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Safety of Statins
Focus on Clinical Pharmacokinetics and Drug Interactions

Stefano Bellosta, PhD; Rodolfo Paoletti, MD, PhD; Alberto Corsini, PhD

Abstract—Statin monotherapy is generally well tolerated, with a low frequency of adverse events. The most important adverse effects associated with statins are myopathy and an asymptomatic increase in hepatic transaminases, both of which occur infrequently. Because statins are prescribed on a long-term basis, however, possible interactions with other drugs deserve particular attention, as many patients will typically receive pharmacological therapy for concomitant conditions during the course of statin treatment. This review summarizes the pharmacokinetic properties of statins and emphasizes their clinically relevant drug interactions.(*Circulation*. 2004;109[suppl III]:III-50–III-57.)

Key Words: drug interactions ■ fibrates ■ rhabdomyolysis ■ safety ■ statins

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are a well-established class of drugs in the treatment of hypercholesterolemia, and members of this class have been shown to reduce the risk of cardiovascular morbidity and mortality in patients with or at risk for coronary heart disease (CHD)[1,2] in several clinical trials. These trials have largely dispelled doubt about the safety and tolerability of statins. In fact, the common adverse effects associated with statin therapy are relatively mild and often transient (gastrointestinal symptoms, headache, rash).[1,3] The most important adverse effects associated with statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) are asymptomatic increases in liver transaminases and myopathy. Based on this clinical evidence, the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III report[3] extended the use of lipid-lowering treatments to a larger number of high-risk CHD patients who often receive more than one medication. Therefore, the potential for drug–drug interactions emerges as a relevant factor in determining the safety profile of statins. Pharmacological differences are evident among the statins, however, and these may affect their safety and potential for drug interactions.[4] Moreover, as pointed out in a recent adverse-event report from the U.S. Food and Drug Administration (FDA),[5] the incidence of side effects might be higher in clinical situations in which patients are not monitored as closely as in clinical trials. The worldwide withdrawal of cerivastatin in August 2001 because of its association with fatal rhabdomyolysis further underscores the importance of considering the safety profile of the available statins.[6] The purpose of this article is to increase awareness of differences that could help clinicians in selecting the appropriate statin for long-term treatment of their patients.

Liver Transaminase Elevations

During initial postmarketing surveillance of statins, elevations in hepatic transaminases were reported at incidences of up to 1%;[1,7] these elevations were dose related and comparable among the various statins, although not significantly increased compared with placebo.[7] The majority of liver abnormalities occur within the first 3 months of therapy and require monitoring.

Myopathy

The term "myopathy" designates any noninherited disorder of skeletal muscle that causes proximal muscle weakness, with difficulty in arising from a chair or raising arms above the head.[8] Duration of statin therapy before the onset of myopathy varies from a few weeks to more than 2 years.[9] Statin-associated myopathy represents a broad clinical spectrum of disorders, from mild muscle aches to severe pain and restriction in mobility, with grossly elevated creatine kinase (CK) levels.[8] However, patients have been described who developed these symptoms while receiving statin therapy despite normal serum CK levels, thus pointing out the inadequacy of CK testing for statin-associated myopathy.[10,11] In statin clinical trials, the reported incidence of myopathy was low (0.1 to 0.2%).[8,12] The symptoms progress toward rhabdomyolysis as long as patients continue to take the drug. Rhabdomyolysis is a syndrome that results from severe skeletal muscle injury and lysis, causing the widespread release of myoglobin with dark brown urine secondary to myoglobinuria.[1,8] An analysis of data from the Adverse Event Reporting System (AERS) of the FDA showed that as of June 2001, fatal rhabdomyolysis had been reported at rates of <1 death per 1 million prescriptions for all statins, except cerivastatin, which had an incidence of >3 deaths per 1 million prescriptions.[6]

