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Effects of HMG-CoA Reductase Inhibitors on Skeletal Muscle

Are all Statins the Same?

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Abstract

The 3-hydroxy-3-methyl coenzyme A (HMG-CoA) reductase inhibitors or statins, specifically inhibit the enzyme HMG-CoA in the liver, thereby inhibiting the rate limiting step in cholesterol biosynthesis and so reducing plasma cholesterol levels. Numerous studies have consistently demonstrated that cholesterol lowering with statin therapy reduces morbidity and mortality from coronary heart disease, whilst recent evidence has demonstrated that benefits of statin therapy may also extend into stroke prevention.

Since hypercholesterolaemia is a chronic condition, the long-term safety and tolerability of these agents is an important issue. Numerous large-scale clinical trials have consistently demonstrated a positive safety and tolerability profile for statins. Hepatic, renal and muscular systems are rarely affected during statin therapy, with adverse reactions involving skeletal muscle being the most common, ranging from mild myopathy to myositis and occasionally to rhabdomyolysis and death. Postmarketing data supports the positive safety and tolerability profile of statins, with an overall adverse event frequency of less than 0.5% and a myotoxicity event rate of less than 0.1%.

The recent withdrawal of cerivastatin from the world market due to deaths from rhabdomyolysis has, however, focused attention on the risk of adverse events and in particular myotoxicity associated with statins. Indeed, initial clinical trial data supports postmarketing data, demonstrating a higher incidence of

myotoxicity associated with cerivastatin, particularly when used in combination with fibrates.

The potential mechanisms underlying statin-induced myotoxicity are complex with no clear consensus of opinion. Candidate mechanisms include intracellular depletion of essential metabolites and destabilisation of cell membranes, resulting in increased cytotoxicity.

Cytochrome P450 3A4 is the main isoenzyme involved in statin metabolism. Reduced activity of this enzyme due to either reduced expression or inhibition by other drugs prescribed concomitantly such as cyclosporin or itraconazole may increase drug bioavailability and the risk of myotoxicity. Such factors may partly account for the interindividual variability in susceptibility to statin-induced myotoxicity, although other as of yet unclarified, genetic factors may also be involved.

The risk of rhabdomyolysis is increased with combination fibrate-statin therapy, with initial evidence suggesting that gemfibrozil-statin combination may particularly increase the risk of myotoxicity, with pharmacodynamic as well as pharmacokinetic mechanisms being involved.

It has long been accepted that lifestyle modification, including a low fat diet, regular exercise and smoking cessation remains the best and most effective approach to cardiovascular disease prevention. High levels of total and low density lipoprotein-cholesterol (LDL-C) are well-recognised risk actors for atherosclerotic disease, in particular coronary heart disease (CHD),[1] with numerous epidemiological studies confirming this association.[2,3] Reduction of total and LDL-C is associated with numerous effects, which attenuate the process of atherogenesis including improved endothelial function, reduced oxidative stress and reduced inflammation.[4,5] Cholesterol reduction is thus associated with a reduced risk of CHD[6,7] and is an important therapeutic target in both primary and secondary prevention.

The development of the 3-hydroxy-3-methyl coenzyme A (HMG-CoA) reductase inhibitors or statins has revolutionised the management of hypercholesterolaemia. In various studies, statins have been shown to reduce total cholesterol by 17 to 29% and LDL-C by between 24 to 61%.[6-11] Associated with these lipid changes the incidence of CHD has been significantly reduced in patients with and without documented CHD.[6,7] Furthermore, recent evidence has also demonstrated that statin therapy may also reduce the risk of stroke by up to 32%.[12]

Cholesterol is an important component of many biological structures and is synthesised from acetyl-CoA in virtually all cells but primarily in liver cells. The rate-limiting step in this process is the formation of mevalonic acid from HMG-CoA (figure 1), catalysed by HMG-CoA reductase an intrinsic membrane protein of the endoplasmic reticulum.[13] Statins inhibit this process resulting in reduced intracellular cholesterol levels and secondary depletion of metabolic intermediates formed during cholesterol biosynthesis.[13] This effect causes reduced plasma cholesterol levels and a secondary increase in LDL receptor expression on the cell surface and thus increased clearance of LDL from plasma.[13]

Since hypercholesterolaemia and atherogenesis are chronic conditions, life-long treatment is required. It is thus important that statins demonstrate a positive safety and tolerability profile, and as with all therapies a benefit-risk assessment to maximise beneficial outcomes and reduce the potential for adverse effects is essential. Various clinical trials have demonstrated that statins are generally

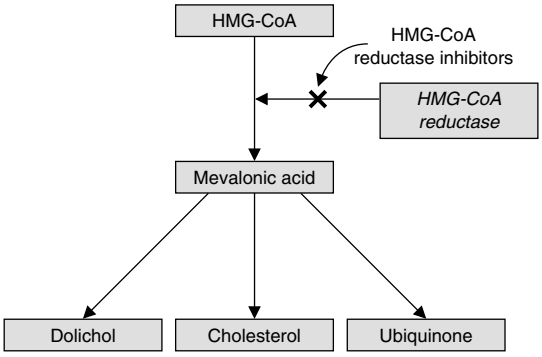

Fig. 1. Products of mevalonic acid and site of action of the 3-hydroxy-3-methyl coenzyme A (HMG-CoA) reductase inhibitors or statins.

