Journal of the American College of Cardiology
Vol. 40, No. 3, 2002

ISSN 0735-1097/02/$22.00
Published by Elsevier Science Inc.
PII S0735-1097(02)02030-2

ACC/AHA/NHLBI CLINICAL ADVISORY ON STATINS

ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins

WRITING COMMITTEE MEMBERS

RICHARD C. PASTERNAK, MD, FACC, FAHA
SIDNEY C. SMITH, JR, MD, FACC, FAHA
C. NOEL BAIREY-MERZ, MD, FACC
SCOTT M. GRUNDY, MD, PHD, FAHA
JAMES I. CLEEMAN, MD
CLAUDE LENFANT, MD, FACC (HON), FAHA

TABLE OF CONTENTS

Preamble....567
Introduction....567
Incidence of Adverse Events....568
Mechanism of Myopathy....569
Diagnosis....569
Management....569
Baseline Measurements....569
Monitoring for Adverse Reactions and Adjusting Therapy....570
Asymptomatic Patients With CK Elevation....570
Prevention....570
Increased Risk States for Statin-Induced Myopathy....570
Clinical Precautions....570
Summary....571
References....571

PREAMBLE

The voluntary withdrawal of cerivastatin (Baycol) from the U.S. market on August 8, 2001, by the manufacturer, in agreement with the Food and Drug Administration (FDA), has prompted concern on the part of physicians and patients regarding the safety of the cholesterol-lowering class of drugs called HMG CoA reductase inhibitors, more commonly known as "statins." This American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute (ACC/AHA/NHLBI) Clinical Advisory is intended to summarize for professionals the current understanding of statin use, *focused on myopathy*, and to provide updated recommendations for the appropriate use of statins, including cautions, contraindications, and safety monitoring for statin therapy. Its purpose is not to discourage the appropriate use of statins, which have life-saving potential in properly selected patients, particularly those with established coronary heart disease (CHD) and others at high risk for developing CHD. Included are recent myopathy information compiled by the FDA, information from clinical trials, and summaries from the recently released report of the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) (1).

INTRODUCTION

In the literature, the general terminology used to describe muscle toxicity is inconsistent. Therefore, for the purpose of this document, the following terms are used as defined here: *Myopathy*—a general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life (Source: NINDS Myopathy Page-http://accessible.ninds.nih.gov/health_and_medical/disorders/myopathy.htm). *Myalgia*—muscle ache or weakness without creatine kinase (CK) elevation. *Myositis*—muscle symptoms with increased CK levels. *Rhabdomyolysis*—muscle symptoms with marked CK elevation (typically substantially greater than 10 times the upper limit of normal [ULN]) and with creatinine elevation (usually with brown urine and urinary myoglobin).

Statins are powerful low-density lipoprotein (LDL)-lowering drugs that are widely used in clinical practice. Results from clinical trials with a mean duration of 5.4 years have demonstrated a decrease in CHD and total mortality, reductions in myocardial infarctions, revascularization procedures, stroke, and peripheral vascular disease (2–8). These trials documented a benefit in both men and women, primarily in middle-aged and older persons treated in the setting of either primary or secondary prevention. More than 50,000 individuals have been randomized to either a placebo or statin in these trials, and no serious morbidity or

This document was approved by the American College of Cardiology Foundation Board of Trustees in May 2002, by the American Heart Association Science Advisory and Coordinating Committee in May 2002, and by the National Heart, Lung and Blood Institute in May 2002.

When citing this document, the American College of Cardiology, American Heart Association, and National Heart, Lung and Blood Institute would appreciate the following citation format: Pasternak RC, Smith SC, Jr., Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI Advisory on the Use and Safety of Statins. J Am Coll Cardiol 2002;40:568–73.

This document is available on the Web sites of the ACC (www.acc.org), the AHA (www.americanheart.org), and the NHLBI (www.nhlbi.nih.gov/guidelines/cholesterol).

