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Adverse Effects of Statins

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Abstract: Statins are competitive inhibitors of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis pathway, which converts HMG-CoA to mevalonate. Statins lower plasma Low Density Lipoprotein (LDL)-bound cholesterol by causing intracellular cholesterol depletion and upregulating the expression of LDL receptors. Apart from cholesterol, mevalonate is also used as the substrate for the synthesis of nonsteroid isoprenoids including farnesylpyrophosphate, geranylgeranylpyrophosphate (both attached to small GTP-binding proteins by protein prenyltransferases), coenzyme Q, dolichol, isopentenylpyrophosphate, etc. Inhibiting the synthesis of these nonsteroid isoprenoids results in so called "pleiotropic" effects of statins which are independent of cholesterol lowering. Although statins are generally well-tolerated, adverse effects may occur in some patients. Myopathy is the most frequent side effect of statins. Other less common include peripheral neuropathy, hepatotoxicity, increased risk of cataract and, according to some studies, increased risk of breast cancer. Some studies suggest that under specific experimental conditions statins may exert detrimental effects also on processes which are generally believed to be favorably modified by these drugs, e.g. vascular reactivity, myocardial performance or atherogenesis. In this review currently recognized mechanisms through which statins could induce side effects are discussed.

Key words: 3-hydroxy-3-methylglutarylcoenzyme A reductase inhibitors, isoprenoids, coenzyme Q, myopathy, hyperlipoproteinemia

INTRODUCTION

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase-a rate limiting enzyme in the cholesterol biosynthesis pathway converting HMG-CoA to mevalonate. Currently available statins may be classified into two groups. Natural statins include lovastatin, which is a fungal metabolite and its synthetic derivatives, pravastatin and simvastatin. Fluvastatin, atorvastatin and rosuvastatin are fully synthetic compounds with completely different chemical structure. Another synthetic statin, cerivastatin, was withdrawn from the market in 2001 due to many reported cases of fatal rhabdomyolysis. Statins decrease plasma Low Density Lipoprotein (LDL) cholesterol by inducing intracellular cholesterol depletion and upregulating hepatic LDL receptors. Many clinical trials have demonstrated that statins effectively prevent acute cardiovascular events and reduce mortality in primary and secondary prevention of ischemic heart disease[1,2]. Initially introduced as cholesterol-lowering drugs, statins posses multiple other lipid-independent or pleiotropic atheroprotective activities such as improvement of endothelial function, inhibition of vascular inflammation, platelet aggregation and thrombosis and amelioration of oxidative stress. Therefore, beneficial effects of statins are observed not only in patients with hyperlipidemia but also in those with normal cholesterol level.

Statins are safe and usually well tolerated. However, no treatment is completely risk-free and statins are not the exception. In this review we will characterize the mechanisms through which statins can exert unfavorable effects and their possible clinical implications.

MEVALONATE CASCADE

Mevalonate is used not only for cholesterol biosynthesis but is also converted to nonsteroid isoprenoids such as farnesylpyrophosphate (FPP), geranylgeranylpyrophosphate (GGPP) and side chain of coenzyme Q (Fig. 1). Statins reduce the synthesis of cholesterol as well as of nonsteroid isoprenoids which play an essential role in cellular physiology. For example, coenzyme Q is a component of mitochondrial respiratory chain and a lipid-soluble antioxidant. Farnesyl-and geranylgeranyl-groups are attached to proteins by protein farnesyltransferase and geranylgeranyltransferase, respectively the process referred to as protein

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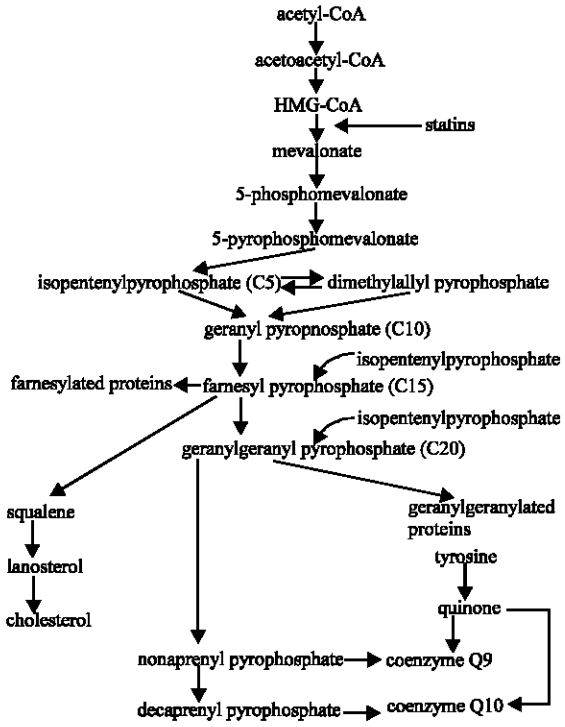

Fig. 1: Mevalonate cascade

isoprenylation. Among isoprenylated proteins are small GTP-binding proteins including Ras, Rho and Rab involved in signal transduction pathways regulating cell proliferation, apoptosis, vascular NADPH oxidase activity, etc. These small G proteins exist in cytosol in their inactive, GDP-bound form. Upon isoprenylation, they exchange GDP to GTP and attach to the plasma membrane. Inhibition of isoprenoid synthesis by statins decreases the activity of these proteins and modifies the respective signaling pathways; the mechanism responsible for cholesterol-independent pleiotropic effects.

