Screening for Statin-Related Toxicity

The Yield of Transaminase and Creatine Kinase Measurements in a Primary Care Setting

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Background: Recommendations for monitoring levels of transaminases (alanine aminotransferase and aspartate aminotransferase) and of creatine kinase (CK) in patients taking 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) vary and are not based on data from clinical practice. We performed a study to determine the yield of routine screening of aminotransferase and CK levels among patients taking statins.

Methods: We performed a retrospective review of a primary care practice’s computerized medical record. A computerized search identified all patients with a statin on their medication list and gave their alanine aminotransferase, aspartate aminotransferase, and CK values for 1998. We reviewed the records of all patients for whom these values were significantly or moderately abnormal to determine the values’ relationship to statin therapy and outcomes.

Results: During the year of the study, 1014 (85%) of the 1194 patients who had a statin on their medication list had at least 1 monitoring test performed. Of these 1014 patients, 10 (1.0%) had a significant elevation and 5 (0.5%) a moderate elevation of transaminase levels, but none of these abnormalities appeared to be related to statin use. Moreover, 6 (0.9%) patients had at least 1 significantly abnormal CK value but it did not appear to be attributable to a statin; and of the 14 (2.1%) patients who had a moderate CK elevation, it was potentially due to a statin in only 2. There were no documented adverse sequelae associated with these abnormal results.

Conclusions: In this study of statin use in a primary care practice, routine monitoring revealed no cases of significantly or moderately abnormal transaminase values attributable to statins. No significantly abnormal and only 2 moderately abnormal CK values were potentially attributable to statin use. This study questions the usefulness of routine measurement of transaminase and CK levels in all patients taking statins.

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The use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, has been shown to reduce major cardiovascular events in both primary and secondary prevention.1-3 Statins have become one of the most widely prescribed classes of medications, with over 76 million prescriptions filled in the United States in 2000. Although HMG-CoA reductase inhibitors generally have a favorable safety profile, controlled trials show increases in serum transaminase values to more than 3 times the upper limit of normal in approximately 1% of patients taking them. The incidence of this abnormality is dose related and, at low doses, is similar to that reached with placebo.3-8 Because of concerns regarding this risk of hepatitis, drug manufacturers have recommended routine screening of serum transaminase values and most physicians follow these recommendations.9,14

In addition to hepatotoxicity, myalgia, myositis, and asymptomatic elevations of serum creatine kinase (CK) have been reported with HMG-CoA reductase inhibitor use. However, clinically significant myopathy—defined in most trials as the association of an elevation of CK levels to more than 10 times the upper limit of the normal range with myalgia or weakness—is infrequent, occurring at a rate equal to that obtained with placebo in most trials.3,8,13 Despite these data, many physicians routinely screen patients for elevations of CK levels. The risk of myopathy increases in a dose-related fashion and is

For editorial comment see page 657
often attributed to concomitant use of other medications.16,17 The risk of myopathy also increases with liver or renal dysfunction, age, and serious infections.18,19 New questions regarding the safety of statins were raised after an increased rate of rhabdomyolysis associated with the use of cerivastatin led to the drug’s withdrawal from the market. While all statins have been associated with rare reports of rhabdomyolysis, these reports were apparently more frequent with cerivastatin. It remains unclear if routine screening would have prevented rhabdomyolysis in these patients.

Data regarding adverse events and recommendations concerning routine monitoring of CK and transaminase values come largely from controlled trials. These trials excluded individuals at increased risk for developing myopathy or hepatitis because of other medications or underlying medical conditions.1,3,6,20-22 In contrast, the controlled trials on statins may have used higher doses of statin medications than the typical starting doses in a primary care practice. Therefore, these trials may have overestimated the rate of complications.3-5,8,23 In addition, many clinicians discontinue statins well before their patients reach the elevations in transaminase or CK values that were considered clinically significant in these trials. Therefore, these studies may not reflect the rate of adverse effects likely to be found with routine use of these medications in a primary care setting. Furthermore, the yield of screening for abnormalities in transaminase or CK levels among patients taking statins in a primary care setting remains uncertain. If the actual risk of the statin medications is sufficiently low, the cost of screening, the evaluation of minor test result abnormalities, and drug discontinuation could all be avoided. Alternatively, if risks are higher than suggested by prior studies, more frequent and rigorous monitoring may be appropriate.

In this study, we analyzed the laboratory results of patients taking statin medications in an academic primary care practice. We determined the frequency of abnormal results (including both significant and moderate serum transaminase and CK elevations), the response of clinicians to these abnormalities, and patient outcomes.

