



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203




Human Journals

Review Article

April 2018 Vol.:12, Issue:1


© All rights are reserved by Micah Susan Mathew et al.

A Review on Statin Induced Myotoxicity



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203



**Micah Susan Mathew^{*1}, Saerah Simon², Sidhi Sunil³,
Renuka R⁴, Elesy Abraham⁵**

1. Micah Susan Mathew, Third Year Pharm D Student, Nazareth College of Pharmacy, Othara P. O, Thiruvalla, Kerala, India

2. Saerah Simon, Third Year Pharm D Student, Nazareth College of Pharmacy, Othara P. O, Thiruvalla, Kerala, India

3. Sidhi Sunil, Third Year Pharm D Student, Nazareth College of Pharmacy, Othara P. O, Thiruvalla, Kerala, India

4. Mrs. Renuka R, Assistant Professor, Nazareth College of Pharmacy, Othara P. O, Thiruvalla, Kerala, India

5. Dr. Elesy Abraham, Principal, Nazareth College of Pharmacy, Othara P. O, Thiruvalla, Kerala, India

Submission: 25 March 2018
Accepted: 02 April 2018
Published: 30 April 2018

Keywords: Statins, rhabdomyolysis, myotoxicity

ABSTRACT

Statin therapy is the cornerstone for prevention and treatment of cardiovascular disease. These drugs are among the most commonly prescribed medicines intended for long-term use. In general, statins are well tolerated. However, muscular adverse effects appear to be the most common obstacle that limits their use, resulting in poor patient compliance or even drug discontinuation. In addition, rare but potentially fatal cases of rhabdomyolysis have been reported with the use of these drugs, especially in the presence of certain risk factors. Previous reports have investigated statin-induced myotoxicity in vivo and in vitro using a number of cell lines, muscle tissues, and laboratory animals, in addition to randomized clinical trials, observational studies, and case reports. Rhabdomyolysis is the most severe adverse effect of statins, which may result in acute renal failure, disseminated intravascular coagulation, and death. Statin-associated rhabdomyolysis causes skeletal muscle injury by self-perpetuating events leading to fatal irreversible renal damage through a series of biochemical reactions. The myotoxicity, which ranges from mild to serious rhabdomyolysis, associated with HMG-CoA reductase inhibitors, during treatment of hypercholesterolemia is of paramount importance. Preferential distribution and action of statins in the liver could be the key to minimize myotoxicity concerns. The exact pathophysiology of statin-induced myopathy is not fully known. Multiple pathophysiological mechanisms may contribute to statin myotoxicity. The management of statin induced myotoxicity involves statin cessation, the use of alternative lipid lowering agents or treatment regimes.



HUMAN JOURNALS

www.ijppr.humanjournals.com

INTRODUCTION

Statins are considered to be safe, well tolerated and the most efficient drugs for the treatment of hypercholesterolemia, one of the main risk factor for atherosclerosis, and therefore they are frequently prescribed medications. The 4S study [3] published in 1994 showed that chronic intake of simvastatin significantly reduced mortality in individuals with hypercholesterolemia and coronary heart disease. These data triggered a great interest in statins. Subsequent studies highlighted the benefits of statin treatment in primary and secondary prevention for coronary heart disease and in individuals with normal cholesterol levels. Currently, the role of statins in reducing the risk of cardiovascular disease is well established. Cerivastatin was withdrawn from the market by the US Food and Drug Administration (FDA) in 2001 due to reports of rhabdomyolysis, which was associated with cerivastatin-gemfibrozil combination therapy.[1-5]

MYOTOXICITY – DEFINITION AND INCIDENCE

The most severe adverse effect of statin therapy is myotoxicity. Its various forms include myopathy, myalgia, myositis, and rhabdomyolysis. The number of muscle complaint incidences varies between studies mainly due to the contradictory definitions of myopathy. According to the US National Lipid Association Statin Safety Assessment Task Force, a meta-analysis of 21 clinical trials providing 180,000 person-years of follow-up found that myopathy, defined by muscle symptoms and creatine kinase (CK) levels above a 10-fold upper limit of normal (ULN), occurs in five patients per 100,000 person-years. Rhabdomyolysis, defined by CK levels above 10,000 IU/l or above a 10-fold ULN with an elevation in serum creatinine or requirement for hydration therapy, occurs in 1.6 patients per 100,000 person-years. Less severe manifestations are much more common. Myalgias with or without CK elevation affect 2–7% of patients and asymptomatic CK elevation up to 10-fold ULN is noted in 11–63% of patients. One recent cohort study confirmed that the risk of myopathy varies with ethnic group, with Caribbean and black African groups having the highest risks [7-10].