TABLE 1. Profile of Reports of Rhabdomyolysis Associated With Statins

Statin	Frequency of Reports/Unique Cases	No. of Cases Associated With Potentially Interacting Drugs* (n)	
Simvastatin	321/215	Mibefradil (48)	Azole antifungals (4)
		Fibrates (33)	Chlorzoxazone (2)
		Cyclosporine (31)	Nefazodone (2)
		Warfarin (12)	Niacin (2)
		Macrolide antibiotics (10)	Tacrolimus (1)
		Digoxin (9)	Fusidic acid (1)
Cerivastatin	231/192	Fibrates (22)	
		Digoxin (7)	
		Warfarin (6)	
		Macrolide antibiotics (2)	
		Cyclosporine (1)	
		Mibefradil (1)	
Atorvastatin	105/73	Mibefradil (45)	
		Fibrates (10)	
		Macrolide antibiotics (13)	
		Warfarin (7)	
		Cyclosporine (5)	
		Digoxin (5)	
		Azole antifungals (2)	
Pravastatin	98/71	Fibrates (6)	
		Macrolide antibiotics (6)	
		Warfarin (5)	
		Cyclosporine (2)	
		Digoxin (2)	
		Mibefradil (1)	
		Niacin (1)	
Lovastatin	51/40	Cyclosporine (12)	Digoxin (2)
		Macrolide antibiotics (11)	Nefazodone (2)
		Azole antifungals (6)	Niacin (1)
		Fibrates (5)	Warfarin (1)
		Mibefradil (3)	
Fluvastatin	11/10	Fibrates (4)	
		Warfarin (2)	
		Digoxin (1)	
		Mibefradil (1)	

*Each case may be associated with 1 or more potentially interacting drugs.
Adapted from Omar MA, Wilson JP. *Ann Pharmacother.* 2002;36:288–295.

It should be noted that the development of myopathy is induced by a complex interaction between drug, disease, genetics, and concomitant therapy.[4,7] Several risk factors that predispose patients to myopathy include increased age, female gender, renal or liver disease, diabetes mellitus, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, and heavy exercise.[13] The mechanism by which statins cause myopathy is not completely understood. However, the clinical association appears to be dose dependent, and the risk is known to increase when statins are prescribed in combination with agents that are also myotoxic when used as monotherapy or that increase the serum concentration of the statin.[4,14] For example, one study reported an 0.15% incidence of myopathy with lovastatin monotherapy, which increased to 2%, 5%, and 28%, respectively, in patients receiving concomitant niacin, gemfibrozil, or cyclosporine plus gemfibrozil.[9] A review by Omar and Wilson[5] of all reports of statin-associated cases reported to the FDA (between November 1997 and March 2001) showed a total of 817 reports and 601 cases of rhabdomyolysis associated with all statins available at that time. As shown in Table 1, in ≈55% of all cases, a drug–drug interaction was suspected.[5] A more extensive FDA search on statin-associated rhabdomyolysis, covering the period from January

TABLE 2.   Clinical Pharmacokinetics of HMG-CoA Reductase Inhibitors

Parameter	Atorvastatin	Fluvastatin	Fluvastatin XL	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
T_{max} (h)	2–3	0.5–1	4	2–4	0.9–1.6	3	1.3–2.4
C_{max} (ng/mL)	27–66	448	55	10–20	45–55	37	10–34
Bioavailability (%)	12	19–29	6	5	18	20	5
Lipophilicity	Yes	Yes	Yes	Yes	No	No	Yes
Protein binding (%)	80–90	>99	>99	>95	43–55	88	94–98
Metabolism	CYP3A4	CYP2C9	CYP2C9	CYP3A4	Sulfation	CYP2C9, 2C19 (minor)	CYP3A4
Metabolites	Active	Inactive	Inactive	Active	Inactive	Active (minor)	Active
Transporter protein substrates	Yes	No	No	Yes	Yes/No	Yes	Yes
$T_{1/2}$ (h)	15–30	0.5–2.3	4.7	2.9	1.3–2.8	20.8	2–3
Urinary excretion (%)	2	6	6	10	20	10	13
Fecal excretion (%)	70	90	90	83	71	90	58

Based on a 40-mg oral dose, with the exception of fluvastatin XL (80 mg).

