Review Article

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Adverse effects of statin therapy and their treatment

Dae Young Cheon[1], Sang-Ho Jo[2]

[1]*Division of Cardiology, Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Dongtan, Korea*
[2]*Division of Cardiology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea*

Statins are one of the most widely used drugs worldwide as first-line drugs for the treatment of hyperlipidemia and the prevention and treatment of cardiovascular diseases. Most of the side effects of statins are known to be mild, and mainly hepatotoxicity and various muscle symptoms are known. Recently, there have been studies on concerns about an increase in the incidence of diabetes after using statins, but it was found that the benefits sufficiently outweigh the risk of side effects. Therefore, the use of statins in the appropriate group should be actively performed, and it seems that the side effects can be prevented through close physical observation and appropriate examination.

Keywords: Statin; Adverse effects; Dyslipidemia; Myalgia; Diabetes mellitus

INTRODUCTION

Statins are a mainstay of therapy for reducing low-density lipoprotein cholesterol levels to prevent cardiovascular events and mortality; therefore, statins are one of the most commonly used classes of drugs worldwide [1–3]. Nonetheless, various side effects, such as hepatotoxicity, muscle disease, acute renal failure, cataracts, and an increased risk of diabetes mellitus, have been reported [4–11]. In this review, we cover the common and important side effects of statins and their management based on the fourth edition of the Korean guidelines for the management of dyslipidemia, which were revised in 2020 [12–14], European guidelines released in 2019 (European Society of Cardiology [ESC] and European Atherosclerosis Society [EAS]) [8,15], United States guidelines released in 2018 (American College of Cardiology [ACC]/American Heart Association [AHA]) [16,17], and Japanese guidelines released in 2019 (Japan Atherosclerosis Society [JAS]) [18,19]. We also compare and summarize those guidelines.

HEPATIC DYSFUNCTION

Hepatotoxicity by statins is usually defined as an increase in alanine aminotransferase (ALT) to 2–3 times higher than the upper normal limit or more than a twofold increase in conjugated bilirubin [20]. A higher dose increases the risk of liver function deterioration, and it is known that statin-induced liver toxicity usually occurs in the first year of statin use [21]. This type of liver injury has no symptoms, represents a temporary increase in liver enzyme levels, and usually improves on its own regardless of drug interruption. Furthermore, it does not cause histological changes in the liver, and it therefore does not fall into the category of actual liver damage. The exact mechanism is not well known, but it is most likely involves an idiosyncratic drug-induced liver

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Correspondence to Sang-Ho Jo, MD
Division of Cardiology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, 22 Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang 14068, Korea. E-mail: sophi5neo@gmail.com

injury or immune-allergic reaction [22].

Clinically meaningful liver toxicity is extremely rare [16]. If ALT continues to rise to more than ten times higher than the upper normal limit, it may be associated with other diseases or interactions with other drugs metabolized via the liver. This is important because statins are mainly metabolized in the liver. Therefore, it is necessary to investigate the possible presence of another medical disease, other medications used, and other possible causes of liver toxicity. Acute liver failure caused by statins is extremely rare, with an incidence rate of 1/114,000 patient-years, similar to the incidence of idiopathic acute liver failure in the general population [23]. The elevation in ALT usually improves naturally because adaptation or tolerance is believed to occur. However, if the ALT level rises to ten times the upper normal limit, most guidelines recommend discontinuing the statin.

Previous guidelines in Korea recommended conducting liver function tests before administering statins and at 6 and 12 weeks after the start of administration, but the recently revised guidelines suggest that measurements can be considered between 4 and 12 weeks. According to the ESC and EAS guidelines, routine liver function tests are not necessary. The ACC/AHA guidelines state that if patients have symptoms suggesting hepatotoxicity, liver enzyme testing is required, including total bilirubin and alkaline phosphatase. In Japan, ALT and total bilirubin levels are recom-

Table 1. Comparison of four guidelines on statin-induced hepatotoxicity and myopathy

