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Managing Statin Intolerance

As more patients become eligible for lipid-lowering treatment, an increasing number seem intolerant to individual statins, with about 5-10% experiencing non-severe side effects. This is an extremely important issue because statin treatment is associated with substantial benefit in patients with or at high-risk for cardiovascular disease (CVD). Unfortunately, dyslipidemia is largely asymptomatic, and any unpleasant side effects of statins can undermine compliance. Patients, who are already scared about statins by TV and magazine articles, underestimate the degree of risk of coronary events associated with high cholesterol. Given these perceptions, a symptom such as myalgia, which is more frequent although less severe than other myotoxicity, can assume an exaggerated role in a patient's decision to discontinue a much-needed lipid-modifying medication. This *Heartbeat* will outline potential differences between statins in their associations with such adverse events, and the diagnostic and treatment strategies to prevent, recognize, and manage these events.

Occurrence of Muscular Complaints

Myalgia, described as muscle pain or soreness and/or weakness in skeletal muscles in the absence of serum creatinine (CK) elevation, is among the most common adverse events associated with statins. In clinical practice, up to 10% of outpatients receiving statins report muscle pain. Symptoms of myalgia are quite variable and include cramping, pain, aches, tenderness, soreness, stiffness, heaviness, and weakness, either at rest or only during physical exertion. Muscle cramping just at night is more likely non-specific leg cramps as opposed to statin related myalgia. Diagnosis is always complicated by the routine aches and pains accompanying aging and/or exercise.

In some the only symptom is weakness, which develops insidiously, sometimes only during physical exertion. *Myositis* is defined as myalgia with an elevated CK. *Rhabdomyoiysis* is defined as pronounced CK elevation (10 times the upper limit of normal) along with myalgia.

In the Prediction of Muscular Risk in Observational Conditions (**PRIMO**) study, the myalgia symptoms tended to occur soon after initiation of high-dose statin regimens or up-titration of statin doses.[1] Discomfort was widespread in 60.1% of patients and was more common in the lower extremities, including the thighs and calves, than in the upper extremities or trunk. The median time to onset of symptoms was about one month. The lowest proportion of patients reporting myalgia on high-dose statins were with fluvastatin (Lescol). Both high-dose atorvastatin (Lipitor) and simvastatin (Zocor) were associated with significantly higher frequencies of reported muscle symptoms compared with high-dose pravastatin (Pravachol)—Table 1.

TABLE 1. Rate of Occurrence of Muscular Symptoms Among Patients Receiving High -Dose Statin Therapy in the PRIMO Study.

statin	# of patients	% of patients with muscular S/S on statin
Pravastatin (40mg)	1901	10.9
Atorvastatin (40 or 80mg)	1844	14.9
Simvastatin (40 or 80mg)	1027	18.2
Fluvastatin (80mg XL)	3121	5.1

PRIMO: A total of 832 patients (10.5%) of the 7,924 enrolled patients reported muscle-related symptoms.

Statin myopathy is thought to be a dose-related phenomenon; as the statin dose and statin systemic exposure increase, the risk of CK elevation increases. Given this relationship, a lower dose of a more potent statin might be less likely to cause myopathy than a higher dose of a less potent statin.

The pharmacokinetics and metabolism of individual statins vary (Table 2), providing a pharmacological basis for trial of alternative statins in those intolerant to a particular statin . Very limited, if any, data exist so far in the management of this subgroup of patients. The first study to document the degree of success in switching from a poorly tolerated statin to another of the same class concluded that nearly two thirds of patients with initial problems with a particular statin are able to take an alternative statin without side effects (average of two more trials with different statins).[2] This figure may have been still higher if more patients were willing to persevere with statin switching. Pravastatin and rosuvastatin were the best tolerated in this study. It is of interest that the two statins that were most frequently tolerated in this study were those which are water soluble. However, the number of patients involved was too small to be able to establish these as the drugs of choice in statin-intolerant patients.