Lowering plasma cholesterol results mainly from the inhibition of hepatic HMG-CoA reductase, whereas cholesterol-independent effects may be exerted in every cell type. Most currently used statins except pravastatin are lipophilic, easily permeate plasma membranes and affect both hepatic and extrahepatic HMG-CoA reductase. Pravastatin is hydrophilic and easily penetrates only into hepatocytes through plasma membrane organic anion transporter. Thus, although pravastatin may be as effective as other statins in reducing plasma cholesterol, it will be much less effective inhibitor of mevalonate cascade in extrahepatic cells.

Although inhibiting nonsteroid isoprenoids is responsible for many favorable effects of statins, one has to realize that depletion of mevalonate derivatives may not be always beneficial. Indeed, recent studies suggest that depletion of mevalonate derivatives contributes to toxic effects of these drugs as well.

The particular toxicity of cerivastatin is attributed to its high affinity to HMG-CoA reductase and lipophilicity which determine its ability to inhibit mevalonate synthesis in extrahepatic tissues. Although rosuvastatin, a recently introduced synthetic statin, is almost equally potent HMG-CoA reductase inhibitor, it is hydrophilic and thus expected to be more safe.

Mechanisms through which statins can induce side-effects

Statins and coenzyme Q: Coenzyme Q (CoQ, 2,3-dimethoxy, 5-methyl, 6-polyisoprene parabenzoqinone) consists of benzoate ring originating from tyrosine and polyisoprene side chain synthesized from farnesyl pyrophosphate. In humans, the predominant form is CoQ_{10} containing 10 isoprene units, while 2-7% of the total is CoQ_9 with 9 isoprene units in its side chain. In rodents, the predominant form is coenzyme Q_9 but 10-30% of the total is CoQ_{10}[3,4]. Coenzyme Q occurs in either reduced (ubiquinol) or oxidized (ubiquinone) form; the transition between them allows it to function as electron carrier in mitochondrial respiratory chain. In addition, ubiquinol is an important lipid-soluble antioxidant protecting plasma membranes and plasma lipoproteins from oxidative damage. Normally, most >80% of CoQ in plasma and tissues exists in oxidized form. Interestingly, CoQ is the only known lipid soluble antioxidant synthesized by mammalian cells and the only one which upon oxidation may be regenerated to its active reduced form by animal enzymes. Apart from de novo synthesis, CoQ may be obtained from alimentary sources.

Willis *et al.*[5] first demonstrated that lovastatin administered for 4 weeks decreases coenzyme Q_9 content in plasma, liver and myocardium in the rat and that this effect is prevented by oral CoQ supplementation. Later it has been demonstrated that lipophilic lovastatin has more marked reducing effect on myocardial CoQ than hydrophilic pravastatin, probably due to its better penetration into myocardial cells[6]. About 20-40% decrease in plasma ubiquinone was found in humans treated with different statins[7-9]. Recently, it has been demonstrated that atorvastatin administered for only 14 days decreases plasma CoQ by about 50% in patients with hypercholesterolemia[10]. Similarly, Passi *et al.*[11] reported reducing effect of atorvastatin, simvastatin and pravastatin therapy on CoQ content in human lymphocytes.

Ubiquinone depletion induced by statin therapy is accompanied by impaired mitochondrial function, as evidenced by reduced oxygen consumption and ATP synthesis[12,13]. In addition, by impairing oxidative metabolism of glucose, statins increase plasma lactate/pyruvate ratio[8], which occasionally may even result in lactic acidosis[14]. The role of CoQ depletion in adverse effects of statins is not completely clear, however, it should be stressed that primary CoQ deficiency leads to mitochondrial encephalomyopathy with recurrent myoglobinuria closely resembling some side effects of these drugs[10].

Prooxidant effect of statins: Oxidative stress, i.e. the imbalance between the amount of Reactive Oxygen Species (ROS) and enzymatic and nonenzymatic antioxidants, plays an important role in the pathogenesis of atherosclerosis, arterial hypertension and heart failure, therefore, the effect of statins on oxidant-antioxidant balance is of special significance. Most studies have demonstrated that statins ameliorate oxidative stress, however, some potential prooxidant effects of these drugs are also known.

Levy *et al.*[15] have demonstrated that one of mevalonate derivatives, presqualene diphosphate, which is synthesized from farnesylpyrophosphate by squalene synthase, is a negative regulator of superoxide generation by human neutrophils. It is not clear whether statins could increase ROS generation by inhibiting production of this compound.

Nitric Oxide (NO), produced constitutively in low amounts by Endothelial NO Synthase (eNOS), plays an important role in the regulation of vascular tone. However, another NOS isoform, i.e. inducible NOS (iNOS) generates NO in much higher amounts in which it can react with superoxide to form peroxynitrite ($ONOO^-$). The latter is a highly reactive free radical which damages proteins, lipids and nucleic acids; the condition referred to as nitrosative stress. iNOS is barely expressed in tissues under baseline conditions but may be induced by inflammatory cytokines, hypoxia, etc. Most studies indicate that statins stimulate eNOS activity, which is beneficial; however, some authors reported their effect also on iNOS which might be detrimental[16-18].

Cytochrome P450 2C isoform is expressed in the vasculature and synthesizes epoxyeicosatrienoic acids (EETs) which function as endothelium-derived hyperpolarizing factor (EDHF). However, cytochrome P450-catalyzed reactions are also a source of reactive oxygen species. Fisslthaler *et al.*[19] have recently demonstrated that cerivastatin and fluvastatin upregulate CYP 2C gene expression in porcine coronary artery endothelial cells. This effect is accompanied by increased O_2^- generation by vascular wall. There are also two reports demonstrating reducing effect of statins on manganese-and extracellular superoxide dismutases in the vascular tissue[20,21].