Table 1: Types of statin induced myopathies

TYPES	SYMPTOMS
Myopathy	Any muscle disease; myalgia, muscle tenderness, weakness, cramps, CK elevation
Myalgia	Muscle aches, CK normal
Myositis	Inflammation, CK elevation
Rhabdomyolysis	Above symptoms and CK elevation, renal insufficiency

MYALGIAS

Symptoms of statin-induced myopathy include any combination of myalgias, muscle tenderness or weakness. Patients describe an aching or cramping sensation in their muscles. Tendon pain and nocturnal leg cramps may also occur. Muscle symptoms are typically more widespread and intense with exercise, and athletes are frequently intolerant to statin therapy. Muscle weakness is usually proximal, but some patients describe difficulty opening jars and snapping their fingers. The incidence of myotoxicity is estimated to be 0.1–0.5% in cases of monotherapy and 0.5–2.5% in cases of multiple medications.[11]

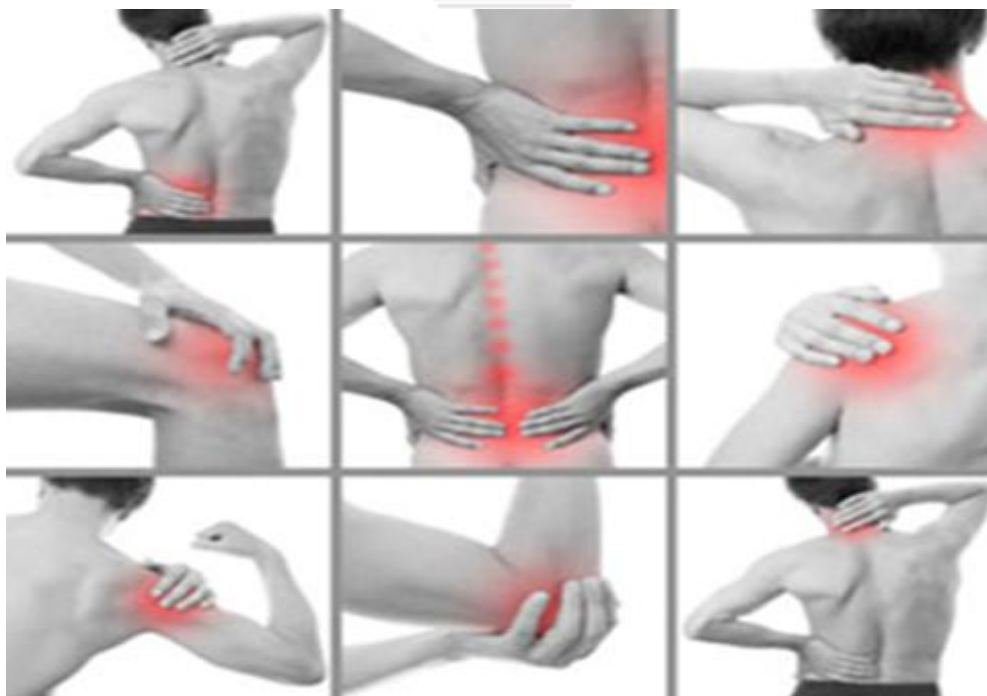


Fig 1: Sites of Myopathy

RHABDOMYOLYSIS

Rhabdomyolysis is a condition in which damaged skeletal muscle breaks down rapidly. Symptoms may include muscle pains, weakness, vomiting, and confusion. There may be tea-colored urine or an irregular heartbeat. Some of the muscle breakdown products, such as the protein 'myoglobin' are harmful to the kidneys and may lead to kidney failure. Rhabdomyolysis is the most severe adverse effect of statins, which may result in acute renal failure, disseminated intravascular coagulation, and death.[12,13]

MECHANISM OF STATIN INDUCED MYOTOXICITY

The mechanism by which statins cause muscle toxicity is not well understood, but genetic studies have provided new insights. They inhibit the conversion of HMG-CoA to mevalonic acid, which is an important early step in cholesterol synthesis.[15]

Individual statins may have distinct effects on the synthesis of coenzyme Q10 (CoQ10, ubiquinone), which plays an important role in muscle cell energy production. It has been speculated that a reduction in ubiquinone in skeletal muscle may contribute to statin-induced muscle injury. Some studies have found that statins decrease skeletal muscle and plasma concentrations of ubiquinone; however, other studies have not and studies have come to different conclusions about whether statin treatment decreases levels of ubiquinone in skeletal muscle. Long-term treatment with simvastatin (10 to 40 mg daily for >12 months) reduced ubiquinone content in skeletal muscles and decreased maximal mitochondrial oxidative phosphorylation capacity [16-17].

One study found increased levels of plant sterols in skeletal muscle in patients treated with high-dose statins. Specifically, sitosterol was increased by approximately 50 percent. The authors of the study proposed that these increased cellular levels could contribute to the muscle toxicity of statins. Beta-sitosterol is an activator of AMP-activated protein kinase, which inhibits acetyl-CoA carboxylase. This results in reduced fat synthesis and increased beta-oxidation. Preliminary evidence suggests that statin-intolerant patients demonstrate increased fatty acid oxidation (FAO) in response to lovastatin, implicating an intrinsic FAO abnormality. Statins increase the expression of mitochondrial carnitine acyl-carnitine translocase and this effect may contribute to the alteration in FAO [17,18-20].