JACC Vol. 40, No. 3, 2002
August 7, 2002:567–72

increase in mortality was observed in the drug treatment groups. These agents reduce the risk of essentially every clinical manifestation of the atherosclerotic process; they are easy to administer, with good patient acceptance. There are very few drug to drug interactions. Although the experience with the safety of statin therapy outside of clinical trials has not been fully reported, it is reasonable to suspect that the incidence of side effects may be higher in clinical situations where patients are not monitored as closely as they are in clinical trials (9).

The NCEP has published updated guidelines for treatment of high blood cholesterol (Adult Treatment Panel III report) (1). These guidelines are endorsed by the ACC and AHA. They identify elevated LDL cholesterol as the primary target of therapy and establish goals for LDL cholesterol that depend on a patient's risk status. The Adult Treatment Panel III report was able to apply rigorous clinical trial evidence to identify additional high-risk individuals for treatment, greatly expanding the number of patients who are candidates for these drugs. These include patients with established CHD, other forms of atherosclerotic disease, diabetes mellitus, multiple risk factors imparting high risk, and severe hypercholesterolemia. In many patients, relatively high doses of statins will be required to achieve LDL cholesterol goals of therapy. In addition, for patients with high triglycerides, non–high-density lipoprotein (HDL) cholesterol (LDL + VLDL [very low density lipoprotein] cholesterol) has been identified as a secondary target of therapy. To achieve the non–HDL cholesterol goal, many patients will require statin therapy as well. This broad expansion of statin use will require that increased attention be given to every aspect of statin therapy (i.e., efficacy, safety, and cost-effectiveness).

In view of the demonstrated safety of these agents, both medical professionals and the public were surprised by the recent withdrawal of a relatively new statin, cerivastatin (Baycol), from the market. Cerivastatin was first approved for use in the U.S. in 1997. In August 2001, the manufacturer, Bayer AG, announced the withdrawal of all dosages of its cholesterol-lowering drug with the brand names Baycol/Lipobay (cerivastatin) because of increasingly frequent reports of serious myopathy, including severe and life-threatening rhabdomyolysis. Rhabdomyolysis was reported most frequently when cerivastatin was used at higher doses and, particularly, in combination with another lipid-lowering drug, gemfibrozil (LOPID and generics). At the time of withdrawal, the FDA had received reports of 31 U.S. deaths due to severe rhabdomyolysis associated with the use of cerivastatin, 12 of which involved concomitant gemfibrozil use (http://www.fda.gov/cder/drug/infopage/baycol/). Subsequently, the Wall Street Journal (1/21/02, pg. A10) reported that Bayer AG had indicated that as many as 100 deaths have been linked to Baycol. The FDA reports that the rate of fatal rhabdomyolysis is 16 to 80 times more frequent for cerivastatin as compared to any other statin (10).

INCIDENCE OF ADVERSE EVENTS

The statins are well tolerated by most persons. Elevated hepatic transaminases generally occur in 0.5% to 2.0% of cases and are dose-dependent (11,12). Whether transaminase elevation with statin therapy constitutes true hepatotoxicity has not been determined. Progression to liver failure specifically due to statins is exceedingly rare if it ever occurs (13). Reversal of transaminase elevation is frequently noted with a reduction in dose, and elevations do not often recur with either re-challenge or selection of another statin (14,15). Cholestasis and active liver disease are listed as contraindications to statin use; however, no specific evidence exists showing exacerbation of liver disease by statins. Furthermore, statins have not been shown to worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C, and treatment of hyperlipidemia may actually improve transaminase elevations in individuals with fatty liver (16). An observational study (16a) has suggested a rare association of statin use with polyneuropathy. This has not been found in the large blinded randomized controlled trials.