Interesting data about possible prooxidant effect of statins *in vivo* have been provided by Sinzinger *et al.*[22]. The authors measured plasma level of isoprostanes-the products of ROS-dependent peroxidation of unsaturated fatty acids-which is a reliable marker of oxidative stress *in vivo*. Baseline concentration of isoprostanes was higher in patients with heterozygous familial hypercholesterolemia than in normolipidemic control group. Although in most patients treatment with various statins reduced plasma isoprostanes consistently with hypolipidemic and antioxidant properties of these drugs, in 10% of them increased isoprostane level was noted after 3 or 6 months of therapy in the absence of any side effects. These data suggest that some persons are especially prone to statin-induced oxidative stress and that prooxidant effect of these drugs precedes clinically relevant adverse effects.

Statins and selenoproteins: One of the products derived from mevalonate, isopentenylpyrophosphate, is attached to adenosine contained in tRNA by tRNA isopentenyltransferase. This posttranscriptional modification is necessary for the synthesis of selenocysteine-tRNA. Selenocysteine is an analogue of cysteine containing selenium instead of sulphur and is incorporated into various selenoproteins such as glutathione peroxidase and thioredoxin reductase (both involved in antioxidant defense) as well as thyroxine deiodinases which catalyze the conversion of thyroxine to triiodothyronine. It has been recently suggested that statins compromise the synthesis of selenoproteins by decreasing the availability of isopentenylpyrophosphate[23,24]. It has been noted that lovastatin decreases selenoprotein content in cultured cells. Moreover, selenium deficiency in animals as well as in humans (Keshan disease observed in rural areas of China) is characterized by myopathy and cardiomyopathy closely resembling statin-induced myopathy. Statin-induced deficiency of selenoproteins could compromise not only antioxidant defense but also thyroid function. Statins have been reported to induce thyroid hypertrophy in the rat[25] and to reduce plasma thyroxine and elevate TSH in hypothyroid patients[26].

STATIN-INDUCED MYOPATHY

Undoubtedly, muscular side effects are the most common and the best known adverse consequence of statin therapy. Various muscular complaints may occur in

up to 8% of treated patients. Statin-induced myopathy has been described in detail in several recent reviews[28-31] and therefore, will be characterized here only briefly.

Several types of statin-induced myopathy have been recognized: (1) myalgia-continuous or exercise-induced muscular pain, tenderness, cramps and/or weakness with normal serum Creatine Kinase (CK) activity, (2) myositis-muscular pain with elevated serum CK activity, (3) asymptomatic elevation of CK activity without myalgia and, (4) rhabdomyolysis.

Myalgia and/or CK elevation usually occur soon after initiation of statin therapy, in most cases within the first month. In the majority of patients remission of symptoms is observed after withdrawing statin therapy. On the other hand, symptoms are unlikely to disappear if treatment is continued.

Rhabdomyolysis is the most severe form of statin-induced myopathy characterized by marked increase in CK activity (>10-times the upper limit of normal), myoglobinemia, myoglobinuria and myoglobin-induced acute renal failure (oliguria, increased plasma creatinine, potassium and phosphorus). Rhabdomyolysis is associated with about 8% risk of death due to hyperkalemia-induced arrhythmias or disseminated intravascular coagulation. Fortunately, rhabdomyolysis is extremely rare. A recent meta-analysis involving almost 34 000 of patients treated with statins in long-term clinical trials revealed the rate of this complication of about 5.3/100 000 patient-year vs. 3.3 in placebo-treated group, i.e. relative risk of only 1.6[32]. However, because total amount of patients treated with statins is large, this complication should not be neglected. About 3300 cases of statin-induced rhabdomyolysis were reported in the USA between 1990 and 2002[30]. Factors which slow the metabolism of statins such as advanced age, renal or hepatic dysfunction, hypothyroidism, perioperative period and diabetes mellitus increase the risk of rhabdomyolysis. Rhabdomyolysis is also more likely to occur following combined therapy with statins and fibrates. Fibrates slow the metabolism of statins because both groups of drugs are metabolized by the common cytochrome P450-dependent mechanisms. In addition, fibrate monotherapy is also associated with the increased risk of myopathy. Thus, both pharmacokinetic and pharmacodynamic interactions between these drugs may be responsible for their synergistic effect[33]. Gemfibrozil is more dangerous in enhancing myotoxic effect of statins than other fibrates. This may be explained by the recently described new pathway of statin metabolism. Simvastatin, atorvastatin and cerivastatin may be condensed with glucuronic acid to form unstable glucuronide which then spontaneously decomposes to biologically inactive statin lactone. It has been demonstrated that only gemfibrozil but not other fibrates inhibits this metabolic pathway [34]. Thus, fibrates other than gemfibrozil, e.g. fenofibrate, are better alternative for patients in whom treatment with both statin and fibrate is considered. Other drugs interfering with statin metabolism include cyclosporine, macrolide antibiotics, warfarin, digoxin and azole antifungals.