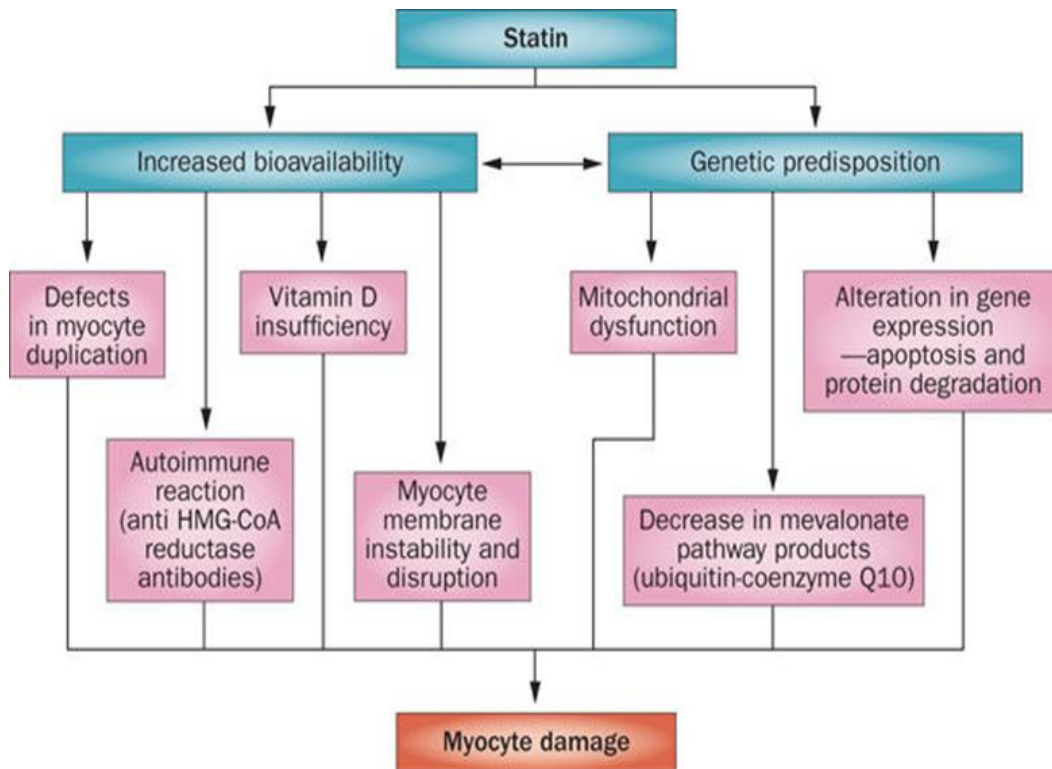


Fig 2: Mechanism involved in statin induced myotoxicity

RISK FACTORS FOR MYOTOXICITY

Anthropometric

- † Age >80 years old
- † Females are more prone to myotoxicity
- † Low body mass index
- † Acute infection
- † Hypothyroidism (untreated or undertreated)
- † Impaired renal function

Hepatic function

- † Biliary tree obstruction
- † Organ transplant recipients

- † Severe trauma
- † Human immunodeficiency virus
- † Diabetes mellitus
- † Vitamin D deficiency
- † Surgery with high metabolic demands.

DIFFERENCES AMONG STATINS

Statins exhibit differences in half-life, systemic exposure (area under the curve), maximum concentration, bioavailability, protein binding, lipophilicity, clearance, metabolic pathways, the presence of active metabolites, and excretion routes. Fluvastatin is available in both immediate-release and extended-release formulations, which have some differences in pharmacokinetic properties. [21]

With the exception of lovastatin and simvastatin, which are administered as prodrugs, all statins are given as the active β -hydroxy acid form. The extent of absorption of statins varies considerably, from 30% to 98%. Following absorption, statins undergo extensive hepatic first-pass metabolism and are excreted mainly via the bile into faeces, resulting in low systemic bioavailability. With the exception of atorvastatin, the elimination half-life of all statins is very short (0.5-4.7 hours), and no drug accumulates in plasma on repeated administration. The quantity of the administered dose of statin that is excreted in urine varies from negligible amounts for atorvastatin to 20% and 30% for pravastatin and cerivastatin, respectively. With their limited renal excretion, fluvastatin and atorvastatin are the statins least affected by alterations in renal function. Immediate-release fluvastatin displays nonlinear increases in its area under the curve and maximum concentration at doses greater than 20 mg, suggesting a saturation of the hepatic first-pass effect. Consequently, there are greater than expected systemic drug concentrations in patients receiving higher doses, although this effect appears to be temporary. Compared with immediate-release fluvastatin, (80 mg), extended-release fluvastatin (80 mg) demonstrates a reduced maximum concentration and bioavailability, resulting in lower systemic drug levels. [22-23]

Table 2: Differences among statins

DRUGS	DOSE RANGE	METABOLISM	DRUG INTERACTIONS
LOVASTATIN	20-80 mg daily	Mainly CYP3A4	Potent inhibitors of CYP3A4
SIMVASTATIN	10-80 mg	Mainly CYP3A4	Potent inhibitors of CYP3A4
PRAVASTATIN	20-80 mg daily	Metabolized by Sulphation. biliary, urinary excretion	Inhibitors of CYP2C9
FLUVASTATIN	40-80 mg daily	CYP2C9	Inhibitors of CYP2C9
ATORVASTATIN	10-80 mg	CYP3A4	Potent inhibitors of CYP3A4
ROSUVASTATIN	5-40 mg daily	Biliary excretion	—

DRUG-DRUG INTERACTIONS

Drug-drug interactions with statins are significantly more likely to be associated with myopathy compared with statin monotherapy. For example, one source reported that the incidence of myopathy for lovastatin monotherapy was 0.15%, but increased to 2%, 5%, and 28% in patients receiving concomitant niacin, niacin plus cyclosporine, or cyclosporine plus gemfibrozil, respectively. [24]