well tolerated in short as well as long-term therapy.[14] The adverse event profile of statins includes constipation, flatulence, dyspepsia and generalised gastrointestinal discomfort; elevated transaminase levels may also occur. More serious adverse events include myotoxic effects, occurring with a reported incidence of between 1 and 7% and ranging from mild myopathy to frank rhabdomyolysis.[15] Myalgia is the most frequently occurring muscular adverse reaction, arthralgia is also a common adverse musculoskeletal adverse reaction accounting for up to 3% of all adverse reactions associated with simvastatin, fluvastatin and pravastatin therapy in Sweden.[15] Both myalgia and arthralgia on the whole appear reversible on statin withdrawal, with symptoms completely resolving within 2 to 3 weeks of drug withdrawal. More serious adverse muscular reactions including myopathy and rhabdomyolysis are rare accounting for 2 to 5% of all muscular adverse events associated with statins.[15] The muscular adverse event frequency associated with statins also appears to be a dose related phenomenon, with increasing muscular toxicity occurring when for example doses of simvastatin were increased from 20 to 30 or 40 mg/day. Peripheral neuropathy has also rarely been described in association with statin therapy, with only three reported cases to date.[16]

The recent withdrawal of cerivastatin from the world market due to rhabdomyolysis and death, coupled with ever increasing use of statins in clinical practice has focused attention on the safety profile statins, particularly with respect to myotoxicity.

In this article we review the pharmacology and safety profiles of the currently available statins, as well as discussing some possible mechanisms underlying the myotoxicity of statins and how these may account for potential safety differences between individual compounds.

1. HMG-CoA Reductase Inhibitors: Pharmacology and Metabolism

The first generation statins (lovastatin, pravastatin and simvastatin) are fungal metabolites sharing the same hydronaphthalene ring structure. Simvastatin and lovastatin are administered as lacton pro-drugs, whereas pravastatin is an active compound. Simvastatin and lovastatin are hydrophobic, whilst pravastatin is hydrophilic.[17,18]

The second-generation statins (fluvastatin, cerivastatin, atorvastatin) are entirely synthetic and are structurally dissimilar. Fluvastatin is a derivative of mevalonolactone and is active in its parent form, a hydroxy side-chain renders the drug more hydrophilic than the other statins.[18] Atorvastatin and cerivastatin are also synthetic compounds and active in their parent form.[19,20] Metabolites of these two agents also have anti-HMG-CoA reductase properties, contributing to their hypolipidaemic effects.[19,20]

There is considerable variation in the pharmacokinetic properties of the various statins after oral administration. Protein binding, metabolism and elimination vary extensively between compounds (table I). The cytochrome P450 (CYP) enzyme system is responsible for the metabolism and elimination of many drugs, including all statins, other than pravastatin [21] (table I). The CYP system is mainly located in the hepatocyte and has various different isoforms, which appear to be involved in the metabolism of different drugs.[22] *In vitro* data

Table I. Pharmacokinetics and metabolism of currently available 3-hydroxy-3-methyl coenzyme A (HMG-CoA) reductase inhibitors (statins)

	Protein binding (%)	Metabolism	Hepatic elimination (%)
Atorvastatin	80	CYP 3A4	NA
Cerivastatin[a]	99	CYP 3A4/2C8	NA
Fluvastatin	98	CYP 2C9	95
Lovastatin	95	CYP 3A4	70
Pravastatin	50	Multiple pathways	50
Simvastatin	95	CYP 3A4	70

a Cerivastatin was recently withdrawn from the market worldwide.

CYP = cytochrome P450 enzyme; **NA** = no available data.

indicate that simvastatin is metabolised by the CYP 3A subfamily,[23] with both CYP 3A4 and 3A5 being capable of metabolising simvastatin. Lovastatin, atorvastatin and cerivastatin are metabolised by CYP 3A4,[20,24,25] whilst cerivastatin is also metabolised by the CYP 2C8 isoform.[26] Pravastatin is unique amongst statins in not being primarily metabolised by the CYP enzyme system. Several different reactions are involved in pravastatin metabolism including isomerisation, sulfation, glutathione conjugation and oxidation.[27]