Adapted from data in Corsini A, et al. *Pharmacol Ther.* 1999;84:413–428, and White CM. *J Clin Pharmacol.* 2002;42:963–970.

1990 through March 2002, showed that among 3339 reports of rhabdomyolysis, ≈58% of the cases were associated with concomitant medications affecting statin metabolism, including mibefradil, fibrates, cyclosporine, macrolides, warfarin, digoxin, and azole antifungals.[15] The incidence of fatal rhabdomyolysis has been estimated using databases from the FDA and is low, resulting in only 0.15 deaths per 1 million prescriptions. This figure uses as the denominator the number of prescriptions, not the number of individuals using the medication.[15] Clinical trial results support a low incidence of severe muscle problems with statin therapy. A compilation of all randomized controlled statin trials revealed that among 83 858 patients randomly assigned to receive either statin treatment or placebo, there were only 49 cases of myositis and 7 cases of rhabdomyolysis in the statin groups, compared with 44 cases of myositis and 5 cases of rhabdomyolysis in the placebo groups.[15] However, these results in volunteer study participants who were monitored by lipid researchers may underestimate the incidence when statins are used in unselected populations monitored with less precision.[15] Thus, although there are significant limitations to the interpretation of the reported adverse events, this information has valuable implications for clinical practice.

Drug Interactions With Statins: Focus on Pharmacokinetic Differences

To understand the molecular bases of statin–drug interactions, it is important to mention that statins are very selective inhibitors of HMG-CoA reductase and usually do not show any relevant affinity toward other enzymes or receptor systems.[4] This suggests that, at the pharmacodynamic level (ie, at their site of action), statins are not prone to interfere with other drugs. However, at the pharmacokinetic level (ie, absorption, distribution, metabolism, and excretion of a given drug), the available statins have important differences, including half-life, systemic exposure, maximum plasma concentration (C_{max}), bioavailability, protein binding, lipophilicity, metabolism, presence of active metabolites, and excretion routes (Table 2).[4,16] The liver biotransforms all statins, which accounts for their overall low systemic bioavailability. The

apparent total body clearance is very high because of an important hepatic first-pass effect. With the exception of pravastatin, which is transformed enzymatically in the liver cytosol, all statins undergo extensive microsomal metabolism by the cytochrome P450 (CYP) isoenzyme systems (Table 3). About half of all drugs currently available in clinical practice are biotransformed in the liver primarily by the CYP450 3A4 system.[17] The CYP3A4 isoenzyme is responsible for the metabolism of lovastatin, simvastatin, and atorvastatin. Fluvastatin is metabolized primarily by the CYP2C9 enzyme, with CYP3A4 and CYP2C8 contributing to a lesser extent.[4] Rosuvastatin is not extensively metabolized, but has some interaction with the CYP2C9 enzyme.[16]

These differences can affect the potential for drug interactions with statins,[4] which can result in markedly increased or decreased plasma concentrations of some drugs within this class. Concomitant use of certain drugs (fibrates, erythromycin, itraconazole, and immunosuppressive drugs such as cyclosporine) can increase blood levels of statins and, consequently, the risk for myopathy.[18] The relationship between altered plasma concentrations and adverse effects or toxicity might not be linear.[10,19] Other variables that affect this concentration–effect relationship include rapid changes in the concentrations, concomitant lipid-lowering therapy, or host genetic factors that code for different forms or amounts of metabolizing enzymes and drug receptors. Special populations at high risk for cardiovascular disease, such as patients with coronary heart disease, dyslipidemia, diabetes, hypertension, nephrotic disease, human immunodeficiency virus (HIV) infection, organ transplant patients, and the elderly, should receive particular attention to avoid clinically relevant interactions. However, because statins have different pharmacological properties, some statins may be more or less likely than others to cause drug interactions.[4] Nevertheless, the incidence of both myopathy and rhabdomyolysis with statins is quite low, despite the common coprescription of these agents with competing substrates or inhibitors of their metabolism.[20,21] Indeed, up to one third of prescriptions issued for statins were in combination with drugs that could poten-

