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A.I. Dyadyk, T.E. Kugler*, Y.V. Suliman, S.R. Zborovskiy, I.I. Zdikhovskaya

Department of Therapy, Faculty of Postgraduate Education, M. Gorky Donetsk National Medical University, Donetsk, Ukraine

STATIN ADVERSE EFFECTS: MECHANISMS, DIAGNOSIS, PREVENTION AND MANAGEMENT

Abstract

Statins are one of the most commonly used lipid-lowering agents in clinical practice. The objective of this review was to systemize the most frequent statin adverse effects, including their pathogenesis, diagnosis, management and prevention. The frequency of statin-associated muscle symptoms is significantly higher in registries and observational studies than in randomized controlled trials. Diagnosis of muscle symptoms is difficult because they are rather subjective. The serum creatine kinase level is often normal or slightly elevated. Association between statin use and the risk of new cases of diabetes mellitus was demonstrated in numerous studies. The drug interaction of statins, high dosage of statins used and comorbidities can lead to a persistent and clinically significant increase of hepatic enzymes levels. A standard blood glucose test, hepatic enzymes and serum creatine kinase levels determination was necessary before statin prescription to identify patients with high risk of adverse effects. The risk of hemorrhagic stroke due to treatment with statins is ambiguous according to randomized controlled trials. It is suggested that statins can inhibit carcinogenesis by inducing apoptosis or reducing cell growth, angiogenesis and invasion. However, the results of preclinical and clinical studies are contradictory. The majority of the studies are observational or of retrospective nature. It is necessary to provide larger prospective randomized placebo-controlled trials with a long-term follow-up. Any specialist should understand the potential negative consequences of statins use taking into account the expansion of their indications for use. Understanding the pharmacokinetics of statins is important for the safety of patients. Dosages, metabolism and risk factors of drug interactions should be considered to minimize statin adverse effects.

Key words: *statins, cholesterol, adverse effects, myopathy, diabetes, liver, stroke, cancer*

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β-blockers — beta-blockers; EAS — European Atherosclerosis Society; ALT — alanine aminotransferase; ARBs — Angiotensin II receptor blockers; AST — aspartate aminotransferase; ATP — adenosine triphosphate; CCBs — calcium channel blockers; ULN — upper limit of normal; HMG-CoA reductase — 3-hydroxy-3-methyl-glutaryl coenzyme A reductase; ACEI — angiotensin converting enzyme inhibitors; BMI — body mass index; IR — insulin resistance; CK — creatine kinase; INR — international normalized ratio; MRI — magnetic resonance imaging; NSAIDs — nonsteroidal anti-inflammatory drugs; NDDM — newly diagnosed diabetes mellitus; AE — adverse effects; RCTs — randomized controlled trials; SAMS — statin-associated muscle symptoms; SIM — statin-induced myopathy; HF — heart failure; CVD — cardiovascular diseases

Introduction

Current national Guidelines in various countries (including Russian guidelines) on the use of lipid-lowering agents in order to reduce the risk of developing atherosclerotic cardiovascular diseases (CVD) and their complications place emphasis on statins — 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors, that are considered as highly effective and safe drugs [1–6]. Due to the wide use of statins, the risk of their adverse effects (AE) is debated a lot. Today we have sufficient evidence of AE, such as statin-associated muscle symptoms (SAMS), newly

*Contacts. E-mail: kugler2@mail.ru

diagnosed diabetes mellitus (NDDM), and insulin resistance (IR), as well as their effect on liver function, hemorrhagic strokes, cancer development, etc. The European Atherosclerosis Society (EAS) proposed the term "statin intolerance", which might be observed in 10–15 % of patients [4].

Not all experts agree on the safety of statins. Criticism has also been leveled against the structure and statistical evaluation of the results of randomized controlled trials (RCTs) as well as close financial ties between researchers and pharmaceutical companies producing lipid-lowering drugs [7–16]. The aim of this overview is to systematize the most common statin AE, presenting the mechanisms of their development, diagnosis, therapeutic approach and prevention.

Statins and Muscle Symptoms

Muscle symptoms due to statin use are usually referred to as SAMS, or "statin-induced myopathy" (SIM) [17–22]. Experts of the National Lipid Association Muscle Safety Expert Panel include in SAMS: 1) "myalgia" (muscle pain); 2) "myopathy" (muscle weakness); 3) "myositis" (muscle inflammation detected with intravital morphological examination of muscle tissue and/or magnetic resonance imaging (MRI)); 4) "myonecrosis" (muscle lesion, based on a significant increase in the serum creatine kinase (CK) level); 5) "rhabdomyolysis" with myoglobulinuria and/or acute kidney injury with the elevated serum creatinine level. Elevated CK levels are classified as follows: mild (> 3 upper limits of normal (ULN)), moderate (≥ 10 ULN) and severe (≥ 50 ULN). Statin-associated autoimmune myopathy is also noted, which is a rare complication accompanied by severe progressive muscle disease even after the drug withdrawal [23].

