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# HMG-CoA Reductase Inhibitors and Myotoxicity

*Memduh Ucar, Tom Mjörndal* and *Rune Dahlqvist*

Division of Clinical Pharmacology, Norrland University Hospital, Umeå, Sweden

## Contents



## Abstract

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors specifically inhibit HMG-CoA reductase in the liver, thereby inhibiting the biosynthesis of cholesterol. These drugs significantly reduce plasma cholesterol level and long term treatment reduces morbidity and mortality associated with coronary heart disease.

The tolerability of these drugs during long term administration is an important

issue. Adverse reactions involving skeletal muscle are not uncommon, and sometimes serious adverse reactions involving skeletal muscle such as myopathy and rhabdomyolysis may occur, requiring discontinuation of the drug. Occasionally, arthralgia, alone or in association with myalgia, has been reported.

In this article we review scientific data provided via Medline, adverse drug reaction case reports from the Swedish Drug Information System (SWEDIS) and the World Health Organization's International Drug Information System (INTDIS) database, focusing on HMG-CoA reductase inhibitor-related musculoskeletal system events.

Cytochrome P450 (CYP) 3A4 is the main isoenzyme involved in the metabolic transformation of HMG-CoA reductase inhibitors. Individuals with both low hepatic and low gastrointestinal tract levels of CYP3A4 expression may be at in increased risk of myotoxicity due to potentially higher HMG-CoA reductase inhibitor plasma concentrations. The reported incidence of myotoxic reactions in patients treated with this drug class varies from 1 to 7% and varies between different agents. The risk of these serious adverse reactions is dose-dependent and may increase when HMG-CoA reductase inhibitors are prescribed concomitantly with drugs that inhibit their metabolism, such as itraconazole, cyclosporin, erythromycin and nefazodone. Electrolyte disturbances, infections, major trauma, hypoxia as well as drugs of abuse may increase the risk of myotoxicity. It is important that the potentially serious adverse reactions are recognised and correctly diagnosed so that the HMG-CoA reductase inhibitor may at once be withdrawn to prevent further muscular damage.

Oxidative modification of low density lipoprotein (LDL) is important in the aetiology and pathogenesis of atherosclerosis,[1] the latter having been identified as a major risk factor for coronary heart disease.[2-5] High plasma levels of total cholesterol and LDL-cholesterol (LDL-C) are risk factors for coronary heart disease;[6] this correlation has been confirmed by numerous epidemiological studies.[7,8] Reductions in plasma levels of total cholesterol and LDL-C are associated with improved endothelial cell function[9] and reduced risk for coronary heart disease.[8,10,11]

As such, the development of HMG-CoA reductase inhibitors has redefined the management of hypercholesterolaemia. In various clinical trials, HMG-CoA reductase inhibitors reduced total plasma cholesterol (17 to 29%) and LDL-cholesterol (24 to 61%) levels in patients with hypercholesterolaemia[5,12-18] and, as a result, reduced the incidence of coronary heart disease.[11,18-20] In patients with hypercholesterolaemia without evidence of previous myocardial infarction (MI), [21] or post-MI,[18,19] long term treatment with HMG-CoA reductase inhibitors has been shown to significantly reduce mortality and recurrent coronary events; these effects were evident relatively early after commencing treatment. In a secondary prevention trial, treatment with HMG-CoA reductase inhibitors significantly reduced the risk of stroke (32%).[22]

Cholesterol is an important structural component of biological membranes and modulates their fluidity.[23] It is synthesised from acetyl-CoA with *de novo* biosynthesis occurring in virtually all humans cells; but primarily in liver cells.[24] A unique step in the pathway of cholesterol biosynthesis is the formation of mevalonic acid from HMG-CoA. This step is catalysed by HMG-CoA reductase, an intrinsic membrane protein of the endoplasmic reticulum, and is the rate-limiting step in cholesterol biosynthesis.[25,26] Other products that are formed

from mevalonic acid are ubiquinone, dolichols and isopentanyl adenine (fig. 1).

## 1. HMG-CoA Reductase Inhibitors

### 1.1 History

Atherosclerosis is now generally accepted as the principal cause of the vascular dysfunction that leads to myocardial and cerebral infarction. Indeed, the relationship between high plasma LDL levels and the occurrence of atherosclerosis is well established. The discovery of LDL receptors, an event awarded the 1995 Nobel prize in medicine, started a new era in the field of lipid research, eventually leading to the development of HMG-CoA reductase inhibitors.

Three generations of HMG-CoA reductase inhibitors, with slight differences between each, are now available. All are selectively targeted to the enzyme HMG-CoA reductase in the liver.

### 1.2 Physical and Chemical Properties

The first generation HMG-CoA reductase inhibitors – lovastatin, simvastatin and pravastatin – share the same hydronaphthalene ring structure (fig. 2). Simvastatin and lovastatin are inactive and are administered as lacton-prodrugs,[27] whereas pravastatin is administered as an active drug.[28] Simvastatin and lovastatin are hydrophobic in nature; pravastatin is hydrophilic.[29]

The first second generation HMG-CoA reductase inhibitor was the entirely synthetic compound fluvastatin.[30] Fluvastatin is a derivative of mevalonolactone but has a fluorophenyl-substituted indole ring;[31] it is active in its parent form. The hydroxy acid side chain renders the drug more hydrophilic than the other HMG-CoA reductase inhibitors.[29]

The third generation of HMG-CoA reductase inhibitors includes the 2 recently marketed drugs atorvastatin and cerivastatin. Both are synthetic and active in their parent form.[16,32,33] Metabolites of these 2 drugs are also have anti-HMG-CoA reductase activity and contribute to the hypocholesterolaemic effect of treatment.[33,34] Cerivastatin is a pure enantiomeric pyridine derivative.[16]