TABLE 3. Human Cytochrome P450 Isoenzymes Known to Oxidize Clinically Used Drugs

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A4
Acetaminophen	Alprenolol	Diazepam	Amitriptyline	Acetaminophen	Amiodarone
Caffeine	Diclofenac	Ibuprofen	Codeine	Etanol	Atorvastatin
Theophylline	Fluvastatin	Mephenytoin	Debrisoquine	Halothane	Clarithromycin
	Hexobarbital	Methylphenobarbital	Flecainide		Cyclosporine
	Phenytoin	Omeprazole	Imipramine		Diltiazem
	Tolbutamide	Phenytoin	Metoprolol		Erythromycin
	Warfarin	Proguanyl	Mibefradil		Itraconazole
			Nortriptyline		Ketoconazole
			Pherexiline		Lacidipine
			Propafenone		Lovastatin
			Propranolol		Mibefradil
			Sparteine		Midazolam
			Thioridazine		Nefazodone
			Timolol		Nifedipine
					Protease inhibitors
					Quinidine
					Sildenafil
					Simvastatin
					Terbinafine
					Verapamil
					Warfarin

tially interact with them, although side effects occurred in only 3% of these patients.[22]

Statin Interactions With CYP450 Inhibitors

Induction or inhibition of CYP450 isoenzymes is an important cause of drug interactions.[4] Competitive inhibition between drugs at the enzymatic level is common and may serve to alter the disposition of statins, leading to increased plasma levels and greater risk of adverse events (Table 4). Pharmacokinetic interactions (eg, increased bioavailability) resulting in myositis and rhabdomyolysis have been reported after concurrent use of statins and several different classes of drugs (Table 5).[4,5,23–26]

Fluvastatin, which is primarily metabolized by CYP2C9, and pravastatin and rosuvastatin, which are eliminated by other metabolic routes, are less subject to this interaction than other statins. Nevertheless, a 5- to 23-fold increase in prava-

statin bioavailability has been reported in the presence of cyclosporine A.[4,27] It has been postulated that competition for carrier-mediated transport across the bile canalicular membrane between pravastatin and cyclosporine leads to a reduced biliary clearance of pravastatin.[4] A cyclosporine–pravastatin interaction may occur also at the level of the transport protein P-glycoprotein.[4] FDA adverse-events reports on statin-associated rhabdomyolysis[5] and postmarketing surveillance[28] have confirmed an increased risk of myopathy when pravastatin is combined with cyclosporine (Table 1). This suggests that cyclosporine may interact with statins via mechanisms not limited to CYP3A4 inhibition. On the other hand, fluvastatin shows a far milder interaction with cyclosporine, most likely because fluvastatin is primarily recognized by CYP2C9 rather than CYP3A4.[4] These findings provided a rationale for the Assessment of Lescol in Renal Transplantation (ALERT) trial in renal transplanted patients

TABLE 4. Inhibitors and Inducers of the Cytochrome P450 Enzymatic Pathway

CYP Substrates (Statins)	Inducers	Inhibitors
CYP3A4		
Atorvastatin, lovastatin, simvastatin	Phenytoin, phenobarbital, barbiturates, rifampin, dexamethasone, cyclophosphamide, carbamazepine, troglitazone, omeprazole	Ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, tricyclic antidepressants, nefazodone, venlafaxine, fluvoxamine, fluoxetine, sertraline, cyclosporine A, tacrolimus, mibefradil, diltiazem, verapamil, protease inhibitors, midazolam, corticosteroids, grapefruit juice, tamoxifen, amiodarone
CYP2C9		
Fluvastatin, rosuvastatin (2C19-minor)	Rifampin, phenobarbital, phenytoin, troglitazone	Ketoconazole, fluconazole, sulfaphenazole