SAMS incidence varies widely and is 7–29 % according to registries and observational studies [20, 24]. In the retrospective PRIMO study (Prediction of Muscular Risk in Observational Conditions) that enrolled 7,924 patients, muscle symptoms were observed in 10.5 % of patients treated with fluvastatin 80 mg, atorvastatin 40–80 mg, pravastatin 40 mg, or simvastatin 40–80 mg daily for at least 3 months [25]. C. Buettner et al. conducted a cross-sectional study of 3,580 patients over the age of 40 years. Twenty-two percent of patients treated with statins reported musculoskeletal pain compared with 16.7 % of patients who did not receive statins [26].

Based on RCTs, SAMS incidence is significantly less than in observational studies. That can be explained by the presence of exclusion criteria, including elderly age, comorbidity, the possible interaction of statins with other drugs, and the presence of previous muscle symptoms, impaired renal and hepatic functions. Up to 30 % of subjects of active pre-randomization phases are excluded from RCTs. Possible mechanisms by which adverse effects can be minimized in clinical trials also include their insufficient identification and selective reporting of adverse drug reactions [18]. In addition, RCTs analyzed are developed mainly to assess the effectiveness of statins and not to record their adverse effects. Only 4 RCTs of 42 reported the CK level of patients enrolled. The STOMP study (The Effect of Statins on Muscle Performance) was the only one that used a questionnaire to identify muscle symptoms, to study the effects of statins on muscle strength and exercise tolerance taking into account the CK level. The STOMP study showed a significant increase in the mean CK levels by 20.8 ± 141.1 U/L ($p<0.001$) in the atorvastatin group. Myalgias were observed in 9.4 % of cases in the atorvastatin group (80 mg/day) and in 4.6 % in the placebo group ($p=0.05$). There were no differences in exercise tolerance and muscle strength between the study groups. The results of the STOMP study are limited by short-term observation (6 months) and a fairly young mean age of subjects (44 years of age) [20, 24].

Mechanisms of SAMS Development

The pathogenesis of SAMS is still poorly understood. There is an ongoing debate over the role of the decrease of ubiquinone (CoQ_{10}) levels in muscle tissue and vitamin D deficiency in the development of SAMS [20, 22, 27]. G.D. Vladutiu identified a 3–4-fold decrease in CoQ_{10} in patients with myopathy as compared with the reference range [28]. Similar results were obtained in a number of other studies. Based on these data, it is assumed that a decrease in the activity of mitochondrial respiratory chains, and, consequently, impairment of energy production and muscle protein degradation play a role in the pathogenesis of SAMS [17, 20, 24]. However, other studies have not detected a decrease in CoQ_{10} levels in patients treated with statins, and its use has not improved statin tolerance and has had no impact on the severity of myalgia [22].

The variability of the pharmacological response to statins depends on polymorphism of genes, the products of which are responsible for pharmacokinetics and pharmacodynamics. Two main mechanisms are suggested: one of them is characterized by impairment of absorption, metabolism, transport and excretion of statins, which leads to an increase in their plasma concentrations and levels in the muscles; the other is a pharmacogenetic one, characterized by mutations leading to impairment of mitochondrial functions. A number of studies have shown an association between the *SLCO1B1* gene polymorphism and pharmacokinetics of statins [27, 29].

Special mention should be made of the pathophysiology of *statin-associated autoimmune myopathy*, a rare but severe and prognostically unfavorable type of SAMS. It usually develops a few months or years after the initiation of the statin therapy [22]. The statin-induced increased activity of HMG-CoA reductase in genetically predisposed patients is thought to produce autoimmune mechanisms against it [20].

Diagnosis of SAMS

Diagnosis of clinical manifestations of SAMS (muscle weakness, pain, tension, cramps, and decreased exercise tolerance) is often based on the subjective assessment of a patient and a physician. They are usually symmetrical, with proximal localization, and involve muscles of upper and lower extremities. SAMS develop more often 4–6 weeks after the beginning of statin therapy, but can develop earlier or later. Plasma CK levels often remain normal or slightly elevated (less than 3-5 ULN) [17, 20, 21, 24, 30, 31].

