News
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****Guidelines for lovastatin use in treating high cholesterol

DALLAS -- When lovastatin was approved by the Food and Drug Administration in October 1987, it was hailed as a breakthrough in the treatment of high cholesterol. The stock of its American manufacturer soared, and physicians were besieged with calls from patients who wanted prescriptions.

Six months later, the New England Journal of Medicine asked Dr. Scott Grundy, director of the Center for Human Nutrition at The University of Texas Southwestern Medical Center at Dallas, to review the results of lovastatin therapy to date and suggest guidelines for its use.

Grundy was one of the first U.S. physicians to test lovastatin on people with high cholesterol levels, and he has conducted many trials since 1983 on the use of lovastatin alone or in combination with other drugs. Of the 1,000 patients who have now taken lovastatin for more than a year, 150 are treated in the Dallas area, the majority under his supervision.

The suggested guidelines for lovastatin treatment published in the July 7, 1988, NEJ reflect very positive results with the drug except in a few instances when side effects can be harmful. Lovastatin is rarely the first and only drug suggested: in most cases dietary changes are the first line of treatment, followed by drugs that have been in use longer, such as niacin or bile acid-binding resins. However, in difficult cases, the addition of lovastatin may make a dramatic difference in the results.

Lovastatin's ability to lower levels of harmful low density lipoprotein (LDL) cholesterol by 25 percent to 40 percent results from its unique action within liver cells. By inhibiting the production of the enzyme HMG CoA reductase, it not only curtails the cell's own production of LDL, but it also causes the cell to send more LDL receptors to its surface to pull LDL out of the bloodstream and into the cell. It has been proven that excess LDL circulating in the blood is the primary cause of atherosclerotic build-up that narrows arteries and leads to heart attack.

Grundy's guidelines say that lovastatin may prove especially effective in treating the following conditions:

*Heterozygous familial hypercholesterolemia occurs when a person inherits only one normal gene for LDL receptors rather than two. Total cholesterol builds up to 300-450 milligrams per deciliter. This genetic disorder accounts for approximately 5 percent of heart attacks before age 60.

*Primary severe hypercholesterolemia has no obvious genetic cause, but results in total cholesterol of 300-375 mg/dl, with LDL-cholesterol of 220-300 mg/dl.

*Primary moderate hypercholesterolemia results in total cholesterol levels of 240-300 mg/dl, with LDL-cholesterol of 160-200 mg/dl, with no known genetic cause. This condition usually calls for lovastatin therapy only in the presence of coronary heart disease (CHD) or obvious risk factors for CHD.

Patients with severe or moderate primary hypercholesterolemia account for approximately 30 percent of heart attacks before age 60.

Suggestions for treating each of these conditions follow approximately the same pattern. First, the physician should evaluate LDL cholesterol following a minimum of six months on a cholesterol-lowering diet in an attempt to bring the

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LDL down to the desirable level of 160 or less. If the LDL-cholesterol remains between 160 and 190 mg/dl. but there is no sign of coronary heart disease (CHD) or risk factors, he should maximize non-drug treatments and consider low doses of bile acid sequestrants.

Stricter treatment is called for if the LDL-cholesterol remains above 190 mg/dl (or above 160 mg/dl in the presence of CHD or two or more risk factors for CHD). In that case, a drug of first choice may be prescribed, usually a bile-acid binder or niacin. If that is not effective, lovastatin may be used in combination with either, but usually with a bile-acid binder. Combined-drug therapy has been shown to lower cholesterol as much as 50 percent to 60 percent.

Some of the risk factors for CHD that a physician should take into account when planning treatment are cigarette smoking, poorly controlled high blood pressure, marked obesity, diabetes, reduced levels of HDL-cholesterol (the "good" cholesterol) and a family history of CHD before the age of 60 in first-degree relatives. Being male also counts as a risk factor because pre-menopausal women have significantly less heart disease than men.

Grundy also discussed other conditions in which lovastatin therapy appears to be helpful although he says more testing is necessary. In families whose members have both high cholesterol and high triglycerides, a combination of lovastatin and gemfibrozil (a drug that is also effective against triglycerides) may prove helpful.

In two rare conditions, lovastatin may prove to be the only cholesterol-lowering drug that can be used safely because other drugs seem to have harmful side effects: one is the case of diabetics with both high cholesterol and high triglycerides and the other is the case of people with nephrotic dyslipidemia (a rare disease in which protein is lost through the kidneys). However, lovastatin needs to be tested further in both conditions.

At the time of FDA approval, harmful side effects of lovastatin were considered minimal. Grundy says experience has shown that most people can tolerate the drug well. "However, it is clear that it's not innocuous for some people," he said. "With people taking other drugs, there may be unfavorable drug interactions. For people with any kind of liver or biliary tract disease, there is a problem getting lovastatin out of the bloodstream and so it builds up and produces myopathy [muscle weakness].

"For the majority of people, it doesn't seem to be a problem. I still think lovastatin has an enormous potential for reducing the risk of heart attacks."

A cost comparison at one Dallas-area drugstore chain showed that lovastatin is more expensive than other commonly prescribed cholesterol-lowering drugs. A month's supply of lovastatin at 20 mg./day, the most common dosage, was $45.99. In comparison, a month's supply of one bulk-form bile-acid binder (Questran) was about $30 for a month's supply. Niacin, which can be bought without prescription, cost about $15 for a month's supply of 250 mg. tablets taken at the rate of 10 a day.

At present, Merck Sharp and Dohme is the only producer of lovastatin under the brand name Mevacor. "Second-generation" HMG CoA reductase inhibitors are presently being developed by several pharmaceutical manufacturers in the United States and Japan.

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Note: The University of Texas Southwestern Medical Center at Dallas comprises Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences and Southwestern Allied Health Sciences School.