EDITORIAL

PCSK9 Inhibitors for Statin Intolerance?

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Statin intolerance is a common problem most clinicians encounter when treating patients taking these drugs. Balancing the symptoms of muscle aches in a patient in need of cholesterol-lowering medication with the clinical trial–proven benefits of statins for reducing cardiovascular events in a broad spectrum of patients can be a difficult clinical challenge.

Muscle-related adverse effects from statins are highly mutable. Considerable evidence suggests that nonpharmacologic mechanisms account for most muscle-related statin intolerance. The prevalence of statin-associated muscle symptoms ranges from 7% to 29% in registries and observational studies.[1] The incidence of muscle symptoms is similar among statin-treated and placebo-treated patients across 26 long-term trials involving 170 000 patients.[2] In a large retrospective cohort study, 6579 of 11 124 patients who discontinued a statin due to adverse effects were rechallenged, with 92% success in restoring therapy, although not necessarily with the same statin or dose.[3] In an international survey, the incidence of intolerable statin-related adverse effects ranged from 2% in Japan, Spain, Italy, and Sweden to 10% to 12% in Canada, the United Kingdom, and the United States.[4] These substantial differences are likely to be modulated by cultural factors and patient perception.

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Nevertheless, statins are capable of causing severe muscle damage, very rarely leading to rhabdomyolysis, with this adverse effect most common with simvastatin. In 2011, the US Food and Drug Administration recommended that the 80-mg dose of simvastatin should only be used in patients who had been taking this medication for a year without adverse effects.[5] Although the underlying mechanism of statin-induced myopathy remains unclear, risk factors include older age, impaired renal or hepatic function, surgery, human immunodeficiency virus infection, genetic susceptibility, and high levels of physical activity.[6] Statins may rarely cause an autoimmune myopathy that persists after the drug is discontinued, with muscle weakness, myocyte necrosis, autoantibodies against the HMG-CoA reductase enzyme, and a need for immunosuppressive therapy.[7]

Guidelines provide common-sense recommendations for the management of statin intolerance.[1,6,8] In some patients the appearance of muscle aches turns the risk-benefit ratio unfavorable, so that stopping the statin and turning to diet and exercise is reasonable. Restarting a different statin at a lower dose after symptoms abate is a widely recommended strategy. Almost all patients will eventually find a tolerable statin and dose, even if it is just a low dose taken once or twice per week. In general, any statin is better than no statin when indicated, and most low-density lipoprotein cholesterol (LDL-C) lowering is obtained with the first 5 to 10 mg of statin.[9]

Nonstatin therapies are available to lower LDL-C levels. Ezetimibe is not approved to prevent cardiovascular events, and data from the only outcomes trial with this drug indicate that the number needed to treat per year to prevent a cardiovascular event is 350.[10] Bile acid sequestrants are poorly tolerated at high doses because of gastrointestinal adverse effects, but these agents lower LDL-C levels synergistically with statins and can play a useful role at low doses. The newest class of drugs, protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, has been shown to markedly lower LDL-C levels. Two of these monoclonal antibodies, evolocumab and alirocumab, were approved by the Food and Drug Administration in 2015 for use in addition to maximally tolerated statin therapy in adults with familial hypercholesterolemia or atherosclerotic cardiovascular disease who require additional lowering of LDL-C levels.

In this issue of *JAMA*, Nissen and colleagues[11] report the results of the GAUSS-3 trial, which used a rigorous protocol to investigate the use of the PCSK9 inhibitor evolocumab among patients with statin intolerance related to muscle-related adverse effects. The results are illuminating, but many unanswered questions remain.

In phase A of the trial, 491 patients with well-documented muscle-related adverse effects to 2 or more statins were randomized to receive either atorvastatin (20 mg daily) or placebo for 10 weeks, followed by a 2-week washout, followed by crossover to the alternate treatment for 10 weeks. Intolerable muscle-related symptoms developed in 209 patients (42.6%) while taking atorvastatin but not placebo, 130 (26.5%) while taking placebo but not atorvastatin, 48 (17.3%) while taking both treatments, and 85 (17.3%) while taking neither treatment. In phase B, 218 patients who had exhibited muscle-related adverse effects while taking atorvastatin but not while taking placebo, or who had experienced a 10-fold increase in creatine kinase level after statin administration, were randomized to receive ezetimibe (10 mg daily) (n = 73 patients) or evolocumab (420 mg monthly) (n = 145 patients). At 24 weeks, LDL-C levels were reduced by 16.7% (from 221.9 mg/dL at baseline to 181.5 mg/dL at 24 weeks) in the ezetimibe group and by 52.8% (from 218.8 mg/dL at baseline to 104.1 mg/dL at 24 weeks) in the evolocumab group ($P < .001$). This result is not surprising; indeed, similar results have been reported with evolocumab or alirocumab in statin-intolerant patients in 3 previous trials, although in this trial Nissen et al followed a precise protocol that identified patients who were truly statin intolerant.[12-14]

Should statin-intolerant patients be treated with PCSK9 inhibitors such as evolocumab? There are several arguments against such an approach. First, PCSK9 inhibitors are not approved for this indication. Although preliminary results are encouraging[15] and large, long-term outcome trials are

well under way, PCSK9 inhibitors have not yet been shown to reduce cardiovascular events. Second, one-fifth of the statin-intolerant patients in GAUSS-3 still reported muscle-related adverse effects while taking evolocumab.[11] Third, a 1-year supply of either alirocumab or evolocumab currently costs approximately $14 000.[16] According to a recent analysis, using a "willingness-to-pay" threshold of $50 000 per quality-adjusted life-year gained, a PCSK9 inhibitor would need to cost $2600 per year to be worthwhile for a statin-intolerant patient with cardiovascular disease and an LDL-level of 70 mg/dL or greater.[16]

Such a categorical financial analysis implies that PCSK9 inhibitors should not be used in any statin-intolerant patients, a conclusion that would be inappropriate. However, a patient at very high risk for a cardiovascular event with intolerable muscle symptoms while taking even a low statin dose should be considered as a candidate for this treatment. Less than 1% of all "statin-intolerant" patients might belong in this group at present. For other patients with statin intolerance, the appropriateness of the use of these agents is less clear.

The management of care for statin-intolerant patients can be frustrating and time-consuming for patients and for physicians. Patients experience their current symptoms but often do not appreciate the cardiovascular events that statins are preventing. Physicians should persist at finding solutions that minimize their symptoms and maximize risk reduction.

The very long-term outcomes reported for early statin primary prevention trials[17,18] are impressive, perhaps even inspiring. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) randomized patients with hypertension and multiple risk factors to receive atorvastatin (10 mg daily) or to placebo and was stopped after a median follow-up of 3.3 years because of benefit.[17] Approximately 8 years later, 11 years after randomization, total mortality, cardiovascular mortality, and noncardiovascular mortality were all significantly reduced in patients who had been in the statin group. In the West of Scotland Coronary Prevention Study (WOSCOPS), pravastatin (40 mg daily) reduced cardiovascular events compared with placebo over 4.9 years of treatment; however, at 20-year follow-up, total and cardiovascular mortality, as well as hospitalizations, were significantly reduced for any coronary event by 18% (P = .002), for myocardial infarction by 24% (P = .01), and for heart failure by 35% (P = .002).[18]

This legacy effect of statins is impressive. PCSK9 inhibitors are just starting out. Whether PCSK9 inhibitors will have the same impressive long-term outcomes will not be known for many years.

ARTICLE INFORMATION

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