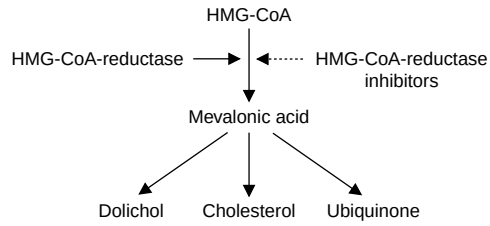



**Fig. 1.** Products of mevalonic acid and site of action of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.

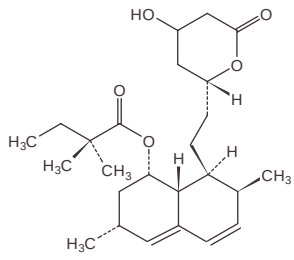
The common characteristic chemical structure for HMG-CoA reductase inhibitors is a side chain analogous to mevalonic acid, either its acid (active) or lactone (inactive) form. The first generation drugs are of fungal origin,[30] with only small differences between them, while drugs in the second and third generations all carry a nitrogen heteroaromatic ring structure with a mevalonic acid-like side chain and a variety of substituents on the heteroaromatic structure (fig. 2).

### 1.3 Pharmacodynamics

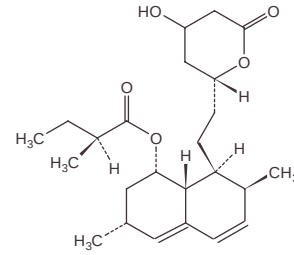
About 50% or more of the total body cholesterol is derived from *de novo* synthesis.[26] The main primary site of endogenous cholesterol biosynthesis is in the liver and it is here that HMG-CoA reductase inhibitors exert their main pharmacological action through a competitive inhibition of HMG-CoA reductase.[35-37] As a result of decreased cholesterol levels in the liver, a compensatory mechanism is activated that increases the synthesis of liver cell LDL-receptors, leading to increased removal of LDL from the circulation.[24]

### 1.4 Pharmacokinetics

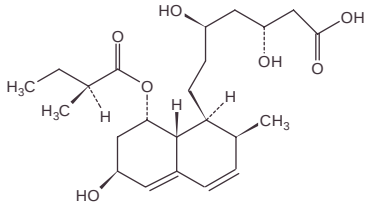
There is considerable variation in the pharmacokinetic properties of the various HMG-CoA reductase inhibitors after oral administration.[30] The protein binding varies between compounds and there are extensive differences between them in terms of elimination (table I).



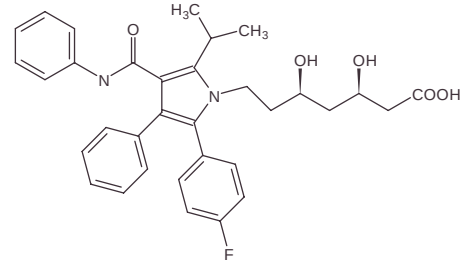

Simvastin



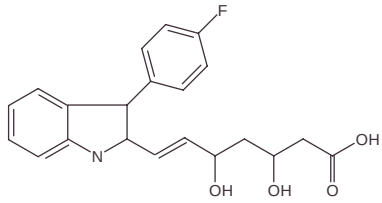

Mevinolin



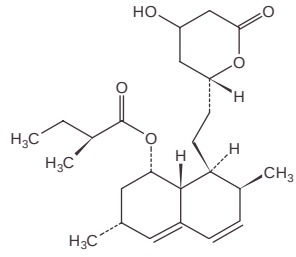

Pravastatin



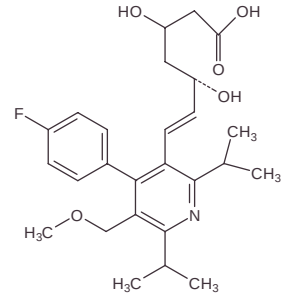

Atorvastatin




Fluvastatin




Lovastatin




Cerivastatin

**Fig. 2.** Structural formulas of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.

**Table I.** Pharmacokinetic comparison of HMG-CoA-reductase inhibitors

| Parameter | Atorvastatin | Cerivastatin | Fluvastatin | Lovastatin | Pravastatin | Simvastatin |
|---|---|---|---|---|---|---|
| Protein binding | 80% [21] | >99% [33] | 98% [32] | 95% [32] | 50% [32] | 95% [32] |
| Metabolism | CYP3A4 | CYP3A4/2C8 | CYP2C9 | CYP3A4 | ? | CYP3A4 |
| Hepatic elimination[a] | NA | NA | 95% [32] | 70% [32] | 50% [32] | 70% [32] |

a Hepatic elimination (% of absorbed dose).

**CYP** = cytochrome P450; **NA** = no data available; **?** = unknown.

The cytochrome P450 (CYP) system is responsible for the metabolism of many drugs. *In vitro* data indicate that simvastatin is mainly metabolised by the CYP3A subfamily.[38] According to present scarce data, both CYP3A4 and CYP3A5 are thought to be capable of catalysing the metabolism of simvastatin. According to one inconclusive study, active simvastatin metabolite(s) might be metabolised by CYP2D6.[39] Lovastatin,[40] atorvastatin[33,41] and cerivastatin[34] are mainly metabolised by CYP3A4. CYP2C8 is also involved in the metabolism of cerivastatin[42]

In a drug interaction study *in vitro*, it has been demonstrated that lovastatin acid, pravastatin and simvastatin acid display moderate affinity for CYP2D6, CYP2C9 and CYP3A4, whereas fluvastatin showed moderate affinity for CYP2D6 and CYP3A4, but higher affinity for CYP2C9.[36]

### 1.5 Clinical Considerations

First generation HMG-CoA reductase inhibitors have been well studied and their efficacy have been proven in several clinical trials – e.g. Scandinavian Simvastatin Survival Study (4S), Expanded Clinical Evaluation of Lovastatin Study (EXCEL), Cholesterol and Recurrent Events (CARE) trial and West of Scotland Coronary Prevention Study (WOSCOP) – to reduce the incidence of fatal and nonfatal myocardial infarctions by 30 to 35% in targeted populations.[22] Second and third generation agents have not been studied as extensively as drugs in the first generation in terms of clinical outcome.

