Severe Events Rare in Statin-Induced Myopathy

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.

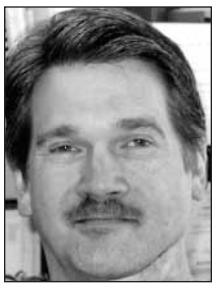
Study subjects were followed until they experienced a myopathic event or until the end of 2005.

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. Also, 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.

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.

DR. NICHOLS

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).

However, 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). ■

Statins Slash Mortality 77% in Nonischemic Cardiomyopathy

BY COLIN NELSON
Contributing Writer

BOSTON — Statin use was associated with startling reductions in mortality and sudden death among patients with nonischemic dilated cardiomyopathy, according to a new subanalysis from a multicenter trial of implantable cardiac defibrillators.

In addition to a 77% decrease in overall mortality (5/110 vs. 64/348), statin use was associated with an 84% reduction in sudden death (1 vs. 18). Statins were also associated with a 22% reduction in appropriate shocks in patients with implantable cardioverter defibrillators (ICDs).

Statins appear to have significant effects beyond lipid lowering. Among patients with coronary artery disease, the lipid-lowering drugs are associated with a reduction in arrhythmic events, appropriate ICD shocks, and mortality. Statins can also improve the clinical status of patients with nonischemic heart failure.

To determine whether statins may be protective against sudden death in patients with nonischemic heart failure, Dr. Jeffrey J. Goldberger of Northwestern University, Chicago, and colleagues compared mortality in the 110 patients who took statins in the multicenter DEFINITE trial with the 348 patients who did not. The patients in both groups were similar at baseline in most clinically important respects.

Dr. Alaa Shalaby of the Pittsburgh VA Healthcare System presented the findings during an oral presentation at the annual meeting of the Heart Rhythm Society.

The DEFINITE trial, published in 2004, randomized 458 patients with nonischemic dilated cardiomyopathy (DCM) and a left ventricular ejection fraction of less than 36% to receive standard medical therapy alone or medical therapy plus an ICD (N. Engl. J. Med. 2004;350:2151-8). The addition of an ICD provided no additional protection against death, the primary end point. But among patients who received ICDs there was a significant (80%) reduction in sudden deaths caused by arrhythmia, the secondary end point.

In the new subanalysis, the ability of ICDs to protect against sudden death remained significant after adjusting for statin use, Dr. Goldberger noted in an interview. Moreover, among patients with ICDs, the use of statin therapy conferred additional protection against sudden death. But Dr. Shalaby cautioned that it is important to put these findings into perspective. "We recognize that these are post hoc analyses."

At the time they released their 2004 findings, the DEFINITE investigators noted that the trial was not powered for subgroup analysis and that such analyses need to be undertaken with extreme care. Statin use was not a prespecified analysis. Of several prespecified subanalyses that they undertook in their 2004 article, none of the differences between subgroups were deemed significant.

The DEFINITE study was funded by a grant from St. Jude Medical. Several of the DEFINITE authors disclosed financial relationships with ICD makers. None of the authors of the current subanalysis disclosed financial relationships with makers of statins. ■

Statin Cut Vascular Events in Patients With Peripheral Arterial Disease

BY MITCHEL L. ZOLER
Philadelphia Bureau

PHILADELPHIA — Treatment with a statin cut the incidence of major vascular events in patients with peripheral arterial disease in a new subanalysis of results from the Heart Protection Study.

The results show that "all patients with peripheral arterial disease [PAD] should be on a statin regardless of their baseline lipid level," Dr. Richard Bulbulia said at the Vascular Annual Meeting.

"This is probably the first study to show the benefit of statin treatment in a predominantly PAD group. [These are] very important data," commented Dr. Thomas F. Lindsay, director of the vascular center at Toronto General Hospital.

The study used data collected in the Heart Protection Study, a British trial with more than 20,000 patients that compared treatment with 40 mg of simvastatin daily with placebo (Lancet, 2002; 360:7-22). The total group included patients with coronary disease, other occlusive arterial disease, or diabetes. In the overall study, treatment with the statin was linked to a relative cut in deaths of 13% and lowered major vascular events by 24% during 5 years of follow-up.

The new analysis focused on the 6,748 patients who entered the study with documented PAD. This subgroup included patients with coincident coronary disease, coincident cerebrovascular disease, coincident diabetes, and more than 1,400 patients who had PAD as their only preexisting disorder.

During 5 years of follow-up of the entire PAD subgroup, the rate of major vascular events (coronary death, nonfatal myocardial infarction, stroke, or revascularization) was 26% in the statin-treated group and 33% in the placebo group, a statistically significant difference, reported Dr. Bulbulia, a researcher with the clinical trial service unit of the University of Oxford (England). The degree of event reduction from statin therapy in this subgroup was very similar to what was seen in the entire study, and in the subset of patients who did not have PAD at entry.

Statin treatment led to a significant reduction in vascular events regardless of whether patients started with a serum level of low-density lipoprotein cholesterol that was above or below 116 mg/dL.

These results also probably underestimated the impact of simvastatin treatment because some patients in the statin group stopped taking their drugs, and some patients in the placebo group were eventually started on a statin, Dr. Bulbulia said.

Another analysis of the data, using the entire study group, looked at the ability of statin treatment to cut the incidence of major peripheral vascular events. These were defined as noncoronary revascularizations, aneurysm repair, major amputations, or deaths due to PAD.

These events occurred in 4.7% of the statin-treated patients and in 5.5% of those on placebo, a statistically significant difference. The impact of statin therapy on reducing peripheral vascular events has not been previously reported in any other statin-treatment study, Dr. Bulbulia said. This effect by simvastatin treatment was primarily driven by a cut in the rate of peripheral revascularization procedures. ■