Alternate day or weekly dosing could also be used in conjunction with non-statin lipid-lowering therapy to reach appropriate lipid goals. This is associated with reasonable success.

Table 2. Clinical Pharmacokinetics of Statins.

Parameter	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin	Lovastatin	Fluvastatin XL
Tmax, h	3.0-5.0	1.0-3.0	1.3-3.0	0.9-1.6	2.0-4.0	4.0
Cmax, ng/mL	37	27-66	10-34	45-55	10-20	55
Bioavailability,%	20	12-14	<5	18	5	6
Lipophilic? (logP)	No (-0.33)	Yes (4.06)	Yes (4.68)	No (-0.23)	Yes(4.27)	Yes
Protein binding, %	88	>95	94-98	43-55	>95	>98
Metabolism	Min CYP; CYP2C9	CYP3A4	CYP3A4	Enzymatic& Non-enzymatic; sulfation	CYP3A4	CYP2C9
Systemic active metabolites (#)	Yes 1 minor	Yes (2)	Yes (3)	No	Yes (3)	No
Transporter protein substrates	NR	Yes	Yes	Yes	Yes	No
T ½, h	19.0	14.0	1.4-3.0	1.3-2.8	2.0	4.7
Renal excretion, %	10	≤ 2	13	20	10	6
Biliary excretion, %	30	70	58	71	83	90

Results are based on 40mg doses with the exception of fluvastatin XL (80mg). C max = max concentration; CYP = cytochrome P; logP = log partition coefficient (octane/water); NR = not reported; T max = time of occurrence of max drug concentration; T ½ = half life. *Expert Open Drug Saf.* 2003; 2(3): 269-286.

And lastly, if muscle symptoms persist after trials of the above strategies with multiple statins and doses, then initiation of non-statin lipid-lowering therapy should be considered. Agents that have been studied in statin-intolerant patients include ezetimibe (Zetia) monotherapy and ezetimibe in conjunction with colesevelam (Welchol) with reasonable reductions of lipids.

Benefit Outweighs Risk

A recent meta-analysis helps delineate the risk-benefit ratio of statin treatment to absolute risks.[3] This analysis, which encompassed 18 trials and 71,108 patients, yielded 316 myopathy-related events (myalgia, myopathy, and asthenia) in the statin group compared with 253 in the placebo group and 81 cases of CK elevation in the statin group, compared with 64 in the placebo group. Rhabdomyoiysis was reported in 9 patients receiving simvastatin, 1 patient receiving lovastatin, and 5 patients receiving placebo. These data indicate that 3,400 was the number needed to treat in order to harm; that is, 3400 patients had to be treated with a statin rather than placebo to observe a single case of statin-related rhabdomyoiysis or CK elevation of 10x ULN or more. The number needed to treat to benefit, or the number of patients who had to be treated with a statin in order to prevent 1 occurrence of myocardial infarction, revascularization, stroke, cardiovascular death, or all-cause mortality, was 27. The absolute risk-benefit ratio was approximately 126:1.

Diagnostic and Management Strategies:

