

# What laboratory monitoring is appropriate to detect adverse drug reactions in patients on cholesterol-lowering agents?

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## ■ EVIDENCE-BASED ANSWER

Recommendations for measuring serum aminotransferase levels before initiating pharmacologic treatment for hypercholesterolemia, after 12 weeks of therapy, and periodically afterward are based on expert opinion. It is not recommended that serum creatine kinase (CK) levels be monitored for elevation indicative of myopathy during cholesterol-lowering therapy. (Grade of recommendation: D, based on expert opinion without explicit critical appraisal)

## ■ EVIDENCE SUMMARY

The current expert recommendations are apparently based on the 0.5% to 3% occurrence of a persistent elevation in aminotransferases (greater than 3 times the upper limit of normal occurring on 2 or more occasions) noted in clinical studies of statins. The incidence of this asymptomatic abnormality increases in a dose-dependent fashion and usually occurs within the first 3 months of therapy. A decreased dose or discontinuation of statin therapy typically results in normalization of aminotransferase values. Yet at least 2 placebo-controlled randomized trials demonstrated no significant difference in the incidence of persistently elevated aminotransferases between statin and placebo treatment.<sup>1,2</sup> Since there has been no study of the natural history and prognosis of persistently elevated aminotransferase values secondary to statin therapy, it is impossible to accurately estimate the need or value of screening for this complication. Gemfibrozil only rarely causes persistently elevated aminotransferase levels.

Myopathy, defined as generalized myalgia with a serum creatine kinase (CK) level greater than 10 times the upper limit of normal is rare (<0.1%), but less so when the statins are used concomitantly with medications such as gemfibrozil, nicotinic acid, antifungal azoles, macrolide antibiotics, and cyclosporine. The myalgia and CK elevation typically resolves after prompt discontinuation from treatment; several fatal cases of rhabdomyolysis, however, have been reported. Remaining alert for the symptoms of myopathy appears to be the best approach to minimize morbidity. The routine determination of serum CK during either statin or gemfibrozil monotherapy is not recommended.

## ■ RECOMMENDATIONS FROM OTHERS

For each of the currently approved statins, the US Food and Drug Administration approved labeling information generally includes liver function testing before, and at 12 weeks following, the initiation of therapy, and at any elevation of dose and periodically thereafter. Periodic liver function monitoring is also recommended for treatment with the fibric acid derivative gemfibrozil.

The Washington Manual of Medical Therapeutics<sup>3</sup> recommends liver function testing every 6 weeks for the first 3 months, then every 6 months afterward. The National Cholesterol Education Program guidelines do not address the appropriateness or frequency of liver function testing.<sup>4</sup>

#### **CLINICAL COMMENTARY**

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I have never had to stop using a statin because of elevated liver function test results. I do check a baseline level of serum alanine aminotransferase (ALT) and then repeat an ALT test when I get my lipid panel a month after initiation of therapy. After that, it is every 6 months with the lipid panel, or sooner with dosage adjustment. I reassure my patients that the problem with "muscle breakdown" is extremely rare, and I tell them to call me with any concerns regarding diffuse muscle pain. As millions of additional patients are put on these medications and experience grows, the recommendations for monitoring may change (remember monitoring captopril with complete blood cell counts?)

#### **R E F E R E N C E S**

1. Downs JR, Clearfield M, Weis S, et al. JAMA 1998;279:1615–22.
2. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–89.
3. Shubhada NA, Flood K, Paranjothi S, eds. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2001.
4. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.