The ability of statins to produce myopathy under some circumstances is well established. A common complaint is non-specific muscle aches or joint pains that are generally not associated with significant increases in creatine kinase. In placebo-controlled trials, the incidence of these complaints (generally reported as about 5%) is similar between placebo and active drug therapy, suggesting they may not be drug-related (12–17). Nonetheless, in some patients, the temporal association with statin therapy is strong enough to implicate these drugs as a cause of these complaints. Other patients can have mild-to-moderate elevations of creatine kinase without muscle complaints. Again, elevations may be non-specific, but a statin effect often cannot be ruled out.

It is rare that patients treated with a statin exhibit severe myositis characterized by muscle aches, soreness or weakness and associated with elevated creatine kinase levels, generally greater than 10 times the ULN. In this setting, failure to discontinue drug therapy can lead to rhabdomyolysis, myoglobinuria, and acute renal necrosis (18). Myositis is most likely to occur in persons who have complex medical problems and/or who are taking multiple medications. It may rarely occur with statin monotherapy, but it occurs more frequently when statins are used in combination with a variety of medications, including cyclosporine, fibrates, macrolide antibiotics, certain antifungal drugs, and niacin (19–21). Some of the drug to drug interactions involve specific interactions with the cytochrome P-450 drug-metabolizing system, especially those involving the 3A4 isozyme (22,23). The combination of statins with a fibrate is attractive for persons who have both high serum cholesterol and high triglycerides or for those who continue to have elevated triglycerides after reaching their LDL-cholesterol target on statin therapy. However, there may be a concern about an increased danger of developing myop-

athy with this combination. In the past, this combination was thought to be "contraindicated" because of the potential danger of myopathy. More recently, it has been used increasingly with apparent safety in the majority of persons. This combination is now presented by the ATP III report as an option, with careful monitoring, for some forms of dyslipidemia.

The FDA report comparing the rate of fatal rhabdomyolsis among different statins is of considerable importance (10). The FDA performed a detailed review of all reports of fatal rhabdomyolysis in their Adverse Event Reporting System and obtained the number of prescriptions dispensed since marketing of each statin began in the U.S. Fatal rhabdomyolysis was extremely rare (less than 1 death/million prescriptions). As previously noted, the rate of fatal rhabdomyolsis for cerivastatin was far greater than that for other statins (16 to 80 times higher). Even after excluding cases in which cerivastatin was administered with gemfibrozil, the reporting rate for fatal rhabdomyolysis with cerivastatin *monotherapy* (1.9 deaths per million prescriptions) was 10 to 50 times higher than for other statins. The FDA report also noted that more than 60% of the fatal cases with cerivastain were associated with use of the highest dose (0.8 mg daily). The FDA notes that the data are reporting rates, *not* incidence rates. Thus, statistically "rigorous comparisons between drugs . . . are not recommended" (10). Nevertheless, review of these data strongly suggests that there were no clinically important differences in the rate of fatal complications among the five statins now available in the U.S. (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin). Clinicians should consider the rates of severe myopathy as equivalent among all of these approved statins.

The following are summary comments reflecting current experience with these issues:

- Statin therapy appears to carry a small but definite risk of myopathy when used alone. According to several large clinical trial databases, the incidence of severe myopathy is reported to be 0.08% with lovastatin and simvastatin (14,15). Elevations of CK greater than 10 times the ULN have been reported in 0.09% of persons treated with pravastatin. All currently marketed statins appear to have a similar potential for causing this adverse effect.
- Fibrate treatment alone appears to be associated with some (probably similar) risk of myopathy.
- Of the nearly 600 persons who have participated in controlled clinical trials of a statin and fibrate combination, 1% have experienced a CK greater than 3 times the ULN without muscle symptoms, and 1% have been withdrawn from therapy because of muscle discomfort (24–31). None of these findings were considered serious by the trial investigators. No cases of rhabdomyolysis or myoglobinuria have been encountered in these clinical trials. The experience in these trials is predominantly with lovastatin and gemfibrozil, but it is reasonable to believe that the experiences with other statin-fibrate combinations would be similar.

