REVIEW

Statin Intolerance: A Mini Review

Rana Zhafira Amanda,[1] Natasha Anindhia Harsas,[2] Sidhi Laksono Purwowiyoto[2,3]

[1]Urip Sumoharjo Hospital, Bandar Lampung, Indonesia
[2]Pertamina Central Hospital, Jakarta, Indonesia
[3]Faculty of Medicine, Universitas Muhammadiyah Prof Dr Hamka, Tangerang, Indonesia

Corresponding Author: Sidhi Laksono, Faculty of Medicine, Universitas Muhammadiyah Prof Dr Hamka, Jl. Raden Patah No.01, RT.002/RW.006, Parung Serab, Kec. Ciledug, Kota Tangerang, Banten 13460 (sidhilaksono@uhamka.ac.id)

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ABSTRACT

Lipid-lowering therapy is crucial for preventing cardiovascular disease—as primary prevention for individuals at increased risk and secondary for reducing the likelihood of disease progression. Statins have proven to be safe and beneficial lipid-lowering therapies in patients with atherosclerotic disease. However, statin intolerance is widely reported in clinical practice. These potential side effects lead to discontinuation or difficulty managing statins at an appropriate dose for achieving the low-density lipoprotein cholesterol (LDL-C) targets. Therefore, it is essential to distinguish patients at risk of or truly with intolerance to statins and determine the best alternative management for reducing LDL-C (without the side effects of statins).

INTRODUCTION

In a cohort of 105,329 patients—hospitalized for myocardial infarction (MI)—statin intolerance was usually identified a year after starting treatment for the MI. This study also suggests that statin intolerance increases the risk of recurrent MI and coronary heart disease (CHD) with 36% and 43% higher rates, respectively.[1] There is currently no broadly-accepted interpretation of statin intolerance. In practice, however, it is common. As a result, identifying people at risk of or with intolerance to statins and determining the best alternative to lower LDL-C—without the statin side effects—is crucial. In this review, we aim to discuss the current knowledge of statin intolerance, focusing on its mechanism, diagnostic assessment, and therapy.

METHODS

Using Google Scholar, a thorough electronic search was carried out. The search was restricted to English-language publications through 2022. Keywords used were “statin intolerance,” “statin-associated muscular symptoms,” and “cardiovascular disease.” Additionally, a direct search of related journals and reference lists was done.

Reviews, original publications, and case reports were all included in the searches. Using Mendeley software, the articles were organized and maintained. After sorting the search results by title and abstract, we reviewed the complete texts. Articles written in languages other than English or with limited access were excluded.

RESULTS AND DISCUSSION

Definition

In 2015, the International Lipid Expert Panel (ILEP) published a paper proposing a definition of statin intolerance which relied upon four criteria. First, a patient is unable to tolerate a minimum of two statins at the lowest available dose. Second, there are confirmed statin-related adverse effects or abnormal biomarker levels that are clinically meaningful. Third, the symptoms get better or resolve after statin dose reduction or discontinuation. Lastly, the observed changes are not due to predisposing factors like drug interactions, thyroid disorders, vitamin D deficiency, or pre-existing neuromuscular disorders.[2]

A 2022 scientific opinion of the National Lipid Association (NLA) described statin intolerance as one or more side effects—related to the statin—that disappear or improve with dose reduction or discontinuation. To qualify as statin intolerant, a patient should try at least two statins, with one (or more) of them at the lowest-approved, daily dose. The NLA definition also categorizes statin intolerance as complete or partial. This classification relies upon a patient's inability to tolerate a sufficient dose of statins to meet their treatment goals. Partial intolerance is the inability to handle the dose needed for specific therapeutic targets, while in complete intolerance, the patient is not able to take any statin dose.[3,4]

Prevalence

The prevalence of statin-related muscle symptoms varies significantly between studies. The Understanding Statin Use in America and Gaps in Education (USAGE) survey examined statin users' attitudes, views, practices, and actions. It evaluated 10,138 respondents who were either present (n=8918) or past (n=1220) statin users. This survey found that muscle-related side effects occurred in 60% of past and 25% of present statin users. As much as 62% of former statin users identified side effects as the reason for discontinuing therapy.[5]