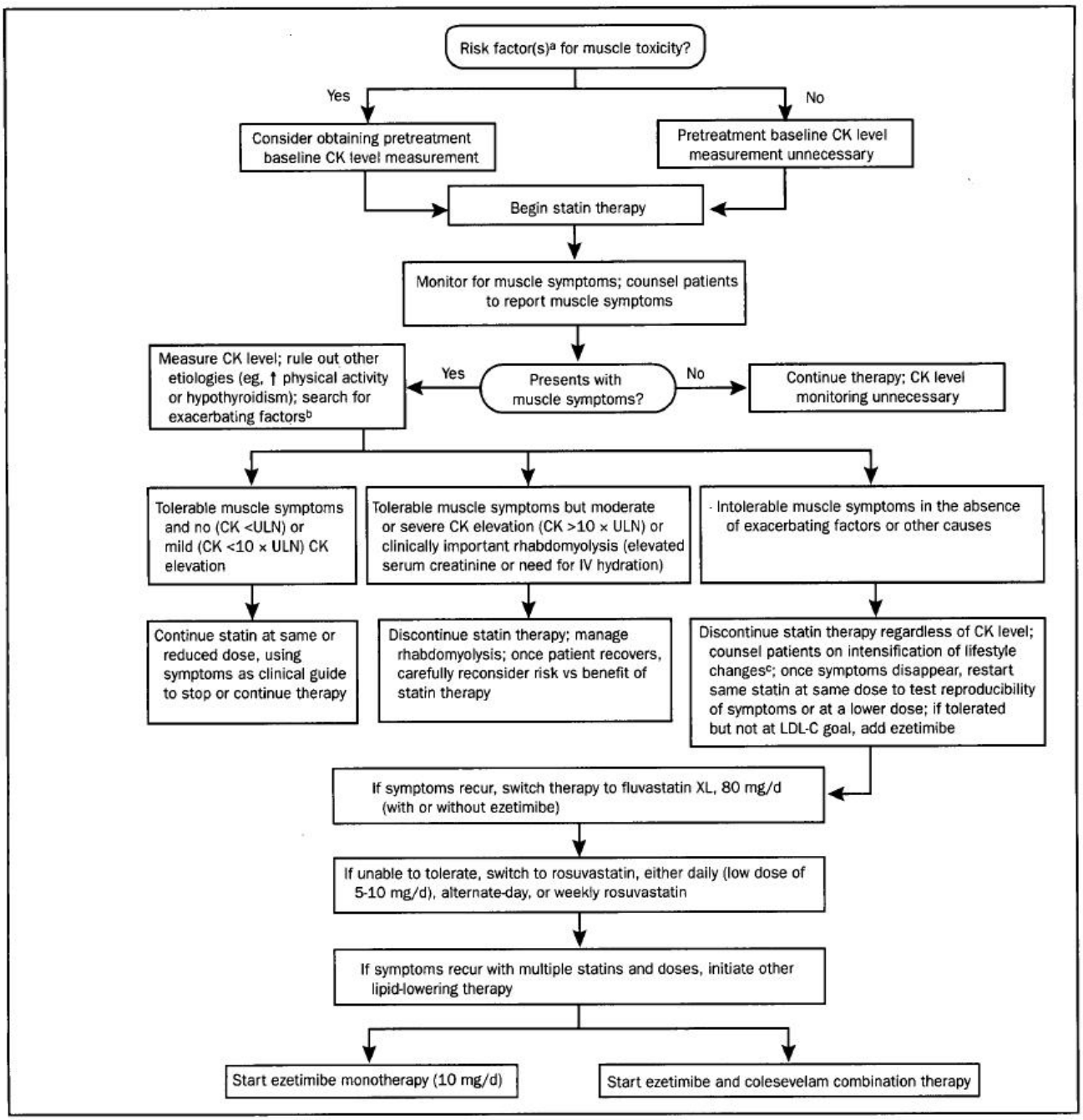
The National Lipid Association has released consensus recommendations to health care professionals regarding muscle and statin safety (Table 3).[4] The clinical algorithm depicted in Figure 1 incorporates some of these recommendations but builds on and extends them. This figure comes directly from a review article from the Mayo Clinic.[5]

TABLE 3. Recommendations to Health Care Professionals Regarding Statin and Muscle Safety