Various statins differ in their ability to induce myopathy. In general, it is appreciated that more potent HMG-CoA reductase inhibitors (i.e. synthetic statins) and more lipophilic ones are more likely to cause muscular side effects. Thus, the reported rate of myopathy in patients treated with different statins is: fluvastatin>atorvastatin>lovastatin=simvastatin> pravastatin. Cerivastatin, the most potent HMG-CoA reductase inhibitor used so far, caused rhabdomyolysis much more frequently than any other statin. Many reported cases of cerivastatin-induced fatal rhabdomyolysis were the reason why this drug was withdrawn from the market in August 2001. Although cerivastatin was introduced in 1997, it was responsible for almost 60% of deaths caused by rhabdomyolysis in statin-treated patients noted in the USA between 1990 and 2002, although in the same period only 2% of statin prescriptions were written for this drug. The estimated rate of rhabdomyolysis is 4.3/100 000 prescriptions for cerivastatin in comparison to <0.2/100 000 prescriptions for other statins[35]. Pravastatin is on the opposite end of this spectrum because it is hydrophilic. In addition, pravastatin is not metabolized by cytochrome P450, therefore, is not expected to interact with other drugs metabolized by this enzymatic system.

The mechanism of statin-induced muscular side effects is unclear at present. Several hypotheses have been raised to explain the pathogenesis of this complication: (1) CoQ deficiency, leading to abnormalities of mitochondrial respiration, (2) oxidative stress, (3) apoptosis, (4) reduced chloride permeability.

Until now, there are few data supporting the role of CoQ in statin-induced myopathy. Although depletion of CoQ in skeletal muscles has been reported in animals treated with statins, there was no correlation between its level and myopathy[36,37]. In addition, no abnormalities of mitochondrial respiration were observed in the animal models of statin myotoxicity. Although statins reduce plasma CoQ in hypercholesterolemic humans, no changes in its content in skeletal muscles were observed[38, 39]. In addition, ATP and phosphocreatine levels in muscular tissue remained intact. Although in the other study depletion of skeletal muscle CoQ was reported following high dose simvastatin or atorvastatin therapy[40], no studies addressed muscular CoQ level in patients with

myopathy in comparison to those without this complication. In addition, no systematic studies investigated whether CoQ supplementation alleviates symptoms of statin-induced myopathy. There are only some case reports suggesting that CoQ administration may reduce the severity (but not the incidence) of myopathy in patients receiving statins[28].

Sinzinger *et al.*[41] observed elevation of plasma and urinary isoprostanes in 18 of 31 patients with statin-induced myopathy. Stopping statin treatment was associated with normalization of isoprostane level and later reexposure to a different statin caused an increase in isoprostane only in those individuals in whom muscular symptoms reappeared. In addition, vitamin E has been reported to ameliorate symptoms of statin-induced myopathy[42]. Taken together, these data strongly support the role of oxidative stress in muscular side effects of statins. Further studies are warranted to investigate whether antioxidants could be effective in the prevention and/or treatment of statin-induced myopathy.

Statins may induce apoptosis of cultured skeletal muscle cells. This effect is reversed by mevalonate, farnesylpyrophosphate and geranylgeranylpyrophosphate but not by squalene or cholesterol, suggesting that depletion of nonsteroid isoprenoids is involved[43]. Finally, it has been suggested that statins may reduce plasma membrane chloride permeability thus favoring membrane depolarization and leading to muscle cramps[44].

The current guidelines[45] suggest that to minimize the risk of myopathy, statin treatment should be started with the lowest available dose of drug. Only if the recommended LDL cholesterol goals can not be achieved, the dose may be gradually increased. Plasma CK activity should be measured in each patient before initiating statin therapy. Routine follow-up CK measurement is not recommended, however, muscle tenderness should be evaluated and if any muscular side effects are suspected, plasma CK should be re-evaluated and compared to baseline values. If muscular symptoms are present and CK activity is normal or moderately elevated (<10 times the upper limit of normal), drug administration may be continued but the patient should be more frequently monitored. If progressive increase in CK activity is observed, statin dose should be reduced or treatment should be temporarily discontinued. When CK activity is elevated above 10 times the upper limit of normal, the drug must be immediately withdrawn. Patients with recognized rhabdomyolysis usually need hospitalization. Treatment of this complication includes parenteral hydration, administration of mannitol and bicarbonates to stimulate osmotic diuresis and alkalinize urine (this inhibits precipitation of myoglobin inside renal tubules) as well as careful monitoring of plasma K^+ since hyperkalemia may induce life-threatening arrhythmias.

NERVOUS SYSTEM DISEASES

One case of simvastatin-induced mitochondrial encephalopathy with lactic acidosis (MELAS) syndrome has been reported in the literature. Stroke-like episode was associated with increased plasma lactate/pyruvate ratio. Neurological abnormalities were accompanied by myopathy and responded to coenzyme Q_{10} therapy[46].

Several epidemiological studies have demonstrated that the risk of peripheral polyneuropathy is increased 2-5 times in statin-treated patients[47-49]. However, the overall risk is low; it is estimated that a single additional case of neuropathy would arise if approximately 14 000 patients received treatment with statin for a year[50]. It seems that in contrast to myopathy, which incidence is clearly dose-dependent, the risk of neuropathy depends on the duration of statin use; i.e. the cumulative dose, rather than the daily dose since this complication develops usually after long time treatment[49]. Statin-induced neuropathy is characterized by paresthesias, sensory loss, hyperesthesia of the extremities, areflexia and muscle weakness. Symptoms of neuropathy are relieved by discontinuation of treatment, however, any attempt to rechallenge with statins are associated with their recurrence[47].

