Statin Discontinuation and Intolerance: The Challenge of Lifelong Therapy

Statins are among the most widely prescribed drugs. They reduce atherosclerotic cardiovascular disease events and improve survival in patients with established disease. Recommendations virtually mandate statin use in secondary prevention and widely advocate use for primary prevention. Clinicians initiate statin therapy with the expectation that the patient will continue lifelong treatment. However, this is a tall order for many persons, and it is not surprising that discontinuation rates are relatively high (1–3). As reported in this issue, Zhang and colleagues (4) explored the frequency of discontinuing statins in 1 hospital system. Combining data from structured electronic medical records and electronic provider notes using validated software from 107,835 patients between 1 January 2000 and 31 December 2008, they found that many patients discontinue statins for various reasons, yet most could tolerate them over the long run if rechallenged.

Patients stop taking statins for many reasons, including fear of side effects, perceived side effects, medication costs, lack of insurance coverage, misunderstanding of the benefits, lack of commitment to treatment, and loss to follow-up (5, 6). Consideration of 2 questions can inform strategies to improve statin adherence. First, why do patients discontinue statins? Second, in what portion of patients who discontinue statins do real side effects (statin intolerance) prevent continuation of therapy?

Most persons are not attuned to taking drugs every day for a lifetime. In 1 large British study, adherence to cardiovascular drugs averaged only approximately 57% (7). Adherence rates were similar for all classes of drugs, suggesting that low adherence was largely unrelated to side effects of specific drugs. A similar lack of adherence to statin therapy has been reported for Medicare beneficiaries in the United States (8). An interesting finding in the Zhang and colleagues report (4) was that a high percentage of persons who had discontinued statins could reestablish and maintain their use when rechallenged, making it unlikely that most of those who discontinued had true statin intolerance.

Surely, the greatest motivation for continuing statins is the presence of atherosclerotic cardiovascular disease. The literature, in fact, confirms that statin adherence is greater in secondary prevention than in primary prevention (1, 9); however, fear of cardiovascular events should be a motivating factor for patients with diabetes or chronic renal disease. Moreover, patients with these disorders are accustomed to regular professional follow-up and medication use. For most of these persons, statins will be only 1 of several drugs that must be taken regularly and indefinitely.

Turning to the question of statin intolerance, persons who take medications commonly blame the medications for various perceived side effects. Many patients know that statins have been reported to cause muscle pain, and because everyone has muscle or joint pain from time to time, blaming the medication is a natural tendency. At least one half of patients referred to the lipid clinic at my institution for statin intolerance have symptoms that are clearly unrelated to the drug. Even so, many patients cannot be convinced that statins are not the problem.

Most lipidologists believe that statins can, in fact, cause myalgia or muscle weakness. These side effects have been disputed by some clinical investigators because muscle symptoms in trial participants on statins were no greater than in those on placebo. It is not entirely clear why clinical experience and clinical trials show this discrepancy. Some trials required documentation of statin tolerance in a run-in phase before randomization. Patients who enter clinical trials may be less susceptible to perceived side effects than the general population. However, whatever the reasons, there is a growing consensus that statin intolerance due to muscle pain or weakness is a real phenomenon despite absence of documentation in trials. The prevalence of true statin intolerance is not well-defined; nevertheless, bona fide intolerance seems to fall in the range of 5% to 10%. A higher percentage of patients, ranging from 10% to 20%, have statin-associated muscle problems. Many of these patients, however, continue to take their medication despite symptoms of discomfort. Mancini and colleagues (10) recently provided a valuable review of statin intolerance that offers a strategy for the management of patients who have side effects. When statin intolerance is real, reestablishing therapy can be very difficult, and when the drug can be tolerated, it is often at “subtherapeutic” doses (that is, giving only modest decreases in low-density lipoprotein cholesterol levels). However, substantial reduction of low-density lipoprotein cholesterol levels can often be achieved by using other cholesterol-lowering drugs.

Besides muscle symptoms, several other adverse effects have been attributed to statins. These include liver injury, memory loss, and increased risk for diabetes. Fortunately, liver injury occurs rarely (if at all), despite occasional increases in aminotransferases. The U.S. Food and Drug Administration notes that some patients who take statins have memory loss, forgetfulness, and confusion and feel “fuzzy” or unfocused. It is difficult to know whether these claims represent true drug side effects. Further, the U.S. Food and Drug Administration brings attention to reports of greater risk for increased blood sugar levels and the development of type 2 diabetes in patients treated with statins.

The highest priority for statin adherence is in secondary prevention or other high-risk states, such as diabetes and chronic kidney disease. Because patients in these cate-
categories regularly see physicians, there is ample opportunity to monitor and promote adherence. Primary prevention in lower-risk persons is another matter. Treatment guidelines for primary prevention are becoming increasingly “aggressive” in use of statins. It is here that adherence will probably emerge as a major issue. In the United States, the health care system is not fashioned to promote long-term drug adherence. With little doubt, good adherence to preventive therapies carries the potential for greatly reducing population prevalence of atherosclerotic cardiovascular disease. Better strategies to promote statin adherence are essential to realizing this potential.

Scott M. Grundy, MD, PhD
Center for Human Nutrition, University of Texas Southwestern Medical Center
Dallas, Texas

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Requests for Single Reprints: Scott M. Grundy, MD, PhD, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Suite Y3.206, Dallas, TX 75390-9052; e-mail, scott.grundy@utsouthwestern.edu.


References