With the exception of pravastatin, which is transformed enzymatically in liver cytosol, statins are extensively metabolized via cytochrome P450 (CYP) pathways. Lovastatin, simvastatin, atorvastatin, and cerivastatin use mainly the CYP3A4 pathway. Fluvastatin has minimal CYP3A4 activity; its metabolism occurs mainly via CYP2C9.[25]

Most of the clinically important drug-drug interactions that occur with statins are attributable to the concurrent use of statins that are recognized by CYP3A4 and other agents that are potent inhibitors or substrates of this enzyme—in particular, the azole antifungals, some macrolide antibiotics, and cyclosporine. Other CYP3A4 substrate agents (eg: the calcium channel antagonists) may compete for the enzyme, thereby also potentially increasing the serum concentration of the statin. An interaction also occurs between statins and coumarin

anticoagulants; the co-administration of statins to patients receiving warfarin causes a small increase in the anticoagulant effect of warfarin that requires monitoring of the international normalized ratio and potentially a reduction in warfarin dosage. The mechanism of the interaction between statins and warfarin is uncertain; given that both CYP3A4 and CYP2C9 isoenzymes are involved in the metabolism of warfarin, competition with statins at this level may be a contributing factor in the potentiation of warfarin effects. Cases of rhabdomyolysis have been reported with the combination of warfarin and any statin, but it is not clear whether these cases were due to a warfarin-statin interaction. However, it should be noted that the risk for myopathy also appears to increase when statins are combined with drugs that may not be metabolized via the CYP3A4 pathway, such as fibrates and niacin. Drug interactions at the excretion level might potentially occur as a consequence of competition for carrier-mediated transport across the bile canalicular membrane.[21]

In addition, 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, P-glycoproteins, are known to affect the disposition and bioavailability of many drugs including 3A4 substrates. P-glycoproteins are transmembrane proteins that function as drug efflux pumps that actively transport drugs from intestinal, renal, brain, and hepatic cells. Lovastatin and simvastatin are very potent and effective inhibitors of P-glycoprotein transport, whereas atorvastatin and pravastatin have less inhibitory activity. In contrast, fluvastatin is not a substrate of P-glycoprotein. Digoxin is a P-glycoprotein substrate, and its narrow therapeutic range makes any drug-drug interaction important. Acute interactions have been observed with simvastatin and co-administration of atorvastatin, 80 mg/d, and digoxin for 20 days increased systemic exposure to digoxin by inhibition of P-glycoprotein; therefore, monitoring digoxin levels is warranted with these agents. Administration of a single 40-mg dose of fluvastatin to patients receiving long-term treatment with digoxin did not result in any clinically significant effect on the digoxin steady-state pharmacokinetics. However, cases of rhabdomyolysis have been reported with the coadministration of digoxin and all statins, although it is not clear whether these cases were related to a digoxin-statin interaction.[26]

When statins are administered concomitantly with other potentially myotoxic drugs or with agents that may increase the plasma concentration of statins, the risk for myopathy increases. Cases of substantial increases in serum drug concentrations of lovastatin and simvastatin have

been reported following clinically significant drug interactions. Spach and colleagues reported a 3-fold increase in the serum concentration of lovastatin (40 mg/d) when given concomitantly with erythromycin, Ayanian and colleagues reported an 8-fold increase in the serum concentration of lovastatin (60 mg/d) in combination with erythromycin and diltiazem, and Mousa and colleagues reported a 3.6-fold increase in the concentration of simvastatin (20 mg/dL) in combination with diltiazem. Interactions have been reported for fluvastatin in combination with the CYP2C9 substrate warfarin, and an increased serum concentration of fluvastatin has been reported when it is coadministered with diclofenac or fluconazole.[25]

Statin Interactions with Cyclosporine

In patients after transplantation, the combination of statins and calcineurin inhibitors (in particular, cyclosporine) often results in increased serum levels of the statin, with the potential for an increased risk for myopathy and rhabdomyolysis, particularly when higher doses of statins are used. Cases of rhabdomyolysis have been reported in patients after transplantation taking cyclosporine with all statins except fluvastatin and pravastatin. Cyclosporine increases plasma exposure to atorvastatin by approximately 6-fold, lovastatin by up to 20-fold, pravastatin by 5- to 23-fold, simvastatin (20 mg/d) by 3-fold, cerivastatin (0.2 mg/d) by 3 to 5 fold, and fluvastatin by approximately 2-fold. The increase in pravastatin bioavailability in the presence of cyclosporine, despite the lack of CYP3A4 interactions, may be due to competition for biliary excretion by these 2 agents resulting in reduced biliary clearance of pravastatin.[21, 27-35]

Despite the risk for statin-cyclosporine interactions, treating dyslipidemia is crucial in the post transplantation population because cardiovascular disease is a major cause of death in these patients, accounting for nearly half of all deaths in kidney graft recipients. Dyslipidemia often worsens during the post transplantation period, with increases in total cholesterol of 25% to 30% commonly found in renal transplant patients, along with concomitant increases in triglyceride and LDL-C levels. Because of the significant clinical benefits of statin therapy in this population, therapy is recommended with close follow-up. In 1992, Ballantyne and colleagues reported that 4 of 5 patients after heart transplantation who were treated with high-dose lovastatin (40-80 mg/d) in combination with another lipid-lowering agent developed rhabdomyolysis and 2 developed acute renal failure. However, lovastatin monotherapy at a dosage of 20 mg/d was well tolerated and did not result in myopathy in 15 similar patients.[35,21]