Concomitant administration of statins with drugs that inhibit or are primarily metabolised by the CYP system may lead to potential interactions, causing an increase in the plasma concentration of drug, which may increase the risk of adverse events. Erythromycin is a potent inhibitor of CYP 3A4 and has been shown to increase plasma concentrations of both simvastatin and cerivastatin.[28] Another well described substrate and competitive inhibitor of CYP 3A4 is cyclosporin, which has been shown to increase plasma concentrations of statins.[29,30] The most potent inhibitors of CYP 3A4 are the azole antifungal agents such as ketoconazole and itraconazole and these have also been shown to significantly increase plasma statin concentrations, although the bioavailability of pravastatin, which is not primarily metabolised by CYP, does not appear to be significantly effected.[30] The potential for interaction between statins and the fibric acid derivatives requires special attention, particularly in view of the increasing evidence supporting the beneficial effects of fibrate therapy on cardiovascular risk[31] and the increasing use of fibrate-statin combination therapy in the treatment of mixed dyslipidaemia.[32] The metabolism of fibrates is complex, and although it is attributed to the CYP 3A4 pathway, the precise mechanisms are controversial.[33,34] Myotoxicity, in particular rhabdomyolysis, is a well-recognised complication of gemfibrozil and statins. The precise cause of this effect is not clear, but mechanisms may be partly pharmacokinetic and perhaps mediated by systems other than CYP 3A4.[34] Indeed displacement/direct drug interactions between gemfibrozil and cerivastatin resulting in increased plasma cerivastatin concentrations indicates that the toxicity of this particular combination is unlikely to be primarily related to CYP 3A4. Part of the hypolipidaemic effect of fibrates is mediated through activation of the peroxisome proliferator activated family of nuclear receptors (PPAR), in particular PPAR-α and γ.[35] This aspect of fibrate action may contribute to the increased risk of interaction with statins, since the PPAR family of receptors have been shown to influence the regulation of CYP 2, 3 and 4,[35] activation has been shown to down-regulate CYP function in rat hepatocytes.[36,37] The potential role of the PPAR system in influencing CYP function also raises important considerations relating to possible interactions between statins and the thiazolidinedione class of oral hypoglycaemic agents (rosiglitazone, pioglitazone), which exert a therapeutic effect by activating the PPAR-γreceptor.[38] Initial short-term studies involving relatively small numbers of subjects appear reassuring,[39] with no evidence of an increase in adverse reactions related to combination statin and thiazolidinedione therapy. These observations are however preliminary and a true evaluation of the safety of statin-thiazoldinedione com-

bination therapy can only be made following larger long-term studies combined with close post-marketing surveillance.

2. Muscle Toxicity: Definition, Subdivision and Classification

Skeletal muscle accounts for around 45% of total bodyweight and has a high metabolic rate and blood flow.[40] As a consequence skeletal muscle is highly exposed to drugs within the circulation. Many drugs bind to skeletal muscle at rates of between 13 and 98%.[41] The muscular toxicity of a drug may thus be related to high plasma drug concentration, which may exert a direct toxic effect on the muscle tissue. Prior to considering potential mechanisms, which may account for the toxic effects of statins on muscle, it is first important to understand the nature of these reactions. Muscle toxicity was one of the first clinically recognised adverse effects of statins. There is a wide spectrum of statin associated myotoxicity ranging from a mild non-specific myalgia to myositis with raised creatinine kinase levels. Myositis can progress to the rare but potentially life-threatening syndrome of rhabdomyolysis, which can lead to irreversible renal failure.

2.1 Myalgia

Myalgia is characterised by diffuse muscle pain, tenderness and weakness. Proximal muscle groups are most often affected and creatinine kinase levels may be normal or slightly elevated. Myalgia is the most common of the myotoxic effects of statins.

2.2 Myopathy

Myopathy is defined as muscle pain, tenderness or weakness associated with abnormal elevations in creatinine kinase levels (>10 times the upper limit of normal). Drug-induced acute or sub-acute myopathy is associated with symptoms predominantly effecting the proximal muscles of the upper limb, although symptoms may be more generalised. Electromyography reveals myopathic changes with prominent spontaneous discharge and muscle biopsy demonstrates muscle-fibre necrosis and regeneration. Immunohistological examination may reveal inflammatory cell infiltration and immunological cell activity.

2.3 Myositis

Myositis may occur with or without elevated levels of creatinine kinase and is usually self-limiting. It is clinically characterised by muscle weakness and biopsy usually reveals variation in fibre size with evidence of necrosis and inflammatory cell infiltration.

2.4 Rhabdomyolysis

Rhabdomyolysis is a syndrome resulting from destruction of skeletal muscle, with a number of different aetiologies (figure 2). Once thought to be rare rhabdomyolysis is now recognised with increasing frequency, in partly due to increased awareness and also partly due to increased availability of routine assays for creatinine kinase and myoglobin. Rhabdomyolysis is characterised by severe muscle destruction resulting in myoglobinuria and clinical features of muscle weakness, pain, swelling and cramps. Myoglobin released from muscles in copious quantities causes a colour change in the urine and may be confirmed by a specific immunoassay. Rhabdomyolysis may cause acute renal failure via direct toxic effects on tubular epithelium or by introducing intratubular cast formation, complicated by hypovolaemia and metabolic acidosis. Myoglobin, by inhibiting nitric oxide synthesis, may promote diffuse intrarenal vasoconstriction and ischaemia. Other serious complications include disseminated intravascular coagulation, cardiomyopathy and respiratory failure. The treatment of rhabdomyolysis is mainly aimed at preventing renal failure and includes judicious intravenous fluid therapy coupled with alkalinisation of urine by sodium bicarbonate infusion. Further treatment includes correction of

