Watch for Statin-Rx Interactions, Side Effects

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.

While hepatotoxicity and rhabdomyolysis are relatively rare, 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 (325.7 patient-years), followed by simvastatin (178.1), fluvastatin (54.0), lovastatin (20.3), and atorvastatin (15.5).

About half of all severe cases of rhabdomyolysis occur when three or more of these agents are taken together. 'It's that third drug that markedly increases the risk.'

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, in the study, 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 very common scenario—it's important to document the reason for using the combination. 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.

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.

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, with certain statins causing more problems than other drugs for some individuals.

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."

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. It may seem highly improbable that the statin is the problem, but 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," Dr. Paauw 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.

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.

Finally, 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.

While small amounts—a half of a grapefruit every 2 weeks, for example—are not likely to be clinically significant, a daily glass of juice at breakfast may cause a significant rise in statin bioavailability. Indeed, one study documented a 15-fold increase in mean peak serum lovastatin in 10 healthy volunteers who drank 200 mL of grapefruit juice, compared with subjects who drank water, three times a day for 3 days; subjects took one 80-mg dose of lovastatin on day 3 (Clin. Pharmacol. Ther. 1998;63:397-402). This highly significant effect may work to the advantage of some patients who have not achieved lipid control on statins, Dr. Paauw noted. ■