Low-dose statin therapy in combination with cyclosporine was well tolerated in heart transplant patients in 2 small open-label trials. Shortly after heart transplantation, Kobashigawa and colleagues randomly assigned 97 patients to pravastatin (20-40 mg/d) or no statin. The pravastatin group had a better survival rate after 12 months (94% vs 78%; $P = .03$), and there were no episodes of CK elevations or myopathy in either group. Similarly, Wenke and colleagues randomly assigned 72 heart transplant patients to receive simvastatin (5-15 mg/d) or no statin. The simvastatin group had a significantly higher survival rate (88.6% vs 70.3%; $P = .05$) and lower incidence of graft complications at 4 years than did patients randomized to no statin. In a 12-month open-label study comparing simvastatin, 20 mg/d, and pravastatin, 40 mg/d, in heart transplant patients receiving cyclosporine there were similar clinical benefits to the 2 trials mentioned previously; however, myopathy or rhabdomyolysis occurred in 6 (13.3%) of the simvastatin-treated patients but in none of the pravastatin-treated patients. Based on these studies, it is recommended that heart transplant recipients receiving cyclosporine should not receive more than 10 mg/d of simvastatin, 20 mg/d of lovastatin, or 40 mg/d of pravastatin, nor should a statin be taken in combination with other lipid-lowering agents.[35-36]

Fluvastatin (at dosages of up to 80 mg/d) has been studied extensively in renal transplant recipients. No instances of rhabdomyolysis have been observed during clinical trials in which patients received fluvastatin and cyclosporine concomitantly. Fluvastatin is currently being investigated in the ongoing Assessment of Lescol in Renal Transplantation (ALERT) trial, which is an RCT designed to assess the effect of fluvastatin (40-80 mg/d) vs placebo on major adverse coronary events and all-cause mortality in renal transplant recipients ($N = 2100$) with mild to moderate hypercholesterolemia. Results of the 6-year trial are expected in early 2003. Following the withdrawal of cerivastatin, ALERT investigators reviewed blinded safety data for all adverse events reported at a mean follow-up of 4 patient-years. Overall, there was only 1 reported asymptomatic CK level greater than $10 \times \text{ULN}$, and there were no cases of rhabdomyolysis.[35]

Statin-Fibrate Combination Therapy

Monotherapy with fibrates appears to pose an independent risk for myopathy that is greater than the risk posed by statin monotherapy. An analysis of data from 17 219 general practice patients in the United Kingdom found that the incidence rate for myopathy observed for the total population was 2.3 per 10 000 patient-years (95% confidence interval, 1.2-4.4), whereas

the incidence rate for the population without hyperlipidemia and not taking lipid-lowering agents was 0.2 per 10 000 patient-years (95% confidence interval, 0.1-0.4). Although rare, myopathy occurred more frequently in patients using either statins or fibrates than in the general population; however, current fibrate users were 5.5 times more likely to develop myopathy than were current statin users.[36]

Fibrates are particularly effective in reducing triglyceride levels and raising high-density lipoprotein cholesterol (HDL-C) levels and have been shown to reduce clinical events in patients with low HDL-C levels. Because patients with mixed hyperlipidemia can rarely be treated successfully with a single drug, statin-fibrate combination therapy may offer a therapeutic advantage in improving lipid profiles, although the potential clinical benefits of this combination have not been reported. Mixed hyperlipidemia is frequently identified in patients with diabetes; it is characterized by a highly atherogenic lipid pattern of increased total cholesterol and triglyceride levels in combination with decreased HDL-C level. For these patients, the absolute risk for a cardiovascular disease event is high, and the benefits of combination therapy are likely to be substantially greater than the risk for an SAE.[37,38]

Drug interactions between statins and fibrates occur frequently, resulting in a relatively large number of reports of severe myopathy and rhabdomyolysis in patients treated with this combination. In a review of 36 clinical trials published between 1988 and 2000 (including RCTs [n = 10], retrospective studies [n = 5], open-label studies [n = 21], and a number of trials of very short duration) with a total combined population of 1674 patients, combination drug therapy with a statin and a fibrate appeared to be associated with an overall 0.12% incidence of myopathy, defined as myalgia with CK levels greater than $10 \times$ ULN.²⁴ Of the studies reviewed, 20 used gemfibrozil and 10 used bezafibrate; the 2 cases of myopathy involved gemfibrozil use. In a subsequent clinical trial, the combination of fluvastatin and bezafibrate was not associated with myopathy or relevant CK elevations in 333 patients with mixed hyperlipidemia who were followed up for 6 months. However, in a 12-month open-label study, myopathy was reported in 2 of 148 patients with type 2 diabetes who received the combination of simvastatin and bezafibrate.[39,40]

Myopathy related to the statin-fibrate combination appears likely to occur by more than a single mechanism and does not always involve CYP3A4 pathways. For example, gemfibrozil was shown to increase plasma concentrations of lovastatin without inhibiting CYP3A4, whereas bezafibrate demonstrated no significant effect on the pharmacokinetics of

lovastatin. 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 use. The concomitant use of gemfibrozil and atorvastatin, lovastatin, pravastatin, or simvastatin has been associated with case reports of rhabdomyolysis, although no cases have been reported for fluvastatin in combination with gemfibrozil. No significant pharmacokinetic differences were observed when comparing the combination of fluvastatin and gemfibrozil with each drug alone. [41]

