December 2003 (Vol. 52, No. 12)

CLINICAL INQUIRIES FROM THE FAMILY PRACTICE INQUIRIES NETWORK

Do statins cause myopathy?

Allen J Daugird, MD, MBA

Department of Family Medicine, University of North Carolina at Chapel Hill;

Karen Crowell, MLIS, AHIP

Health Sciences Library, University of North Carolina at Chapel Hill

EVIDENCE-BASED ANSWER

If statins (HMG-CoA reductase inhibitors) cause myopathy, the risk is very low (strength of recommendation [SOR]: **A**). There is no direct evidence to answer this question. A pooled analysis of randomized controlled trials found similar myopathy rates in patients taking statins and placebo. However, a large cohort study revealed a very small but statistically significant increased risk of myopathy in patients taking statins (number needed to harm=10,000/year).

Case reports suggest a myopathy risk for all statins, including fatal rhabdomyolysis. Risk of myopathy may increase with higher statin doses, certain comorbid states (eg, hypothyroidism, renal insufficiency [especially with diabetes], recent trauma, perioperative periods, advanced age, small body frame) and concurrent medications, including fibrates, cyclosporine, azole antifungals, and macrolide antibiotics (SOR: **B**). No studies have directly compared myopathy rates among statins, and there is no good evidence to suggest any differences. No controlled study has directly examined statin rechallenge in patients with previous myopathy; however, case reports and expert opinion support this practice (SOR: **B**).

EVIDENCE SUMMARY

There is little evidence that statins cause myopathy. Synthesis is difficult because definitions of myopathy types differ among investigators. Proposed clinical syndrome definitions are myalgia (muscle weakness or ache with normal creatine kinase), myositis (symptoms with increased creatine kinase), and rhabdomyolysis (symptoms, markedly elevated creatine kinase, and renal insufficiency) as subsets of the more general term myopathy.[1] The **Table** summarizes myopathy data from 30 statin trials analyzed in a recent systematic review, showing similar myopathy rates in statin and placebo patients.[2] There may be a lower myopathy rate in these trials than in routine clinical practice because of stricter exclusion criteria and more intense monitoring.

A large well-done British epidemiologic cohort study (n=96,193) found an increased rate of myopathy (broadly defined, not requiring creatine kinase elevation) among patients taking statins, with an absolute rate difference of 1 per 10,000 person-years.[3] A small study of 21 patients on statins with muscle symptoms but normal

creatine kinases described 4 patients who were able to distinguish statins from placebo, with objective reversible weakness and abnormal muscle biopsies.[4] Postmarket voluntary clinician reports point to statin myopathy in this and other countries;[5-7] these include 3339 rhabdomyolysis FDA reports (1990 to March 2002).[2]

Though some assert differential myopathy rates among statins based on cell research, case reports, or differences in metabolic clearance, no studies directly compare clinical myopathy rates among statins. There is no good evidence of a differential myopathy risk among statins currently available in the US.[1-2] Cerivastatin, however, was withdrawn from the US market because of a fatal rhabdomyolysis rate 16 to 80 times higher than other statins based on FDA reports using a denominator of prescription volume (3.16 fatal cases/million prescriptions vs 0.15 for the statin class as a whole).[6]

It is unknown whether previous myopathy, however defined, increases the risk of future myopathy with statin rechallenge. A tabular analysis of 74 published case reports of statin-associated rhabdomyolysis from a MEDLINE search covering 1985 to 2000 reported that in most cases the statin was safely restarted after stopping presumed interactive drugs (exact numbers not reported).[8] In the AFCAPS/TexCAPS trial, 20 of 21 statin patients (out of a study population of 3304) who had elevated creatine kinase (>10 times the upper limits of normal) recovered with continued lovastatin treatment, while the other patient resumed treatment after a brief interruption without further elevations.[9] The EXCEL trial (n=8245) of various lovastatin dosages included routine creatine kinase tests every 6 weeks for 48 weeks. Five lovastatin patients had muscle symptoms with creatine kinases >10 times the upper limits of normal, and in the 2 who continued treatment, symptoms and creatine kinase became normal.[10] Of note, creatine kinase elevation of any kind at least once during 48 weeks occurred in 28.9% of placebo patients, arguing against routine creatine kinase screening in statin patients.

