450 enzymes caused by genetic polymorphisms may considerably change statin pharmacokinetics and, as a result, either lead to increased toxicity or decreased lipid-lowering efficacy. The most important CYP isoforms for statin metabolism are CYP3A and CYP2C subfamilies.[11] CYP enzyme system is the main phase I metabolic pathway for the biotransformation of both endogenous compounds and xenobiotic in humans. Out of its many isoforms, CYP3A4 and CYP3A5 are the most significant ones in the pharmacokinetics of statins, as they are the enzymes participating in the oxidative metabolism of several lipophilic statins. CYP3A4 is the major CYP enzyme for the human liver and is also very highly expressed in the intestinal epithelium, where it is a foremost contributor to first-pass metabolism. On the other hand, the expression of CYP3A5 is quite variable and mostly influenced by genetic polymorphisms; a large number of people have alleles that result in low or no enzyme activity. The most remarkable is the difference in the functional expression of CYP3A5 among different ethnic groups. The percentage of the population with a functional enzyme is higher in the African and Asian populations than in those of European descent.[12]

Atorvastatin undergoes extensive metabolism in the liver, and most of the metabolism involve CYP3A4-mediated oxidation of atorvastatin to active metabolites such as ortho-hydroxy atorvastatin and para-hydroxy atorvastatin. The CYP3A41B promoter polymorphism (rs2740574) is linked with low enzyme production and activity, causing a higher systemic concentration of atorvastatin. On the other hand, the CYP3A53 allele (rs776746) that leads to the loss of CYP3A5 expression in most individuals of European origin, removes the alternative pathway of metabolism and hence contributes to high plasma concentrations of atorvastatin.[13] Several populations, based cohorts have found that the genetic variants in CYP3A4 and CYP3A5 that alter these enzymes pharmacokinetics result in significant changes in atorvastatin pharmacokinetics and have important implications for drug accumulation and toxicity. For instance, the research in Egyptian patients found that those who carried the genotypes CYP3A41B (T/T) and CYP3A53 (C/C) had higher levels of atorvastatin and total bilirubin was increased more; thus, suggesting that these genetic subgroups might be at higher risk of statin-induced toxicity.[14]

Inactivating mutations in CYP3A enzymes lead to decreased systemic statin exposure. Theoretically, this could increase the reduction of LDL-C. Still, the net clinical effect is often ambiguous. The literature abounds with reports of enhanced hypolipidemic efficacy in variant allele carriers, as well as accounts of lower or variable responses, which may indicate that dose-response relationships are nonlinear and complex. Significantly, a decrease in CYP3A activity elevates the risk of statin-associated muscle side effects due to drug accumulation. Therefore, patients with these genetic variations might need a lower statin dose to strike a good efficacy-safety ratio.[14]

CYP2C9 Genetic Polymorphisms

CYP2C9 is a Phase I enzyme involved in metabolism, with a narrower substrate specificity than CYP3A4, but it is very important to the metabolism of certain statins, especially fluvastatin. In comparison to the wild-type CYP2C9*1 allele, the frequently occurring CYP2C9 2 (rs1799853; Arg144Cys) and CYP2C9 3 (rs1057910; Ile359Leu) alleles are concomitant with decreased enzyme action.

Statins that are metabolized by CYP2C9 are more prevalent in the plasma of variations. The pharmacokinetics of fluvastatin, which is the least among statins and is predominantly metabolized by CYP2C9, are significantly changed in poor metabolizers, and as a result, systemic exposure is increased, and the risk of statin-associated myopathy is also elevated.[15]

CYP2C19 Genetic Variability

Presently, CYP2C19 is just a minor contributor to statin metabolism; however, new data indicate that its genetic polymorphisms may modify the clinical response to atorvastatin in certain situations. Among acute coronary syndrome patients, a poor metabolizer genotype of CYP2C19, which is characterized by loss of function alleles such as *2, *4, and *8, is related to diminished LDL-C lowering after atorvastatin treatment. Those individuals were at a higher risk of not reaching stringent LDL-C goals, thereby implying that the CYP2C19 genotype might significantly help in predicting statin response in populations with a considerable risk of cardiovascular diseases.[16]