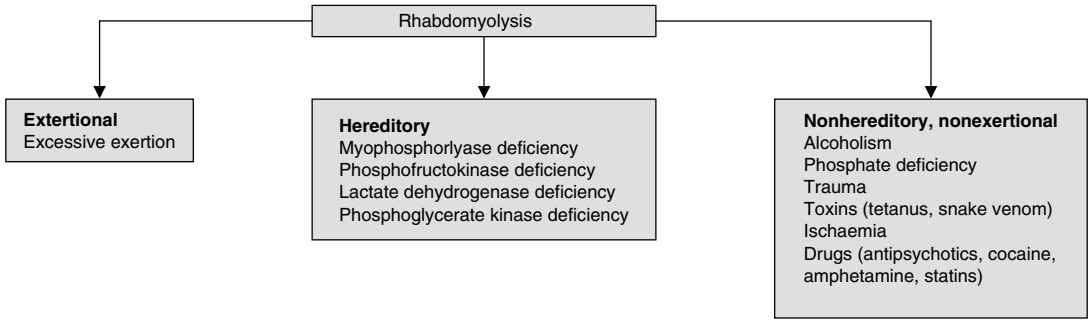

Fig. 2. Classification of rhabdomyolysis.

electrolyte abnormalities including hypocalcaemia, hyperkalaemia and hypophosphataemia.

The incidence of rhabdomyolysis of any cause is increased in patients with underlying metabolic myopathies. Around 25% of patients with recurrent rhabdomyolysis have enzymatic defects[42] and may thus be at increased risk of adverse effects from drugs, including statins, which may effect muscle. Muscle biopsies from cases of rhabdomyolysis associated with statin therapy reveal characteristic changes in muscle cells, with loss of cross-striations and nuclei, partial regeneration and a lack of inflammatory cell infiltrate.[43,44]

3. Clinical Considerations of Statin Therapy

The first generation statins have been well evaluated from the perspective of both efficacy and safety in a series of large clinical trials involving more than 39 000 patients. Table II summarises the safety data from the major trials, which represent the main evidence base supporting the clinical benefits of the individual statins. Such studies including the Scandinavian Simvastatin Survival Study (4S),[6] Expanded Clinical Evaluation of Lovastatin (EXCEL),[45] Cholesterol and Recurrent Events trial (CARE)[46] and the West of Scotland Coronary Prevention Study (WOSCOPS)[7,47] have demonstrated reduced cardiovascular morbidity and mortality with no increased rates of myotoxicity compared to placebo. The cardiovascular benefits of long-term statin therapy have been further illustrated by Heart Protection Study (HPS),[48] in which 10 000 patients treated with simvastatin 40 mg/day for an average of 5.5 years. This study, which was presented at the American Heart Association in 2001, and is currently in press, demonstrated a 24% reduction in all cause cardiovascular events, with similar adverse event rates, including myotoxicity (0.09%) and elevation in liver enzymes (0.8%) in both placebo and simvastatin groups. The low adverse event rate in the HPS supports the safety of simvastatin at higher doses, but may be somewhat overstated since this study included a pre-screening phase prior to entry into the study.

In the prospective pravastatin pooling project,[51] which analysed over 112 000 patient-years of drug exposure from three large clinical trials, pravastatin treatment was withdrawn from only three subjects due to elevated creatine kinase concentrations, whilst no cases of rhabdomyolysis were reported. In the 4S study increases in creatinine kinase to greater than ten times the normal upper limit occurred in six patients, with rhabdomyolysis occurring in only one subject.[6] In the Air Force/Texas Coronary Prevention study involving 6605 patients, the rate of myotoxicity (0.7%) was similar in both lovastatin and placebo groups.[49] Two cases of rhabdomyolysis occurred

Table II. Serious adverse events in various major 3-hydroxy-3-methyl coenzyme A (HMG-CoA) reductase inhibitors (statin) studies