Simvastatin has been proven cost-effective as treatment for hypercholesterolaemia in patients postmyocardial infarction, or with angina pectoris.[43] Further analysis of primary prevention of cardiovascular disease in patients with hypercholesterolaemia indicates that treatment with pravastatin is of substantial clinical benefit at reasonable cost.[44]

### 1.6 Tolerability and Adverse Drug Reactions

Hypercholesterolaemia is primarily a chronic disease necessitating long term therapy; thus pharmacological treatments with a good tolerability profile are desirable. Various clinical trials have shown that HMA-CoA reductase inhibitors are generally well tolerated in short as well as long term therapy,[12,13,18,45-47] findings that have made this the drug class of choice in for the treatment of hypercholesterolaemia when dietary control and other nonpharmacological interventions have failed to elicit the required level of control.

The adverse event profile of HMG-CoA reductase inhibitors includes constipation, flatulence, dyspepsia, nausea, and gastrointestinal pain; elevated serum transaminase levels may also occur. More serious adverse events include myotoxic adverse reactions including rhabdomyolysis.

### 1.7 Drug Interactions

Concomitant administration of HMG-CoA reductase inhibitors with drugs that inhibit CYP3A4 may result in increased plasma concentrations of HMG-CoA reductase inhibitors. Erythromycin, a potent inhibitor of CYP3A4, has been shown to cause an increase in the plasma concentration of simvastatin[48] or cerivastatin[34] when given concomitantly. Cyclosporin is another substrate and potential competitive inhibitor of CYP3A4;[49] in 1 study the concentration of simvastatin was significantly higher in kidney transplant recipients

treated with cyclosporin and simvastatin than in those treated with simvastatin alone.[50] In contrast to lovastatin, pravastatin did not accumulate during concomitant therapy with cyclosporin in stable kidney graft recipients.[51] In a recent study in volunteers, concomitant administration of itraconazole with simvastatin or pravastatin caused a significant increase in the bioavailability of simvastatin, but not pravastatin.[52]

Grapefruit juice is also known to be an inhibitor of CYP3A4 and concomitant ingestion of grapefruit juice with lovastatin and simvastatin has been reported to increase the bioavailability of these 2 drugs.[53,54]

## 2. Signs of Skeletal Muscle Damage

### 2.1 Creatine Kinase

Creatine kinase (CK) generates adenosine triphosphate (ATP) via phosphorylation of adenosine diphosphate (ADP). The main source of CK is skeletal muscle and myocardium.[55] In many conditions, acute muscle necrosis seems to be related to failure of energy production and possibly depletion of the ATP reserves necessary to maintain the integrity of the sarcolemma.[56] HMG-CoA reductase inhibitors may inhibit mitochondrial production of ATP which will lead to an inadequate synthesis of coenzyme Q and heme A in the inner mitochondrial membrane.[57]

Ubiquinone, synthesised from mevalonic acid, is utilised by mitochondria for electron transport, a mechanism that theoretically might be impaired by HMG-CoA reductase inhibitors. In 1 study, mevastatin treatment caused no decrease of ubiquinone;[58] however, more recent data indicate the opposite. In 1 clinical trial, 38 and 27% decreases in ubiquinone levels occurred in association with atorvastatin and lovastatin treatment, respectively.[59] HMG-CoA reductase catalyses the formation of mevalonate from HMG-CoA. Mevalonate is an important precursor of cholesterol, ubiquinone, dolichols and isopentanyl adenine. All these products are involved in cell replication.[60] Dolichol is required for glycoprotein synthesis and a deficit may cause an instability of the plasma membrane. This may lead to an unstable action potential and disruption of the muscle cell membrane; and leakage of CK to the circulation system may follow.

### 2.2 Myotoxicity

Skeletal muscle constitutes about 45% of total bodyweight.[61] Because of its mechanical function, muscle has a high metabolic rate and a high blood flow. This may explain why skeletal muscle is highly exposed to drugs available in the circulation. Many drugs bind to muscle tissue, with binding rates of 13 to 98% having been reported.[62] The muscular toxicity of a drug may be associated with a high plasma drug concentration that may exert a direct toxic effect on the muscle tissue itself. High serum concentrations of HMG-CoA reductase inhibitors have been reported in several experimental studies during concomitant administration with certain drugs.[34,48,50-52,63] The physicochemical properties of the HMG-CoA reductase inhibitors may also govern the frequency of adverse effects. Drugs with hydrophobic (simvastatin, lovastatin) properties may more easily permeate the biological membranes than the hydrophillic drugs (pravastatin, fluvastatin).[29]

### 2.3 Subdivisions and Definitions of Myotoxic Reactions

#### *2.3.1 Myalgia*

Myalgia is clinically characterised mainly by proximal or diffuse muscular pain, tenderness and/or muscle weakness, or both muscle pain and weakness. CK may be normal or slightly increased in the serum.

