Severe Statin-Induced Problems Rare in Diabetes

Statin users had higher myopathy and myalgia rates, but not higher myositis and rhabdomyolysis rates.

BY MIRIAM E. TUCKER
Senior Writer

WASHINGTON — Statin-induced myopathy and myalgia may be higher than reported previously in patients with diabetes, but myositis and rhabdomyolysis are rare, Gregory A. Nichols, Ph.D., and Carol E. Koro, Ph.D., reported in a poster at the annual scientific sessions of the American Diabetes Association.

Clinical trial results suggest that statin-induced myopathy occurs in less than 1% of patients, but no previously published reports of muscle syndromes following statin initiation have come from real-world settings, said Dr. Nichols and Dr. Koro, both of Kaiser Permanente Northwest, Portland, Ore.

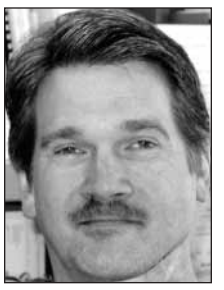
They compared electronic pharmacy records for 10,247 Kaiser enrollees who have type 2 diabetes and initiated statins between 1997 and 2004. Their results were compared with those of the same number of diabetic patients who did not take statins during that time period. Study subjects were followed until they experienced a myopathic event or until the end of 2005.

Kaiser Permanente recommends that any patient who presents with muscle complaints while taking statins undergo a creatine kinase (CK) test and suspend statin use pending the results.

Therefore, myopathy was defined as the presence of any creatine kinase test during a break in statin dispense records, any CK test greater than three times the upper limit of normal (ULN), or any diagnosis of myopathy. Myalgia was defined as the presence of a normal CK test during a break in the statin dispense records or a diagnosis of myalgia.

During the study period, myopathy developed in 7.1% of the statin initiators and 5.5% of the controls, a statistically significant difference. The unadjusted incidence of myopathy/1,000 person-years was also significantly greater for the statin users, 21.9, than for the nonusers, 18.1. In addition, the rates of CK levels between 1 and 3 times the ULN were significantly different, seen in 1.7% of the statin users and 0.6% of the controls, translating to unadjusted incidence rates of 5.5/1,000 vs. 2.0/1,000 person-years.

Similarly, the proportion developing myalgia was also significantly greater with statins (5.8%), compared with controls (4.7%), as was the incidence rate of myalgia (18.3/1,000 vs. 15.4/1,000), Dr. Nichols and Dr. Koro reported.



Rates of CK levels 1-3 times the upper limit of normal were significantly higher for statin users than nonusers.

DR. NICHOLS

On the other hand, myositis—defined as a CK test with a result 3-10 times the ULN or a diagnosis—was not significantly more common among statin users, occurring in 0.21% of statin users and 0.14% of controls, with rates of 0.70/1,000 vs. 0.46/1,000. Similarly, comparable rates of rhabdomyolysis, defined as a CK test result more than 10 times above the ULN (0.13% vs. 0.12%) or a diagnosis (0.41/1,000 vs. 0.17/1,000), were seen.

Concurrent use of fibrates and corticosteroids were the strongest predictors of myopathy (hazard ratios 2.11 and 1.80, respectively). Older age, presence of cardiovascular disease, and higher body-mass index also contributed to the myopathy risk. After adjustment for those factors, the incidence rates were not significantly different between statin users and controls (21.1/1,000 vs. 19.4/1,000).

Older age, higher BMI, concurrent fibrate use, concurrent corticosteroid use, and the presence of cardiovascular disease also increased the risk for myalgia; male sex and metformin use appeared to be protective. As with myopathy, adjusting for those factors eliminated the difference between statin users and nonusers (17.3/1,000 vs. 16.4/1,000).

But the rates of elevated CK test results of 1-3 times the ULN remained significantly higher for statin users even after adjusting for predictors such as younger age, longer duration of diabetes, male sex, concurrent fibrate use, higher BMI, and poor kidney function (4.1/1,000 vs. 1.3/1,000). Differences between statin users and controls in rates of myositis and rhabdomyolysis remained insignificant after adjusting for male sex (a predictor of both) and for concurrent use of diuretics (a predictor of rhabdomyolysis). ■

Maintain Good Vigilance for Statin Side Effects, Interactions

BY MIRIAM E. TUCKER
Senior Writer

PHILADELPHIA — Be alert for potential interactions and side effects when prescribing statins, Dr. Douglas S. Paauw advised at the annual meeting of the American College of Physicians.

Hepatotoxicity and rhabdomyolysis are relatively rare, but myalgias are quite common and often prompt patients to discontinue the drugs, said Dr. Paauw, professor of medicine at the University of Washington, Seattle.

And, although the overall risk of rhabdomyolysis is low, the chance is greater with the addition of other drugs.