When muscle symptoms appear, risk factors for the development of SAMS should be taken into account, as well as the possibility of alternative diagnosis. Data of clinical studies suggest that statin therapy can be a trigger for metabolic myopathy. Some patients with arthritis, tendinitis, lumbar radiculopathy report an increased pain syndrome when taking statins, perhaps because muscle weakness exacerbates arthropathy or tendinopathy [18]. In addition, physically active patients are more likely to suffer from SAMS [25], which is consistent with H. Sinzinger and J. O'Grady [32] data which show worse tolerance to lipid-lowering therapy among athletes. The study of CK, thyroid-stimulating hormone, C-reactive protein, and ESR values is necessary for the purpose of differential diagnosis.

Diagnosis of *statin-associated autoimmune myopathy* has unique features. CK levels usually (but not always) are significantly elevated and exceed 10 ULN. Low voltage motor potentials are recorded during electromyography with increased spontaneous activity, which is characteristic of the active myopathic process. Muscular and fascial edema can be detected on MRI. Muscle cell necrosis and regeneration are the most typical histological signs in biopsy specimens of patients with statin-associated autoimmune myopathy [20–22].

Rhabdomyolysis is the most aggressive and severe form of SAMS with development of skeletal muscle necrosis with a slight increase in serum CK levels (> 10 ULN), myoglobinemia, myoglobulinuria, myoglobin-induced acute kidney injury [20, 21].

Therapeutic Approach and Prevention of SAMS

To prevent SAMS, it is necessary to detect the presence of risk factors for their development before statin administration, including the administration of potentially dangerous drug combinations. If these factors cannot be eliminated, special care should be taken for the patients at risk: elderly age, alcohol abuse, high physical activity, a history of skeletal muscle diseases, hypothyroidism, diabetes mellitus, impaired renal and hepatic functions [1–6, 20, 21, 24, 27, 30, 33, 34].

According to the 2017 guidelines of RSC (Russian Society of Cardiology), RNAS (Russian National Atherosclerosis Society), RSCRSP (Russian Society of Cardiosomatic Rehabilitation and Secondary Prevention) on diagnosis and correction of lipid metabolism disorders [1], the serum CK level should be determined before prescription of statins. If the CK level is > 4 ULN, the test should be repeated. Routine monitoring of the CK level is not necessary if there are no muscle symptoms. When they appear, CK should be determined to assess the severity of muscle injury and to decide whether to continue statin therapy or change the dose.

Reduction in the severity of SAMS or their complete elimination is often observed with a decrease in the dosages of statins and/or their use on alternate days or 1–2 times a week (preference should be given to statins with a longer half-life: atorvastatin,

rosuvastatin), and switching to another statin (e. g., switching from lipophilic statin to hydrophilic statin) or combination with other lipid-lowering agents (e. g., ezetimibe, niacin) [1, 20, 34].

After confirming the presence of statin-associated autoimmune myopathy, immunosuppressive therapy including oral administration of glucocorticoids (in prednisolone equivalent of 1 mg/kg body weight) with possible combination with cytotoxic agents at conventional doses (azathioprine, methotrexate, or mycophenolate mofetil) is indicated. When the clinical effect, normalization or significant reduction in plasma CK levels are achieved, the dose of immunosuppressive agents should be decreased slowly [20, 24, 35]. In some patients treated with statins, muscle weakness persists even after the CK levels become normal [30].

If rhabdomyolysis develops, immediate discontinuation of the statin, monitoring of the blood creatinine, potassium and the glomerular filtration rate are required, as well as evaluation of daily diuresis and urinalysis [21, 24].

Statins and NDDM

At present, strong evidence of the relationship between statin therapy and the development of IR and NDDM has been obtained. This is reflected in the national Guidelines of various countries [1–6]. This position is based on the results of RCTs, their meta-analyses and observational studies. In 2012, the Food and Drug Administration and the European Medicines Agency decided to supplement the instruction with information on the risk of elevation of fasting glucose and the level of glycated hemoglobin during statin therapy [36, 37].