TRANSPORTER GENE POLYMORPHISMS AND STATIN RESPONSE

Membrane transporters are the main determinants of pharmacokinetics of statins since they regulate the uptake of drugs into hepatocytes and their efflux from cells. Polymorphic variations in the genes encoding the transporters may have major impact on the concentration of statins in plasma, response to treatment, and risk of side effects. Among these transporters, the one that contributes the most to the clinical variability of drug disposition is the SLCO1B1 that encodes the organic anion transporting polypeptide 1B1 (OATP1B1).[17]

SLCO1B1 (OATP1B1): A Central Determinant of Hepatic Statin Uptake

OATP1B1 is a major physiologic transporter that mediates the high-affinity uptake of various endogenous and exogenous compounds. SLCO1B1 gene encoded the transporter, which is particular for the liver and normally fluoresces in the presence of inhibition outside of the (sinusoidal) membrane of hepatocytes. The transporter facilitates the sodium-independent uptake of a variety

of both endogenous and exogenous compounds, which include cholest-4-en-3-one, bilirubin, gluconide, and more than five statins. Without the statins being taken efficiently into the liver via OATP1B1, they would not be able to inhibit HMG-CoA reductase and thus achieve their lipid-lowering effect.[18] The SLCO1B1 gene encodes the organic anion, transporting polypeptide 1B1 (OATP1B1), one of the main hepatic uptake transporters that is mostly found within the basolateral (sinusoidal) membrane of hepatocytes (Table 1). OATP1B1 is sodium, independent transporter; thus, it does not require sodium for transport. It enables the liver to take in a large variety of naturally occurring compounds and foreign substances such as bile acids, steroid hormones, thyroid hormones, and various drugs that are of therapeutic importance. In pharmacokinetics of statins, OATP1B1 plays a key role in the process by which statins are transferred from the blood circulating system to hepatocytes; thus, the essential step for both therapeutic action and metabolism follows. SLCO1B1-mediated uptake is thus often the rate-limiting step in statin elimination since the liver is the foremost site of statin accomplishment and clearance. Due to this reason, the impact of genetic disparity in this transporter on statin plasma concentrations, efficacy and side effects potential is indeed significant.[19]

The SLCO1B1 gene has many variations, and one or more of its variants have been shown to alter transporter function and statin pharmacokinetics significantly. Out of these, only two variants matter the most from a clinical point of view. SLCO1B1 c.521T>C (rs4149056; Val174Ala). One of the most extensively investigated features of SLCO1B1 in connection with statin therapy is a c.521T>C change that leads to a single amino acid mutation in the protein. The c.521T>C replacement causes the amino acid alanine to replace valine at position 174 of the OATP1B1 protein chain. Various studies on protein functions have shown that the c.521C allele is responsible for reducing transporter activity. This is the reason why the c.521C, mediated hepatic uptake of statins is low. The plasma levels of statins in patients carrying the c.521C allele in a homozygous state can be several-fold higher than those who are c.521T/T carriers. This genotype has a frequency range of approximately 37% in populations of Europeans and is higher in a number of Asian populations. Without reference to any preconceived hypothesis, a genome-wide association study pinpointed this variant as a major factor for simvastatin-induced myopathy. Patients with c.521C/C homozygotes showed an increased risk of about 16 times compared with individuals with the wild-type gene.[20] The association's magnitude led to regulatory safety alerts concerning simvastatin dosing in patients having this genotype. SLCO1B1 c.388A>G (rs2306283; Asn130Asp) The c.388A>G variant leads to higher expression of the OATP1B1 transporter and, therefore, more activity. The polymorphism c.388A>G is in opposite to the c.521T>C variant, with the former being correlated with enhanced OATP1B1 transporter expression and functional activity increase (Table 1). Those who have the c.388G allele more effectively absorb the statins in the liver, thus, the drug is better delivered to the area where it works in the hepatocytes. Investigations have associated this change with better lipid-lowering effects, mainly when atorvastatin is used. To illustrate, the research in the Chilean population showed that people with the c.388G allele had a higher increase in HDL-C level, which is in line with that allele being a factor that changes statin effectiveness.[21]