TABLE 5.   Selected Drugs That May Increase Risk of Myopathy and Rhabdomyolysis When Used Concomitantly With Statins

CYP3A4 Inhibitors/Substrates	Others
Cyclosporine, tacrolimus	Digoxin
Macrolides (azithromycin, clarithromycin, erythromycin)	Fibrates (gemfibrozil)
Azole antifungals (itraconazole, ketoconazole)	Niacin
Calcium antagonists (mibefradil, diltiazem, verapamil)	
Nefazodone	
Protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir)	
Sildenafil	
Warfarin	

Adapted from Corsini A, et al. *Pharmacol Ther*. 1999;84:413–428.

with hypercholesterolemia who were treated with cyclosporine and randomized to receive either fluvastatin or placebo.[29] Adverse-event rates were similar in both treatment groups, as were rates of discontinuation because of adverse events. The incidence of alanine aminotransferase elevations ≥ 3 times the upper limit of normal (ULN) or CK elevations ≥ 5 times the ULN was similar in fluvastatin-treated and placebo-treated patients, and no elevations were accompanied by musculoskeletal symptoms. The safety profile is perhaps the most remarkable aspect of this trial, as all the renal transplant patients enrolled were taking cyclosporine, 80% were taking prednisone, and 95% received concomitant cardiovascular medications.[29] However, caution should be exercised when fluvastatin is combined with substrates for CYP2C9. For example, potentiation of the anticoagulant effects of warfarin,[4] and increased bioavailability, peak plasma concentrations, and plasma half-life of fluvastatin have been reported when fluvastatin is coadministered with diclofenac and fluconazole.[30,31]

Dyslipidemia, one of the major metabolic abnormalities associated with HIV infection, appears to be related to the use of protease inhibitors, due to increased hepatic triglyceride synthesis.[32] Statins are being used increasingly in HIV-infected patients. However, cases of myalgia, rhabdomyolysis, and transaminase elevations have been reported with statins[26,33] because of the fact that protease inhibitors also inhibit the CYP3A4/5 isoenzymes (Table 3).

Finally, inhibitors of CYP3A4 isoenzyme activity, such as cimetidine and grapefruit juice, increase the oral availability and pharmacokinetic parameters of statins, thus potentially increasing their systemic exposure and side effects. In particular, the administration of 200 mL of double-strength grapefruit juice 3 times a day for 2 days, followed on day 3 by the administration of lovastatin together with 200 mL of juice, and additional doses of 200 mL 30 minutes and 90 minutes after statin intake, increased the lovastatin concentration–time curve (AUC) and C_{max} 15-fold and 12-fold, respectively.[34] The same experiment was performed with simvastatin, and the AUC and C_{max} increased 16-fold and 9-fold, respectively.[35] However, despite the high concentrations of simvastatin and simvastatin acid when coadministered with grapefruit

juice, the HMG-CoA reductase inhibitory activity AUC and C_{max} increased only from 3-fold to 5-fold.[35] Under the same experimental conditions, grapefruit juice significantly increased up to 3.3-fold the AUC of atorvastatin, whereas no changes were observed in the pharmacokinetics of pravastatin.[36] The interaction potential of even high amounts of grapefruit juice with CYP3A4 substrates dissipates within 3 to 7 days after ingestion of the last dose of juice.[37] However, daily consumption of a glass of regular-strength grapefruit juice has a minimal effect on plasma statin concentrations (approximately 30% to 40% increase) after a 40-mg evening dose of lovastatin.[38] It may be concluded that the interaction between grapefruit juice and statins does not represent a great concern, unless >1 quart per day of juice is consumed.[37]