MECHANISM OF MYOPATHY

Because it occurs so rarely, little is known about the fundamental mechanisms of statin-associated myopathy. It has been suggested that statins lead to inhibited synthesis of compounds arising from the synthetic pathway of cholesterol. In theory, this could lead to ubiquinone (an essential intracellular energy component) deficiency in muscle cell mitochondria, disturbing normal cellular respiration and causing adverse effects including rhabdomyolysis. Despite in-vitro support for this concept (32,33), a human study of six months of simvastatin treatment (20 mg per day) on skeletal muscle concentrations of high-energy phosphates and ubiquinone demonstrated that the muscle high-energy phosphate and ubiquinone concentrations assayed after simvastatin treatment were similar to those observed at baseline and did not differ from values in control subjects (34). No clinical study has yet provided support for the hypothesis of diminished isoprenoid synthesis or energy generation in muscle cells during statin therapy. Some have proposed that statin interaction with the cytochrome P-450 hepatic enzyme system might be related to myopathy (22). Support for this concept comes, in part, from the known enhanced toxicity when statins are administered with agents sharing metabolism by the same cytochrome isoforms. Finally, it has been shown that exercise in combination with lovastatin produces greater creatine kinase elevations than those produced by exercise alone, suggesting that statins can exacerbate exercise-induced skeletal muscle injury (35).

DIAGNOSIS

Routine laboratory monitoring of CK is of little value in the absence of clinical signs or symptoms. Therefore, all persons beginning to receive statins should be instructed to report muscle discomfort or weakness or brown urine immediately, which should then prompt a CK measurement.

MANAGEMENT

Baseline Measurements

Before initiating statin therapy, baseline measurements, including a lipid and lipoprotein profile, that will be used to follow the drug's efficacy and safety should be documented. Current labeling for all statins requires baseline measurements of liver function, including alanine transferase and aspartate transferase, although this is not agreed on by many liver experts and will likely undergo review in the future. Modest transaminase elevations (less than 3 times the ULN) are not thought to represent a contraindication to initiating, continuing, or advancing statin therapy, as long as patients are carefully monitored. Many experts also favor,

JACC Vol. 40, No. 3, 2002
August 7, 2002:567–72

and the ATP III report recommends, baseline CK measurement, reasoning that asymptomatic CK elevations are common and pre-treatment knowledge of this condition can aid in later clinical decision making.

Monitoring for Adverse Reactions and Adjusting Therapy

Once therapy has been initiated, symptoms may appear at any time. If myositis is present or strongly suspected, the statin should be discontinued immediately. Several key points should be kept in mind.

Obtain a CK measurement if the patient reports suggestive muscle symptoms, and compare to CK blood level prior to beginning therapy. Because hypothyroidism predisposes to myopathy, a thyroid-stimulating hormone level should also be obtained in any patient with muscle symptoms.

If the patient experiences muscle soreness, tenderness, or pain, with or without CK elevations, rule out common causes such as exercise or strenuous work. Advise moderation in activity for persons who experience these symptoms during combination therapy.

Discontinue statin therapy (or statin *and* niacin or fibrate if the patient is on combination therapy) if a CK greater than 10 times the ULN is encountered in a patient with muscle soreness, tenderness, or pain.

If the patient experiences muscle soreness, tenderness, or pain with either no CK elevation or a moderate elevation (3 to 10 times the ULN), follow the patient's symptoms and CK levels weekly until there is no longer medical concern or symptoms worsen to the situation described previously (at which point therapy should be discontinued). For patients who develop muscle discomfort and/or weakness and who also have progressive elevations of CK on serial measurements, either a reduction of statin dose or a temporary discontinuation may be prudent. A decision can then be made whether or when to reinstitute statin therapy.