Effects on Hepatic Uptake and Systemic Exposure

The SLCO1B1 polymorphisms impact pharmacokinetics and can be seen in the large differences in systemic statin exposure. Plasma statin concentrations in individuals homozygous for the c.521C allele are so increased that area-under-the-curve (AUC) values are changing approximately two-to-five folds, depending on the statin and its OATP1B1-mediated uptake (Table 1). The heightened systemic exposure is, therefore, the main cause that is strongly correlated to an increased risk of statin-persuaded muscle toxicity, which is a dose, and attentiveness, reliant type of side effect. On the other hand, a c.388G allele carrier is usually having a better hepatic clearance and, thus, lowers drug levels in the blood, and it is theoretically possible for such a carrier to attain effective LDL, C lowering with almost no risk of myopathy.[22]

Relationship with Non Response and Myopathy Risk

Variants in SLCO1B1 are the major influencers of both the effectiveness and statin therapy safety. Patients defined as non-responders may have variants that are related to increased transporter activity, thus they may experience rapid hepatic clearance and insufficient systemic drug exposure at standard doses. Meanwhile, those with reduced, function variants, especially c.521C/C homozygotes, are a great way to have muscle, related side effects even though a strong lipid-lowering effect can be present and so, dose adjustments or a different statin selection are the most common solutions. The UK Biobank data show that muscle symptoms caused by statin therapy are likely associated with certain SLCO1B1 haplotypes. The most significant thing is, the authors claimed that it could be about 18% muscle, related adverse events which could be avoided if the prescribing decision was facilitated by the SLCO1B1 genotype.[23]

ATP, BINDING CASSETTE (ABC) TRANSPORTERS AND STATIN RESPONSE

The ABCB1 gene, commonly referred to as multidrug resistance protein 1 (MDR1), encodes P, glycoprotein (P, gp), an ATP-driven efflux transporter found on the outermost layer of intestinal epithelial cells, at the protective blood tissue obstacles, and on the canalicular cell membrane

of hepatocytes. P, gp, in an energy, dependent manner, transports out many types of substrates, among which are a number of statins, thus it limits their intestinal absorption and promotes biliary excretion.[24] The synonymous ABCB1 C3435T polymorphism (rs1045642) has been put forward as a candidate variant for its potential role in statin response. However, the observed results are contradictory. A few studies indicate that lowered P, gp levels resulting from certain genotypes might raise statin bioavailability and hence, the LDL, C reducing effect would be stronger, whereas some other studies have found little or no effects of clinical significance.[25] The protein breast cancer resistance protein (BCRP), one of the components expelled by the cell, is coded for by the ABCG2 gene. Among other things, this protein is of great significance for the disposition of rosuvastatin. Compared to statins that are mainly metabolized by cytochrome P450 enzymes, rosuvastatin, and pravastatin are more dependent on active transport mechanisms. The ABCG2 c.421C>A polymorphism (rs2231142; Gln141Lys) is the change that is mostly linked to the least transporter activity, thus the patient is exposed to the drug systemically in a very high amount. The presence of the c.421A allele results in significantly higher plasma drug concentrations and, consequently, the risk of statin-associated myopathy increases. So as to lessen adverse effects yet maintain the therapeutic effectiveness, the Clinical Pharmacogenetics Implementation Consortium (CPIC), based on extensive clinical data, has published genotype, guided dosing recommendations for rosuvastatin, which advises dose reductions in A allele carriers (Table 1). These recommendations are supported by a study on the pharmacokinetics of healthy Chinese volunteers. The results showed that rosuvastatin AUC values were considerably greater in C/A and A/A genotype people than in C/C wild-type individuals.[26]