Cardiologists and lipidologists are the primary prescribers of statin-fibrate therapy, but primary care providers, particularly in the United States, also increasingly prescribe the combination. In 1998, a consensus paper on the clinical use of fibrates in the treatment of dyslipidemia and CHD affirmed the benefits of statin-fibrate therapy in patients with type IIB hyperlipidemia; however, it cautioned that this combination should not be used by the following groups: elderly patients (older than 70 years), patients taking multiple medications, patients with renal disease or other severe illnesses, and patients who may not fully understand the risks of therapy. Fibrate monotherapy may impair liver function independently; therefore, patients with impaired liver function should not receive combination statin-fibrate therapy. Furthermore, fibrates, which are excreted primarily through the kidneys, may increase the risk of myopathy in patients with even mild renal impairment.[42]

Statin-Niacin Combination Therapy

Nicotinic acid (niacin) monotherapy is used infrequently to lower LDL-C level, primarily because it is poorly tolerated at the high doses required for monotherapy. However, as with the statin-fibrate combination, statin-niacin therapy is used to augment reductions in LDL-C and triglycerides and increases in HDL-C. In 5 major clinical trials, various combinations of statins and niacin preparations have demonstrated efficacy in reducing cardiovascular and total mortality and in slowing the progression of coronary lesions.[42]

Niacin monotherapy has not been associated with myopathy. Clinical trials in which patients have received niacin in combination with fluvastatin, pravastatin or simvastatin have also not reported myopathy; however, the number of patients in these trials was low. A recent open-label study did not find any cases of myopathy with a new drug formulation containing once-daily extended-release niacin and lovastatin. The concomitant administration of fluvastatin

with niacin demonstrated no effect on the bioavailability of either drug. However, in case reports, niacin has been associated with rhabdomyolysis in combination with lovastatin, pravastatin, or simvastatin use, but not with atorvastatin or fluvastatin. Myopathy has been reported in 2% of patients taking lovastatin and niacin concomitantly.[43-48,21,24]

While hepatic toxicity with statin-niacin therapy has been minimal, transaminase elevations are frequently encountered, particularly with the use of a sustained-release niacin preparation given twice daily. As with monotherapy with either agent, patients being treated with statin-niacin combination therapy should have liver transaminase levels monitored and should be cautioned to report any symptoms that suggest myopathy.

Calcium Channel Antagonists

Many patients with hypercholesterolemia are also hypertensive 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. Several cases of statin-associated rhabdomyolysis were reported in patients receiving mibefradil. Verapamil and diltiazem, which are weak inhibitors of CYP3A4, have been shown to increase the plasma concentration of simvastatin up to 4-fold, and diltiazem has been shown to increase the plasma concentration of lovastatin to the same magnitude.[49-53]

A review of data from clinical outcome trials in which more than 12 000 patients received simvastatin for several years revealed that approximately one-third of patients randomized to simvastatin were receiving concomitant therapy with a calcium channel antagonist. There was no evidence that the concomitant use of calcium channel antagonists, including diltiazem and verapamil, increased the risk of simvastatin-associated myopathy in these trials. However, more recently, enhanced cholesterol reduction has been reported with simvastatin use in combination with diltiazem, and 2 cases of rhabdomyolysis have also been reported in association with this combination, suggesting a need for some caution in using the 2 agents simultaneously.[50,54-55]

Management of statin-associated muscle symptoms

† Ensure that there is an indication for statin use and that the patient is fully aware of the expected benefit in cardiovascular disease risk reduction that can be achieved with this treatment

† Ensure that there are no contraindications to statin use

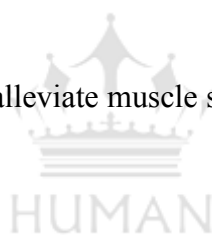
† Counsel patients regarding the risk of ‘side effects’ and the high probability that these can be dealt with successfully

† Emphasize dietary and other lifestyle measures

† Use statin-based strategies preferentially not with-standing the presence of statin-attributed muscle-related symptom

† Use non-statin therapies as adjuncts as needed to achieve low-density lipoprotein cholesterol goal

† Do not recommend supplements to alleviate muscle symptoms as there is no good evidence to support their use.



CONCLUSION

Statins play a vital role in the prevention of atherosclerotic cardiovascular complications, and statin therapy continues to be a mainstay in treating patients with dyslipidemia. However, statin-associated myopathy affects up to 10% of patients receiving statin therapy. Although considered a minor adverse effect, it may have a significant effect on patient adherence to statin therapy. While some patients may elect to discontinue therapy after consulting their health care provider, many patients may be able to continue statins with proper management of the adverse effects. Proper assessment of patients will assist in the recognition of patients at risk. Knowledge of the currently available statins and their properties will enable pharmacists to provide appropriate recommendations for individualized treatment regimens. Once patients are initiated on statin therapy, pharmacists have the opportunity to monitor patient adherence, treatment response, and medication safety, in addition to providing ongoing patient education on statin therapy and its adverse effects. Pharmacists should continue to counsel patients on the risk and warning signs of statin-associated myopathy, as

the incidence underscores the need for pharmacists to play a direct role in the monitoring of statin therapy in the inpatient and outpatient setting.