Documented statin intolerance is less prevalent in randomized controlled trials (RCTs) than in observational studies. A global meta-analysis of 176 studies involving 4,143,517 patients estimated that the global prevalence of statin intolerance is 9.1%. The prevalence was comparable when using the NLA, ILEP, and EAS (European Atherosclerosis Society) criteria (7.0% [6.0-8.0%], 6.7% [5.0-8.0%], and 5.9% [4.0-7.0%], respectively). RCTs may underestimate prevalence by omitting elderly patients and individuals with comorbid conditions—such as chronic liver or kidney disease—and laboratory abnormalities, which may increase the risk of statin intolerance.[3,6]

The Statin Adverse Treatment Experience (STATE) study looked at 1,500 patients with high cholesterol who had taken statins in the previous two years and had at least one statin-related adverse event within the preceding six months. It reviewed their statin use and discontinuation reasons. 332 (22.1%) study participants reported stopping statin therapy because of their inability to tolerate side effects. This issue was the most common reason for treatment discontinuation. Although we cannot use the study data to predict the prevalence of statin intolerance in clinical practice, it supports the idea that the existence of statin-related

adverse events may interfere with continuing therapy.[7]

Risk Factors

Intolerance can be avoided or managed by recognizing at-risk patients and predisposing conditions. Screening for modifiable risk factors for statin intolerance is, thus, necessary when prescribing statins or upon identifying intolerance. Known risk factors for clinically-relevant side effects of statins are in Table 1.[6,8]

Table 1. Risk factors for statin adverse effects [8]

Female gender
Advanced age (>75 years)
Asian and African-American race
Chronic kidney disease
Pre-existing liver disease
Metabolic muscle disorder
Family history of statin intolerance and personal history of intolerance to other statins and lipid-lowering therapies
Abdominal obesity and metabolic syndrome
Vitamin D deficiency
Excessive alcohol intake
Excessive physical activity
Uncontrolled hypothyroidism
Drugs affecting statin metabolism increasing their plasma levels (inhibitors of CYP3A4: macrolides, fluoxetine, verapamil, protease inhibitors, grape fruit juice, etc.; inhibitors of CYP2C9: ketoconazole, fluconazole, fluoxetine, amiodarone, etc.; inhibitors of organic anion transporting peptide 1B1: gemfibrozil)

Age is a key predisposing factor, as it correlates to various comorbidities (renal or hepatic impairment), simultaneous drug use, weight loss, cognitive deficits, and susceptibility to other stressors.[9]

Molecular Mechanism

The exact mechanism of statin myopathy is unknown. As the subject of active research, though, there are several hypotheses. Polymorphisms in the following genes have been correlated with an increased risk of myopathy: solute carrier organic anion transporter family member 1B1 (SLCO1B1), cytochrome P450 isoenzyme, coenzyme Q10, carnitine palmitoyltransferase 2, ATP-binding cassette subfamily B (MDR/TAP)-member 1 (ABCB1), and ATP-binding cassette subfamily G member 2 (ABCG2).[10, 11]

Statin intolerance can result from two mechanisms: increased bioavailability (defects in muscle cell duplication, autoimmune reaction like anti-HMG-CoA reductase antibodies, vitamin D deficiency, and myocyte membrane instability and disruption) and genetic predisposition (mitochondrial dysfunction, reduction in mevalonate pathways products like ubiquitin – coenzyme Q10, modification in gene expression for apoptosis and protein degradation). The following etiologies may be associated with the development of statin myopathy: reduced production of ubiquinone or coenzyme Q10, failure to replace damaged muscle protein via the ubiquitin pathway, reduced sarcolemmal or sarcoplasmic reticular cholesterol, increased uptake of cholesterol or phytosterols, diminished production of prenylated proteins, disruption of calcium metabolism in the skeletal muscle, alterations of fat metabolism and inhibition of selenoprotein synthesis. Furthermore, induction of skeletal muscle fiber apoptosis, mitochondrial dysfunction, and terpenoid depletion may mediate statin-associated myopathy.[11]

The side effects of statins are dose related. Medication use and certain conditions can increase statin levels. Drug interactions are often caused by the induction or inhibition of CYP450 isoenzymes. Statin

clearance might change because of conflicting medication effects. Enzymatic inhibition might elevate plasma levels and increase the possibility of adverse effects. Apart from pravastatin, all statins undergo considerable microsomal metabolism via the cytochrome P450 (CYP) isoenzyme systems. The CYP3A4 isoenzyme is responsible for lovastatin, simvastatin, and atorvastatin metabolism. Similarly, the CYP2C9 enzyme is primarily responsible for metabolizing fluvastatin, with CYP3A4 and CYP2C8 playing a minor role. Although rosuvastatin is only mildly metabolized, it does interact with the CYP2C9 enzyme. Data suggests that simvastatin, and lovastatin have the greatest potential for drug interactions with CYP3A4 inhibitors.[10,12]