METHODS

After obtaining approval from the Committee on Clinical Investigations, New Procedures and New Forms of Therapy at Beth Israel Deaconess Medical Center, we performed a retrospective review of the computerized medical records of patients who received their primary care at this center during 1998. Patients who had an HMG-CoA reductase inhibitor (by brand name or generic name) on their medication list were identified through a computerized search. This hospital-based practice cares for approximately 30,000 patients in an urban academic setting.

All patients who were taking statins and for whom test results showed significantly or moderately elevated serum levels of transaminase or CK were identified. Significant elevations were defined as more than 3 times the upper limit of the normal range (110-120 U/L) for transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) and more than 5 times the upper limit of the normal range (501-1000 U/L) for CK. This is consistent with (or more cautious than) prior studies of statin safety.8,9 We defined moderately abnormal transaminase values as 2 to 3 times the upper limit of the normal range (81-120 U/L) and moderately abnormal CK values as 2.5 to 5 times that limit (301-1000 U/L).

A detailed review of the record of every patient with significant or moderate elevations of serum transaminase or CK values was performed to identify whether the abnormalities appeared to be directly attributable to statin use. An abnormal test result was considered attributable to statin use if it could be reasonably explained by no other medical condition or medication use, or if it resolved when the medication was discontinued. For example, if a patient had both an elevated CK serum level and a myocardial infarction, or both an elevated transaminase serum level and symptomatic cholecystitis, and if the abnormalities resolved over time despite continuation of the statin medication, the medication was not considered the cause of abnormal blood test results. In cases when the statin was discontinued because of abnormal laboratory findings, follow-up laboratory results and medical records were reviewed to determine the outcome.

Detailed information was obtained for every patient with significantly or moderately abnormal test results, including dose and type of statin; medical conditions such as liver disease, kidney disease, or the presence of human immunodeficiency virus; alcohol consumption; concurrent medications such as antiretroviral agents, azole antifungals, cyclosporine, fibrates, macrolide antibiotics, and niacin; symptoms experienced with abnormal laboratory findings; and adverse outcomes.16,17 The computerized medical record used for all patients at this practice includes office notes, discharge summaries, current and past medications, medical problem lists, and laboratory data.

A random sample of the patients taking statins was used to provide demographic data and an estimate of the rate of transaminase and CK monitoring (for patients taking statins for 6 months or longer). We calculated 1-sided confidence intervals based on the exact binomial distribution to provide an upper confidence bound on the probability of statin-related abnormalities.

RESULTS

Of the 1194 patients identified in our primary care practice with a statin on their medication list in 1998, 53% were female (with a mean age of 61 years). Thirty-seven percent of the patients were taking atorvastatin, 23% lovastatin, 20% pravastatin, and 20% simvastatin. No patients were taking cerivastatin or fluvastatin at the time of this study.

The number and proportion of patients taking statins who had both transaminase and CK values measured during 1998, though not necessarily because of their statin use; who had a transaminase measurement without CK testing; and who had no testing performed are shown in the tabulation.

<table>
<thead>
<tr>
<th>Laboratory Monitoring</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine kinase and transaminase</td>
<td>632 (53)</td>
</tr>
<tr>
<td>Transaminase only</td>
<td>371 (31)</td>
</tr>
<tr>
<td>Creatine kinase only</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Neither creatine kinase nor transaminase</td>
<td>180 (15)</td>
</tr>
<tr>
<td>Total</td>
<td>1194</td>
</tr>
</tbody>
</table>

At the time of this study, 29% of the patients in the study population were prescribed a statin dosage higher than the recommended starting dosage; moreover, 16% of them had medical conditions or were taking medications associated with an increased risk of myositis or hepatitis in individuals taking statins.
TRANSAMINASE ABNORMALITIES

Of the 1002 patients for whom serum transaminase level was tested, 10 (1.0%) were identified as having a significantly abnormal value; however, these values did not appear to be directly attributable to the statin medication (Table 1).

Five additional individuals (0.5%) were identified as having a moderate elevation of serum transaminase. As outlined in Table 2, none of these elevations appeared to be directly related to statin use, and there were no adverse patient outcomes related to these abnormal laboratory findings. The upper bound of the 95% confidence interval for moderately or severely abnormal, statin-related, transaminase serum levels was less than 0.3%.