ACKNOWLEDGMENT

We would like to thank God Almighty who gave us the strength to complete the work.

We would like to express our heartfelt thanks to our Beloved Parents who supported us throughout this work.

It gives us great pleasure to express our deep sense of gratitude and immense respect to our esteemed guide, Mr. Renuka R, Assistant Professor, Dept of Pharmacy Practise, Nazareth College of Pharmacy, Othra for her inspiring guidance, sound advice, timely help, encouragement and kind support throughout this review article.

I am indebted to Dr. Elessy Abraham, Principal Nazareth College of Pharmacy, Othra for her keen interest, timely help, valuable suggestions and constant encouragement throughout this work.



REFERENCES

1. Klopstock T: Drug-induced myopathies. *Curr Opin Neurol*, 2008, 21, 590–595.
2. Kuncl RW: Agents and mechanisms of toxic myopathy. *Curr Opin Neurol*, 2009, 22, 506–515.
3. Scandinavian Simvastatin Survival Study (4S) Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*, 1994, 344, 1383–1389.
4. Heart Protection Study Collaborative Group: MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet*, 2002, 360, 7–22.
5. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM et al.: Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*, 2005, 352, 1425–1435.
6. Staffa JA, Chang J, Green L: Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med*, 2002, 346, 539–540.
7. McKenney JM, Davidson MH, Jacobson TA, Guyton JR: National Lipid Association Statin Safety Assessment Task Force. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol*, 2006, 97, 89C–94C.
8. Law M, Rudnicka AR: Statin safety: a systematic review. *Am J Cardiol*, 2006, 97, 52C–60C.
9. Baer AN, Wortmann RL: Myotoxicity associated with lipid-lowering drugs. *Curr Opin Rheumatol*, 2007, 19, 67–73.
10. Hippisley-Cox J, Coupland C: Individualising the risks of statins in men and women in England and Wales: the population-based cohort study. *Heart*, 2010, 96, 939–947.
11. Sirvent P, Mercier J, Lacampagne A: New insights into mechanisms of statin-associated myotoxicity. *Curr Opin Pharmacol*, 2008, 8, 333–338.
12. Bell DS: Resolution of statin-induced myalgias by correcting vitamin D deficiency. *South Med J*, 2010, 103, 690–692.

13. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B: Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients – the PRIMO study. *Cardiovasc Drugs Ther*, 2005, 19, 403–414.
14. World Health Organization. International Drug Monitoring: The Role of the Hospital. Geneva, Switzerland: World Health Organization; 1966. Technical Report Series No. 425.
15. Elam MB, Majumdar G, Mozhui K, et al. Patients experiencing statin-induced myalgia exhibit a unique program of skeletal muscle gene expression following statin re-challenge. *PLoS One* 2017; 12:e0181308.
16. Ghirlanda G, Oradei A, Manto A, et al. Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. *J Clin Pharmacol* 1993; 33:226.
17. Päivä H, Thelen KM, Van Coster R, et al. High-dose statins and skeletal muscle metabolism in humans: a randomized, controlled trial. *Clin Pharmacol Ther* 2005; 78:60
18. Larsen S, Stride N, Hey-Mogensen M, et al. Simvastatin effects on skeletal muscle: relation to decreased mitochondrial function and glucose intolerance. *J Am Coll Cardiol* 2013; 61:44.
19. Phillips PS, Ciaraldi TP, Kim DL, et al. Myotoxic reactions to lipid-lowering therapy are associated with altered oxidation of fatty acids. *Endocrine* 2009; 35:38.
20. Iacobazzi V, Convertini P, Infantino V, et al. Statins, fibrates and retinoic acid upregulate mitochondrial acylcarnitine carrier gene expression. *Biochem Biophys Res Commun* 2009; 388:643.
21. Corsini A, Bellocosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. *Pharmacol Ther*. 1999; 84:413- 428.
22. Desager J, PHorsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. *Clin Pharmacokinet*. 1996;31:348- 371.
23. Sabia H, Prasad P, Smith H T, Stoltz R R, Rothenberg P Safety, tolerability, and pharmacokinetics of an extended-release formulation of fluvastatin administered once daily to patients with primary hypercholesterolemia. *J Cardiovasc Pharmacol*. 2001;37:502- 511.
24. Tobert J A Efficacy and long-term adverse effect pattern of lovastatin. *Am J Cardiol*. 1988; 62:28J- 34J.
25. Scripture C D, Pieper J A, Clinical pharmacokinetics of fluvastatin. *Clin Pharmacokinet*. 2001; 40:263- 281.
26. Yu DK, The contribution of P-glycoprotein to pharmacokinetic drug-drug interactions. *J Clin Pharmacol*. 1999; 39:1203- 1211.
27. Corpier C L, Jones P H, Suki W N et al. Rhabdomyolysis and renal injury with lovastatin use: report of two cases in cardiac transplant recipients. *JAMA*. 1988; 260:239- 241.
28. East C, Alivizatos P A, Grundy S M, Jones, PHFarmer JA, Rhabdomyolysis in patients receiving lovastatin after cardiac transplantation. *N Engl J Med*. 1988;318:47- 48.
29. Rodriguez ML, Mora C Navarro J F, Cerivastatin-induced rhabdomyolysis [letter]. *Ann Intern Med*. 2000;132:598.
30. Holdaas H, Jardine, AG Wheeler DC et al. Effect of fluvastatin on acute renal allograft rejection: a randomized multicenter trial. *Kidney Int*. 2001;60:1990- 1997.
31. Olbricht C, Wanner C Eisenhauer T et al. Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses. *Clin Pharmacol Ther*. 1997;62:311- 321.
32. Regazzi MB, Iacona I Campana C et al. Altered disposition of pravastatin following concomitant drug therapy with cyclosporin A in transplant recipients. *Transplant Proc*. 1993; 25:2732- 2734.
33. Arnadottir M, Eriksson LO, Thysell HK, Karkas JD; Plasma concentration profiles of simvastatin 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without cyclosporine. *Nephron*. 1993;65:410- 413.
34. Ichimaru N, Takahara S, Kokado Y et al. Changes in lipid metabolism and effect of simvastatin in renal transplant recipients induced by cyclosporine or tacrolimus. *Atherosclerosis*. 2001; 158:417- 423.
35. Muck W, Mai Fritsche L et al. Increase in cerivastatin systemic exposure after single and multiple dosing in cyclosporine-treated kidney transplant recipients. *Clin Pharmacol Ther*. 1999;65:251- 261.
36. Gaist D, Rodriguez LA, Huerta CHallas, J, Sindrup SH; Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology*. 2001;12:565- 569.
37. Rubins HB, Robins SJ, Collins D et al. for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group, Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med*. 1999;341:410- 418.

