Chapter

Reviews on Statin-Associated Side Effects

Qiutong Wu, Lu Fang, Yujie Zhu and Lemin Zheng

Abstract

Statins are a class of drugs widely used worldwide to manage hypercholesterolemia and prevent secondary heart attacks. They have an important role in reducing morbidity and mortality in patients with cardiovascular disease. Due to their wide range of biological effects, some potential therapeutic effects of statins have also attracted increasing attention, such as the treatment of multiple sclerosis, systemic lupus erythematosus, Alzheimer's disease, and chronic liver disease. However, a major problem with these kinds of applications is that long-term use of statins also has certain adverse reactions. These adverse effects include liver injury, myopathy, new-onset type 2 diabetes, renal dysfunction, interstitial lung disease, and other reactions. This article mainly reviews the adverse reactions of statins in clinics, aiming to provide a reference for the clinical application of these drugs.

Keywords: statins, side effects, serum cholesterol, adverse reactions, LDL

1. Introduction

Statins are a class of widely used oral lipid-lowering drugs in clinical practice. At present, in terms of their pharmacokinetic and pharmacodynamic profiles, available statins show various characteristics. Despite the primary target of statins serving as the inhibition of HMG-CoA reductase (HMGR), the rate-limiting enzyme in cholesterol biosynthesis, many pleiotropic effects can be easily found in statins in the downstream of the mevalonate pathway. Although these pleiotropic effects of statins may be a cause for enthusiasm, there are many adverse effects that, for the most part, are unappreciated and need to be highlighted. These adverse effects may be relatively uncommon, considering the number of people worldwide who use statins daily, and the actual number of people affected becomes quite large. In this overview, we mainly focus on the potential adverse effects of statins (**Figure 1**).

2. Adverse events of statins

Even though statins are prominently used in treating hypercholesterolemia and boast lots of pleiotropic effects, they also bear plenty of dose-dependent adverse effects. Therefore, it needs to be treated with caution when extensively utilized.