Cognitive impairment and memory loss were occasionally observed in statin-treated patients[51-53]. The mechanism of this effect was partially explained by the experimental study of Matthiews *et al.*[54] who demonstrated that statins diminished long-term potentiation of synaptic transmission in the hypoccampal slices-the model of activity-dependent synaptic plasticity which is one of the principal mechanisms of learning in higher vertebrates.

UNBENEFICIAL EFFECTS IN THE CARDIOVASCULAR SYSTEM

The majority of studies have documented beneficial effects of statins on various aspects of cardiovascular function, i.e. improvement of endothelium-dependent vasorelaxation, reduced oxidizability of plasma lipoproteins, inhibition of growth and stabilization of atherosclerotic plaque, etc. However, there are some data suggesting that under specific experimental conditions detrimental effects of statins on cardiovascular pathophysiology may be observed.

Vascular reactivity: It has been observed that fluvastatin augmented the vasoconstricting effect of KCl or adrenaline in apolipoprotein E-knockout mice[55]. Treatment of rats with atorvastatin, pravastatin or simvastatin impaired acetylcholine-induced relaxation of isolated aorta, which was normalized by superoxide dismutase[56]. Fisslthaler *et al.*[19] have demonstrated that cerivastatin impairs NO-dependent relaxation of porcine coronary arteries. In both Spontaneously Hypertensive Rats (SHR) and in control normotensive Wistar-Kyoto (WKY) rats lovastatin increased whereas mevalonate decreased blood pressure[57]. In addition, mesenteric arteries isolated from lovastatin-treated animals showed increased contractile response to noradrenaline and impaired NO-dependent relaxation to acetylcholine. These effects were also reproduced when isolated arteries were treated with lovastatin or mevalonate *in vitro*. Further studies by this group confirmed these observations in rat conduit arteries and in human resistance arteries[58].

Two mechamisms may contribute to deleterious effects of statins on vascular reactivity. First, as previously stated, statins may stimulate vascular cytochrome P4502C-derived ROS which inactivate nitric oxide[19,56]. Second, statin-induced deficiency of farnesol may be important. Farnesol, the product of mevalonate cascade, inhibits norepinephrine-induced vasoconstriction of rat and human mesenteric arteries[59]. Later studies have demonstrated that farnesol inhibits Ca^{2+} entry to vascular smooth muscle cells by blocking L-type calcium channels[60,61]. Defect of mevalonate cascade (decreased activity of mevalonylpyrophosphate decarboxylase) leading to decreased plasma cholesterol and nonsteroid isoprenoids is observed in SHR[62]. In addition, oral administration of farnesol or mevalonate normalizes blood pressure in this strain[61]. Collectively, these data suggest that farnesol deficiency may contribute to the pathogenesis of hypertension in SHR.

LDL oxidizability and atherogenesis: Peroxidation of unsaturated fatty acids contained in plasma LDL plays an important role in atherogenesis. Oxidized LDLs do not bind to LDL receptors but are taken up by macrophage scavenger receptors, leading to cholesterol overload and formation of foam cells-a major constituent of early atherosclerotic plaque. In addition, oxidized LDL inhibit endothelial NO production, are chemotactic for inflammatory cells, stimulate proliferation of vascular smooth muscle cells and induce the immune response. Thus, modulating LDL oxidation may have an important impact on atherogenesis. Although most studies demonstrated reduced oxidizability of plasma LDL following statin treatment, some authors reported the opposite data. For example, oxidizability of LDL challenged with oxidants *ex vivo* increased following 1-year fluvastatin therapy in hypercholesterolemic renal transplant recipients[63]. The similar effect was noted in patients with ischemic heart disease receiving cerivastatin[64] and lovastatin[65]. Increased LDL oxidizability is associated with reduced ubiquinone content in these lipoproteins[66]. Indeed, coadministration of exogenous ubiquinone normalized LDL resistance to oxidative damage in some of these studies[67,68].

The susceptibility of isolated LDL to oxidation *in vitro* is at best only a crude estimate of processes occurring *in vivo*. Recently, Vasankari *et al.*[69] have investigated the effect of atorvastatin or simvastatin treatment on baseline content of Conjugated Dienes (CD) in LDL - a marker of LDL oxidation *in vivo* - in patients with hypercholesterolemia and coronary heart disease. They observed that although LDL cholesterol decreased in statin-treated patients by almost 50%, the amount of CD in these lipoproteins dropped by only 10-12% after 12 weeks of therapy. Moreover, after 12 months of statin administration CD returned to pretreatment values which resulted in 50% elevation of CD/LDL-cholesterol ratio; the results indicative of increased LDL oxidizability.

Reverse cholesterol transport from peripheral tissues to the liver driven by plasma High Density Lipoproteins (HDL) plays an important role in tissue cholesterol homeostasis and is responsible for antiatherosclerotic properties of this lipoprotein fraction. This process is initiated by cholesterol transfer from the plasma membrane to HDL by ABCA1 (ATP binding cassette A1) transporter protein. A recent study has demonstrated that statins reduce ABCA1 expression in cultured human macrophages which is accompanied by impaired cholesterol efflux[70]. The mechanism of this effect was also elucidated. Statins decrease the synthesis of 24(S),25-epoxycholesterol which, like other oxysterols, is an activator of Liver X Receptor (LXR)-the ligand-activated transcription factor which stimulates the expression of genes involved in reverse cholesterol transport including ABCA1.