GENETIC INFLUENCE ON INDIVIDUAL STATINS

Rosuvastatin is unlike many other statins in that it has a unique metabolic pathway. In contrast to atorvastatin and simvastatin, which are metabolized to a large extent by the CYP3A4 enzyme, rosuvastatin is a drug that is only to a very small extent (less than 10%) metabolized by cytochrome P450 and CYP3A4 is responsible for less than 10% of its biotransformation. The majority of the drug is converted through direct glucuronidation, which is mainly catalyzed by UGT1A1 and UGT1A3 enzymes. Therefore, polymorphisms in the genes that encode for CYP3A4 that change the enzyme activity have almost no impact on the pharmacokinetics of rosuvastatin. Obviously, the absorption, distribution, metabolism, and excretion and clinical effects of rosuvastatin are mainly dependent on transporters.[27]

The most notable pharmacogenetic element that dramatically changes the rosuvastatin plasma level is the ABCG2 c.421C>A polymorphism (rs2231142) that essentially changes the efflux transporter function and drug bioavailability. A variant impacts the BCRP to change one amino acid from glutamine to lysine at position 141. This leads to a less active transporter. Hence, those who have the c.421A allele show a drop of drug elimination and, as a result, elevated rosuvastatin exposure in plasma is observed to them. The variants in SLCO1B1 manipulating hepatic uptake also change rosuvastatin pharmacokinetics, however, their influence is normally less for statins that are metabolized by CYP3A4 to a great extent than for those that are highly dependent on CYP3A4. The SLCO1B1 c.521T>C polymorphism has been linked to the change of the rosuvastatin response and the risk of muscle damage, but the sizes of the effects are much smaller in comparison with simvastatin ones.[28]

Rosuvastatin is a very potent drug to LDL, C; it is common for it to use standard doses of therapeutic to achieve a reduction of 45-55% (Fig 1). However, pharmacogenetic variability still plays an important role in the optimization of treatment. Those who are homozygous for ABCG2 c.421A allele have a considerable increase in the risk of statin, induced myopathy and, as a result, frequently need to lower their dose in order to improve their tolerance. On the other hand, subjects with a wild-type c.421C/C genotype are mostly capable of handling normal or even higher doses without any major side effects. Furthermore, individuals carrying SLCO1B1 variants that result in increased transporter activity should be given more doses to obtain the desired lipid-lowering effects. Also, due to its lesser dependence on CYP3A4 metabolism, rosuvastatin is the drug of the choice in patients who are given CYP3A4 inhibitors or in those who have genetic variants that result in decreased CYP3A4 activity.[28]

Pharmacogenetics of Atorvastatin

Atorvastatin is a drug that is largely broken down in the liver and among the enzymes that cytochrome P450 3A4 (CYP3A4) plays a major role in the production of its active metabolites. For that matter, the pharmacokinetics of atorvastatin are very dependent on the genetic polymorphism that affects the activity of CYP3A4, as well as on the geographical factors and drugdrug interactions that change the activity of this enzyme. The CYP3A41B promoter polymorphism and the CYP3A53 loss, of, function allele are such examples that cause the reduction of metabolic capacity and thus the increase of atorvastatin plasma concentrations. In addition, OATP1B1 is the protein accountable for the uptake of atorvastatin into hepatocytes and genetic variations in SLCO1B1 determine not only the therapeutic response but also the menace of muscle, related side effects. There is some evidence pointing to the fact that the carriers of the SLCO1B1 c.521T>C variant have around a twofold increase in the risk of myopathy during therapy with atorvastatin, however, this risk is still lower than the one associated with

simvastatin, thus, careful dose adjustment is advised in individuals at high risk.[29] Besides metabolism by CYP3A4, transporter proteins are very important to the atorvastatin disposition. The hepatic uptake by OATP1B1 is the main factor of systemic exposure, with the SLCO1B1 c.388A>G variant characterized by increased transporter activity being associated in some populations to a more potent LDL, C lowering effect. On the other hand, the c.521T>C variant with reduced function is correlated with higher levels of circulating atorvastatin and a greater probability of adverse effects. A pharmacokinetic study of healthy volunteers has recognized the SLCO1B1 c.521T>C genotype as the most influential factor for atorvastatin bioavailability, thus, it explained a large part of the interindividual variability.[30] In contrast to rosuvastatin, which shows almost no dependence on CYP3A4, atorvastatin depends this enzyme significantly for its metabolism. Consequently, a genetic change in CYP3A4 has a much greater effect on the effectiveness and safety of atorvastatin. Both statins are affected by SLCO1B1 polymorphisms; however, the effect mostly goes to atorvastatin and simvastatin, while for rosuvastatin it is less. In addition, atorvastatin is more vulnerable to the condition of being a source of clinically significant drug-drug interactions accompanied by the CYP3A4 inhibitors like clarithromycin, ketoconazole, and ritonavir. The analyses of statin macrolide interactions have found that clarithromycin substantially elevates plasma concentrations of atorvastatin and the risk of myopathy, thus, it is advised to avoid co administration or to use further agents.[31]