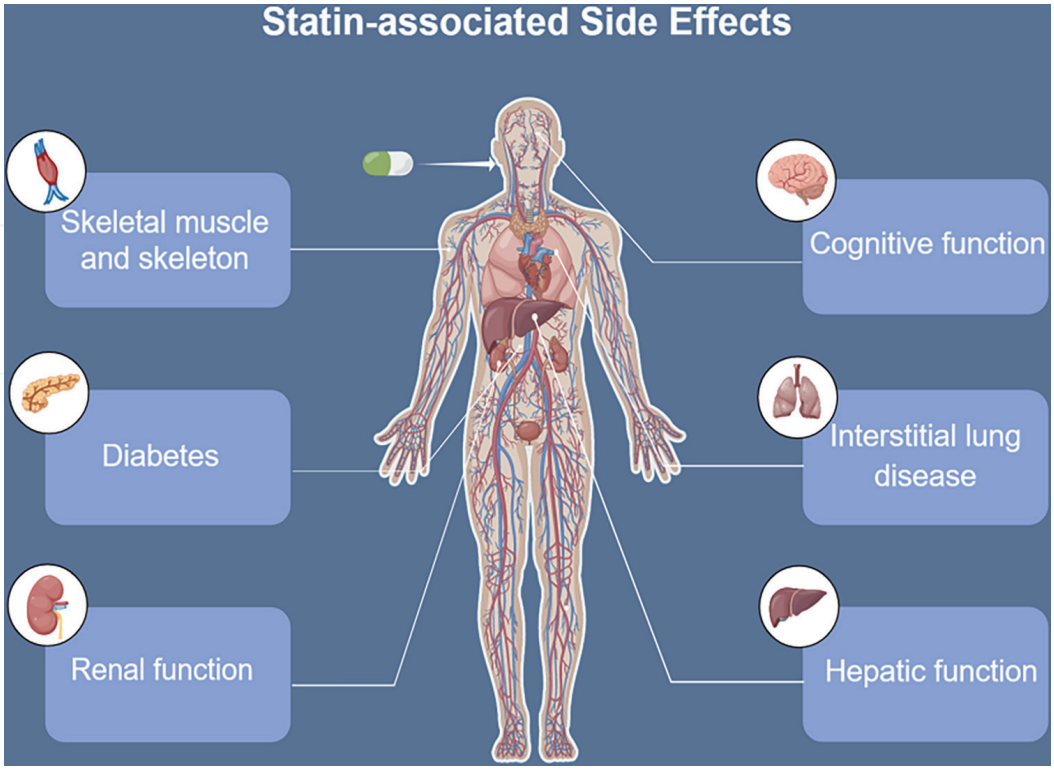

Figure 1.
Statin-associated side effects mainly include liver injury, skeletal muscle impairment, new-onset diabetes, cognitive function, renal dysfunction, and interstitial lung disease.

Statin-associated liver injury, muscle symptoms, new-onset type 2 diabetes, cognitive and renal dysfunctions, interstitial lung disease, and other reactions are among them. We aim to underscore these potential effects, some of which can be life-threatening.

2.1 Liver injury

In early clinical trials, the elevation of aminotransferase levels caused by the use of statins raised concerns about statin hepatotoxicity, which severely limited the clinical application of statins. There is no distinction between statin type and the incidence of transaminitis. Transaminitis may be related to changes in the hepatocyte membrane. When the lipid concentration of the hepatocyte membrane decreases, the cellular membrane subsequently becomes more permeable and allows lipophilic enzymes to leak [1].

The use of statins can also be associated with rare but severe liver injury and even sometimes severe hepatotoxicity. After recovery, similar symptoms of liver injury may recur in re-episodes. Liver injury develops in most patients 3–4 months after treatment. The statins, such as atorvastatin and simvastatin, are most commonly tied in with drug-induced liver injury (DILI). And only the liver damage caused by atorvastatin and simvastatin among statins has been linked to a catastrophic outcome. That is probably because these are the most utilized statins. Atorvastatin-associated liver injury has decreased biliary flow from the liver to the duodenum, whereas simvastatin has been associated with hepatocellular injury [2]. The likelihood of statin-induced hepatotoxicity may probably rise if the other hepatotoxic substances, such as alcohol, calcium channel blockers, and fibrates, are used in combination

with statin therapy [3]. Although liver injury can occur in patients treated with statins, actually this is rare [4]. In addition, there is evidence that specific liver injury caused by statins is dose-independent and is not more common in patients with liver disease than in other patients [5]. Whether statins can cause specific drug-induced liver injury in patients with chronic liver disease is not clear and still needs further research [5]. Patients, even though with potential liver pathology, are also supposed to be treated with statins as long as they have a solid indication. That is because many of these patients have a higher risk of cardiovascular death than those with liver disease [4].

2.2 Skeletal muscle impairment

Approximately 10–15% of patients experience different degrees of adverse reactions, such as myalgia, after taking statins. Muscle pain often causes patients to stop taking statins, which is known as statin intolerance. Myopathy, including myalgia, is a common dose-dependent side effect associated with statins. It is characterized by stiffness, cramps, weakness, or loss of strength during exertion [6]. The muscular toxicity of statins is manifested as muscle pain and aching (myalgia), myositis, and rhabdomyolysis, depending on the presenting symptoms and levels of creatine kinase (CK) [7].

Myopathy is defined as symptomatic muscle pain in which CK is elevated to greater than four times the upper limit of normal value (ULN), while severe myopathy is classified as muscle symptoms with CK between 10 and 50 times ULN [8]. There are no validated tests or clinical criteria, except for increases in CK, but CK increases are absent in most myalgia patients. Statin-associated muscle symptoms (SAMSs) can occur without creatine kinase (CK) elevations, and this is the most frequent SAMS presentation. Therefore, the diagnosis of SAMS is difficult and only based on clinical criteria.