Inhibition of LXR-dependent signaling may be an important mechanism also of other side effects of statins. In particular, Gouedard *et al.*[71] have demonstrated that statins inhibit the expression of paraoxonase 1 (PON1) in cultured human hepatocytes. PON1 is synthesized in the liver and circulates in plasma attached to HDL. The enzyme plays an important role in atheroprotection by inhibiting oxidative modification of LDL and HDL as well as by reducing cholesterol synthesis in macrophages[72].

We observed that treatment of rats with various statins reduces PON1 activity in plasma, liver and kidney[73-75], suggesting that this effect of statins may be relevant *in vivo*. The effect of statins on PON1 was reversed by exogenous LXR agonists, suggesting that it may result from deficiency of oxysterols[71] .

Another potentially proatherogenic effect of statins was recently discovered by Ruiz-Velasco *et al.*[76] who have demonstrated that in cultured macrophages statins stimulate the expression of CD36, one of scavenger receptors involved in the uptake of oxidized LDL. Finally, enhancing effect of statins on the expression of adhesion molecules by endothelial cells may contribute to the migration of monocytes to subendothelial space, which is an important step in plaque formation[77].

Are these potentially proatherogenic effects relevant *in vivo*? Although most studies documented antiatherosclerotic effect of statins, the opposite data are also available. For example, Choudhury *et al.*[78] have demonstrated that treatment with simvastatin worsens neointimal proliferation after wire-induced injury of the femoral artery in apolipoprotein E knockout mice. In addition, high fat-fed apo-$E^{-/-}$ animals treated with simvastatin develop more atherosclerotic lesions[79]. These data suggest that under certain experimental conditions statins may be proatherogenic. Interestingly, several mutations of nuclear lamins are associated with accelerated atherosclerosis in humans[80]. Lamins are proteins contained in the nuclear membrane which are farnesylated by protein farnesyltransferase. Statins, by depleting intracellular farnesylpyrophosphate pool, will be expected to decrease lamin activity.

Myocardial contractility: It has long been recognized that CoQ deficiency leads to the impairment of myocardial contractility and that its supplementation can improve cardiac function[81]. In the rat, lovastatin decreased not only plasma but also myocardial CoQ concentration[5]. Diebold *et al.*[82] observed that lovastatin decreased CoQ_{10} level in cardiac muscle of the older guinea-pigs and this was accompanied by impaired phosphorylation of ADP to ATP. These effects were not observed in young animals, although the reducing effect on plasma cholesterol was not age-dependent. These results suggest that older myocardium may be more sensitive to the adverse effect of statins.

Pretreatment with lipophilic simvastatin but not with hydrophilic pravastatin worsened myocardial stunning induced by experimental occlusion of left coronary artery in dogs[83]. Simvastatin treatment was also associated with lower myocardial CoQ_{10} and greater drop in tissue ATP during ischemia and reperfusion in rat and dog hearts[12,13]. The same was observed with other lipophilic statins including fluvastatin, atorvastatin and cerivastatin[84]. It is suggested that reducing effect of lipophilic statins on myocardial CoQ production may account for the paradox that in most clinical trials lipophilic statins had less favorable effect on all-cause mortality than hydrophilic ones despite similar or even greater reduction of coronary artery stenosis[85]. In hamsters with inherited cardiomyopathy lovastatin but not pravastatin shortened the medium survival during heart failure phase from 89 to 30 days[86].

Simvastatin treatment decreased myocardial concentration of CoQ_9 and CoQ_{10} in rats with arterial hypertension induced by chronic NOS blockade. Interestingly, although simvastatin decreased blood pressure in this model, it did not prevent myocardial hypertrophy (in contrast to other equally effective hypotensive drugs), suggesting that simvastatin has blood pressure-independent unbeneficial effect on myocardial remodeling[87].

The effect of statins on the progression of human heart failure is not entirely clear because no trials were specifically designed to test it. However, in patients with cardiac failure administration of lovastatin has been demonstrated to impair myocardial performance as evidenced by reduced left ventricular ejection fraction and this effect was prevented by coadministration of coenzyme Q[7]. More recently, Silver *et al.*[88] have demonstrated that atorvastatin treatment for 3 or 6 months worsened at least 1 echocardiographic marker of left ventricular diastolic function in 70% of treated patients with no clinical features of heart failure. In most of them unbeneficial effect of atorvastatin was ameliorated by CoQ supplementation. Interestingly, plasma CoQ was higher in those who did not present the impairment of cardiac function during statin therapy. In one prospective study[89], a trend toward more admissions due to heart failure was observed in patients with average or low plasma cholesterol treated with atorvastatin in comparison to placebo group. De Lorgeril *et al.*[90] reported that 12-week simvastatin treatment had no effect on left ventricular ejection fraction, however, myocardial reserve, i.e. the response of ejection fraction to physical exercise, was impaired. These data suggests that in some circumstances, especially in patients with previously impaired myocardial contractility, statins could worsen heart failure by inhibiting coenzyme Q formation.

Cardiovascular effects of statin withdrawal: It has been demonstrated that rapid withdrawal of atorvastatin increases aortic ROS generation by 2-fold. Statins inhibit geranylgeranylation of Rac1-an essential regulator of

vascular NADPH oxidase. Since during statin treatment Rac1 is not geranylgeranylated (and thus inactive), synthesis of this protein is compensatorily upregulated. After statin withdrawal, this increased Rac1 pool is rapidly activated, translocates to the plasma membrane and activates NADPH oxidase even above pretreatment level. The effect is accompanied by impaired endothelium-dependent vasorelaxation due to O_2^--mediated inactivation of NO[21]. Other studies demonstrated that statin withdrawal may induce also other rebound phenomena such as downregulation of endothelial NO synthase[91], platelet hyperactivity[92], increased expression of Monocyte Chemoattractant Protein-1 (MCP-1) in endothelial cells[93] and elevation of plasma C-reactive protein reflecting systemic proinflammatory state[94]. All these events may contribute to the impairment of endothelium-dependent vasorelaxation[95] and to increased prevalence of acute cardiovascular events[96] observed in humans after statin withdrawal. These data suggest that like some other cardiovascular drugs such as β-adrenergic antagonists, statins should not be withdrawn rapidly, but rather their dose should be gradually reduced.