Randomized controlled trials

One of the large-scale RCTs which demonstrated the risk of NDDM was the JUPITER study (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin), focused on the primary prevention of CVD. The JUPITER study enrolled 17,802 subjects (11,001 men aged 50 years and older, and 6,801 women aged 60 years and older) with low-density lipoprotein cholesterol (LDL-C) values < 3.4 mmol/L, but with elevated values of highly-sensitive C-reactive protein (≥ 2 mg/L), randomized into a rosuvastatin group (20 mg/day) and a placebo group. After 1.9 years of follow-up, there was an increase in NDDM incidence in patients of rosuvastatin group compared with the control group (odds ratio (OR) = 1.26, 95 % confidence interval (CI) 1.04–1.51) with no differences in fasting glucose values between groups. However, elevation of the glycated hemoglobin values was detected (5.9 % versus 5.8 %; p=0.001). A higher incidence of NDDM in women was noted [38].

In the PROSPER study (PROspective Study of Pravastatin in the Elderly at Risk), there was a 32 % increase in NDDM incidence in the pravastatin group (40 mg/day) compared with the control group (OR=1.32, 95 % CI 1.03–1.69) [39].

Supportive analysis of the PROVE-IT TIMI 22 study (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) has shown a significant increase in glycated hemoglobin > 6 % in patients with or without DM when treated with statins [40].

Kwang Kon Koh et al. conducted an RCT in order to study the effect of various doses of atorvastatin on fasting plasma insulin and glycated hemoglobin values: 44 subjects received a placebo, 42, 44, 43 and 40 subjects received atorvastatin 10, 20, 40 and 80 mg/day, respectively, for 2 months. There was a significant increase in plasma fasting insulin value by 25 %, 42 %, 31 % and 45 % on average under the effect of atorvastatin 10, 20, 40 and 80 mg, respectively, (p=0.009) and glycated hemoglobin level by 2 %, 5 %, 5 % and 5 %, respectively, compared with the placebo group (p=0.008). Atorvastatin 10, 20, 40 and 80 mg significantly decreased insulin sensitivity by 1 %, 3 %, 3 % and 4 %, respectively, compared with the placebo group (p=0.033) [41].

Meta-analyses

A number of large-scale meta-analyses seek to study of the relationship between statin therapy and the risk of development of NDDM. For example, N. Satar et al. [42] after analyzing 13 RCTs with 91,140 subjects enrolled, noted a 9 % increase in the risk of DM in groups of patients who received statins compared with control group results (OR=1.09; 95 % CI 1.02–1.17). The risk factors of DM were a high body mass index (BMI), elderly age, heart failure (HF), a history of myocardial infarction in the last six months, and a high cardiovascular risk. The authors of this meta-analysis concluded that the use of statins in 255 patients for 4 years was associated with a risk of developing NDDM in one patient.

D. Preiss et al. [43] analyzed 5 RCTs with 32,752 subjects without DM enrolled (the study lasted for more than 1 year). During follow-up, 2,749 subjects developed DM, of which 1,449 received intensive statin therapy (atorvastatin 80 mg, simvastatin 40 and 80 mg), 1,300 received moderate statin therapy (pravastatin 40 mg, simvastatin 20 mg, atorvastatin 10 mg). This study demonstrated that intensive statin therapy was associated with a higher incidence of NDDM (OR=1.12, 95 % CI 1.04–1.22). The authors concluded that the possibility of developing NDDM was 1 in 498 treated patients per year. According to D. Preiss, the results of the meta-analysis indicate a dose-dependent risk of the development of NDDM on statin use.

Cohort and observational studies

Numerous observational and cohort studies have demonstrated the association between statin use and the risk of the NDDM development. A. Macedo et al. [44] conducted a population cohort study with 2,016,094 subjects enrolled, 430,890 of which received statins. 130,395 subjects developed type 2 diabetes during the follow-up period (5.4 years on average). The use of statins was associated with a higher risk of NDDM development (hazard ratio (HR) = 1.57, 95 % CI 1.54-1.59), which increases with longer statin therapy. Risk was higher in persons without hypertension and other CVD.

C. Dormuth et al. analyzed 8 cohort studies and a meta-analysis which enrolled 136,966 subjects aged ≥ 40 years, who received statins. The risk of NDDM development was higher when rosuvastatin, atorvastatin and simvastatin were used [45].

A. Culver et al. analyzed data on 153,840 postmenopausal women. Development of NDDM was identified in 10,242 cases. In addition, the risk of NDDM development occurred with the use of various statins, which suggests the effect of the class [46].

In a cohort study conducted by D. Yoon et al. [47] (8,265 patients treated with statins and 33,060 patients in the control group) NDDM incidence was higher in the statin group compared with the control group (OR=1.872, 95 % CI 1.432–2.445). The highest risk was found for atorvastatin (OR=1.939, 95 % CI 1.278).