Case studies suggest an increased myopathy risk when statins are given with various medications, including fibrates, cyclosporine, azole antifungals, warfarin, nefazodone, and macrolide antibiotics.[4,6,8] Pravastatin and fluvastatin, which are not metabolized by the P450 CYP3A4 pathway, may be safer to use because of fewer drug interactions.[2,8] Likewise, certain comorbid states such as hypothyroidism, renal insufficiency (especially in patients with diabetes), recent trauma, and perioperative periods, as well as advanced age, small body frame, and multiple medications may increase statin myopathy risk.[1,2,7,8]

Pooled myopathy data from 30 randomized controlled statin trials

	Trials	Total patients	Statin patients	Placebo patients
Myalgia	5	33,929	0.3–32.9%	0–33.3%
Creatine kinase elevation	9	33,921	0–0.64%	0–0.58%
Myositis*	18	58,237	0.17%	0.15%

Rhabdomyolysis	20	70,126	0.020%	0.014%
*Creatine kinase >10 times upper limit of normal				
Adapted and calculated from Thompson PD, et al. *JAMA* 2003; 289:1681–1690.[2]				

RECOMMENDATIONS FROM OTHERS

A 2002 Clinical Advisory, jointly issued by the American College of Cardiology, the American Heart Association, and the National Heart, Lung and Blood Institute, asserted that statins carry a small but definite myopathy risk.[1] It recommended against routine creatine kinase tests, reserving them for patients who develop muscle symptoms. It also recommended stopping statins when muscle symptoms with creatine kinase elevations >10 times the upper limits of normal occur, with consideration of restarting statins later at a lower dose if symptoms and elevated creatine kinase resolve. Careful monitoring of patients at higher risk of statin myopathy is also recommended.

CLINICAL COMMENTARY

Benefits of statins outweigh the risks

Joseph Saseen, PharmD, BCPS

University of Colorado Health Sciences Center, Denver

Contrary to popular belief, statin-associated myopathy is a rare adverse event. Drug-drug interactions and comorbid diseases (especially chronic kidney disease) increase myopathy risk. Given the overwhelming evidence demonstrating reduced morbidity and mortality with statins, benefits outweigh risks in patients with elevated low-density lipoprotein cholesterol. Data supporting myopathy management strategies are limited, but support stopping statin therapy in patients with myopathy (muscle aches/pain with elevated creatine kinase), and restarting, possibly with a different statin, after symptoms resolve. Myopathy should not be confused with myalgia (muscle aches/pain with normal creatine kinase). Myalgia requires interrupting treatment only for patients with persistent muscle aches/pain while on statin therapy.

REFERENCES

1. Pasternak RC, Smith SC Jr, Biarey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567–572.
2. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681–1690.
3. Gaist D, Rodriquez LA, Huerta C, Hallas J, Sindrup SH. Lipid-lowering drugs and

risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;12:565–569.

4. Phillips PS, Haas RH, Bannykh S , et al. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 2002;137:581–585.
5. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288–295.
6. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002;346:539–540.
7. Ucar M, Mjorndal T, Dahlqvist R. HMG-CoA reductase inhibitors and myotoxicity. *Drug Saf* 2000;6:441–447.
8. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001;35:1096–1107.
9. Downs JR, Clearfield M, Tyroler HA , et al. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): Additional perspectives on tolerability of long-term treatment with lovastatin. *Am J Cardiol* 2001;87:1074–1079.
10. Bradford RH, Shear CL, Chremos AN , et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholes-terolemia. *Arch Intern Med* 1991;151:43–49.