Gemfibrozil, notably its glucuronide metabolite, are powerful inhibitors and inactivators of CYP2C8. Despite the two being CYP3A4 substrates, none are inhibitors. Gemfibrozil has been observed to raise the area under the curve (AUC) of simvastatin, lovastatin, and pravastatin in their open acid form, while it has no impact on the AUC of their lactone form. The most likely reason for these interactions is the inhibition of OATP2-mediated hepatic uptake. The membrane transporter OATP1B1 may also play a role in the reported interactions between gemfibrozil and some statins. Because of the likelihood of side effects, gemfibrozil shouldn't be taken with lovastatin, pravastatin, or simvastatin.[12,13]

Fenofibrate and fenofibric acid are mild inhibitors of CYP2C8, CYP2C19, and CYP2A6 and weak to moderate inhibitors of CYP2C9. They do not hinder the activity of CYP3A4, CYP2D6, CYP2E1, or CYP1A2. Combining fenofibrate with statins has not been found to have noteworthy effects on glucuronidation, oxidation, or plasma levels of statins.[13]

Clinical Presentation

Muscle-related statin side effects are the most cited reason for dissatisfaction. In a 2014 article, Rosenson et al. described the spectrum of statin-related muscle effects. It consists of the following conditions (listed in order of increasing severity): myalgia, a condition that causes flu-like symptoms, muscle aches, and cramps; myopathy or muscle weakness; myositis, which is muscle inflammation accompanied by pain and tenderness; myonecrosis, characterized by elevated muscle enzyme levels; and clinical rhabdomyolysis.[14]

In the case of myalgia, muscle pain is commonly bilateral. It affects large proximal muscles and may worsen with exercise. By contrast, cramps typically are unilateral and may impact small muscles of the hands and feet. Myalgias tend to resolve after stopping the statin.[15,16]

Severe muscle damage or rhabdomyolysis is rare, affecting 1 in 23 million people prescribed atorvastatin. Patients using statins may occasionally experience mild to moderate elevations in creatine kinase (CK) without any negative effects on their muscles. These laboratory abnormalities are typically not a reason for discontinuing statins.[15]

A recent statement from the European Atherosclerosis Society (EAS) categorizes all muscle-related complaints as “statin-associated muscular symptoms (SAMS)” and subdivides them by CK elevation. Patients with muscle symptoms—such as myalgia and myopathy with no or minimal CK elevation or evidence of muscle weakness—are classified as SAMS. Statin-associated myotoxicity (SAMT), then, occurs in patients with statin-induced CK elevation that resolves after discontinuation of the drug.[17,18]

Apart from the statin side effects mentioned previously, liver toxicity, peripheral neuropathy, cognitive decline, tendonitis, arthritis, diabetes, insomnia, joint

pain, or cataracts can occur in some cases. It may also be associated with an increased risk of insomnia. In addition, people who are unable to tolerate statins encounter side effects such as hair loss, gastrointestinal upset, joint pain, peripheral neuropathy, pseudo-lupus syndrome, sexual problems, and weight changes.[11]

Diagnosis

Diagnosing statin intolerance is challenging due to the subjective complaints and the absence of a diagnostic test considered to be the "gold standard." A diagnosis of statin intolerance covers a systematic strategy of statin de-escalation and reescalation to assess the cause, establish a diagnosis, and eliminate other possible causes of the adverse effects.[9]

The European Atherosclerosis Society suggested that assessment of SAMS probability should consider the type of muscle manifestations, elevation in creatine kinase (CK) levels, and a relationship between the symptoms and the start of statin therapy, discontinuation of treatment, and reintroduction of the statin.[8,17]

Based on the STOMP trial and the PRIMO survey, the National Lipid Association proposed a symptom scoring system. However, there is still no validated muscle symptom questionnaire. The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI) was proposed by the NLA Statin Muscle Safety Task Committee as a novel technique for assessing if a patient's myalgia or myopathy was brought on by or made worse by a statin. SAMS-CI has several components: the site and patterns of muscle complaints and the timing of symptoms in relation to the onset, discontinuation, and reintroduction of the statin. [15]