Opinions differ on the risk of development of NDDM for various statins. Some researchers have found no difference between lipophilic (atorvastatin, simvastatin and lovastatin) and hydrophilic statins (rosuvastatin, fluvastatin and pravastatin) but others reported this difference [42]. N. Zaharan et al. showed a high risk of development of NDDM for atorvastatin (OR=1.23, 95 % CI 1.19–1.27), simvastatin (OR=1.15, 95 % CI 1.05–1.25) and rosuvastatin (OR=1.41, 95 % CI 1.31–1.52), in contrast to fluvastatin and pravastatin [48]. A. Carter et al. demonstrated similar results in the retrospective study in 471,250 patients over the age of 66 years without DM (follow-up period was 14 years). It was shown that there was an increase in the risk of NDDM development by 22 % in patients who received atorvastatin, by 18 % in patients who received rosuvastatin, by 10 % in patients who received simvastatin, in comparison with pravastatin. In contrast, the use of lovastatin and fluvastatin was not associated with an increased risk of DM [49].

Mechanisms of NDDM and IR development

Several mechanisms are proposed that explain the association of statins with the risk of NDDM development. They include blocking calcium channels in pancreatic β-cells, decreasing levels of CoQ_{10}, reducing expression of glucose transporter type 4 (GLUT4), immune-mediated inflammation in pancreatic β-cells [10, 20, 50–53].

Evidence is presented on the adverse effects of statins on insulin sensitivity and pancreatic β-cell secretion [50]. In the population METSIM study (Metabolic Syndrome in Men) (8,749 patients aged 45–73 years) [54], statin therapy increased the risk of DM type 2 development by 46 % (OR=1.46, 95 % CI 1.22–1.74). Insulin sensitivity decreased by 24 %, and insulin secretion — by 12 % in persons treated with statins (at fasting glucose levels and postprandial glycemia < 5.0 mmol/L) compared to those who did not receive lipid-lowering therapy ($p<0.01$).

Glucose is the most important regulator of insulin release. It enters β-cells using glucose transporter type 2 (GLUT2). In β-cells, glucose is phosphorylated to glucose-6-phosphate by glucokinase enzyme. Adenosine triphosphate (ATP) is produced in the next metabolic process, leading to the closure of potassium channels and, consequently, depolarization of cell membranes, resulting in calcium flowing into the cell through the L-type calcium channels. In the experiment, it was shown that a decrease in the content of cholesterol in cells can lead to a decrease in insulin secretion due to impairment of the functioning of L-type voltage-gated calcium channels in pancreatic β-cells [10, 50, 51, 52].

Mitochondrial dysfunction in pancreatic β-cells, skeletal muscles and adipocytes plays an important role in the DM pathogenesis. Statins decrease levels of CoQ_{10}, which is an essential factor that ensures electron transport in mitochondria, leading to slowed ATP production in the pancreatic β-cells and, accordingly, impairment of insulin secretion. Inhibition of isoprenoid synthesis by statins leads to a decrease of GLUT4 expression in adipocytes and development of peripheral insulin resistance [20, 51].

HMG-CoA reductase inhibition, oxidation of LDL-C, which enters β-cells from plasma, promotes activation of intracellular systems of congenital and acquired immunity, inflammation in β-cells, impairment of their structure and function, and ultimately, a decrease in insulin secretion [52, 53]. Statins can induce apoptosis of β-cells due to excessive NO production [53].

Therapeutic approach and prevention of NDDM and IR

Primarily, patients should be recommended to adhere to a healthy lifestyle (Mediterranean diet, regular physical activity, body weight control) [1–6, 10, 51]. In case of vitamin D deficiency, its replacement therapy should be administered. In case of ineffectiveness of these recommendations, the risk and benefit ratio should be assessed and statins should be prescribed according to strict indications, without considering them as a panacea ("magic bullets", in the words of Umme Aiman) [51].

Before prescription of statins, a patient should be informed about the risk of DM development and basic glycemic parameters (fasting glucose and glycated hemoglobin) should be determined, especially in individuals with risk factors for DM (female, elderly age, BMI > 30 kg/m^2, hypertension, triglyceride levels > 1.69 mmol/L, fasting glucose levels 5.6–6.9 mmol/L, family history of type 2 DM, Asian race, smoking, and alcohol abuse) [1–6, 10, 20, 36, 51, 52].

Parameters of carbohydrate metabolism should be monitored during statin therapy (especially in case of intensive therapy). High doses of statins are associated with an elevated risk of NDDM development. In this regard, in order to achieve the target LDL-C level, the treatment should be started at low doses. A combination of moderate doses of statins with ezetimibe is possible, which allows further decrease in LDL-C by 20 % [10, 51]. The detection of glycemic disorders without testing the essential parameters permits to consider these abnormalities as statin-induced [10].