#### *2.3.2 Myositis*

Myositis, with or without CK elevations in the serum, is usually self limiting and is characterised by muscle weakness.[31] Biopsy usually indicates cell damage with variation in fibre size, muscle fibre necrosis with inflammatory cell infiltration.[64,65]

#### *2.3.3 Myopathy*

Myopathy can be clinically defined as muscle pain, tenderness and muscle weakness, or both

muscle pain and weakness, accompanied by abnormal elevations in CK levels (>10 times the upper limit of normal) in the serum.[66] In rabbits, experimentally induced myopathy by HMG-CoA reductase inhibitors is characterised by high serum CK levels, necrotic and degenerating muscle fibres, and electromyographic myotonic discharge.[67]

Drug-induced acute or subacute myopathy is characterised by a syndrome of muscle pain, tenderness and weakness, principally of the proximal limb, but at the times it may also be more generalised.[61] Electromyography reveals myopathic changes with prominent spontaneous potentials. Muscle biopsy is characterised by multifocal muscle-fibre necrosis and regenerative activity may be observed.

Morphologically HMG-CoA reductase inhibitor–induced myopathy is characterised by a variation in fibre size, muscle-fibre necrosis and fragmentation with inflammatory cell infiltration in the perivascular and endomysial areas. In addition, CK levels are increased in the serum.[64,65] Immunohistological examination of muscle specimens may reveal immunological cell activity.[64,65]

#### *2.3.4 Rhabdomyolysis*

Rhabdomyolysis is an acute, fulminating, potentially fatal condition of skeletal muscle characterised by destruction of skeletal muscle as evidenced by myoglobinaemia and myoglobinuria plus a CK level in the serum of at least 10 times the upper limit of normal. Muscle biopsies from clinically diagnosed cases of rhabdomyolysis associated to HMG-CoA reductase inhibitor therapy reveal changes in muscle cells characterised by loss of cross-striations and nuclei, with regeneration in part, and no infiltration of inflammatory cells.[68,69] Serious complications that may follow acute rhabdomyolysis include hyperkalaemia, hyperuricaemia, disseminated intravascular coagulation, metabolic acidosis, cardiomyopathy, respiratory and renal failure.[70]

## 3. Data from Spontaneous Reporting Systems

### 3.1 General Consideration

In Sweden, it is compulsory for physicians to report all new suspected adverse reactions related to drug therapy to the Swedish Adverse Drug Reactions Committee (SADRAC). Each reported event is assessed by the committee for causality related to the drug exposure and a probability of certain, probable, possible or unclassifiable is assigned. The report is then registered in the Swedish Drug Information System (SWEDIS) database. In a systematic search of this database up to April 1998, we identified 458 reports of adverse events related to HMG-CoA reductase inhibitors (fluvastatin, pravastatin, simvastatin) therapy. All reports of musculoskeletal adverse reactions with causality assessments certain, probable or possible and classified as myalgia (98 cases), arthralgia (14 cases) and myopathy (6 cases) were collected. No cases of rhabdomyolysis were identified.

### 3.2 Myalgia, Arthralgia

In a survey of HMG-CoA reductase inhibitor–induced myotoxic adverse reactions in the SWEDIS database, 74 reports of simvastatin- (2 classified as certain, 22 probable, 50 possible), 11 reports of pravastatin- (1 classified as certain, 2 probable, 8 possible) and 13 reports of fluvastatin- (7 classified as probable and 6 as possible) associated myalgia were found. Atorvastatin and cerivastatin were recently registered in Sweden and 3 reports of atorvastatin-associated myalgia were found. In 6 cases cholestyramine, and in 2 cases gemfibrozil, was given concomitantly with simvastatin. In 3 reports the patients also had paresthesias (including 1 who received concomitant cholestyramine). 64 reports indicated patients fully recovered after cessation of simvastatin (in 3 cases the patient still had symptoms at the time the report was prepared and the outcome was not reported in 7 cases).

Myalgia is the most frequently occurring muscular adverse reaction in SWEDIS (table II). The described symptoms were mainly proximal or dif-

**Table II.** Number of adverse reactions associated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors reported to the Swedish Drug Information System[a]

| Agent | TNR | Arthralgia (%) | Myalgia (%) | Myopathy (%) | PN (%) | Neuropathy (%) | T-MAR (%) |
|---|---|---|---|---|---|---|---|
| Simvastatin | 344 | 11 (3) | 74 (22) | 5 (2) | 2 (-) | 1 (-) | 92 (27) |
| Pravastatin | 62 | 2 (3) | 11 (19) | NA | NA | NA | 14 (23) |
| Fluvastatin | 52 | 1 (2) | 13 (25) | 1 (2) | 1 (2) | NA | 15 (29) |

a Between 1988 and 1997 (simvastatin), 1991 and 1997 (pravastatin), and 1994 and 1997 (fluvastatin).

**NA** = no cases were reported; **PN** = peripheral neuropathy; **T-MAR** = total number of musculoskeletal adverse reactions; **TNR** = total number of reactions; **%** = percentage of all TNR for that drug.

fuse muscle pain, tenderness, muscle weakness or muscle pain and muscle weakness together.

Simvastatin, the most commonly prescribed HMG-CoA reductase inhibitor in Sweden, also had the highest number of reported adverse reactions, followed by pravastatin and fluvastatin (fig. 3). CK levels in the serum were slightly increased in a few cases classified as myalgia. In most cases, however, symptoms disappeared within days to weeks after withdrawal of the drug.