STATIN THERAPY RESPONDER AND NON-RESPONDER PHENOTYPES

The classification of patients into statin responders and non-responders mainly depends on the extent of low, density lipoprotein cholesterol (LDL, C) lessening that is achieved during therapy. Modern clinical guidelines consider statin therapy as effective when patients either reach the recommended LDL, C targets based on their cardiovascular risk category or show a decrease of about 40, 50% from the baseline values. Those individuals who achieve a reduction of 50% or more or those who reach LDL, C levels below 1.0 mmol/L with standard dosing are usually referred to as very good responders. On the other hand, non, responders are generally considered to be patients who have only a slight decrease in LDL, C (usually less than 10%) despite the use of statin doses that are maximally tolerated and are also unable to get to target LDL levels even with high, intensity statin regimens.[31]

Clinical and Biochemical Indicators of Response

Evaluation of statins effect is not limited to the reduction of LDL, C only. Additional biochemical markers may also be considered, such as alterations in apolipoprotein B, lipoprotein(a), triglycerides, and high, density lipoprotein cholesterol (HDL, C). In addition, the ability to tolerate the drug is very important to delineate the response. The most frequent statin-associated muscle symptoms, along with other adverse effects, may cause the patient to stop the treatment and thus reduce the therapeutic benefits. As a result, a patient may show a great lipid-lowering response, but due to therapy discontinuation, he/she may still be considered a functional non-responder. Hence, a thorough review of statin response should combine effectiveness results with safety issues.[32]

Relationship between Genotype and Statin Response

Certain genetic polymorphisms can contribute to the situation where statins are less effective in some individuals by the mechanisms that increase drug clearance or decrease liver uptake of the drug. It has been found that variants in SLCO1B1 that lessen transporter, mediated hepatic uptake and also genetic factors that lead to increased metabolic activity are allied with an attenuated LDL, C reduction and a higher probability of non, response. The SLCO1B1 *15 haplotype, which comprises the c.521C allele, is related to a lower statin delivery to hepatocytes and, therefore, decreased lipid-lowering effectiveness. Also, the genetic variation that affects CYP3A4 activity might cause statin exposure at subtherapeutic levels, which in turn results in low LDL, C reduction even when the dose is correct.[33] On the other hand, genetic variants that facilitate efficient liver uptake or maintain an ideal metabolic balance are in most cases linked with better statin responses. As an illustration, individuals with the SLCO1B1 c.388G allele usually achieve more significant LDL, C reductions because the transporter activity is enhanced and the delivery of statins to the site of action is facilitated. Some CYP2C9 genotypes may also affect the response, especially for the statins like fluvastatin that are extensively metabolized by this enzyme. Nonetheless, in comparison with the variation of the transporter gene, the polymorphisms of CYP2C9 only account for a very small fraction of the entire variability in the statin response.[34] Various lines of evidence indicate that multi-gene pharmacogenetic models have a better predictive power than single, variant analyses. A composite genetic profile including SLCO1B1 polymorphisms, CYP3A4/CYP3A5 variants, apolipoprotein E (APOE) genotype, and lifestyle factors was found to account for about 15-20% of the variation in LDL, C response to statin therapy. Although this is a substantial contribution, it also shows that genetic factors cannot be used alone to accurately predict statin response, thus the need to combine genetic and non, genetic factors.[35]

