Needed: Pragmatic Clinical Trials for Statin-Intolerant Patients

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Statins are the most commonly prescribed drugs for lowering low-density lipoprotein (LDL) cholesterol levels. They've been amply studied in phase 3, randomized clinical trials and have been shown in primary and secondary prevention trials to reduce the risk of cardiovascular events. Statin use has increased dramatically in the past decade and will probably increase further because of lowered LDL cholesterol goals, new indications for treatment (increased C-reactive protein levels despite low or normal LDL levels), the introduction of generic versions of brand-name statins, and treatment recommendations for younger age groups. And since statin use has become the standard of care, pay-for-performance incentives may begin to incorporate the prescribing of statins in order to meet preestablished targets for health care delivery.

Yet all statins are associated with adverse events, especially at higher doses. Muscle-related adverse events, cognitive and memory problems, and elevation of liver enzymes have all been described. Such events reportedly occur with a frequency of less than 5% among patients in randomized clinical trials but in as many as 20% of patients in clinical practice.[1] The discrepancy may be largely attributable to patient selection in randomized trials, which may exclude older subjects or enroll insufficient numbers of women, two groups reported to have a higher incidence of statin-related adverse events. Patients who consume substantial amounts of alcohol, have multiple coexisting conditions, or take several other medications are also generally excluded. In clinical practice, however, such patients might well be prescribed statins. It's unlikely that a randomized clinical trial would or could be designed to include all these patients.

Another reason for the discrepancy in the reported frequency of adverse events may be the lack of a standard definition for statin-associated myopathy, the most common adverse event. Elevated serum creatine kinase levels (at least 10 times the upper limit of the normal range) are typically used to identify statin-associated myopathy in most studies, but this condition is not necessarily accompanied by elevated serum creatine kinase levels.[2] In addition, statin-associated myopathy may present not only as pain, but also as fatigability and weakness, which are not assessed in routine physical examination. Impaired cognition, the most common neurologic problem associated with statin use, is also not measured in most clinical settings, and reports of such symptoms are often dismissed as related to aging.

Possible further evidence of statin toxicity comes from the low rates of adherence to statin therapy over a 2-year period — 25.4% among patients taking the statin for primary prevention and 40.1% among patients taking it because of a history of coronary disease.[3] It's been assumed that poor adherence is due to barriers to therapy, but the occurrence of adverse events is also a possibility. Whether the frequency of adverse events is closer to 5% or 20%, statins are used so widely that side effects can translate into substantial public health problems.

The complexity of statin intolerance is certainly a hindrance to designing randomized clinical trials for these patients. The lack of standard definitions and relevant biomarkers makes it difficult to define a statin-intolerant group. Moreover, patients are often excluded from trials if they have adverse effects during the run-in phase, have a history of statin-associated adverse events, or are considered to be at high risk for such events. Management of dyslipidemia and outcomes in this group are therefore virtually unstudied, and clinicians and policymakers must turn to observational research or expert opinion for alternative strategies for achieving LDL cholesterol goals. These include reducing the dose or the frequency of administration of a statin, shifting to another statin, taking nonstatin lipid-altering medications, and alternative therapies such as very-low-calorie vegetarian diets. There are currently no data to support the superiority of one of these treatment regimens over another for the lowering of LDL levels or for cardiovascular and survival benefits for statin-intolerant patients.

Meanwhile, recent trials of lipid therapies aren't addressing the needs of this large group of patients, because nonstatin lipid-altering drugs are tested in phase 3 randomized clinical trials almost exclusively as additive therapy to statins, which are the standard of care. A recent example is the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health; ClinicalTrials.gov number, NCT00120289), in which 94% of

patients were already taking a statin at study entry. In this study, the addition of extended-release niacin to a statin regimen with or without ezetimibe that had already lowered LDL cholesterol levels to 40 to 80 mg per deciliter (1.03 to 2.07 mmol per liter) had no additional cardiovascular benefits and resulted in an increased incidence of ischemic strokes (see the article by the AIM-HIGH Investigators, pages 2255–2267).

The broad message was that perhaps niacin was not useful and might even be harmful. However, niacin was previously shown to be beneficial as a stand-alone treatment without increasing the incidence of ischemic strokes, and we believe it should still be considered for patients who cannot tolerate statins. If a new drug were tested only in addition to statins with the same result, it would be impossible to determine whether it had stand-alone benefits, and its value would be lost for statin-intolerant patients. Indeed, since cholesterol-absorption inhibitors and cholesteryl ester transfer protein inhibitors are being tested in this way, we won't know what their stand-alone effects might be. Since statins have consistently been shown to reduce the risk of cardiovascular events, some experts consider it unacceptable to use a placebo control in trials of new lipid-altering drugs. However, we suggest that placebo controls are necessary and valuable for studying patients who cannot tolerate statins. There is no accepted standard of therapy for this group, and many such patients are taken off lipid-lowering medications in clinical practice.

Pragmatic clinical trials may be well suited to determining the best treatment options for patients who have adverse effects from statins, because such trials are performed in the context of usual care, use broad eligibility criteria, and recruit patients from varied practice settings.[4] In pragmatic trials, physicians and patients are often not blinded to the treatment assignment and have the flexibility to adjust or discontinue treatment. Although less rigidly controlled than randomized trials in terms of study design, pragmatic trials are conducted in real-world settings and provide valuable information and guidance for clinical practice.

How might a pragmatic clinical trial for statin-intolerant patients be designed? Given the lack of standard definitions and relevant biomarkers, we propose a simple definition of statin-intolerant patients as those in whom statin-associated adverse effects develop that are either recognized by a physician or identified by the patient and who find their quality of life so diminished by these effects that they discontinue or modify their lipid-lowering regimen. To optimize treatment for statin-intolerant patients, such a study might be undertaken in referral clinics, such as lipid clinics, which see many patients who have not tolerated statins prescribed in primary care settings. Patients of a particular clinic or entire lipid clinics could be randomly assigned to one management approach or another, and the efficacy of the approaches could be compared. However, after randomization, treatments could be adjusted as necessary. A key component of such studies would be the use of quality-of-life questionnaires as additional screening tools to determine patients' perception of their symptoms, quantify the effects of statin intolerance on daily activities, and monitor changes in quality of life.

Certain key variables should be considered in designing such a trial. Study patients could be stratified according to cardiovascular risk level; they could include all statin-intolerant patients or just those with specific muscle or neurologic effects. Outcomes could include lowering of lipid levels, cardiovascular outcomes, quality of life, adherence to assigned therapy, and recurrence of old or appearance of new adverse effects. Therapeutic options might be those mentioned above, in a comparison with each other or with placebo. Of course, statistical issues would determine sample size and cost, and the investigators would determine whether to conduct a superiority, equivalence, or noninferiority trial.

We're not suggesting that a pragmatic clinical trial for statin-intolerant patients would be easy or inexpensive, but this population's needs are not being met, and it's time to begin a dialogue on the best way to meet them.

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