Asymptomatic Patients With CK Elevation

Prior to the withdrawal of cerivastatin, the ATP III report did not recommend routine ongoing monitoring of CK in asymptomatic patients. If a physician chooses to obtain CK values in asymptomatic patients, particularly those on combination therapy, and CKs are elevated to more than 10 times the ULN, strong consideration should be given to stopping therapy. Following discontinuation, wait for symptoms to resolve and CK levels to return to normal before reinitiating therapy with either drug and use a lower dose of the drug(s) if possible.

Some asymptomatic patients will have moderate (i.e., between 3 and 10 times the ULN) CK elevations at baseline, during treatment, or after a drug holiday. Such patients can usually be treated with a statin without harm. However, particularly careful monitoring of symptoms and more frequent CK measurements are indicated.

PREVENTION

Increased Risk States for Statin-Associated Myopathy

Prevention of statin-associated myopathy can best be accomplished by attention to those factors that might increase the risk for such myopathy:

- Advanced age (especially more than 80 years) in patients (women more than men)
- Small body frame and frailty
- Multisystem disease (e.g., chronic renal insufficiency, especially due to diabetes)
- Multiple medications
- Perioperative periods
- Specific concomitant medications or consumption as listed below (check specific statin package insert for warnings)
  - Fibrates (especially gemfibrozil, but other fibrates too)
  - Nicotinic acid (rarely)
  - Cyclosporine
  - Azole antifungals
  - Itraconazole and ketoconazole
  - Macrolide antibiotics
  - Erythromycin and clarithromycin
  - HIV protease inhibitors
  - Nefazodone (antidepressant)
  - Verapamil
  - Amiodarone
  - Large quantities of grapefruit juice (usually more than 1 quart per day)
  - Alcohol abuse (independently predisposes to myopathy)

Clinical Precautions

Most myopathy associated with statins appears to occur in patients who are at risk for the condition. For this reason, physicians should be aware of several caveats when prescribing statin therapy. Myopathy is more likely to occur at higher statin doses than at lower doses. For this reason, doses should not exceed those required to attain the ATP III goal of therapy. As a rule, statin therapy should be employed more cautiously in older persons, particularly older thin or frail women, but it is not contraindicated in these or other high-risk patients. Among older persons, those with multisystem disease apparently are at higher risk. Patients with diabetes combined with chronic renal failure also appear to be at higher risk for myopathy—such patients should be monitored carefully. In several instances, myopathy has developed when patients were continued on statin therapy during hospitalization for major surgery. Therefore, it probably is prudent to withhold statins during such periods.

Particular attention should be given to drug interactions when employing statin therapy. Although the combination of statin plus fibrate is accompanied by an increased danger of myopathy, the use of moderate statin doses combined

Table 1. Summary of HMG CoA Reductase Inhibitors

Available drugs	Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin
Lipid/lipoprotein effects	LDL cholesterol ↓ 18–55 percent HDL cholesterol ↑ 5–15 percent Triglycerides ↓ 7–30 percent
Major use	To lower LDL-cholesterol
Contraindications	
Absolute	Active or chronic liver disease
Relative	Concomitant use of cyclosporine, gemfibrozil, or niacin, macrolide antibiotics, various anti-fungal agents, and cytochrome P-450 inhibitors
Efficacy	Reduce risk for CHD and stroke
Safety	Side effects minimal in clinical trials
Usual starting dose	Lovastatin - 20 mg Pravastatin - 20 mg Simvastatin - 20 mg Fluvastatin - 20 mg Atorvastatin - 10 mg
Maximum FDA-approved dose	Lovastatin - 80 mg Pravastatin - 80 mg Simvastatin - 80 mg Fluvastatin - 80 mg Atorvastatin - 80 mg
Available preparations	Lovastatin - 10, 20, 40 mg tablets Pravastatin - 10, 20, 40, 80 mg tablets Simvastatin - 5, 10, 20, 40, 80 mg tablets Fluvastatin - 20, 40, 80 (xl) mg tablets Atorvastatin - 10, 20, 40, 80 mg tablets

with fibrate appears to have a relatively low incidence of myopathy, especially when used in persons without multisystem disease or multiple medications. The combination of statin plus nicotinic acid seemingly carries a lower risk for myopathy than does statin plus fibrate. Finally, physicians should be aware of the dangers of interactions of statins with the other drugs previously listed. These combinations should also be used with caution or avoided altogether. Furthermore, it is important for clinicians prescribing statins to make sure that their patients are aware of these potential drug interactions, because in current practice, a patient may receive prescriptions from many different caregivers.