In case of hypertension, a differentiated approach to the choice of antihypertensive agents is needed. It should be taken into account that beta-blockers (β-blockers) and thiazide diuretics increase the risk of NDDM by 22 % and 43 %, respectively. If it is necessary to use β-blockers, drugs with vasodilating properties should be preferred. At the same time, angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) can increase insulin sensitivity and reduce DM incidence, and calcium channel blockers (CCBs) are neutral in terms of glycemia [10].

Statins and Hemorrhagic Stroke

The association between low values of cholesterol and an increased risk of hemorrhagic stroke development is observed in epidemiological studies [20, 55]. The meta-analysis of 23 trials which included 1.4 mln patients with 7,960 cases of hemorrhagic stroke showed that the risk of stroke decreased by 10 % with an increase in LDL-C by 1 mmol/L [20]. The results of a number of RCTs on the risk of hemorrhagic strokes during statin therapy are inconclusive. In some studies, there was no increase in the frequency of hemorrhagic strokes with a decrease in LDL-C to 1.8 mmol/L and lower [55]. The supportive analysis of the SPARCL study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) showed an increase in the incidence of hemorrhagic strokes in patients receiving atorvastatin, compared with the placebo group. The risk of hemorrhagic strokes increased with age, in males and in case of stage 2 hypertension [56]. The HPS study (Heart Protection Study) showed an increase in the frequency of hemorrhagic strokes in patients with cerebral atherosclerosis who received simvastatin 40 mg/day [57].

The mechanisms by which statins can increase the incidence of hemorrhagic strokes have not been sufficiently studied. Statins are characterized by pleiotropic effects, including antithrombotic and fibrinolytic activities, due to which they can increase the activity of other fibrinolytic agents [58].

Thus, summarizing the results of the studies, it should be noted that statins decrease incidence of ischemic stroke and other atherosclerotic cerebral diseases, but increase the risk of hemorrhagic stroke

in patients after ischemic strokes. In this regard, the potential risk of hemorrhagic stroke development in these patients should be considered [20, 55, 56].

Statins and the Liver

Asymptomatic increase in the level of hepatic transaminases is one of the most frequent AE of statins and is observed in 0.5–2.0 % of patients. This class effect is dose-dependent, is usually observed within the first 12 weeks of statin use, and is normalized with reduction of statin doses. Moderate increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels is not an indicator of liver dysfunction and does not require discontinuation of statins [1–6, 21, 53].

A clinically significant increase in ALT/AST level implies a three-fold increase from ULN in two consecutive measurements, which are usually performed with a short time interval between them. A persistent and significant increase in the level of transaminases is often due to the interaction of statins with other drugs, the use of high doses and the presence of concomitant diseases. The risk of liver failure is extremely low [1–6, 20, 21, 53].

The mechanism of hepatic transaminase elevation is not well understood. The increase in ALT levels is associated with a decrease in CoQ_{10} levels, changes in the lipid components of the hepatocyte membrane and the generation of free radicals, which leads to an increase in the permeability of their membranes and, consequently, vulnerability to other toxins [21, 53].

Based on the results of numerous studies, routine monitoring of ALT/AST levels is not recommended by the experts during statin therapy [1, 4]. At the same time, it is recommended to measure ALT/AST levels before prescription of statins and 4–12 weeks after initiating or modifying drug therapy. In case of increase in the level of transaminases > 3 ULN, treatment should be discontinued or the dose of the drug should be reduced. If ALT/AST activity is ≤ 3 ULN, treatment can be continued, and the enzyme level should be re-tested after 4–6 weeks [1]. If a clear causal relationship is established between an increase in transaminases and the administration of a statin, the drug should be withdrawn and patient should be switched to alternative therapy (ezetimibe) [2].

In addition, to reduce the risk of hepatotoxicity, thorough questioning of the patient is necessary in order to exclude the intake of alcohol, drugs that are metabolized by cytochrome P450 3A4 (e. g., amiodarone, sulfonamides, methyldopa, cyclosporine, etc.). [21, 53].

Statins should not be prescribed to patients with acute and active viral hepatitis until the serum levels of AST/ALT, total bilirubin and alkaline phosphatase are back to normal. According to EAS, a moderate increase in liver enzyme activity in patients with non-alcoholic fatty liver disease and high CVD risk should not be an obstacle to the administration of statins [21].

