Statin Intolerance

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Statin therapy is one of the greatest therapeutic advances in modern medicine. As a consequence of their proven ability to prevent cardiovascular disease and to extend life, statins are among one of the most widely prescribed medications. Although statins are generally extremely well tolerated, statin intolerance occurs in some patients and requires careful consideration. In addition, patients are sometimes concerned about the potential risk of statins causing diabetes mellitus, cancer, and memory loss and often question whether they should continue with their medication. This Cardiology Patient Page aims to assist patients with the overall approach to statin intolerance and to better understand the benefits and risks involved.

What Are the Benefits of Statins?

Statins (eg, atorvastatin [Lipitor], rosuvastatin [Crestor], and simvastatin [Zocor]) are medications that reduce the production of cholesterol in the liver and, as a result, lower cholesterol levels in the bloodstream. By lowering the levels of low-density lipoprotein (LDL) cholesterol (the "bad" cholesterol) in particular, statins reduce the rates of heart attack and stroke and improve long-term survival. Large-scale analyses of more than 170 000 patients have demonstrated that for each 1.0-mmol/L (39-mg/dL) reduction in LDL cholesterol, statins reduce the rates of major adverse cardiovascular events by about a quarter (20% to 25%).[1] Treated patients also live longer. Importantly, the lower the level of LDL cholesterol achieved, the greater the degree of cardiovascular protection.[1] Even in lower-risk patients, the cardiovascular benefits of statins greatly outweigh any real or perceived side effects. For these reasons, clinical practice guidelines throughout the world strongly recommend statins for patients at risk of cardiovascular disease and emphasize the need to use potent statins at doses that have the ability to lower LDL cholesterol by 50%.

What Is Statin Intolerance?

As the name suggests, statin intolerance occurs when a patient is unable to continue to use a statin, either because of the development of a side effect or because of evidence on a blood test that certain markers of liver function or muscle function (creatine kinase) are sufficiently abnormal to cause concern.[2] The intolerance can be either partial (ie, only some statins at some doses) or complete (ie, all statins at any dose).

The most common presentation of statin intolerance is muscle aches, pains, weakness, or cramps, often called myalgias; these can occur in up to 15% of treated patients. In most instances, the symptoms are mild and are rarely associated with muscle inflammation (myositis) and markers of muscle injury (creatine kinase).[2] Importantly, the symptoms are completely reversible shortly after the statin is stopped. Serious muscle damage or rhabdomyolysis associated with statin treatment is extremely rare, for instance, occurring in 1 in 23 million individuals with prescriptions for atorvastatin. Mild to moderate increases in creatine kinase may occasionally be seen in patients taking statins who have no muscle-related side effects, but this should not be grounds to stop statin therapy. It is theorized that some of the muscle side effects may be related to the effects of statins on energy metabolism[2] or that the symptoms are

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attributable to reduced levels of coenzyme Q10 in muscles.

What Are the Risk Factors That Can Cause Statin Intolerance?

Table 1 lists some factors that have been associated with an increased risk of developing statin-related intolerance, primarily myalgias.[2] These factors are either endogenous, that is, intrinsic to the patient, or exogenous, that is, external factors that can amplify the symptoms.

What Are the Other Side Effects of Statins?

Fortunately, statins are generally very well tolerated with a very low risk of serious adverse outcomes. A general issue with side effects of any medication is determining a cause-and-effect relationship. For medications that are as widely used as statins, there can be a tendency to blame the medication when certain symptoms develop, even though these symptoms would have arisen anyway without the patient being on the drug. Rather than relying on anecdotes reported by individual patients, there are careful systematic studies that monitor the development of a wide range of symptoms in matched groups of patients on and off statins. We now have 20-year follow-up data from these types of scientific studies, which indicate no increase in the rate of serious side effects over the long term.

Adverse effects of statin therapy for which there is solid evidence are shown in Table 2. However, numerous other adverse effects that have been anecdotally attributed to statin treatment have no objective evidence to support any cause-and-effect relationship (Table 2). For instance, careful long-term controlled follow-up of 170 000 patients showed that statins had no effect rates of cancer, cerebral hemorrhages ("bleeding" strokes), kidney disease, liver disease, dementia or memory impairment, or fatigue.[2–4] Although biochemical tests for liver function may be outside the normal range in 0.1% to 3% of subjects receiving high doses of a statin, the blood tests soon return to the normal range when the statin is stopped, and permanent liver damage is extremely rare (<1 in 2 million treated subjects).

Recently, statin has been found to be associated with the diagnosis of new-onset diabetes mellitus. However this risk is very small and is almost completed outweighed by the benefits of statins. Treatment of 255 people with statins for 4 years results in 1 additional case of diabetes mellitus. In those 255 individuals, statin treatment over the same time period would have prevented at least 5 serious cardiovascular events such as heart attack and stroke.

What Should I Do if I Am Concerned With Statin Intolerance?