There have been 13 reports of myalgia with fluvastatin (1 patient received concomitant gemfibrozil and another received erythromycin). In 1 report arthralgia was reported in addition to myalgia. All patients recovered after cessation of fluvastatin therapy. One of 11 patients treated with pravastatin also received gemfibrozil. Arthralgia was reported in 2 cases (classified as possible). Nine patients (including 2 with arthralgia) recovered, symptoms persisted in 2 and outcome was unknown in 1, after the cessation of pravastatin therapy. However, CK was increased in the serum (13.8 and 48.5 μcat/L) in 2 cases.

Arthralgia accounted for 2 to 3% (table II) of reports associated with these 3 drugs (simvastatin, pravastatin, fluvastatin) and was the primary diagnosis in 11 patients (in 5 cases myalgia was also present, 1 in a patient treated concomitantly with cholestyramine) treated with simvastatin. The main symptom was pain localised to knee, foot, hand and or finger joints. In all cases symptoms disappeared after simvastatin cessation, however, in some patients symptoms did not resolve until almost 2 months thereafter.

### 3.3 Myopathy and Rhabdomyolysis

Five (2 classified as probable, 3 possible) cases of myopathy associated with simvastatin treatment were located in SWEDIS. CK levels in the serum were >10 times the upper limit of normal in all cases. The main symptoms recorded were muscle pain, muscle weakness, feeling of numbness in the lower limb and chest pain. Three of the patients were concomitantly treated with cyclosporin (1 after kidney and 2 after cardiac transplantation) and 2 with gemfibrozil.

Data derived from World Health Organization's International Drug Information System (INTDIS) database, which includes reports related to drug adverse reactions from different countries, clearly demonstrate that both HMG-CoA reductase inhibitors (table III) and other (table IV) hypolipidaemic drugs have the ability to induce myotoxic adverse reactions in combination with each other and in monotherapy. Although some of these reports of myotoxic adverse reactions were poorly documented, all were considered suitable for analysis.

Reports of more serious myopathy and rhabdomyolysis also appear in the World Health Organization's INTDIS database (table III). In 75 cases of rhabdomyolysis in patients (median age 50 years, range 16 to 84, age not recorded in 5 cases) treated with simvastatin, the median dosage of the drug was 23 mg/day (range 5 to 80mg), dose not specified in 21 cases]. In 40 cases of rhabdomyolysis, simvastatin was the only suspected drug. In addition to rhabdomyolysis, arthralgia were reported in 4 cases. Among 56 reports of rhabdomyolysis, in 30 (median age 61, range 31 to 78 years old) lovastatin (median dose 32mg, range: 20 to 80mg) was the

only suspected drug. Three cases of renal failure were reported in association with lovastatin given as monotherapy.

In 19 of 20 cases of rhabdomyolysis associated with pravastatin (median age 61, range 17 to 85 years old, age was not given in 1 report), pravastatin was the only suspected drug. The median dosage was 23 mg/day (range 10 to 40mg) but was only specified in 6 reports. Abnormal renal function was reported in 2 cases. In 2 reports the patient had died because of adverse reactions. Of 12 cases associated with fluvastatin monotherapy, 3 reported abnormal renal function.

In a complementary search up to March 1999, 15 cases of rhabdomyolysis associated with atorvastatin and 8 associated with cerivastatin were found (tables III and V). In 1 report, cross reaction between simvastatin and atorvastatin had occurred.

Non-HMG-CoA reductase inhibitor antihyperlipidemic drugs have been reported to cause muscular adverse effects. There were 125 reports of myopathy and 14 reports of rhabdomyolysis associated with gemfibrozil (2 acute renal failure, 2 abnormal renal function) and 28 reports of myopathy and 26 of rhabdomyolysis (2 with abnormal renal function and 4 with acute renal failure), where bezafibrate was the main suspected drug (table IV). Only 1 report of rhabdomyolysis linked to nicotinic acid was found.

Rhabdomyolysis with myoglobinuria is potentially serious. Symptoms consist mainly of gradually decreased muscle strength, proximal or generalised muscle weakness. These symptoms can develop within days, or may not occur for to up to 2 years after starting therapy. If the condition remains untreated renal failure may occur. The mechanism underlying rhabdomyolysis with myoglobinuria has been defined as impairment of renal vascular flow, tubular obstruction by myoglobin casts or crystals of uric acid and direct toxicity from ferrihemate.[70] At postmortem autopsy in individual patients who died after experiencing drug-induced rhabdomyolysis with renal failure, amorphous sediment consistent with myoglobin casts in the renal tubules have been found.[71]

Neuropathy and peripheral neuropathy as well as myositis have been associated with lipid lowering drugs (tables III and IV). Compared with other myotoxic adverse reactions, neuropathy and peripheral neuropathy are much less common as adverse reactions in patients treated with HMG-CoA reductase inhibitors. Only 3 published case reports

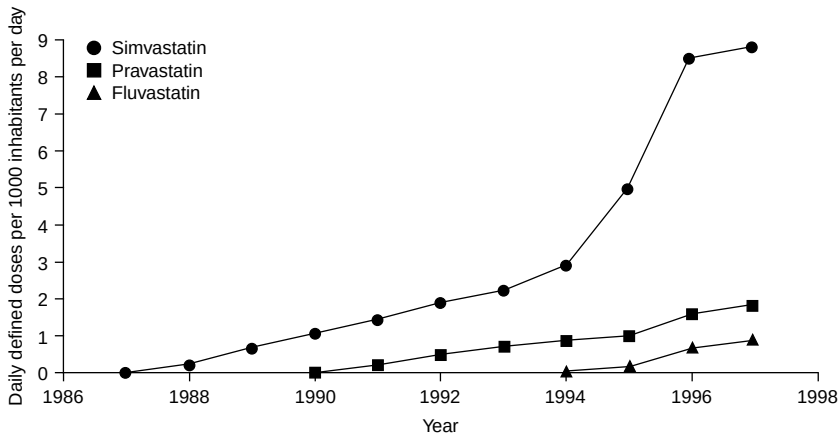



**Fig. 3.** Use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors in Sweden. Defined daily doses of simvastatin, pravastatin and fluvastatin per 1000 inhabitants per day between 1987 and 1997. Data are from the Swedish Drug Information System.

of neuropathy and 2 cases of peripheral neuropathy were found in the English literature.[72,73]

HMG-CoA reductase inhibitors were associated with death in 4 reports in patients with rhabdomyolysis. In 2 reports each pravastatin and simvastatin (the latter concomitant with gemfibrozil) were judged to have contributed to the fatal outcome.