	Korea (KSoLA)	Japan (JAS)	United States (ACC/AHA)	Europe (ESC/EAS)
Revised year	2018	2019	2018	2019
Detect of hepatotoxicity	Pretreatment Consider at 4–12 weeks (not routinely)	Pretreatment At 4 weeks (ALT + T.bil)	Pretreatment Consider if symptoms are present (AST+ALT, not routinely)	Pretreatment At 8–12 weeks
Definition of hepatotoxicity	ALT ≥ 3× UNL, two times	ALT > 3× UNL or T.bil > 2× UNL	ALT ≥ 3× UNL	ALT ≥ 3× UNL
Coping with hepatotoxicity	ALT ≥ 3× UNL → Recheck → ALT ≥ 3× UNL, stop	ALT > 3× UNL and T.bil > 2× UNL → Stop ALT ≤ 3× UNL or T.bil ≤ 2× UNL → Consider stop ALT ≤ 3× UNL and T.bil ≤ 2× UNL → Recheck at 2–4 weeks	ALT ≥ 3× UNL → Dose reduction or alternative statins	ALT ≥ 3× UNL → Stop → Recheck at 4–6 weeks ALT < 3× UNL → Continue
Detect of myopathy	Pretreatment Consider if symptoms are present (not routinely)	Pretreatment At 4 weeks	Identify predisposing factors Consider if symptoms are present (not routinely)	Pretreatment Consider if symptoms are present (not routinely)
Coping with myopathy	CK ≥ 10× UNL → Stop 4× UNL ≤ CK < 10× UNL → Stop, monitor CK < 4× UNL → Restart after 2–4 weeks	CK ≥ 10× UNL and symptoms → Stop, refer to specialist CK ≥ 10× UNL and no symptoms → Stop, recheck at 4-6 weeks 4× UNL ≤ CK < 10× UNL and symptoms → Stop, recheck at 4-6 weeks 4× UNL ≤ CK < 10× UNL and no symptoms → Continue, recheck at 2–4 weeks CK < 4× UNL and symptoms → Continue, recheck at 2–4 weeks CK < 4× UNL and no symptoms → Continue	Not specifically mentioned → Statin discontinuation until symptoms improve → Rechallenge with a reduced dose, alternative agent, or alternative dosing regimen	CK ≥ 10× UNL → Stop, check every 2 weeks CK < 10× UNL and symptoms → Stop, monitor CK < 10× UNL and no symptoms → Continue, check every 2 weeks CK < 4× UNL → Continue, if symptoms occur, monitor CK regularly

KSoLA, Korean Society of Lipid and Atherosclerosis; JAS, Japan Atherosclerosis Society; ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; EAS, European Atherosclerosis Society; ALT, alanine aminotransferase; T.bil, total bilirubin; AST, aspartate aminotransferase; UNL, upper normal limit; CK, creatinine kinase.bin.

mended to be measured at 4 weeks. According to the Korean guidelines, if the ALT level rises more than three times, and if it is still elevated after re-measurement, the cause is to be examined after stopping the statin. In the United States, if the ALT level increases more than three times, it is recommended to change the drug or reduce the dose without stopping the statin immediately, and in Europe, it is recommended to check liver enzyme levels again after stopping the statin for 4 to 6 weeks. In Japan, total bilirubin is included in the diagnostic criteria, and if both levels are elevated, stopping the drug is considered, while if only one is elevated, both are to be re-measured after 2 to 4 weeks to decide whether to stop the statin (Table 1) [8,12–19].

MYOPATHY

Statin-induced myopathy, also known as statin-associated muscle symptoms, is the most common complication of statins and is usually the most important reason for their discontinuation [24]. Myopathy has a wide variety of patterns, ranging from minor muscle pain to rare but life-threatening rhabdomyolysis. Most cases of statin-induced myopathy appear as muscle enzyme elevation without symptoms, or as bilateral muscle pain involving a proximal muscle such as the thigh. Twenty-five percent of patients complain of whole-body pain. The muscle pain patterns are non-specific and diverse, involve intermittent complaints of pain, and last for several different periods [25]. Most studies have reported that side effects occur after 1 to 12 months of use, and disappear within about 2 months of discontinuation of the drug. The risk factors for muscle side effects are old age and intense physical exercise, with the concomitant intake of various drugs. It has been reported that no difference exists in the risk for myopathy among statins. The rhabdomyolysis risk is high when creatine kinase (CK) is more than ten times the normal value with high doses [26].

The predisposing factors are known to include age, female sex, a low body mass index, Asian descent, excess alcohol consumption, high levels of physical activity, and trauma. The drug interactions of statins are also associated with myopathy. Since simvastatin, lovastatin, and atorvastatin are metabolized by cytochrome P450 3A4 (CYP3A4), drugs that suppress CYP3A4, such as cyclosporin A or protease inhibitors, can increase the serum concentration of statins and consequently cause rhabdomyolysis. In cases of mixed dyslipidemia, gemfibrozil or fenofibrate can be additionally used. Gemfibrozil can double the serum concentration of statins and is reported to be associated with a 15-fold higher risk of rhabdomyolysis than fenofibrate; therefore, it is recommended to use fenofibrate as add-on therapy. Pravastatin is excreted by the kidneys, while fluvastatin and rosuvastatin are metabolized by another pathway within the liver (CYP4502C9); therefore, these drugs are relatively safe from the standpoint of drug interactions and can be an alternative if the dose of statin should be sustained [27].

In order to check the side effect of statins on muscle, all four guidelines recommend testing basal CK levels before prescribing a statin. After starting a statin, only the Japanese guidelines recommend performing routine tests of CK levels at the fourth week, while all other guidelines recommend testing only if symptoms occur. The ACC/AHA guidelines from the United States recommend measuring CK levels in individuals with severe statin-associated muscle symptoms or objective muscle weakness [8,12–19].