Table 1. Causes of Significant Serum Transaminase Elevation in Patients Taking Statin Medications

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Medications Contributing to Abnormality</th>
<th>Diseases Contributing to Abnormality</th>
<th>Comments</th>
<th>Test Result Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Azithromycin, protease inhibitors, antiretrovirals</td>
<td>HIV, fatty liver</td>
<td>Transaminase elevation predated statin use, statin treatment continued</td>
<td>Unchanged</td>
</tr>
<tr>
<td>2</td>
<td>Protease inhibitors, antiretrovirals</td>
<td>HIV</td>
<td>Transaminase elevation predated statin use, statin treatment discontinued</td>
<td>Normalized</td>
</tr>
<tr>
<td>3</td>
<td>Acute cholecystitis</td>
<td>Gallstone pancreatitis</td>
<td>Statin treatment continued</td>
<td>Normalized</td>
</tr>
<tr>
<td>4</td>
<td>Troglitazone</td>
<td></td>
<td>Troglitazone treatment discontinued; statin treatment continued</td>
<td>Normalized</td>
</tr>
<tr>
<td>5</td>
<td>Fatty liver</td>
<td></td>
<td></td>
<td>Unchanged</td>
</tr>
<tr>
<td>6-9</td>
<td>Alcohol abuse</td>
<td>Transaminase elevation predated statin use; statin treatment continued</td>
<td>Normalized</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Myocardial infarction</td>
<td>Transaminase elevation predated statin use; statin treatment continued</td>
<td>Normalized</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AST, aspartate aminotransferase; HIV, human immunodeficiency virus.

Table 2. Causes of Moderate Elevation of AST or ALT in Patients Taking Statin Medications

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diseases Contributing to Abnormality</th>
<th>Comments</th>
<th>Test Result Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alcohol abuse</td>
<td>Transaminase elevation predated statin use; statin treatment continued</td>
<td>Unchanged</td>
</tr>
<tr>
<td>2</td>
<td>Alcohol abuse</td>
<td>Abnormalities in test results predate statin use; statin treatment continued</td>
<td>Normalized after abstinence from alcohol</td>
</tr>
<tr>
<td>3</td>
<td>Acute cholecystitis</td>
<td>Statin treatment continued</td>
<td>Normalized</td>
</tr>
<tr>
<td>4</td>
<td>Hepatitis C, possible autoimmune hepatitis</td>
<td>Transaminase elevation predated statin use; statin treatment continued</td>
<td>Unchanged</td>
</tr>
<tr>
<td>5</td>
<td>Statin treatment continued</td>
<td></td>
<td>Normalized</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

The upper bound of the 95% confidence interval for moderate statin-related CK abnormalities was less than 1.0%.

CK ABNORMALITIES

The CK serum concentration of 6 (0.9%) of the 645 patients for whom it was measured (54% of those taking a statin) was identified as severely abnormal (>1000 U/L), but for none of them did it appear to be attributable to statin medication. It was due to a myocardial infarction in 5 patients and related to surgery in the sixth. All values returned to normal at subsequent measurements despite continued statin therapy. The upper bound of the probability for severe statin-related abnormalities in CK serum levels was less than 0.5%, with 95% confidence. Fourteen (2.1%) of the patients monitored had a moderate elevation of serum CK (501-1000 U/L), and it was considered to be potentially due to statin medication in only 2 (0.3%) of them, although neither had new myalgia or weakness. In one of them, testing was prompted by long-standing musculoskeletal complaints that predated statin use and persisted after discontinuation; the patient was noted to have mild and persistent serum elevations of CK (250-500 U/L) even after the statin was discontinued. The second patient’s CK elevation was noted in testing performed during an office visit following a traumatic injury requiring sutures, and the CK level quickly returned to normal. In both instances statin therapy was later resumed and CK levels remained normal.

The upper bound of the 95% confidence interval for moderate statin-related CK abnormalities was less than 1.0%.

COMMENT

This study suggests that among patients receiving statin medications in a primary care practice, the risk of severe transaminase or CK abnormalities attributable to statins is low. These results question the necessity of routine laboratory measurements of transaminase and CK values in all patients taking these medications. While the overall incidence of significant transaminase abnormalities is similar in this study (1%) to what has been described in prior randomized controlled trials, the detailed chart review of cases included in this study...
determined that these abnormalities appeared unrelated to the statin medication.