## 4. Data from Large-Scale Clinical Trials

HMG-CoA reductase inhibitors have been associated with a low to moderate frequency of muscular adverse effects clinical trials. The incidence of musculoskeletal complaints was reported to be between 2 and 7% for simvastatin and 3% for atorvastatin.[17,46,74] Approximately 0.1 to 0.2% of lovastatin or pravastatin recipients experienced myopathy.[75,76] The incidence increased to 0.5% when certain other drugs were given concomitantly.[66]

In a trial (n = 2085) with simvastatin (10 to 20 mg/day), musculoskeletal toxicity was reported in 41 (1.3%) patients [myalgia (n = 28), muscle weakness (7), muscle cramp (6), arthralgia (4) and gout (1)].[77] In 2 (0.1%) cases a slight increase in serum CK above the upper normal limit was noted. No cases of myopathy were reported in this study.

Lovastatin-associated myopathy was reported with an incidence of >0.5% (17 of 4000 participants: 5 treated concomitantly with cyclosporin, 6 with gemfibrozil, 2 with niacin, 2 with both cyclosporin and niacin, and 6 with lovastatin only (some participants received more than 1 drug).[66] In the EXCEL study, >8000 patients were randomised to receive placebo or lovastatin 20 to 40 or 40 to 80 mg/day for 48 weeks. One case of myopathy occurred during the second treatment year among over 4500 patients receiving lovastatin 20 to 40 mg/day. Over the 2 year study 2 new cases occurred in patients receiving lovastatin 40 mg/day and 4 cases (0.3%) in patients receiving 80 mg/day. More than 1500 patients had their lovastatin dosage increased to 80 mg/day.[47]

## 5. Possible Mechanism

Myotoxic adverse reactions resembling rhabdomyolysis have, albeit rarely, been associated with HMG-CoA reductase inhibitors[57,68,69,78] and other hypolipidaemic drugs.[55,79,80] Needle biopsies from 15 patients with myopathy treated with either simvastatin (10 to 20 mg/day) or pravastatin (40 mg/day) and without notable CK increase in the serum, revealed light microscopic changes of mitochondrial myopathy.[81] The mechanism behind this complication is unknown, but different hypotheses have been proposed. These include: decreased hepatic clearance,[24] HMG-CoA reductase inhibitor–induced interruption of glycoprotein synthesis in the normal muscle membrane[82] and deficiency of the chloride channels in the muscle membrane.[83] Immunohistological mechanisms may also be of importance in the HMG-CoA reductase inhibitor-induced myotoxicity.[64,65] Morphologic observations suggest that dividing myoblasts are sensitive to the effect of HMG-CoA reductase inhibitors[37]

**Table III.** Number of adverse reactions associated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors reported to the World Health Organization's International Drug Information System (INTDIS) database

| Agent | TNR | Arthralgia (%) | Myalgia (%) | Myopathy (%) | PN (%) | Neuropathy (%) | Rhabdomyolysis (%) | T-MAR (%) |
|---|---|---|---|---|---|---|---|---|
| Atorvastatin[a] | 3188 | 42 (1.3) | 243 (7.6) | 3 (0.1) | 4(0.1) | 4 (0.1) | 16 (0.5) | 312 (10) |
| Cerivastatin[a] | 387 | 12 (3.1) | 56 (14.4) | 1 (0.02) | NA | NA | 8 (2.1) | 20 (14) |
| Fluvastatin[b] | 2061 | 35 (1.6) | 188 (9.1) | 25 (1.2) | 2 (0.0) | 4 (0.1) | 12 (0.5) | 266 (13) |
| Lovastatin[b] | 21541 | 281 (1.3) | 1350 (6.2) | 395 (1.8) | NA | 66 (0.3) | 56 (0.2) | 2148 (10) |
| Pravastatin[b] | 6208 | 91 (1.4) | 403 (6.4) | 63 (1.0) | NA | 14 (0.2) | 20 (0.3) | 591 (10) |
| Simvastatin[b] | 15149 | 261 (1.7) | 1286 (8.4) | 148 (0.9) | 11(0.0) | 48 (0.3) | 75 (0.4) | 1829 (12) |

a Updated search to March 1999.

b Updated search to April 1998.

**NA** = no cases were reported; **PN** = peripheral neuropathy; **T-MAR** = total number of musculoskeletal adverse reactions; **TNR** = total number of adverse reactions; **%** = percentage of all TNR.