Table 2. Monitoring Parameters and Follow-Up Schedule

	Monitoring Parameters	Follow-Up Schedule
Statins	Headache, dyspepsia	Evaluate symptoms initially, 6 to 8 weeks after starting therapy, then at each follow-up visit
	Muscle soreness, tenderness, or pain	Evaluate muscle symptoms and CK before starting therapy. Evaluate muscle symptoms 6 to 12 weeks after starting therapy and at each follow-up visit. Obtain a CK measurement when persons have muscle soreness, tenderness, or pain.
	ALT, AST	Evaluate ALT/AST initially, approximately 12 weeks after starting therapy, then annually or more frequently if indicated.

ALT = alanine transferase; and AST = aspartate transferase.

SUMMARY

Statin therapy holds great promise for reducing the incidence of major coronary events, coronary procedures, and stroke in high-risk patients. At present, this potential has not been fully realized, because many patients at heightened risk are not being treated with these drugs. There is a well documented under-use of statins in clinical practice. Statins have proven to be extremely safe in the vast majority of patients receiving them. Few significant side effects were observed in clinical trials, and post-marketing reports of adverse events have been very limited when considered in comparison to the very large number of persons safely receiving these drugs. Even so, these drugs are not *entirely free* of side effects, and as for all drugs, they should be used appropriately and judiciously. This advisory encourages the appropriate use of statins while pointing out the possibility of side effects in certain patients. If statins are used with appropriate caution in these selected patients, the likelihood of developing clinically important myopathy should be substantially reduced. (See Tables 1 and 2.)

REFERENCES

1. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
2. Collins R. Results of the Heart Protection Study. Oral presentation at the American Heart Association Annual Scientific Sessions, Anaheim, CA, November 2001.
3. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998;279:1615–22.
4. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301–7.
5. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001–9.
6. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 1999;282:2340–6.
7. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
8. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998;339:1349–57.
9. Gaist D, Rodriguez LA, Huerta C, Hallas J, Sindrup SH. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. Epidemiology 2001;12:565–9.
10. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. N Engl J Med 2002;346:539–40.
11. Hsu I, Spinler SA, Johnson NE. Comparative evaluation of the safety and efficacy of HMG-CoA reductase inhibitor monotherapy in the