Drug	Study	No. patients	Adverse events	No. affected (treatment/dosage)
Lovastatin	EXCEL[45]	8000	↑ Liver enzyme levels (>3 × ULN)	0.1% with placebo
				0.1% with lovastatin 20 mg/day
				0.9% with lovastatin 40 mg/day
				1.5% with lovastatin 80 mg/day
			Myositis (creatinine kinase >10 × ULN)	0.1% with lovastatin 40 mg/day
				0.2% with lovastatin 80 mg/day
	AFCAPS/TEXCAPS[49]	6605	↑ Liver enzyme levels (>3 × ULN)	0.3% with placebo
				0.6% with lovastatin
			Myositis (creatinine kinase >10 × ULN)	0.3% with placebo
				0.3% with lovastatin
			Rhabdomyolysis	1 patient with lovastatin
				2 patients with placebo
Pravastatin	WOSCOPS,[47] CARE,[46] LIPID,[50] (Pravastatin Pooling Project)[51]	19 592	↑ Liver enzyme levels (>3 × ULN)	129 patients with placebo
				65 patients with pravastatin
			Myositis (creatinine kinase >10 × ULN)	3 patients with pravastatin
				7 patients with placebo
			Rhabdomyolysis	0 patients with pravastatin
				0 patients with placebo
Simvastatin	4S[6]	4444	↑ Liver enzymes (>3 × ULN)	23 patients with placebo
				20 patients with simvastatin
			Myositis (creatinine kinase >10 × ULN)	1 patient with placebo
				6 patients with simvastatin
			Rhabdomyolysis	1 patient with simvastatin
	HPS[48]	20 000	Myositis (creatinine kinase >10 × ULN)	0.09% with simvastatin
				0.05% with placebo
			↑ Liver enzymes (> 3 × ULN)	0.8% with simvastatin
				0.6% with placebo
Fluvastatin	LCAS[52]	429	↑ Liver enzymes (>3 × ULN)	1 patient with placebo
				5 patients with fluvastatin
			Myositis (creatinine kinase >10 × ULN)	2 patients with placebo
				1 patient with fluvastatin
Atorvastatin	AVERT[53]	341	↑ Liver enzymes (>3 × ULN)	0 patients with 'usual care'
				4 patients with atorvastatin
			Myositis (creatinine kinase >10 × ULN)	0 patients with 'usual care'
				0 patients with atorvastatin
	MIRACL[54]	3086	↑ Liver enzymes (>3 × ULN)	9 patients with placebo
				38 patients with atorvastatin
			Myositis (creatinine kinase >10 × ULN)	0 patients with placebo
				0 patients with atorvastatin

4S = Scandanavian Simvastatin Survival Study; **AFCAPS/TEXCAPS** = Air Force/Texas Coronary Atherosclerosis Prevention Study; **AVERT** = Atorvastatin Versus Revascularisation Treatments; **CARE** = Cholesterol and Recurrent Events; **EXCEL** = Expanded Clinical Evaluation of Lovastatin; **HPS** = Heart Protection Study; **LCAS** = Lipoprotein and Coronary Atherosclerosis Study; **LIPID** = Long-Term Intervention with Pravastatin in Ischaemic Disease; **MIRACL** = Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering; **ULN** = upper limit of normal; **WOSCOPS** = West Of Scotland Coronary Prevention Study; ↑ = increase.

in the placebo group and one in the lovastatin group, whilst patients receiving lovastatin and a CYP 3A4 inhibitor demonstrated no increased incidence of myotoxicity. There is thus significant clinical trial evidence supporting a highly favourable benefit-risk ratio.

However, a similarly large evidence base does not exist for the second-generation statins (atorvastatin, fluvastatin and cerivastatin). Atorvastatin is a synthetic statin that has been generally well tolerated in clinical studies of up to 52 weeks duration.[55] In total <2% of 2502 patients withdrew from treatment with atorvastatin in clinical trials due to adverse effects. In the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study[54] in which over 1500 patients received atorvastatin 80 mg/day over 16 weeks following presentation with an acute coronary syndrome, there was a significant reduction in further vascular events with an adverse event frequency of <1%. This adverse event rate was comparable with that seen in the placebo group and was mainly due to elevated liver transaminase levels, which reverted to normal following discontinuation of the drug, with no cases of myositis being reported.

Fluvastatin has demonstrated a safety profile similar to that of other statins. In a small double blind study comparing fluvastatin monotherapy and combination therapy with nicotinic acid, there was no evidence of serious muscle or hepatic toxicity.[56] The Lipoprotein and Coronary Atherosclerosis Study (LCAS) was a randomised, double-blind controlled trial of fluvastatin 20 mg/day, following 429 patients with angiographically detectable atherosclerosis for 2.5 years.[52] Significant reductions in CHD events were recorded, with adverse events occurring at a similar rate to other studies (table II).