PROINFLAMMATORY EFFECT OF STATINS AND THEIR IMPACT ON THE IMMUNE RESPONSE

Most studies performed to date reported that statins inhibit inflammatory reaction, however, data about possible proinflammatory effect of HMG-CoA reductase inhibitors are also available. For example, fluvastatin induced the release of interleukin-1β (IL-1β), interferon-γ and interleukin-18 by human peripheral blood monocytes[97]. In human umbilical vein endothelial cells, simvastatin enhanced the expression of adhesion molecules: E-selectin, ICAM-1 and VCAM-1 induced by IL-1β or tumor necrosis factor-α[77]. It should also be noted that inherited mevalonate kinase deficiency-the rare disease associated with lower production of cholesterol and nonsteroid isoprenoids which mimics the effect of statins-is characterized by recurrent episodes of fever and other features of generalized inflammation. The symptoms may be stabilized by CoQ whereas lovastatin induced severe crises in these patients, suggesting that shortage of isoprenoids rather than excess of mevalonate is responsible for proinflammatory state[98] .

Recently, Sinzinger[99] described 5 cases of flue-like response to statins, characterized by myalgia, weakness, paining joints, fever and increased acute phase reactants. Plasma CK was normal, excluding statin-induced myopathy. In 4 of these patients severe increase in plasma and urinary isoprostanes was observed, suggesting the involvement of oxidative stress.

There are several case reports of statin-induced autoimmune diseases, in particular Systemic Lupus Erythematosus (SLE) and less frequently dermatomyositis, autoimmune hepatitis or pemphigoides[100]. Interestingly, these complications may develop many months or even years after starting statin therapy and frequently do not improve following drug discontinuation. In many cases antinuclear antibodies, a hallmark of SLE, are detected in patient sera many months after interruption of treatment. Therefore, the causal relation between statin and autoimmune reaction may be difficult to established and consequently, these side effects are probably underreported. It is not entirely clear how statins could induce the autoimmune reactions. Statins induce apoptosis in many cell types and thus could release intracellular antigens such as histones or nucleic acids which then may trigger the immune response. In addition, statins shift the immune response from Th1-mediated (cellular) toward Th2-mediated (humoral) and thus may facilitate formation of autoantibodies[101].

Hyperlipidemia is a common complication in HIV-infected patients treated with antiretroviral drugs. According to some statistics, hyperlipidemia-induced cardiovascular complications may be significant contributor to mortality, comparable to or even exceeding the developed AIDS. Statins are widely used in the management of hyperlipidemia in these patients, however, they may impair the beneficial effect of antiretroviral therapy on the amount of CD4+ (T-helper) lymphocytes[102]. It should be mentioned that patients with the Griscelli syndrome caused by the mutation of Rab27a protein are characterized by immune deficiency. Rab27a is involved in fusion of lytic granules of cytotoxic lymphocytes with their plasma membrane, which explains the immune deficit in these patients. Rab27a is a geranylgeranylated protein and thus its activity may be impaired in statin-treated individuals. Apart from the effect on lymphocytes, statins have been reported to inhibit phagocytosis[103].

HEPATOTOXICITY

Four main statin-induced hepatic syndromes have been recognized, however, the overlapping forms are common: (1) asymptomatic elevation of serum transaminases, (2) hepatitis, (3) cholestasis and (4) acute liver failure.

Elevation of transaminases is observed in 0.5-2% of patients treated with statins[104]. However, in most prospective trials the incidence of transaminase elevation was not significantly different between statin and placebo groups. Thus, whether the causal relationship exists

between statin administration and liver damage remains an open question. Moreover, during the follow-up transaminase activity usually returns to normal despite continuation of statin therapy. It is likely that in many patients high transaminase activity results from fatty liver disease which is common in subjects with hyperlipidemia, obesity and diabetes mellitus, who are frequently treated with statins. The recent meta-analysis[105] involving 13 statin trials in which almost 50 000 of patients were included revealed that among currently used statins only fluvastatin increased transaminases more frequently than placebo. Asymptomatic elevation of transaminases is not an indication to discontinue potentially life-saving statin therapy. Currently, monitoring of serum transaminases is not recommended in statin-treated patients.

Statin-induced hepatitis, associated with higher transaminase activity (>3 times the upper limit of normal), hyperbilirubinemia and clinical symptoms of liver dysfunction, is much less common and is estimated to occur in about 10/1 million patient-years[106]. Early animal studies have demonstrated that statins may induce hyperplasia of bile canaliculi, diminute bile flow, induce gallstone formation and elevate plasma concentration of bile acids and conjugated bilirubin[107]. The incidence of cholestasis, associated with pruritus, jaundice, increased activity of alkaline phosphatase and γ-glutamyltranspeptidase, in statin-treated individuals is about 1/150 000 patient-years[108]. Acute Liver Failure (ALF) is a life-threatening complication which develops with the incidence of about 10/1 million patient-years[109]. ALF is an idiosyncratic reaction which, unlike other side effects of statins, is dose-and time-independent and therefore virtually impossible to predict. It remains an important challenge for future research to establish what mechanism(s) determine the susceptibility of a given patient to this potentially fatal complication and to develop the methods which could allow identifying those who are predicted to develop it. It should be mentioned that clinically silent elevation of serum transaminases has no value in predicting ALF.