In one frequently cited study, rates of toxicity were very low (2% myalgias, 0.4% myositis, and 0.4% hepatotoxicity) among 252 atherosclerotic patients receiving a statin plus gemfibrozil, leading the authors to conclude that the combination could be used safely in high-risk patients (Am. Heart J. 1999;138:151-5).

But those results may not reflect current clinical experience. Pravastatin, which is used less often today, was the statin most commonly used in the study. Simvastatin and lovastatin, both used more often today, are metabolized by a subunit of the cytochrome P450 system that is affected to a greater degree by gemfibrozil than are pravastatin or fluvastatin. Thus, the investigators were using "safer statins" in terms of drug interactions, Dr. Paauw noted.

If it is necessary to use both gemfibrozil and a statin—a common scenario—it's important to document the reason. Also, educate the patient about myalgias and rhabdomyolysis, including the importance of stopping the drug right away when muscle pain starts and then calling the physician afterward—especially if the symptoms occur during weekends or holidays. "I tell patients to stop the drug if there's any question. It's not going to be a problem if they're off the statin for 24 hours."

Always ask patients about muscle pain, and monitor signs and symptoms at every office visit. There is no set policy about blood monitoring, but it's a good idea to measure creatinine phosphokinase (CPK) levels periodically and any time that symptoms develop, he advised.

'Take very seriously any pain syndrome in a patient on statins. If you can't find an alternative diagnosis, consider a short drug holiday'; see what happens.

Fibrates top a long list of other drugs that can increase statin toxicity, including azole antifungals, niacin, erythromycin/clarithromycin, protease inhibitors, verapamil/diltiazem, and cyclosporine. About half of all severe cases of rhabdomyolysis occur when three or more of these agents are taken together, such as in a patient who is already taking a fibrate plus a statin who is then prescribed erythromycin for 2 weeks.

"It's that third drug that markedly increases the risk," Dr. Paauw said.

Less attention has been paid to simple muscle pain and weakness. Published data suggest that this side effect occurs in only 1%-5% of patients on statins. "I really believe that that number is higher. In my practice, it's probably 20% at least," he said.

Indeed, patients will often take themselves off the drug and report that the pain goes away. The problem appears to be both dose- and drug-related.

In one study, muscle cell abnormalities were found on biopsy in patients who had normal CPK levels but who complained of muscle pain (Ann. Intern. Med. 2002; 137:581-5). "If a CPK comes back normal, it doesn't tell us that the pain isn't from the statin. It simply tells us that the magnitude of the muscle problem doesn't put them at risk for rhabdomyolysis right now, but they could still be severely debilitated by the pain," Dr. Paauw said.

Further complicating the picture, statin-induced muscle pain isn't necessarily uniform throughout the body. For example, a patient may complain of severe pain only in the left thigh. Quite often, the pain goes away if you take the patient off the drug. "Take very seriously any pain syndrome in a patient on statins. If you can't find an alternative diagnosis, consider a short drug holiday and see what happens," he recommended.

Once the pain resolves—typically in 1-2 weeks—you can restart the same statin at a low dose, or try switching to a different one. If the patient still experiences muscle pain after trying two different statins, it may be necessary to consider a different category of lipid-lowering drug.

In contrast to muscle problems, hepatotoxicity appears to be less of an issue with statins than was originally thought. In a retrospective cohort study of 23,000 adult HMO patients who received statins over a 5-year period, just 0.3% had severe transaminitis, defined as an alanine aminotransferase (ALT) level 10 times greater than normal. Of those 62 patients, only 17 had ALT elevation due to the statin, and the problem resolved after stopping the statin in 16 of those 17. Most patients were symptomatic at the time of the elevation, which usually occurred within 4 weeks of starting or changing therapy (Am. J. Med. 2005;118:618-24).

Another study, which included 1,014 primary care patients taking statins who had at least one transaminase measurement, only 1% (10) had a significant elevation and another 5 had moderate elevations, but none of those cases appeared to be related to statin use (Arch. Intern. Med. 2003;163:688-92).

Based on the data, it's reasonable to monitor liver function within the first 12 weeks of therapy and perhaps annually thereafter for the first 3-4 years. After that, if the patient has been on a stable dose and has not had an ALT elevation, it's not necessary to keep going. "I don't continue to monitor for years and years," Dr. Paauw said.

And finally, there's the grapefruit juice problem. Grapefruit juice increases the bioavailability of drugs known to be metabolized by the CYP3A4 subunit of the P450 system, including simvastatin, lovastatin, and to a lesser degree, atorvastatin. Pravastatin, fluvastatin, and rosuvastatin do not rely on CYP3A4 and therefore do not interact with grapefruit juice.

Small amounts—a half of a grapefruit every 2 weeks, for example—are not likely to be clinically significant, but a daily glass of juice at breakfast may increase statin bioavailability. ■