An elevated CK level is not a requirement for the diagnosis of SAMS. Monitoring serum CK in individuals taking statin medications is not advised unless symptoms arise. [16]

Management

It is crucial to emphasize the benefits of statins to the patient. In order to prevent premature discontinuation of statin treatment because of muscle symptoms in high-risk patients, one should convey that myopathy is a rare adverse effect (AE) and usually resolves after cessation of the drug. When re-evaluating the rationale for taking statins, the threshold for discontinuation in patients with SAMS is higher for individuals with very high cardiovascular (CV) risk.[8]

The initial step in addressing SAMS patients is to exclude secondary causes of myalgias—for example, hypothyroidism, low vitamin D levels, polymyalgia rheumatic, or a greater level of exercise—and to assess all concurrent drugs that may interact with statins. It is important to check the levels of CK, creatinine, TSH, and vitamin D in the blood. Statin side effects can be predicted by increases in CK levels (defined as more than ten times the Upper Limit of Normal [ULN]) and hepatic transaminases (defined as more than three times the ULN).[19]

The decision to discontinue statins in patients with probable SAMS is based on symptom severity and degree of CK level abnormality. If muscle complaints are: 1) moderate/severe symptoms that interfere with everyday life, then statins should be discontinued, irrespective of CK levels; 2) minor symptoms with mildly increased CK levels (less than four times the ULN), then the statin can be maintained under close observation; 3) minor symptoms and the CK levels are more than four times the ULN without preceding physical exercise, then statins should be discontinued. We must consider the likelihood of rhabdomyolysis if CK levels are more than ten times the ULN. The typical symptoms of rhabdomyolysis include intense muscle pain, generalized weakness, evidence of renal impairment and/or myoglobinuria, and a significant CK

increase (greater than forty times the ULN). Although the incidence of rhabdomyolysis is 1-3 per 100,000 patients per year, it has a 10% fatality rate due to disseminated intravascular coagulation or hyperkalemia-induced arrhythmias.[16]

After stopping the statin, the patient's symptoms and CK level should be reassessed after 4 to 6 weeks. [19] Once the patient is symptom-free and the CK level has returned to normal, reintroduction of a statin should be considered, typically at a lower dose. In most cases, a re-challenge of a statin after a short period of drug discontinuation may be successful.[14,16]

The American Association of Clinical Endocrinology (AACE) suggests several strategies, such as using lower statin dosages and/or less potent statins with a decreased risk of myopathy—along with cautious dose up-titration. It is crucial to inform patients that they should mention muscular symptoms of any severity and discontinue the medicine if they are deemed clinically relevant. These instructions can be given when initiating a statin, increasing the dose, or switching to a different statin type. Once their symptoms subside, the patient can do a trial, incorporating a reduced dose of the same statin, a different statin, or another one with a relatively low lipid solubility (pravastatin, rosuvastatin). Other strategies include decreasing the frequency of use (e.g., one or three times each week) and/or utilizing lipid-lowering nutraceuticals, such as coenzyme Q10, with the addition or replacement of non-statin, lipid-lowering medications as necessary.[8,19,20]

Lipid-lowering nutraceuticals

Healthier lifestyle changes are necessary to lower cholesterol levels and improve other cardiovascular-related risks. For statin-intolerant patients, these options may include foods rich with viscous fiber (oats and barley) and plant sterols, high protein vegetables (soy), and nuts (almonds). A nutritious diet that includes plant sterols and stanols can lower LDL-C levels. Dietary supplements such as CoQ10, vitamin E, and magnesium are often tried. But there is still little data to support their use.[8,10,19]

Moreover, adding nutraceuticals can enhance the effectiveness of these dietary interventions. Nutraceuticals are naturally derived foods that provide health benefits for a medical condition and are generally well-tolerated. Two of the most widely studied foods for cholesterol-lowering therapy are red yeast rice (which contains monacolin K, the active component in lovastatin) and berberine.[21]

Switching therapy

There is no consensus on the standards for choosing a new statin when switching therapies. Common choices include changing from: a mild to highly lipophilic statin, a cytochrome P450 metabolized to a non-cytochrome P450 metabolized statin, and to a smaller dose of a more effective statin. Pilot research suggests that rosuvastatin (a novel and potent non-cytochrome P450 metabolized statin) at 5 and 10mg was well-tolerated, safe, and potent for patients with high LDL-C and intolerance to another statin. Meanwhile, a study by Alexandra et al. did not demonstrate that hydrophilic statins had a lower incidence of muscle events, in contrast to lipophilic statins at the same lipid-lowering doses.[19,22,23]