38. Kane JP, Havel RJ; Disorders of the biogenesis and secretion of lipoproteins containing the B apolipoproteins. Scriver CR, Beaudet ALSy WS et al. eds. The Metabolic and Molecular Bases of Inherited Disease 8th ed. New York, NY McGraw-Hill 2001; 2717- 2752.
39. Pauciuolo P, Borgnino C, Paoletti R, Mariani M, Mancini M; Efficacy and safety of a combination of fluvastatin and bezafibrate in patients with mixed hyperlipidemia (FACT study). *Atherosclerosis*. 2000;150:429-436.
40. Gavish D; Leibovitz E; Shapira I Rubinstein A; Bezafibrate and simvastatin combination therapy for diabetic dyslipidemia: efficacy and safety. *J Intern Med*. 2000;247:563- 569.
41. Kyrklund C, Backman JT, Kivisto KT, Neuvonen M, Laitila J, Neuvonen PJ; Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther*. 2001;69:340- 345.
42. Duell PB, Connor W, Eillingworth DR; Rhabdomyolysis after taking atorvastatin with gemfibrozil. *Am J Cardiol*. 1998;81:368- 369.
43. Guyton JR, Capuzzi DM; Treatment of hyperlipidemia with combined niacin-statin regimens. *Am J Cardiol*. 1998;82:82U- 84U.
44. Jacobson TA, Chin MM, Fromell GJ, Jokubaitis L, AA morosa LF; Fluvastatin with and without niacin for hypercholesterolemia. *Am J Cardiol*. 1994;74:149- 154.
45. Arntz HR, Agrawal R, Wunderlich W et al; Beneficial effects of pravastatin (+/- colestyramine/niacin) initiated immediately after a coronary event (the randomized Lipid-Coronary Artery Disease [L-CAD] Study). *Am J Cardiol*. 2000;86:1293- 1298.
46. Brown BG, Zhao X Q, Chait A et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583- 1592.
47. Kashyap ML, McGovern M, EBerra K et al. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. *Am J Cardiol*. 2002;89:672- 678.
48. Garnett WR; Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors. *Am J Health Syst Pharm*. 1995;52:1639- 1645.
49. Reaven P; Witztum JL; Lovastatin, nicotinic acid, and rhabdomyolysis. *Ann Intern Med*. 1988;109:597- 598.
50. Schmassmann-Suhjar D, Bullingham R, Gasser R et al. Rhabdomyolysis due to the interaction of simvastatin with mibefradil. *Lancet*. 1998;351:1929- 1930.
51. Gruber PJ, Vega JM, Mercuri MF, Dobrinska MR, Tobert JA; Concomitant use of cytochrome P450 3A4 inhibitors and simvastatin. *Am J Cardiol*. 1999;84:811- 815.
52. Azie NE, Brater D, C Becker PA et al. The interaction of diltiazem with lovastatin and pravastatin. *Clin Pharmacol Ther*. 1998;64:369- 377.
53. Yeo KR, Yeo WW; Inhibitory effects of verapamil and diltiazem on simvastatin metabolism in human liver microsomes. *Br J Clin Pharmacol*. 2001;51:461- 470.
54. SoRelle R, Baycol withdrawn from the market. *Circulation*. 2001;104:E9015- E9016.
55. Peces R, Pobes A; Rhabdomyolysis associated with concurrent use of simvastatin and diltiazem. *Nephron*. 2001;89:117- 118.
56. Kanathur N, Mathai MG, Byrd RP, Jr Fields CL, Roy TM; Simvastatin-diltiazem drug interaction resulting in rhabdomyolysis and hepatitis. *Tenn Med*. 2001;94:339- 341.