Statin-intolerant patients need a different type of clinical trial

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(Medical Xpress) -- Millions of people take statins, the blockbuster drug that lowers low-density lipoprotein (LDL), the so-called bad cholesterol. But as many as 20 percent of them develop adverse effects such as muscle fatigue and weakness and impaired cognition. Rockefeller University scientists Patricia Maningat and Jan L. Breslow, writing in this week's issue of the *New England Journal of Medicine*, argue that clinical trials need to be designed to address the needs of statin-intolerant patients.

"Statins are so widely used that side effects can translate into substantial public health problems," says Breslow, Frederick Henry Leonhardt Professor and head of the Laboratory of Biochemical Genetics and Metabolism. "It's imperative that we design special clinical trials, such as pragmatic trials, to determine the best treatment options for patients who have adverse effects from statins."

Statins, first introduced in 1987, work by blocking an enzyme called HMG-CoA reductase, which plays a key role in the liver's production of cholesterol. Randomized clinical trials have shown that side effects occur in less than 5 percent of patients who take statins, although as many as 20 percent are reported to experience side effects in clinical practice. Maningat and Breslow attribute this discrepancy to how patients are selected for clinical trials, which typically under enroll two groups likely to experience statin-related side effects — older patients and women — as well as patients who drink large amounts of alcohol, take several other medications, or have complicated medical conditions.

The problem, the researchers say, is that these groups are likely to be prescribed statins in the real world.

According to the researchers, the most common side effect of statin use, a muscular condition known as statin-associated myopathy, lacks a standard definition, which also leads to the discrepancy of reported adverse effects. For example, high levels of an enzyme called creatine phosphokinase typically indicate statin-associated myopathy, but this condition is not necessarily accompanied by elevated levels of this enzyme. Finally, cognitive impairment, the most common neurologic problem associated with statin use, is generally not measured in the clinic or it's disregarded as a consequence of aging.

Maningat and Breslow argue that introduction of new drugs for people who can't tolerate statins lags because most non-statin therapies are tested in clinical trials as additive therapies on top of statins. For example, in a recent trial on the benefits of combining niacin with statins, called the AIM-HIGH trial, 94 percent of those enrolled were taking a statin drug at the time they were enrolled. In this study, niacin combined with a statin was found to have no cardiovascular benefits and a trend towards increased risk of ischemic strokes.

"In the AIM-HIGH trial, niacin was not found to be useful when combined with a statin, and indeed, it might be harmful," says Breslow. "Fortunately, we do know that niacin alone can be beneficial. However, if a new drug was tested with a statin and the same result was found, it would be impossible to determine if it had standalone benefits and its value would be lost for statin-intolerant patients."

Since statins have been shown to reduce the risk of cardiovascular disease and have become standard of care, placebos are considered by some experts to be unacceptable when studying the effectiveness of new cholesterol modifying drugs, and therefore most studies employ the

study drug as an add-on to statin therapy. That severely complicates the conduct of meaningful trials for statin-intolerant patients. But Maningat and Breslow say that pragmatic trials, which occur in the context of usual care and recruit patients from broad a variety of practice settings, may be well suited for determining the best treatment options for patients who experience side effects from statins. In pragmatic trials, patients and doctors usually aren't blinded to the treatment and have the option to adjust or discontinue the treatment.

"Although less rigidly controlled than randomized trials, pragmatic trials are conducted in real-world settings and provide valuable information and guidance for clinical practice," Breslow says. "Given the complexity of statin intolerance, physicians need a simple way to identify patients who experience side effects." Maningat and Breslow suggest that patients who find their quality of life diminished to the point where they discontinue or change their statin regimen be defined as statin intolerant.

Enrolling patients in pragmatic trials, the researchers say, would involve, among other things, simplifying the definition of statin intolerance and screening patients to determine their perception of their symptoms, quantify the effects of statin intolerance on their daily activities and monitor changes in quality of life.

"We're not suggesting that pragmatic clinical trials for statin-intolerant patients would be easy or inexpensive, but this population's needs are not being met," says Maningat, who is a research associate in Breslow's lab. "It's time to begin a dialogue on the best way to meet them."

More information: *The New England Journal of Medicine* online: November 15, 2011, Needed: Pragmatic Clinical Trials for Statin-Intolerant Patients, Patricia Maningat and Jan L. Breslow