Additionally, myalgia may be associated with statin treatment, which could be linked to reduced coenzyme Q10 (CoQ10) in skeletal muscle and impaired mitochondrial function. In the mitochondria, CoQ10 is an essential electron carrier in the electron transfer system. Therefore, a lack of muscle CoQ10 may impair the function of mitochondrial respiratory chain and increase the production of reactive oxygen species (ROS) [9]. Previous studies have found that mitochondrial respiratory dysfunction and increased ROS production are related with nociceptor activation and pain [10]. Therefore, although not supported by the literature, the link between statins, low levels of muscle CoQ10, mitochondrial dysfunction, and myalgia is biologically probable. Study found no differences in muscle CoQ10 levels or mitochondrial function in statin users with or without myalgia. Individual variations in muscle CoQ10 levels were not associated with variations in myalgia intensity in statin users with mild-to-moderate myalgia. Further studies are warranted to create methods to alleviate myalgia for statin users [11].

Recently, a study identified that in statin-treated human and rat, statin leads to the fact that the FK506-binding protein (FKBP12) dissociates from the ryanodine receptor 1 (RYR1) in skeletal muscle. This relates to increased unwarranted calcium release sparks. Nevertheless, despite the calcium sparks relating to upregulation of pro-apoptotic signaling markers (caspase-3 and the proportion of TUNEL positive nuclei), statins had no influence on muscle force production. So other factors are likely required for myotoxicity. And moderate exercise may mitigate the effects of statins on skeletal muscle [12].

Clinically important muscle symptoms, including rhabdomyolysis and statin-induced necrotizing autoimmune myopathy (SINAM), are rare. Particularly, rhabdomyolysis is the most feared complication of statin use. The risk of statin-induced rhabdomyolysis increases with age, administration of interacting drugs (e.g., fibrinolytic drugs), and hypothyroidism. The current incidence of rhabdomyolysis is approximately one case per 10,000 person-years [13]. Rhabdomyolysis is also associated with renal failure and a high mortality rate reported as 0.3 per 100,000 person-years [8].

2.3 New-onset diabetes

The first indication that statins may precipitate new-onset diabetes was reported in 2008 (JUPITER study), when the beneficial effects of rosuvastatin were evaluated in people with elevated high-sensitivity C-reactive protein (hs-CRP) levels but without hyperlipidemia [14]. This study indicated that rosuvastatin did not cause a significant increase in myopathy or cancer but did cause a higher incidence of diabetes, possibly because inclusion required elevated hs-CRP, a marker for insulin resistance.

Stains, especially lipophilic stains, can raise blood glucose levels and cause diabetes through a variety of potential mechanisms, such as inhibiting the synthesis of ATP and coenzyme Q10, increasing the uptake of plasma-derived LDL-C, decreasing the expression of glucose transporter 4 and the L-type calcium channel, and causing β-cell inflammation, oxidation, and apoptosis. However, the exact mechanism by which statins increase the risk of diabetes is unclear. It has been suggested that the inhibition of HMGCoAR may be a key mechanism for the increased risk of diabetes induced by statins [15].

Although statin does have an association with an increased risk of type 2 diabetes, not all statins display this effect. However, based on the current evidence, the cardiovascular protective benefits of statins still outweigh this risk, and it is necessary to strengthen the prevention and treatment of diabetes. Blood glucose should be monitored and adjusted in a timely manner when statins are used in clinics.

2.4 Cognitive function

It is unclear whether statins affect cognitive function in a positive or negative manner. Although there is evidence supporting the neuroprotective effects of statins, there are also reports suggesting that statins may adversely affect cognitive function [16]. Several epidemiological studies and meta-analyses reported a lower risk of dementia in statin users. Other studies also documented the reversible cognitive impairment, manifesting in restlessness, mental confusion, and short-term memory loss after beginning statin therapy or increasing the dosage [17, 18].

Poor cognitive performance has also been correlated with decreased serum cholesterol [18]. Higher doses of lipophilic statins, which can successfully pass the blood–brain barrier (BBB) and lower cholesterol levels in the central nervous system (CNS), are thought to cause negative consequences when exposed to the CNS [1]. In this context, cholesterol has many important functions in the brain, including myelin sheath formation, neuron signaling processes, and mitochondrial function [19]. In perspective, the FDA has put a neurological side effect warning label on statins due to the possibility of increased dementia, mild cognitive impairment, or cognitive performance decline [20]. However, several systematic reviews have shown that the effects

of statins on cognitive dysfunction are negligible [21]. Thus, the cognitive effects of statins have not been fully elucidated.