Gene–Gene and Gene–Environment Interactions

The human body reaction to the variation of pharmacogenetics is usually complicated by the fact that multiple genes interact with each other. For example,

individuals who have both reduced function of SLCO1B1 variants and polymorphisms associated with the decrease of CYP3A4 expression may as a result have enormous statin accumulation and a sophisticated menace of toxicity. In contrast, the occurrence of variants that facilitate hepatic uptake and increase metabolic clearance may lead to very fast statin elimination and low drug concentration in the body. Such gene-gene interactions reveal the differences of statin response to which account cannot be given to the existence of single genetic variants only.[36] Non-genetic factors significantly alter statin efficacy and tolerability. Healthy or unhealthy eating habits, physical activity, and general metabolic health have an influence on lipid metabolism and the risk of cardiovascular diseases. Overweight and metabolic syndromes are, in particular, allied with abridged LDL, C response to statin therapy, showing a gene environment interaction whereby genetic predisposition interacts with negative metabolic states. The presence of such diseases as chronic kidney disease, hepatic impairment, and endocrine disorders influences further the pharmacokinetics of statins by changing drug metabolism, protein binding, and transporter expression. Hence, a thorough evaluation of statin response should take into account not only genetic background but also clinical context.[37] Statin response is oftentimes a consequence of the influence of a medication regimen that inhibits or induces metabolic enzymes and transporter processes and is on polypharmacy, especially those patients. As a consequence, individuals with variants of the SLCO1B1 gene with reduced function and who are given CYP3A4 inhibitors such as clarithromycin or ketoconazole may have their statin exposure increased to a very high level and thus be more liable to develop myopathy. This is drug-drug gene interaction, where genetic vulnerability and pharmacological inhibition reinforce each other, to the extreme. The examples of severe rhabdomyolysis caused by statin and interacted drug and genetic case backgrounds make the integration of pharmacogenetic into clinical decision, making most important. Genotyped patients who have risk factors should be closely monitored and, in any case, be given drug substitutes with less interaction potential.[38]

Clinical Applications of Personalized Statin Therapy

Pharmacogenetic testing in the case of statin therapy has been a major focus of interest in the clinic. This is because there have been clear connections made between different genetic variants and how the drug works in the body; also, these genetic variants have been linked to the occurrence of adverse effects. In 2022, the Clinical Pharmacogenetics Implementation Consortium (CPIC) communicated a set of guidelines based on scientific evidence. The guidelines dealt with the impact of changes in the genes SLCO1B1 c.521T>C, ABCG2 c.421C>A, and CYP2C9 on the probability of muscle, related side effects caused by statins. This publication was a significant step forward towards a more organized, evidence, driven approach to using pharmacogenetics in lipid-lowering therapy.[39] At the same time, the Dutch Pharmacogenetics Working Group has issued recommendations that support genotype, informed statin prescribing. However, a few healthcare providers have been reluctant to perform statin pharmacogenetic testing routinely in their clinical practice, which is still a minority, and this is mainly due to concerns about the test's cost, effectiveness, availability, and the small benefit that comes on top of the clinical risk assessment. Currently, most practice of statin pharmacogenetic testing calls for a limited panel that is mainly concerned with SLCO1B1 c.521T>C (rs4149056), SLCO1B1 c.388A>G (rs2306283), ABCG2 c.421C>A (rs2231142), and the CYP2C9 *2 and *3 alleles. A larger testing panel may include variants in CYP3A4, CYP3A5, CYP2C19, and other transporter genes, but the clinical significance of these variants for the determination of statin dose is not very certain. Testing can also be done as a preventive measure before starting statin therapy or as a follow, up in patients who have not been able to tolerate the medication or have not achieved sufficient lipid lowering even though they have been properly dosed. To be sure, these results must be considered together with other clinical factors such as other drugs taken, diseases, prior statin exposure, and the statin used because the genetic variants may function differently for different statins.[40]