Table 3 highlights the approach and general principles for patients to follow when they face statin intolerance. First, remember that the benefits of statins are large and potentially lifesaving and any risks are small, not life threatening, and reversible. The reduction in fatal and nonfatal heart attack and stroke by statin treatment cannot be achieved with other currently available medications, nutraceuticals, or dietary modifications. Patients, together with their healthcare providers, must weigh the risk of drug discontinuation versus the benefits before making permanent decisions about the management of statin intolerance. Before considering the use of a second-line alternative drug, patients should try statin rechallenge, alternative regimens, doses, or types of statins. In most cases, rechallenge with a statin after a brief period of drug discontinuation ("drug holiday") can be successful. In a study of 11 124 patients in whom statins were discontinued at least temporarily because of clinical events or symptoms believed to have been caused by statin use, 92% of those who were rechallenged were still taking a statin 12 months after the statin-related event.[2,5] Studies to date do not support the use of vitamins and minerals such as coenzyme Q10 supplements to reduce the rates of muscle side effects.[2]

Table 1. Factors Associated With Increased Risk of Statin Intolerance

Endogenous factors or features that are intrinsic to the patient
Advanced age (>80 y)
Female sex
Asian ethnicity
Pre-existing neuromuscular condition
Known history of myopathy or family history of myopathy syndrome
Pre-existing liver disease
Pre-existing kidney disease
Pre-existing untreated hypothyroidism (underactive thyroid)
Certain rare genetic polymorphisms regulating liver cytochrome enzyme pathways
Exogenous factors or factors that are potentially modifiable
High-dose statin therapy
Excessive alcohol intake
Drug interactions (notably the use of gemfibrozil, antipsychotics, amiodarone, verapamil, cyclosporine, macrolide antibiotics, azole antifungals, protease inhibitors)
Excessive exercise
Excessive grapefruit juice intake

Table 2. Potential Adverse Effects of Statins

Adverse effects for which there is good supportive evidence
Myopathy (muscle aches/cramps, myositis, rhabdomyolysis)
Increase in liver function enzymes
New-onset diabetes mellitus
Adverse effects for which there is little or no supportive evidence
Cancer
Intracerebral hemorrhage (bleeding stroke)
Cognitive decline (Alzheimer disease)
Lung disease
Erectile dysfunction
Fatigue, headaches, or dizziness
Psychiatric illness
Cataracts
Rheumatoid arthritis
Gastrointestinal upset, abdominal cramping
Permanent liver or kidney damage

Table 3. How to Manage Statin Intolerance

Make sure there is no reversible cause (see Table 2) such as:
Medication interaction
Hypothyroidism
With mild symptoms, try reducing the dose of statin
With intolerable symptoms, stop the statin
When symptoms resolve, attempt rechallenge:
Low dose of same or different statin
Dose statin intermittently, for instance, 2–3 times a week
Use an alternative statin (eg, fluvastatin or pravastatin) plus ezetimibe or bile acid sequestrant
If symptoms return, use non–statin-based cholesterol-lowering medication such as ezetimibe or bile acid sequestrant (cholestyramine or colesevelam)
Encourage a healthy lifestyle in any event in all patients such as smoking cessation, weight loss, diet low in saturated fat, increased physical activity

Table 4. Second-Line Statin Alternatives

Pharmacological agents currently available
Cholesterol absorption inhibitors (ezetimibe)
Bile acid sequestrants (colesevelam, colestipol, cholestyramine)
Niacin
Fibrates
Pharmacological agents under development
Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors
Cholesterol ester transfer protein (CETP) inhibitors
Nonpharmacological approaches
Reduce intake of saturated and trans fats
Choose monounsaturated and polyunsaturated fats
Portfolio diet or Mediterranean diet
Plant sterols
Red rice yeast
Viscous fiber

The alternatives to statins are listed in Table 4. The available pharmacological agents are associated with only modest reductions in LDL cholesterol, and most of them do not have the same compelling evidence of protection against cardiovascular disease as statins. Among newer agents under development, the injectable proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can reduce LDL cholesterol substantially (by 60% or more) and are likely to become available within the next few years,[6] whereas oral cholesteryl ester transfer protein (CETP) inhibitors reduce LDL cholesterol levels by about 20%.[7] However, these newer agents have not been proven to prevent cardiovascular disease, and their long-term side effects are unknown. Nonpharmacological therapies should be part of every patient's lifestyle, and they become particularly important when a patient is faced with statin intolerance. A diet low in saturated fats, the use of polyunsaturated and monounsaturated fats, specific diets (such as the Portfolio diet or Mediterranean diet), plant sterols, and viscous fiber are all associated with modest reductions in LDL cholesterol[8] and can help to keep the dose of statin low.

Disclosures

Dr Fitchett has received consultation and CME lecture honoraria from Amgen, AstraZeneca, Pfizer, Sanofi, and Valeant. Dr Hegele has received consultation and CME honoraria from Aegerion, Amgen, Sanofi, and Valeant. Dr Verma has received consultation and CME lecture honoraria from AstraZeneca, Merck, Tribute, and Valeant.

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