2.5 Renal function

In patients with chronic kidney disease (CKD), statins have generally been universally acknowledged for their renal protective functions. So they are strongly recommended for non-dialysis patients in stage 3 CKD [22]. A network meta-analysis of 43 randomized controlled trials (RCTs) revealed that statins slowed the progressive decline of estimated glomerular filtration rate (eGFR) and reduced proteinuria in CKD patients [22]. Although statins generally have a positive effect on renal function in these patients, there still exist some adverse effects concerning the kidneys that require special attention. Since myoglobin is released from muscle tissues, renal failure can be typically induced by rhabdomyolysis, one statin-associated muscle symptoms mentioned above. Myoglobin can then lead to renal dysfunction through inducting renal vasoconstriction, intratubular cast formation, and tubular cell toxic effects mediated by ROS [23]. This adverse effect, however, is exceedingly uncommon in the general population. There is also an increased risk of hospital admission in patients with acute kidney injury taking high-intensity statins compared with low-intensity statins [24], with the strongest effect observed within the first 4 months of starting statin therapy [25]. This suggests a dose-dependent injury of statin therapy on renal function. There are also reports indicating that kidney damage caused by statins may inhibit receptor-mediated endocytosis, hinder the reabsorption of protein by the proximal tubule, and lead to proteinuria [26]. Although there is a report that the relative hazard ratio for acute kidney injury in patients using statins for more than 1 year versus nonusers was 1.5 [25], clinical studies such as CARE debunked this notion. In reviewing the previous literature, no strong enough evidence-based medical evidence was found that statins affect the kidney and urinary system by inducing proteinuria. Overall, available studies do not suggest that statins deleteriously affect renal function.

2.6 Interstitial lung disease

The first case of interstitial lung disease (ILD) linked to statin was reported in 1995 [27]. Statin-induced ILD is a potential, recently identified side effect of statin medication, according to the FDA-AER. However, the mechanism of lung damage is not known [28]. In contrast, a cohort [29] and case-control study [30] both found no association between statin use and ILD. The only large study linking statin use and ILD is COPDGene [31]. In accordance with the COPDGene study, statin use is associated with ILA among smokers and promotes bleomycin-induced lung inflammation and fibrosis in mice via a mechanism involving heightened NLRP3 inflammasome activation. How statins can exacerbate ILD is unknown, but the effects on lipid metabolism via phospholipidosis [32] and the immune system via cytokine enhancement [33] have been considered possible mechanisms. Nevertheless, the relationship between statins and ILD is largely anecdotal and speculative. It is suggested that such adverse reactions should be treated in time and relevant cases should be recorded.

2.7 Other reactions

Studies have shown that the common adverse reactions of statins also include pancytopenia, stomatitis, irritability, increased blood urea, decreased blood pressure,

decreased white blood cell count, mental distress, cystitis, and so on. However, the study has limitations. One of the limitations with these conclusions is that the method used relies on a spontaneous adverse reaction monitoring system. The causal relationship between adverse reactions and drugs only depends on the judgment of the reporter, and the number and quality of reports are difficult to control. Therefore, the interpretation of data mining results should be cautious, and comprehensive judgment should be combined with evidence-based medical evidence. More crucially, a new study suggests the existence of potential for enhancement in how medical facilities consistently capture statin-associated side effects (SASEs) [34].

3. Conclusion and perspectives

In recent years, with the increasing evidence of preclinical and clinical research, the concept of using statins in patients has been constantly changing. Statins are widely used in clinical practice and have high safety in practical applications, but there are still adverse reactions in liver injury, renal function, myopathy, new-onset diabetes, cognitive impairment, and other aspects, which affect the treatment effect and the quality of life in patients. Therefore, we should attach great importance to the occurrence of adverse reactions in the process of actual clinical drug use, clarify their characteristics, and take more targeted prevention and treatment measures to ensure that the effect of clinical drug use can be improved. At present, research on statins in patients is still hot. It is believed that shortly, the role of statins will be clearer, and the use of drugs will be more standardized.

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