Adjusting Dose

For people who cannot handle daily statins, alternating days or twice-a-week dosing is a good alternative. Statins with a longer half-life (rosuvastatin and atorvastatin) have a long-lasting, lipid-lowering effect, which allows for alternate-day dosing strategies. Various studies have demonstrated that administration of rosuvastatin one or two times a week in patients with a history of

adverse effects results in a moderate LDL-C decrease (up to 26%). It is acceptable in greater than 70% of patients.[16,19]

Patients are re-evaluated after 4 to 6 weeks. If the new regimen is well-tolerated, the dose will be increased gradually to reach LDL-C targets with little to no muscle discomfort. However, this approach has drawbacks. There is a smaller LDL-C decrease (up to 10-15% less) than the daily dosage regimen. Moreover, clinical trials have not supported this method. Therefore, the alternate-day method should only be utilized as a backup plan in certain high-risk patients who cannot tolerate lower statin doses.[19]

Non-statin lipid-lowering drugs

Based on the Endocrine Society guidelines, non-statin, lipid-lowering medications are recommended as a single therapy or adjunct to the highest-tolerated statin dose to achieve LDL-C targets. The initial choice is to incorporate ezetimibe (an intestinal cholesterol absorption inhibitor) and a low-dose statin or ezetimibe monotherapy. A daily dose of 10mg of ezetimibe decreases LDL-C by 15-20% and doesn't seem to cause any muscle discomfort. If ezetimibe is insufficient for meeting LDL-C goals, adding fibrates or resins is an option. When ezetimibe and bile acid sequestrants are taken together, LDL-C levels are further lowered without any negative side effects—in comparison to monotherapy of bile acid sequestrants.[8,19,24,25]

Co-administration of ezetimibe and an injectable proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has additional effects. PCSK9 inhibitors are effective at lowering LDL-C levels. It has also been noted that PCSK9 inhibitors reduce lipoprotein (a) (Lp(a)) levels, although the exact mechanism is unknown. Alirocumab and evolocumab, two monoclonal PCSK-9 antibodies, can be given subcutaneously (every two weeks or once a month) with either a statin or a statin with ezetimibe. These medications stop the degradation of the liver's LDL receptors caused by PCSK9, a proprotein convertase. They are prescribed as an adjuvant to diet, alone or in combination with other lipid-lowering drugs. Large RCTs have demonstrated that PCSK9 inhibitors' adverse effects are mild and generally well tolerated. [24-26]

A systematic review of ten papers concluded that adding PCSK9 inhibitors to baseline treatments for selected high-risk patients significantly reduced overall CV morbidity and mortality following acute coronary syndrome (ACS). Several studies have also demonstrated the medications' short-term safety for achieving low LDL-C levels. However, additional research is required to evaluate long-term safety. The use of these medications though—even when given to patients at very high risk—would be inefficient financially, according to numerous modeling studies. Cost is still a major factor in PCSK9 inhibitor use.[26,27]

In addition, the United States Food and Drug Administration (FDA) authorized bempedoic acid in 2020 for patients with heterozygous familial hypercholesterolemia (FH) or established atherosclerotic cardiovascular disease (ASCVD) who need further reduction in LDL-C beyond diet and maximally-tolerated statin therapy. Investigations are being conducted to establish whether bempedoic acid has any impact on CV morbidity and mortality.[24,25]

The available non-statin pharmacological agents are mostly associated with moderate reductions in LDL cholesterol. Moreover, the majority of them do not have the same evidence of cardiovascular disease protection as statins, and the long-term side effects are still unknown.[14]

CONCLUSION

Due to their cardioprotective effect, statins have become a vital medication for treatment of atherosclerotic vascular disease. However, some patients encounter intolerance to statins. The most frequently reported symptoms are muscle-related. While diagnosing statin intolerance is a complex process, it is a necessary step for avoiding early discontinuation. Further, lifestyle changes are essential and provide benefits for patients with statin intolerance. Other strategies like switching statin therapy and adjusting doses are used to address the side effects. There is ongoing research about managing statin intolerance. Besides ezetimibe, novel drugs such as PCSK9 inhibitors and bempedoic acid are currently being studied as an alternative for patients with complete statin intolerance.

Notes
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