**Table IV.** Number of adverse reactions associated with non 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor hypolipidemic agents reported to the World Health Organzation's International Drug Information System (INTDIS) database

| Agent | TNR | Arthralgia (%) | Myalgia (%) | Myopathy (%) | PN (%) | Neuropathy (%) | Rhabdomyolysis (%) | T-MAR (%) |
|---|---|---|---|---|---|---|---|---|
| Bezafibrate | 2959 | 27 (0.9) | 217 (7.3) | 28 (1.0) | 5 (0.2) | 9 (03.) | 26 (0.9) | 312 (11) |
| Clofibrate | 1212 | 6 (0.4) | 62 (5.1) | 27 (2.2) | NA | 3 (0.2) | 3 (0.2) | 101 (8.0) |
| Colestipol | 584 | 9 (1.5) | 7 (1.1) | 2 (0.3) | 1 (0.1) | NA | NA | 19 (3.0) |
| Colestyramine | 2850 | 27 (0.9) | 34 (1.1) | 7 (0.2) | 1 (0.0) | 7 (0.2) | 2 (0.0) | 78 (3) |
| Gemfibrozil | 7639 | 18 (1.0) | 304 (3.9) | 125 (1.6) | NA | 14 (0.1) | 33 (0.4) | 494 (7.0) |
| Nicotinic acid | 1419 | 5 (0.3) | 14 (0.9) | NA | NA | 1 (0.0) | 1 (0.0) | 21 (2) |
| Niceritol | 50 | NA | 1 (2.0) | NA | NA | NA | NA | 1 (2.0) |
| Questran | 8 | NA | NA | NA | NA | NA | NA | NA |

**NA** = no cases were reported; **PN** = peripheral neuropathy; **T-MAR** = total number of musculoskeletal adverse reactions; **TNR** = total number of adverse reactions; **%** = percentage of all TNR for that drug.

and that myotoxicity may be related to the intracellular $Ca^{2+}$ level elevation induced by these drugs.

Since membrane lipids are in dynamic equilibrium with plasma lipids, a low concentration of cholesterol in the cell may cause a decrease in membrane fluidity[84-86] and a decreased content of mevalonic acid derivatives (isopentenyl-adenine, dolichol, ubiquinone cholesterol).[37,59] A reduction in cholesterol content of ≤60% has been noted in the cells of patients treated with simvastatin.[84] The lower amount of intracellular cholesterol results in reduced levels of membrane cholesterol, which in turn may cause physical modification of membrane fluidity and a decrease in cell proliferation.[84-86]

Reduced cholesterol levels in erythrocyte and platelet membranes has been observed in patients with hypercholesterolaemia treated with pravastatin.[87] This change was accompanied by a decrease in erythrocyte and platelet $Na^+$ level and increased activity of the $Na^+$-$K^+$ pump. In the long term, such basic changes may cause irreversible cell damage leading to enzyme leakage and dysfunction with cell dispersion.

## 6. Risk Factors

### 6.1 Myotoxicity is a Class Effect

The spectrum of myotoxic adverse reactions related to HMG-CoA reductase inhibitors is quite similar, and cross-reactivity between different drugs in the class should be expected. In 2 SWEDIS case reports, patients treated with simvastatin (10 mg/day) who complained of muscle pain (which resolved on withdrawal of the drug) were subsequently prescribed pravastatin (20 mg/day in 1 case, dosage not reported in the other). In both cases muscle pain recurred within weeks; again resolution occurred on withdrawal of the drug. CK level was normal in both individuals with each drug.

### 6.2 Myotoxicity is Dose-Dependent

The incidence of myotoxic adverse events related to HMG-CoA reductase inhibitor therapy is dose-dependent.[77,88] In rats, dose-dependent skeletal myotoxicity was observed for simvastatin, lovastatin or pravastatin. The effect was potentiated by concomitant cyclosporin administration.[89]

Pravastatin is less myotoxic than lovastatin and simvastatin, a finding most likely related to its relatively poor uptake by muscle cells.[90] The lipophilicity of the HMG-CoA reductase inhibitors may be another important factor for their penetration into muscle tissue.[91]

In a recently published clinical trial (n = 156) with simvastatin (40, 80 and 160 mg/day), 10 patients discontinued treatment because of adverse events, which were considered drug related in 8. Of these, 1 patient was receiving simvastatin 40 mg/day (diffuse body pain), 3 were receiving 80 mg/day (2 myalgia, 1 increased CK level), and 5

**Table V.** Cases of rhabdomyolysis reported to the World Health Organzation's International Drug Information System (INTDIS) database with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors during combined treatment with other drugs

| Agent | Itraconazole | Cyclosporin | Warfarin | Erythromycin | Fibrate | Cholestyramine | Niacin | Nefazodone |
|---|---|---|---|---|---|---|---|---|
| Cerivastatin[a] | | | | | 1[c,d] (1) | | | |
| Fluvastatin[b] | | | | | 1[c] | | | |
| Lovastatin[b] | 2 | 1 | 1 | 4 | 7[c] (3) | 3 | 3 | 1 (1) |
| Pravastatin[b] | | 1 | | | 2[c,e] | | | |
| Simvastatin[b] | 2 | 5 (2) | 4 | 4 (1) | 9 (5) | 2 | 1 | |

a Updated search to March 1999.
b Updated search to April 1998.
c Gemfibrozil.
d Bezafibrate.
e Fenofibrate.
**( )** = number of cases with renal failure or reduced renal function.

received 160 mg/day (1 case of myopathy, 2 cases of elevated CK levels, 1 with muscle aches).[88] Data from SWEDIS supports this view with case reports documenting good tolerability with 20 mg/day simvastatin and muscular toxicity after the dosage was increased to 30 or 40 mg/day.

