Dose-related statin myopathy: Is it an issue?

ROBERT L. WORTMANN, MD
Professor and C.S. Lewis, Jr., MD, Chair of Medicine,
The University of Oklahoma College of Medicine, Tulsa

ARGUABLY one of the most important medical breakthroughs in the last 20 years has been the development of HMG-CoA reductase inhibitors, commonly termed statins. Used properly, these agents reduce atherosclerotic disease events and prolong lives. These positive effects are attributed to alterations in serum lipid profiles and to anti-inflammatory effects.[1,2]

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Although the actions of statins are complex and not completely understood, targets have been established for their use. The primary target is lowering the concentration of low-density lipoprotein cholesterol (LDL-C), and a secondary target is lowering non-high-density lipoprotein cholesterol (LDL-C plus very-low-density lipoprotein cholesterol) in people with elevated triglycerides.

Reaching and maintaining these target levels significantly improves the prognosis for people at risk of atherosclerotic events.[3–5] The prognosis is also better if high-density lipoprotein cholesterol (HDL-C) levels increase.

In this issue of the *Cleveland Clinic Journal of Medicine*, Dr. Peter Jones reports the benefits of starting statin therapy with doses stratified on the basis of the patient's global risk for coronary artery disease, baseline LDL-C level, and degree of LDL-C reduction required.[6] As Dr. Jones points out, the rationale for this approach comes from numerous studies showing prevalent "undertreatment" (ie, large percentages of patients not attaining recommended serum cholesterol targets) and trials in which a higher percentage of patients reached the desired cholesterol level when a targeted strategy was employed.

Clearly, the available data indicate that one should try to reduce LDL-C to lower and lower levels, that higher doses of statins are more effective, and that many people require those higher doses for optimal results.

Current guidelines recommend LDL-C levels of less than 100 mg/dL as the target for patients with stable coronary heart disease, and less than 70 mg/dL for those at very high risk.[4] Some experts now also advocate the target of 70 mg/dL for those with stable disease.

Lower LDL-C is good, but how fast do we need to get there?

This opinion is derived from the findings of epidemiologic studies and the recognized efficacy of high doses of statins in acute coronary syndromes.[7] Indeed, results from the recently published Treating New Targets (TNT) trial support the efficacy and safety of reaching levels of 70 mg/dL in patients with stable coronary heart disease, which are attained by using higher doses of statins, compared with reaching 100 mg/dL.[8]

TWO RISKS OF A TARGETED APPROACH

So what are the risks of using this targeted approach compared with starting with a low dose and titrating as needed to reach the desired LDL-C concentration?

First, some patients would be taking doses higher than necessary, because they could have reached the target value at a lower dose. Those people would be paying more for their

The author has indicated that he serves as a consultant to Merck and Company.

medication than necessary and would have a lower benefit-to-risk ratio.

Second and more important, the higher the dose of statin, the greater the risk of statin-related myopathy, which can cause a variety of symptoms, including myalgia, cramps, muscle weakness, and fatigue.

MYOPATHY CAN BE SERIOUS, BUT IS UNCOMMON

Statin myopathies are perplexing. They can occur with normal or with elevated serum creatine kinase (CK) levels. Whereas most statin myopathies resolve after the offending agent is stopped, some do not, and statin myopathy can result in renal failure and death.

In placebo-controlled trials, approximately 5% of patients who take statins report myopathic symptoms, but a similar percentage of patients who take placebo also report those symptoms.[8–13] The percentage of patients with elevated CK levels is also similar for those taking a statin vs a placebo.[8,9,12] Although these data suggest that the myopathic symptoms are not related to statin use, the temporal relationship between statin use and the onset of symptoms is strong enough to implicate the drug as the cause of the complaints in many cases.

If more patients take higher doses, more myopathy will occur

Fortunately, rhabdomyolysis with renal failure, the most severe form of statin myopathy, is rare with the statins available today. The rate of hospitalization for rhabdomyolysis from the use of statin monotherapy is low, 0.44 cases per 10,000 person-years.[14] The risk is higher if statins are used in combination with a fibrate or niacin.

Nevertheless, even though the risk for the individual patient is low, many cases will occur because of the large number of patients who take these agents. Think of the number we would see if we were to treat all 105 million people the American Heart Association[15] says have LDL-C concentrations greater than 200 mg/dL!

HOW DO STATINS CAUSE MYOPATHY?

A variety of mechanisms have been proposed to explain statin myotoxicity.[16]

Blocking mevalonic acid production

Statins lower cholesterol levels by inhibiting HMG-CoA reductase, which catalyzes the conversion of 3-hydroxyl-1-3-methylglutaryl-coenzyme A to mevalonic acid, a rate-limiting step in cholesterol biosynthesis.

Mevalonic acid is a precursor for isoprenoids, which are necessary for prenylation reactions in post-transcriptional lipid modification of proteins and other compounds. Important isoprenoids include dichols, which are required for glycoprotein synthesis; isopentyl adenosine, which is required for transfer-RNA synthesis; and heme and ubiquinone (coenzyme Q10), which are components of the respiratory chain.

Thus, blocking mevalonic acid synthesis could have a variety of consequences.

Depleting coenzyme Q10

Of these consequences, the potential effect on coenzyme Q10 is of major interest because of its role in energy metabolism.