The seminal study performed recently[110] addressed the question whether preexisting liver disease (elevated serum transaminases before starting statin therapy) increases the risk of statin-induced hepatotoxicity. Three groups of patients have been studied: statin-treated with initially normal transaminases, statin-treated with initially elevated transaminases and patients with elevated transaminases who were not treated with statins. During 6-month follow-up increase in serum transaminases in statin-treated group with preexisting liver diseases was observed more frequently than in those with initially normal transaminases, however, it was not higher than in the group with initially elevated transaminases not treated with statins. These results suggest that increase in transaminases during therapy results from the progression of liver disease rather than from statin administration. These data suggest that pretreatment increase in serum transaminases does not increase the risk of statin-induced hepatotoxicity and thus is not a contraindication for therapy.

OTHER SIDE EFFECTS

Insulin stimulates the activities of protein farnesyltransferase and geranylgeranyltransferase both *in vitro* and *in vivo*[111,112]. It has been shown that statins may impair insulin signaling *in vitro*[113-115]. Some studies suggest decreased insulin sensitivity and elevation of plasma insulin concentration following statin therapy in animals and human subjects with previously normal insulin sensitivity[116,117].

Increased breast cancer rates have been observed in some statin trials[118-121]. The relationship between low CoQ level and the incidence of breast cancer has been reported[122]. Therefore, some authors suggest that statins may increase the risk of breast cancer by inhibiting coenzyme Q synthesis[123]. Muscaritoli *et al.*[124] have demonstrated that simvastatin administration worsens cachexia in rats inoculated with Yoshida AH-130 ascites hepatoma cells. Simvastatin had no effect on body weight in control animals, however, aggravated weight reduction in tumor-bearing rats, although it had no effect on either tumor growth or food intake.

Although many clinical studies suggest renoprotective effect of statins, i.e. slowing the progression of chronic nephropathy especially in patients with diabetes mellitus, it was occasionally observed that statins may induce moderate proteinuria and sometimes hematuria. This was particularly common in patients taking the highest available dose of rosuvastatin (80 mg day^{-1})-the most potent HMG-CoA reductase inhibitor currently used in clinical practice[125]. Generally, proteinuria has a detrimental effect on the progression of nephropathy since it stimulates interstitial inflammation and fibrosis. Although in statin-treated patients proteinuria was not accompanied by the deterioration of renal function, high doses of statins may induce tubular degeneration in experimental animals[126]. The mechanism of statin-induced proteinuria was recently clarified. Two experimental studies performed on cultured opossum kidney cells[127] and on human tubular cells[128] have demonstrated that statins inhibit protein endocytosis. This is consistent with the tubular type proteinuria in statin-treated patients, i.e. preferential excretion of

low-molecular weight proteins which are normally filtered in glomeruli and then reabsorbed by the proximal tubules. However, the significance of these observations for the potential nephrotoxic effect of statins is not entirely clear because inhibiting protein endocytosis could actually protect tubular cells from detrimental effect of endocytosed proteins.

Both experimental[129-131] and some clinical studies[132,133] suggest that statin treatment may increase the risk of cataract. Finally, statins are contraindicated during pregnancy since they increase embryonic lethality as well as induce central nervous system and limb developmental anomalies[134].

CONCLUSIONS

Statins are now among most frequently prescribed medications and are currently used by about 25 million people worldwide. The population treated with statins is likely to increase dramatically in the near future because they are now recommended also for persons with average or low cholesterol level, especially in secondary prevention. Recently, the lowest dose of simvastatin was introduced to the UK market as the other-the-counter drug available without prescription.

There is no doubt that statins have marked net beneficial effect by substantially reducing cardiovascular risk. In most patients statins are safe and well tolerated. However, essential role of many mevalonate derivatives in cell physiology suggests that inhibiting their production may not be exclusively beneficial. Many potentially negative effects of statins have been observed in experimental studies. Some of them may lead to rare potentially fatal adverse effects such as rhabdomyolysis or acute liver failure, whereas others may only reduce, to some extent, the overall benefit. Although in all statin trials published to date the net benefit far exceeds any potential risk, patients selected for randomized placebo-controlled trials are carefully selected, screened for any contraindications and systematically monitored. The amount of side effects in routine clinical practice may be slightly higher. Moreover, statins are recommended as a lifelong therapy whereas most trials were relatively short ($\leq$5 years). With growing number of patients taking these drugs for the increasing period of time, we should be prepared for more side effects in the future.

It should also be noted that the benefit of statins was the largest in high-risk patients, i.e. those with hyperlipidemia, especially in secondary prevention. The benefit/risk ratio in low-risk groups (normolipidemia and primary prevention) seems to be less favorable and some of these studies observed in fact the trend toward harm in statin-treated vs. placebo arm[135]. Of course, the usefulness of statin therapy can not be questioned, however, studies demonstrating their unbeneficial effects should not be neglected. The important challenge for future research is to identify factors which predispose a given person for certain side effects of statins. This would allow to select for therapy the patients who may obtain the greatest benefit and to prevent or at least minimize the risk of adverse effects.

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