### 6.3 Pharmacokinetics and Drug Interactions

CYP3A4 is an important enzyme in the metabolism of HMG-CoA reductase inhibitors.[33,34,38,40,41,92] Concomitant use of certain other drugs (itraconazole, cyclosporin, erythromycin) that inhibit CYP3A4 may lead to an increase in the bioavailability of HMG-CoA reductase inhibitors.[48-50,63,92,93] Data from INTDIS (tables V and VI) confirm this. Two cases of rhabdomyolysis following concomitant therapy with simvastatin and cyclosporin have been described.[92,94] P-glycoprotein in the intestine, which has an important role in the first pass metabolism of cyclosporin together with CYP3A4 in cyclosporin absorption, also has an interindividual variation in expression.[95]

Interindividual pharmacokinetic variability may influence the occurrence of HMG-CoA reductase inhibitors-related adverse effects. CYP3A4 is the main isoenzyme expressed in the adult liver and in some adult individuals can account for as much as 50% of the total CYP proteins.[49] There are large interindividual variations in the concentration and activity of this isoenzyme in the liver,[96] and in the gastrointestinal tract.[95,97] In *ex vivo* analysis of hepatic biopsy tissue from 21 organ donors, a 37-fold variation in the concentrations of CYP3A4 was observed.[98] The clearance of certain HMG-CoA reductase inhibitors (atorvastatin, cerivastatin, lovastatin, simvastatin) is due to a metabolic transformation catalysed mainly by CYP3A4 in the liver; however, CYP3A4 in the gastrointestinal tract will be of significant importance in the first-pass metabolism.[99] Low intestinal expression of CYP3A4 may lead to higher plasma concentration of these HMG-CoA reductase inhibitors, and vice versa. Individuals who have both low hepatic and low gastrointestinal tract levels of CYP3A4 expression could thus be at increased risk of adverse events.

### 6.4 Combination with Other Potentially Myotoxic Drugs

Data from SWEDIS and INTDIS indicate that hypolipidaemic agents (HMG-CoA reductase inhibitors and other classes) have the ability to induce myotoxic adverse reactions (tables II, III, IV). Patients who do not respond to dietary modifications and HMG-CoA reductase inhibitor therapy may require additional treatment with other hypolipidaemic drugs to achieve an appropriate response. This may increase the risk of adverse reactions including myotoxicity. This risk is increased when HMG-CoA reductase inhibitors are adminis-

tered concomitantly with gemfibrozil,[69,100-103] bezafibrate,[104] cyclosporin,[50] erythromycin,[48,105] verapamil,[48] mibefradil,[105] itraconazole[63,78,92,106] and nefazodone.[107] The incidence of myotoxicity associated with lovastatin combined with gemfibrozil has been reported to be 5%, whereas when lovastatin was combined with immunosuppressive drugs, including cyclosporin, the estimated risk was 30%.[82]

Other drugs that have been associated with myotoxicity are corticosteroids, β-blockers,[61,108] diuretics that cause hypokalaemia,[61] cimetidine, theophylline, terbutaline, barbiturates and colchicine.[70]

### 6.5 Other Risk Factors

Other factors that may predispose to the occurrence of myopathy and rhabdomyolysis are electrolyte disturbances,[109] major trauma,[110] defective lipid metabolism,[111] seizures, hypothermia, metabolic acidosis, hypoxia, viral infections (Epstein-Barr, influenza and coxackie virus, Q fever), and drugs of abuse (alcohol, amphetamine, cocaine, ecstasy, lysergide, etc).[70,112]

Patients treated with HMG-CoA reductase inhibitors may experience an increase in plasma CK levels following exercise. This increase may be associated with disruption of the muscle cell membrane.[113] Among 14 men taking lovastatin, CK levels were increased in 2 (by 183 and 242%) 24 hours after exercise.[114]

**Table VI.** Number of cases of rhabdomyolysis reported to the World Health Organzation's International Drug Information System (INTDIS) database where 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors had been given in combination with more than one drug

| Concomitant drugs | Lovastatin[a] | Simvastatin[a] | Atorvastatin[b] |
|---|---|---|---|
| Gemfibrozil + cyclosporin | | | 1 |
| Colestyramine + cyclosporin | | 1 | |
| Gemfibrozil + nefazodone | | 1 | |
| Gemfibrozil + warfarin | | 1 | |
| Gemfibrozil + erythromycin | | 2 | |
| Gemfibrozil + nicotinic acid | (1) | | |
| Colestyramine + erythromycin | 1 | | |
| Nicotinic acid + itraconazole | 1 | | |
| Cyclosporin + itraconazole | 1 | | |
| Cyclosporin + warfarin | 2 (1) | | |

a Updated search to April 1988.

b Updated search to March 1999.

**( )** = number of cases with renal failure or reduced renal function.

## 7. Conclusion

HMG-CoA reductase inhibitors have been associated with myopathy and rhabdomyolysis in experimental models as well as in humans. The pathophysiological mechanism for the occurrence of myopathy and rhabdomyolysis is not known. The risk of these potentially serious adverse reactions is dose-dependent and may increase when HMG-CoA reductase inhibitors are prescribed concomitantly with certain other drugs; these include itraconazole, cyclosporin, gemfibrozil and erythromycin. In light of available data, it is evident that myotoxic adverse reactions related to treatment with HMG-CoA reductase inhibitors is a class effect. To identify those groups of patients at particular risk, i.e. those who have had infections or experienced major trauma, is of fundamental importance. The physician should suspect an adverse drug reaction when an abnormal response, such as subacute proximal or diffuse muscle pain, tenderness, muscle weakness with or without elevations in serum CK levels, presents in any patient prescribed HMG-CoA reductase inhibitors. In such cases the drug should be withdrawn. Once myopathy or rhabdomyolysis is suspected the drug should be stopped and CK plasma activity should be monitored until a normal level is established.

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Correspondence and offprints: Dr *Memduh Ucar*, Division of Clinical Pharmacology, Norrland University Hospital, S-901 85 Umeå, Sweden.
E-mail: memduh.ucar@vmo.ltjkpg.se