Statins and Cancer

It is believed that statins can inhibit carcinogenesis by inducing apoptosis or inhibiting cell growth, angiogenesis, and invasion. Antiproliferative effects were the basis for mass preclinical studies to elucidate the functional role of statins in carcinogenesis. However, the results of preclinical and clinical studies contradict each other, although there is evidence that statins can suppress and reduce the incidence and relapse of certain cancers [59]. Taylor et al. have identified a relation between statins and breast, colon, lung, prostate and other cancers in the meta-analysis of 20 case-control studies that included 100,129 cases of cancer. When stratifying by the type of cancer, a statistically significant carcinoprotective effect was detected only in case of colon cancer (OR=0.89, CI 0.82-0.97) [60]. However, there were no data on what other drugs the patients took besides statins. As is known, low-dose acetylsalicylic acid with anti-inflammatory effect is often used for the prevention of CVD. Some studies showed that statins and nonsteroidal anti-inflammatory drugs (NSAIDs) can act synergistically, inhibiting the cell cycle and promoting apoptosis [61]. The disadvantages of observational studies are also the presence of random factors that are unevenly distributed among patients in the "case" and "control" groups and can affect the outcome. For example, differences in lifestyle, dietary habits, smoking and alcohol use are often not recorded in population databases, which makes it impossible to adjust them.

In the "pre-statin" era, reverse causality between the levels of plasma cholesterol and the potential risk of cancer (especially in the elderly patients) was actively discussed [7, 62, 63]. A number of cohort studies have shown that low cholesterol levels are

risk factors for cancer development. U. Ravnskov et al. analyzed 9 studies, which included more than 140,000 persons, and identified an increase in the incidence of cancer at low levels of cholesterol [63]. The risk of cancer has been noted in a number of RCTs devoted to the prevention of CVD diseases. In the aforementioned PROSPER study [62], the authors identified a reduction in cardiovascular mortality in the pravastatin group by 24 % (p=0.043). However, this effect was offset by a significant increase in mortality from cancer in the pravastatin group. The total number of patients with cancer in the pravastatin group was 245 versus 199 in the placebo group (p=0.02). The difference increased with a longer follow-up period. Commenting on the findings, the authors associate them with inclusion of patients with severe comorbid diseases in the study.

In the SEAS study (The Simvastatin and Ezetimibe in Aortic Stenosis) which enrolled 1,873 patients with aortic stenosis (mean age 67.6 years, follow-up duration 4.3 years), one group of patients received lipid-lowering therapy with simvastatin (40 mg/day) in combination with ezetimibe (10 mg/day) and another group received a placebo. In the pravastatin-ezetimibe group, prostate cancer was diagnosed in 105 patients (11.1 %) versus 70 patients (7.5 %) in the placebo group (p=0.01) [64]. At the same time, there was no significant difference when comparing both the total (p=0.80) and the cardiovascular (p=0.34) mortality.

In the 4S (Scandinavian Simvastatin Survival Study) and HPS studies focused on the secondary prevention of CVD, an increase in the incidence of skin cancer was revealed. When combining the results of these two studies, the increased risk of skin cancer in patients who received simvastatin was statistically significant compared with those who received placebo (p=0.028) [63].

According to D. Diamond, U. Ravnskov, the risk of cancer with prolonged use of statins may be higher than in the results of RCTs, the duration of which in the vast majority is no more than 2-5 years [7]. J.A. Mc Dougall et al. in the population study revealed a two-fold increase in the risk of breast carcinoma in women aged 55–74 years who received statins for 10 years or more [65]. The authors noted that the risk was highest among long-term users and suggested that statins could act as promoters of breast carcinogenesis. The detection of an increased risk only with prolonged use of statins suggests that chronic dysregulation of the mevalonate pathway and/or a long-term decrease in serum cholesterol levels may contribute to breast carcinogenesis.

Previous studies of statins did not reveal an increased risk of breast cancer, except for the RCT CARE (Cholesterol And Recurrent Events), which was focused on the secondary prevention of CVD (the duration was 5 years). However, it should be noted that most statin users in these studies took statins for less than 3 years. In the CARE study, patients were randomized into two groups: 2,078 in the placebo group and 2,081 in the pravastatin (40 mg/day) group. Plasma levels of total cholesterol were less than 6.2 mmol/L, LDL values were between 3.0 and 4.5 mmol/L. There were no significant differences in overall mortality (9 % decrease in the risk of death, 95 % CI 12 to 26 %, p=0.37). However, there was a 12-fold increase in the risk of breast cancer (12 cases in the pravastatin group versus 1 case in the placebo group, p=0.002). There were no other statistically significant differences between the groups in the incidence of cancer (gastrointestinal cancer, melanoma, lymphoma) [66].