Statins and Calcium Antagonists
Many patients with hypercholesterolemia also have high blood pressure and may be receiving antihypertensive therapy with calcium channel antagonists. Of particular note is the interaction of statins with mibefradil, which was withdrawn from the global market because of a range of serious drug–drug interactions.[4] Several cases of statin-associated rhabdomyolysis were reported in patients receiving mibefradil.[39]

Both verapamil and diltiazem, which are weak inhibitors of CYP3A4,[28] increase the plasma concentration of simvastatin up to 4-fold, and diltiazem increases the plasma concentration of lovastatin to the same magnitude.[40,41] Cases of rhabdomyolysis have also been reported with the association of diltiazem with atorvastatin or simvastatin,[42,43] suggesting a need for some caution in using these agents simultaneously.

Statin Interactions With CYP450 Inducers
Cytochrome P450 inducers (Table 4) may decrease statin plasma levels. This seems to be the case with troglitazone (now withdrawn from the U.S. market), a thiazolidinedione antidiabetic agent that induces the CYP3A4 enzyme.[44] Analogously, it has been shown that rifampicin, another inducer, greatly decreases the plasma concentrations of simvastatin.[45]

Phenytoin, another inducer of CYP3A4, can alter the lipid-lowering efficacy of both atorvastatin and simvastatin.[46] It has also been reported that the herbal supplement St. John's wort decreases plasma concentrations of simvastatin but not of pravastatin;[47] this interaction most likely is caused by the enhancement of the CYP3A4-mediated first-pass metabolism of simvastatin in the small intestine and liver by this herbal supplement.

Interactions Between Statins and Fibric Acid Derivatives
The interaction of statins with fibrates deserves particular attention because myopathy can occur with either drug alone, and the effects may be additive.[4] The rate of fatal rhabdomyolysis was 16 to 80 times higher with the withdrawn statin, cerivastatin, than with the other statins then in clinical use; this difference appears to be related to the marked interaction (relative to that of other statins) between cerivastatin and gemfibrozil.[6] A review[13] of 36 published clinical trials involving statin–fibrate combination therapy and 29 case

reports of rhabdomyolysis found that the prevalence of myopathy associated with statin–fibrate combination therapy was 0.12%. Although all fibrates have been associated with cases of CK elevations and myopathy in combination with statins, the risk for the development of myopathy may be greater for gemfibrozil compared with bezafibrate or fenofibrate. The concomitant use of gemfibrozil and atorvastatin, lovastatin, pravastatin, or simvastatin has been associated with case reports of rhabdomyolysis.[5,48,49]

It is generally believed that the adverse effects of combination therapy with a statin plus a fibrate is based on pharmacodynamic interactions. However, gemfibrozil was shown to increase plasma concentrations of active simvastatin and lovastatin acid forms but minimally the lactone forms, whereas bezafibrate demonstrated no significant effect on the pharmacokinetics of lovastatin. Recently, it was shown that gemfibrozil can modulate the pharmacokinetics of statins more via inhibition of statin hydroxy acid glucuronidation than via inhibition of CYP3A4-mediated oxidation.[50] Glucuronidation is a previously unrecognized, but common, metabolic pathway for the conversion of active open acid forms of several statins (including atorvastatin and rosuvastatin) to their lactone form. The lactone form, in turn, plays a critical role in the subsequent statin metabolism catalyzed by CYP3A4.[51] Consistent with the severe interactions reported with gemfibrozil, cerivastatin was shown to be more susceptible than simvastatin and atorvastatin to metabolic interaction with gemfibrozil at the level of glucuronidation.[50] Additionally, a potential difference between gemfibrozil and fenofibrate in their ability to alter the pharmacokinetics of statins has been shown in human hepatocytes in which fenofibrate was much less effective than gemfibrozil in affecting simvastatin metabolism.[50] Finally, the interaction between gemfibrozil and pravastatin could occur at the transport protein level.[52] Altogether, these studies provide a possible explanation for the difference in the interactions observed among various statin–fibrate combinations.