Whenever muscle symptoms or an increased CK level are encountered in patients receiving statin therapy, health professionals should attempt to rule out other causes, because these are most likely to explain the findings. Other common causes include increased physical activity, trauma, falls, accidents, seizure, shaking chills, hypothyroidism, infections, carbon monoxide poisoning, polymyositis, dermatomyositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, or PCP).
Obtaining a pretreatment, baseline CK level can be considered in patients who are at high risk of experiencing muscle toxicity (eg, older patients or those combining a statin with an agent known to increase myotoxicity), but this is not routinely necessary in other patients.
It is unnecessary to measure CK levels in asymptomatic patients during the course of statin therapy, because significant, clinically important CK elevations are rare and are usually related to physical exertion or other causes.
Patients receiving statin therapy should be counseled about the increased risk of muscle symptoms, particularly if initiation of vigorous, sustained endurance exercise or a surgical operation is being contemplated; they should be advised to report such muscle symptoms to a health professional.
Creatine kinase (CK) measurements should be obtained in symptomatic patients to help gauge the severity of muscle damage and facilitate a decision of whether to continue therapy or alter doses.
In patients who develop intolerable muscle symptoms with or without CK elevation and for whom other etiologies have been ruled out, the statin should be discontinued. Once symptoms disappear, the same or different statin at the same or a lower dose can be restarted to test the reproducibility of symptoms. Recurrence of symptoms with multiple statins and doses requires initiation of other lipid-altering therapy.
In patients who develop tolerable muscle symptoms or have no symptoms but have a CK level <10 x ULN, statin therapy may be continued at the same or reduced doses and symptoms may be used as the clinical guide to stop or continue therapy.
In patients who develop rhabdomyoiysis (CK >10,000 IU/L or >10 x ULN with an elevation in serum creatinine or need for intravenous hydration therapy), statin therapy should be stopped. Intravenous hydration therapy in a hospital should be instituted if indicated for patients experiencing rhabdomyoiysis. Once patients recover, risk vs benefit of statin therapy should be carefully reconsidered.

CK = creatine kinase; PCP = phencyclidine; ULN = upper limit of normal. From AJC[4]

Figure 1. Algorithm for monitoring and management of suspected statin-associated myopathy.



CK = creatine kinase; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; PCP = phencyclidine; ULN = upper limit of normal; XL = extended release. From Mayo Clin Proc[5]

► [a] Risk factors for muscle toxicity include advanced age and frailty, small body frame, deteriorating renal function, infection, untreated hypothyroidism, interacting drugs, perioperative periods, alcohol abuse.

► [b] Causes for elevated CK levels/muscle toxicity are as follows: increased physical activity, trauma, falls, accidents, seizure, shaking chills, hypothyroidism, infections, carbon monoxide poisoning, polymyositis, dermatomyositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, or PCP).

► [c] Patient counseling regarding intensification of therapeutic lifestyle changes (reduced intake of saturated fats and cholesterol, increased physical activity, and weight control) should be an integral part of management in all patients with statin-associated intolerable muscle symptoms.

Summary/Conclusions:

Statin intolerance is becoming a more prevalent and important issue, with myalgia the most common symptom associated with discontinuing the drug.

The best ways to avoid symptoms are to use the lowest statin dose required to achieve therapeutic goals and, when possible, to avoid concomitant therapy with drugs known to increase the risk of myopathy. A lower dose of a more potent statin is usually associated with decreased side effects. Alternate day or weekly dosing would be the last gambit (reasonably successful in my experience). Another possible treatment for some patients is the addition of Coenzyme Q_{10} to statin therapy to decrease symptoms of statin-associated myalgia. Adjunctive Coenzyme Q_{10} treatment is not mentioned in the algorithm because studies have yielded equivocal results.

Fluvastatin, Rosuvastatin and Pravastatin seem to be the best tolerated, in that order. We should always try to prescribe generics when possible to reduce costs. **We need to emphasize two things to our patients: 1) statins have undeniably fantastic benefits in decreasing CV events, and 2) the effort to find a statin which they can tolerate is definitely worth it.**

If muscle symptoms recur with trials of multiple statins and doses, then initiation of non-statin lipid-lowering therapy, like ezetimibe monotherapy and ezetimibe in conjunction with colesevelam, must be considered. Other alternatives would be Niaspan or fibrates. Lifestyle changes take on even greater importance in the management of hyperlipidemia in patients who are intolerant of statins. Dietary options include plant stanols and sterols and soluble fiber.

The risk and severity of statin-associated myopathy can be minimized by following the recent National Lipid Association guidelines for prevention and management of statin-associated myopathy, along with treatment options for those who develop intolerable muscle symptoms secondary to statin treatment.

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