It therefore remains an open question whether statins have carcinogenic or carcinoprotective effect. While the growth of tumor cells *in vitro* is usually suppressed in the presence of lipophilic statins, the clinical data on their antitumor effects are contradictory. Most of the studies are observational or retrospective. There is a need for more extensive prospective, randomized, placebo-controlled trials with a long follow-up period. In the systematic review, M. Künzl et al. come to the conclusion that the use of statins for the prevention of cancer can not be recommended due to the lack of convincing data [59].

Drug Interactions of Statins

Patients with CVD often need a concomitant prescription of a number of drugs. Drug interactions may lead to a change in the effectiveness of the drug or its toxicity due to impairment of absorption, distribution, metabolism and/or excretion. Risk factors for drug interactions include anthropometric factors (advanced age, female sex, low BMI, Asian race), comorbid states, and genetic polymorphisms that cause differences in the expression of enzymes and the ability of the body to participate in drug metabolism (i. e., impaired renal or hepatic function, HF).

An elevated risk of the development of statin therapy AE occurs with the concomitant use of drugs including macrolides, protease inhibitors, immunosuppressive drugs, as well as those inhibiting cytochrome P 450 isoenzymes, organic anions transporting polypeptide 1B1 (OATP1B1) or P-glycoprotein 1 [67].

Co-administration of statins with CCB is possible. However, doses of lovastatin or simvastatin > 20 mg/day when combined with amlodipine, diltiazem or verapamil are not recommended. If high doses are required (80 mg/day), clinicians should switch to statin, which is not associated with cytochrome P450 3A4 (pravastatin, rosuvastatin or pitavastatin) if treatment with diltiazem or verapamil is initiated [67].

Combined therapy of rosuvastatin, atorvastatin, pitavastatin, fluvastatin or pravastatin with amiodarone is acceptable. In this case, the dose of lovastatin should not exceed 40 mg/day and simvastatin — 20 mg/day. Concomitant use of statin with dronedarone is possible. It should be taken into account that dronedarone potentiates the action of simvastatin and lovastatin, and digoxin potentiates the action of atorvastatin. In this regard, more careful control of the risk of digitalis intoxication is recommended for patients taking high doses of atorvastatin [67].

Warfarin may be combined with statins. Careful monitoring of the international normalized ratio (INR) is needed after initiating therapy and/or modifying a dose. Effects on INR are minimal for pitavastatin and atorvastatin. Ticagrelor can be used in combination with atorvastatin, pravastatin, fluvastatin, pitavastatin or rosuvastatin without dose restrictions. When prescribing a combination of ticagrelor with simvastatin and lovastatin, their dose should not exceed 40 mg/day [67].

Combination therapy of lovastatin, simvastatin or pitavastatin with cyclosporine, everolimus, tacrolimus or sirolimus is potentially dangerous and should be avoided. The combined use of immunosuppressants with fluvastatin, pravastatin and rosuvastatin at doses of 40, 20 and 5 mg/day, respectively, is possible. It is not recommended to administer atorvastatin > 10 mg/day when combined with cyclosporine, tacrolimus, everolimus or sirolimus without careful monitoring of CK and muscle symptoms [67].

Patients receiving combination therapy of statins with colchicine should carefully monitor the condition of the musculoskeletal system, taking into account the potential for synergistic muscle toxicity. It is recommended to adjust the dose of colchicine (no more than 0.6–1.2 mg at the start of therapy and maintaining doses of 0.3–0.6 mg/day) when co-administered with a cytochrome P450 3A4 or P-glycoprotein inhibitor, as well as in patients with impaired renal function. Dose reduction is recommended for atorvastatin, simvastatin and lovastatin when combined with colchicine [67].

Understanding the pharmacokinetics of statins and other drugs that are often prescribed in combination is a high priority to ensure patient safety. In this case, dosages, metabolic pathways and risk factors for drug interaction should be taken into account in order to minimize the AE of statin therapy.

Conclusion

Providing lipid-lowering therapy, especially for the primary prevention of atherosclerotic CVD, requires an assessment of the risk/benefit ratio due to the high probability of statin-associated AE. Before prescription of statins, it is necessary to determine the baseline glycemic parameters, ALT/AST and CK levels, and risk factors for AE development, that will allow to reduce their incidence and severity.

Conflict of interests

The authors declare no conflict of interests.

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