The criteria of severe myopathy are simply defined as a CK increase to ten times or more than upper normal limit along with symptoms. Most myopathy patients have 3 to 10 times higher serum levels of CK than normal. In the Korean guidelines, regardless of symptoms, the CK level is regarded as the most important criterion. If the CK level is ten times higher than the upper normal limit or more than 10,000 IU/L, statins have to be immediately stopped. If the CK level is 4 to 10 times higher than the normal limit, the drug should be stopped, but can be used again if necessary while monitoring the CK level. If CK levels decrease to under four times the upper normal limit, it is possible to restart the drug about 2 to 4 weeks after stopping. The ACC/AHA guidelines describe that objective muscle weakness (myopathy) and an associated significant increase in CK levels (myositis) are rare but recommend prompt statin cessation. However, if the symptoms are not severe and tolerable, they recommend reassessing and conducting a statin rechallenge. In other words, these guidelines state that symptoms are the main criteria for statin cessation regardless of the CK level. After that, the ACC/AHA guidelines recommend measuring and monitoring CK levels and symptoms every week. If either of them worsens, statin should be stopped for a while or be reduced in dose until symptoms improve. In the European ESC/EAS guidelines, the CK limit is stricter (four times

the upper normal limit). If the CK level is four times or more higher than the upper normal limit with symptoms, statins have to be stopped for 6 weeks. If it rises to less than four times the normal upper limit with accompanying symptoms, the drug must be stopped for 2 to 4 weeks. However, if the CK level rises to less than ten times the upper normal level with no symptoms, statins can be continued and CK levels should be monitored every 2 weeks. According to the Japanese guidelines, if the CK level increases to more than ten times the upper normal limit with muscle-related symptoms, the statin should be stopped and the patient should be referred to a specialist. If the CK level rises to more than ten times the upper normal limit with no symptoms or to four to ten times the upper normal limit accompanied with symptoms, it is recommended to stop the drug for 4 to 6 weeks. If there are symptoms, but the CK level rises to less than four times the upper normal limit, or if the CK level rises to four to ten times the upper normal limit with no symptoms, the guidelines recommend continuing to take statins with appropriate follow-up (Table 1) [8,12–19].

Most of the guidelines present the same recommendations for restarting statins, stating that patients should start at a low dose or start with an alternative statin, and that symptoms and CK levels should be monitored more frequently after the CK level normalizes. Once the CK level normalizes, any other statin can usually be tried at a small dose, and there will generally be no side effects in 40% of cases. Some guidelines recommend taking the drug only once or twice a week. Fluvastatin alone or statin plus ezetimibe combination therapy is considered more useful than lovastatin, simvastatin, or atorvastatin if there is an intolerance due to previous statin-induced myopathy symptoms [28]. In addition, considering that muscle disease occurs due to drug interactions, especially at high doses, rosuvastatin (which is metabolized through the CYP2C9 pathway) may be an alternative [29].

DIABETES

Meta-analyses of prospective randomized clinical studies have reported that statin use can increase the risk of diabetes by 9% to 13%, and higher doses increase the risk of developing diabetes [30,31]. No significant differences in the risk of diabetes by statin type were found in meta-analyses that synthesized the results of prospective randomized clinical studies, although some studies showed contradictory results [32–35]. Nonetheless, it is appropriate to interpret these findings as indicating that all statins have a class effect [36]. Because statins have much greater efficacy for preventing cardiovascular events and deaths than their risk of new-onset diabetes, most guidelines recommend maintaining statin use if the benefits outweigh the risk [8,12–19]. The risk factors of developing diabetes are high-intensity statin use, high basal fasting blood glucose and triglyceride levels, body mass index, diuretic administration, metabolic syndrome, hypertension, and old age. It is necessary to emphasize aspects of lifestyle management such as diet control and exercise by identifying high-risk individuals for diabetes development after statin administration. If patients are in a high-risk group or have arteriosclerotic cardiovascular disease, it is necessary to prescribe high-intensity statin treatment without hesitation. This is because the effect of reducing cardiovascular events is more than three times greater than the risk of statin-induced diabetes, and the clinical prognosis of patients who develop diabetes during statin administration is not significantly different from that of patients without diabetes [31].

CONCLUSIONS

Elevated levels of liver and muscle enzymes, the most common side effects associated with the use of statins, are sometimes detected by blood tests or when patients complain of symptoms. However, if the elevation is not very high, statin use can be continued and the elevated enzyme levels usually normalize on their own. Fatal rhabdomyolysis or liver failure is very rare and unpredictable, but drug interactions should be minimized and the possibility of occurrence should be kept in mind by reducing the number of concomitant drugs in elderly patients. New-onset diabetes is generally considered to be a side effect of all statins, but the benefit of statins in reducing cardiovascular events is generally greater than their adverse effects. Thus, statin use should be continued if it is indicated. In conclusion, although statins have limitations in terms of their adverse effects, these adverse effects are generally of minimal clinical significance and can be avoided by taking appropriate precautions. Clinicians should pay appropriate attention to these side effects when prescribing statins. We do not need to hesitate using statins due to fear of these adverse effects,

because the benefits generally outweigh the risks.

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ORCID
Dae Young Cheon, https://orcid.org/0000-0001-6713-4300
Sang-Ho Jo, https://orcid.org/0000-0002-2063-1542

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