Prior controlled trials of statin therapy defined clinically significant abnormal laboratory findings as greater than 3 times the upper limit of the normal range for transaminase values and greater than 10 times the upper limit of normal range for CK values with concurrent muscle pain, tenderness, or weakness.\(^{24}\) However, many physicians may actually discontinue statin therapy well before values reach these levels of abnormality. We addressed this possibility by reviewing all moderately abnormal transaminase or CK values for patients taking statins. In this population, not even cases of moderately abnormal transaminase values could be attributed to statin medication. We identified 2 patients (representing 0.3% of the monitored patients) with moderately abnormal CK values that might have been attributable to statin use; however, these abnormalities were not associated with symptoms or adverse outcomes. It is unclear even in these cases whether detection of the moderate elevations in CK serum concentrations and discontinuation of statin therapy were beneficial to these patients (by preventing myopathy) or harmful (by discontinuing a beneficial medication).

Already one of the most commonly prescribed classes of medications, statins are likely to be increasingly used given the National Cholesterol Education Program’s recent recommendations for an even more aggressive cholesterol management.\(^{24}\) The use of these medications will probably increase even more dramatically if the proposals by pharmaceutical companies to make low-dose statins available without a prescription are accepted by the Food and Drug Administration. Given the prevalence of statin use in a wide range of patients, it is important to identify their actual risk in clinical practice and to establish appropriate monitoring guidelines.

The recent withdrawal of cerivastatin from the market due to reports of an increased rate of rhabdomyolysis raises concerns regarding the safety of this class of medication. While rare cases of rhabdomyolysis have been reported with all statins, the number of events associated with cerivastatin use was significantly higher than for other approved statins. This study further supports the safety of the other drugs in this class, as there were no significant abnormalities in CK serum concentrations attributable to statins. No patients in this study were taking cerivastatin.

Unlike prior randomized controlled trials that evaluated statins for safety and efficacy, our study included individuals at an increased risk for complications due to preexisting medical conditions or concomitant medication use. Despite the broader population evaluated in this study, our data indicate that the incidence of statin-related serum transaminase or CK serum concentration elevations is quite low, even when a more rigorous definition of abnormal laboratory findings is applied.

While careful laboratory monitoring will certainly be needed in individuals at increased risk for hepatitis or myopathy, the data provided by this study question the utility of routine screening in all patients. A reduced need for routine screening would provide a substantial reduction in the overall cost associated with statin use and would prevent the unnecessary evaluation of slightly abnormal laboratory findings as well as the unnecessary discontinuation of a highly effective medication. Statin underutilization is reportedly common\(^{25-29}\) and perhaps even more prevalent in light of the new National Cholesterol Education Program’s recommendations. The costs associated with an increase in appropriate administration of these drugs could be offset, at least in part, by a reduction in monitoring costs and follow-up of abnormalities.

In our practice, approximately 4.1% of 29000 patients are taking statin medications. Assuming an average cost of $32 and $23 for measurement of ALT and CK, respectively, the semiannual screening of all patients in our practice who take statin medications would cost in excess of $130000 a year. This cost does not include the additional expense expected from further laboratory testing associated with minor abnormalities discovered during screening; more frequent monitoring, as practiced by many clinicians, would also increase the cost. If, however, only high-risk and symptomatic patients were evaluated, a significant reduction in overall cost and inappropriate drug discontinuation would likely follow, without compromising quality of care.

One of our study’s limitations is that 84% of the patients had transaminase values measured, that 54% had CK values measured, and that abnormalities could have occurred in those who did not have routine screening during the year. However, given the awareness of clinicians regarding the reported risks of hepatitis and myopathy among patients taking statins, it is likely that patients with any significant adverse events or outcomes would have been tested and identified. Furthermore, because only 29% of our patients were prescribed a dosage higher than the usual starting dose, a larger sample of patients may be needed to establish more clearly how often important toxic effects related to statin use or dosage occur, and whether any specific monitoring practice could identify and prevent them. Our inclusion of moderately abnormal laboratory findings helps minimize this potential effect of sample size. However, a larger sample size would also help determine if one particular statin has a higher incidence of toxic effects, as has been suggested by recent reports linking cerivastatin with rhabdomyolysis. While prior studies have viewed transaminase values less than 3 times and CK values less than 10 times the upper limit of normal as not clinically relevant, a much longer follow-up would be needed to determine the long-term effect of these abnormalities. Finally, statins could be contributing to these abnormalities in patients with abnormal laboratory findings that persist and are attributed to other causes (such as hepatitis C or alcohol use). The safety of treating such patients with statin medications deserves further investigation.

This study further supports the safety of statin use in a primary care setting and provides evidence that the yield of routine monitoring of serum concentrations of transaminases and CK in all treated patients is quite low. If these results are confirmed by other large series, it is possible that transaminase and CK monitoring could be eliminated altogether in asymptomatic patients without significant risk factors for hepatitis or myopathy.

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REFERENCES