Cerivastatin was developed as a highly potent lipophilic, pure enantiomeric agent and has been evaluated in studies since 1993.[57] It has a dual excretory mechanism involving both CYP 2C8 and CYP 3A4, which was originally thought to improve its safety profile compared to statins exclusively metabolised by CYP 3A4. Despite this, initial studies with cerivastatin combined with other agents (e.g. cyclosporin) a significant potential for drug interactions was noted with increases in cerivastatin concentrations observed of between 40 and 300%.[57,58] Premarketing clinical trials at doses of up to 0.4mg daily demonstrated no evidence of increased myotoxicity and rhabdomyolysis. In studies using higher daily doses of cerivastatin (0.4 to 0.8 mg) there was a significant increase in adverse events including myotoxicity.[59] Postmarketing surveillance, however, demonstrated increased rates of rhabdomyolysis, particularly when cerivastatin was used in combination with gemfibrozil. As a consequence of these observations the US Food and Drug Administration agency issued a specific contraindication for the use of cerivastatin in combination with gemfibrozil. Cases of rhabdomyolysis associated with cerivastatin continued to accumulate and after 52 worldwide deaths were recorded cerivastatin was withdrawn.[60] Twelve of these deaths were associated with the cerivastatin-gemfibrozil combination.[61] In the majority of those cases associated with cerivastatin alone, higher doses of 0.8mg daily had been used.[62] The rate of rhabdomyolysis with cerivastatin was at least 10-fold higher than with first generation statins and indicates a weakness in post-release regulation and surveillance of drugs with the potential for rare, but lethal adverse events. In order to reduce the risk of such adverse drug effects, an understanding of the pathophysiological mechanisms underlying these effects should be sought. This is particularly true with respect to the statins and in the following discussion (section 4) we present an overview of the current understanding relating to potential mechanisms underlying statin-induced rhabdomyolysis.

Table III illustrates the frequency of all cause musculoskeletal adverse events and rhabdomyolysis in the statins available in the UK since 1994 as a function of the total number of prescriptions of each agent over this period. Musculoskeletal ad-

Table III. Total number and frequency of all-cause musculoskeletal adverse events and total number and frequency of rhabdomyolysis associated with the available statins in the UK from 1994 to 2002[a]

Statin	Total number of prescriptions (1 Jan 1994 to 1 Jan 2002)	Total number of musculoskeletal adverse events	Frequency of musculoskeletal adverse events (% total prescriptions)	Total number of reported cases of rhabdomyolysis	Frequency of rhabdomyolysis (% total prescriptions)
Simvastatin	23 836 747	875	0.004	38	0.0002
Pravastatin	6 016 920	177	0.003	3	0.00005
Fluvastatin	2 830 006	129	0.005	2	0.00007
Atorvastatin	12 704 854	438	0.003	13	0.0002
Cerivastatin	2 541 792	258	0.01	12	0.0004

a Adverse event data obtained from the UK Medicines Control Agency. Prescription data as assessed by Merck Sharp & Dohme using UK Mediplus data from IMS Health (February 2002 update).

verse events include all muscle disorders including myopathy, myalgia, myositis and increased creatine phosphokinase as well as rhabdomyolysis. These data illustrate a significantly higher frequency of musculoskeletal adverse events associated with cerivastatin, while the frequency of both rhabdomyolysis and all cause muscle toxicity associated with simvastatin, pravastatin, atorvastatin and fluvastatin appears reassuring and supports the safety profiles and low incidence of myotoxicity reported in the major clinical trials.

4. Mechanisms of Statin-Induced Myotoxicity

Myotoxic adverse reactions including rhabdomyolysis are among the most well documented adverse reactions associated with both statins and other hypolipidaemic drugs.[63-66] However, the precise mechanisms behind the myotoxic effects of statins and the increased risk of rhabdomyolysis associated with statin-fibrate combination therapy remain unclear and there is no clear consensus of opinion regarding which is the more likely to be responsible.

A variety of different hypotheses have been suggested to account for the myotoxic effects of statins. These include statin-induced interruption of glycoprotein synthesis in the muscle membrane,[67] deficiency in chloride channel activation in the muscle membrane[68] and increased intracellular calcium concentrations leading to impaired membrane function[69] all of which may result in myocyte injury. Morphologic observations suggest that dividing myoblasts are sensitive to the effect of statins contributing to a myotoxic effect.[68] Since membrane lipids are in dynamic equilibrium with plasma lipids, a low concentration of plasma cholesterol associated with decreased intracellular cholesterol may result in reduced membrane lipid content, which in turn may cause physical modification of membrane fluidity and a decrease in cell proliferation[70-72] reduction in cholesterol content of up to 60% has been noted in myocytes of patients treated with simvastatin,[71] whilst reduced cholesterol levels have also been noted in erythrocyte and platelet membranes of patients treated with pravastatin.[72] Such changes in membrane composition may result in alterations in membrane Na^+/K^+ channels thus causing irreversible cell damage.[72]

Muscle injury leads to the release of creatinine kinase, an enzyme that generates adenosine triphosphate (ATP) via phosphorylation of adenosine diphosphate (ADP). Acute muscle necrosis as seen in rhabdomyolysis may be related to depletion of ATP reserves required to maintain cell integrity,[73] since statins may inhibit production of mitochondrial ATP[74] this effect may predispose to myocyte disruption.

