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REVIEW

Resistance and intolerance to statins

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Abstract *Background and aims:* Many patients treated with statins are considered statin-resistant because they fail to achieve adequate reduction of low density lipoprotein cholesterol (LDL-C) levels. Some patients are statin-intolerant because they are unable to tolerate statin therapy at all or to tolerate a full therapeutic statin dose because of adverse effects, particularly myopathy and increased activity of liver enzymes.
Results: The resistance to statins has been associated with polymorphisms in the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA-R), P-glycoprotein (Pg-P/ABCB1), breast cancer resistance protein (BCRP/ABCG2), multidrug resistance-associated proteins (MRP1/ABCC1 and MRP2/ABCC2), organic anion transporting polypeptides (OATP), RHOA, Nieman-Pick C1-like1 protein (NPC1L1), farnesoid X receptor (FXR), cholesterol 7alpha-hydroxylase (CYP7A1), Apolipoprotein E (ApoE), proprotein convertase subtilisin/kexin type 9 (PCSK9), low density lipoprotein receptor (LDLR), lipoprotein (a) (LPA), cholesteryl ester transfer protein (CETP), and tumor necrosis factor α (TNF-α) genes. However, currently, there is still not enough evidence to advocate pharmacogenetic testing before initiating statin therapy. Patients with inflammatory states and HIV infection also have diminished LDL-C lowering as a response to statin treatment. Pseudo-resistance due to nonadherence or non-persistence in real-life circumstances is probably the main cause of insufficient LDL-C response to statin treatment.
Conclusions: If a patient is really statin-resistant or statin-intolerant, several other treatment possibilities are nowadays available: ezetimibe alone or in combination with bile acid sequestrants, and possibly in the near future mipomersen, lomitapide, or monoclonal antibodies against PCSK9.

Introduction

Statins are today accepted as the treatment of choice for lowering low density lipoprotein cholesterol (LDL-C) in the vast majority of individuals with increased risk for cardiovascular disease (CVD) and associated mortality. As CVDs are the leading cause of death as well as disease burden worldwide, and almost one-third of adult persons without CVD have dyslipidemia while most of the CVD patients have an increased plasma LDL-C, it is quite comprehensible why the statins are among the most commonly prescribed drugs [1]. They are available on the market for almost three decades and are among the most studied drugs in CVD prevention.

Based upon a number of large-scale randomized clinical trials and meta-analyses, it has been established beyond any doubt that statins reduce CVD morbidity and mortality in secondary prevention [3]. This is also something where both the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidemias and the recently published American College of Cardiology/American Heart

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Association (ACC/AHA) guidelines on the treatment of blood cholesterol agree [2,3]. However, the expanding use of statins in primary prevention, that is, in individuals without documented CVD, still seems to raise some questions. Although their use for primary prevention in high-risk individuals is undoubtedly justified, their use in individuals at low or moderate risk is not so certain and an individualized approach is recommended [4]. Because statins are so broadly used, the issue of statin resistance and intolerance is coming more and more into the focus and is widely discussed, but there are not many hard data on this.

What is statin resistance and what is statin intolerance?

According to the National Library of Medicine – Medical Subject Headings – drug resistance is diminished or failed response of an individual to the intended effectiveness of a drug. It should be differentiated from drug intolerance which is the progressive diminution of the susceptibility of a patient to the effects of a drug, as a result of continued administration, or excess of adverse effects which prevent the patient from further treatment or using the adequate drug doses.

Although the definition of resistance seems to be quite clear, it is very difficult to determine what really statin resistance is. Generally, patients who fail to reach LDL-C target values despite best available therapy, mostly a highest tolerable dose of a more potent statin, are considered to be statin-resistant. It is well known that the reduction of LDL-C in response to statin therapy can vary by as much as 5–70% from person to person, even when compliance is taken into account, with many individuals not reaching LDL-C target values [5,6]. It is also known that LDL-C response can be influenced by many factors, for instance racial ancestry, with attenuated response in blacks compared with whites. The problem is also that there are almost no studies which compared statin-resistant patients with statin nonresistant patients.

Millions of statin-treated patients are considered statin-intolerant because they are unable to tolerate statin therapy at all or, much more often, they may not tolerate a full therapeutic statin dose having adverse effects, mostly myopathy. Again, pinning down a definition for statin intolerance is a big challenge.

Even though the most recent ACC/AHA guidelines http://www.medscape.com/viewarticle/814579 indicate that the evidence is not to set any lipid target value, which is different from the European ESC/EAS guidelines for the management of dyslipidemias published in 2011 and the European guidelines for CVD prevention published in 2012 [2,3,7], setting of lipids target has not at all been eliminated as a way to treat patients with dyslipidemias [8]. This is for sure true in Europe but most probably also in the US, at least it will be so in the near future. Therefore, the problem of resistance as an inability to reach the LDL-C target values is a reality. When discussing these guidelines, in none of them, the term “statin resistance” is mentioned and the term “statin intolerance” does exist but without any further explanation or data concerning this issue.

The aim of this review is to present the available data concerning these intriguing questions of statin resistance and intolerance. Although it is known that in some individuals statins are unable to prevent atherosclerotic changes and reduce clinical outcomes which might also be called “resistance,” for the sake of space, this review will focus only on their effects on LDL-C lowering and not to their effectiveness to reduce the CVD events.

Resistance to statins can be related to differences in drug absorption, drug transport, intrahepatic drug metabolism, drug metabolism within other organs, and finally drug excretion mechanisms. In addition, resistance can occur due to differences in the level of the various target pathways that are unrelated to pharmacokinetics, including HMG-CoA reductase, as well as various points along the cholesterol biosynthesis and lipoprotein metabolic pathways. Only some of them will be discussed more in depth.

The impact of genetic factors on statin resistance

It has been mentioned already that the same dose of the same statin in different individuals produces different LDL-C decreases, but it has been also shown that the time to reach maximum LDL-C decrease differs significantly between individuals [5,6]. Such a wide interindividual variation as the response to statins is more and more attributed, at least partly, to the polymorphisms in genes affecting statin pharmacodynamics and pharmacokinetics. Pharmacogenetics seeks to determine the role of genetic factors in variation of statin response. However, it has to be frankly stated that today the origins of the notable inter-individual variation in response to statins are still poorly understood. In a number of studies, genetic variability has been shown to affect statin responsiveness thus influencing statin resistance and intolerance. These studies have identified numerous candidate genes (>50) and dozens of single-nucleotide polymorphisms (SNPs) that have been reported to be associated with differing aspects of statin response and are related to pharmacokinetics and pharmacodynamics of statins being potential determinants of drug responsiveness in terms of LDL-C lowering (Table 1). Although genes are supposed to be associated with statin cholesterol-lowering efficacy, the magnitude of variation in statin response that could be explained by these associations is still questionable.

The association between SNPs in genes involved in lipid metabolism and total cholesterol and LDL-C response to statin therapy is of particular interest. The 3-hydroxyl-3-methylglutaryl coenzyme A reductase (HMG-CoA-R) gene encoding the enzyme HMG-CoA-R which is the principal target of statins because the foremost pharmacological action of these drugs is exactly the competitive inhibition of HMG-CoA-R, might be one of the candidate genes when analyzing the SNPs as a possible cause of diminished statin responsiveness. When SNPs and the common haplotypes inferred from them were tested for association with plasma LDL-C levels and LDL-C response to statin treatment, it has been shown that HMG-CoA-R gene