Genotype-Based Dose Individualization

Guideline-based recommendations for genotype-directed statin dosing can be most easily seen in the case of SLCO1B1 variants. CPIC guidelines signal out simvastatin as the drug that needs the most careful handling, thus, in patients homozygous for the SLCO1B1 c.521C allele, it is either recommended that the drug be avoided or a maximum daily dose of 20 mg be given, as the risk of myopathy is very high in these cases as compared to a dosing range of 4080 mg that is usually standard. As far as atorvastatin is concerned, CPIC provides a rather different picture where it only talks about possible lower starting doses and monitoring being intensified in the presence of the C allele. The Dutch Pharmacogenetics Working Group has suggested a set of more cautious recommendations for the case of c.521C/C genotype in which atorvastatin dose limitation or use of an alternative statin is indicated. These conflicting recommendations illustrate that the connotation amid SLCO1B1 variants and atorvastatin, induced myopathy is less strong as compared to that between SLCO1B1 variants and simvastatin, although the pharmacokinetic effects are clearly seen.[41]

ABCG2-Based Considerations for Rosuvastatin

According to CPIC guidelines, a person with an ABCG2 c.421C>A variant in rosuvastatin treatment, especially those

Table 1: Pharmacogenetic determinants influencing statin response and safety

This table summarizes the key genetic polymorphisms in drug-metabolizing enzymes and transporter genes that influence statin pharmacokinetics, therapeutic response, and adverse effects. Genetic variants affecting cytochrome P450 (CYP450) enzymes, hepatic uptake transporters, and efflux transporters are presented along with their functional consequences, clinical phenotypes, and implications for personalized statin therapy. (↑ = Increased, ↓ = Decreased).

Category	Gene	Key Polymorphism(s)	Primary Statins Affected	Functional Consequence	Effect on Statin Exposure	Clinical Phenotype	Clinical Implication	References
Drug-Metabolizing Enzymes (CYP450)	CYP3A4	CYP3A4*1B (rs2740574)	Atorvastatin, Simvastatin, Lovastatin	Reduced enzyme expression	↑ Plasma statin levels	↑ LDL-C reduction but ↑ SAMS risk	Lower starting dose; monitor toxicity	11,13,14
	CYP3A5	CYP3A5*3 (rs776746)	Atorvastatin, Simvastatin	Loss of functional enzyme	↓ Metabolic clearance	Variable efficacy; ↑ toxicity risk	Dose individualization recommended	12-14
	CYP2C9	*2 (rs1799853), *3 (rs1057910)	Fluvastatin (major), Rosuvastatin (minor)	Reduced catalytic activity	↑ AUC and half-life	↑ Myopathy risk	Prefer lower dose or alternative statin	15,43
	CYP2C19	*2, *4, *8	Atorvastatin (minor)	Altered metabolic contribution	Variable statin exposure	Poor LDL-C response in some carriers	Limited but emerging relevance	16
Hepatic Uptake Transporters	SLCO1B1 (OATP1B1)	c.521T>C (rs4149056)	Simvastatin, Atorvastatin, Rosuvastatin	Reduced hepatic uptake	↑ Systemic exposure	Strong association with SAMS	Avoid high-dose simvastatin; CPIC-guided dosing	17-19,39,41
	SLCO1B1 (OATP1B1)	c.388A>G (rs2306283)	Atorvastatin	Increased transporter activity	↑ Hepatic drug delivery	Enhanced LDL-C reduction	Favorable responder genotype	21,22
Efflux Transporters (ABC family)	ABCB1 (P-gp)	C3435T (rs1045642)	WAtorvastatin, Simvastatin	Altered intestinal efflux	Variable bioavailability	Inconsistent LDL-C response	Limited standalone clinical value	24,25
	ABCG2 (BCRP)	c.421C>A (rs2231142)	Rosuvastatin (major)	Reduced efflux transport	↑ Plasma rosuvastatin	↑ Myopathy risk	Lower dose recommended (CPIC)	26,28,39,42
Overall Clinical Phenotype	—	Multigene profiles	All statins	Combined PK/PD effects	Marked variability	Responder vs Non-responder	Best prediction with combined genetic + clinical data	33-38

with C/A or A/A genotypes, could be equally or more likely to develop muscle discomfort or pain associated with the statin and therefore, their condition should be regularly checked, or they could be dosed differently or given another type of statin, for example, if there are some additional risk factors present. While doses of rosuvastatin are not so clearly defined as those of simvastatin, conservative dosing is generally recommended for high-risk genotypes. As the frequency of ABCG2 A/A homozygosity is fairly low in most populations, it is expected that a majority of individuals will be heterozygous and thus, standard dosing with proper clinical monitoring may be tolerated by them.[42]