HMG-CoA reductase catalyses the formation of mevalonate from HMG-CoA. Mevalonate is an important precursor not only of cholesterol but also of ubiquinone (co-enzyme Q), dolichols and isopentenyl adenine. All these products are in-

volved in cell replication and dolichol is required for glycoprotein synthesis.[75] Deficit in these products may adversely effect myocyte duplication and cause disruption of the myocyte cell membrane, predisposing to myotoxic consequences. Ubiquinone is utilised by mitochondria for electron transport, reduced levels of ubiquinone are found in some mitochondrial myopathies[76] and reduced synthesis of ubiquinone may result in defective mitochondrial ATP synthesis predisposing to myocyte instability.[77] Furthermore needle biopsies from a series of patients with myopathy related to either simvastatin or pravastatin revealed light microscopic changes similar to those of a mitochondrial myopathy,[78,79] which may be related to reduced ubiquinone concentrations. The role of ubiquinone in statin-associated myotoxicity is however contentious, since some studies have failed to show a reduction in ubiquinone levels with statin therapy and therapeutic trials of ubiquinone in patients with muscle disorders or congestive cardiac failure have failed to show any benefit.

The fact that the rate of myotoxicity was much higher with cerivastatin than with any other statin has raised the issue of whether there are differences in the myotoxic potential of the various statins and whether these relate to specific physicochemical properties of the drug. Lipophilic statins have been postulated to be more myotoxic because of possible enhanced penetration of the myocyte. *In vitro* studies in mouse myoblasts demonstrated that pravastatin, (a relatively hydrophilic statin) appears to have poor penetration of the cell membrane.[68] Clinically significant myopathy is, however, rare in association with lipophilic statins, with an analysis of simvastatin megatrials demonstrating an overall myotoxic rate of <0.025%. Furthermore, myotoxicity has been reported with all statins (tables II and III) and there have been no clinical safety trials that directly compare statins.

Differences in myotoxicity between the statins may also be related to the CYP enzyme system. Various isoforms of the CYP system are the primary mechanisms involved in the metabolism of all statins other than pravastatin. The CYP 3A4 isoform is the main isoenzyme expressed in human liver, accounting for up to 50% of total CYP protein and is the predominant isoform for the metabolism of simvastatin, atorvastatin, and lovastatin.[23,24] Reduced function of CYP mediated statin clearance due for example to concomitant use of other drugs that inhibit CYP (cyclosporin, itraconazole, and erythromycin) leads to increased bioavailability of statins, thereby increasing the potential for myotoxicity.[80] There is large interindividual variation in expression of the CYP 3A4 isoenzyme,[81] which may partly account for any possible differences in myotoxic potential between individual patients and drugs, since other CYP isoforms including CYP 2C8 (cerivastatin) and CYP 2C9 (fluvastatin) are also involved statin metabolism. Variability in CYP isoform activity does not, however, explain adequately the susceptibility to develop statin-induced myotoxicity. Cerivastatin demonstrates higher rates of myotoxicity despite being metabolised by both CYP 2C8 and CYP 3A4 isoforms. Furthermore rates of myotoxicity are similar with simvastatin and pravastatin, the latter not being metabolised by the CYP system.

Statin-induced myotoxicity is also a dose-dependent phenomenon.[82] In rats dose-dependent myotoxicity has been seen with simvastatin, lovastatin and pravastatin, an effect that was potentiated by concomitant cyclosporin administration.[83] Pravastatin, however, appeared less myotoxic than simvastatin or lovastatin, a finding, which is most likely, related to hydrophilicity and thus lower uptake by myocytes.[83] Clinical data also support the dose relationship of statin myotoxicity, with a recent simvastatin study at doses of 40, 80 and 160 mg/day demonstrating increased myotoxic symptoms with increasing dosage.[82]

There are also multiple complex metabolic causes of rhabdomyolysis including malignant hyperthermia, organic aciduria and various genetic myopathies. The role of heterozygosity for such

gene defects in inter-individual susceptibility to develop myotoxicity and rhabdomyolysis in response to statin therapy is unclear and requires further evaluation.

5. Fibrate-Statin Associated Myotoxicity

Myotoxicity, in particular rhabdomyolysis, is a well-recognised complication of the combination of statins and fibrates,[84,85] approximately 25% of the rhabdomyolysis-related mortality due to cerivastatin was associated with cerivastatin-gemfibrozil combination therapy. How this combination causes rhabdomyolysis is not known. Initial evidence suggested that this interaction was purely pharmacodynamic. The fact that both statin and fibrate monotherapy each cause myopathy, could explain the observed higher risk of muscle toxicity when both drugs were taken together. Gemfibrozil and other fibrates are not known to inhibit CYP 3A4-mediated statin elimination and thus should have no effect on systemic statin levels. Furthermore, statins are not known to significantly inhibit any CYP pathways, thus statins should not significantly effect plasma fibrate levels and should not act as perpetrators in any pharmokinetic fibrate-statin interaction.