Statin–fibrate combination therapy should be undertaken cautiously and reserved for patients with severe or refractory hyperlipidemia. In addition, because fibrates may impair liver function, which could lead to higher plasma levels of statins, patients with impaired liver function should not receive this combination. Furthermore, mild renal impairment may increase the risk of myopathy because fibrates are primarily excreted renally.

Other Statin Interactions

Changes in the absorption and excretion of drugs independent of CYP metabolism can alter drug disposition and may contribute to the interaction potential of statins. A newly recognized class of active drug transporters, including the P-glycoproteins,[4,53] is known to affect the disposition and bioavailability of many drugs, including CYP3A4 substrates. Transport proteins are, at least in part, responsible for the low and variable oral bioavailability of atorvastatin, lovastatin, simvastatin, and pravastatin (Table 2).[54] Indeed, interactions with other drugs at the P-glycoprotein level could potentially be responsible for the rhabdomyolysis observed after statin–

digoxin combination therapy. Digoxin is a P-glycoprotein substrate/inhibitor, and its narrow therapeutic range makes any drug–drug interaction important, warranting the monitoring of digoxin levels. In fact, acute interactions have been observed with simvastatin,[55] and coadministration of atorvastatin 80 mg/d and digoxin 0.25 mg/d for 20 days increased systemic exposure to digoxin by inhibition of P-glycoprotein.[56] However, administration of atorvastatin 10 mg/d with digoxin did not affect mean steady-state concentrations of digoxin.[56] Rosuvastatin, but not fluvastatin, has been shown to be recognized by these transporters.[14,16]

Clinical trials in which patients have received niacin in combination with fluvastatin, pravastatin, or simvastatin have also not reported myopathy,[4,57,58] although the number of patients in these trials was low. However, in case reports, niacin has been associated with rhabdomyolysis in combination with lovastatin, pravastatin, or simvastatin, but not with atorvastatin or fluvastatin.[4,5,9] A lovastatin and extended-release niacin combination product has recently become available, and no cases of myopathy have been reported in an open-label study with this combination.[59] No clinically important interactions have been observed between statins and other drugs used in cardiovascular diseases, such as propranolol, angiotensin-converting enzyme inhibitors, and thiazide diuretics.

An interaction also may occur between statins and antithrombotic agents.[4] The administration of statins to patients receiving warfarin caused a small potentiation of the anticoagulant effect, requiring a warfarin dosage reduction, and a recent FDA report has documented cases of rhabdomyolysis when all statins were given in combination with warfarin.[5] The mechanism underlying the interaction between statins and warfarin is due to a competition at the cytochrome level.[4]

Finally, evidence suggests that genetic polymorphisms play a potentially key role in the efficacy, safety, and tolerability of all medications.[60] For example, findings indicate that CYP2D6 polymorphisms influence the efficacy and tolerability of simvastatin.[61]

Conflicting data have been reported on the effect of statins on clopidogrel-inhibited platelet aggregation in patients undergoing coronary stenting; at the moment, there are no clear reasons to exclude the coadministration of these two classes of drugs in patients who are at high risk for coronary events.[62–65]

Conclusion

The safety and tolerability of statins supports their use as first-line treatment for hypercholesterolemia. Myopathy and its serious complication, rhabdomyolysis, are a potential effect of therapy with the available statins, but occur very rarely. The molecular and biochemical mechanisms of myopathy and rhabdomyolysis caused by statins are yet to be fully elucidated. Appropriate awareness and attention to the potential for myopathy with statin therapy, in particular when they are given in combination with other drugs, should reduce the risk of this adverse event considerably. The different pharmacokinetic profiles among the statins should be carefully considered to understand the different spectrum of drug

interactions. These interactions are important determinants of safety in patients with hypercholesterolemia, especially in those requiring long-term therapy with drugs that are well-known CYP3A4 substrates and/or inhibitors.

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