Coenzyme Q10 is a component of complexes I and II of the electron transport chain and is an important antioxidant in mitochondrial and other lipid membranes. Perhaps statins cause myopathy by depleting coenzyme Q10, resulting in decreased production of adenosine triphosphate or enhanced membrane damage from free radicals.[17] Decreased coenzyme Q10 has been observed in the serum of some[18,19] but not all[20] patients using statins.

Blocking Rho, Rac, and Ras activation

Additional regulatory compounds that are activated by prenylation are small proteins that bind guanosine triphosphate (GTP). Rho, Rac, and Ras are GTP-binding proteins that promote cell maintenance and attenuate apoptosis.[21] Thus, blocking the activation of Rho, Rac, or Ras could promote apoptosis. This may be good if the apoptosis occurs within an atherosclerotic plaque, but bad if it occurs in skeletal muscle.

Inducing selenoprotein dysfunction

In addition, HMG-CoA reductase inhibition could lead to myopathy by interfering with the formation of selenocysteine-tRNA and by causing abnormalities in selenoproteins.[22]

Selenoprotein dysfunction has been linked to multiminicore disease, a congenital myopathy that is characterized histologically by minicore lesions (focal areas of myofibrillar disorganization) and loss of mitochondrial function. In addition, selenium deficiency can cause a painful myopathy with thinned myofibrils, vacuolization without fibrosis, and mitochondrial abnormalities—clinical and histologic features seen with statin myopathy.

Reducing cholesterol per se

Statins have been found to cause a lipid storage myopathy in some patients,[23] and a reduction in cholesterol levels alone may also have a deleterious effect. Cholesterol is an important structural component of cell membranes. Thus, statin use might alter membrane fluidity, electrical properties, sodium-potassium pump density, excitation-contraction coupling, or cell-surface receptor transduction cascades.[16]

Predisposing factors

Each of these mechanisms may cause statin myopathy in a given patient. But given the small percentage of people who experience myotoxicity, those who do experience these complications likely are predisposed to them.

Recent observations indicate that statin use triggers myopathy in people with previously asymptomatic deficiencies of myophosphorylase and carnitine palmitoyltransferase (CPT) and in some carriers of these disorders.[24] This same study found abnormalities in muscle L-carnitine content and decreased activities of CPT and respiratory chain enzymes in some patients. Whether these changes are primary and set the stage for statin myopathy or are secondary to the agents is not known. Regardless, they implicate abnormalities in energy metabolism as playing a role in statin myopathy.

Contributing factors

Although the causes of statin myopathy are unknown, recognized factors contribute to its development.[25–27] The risk is greater in patients with advanced age, small body frames, frailty, multisystem disease, and polypharmacy and in the perioperative period. Hepatic and renal dysfunction can contribute. The risk is also increased in patients who have diseases that affect skeletal muscle (such as hypothyroidism) or who use medications that can induce myopathy (eg, glucocorticoids, hydroxychloroquine, colchicine, alcohol, and antiretroviral agents).

But by far and away, the greatest risk of developing a myopathy correlates with exposure to the drug, either by simply taking a higher dose or by using another medication that interferes with the metabolism of the statin. Such drugs include gemfibrozil, cyclosporine, macrolide antibiotics, azole antifungal agents, nefazodone, some calcium channel blockers, and antiretroviral agents. Grapefruit juice can also have this effect if more than 1 quart a day is consumed.

CONSIDER OTHER CAUSES OF MYOPATHY

Because I am a rheumatologist with a special interest in muscle diseases, I have been referred a number of patients with the diagnosis of persistent statin myopathy. Interestingly, one of them proved to have hypothyroidism and was able to resume the use of a statin without difficulty after his symptoms resolved and his CK level returned to normal with thyroid hormone replacement. Others have reported the same occurrence.[28] Therefore, one should always consider other causes of myopathy even in patients taking a statin.

DOES ANYTHING HELP BESIDES STOPPING THE STATIN?

Coenzyme Q10 supplementation has been helpful to some patients with statin myopathy, but certainly not to all. Although a dose of 60 mg orally twice a day has been recommended, doses in excess of 300 mg twice a day may be required.[29]

Whether L-carnitine supplementation will prove helpful remains speculative, but this agent has a logical rationale and ought to be tested in clinical trials.[24]

An aerobic exercise program is recommended. Patients should start with low levels of exercise and increase to higher levels gradually as tolerated.

An aerobic exercise program is recommended, starting at a low level

REACHING LDL-C GOALS: QUICKLY OR GRADUALLY?

One cannot argue against the goal of having patients reach their ideal cholesterol targets. After all, any reduction in LDL-C and increase in HDL-C provides benefit. By one estimate, the risk of a coronary heart event is reduced by 1% for every 1-mg/dL reduction in LDL-C. One can, however, question how important it is to reach those targets rapidly if the use of the higher doses that are required to produce the rapid reduction increases the potential for myotoxicity.

If more patients take higher doses of statins, more myopathic complications will occur. This increase must be balanced against the improved outcomes that would be derived. Regardless of the approach chosen, the starting dose used may not provide the desired result, and further modification will be necessary. According to Dr. Jones's report, many physicians need to be reminded of that fact.

What is important is that we strive to help our patients achieve the optimal LDL-C level. Whether one chooses to start low and titrate the dose of a statin or to begin with a dose stratified according to baseline risks remains a matter of clinical judgment.

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ADDRESS: *Robert L. Wortmann, MD, The University of Oklahoma College of Medicine, 4502 East 41st Street, Tulsa, OK 74135; e-mail robert-wortmann@ouhsc.edu.*