Recent evidence has, however, demonstrated that concomitant gemfibrozil and simvastatin therapy leads to increased plasma concentrations of simvastatin through non-CYP 3A4 mechanisms as *in vitro* evidence suggests that gemfibrozil has no effect on CYP 3A4 function.[86] A further study demonstrates that gemfibrozil also leads to increased plasma levels of lovastatin, whilst bezafibrate has no effects on plasma lovastatin levels,[87] an observation that supports the notion that there may be differences between individual fibrates. The mechanisms mediating these observations at present remain unclear. Glucuronidation is a metabolic pathway for simvastatin, atorvastatin and cerivastatin (but not pravastatin), and part of the effect of gemfibrozil on statin metabolism may be mediated by its ability to inhibit this process. Some preliminary *in vitro* data suggest that glucuronidation of cerivastatin may be more susceptible to inhibition by gemfibrozil than is the case with simvastatin and atorvastatin. Furthermore, there are accumulating *in vitro* data suggesting that CYP 2C8-mediated metabolism of cerivastatin, but not CYP 3A4-mediated metabolism of atorvastatin or simvastatin, is inhibited by gemfibrozil and that these effects are more pronounced with gemfibrozil than with fenofibrate. Recently published studies also suggest that gemfibrozil may also inhibit the CYP 2C9 isoform,[88] thus leading to potential interaction problems with fluvastatin.

Despite these observations, in a recent review of 36 published clinical trials and 29 case reports involving combination statin-fibrate therapy,[89] an incidence of myotoxic reactions of only 0.12% was noted, with higher incidences of myotoxicity having been reported with statin monotherapy.[15] Risk factors that predisposed patients to myopathy caused by combination therapy included increased age, female gender, renal or liver disease, diabetes mellitus, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, and heavy exercise.

6. Conclusion

Statins have been associated with myotoxicity in experimental as well as human models. The pathophysiological mechanism for the development of myopathy and rhabdomyolysis is not established. The risk of these potentially life-threatening adverse reactions appears to be a class effect and dose related. The 10-fold higher rate of rhabdomyolysis with cerivastatin suggests that there are real differences in the risk of myotoxicity, which may relate to both physicochemical as well as pharmacokinetic properties of the drugs. A significant proportion of the cerivastatin-related rhabdomyolysis was associated with combination therapy with gemfibrozil. Although well recognised, the mechanisms underlying the increased incidence of rhabdomyolysis with combination fibrate-statin therapy are unclear. Initial evidence suggests that the effects of gemfibrozil may be pharmacody-

namic as well as pharmacokinetic and the effects of gemfibrozil may be different from other fibrates. Although there are growing data demonstrating pharmacodynamic and metabolic differences between individual fibrates, there are, however, no definitive data at present other than that with gemfibrozil and cerivastatin to suggest that an individual fibrate has greater potential to cause myotoxicity either alone or in combination with a statin than any other. The clinical indications for statin-fibrate combination therapy are unclear and at present combination therapy is used when statin monotherapy fails to control mixed hyperlipidemia. Niacin may be added before a fibrate is considered, as it appears to have less risk of myopathy. Statin-fibrate combination therapy must be undertaken cautiously and only after careful benefit-risk analysis. Patient counselling on the risks and warning signs of myopathy is extremely important.

The increased risk of rhabdomyolysis associated with cerivastatin was not identified in premarketing clinical trials and only became apparent on postmarketing surveillance. In 1999 the product information for cerivastatin was amended to include a contraindication for combination with gemfibrozil. Despite this, cases of rhabdomyolysis continued to occur, which, coupled with the recent troglitazone experience, indicates weaknesses in post-release surveillance of drugs with the potential to cause rare, but potentially fatal adverse events. In order to assess whether more stringent labelling, dose restrictions and safety measures are required for the statins, the results of the European Agency for Evaluation of Medicinal Products safety assessment of statins are eagerly awaited.

Appropriate measures to reduce the risk of adverse drug effects with the statins, need to be based on a detailed understanding of the mechanisms by which these toxic effects are produced. This is particularly needed for statin-induced rhabdomyolysis.

The overwhelming clinical outcome evidence supporting the long-term use of statin therapy in patients at risk of coronary heart disease together with the long-term safety data, particularly relating to simvastatin and pravastatin, support the predicted worldwide increase in long-term use of these agents. The choice of statin, therefore, should be based on several criteria including outcome evidence, long-term safety and cost effectiveness analysis.

With the imminent release and marketing of more lipid lowering agents, the cerivastatin experience illustrates the importance of postmarketing surveillance of drug-related adverse effects. This episode also highlights the need for such information to be appropriately and rapidly communicated to physicians to ensure that confidence in this class of drugs is not needlessly undermined.

From the perspective of clinical practice when considering the use of newer, potent lipid lowering agents such as rosuvastatin, a detailed benefit-risk assessment needs to be made with close attention paid to assessing the presence of factors predisposing to myotoxicity such as age, female gender, renal or liver disease, diabetes mellitus, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, and heavy exercise. The small risk of myopathy as illustrated by both clinical trial and postmarketing safety data, however, rarely outweighs the established morbidity and mortality benefits of achieving lipid goals. Patient counselling on the risks and warning signs of myopathy is extremely important and in subjects at high-risk regular clinical and biochemical screening may be required.

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