CYP2C9-Guided Fluvastatin Therapy

Fluvastatin among the statins on the market is the one that shows the strongest correlation between its metabolism and CYP2C9. As a result, the genotype, phenotype relationships are very clear. Patients with genotypes CYP2C9 *2/*2 or *2/*3 that indicate a decreased metabolic capacity, have plasma fluvastatin concentrations that are about two to three times higher than those of a wild-type (*1/*1) carrier. In such cases, the guidelines that are currently in use, suggest that the dose may be reduced or that an alternative statin may be selected in directive to subordinate the menace of the attentiveness, reliant side effects, especially when there are additional clinical risk factors for statin intolerance.[43]

CONCLUSION

Inter-individual differences in how well statins work and are tolerated are a major problem in the clinical treatment of Hyperlipidemia and cardiovascular diseases. This paper emphasizes the decisive influence of pharmacogenetic factors that determine the responder and non-responder phenotypes. It focuses mainly on genetic polymorphisms of drug-metabolizing enzymes and membrane transporters. Mutations in genes like **SLCO1B1, ABCG2, CYP3A4,

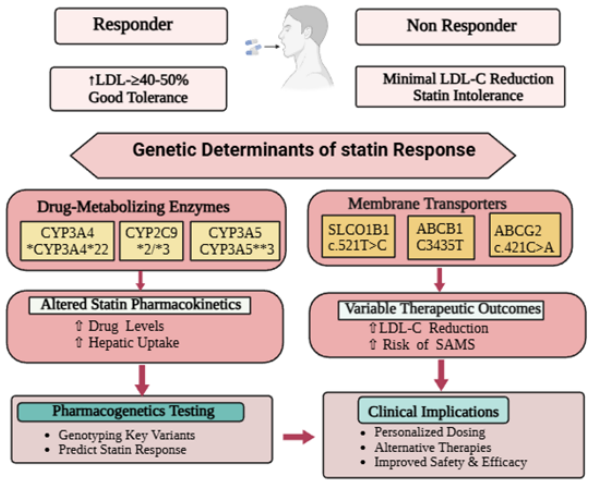

Figure 1: Genetic determinant of responder and non-responder phenotypes in statin therapy.

CYP3A5, and CYP2C9** can have a strong impact on the pharmacokinetics of statins, their systemic exposure, the therapy outcome, and the occurrence of side effects, in particular, statin-associated muscle symptoms. Out of these, the genetic variant **SLCO1B1 c.521T>C** is considered the most significant one, and there is convincing evidence for genotype, guided dosingmainly for simvastatin and, to a lesser degree, atorvastatin. In the same way, the **ABCG2 c.421C>A** is very important for the rosuvastatin elimination, and the **CYP2C9 polymorphisms** are quite relevant for fluvastatin therapy. The presence of drug therapy guidelines grounded on scientific evidence by the **Clinical Pharmacogenetics Implementation Consortium (CPIC)** and other professional organizations is an indicator of the advance level of statin pharmacogenetics and its possible application in real life medicine. Nevertheless, the use pharmacogenetic testing regularly to guide the use of statin therapy is still low. Some of the barriers to this include: a lack of confidence in the cost, the test's efficacy, that a single genetic variant cannot fully predict, and that genetic data need to be combined with clinical factors such as comorbidities, drug interactions, and patient adherence before any definitive conclusion can be drawn. Significantly, new evidence indicates that multigene models, together with clinical and environmental factors, have better predictive power than single genetic markers. To sum up, pharmacogenetic profiling is a potential source of great power to optimize statin selection and dosing, lessen adverse effects, and increase long, term treatment adherence. When genotyping will be more widely available and part of the clinical work, personalized statin therapy will probably be a routine way rather than a special approach of precision cardiovascular medicine. The next step in research should be outcome, based prospective studies, cost, effectiveness analyses, and the creation of clinical decision, support tools that will make the use of pharmacogenetics in guiding statin therapy convenient, accessible, and equitable.

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