treatment of primary hypercholesterolemia. Ann Pharmacother 1995; 29:743–59.
12. Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. Arch Intern Med 1991; 151:43–9.
13. Pedersen TR, Tobert JA. Benefits and risks of HMG-CoA reductase inhibitors in the prevention of coronary heart disease: a reappraisal. Drug Saf 1996;14:11–24.
14. Cressman MD, Hoogwerf BJ, Moodie DS, Olin JW, Weinstein CE. HMG-CoA reductase inhibitors. A new approach to the management of hypercholesterolemia. Cleve Clin J Med 1988;55:93–100.
15. Hunninghake DB. Drug treatment of dyslipoproteinemia. Endocrinol Metab Clin North Am 1990;19:345–60.
16. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;346: 1221–31.
16a. Gaist D, Jeppesen U, Anderson M, et al. Statins and risk of polyneuropathy: a case-control study. Neurology 2002;58:1333–7.
17. Farmer JA. Learning from the cerivastatin experience. Lancet 2001; 358:1383–5.
18. Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. JAMA 1990;264:71–5.
19. Goldman JA, Fishman AB, Lee JE, Johnson RJ. The role of cholesterol-lowering agents in drug-induced rhabdomyolysis and polymyositis. Arthritis Rheum 1989;32:358–9.
20. Wanner C, Kramer-Guth A, Galle J. Use of HMG-CoA reductase inhibitors after kidney and heart transplantation: lipid-lowering and immunosuppressive effects. BioDrugs 1997;8:387–93.
21. Hanston PD, Horn JR. Drug interactions with HMG CoA reductase inhibitors. Drug Interactions Newsletter 1998:103–6.
22. Davidson MH. Does differing metabolism by cytochrome p450 have clinical importance? Curr Atheroscler Rep 2000;2:14–9.
23. Gruer PJ, Vega JM, Mercuri MF, Dobrinska MR, Tobert JA. Concomitant use of cytochrome P450 3A4 inhibitors and simvastatin. Am J Cardiol 1999;84:811–5.
24. Shepherd J. Fibrates and statins in the treatment of hyperlipidaemia: an appraisal of their efficacy and safety. Eur Heart J 1995;16:5–13.
25. Ellen RL, McPherson R. Long-term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. Am J Cardiol 1998;81:60B–5B.
26. Rosenson RS, Frauenheim WA. Safety of combined pravastatin-gemfibrozil therapy. Am J Cardiol 1994;74:499–500.
27. Murdock DK, Murdock AK, Murdock RW, et al. Long-term safety and efficacy of combination gemfibrozil and HMG-CoA reductase inhibitors for the treatment of mixed lipid disorders. Am Heart J 1999;138:151–5.
28. Iliadis EA, Rosenson RS. Long-term safety of pravastatin-gemfibrozil therapy in mixed hyperlipidemia. Clin Cardiol 1999;22:25–8.
29. Zambon D, Ros E, Rodriguez-Villar C, et al. Randomized crossover study of gemfibrozil versus lovastatin in familial combined hyperlipidemia: additive effects of combination treatment on lipid regulation. Metabolism 1999;48:47–54.
30. Napoli C, Lepore S, Chiariello P, Condorelli M, Chiariello M. Long-term treatment with pravastatin alone and in combination with gemfibrozil in familial type IIB hyperlipoproteinemia or combined hyperlipidemia. J Cardiovasc Pharmacol Ther 1997;2:17–26.
31. Farnier M, Dejager S. Effect of combined fluvastatin-fenofibrate therapy compared with fenofibrate monotherapy in severe primary hypercholesterolemia. French Fluvastatin Study Group. Am J Cardiol 2000;85:53–7.
32. Flint OP, Masters BA, Gregg RE, Durham SK. HMG CoA reductase inhibitor-induced myotoxicity: pravastatin and lovastatin inhibit the geranylgeranylation of low-molecular-weight proteins in neonatal rat muscle cell culture. Toxicol Appl Pharmacol 1997;145:99–110.
33. Gadbut AP, Caruso AP, Galper JB. Differential sensitivity of C2-C12 striated muscle cells to lovastatin and pravastatin. J Mol Cell Cardiol 1995;27:2397–402.
34. Laaksonen R, Jokelainen K, Laakso J, et al. The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle. Am J Cardiol 1996;77:851–4.
35. Thompson PD, Zmuda JM, Domalik LJ, Zimet RJ, Staggers J, Guyton JR. Lovastatin increases exercise-induced skeletal muscle injury. Metabolism 1997;46:1206–10.

CDER - Center for Drug Evaluation and Research Logo

Drug Information

Search Go

Side Navigational Buttons

Baycol Information

FDA announced on August 8, 2001 that Bayer Pharmaceutical Division is voluntarily withdrawing Baycol (cerivastatin) from the U.S. market because of reports of sometimes fatal rhabdomyolysis, a severe muscle adverse reaction from this cholesterol-lowering (lipid-lowering) product. The FDA agrees with and supports this decision.

- Baycol Talk Paper (8/8/2001)
- Baycol Questions and Answers (8/8/2001)
- Dear Healthcare Professional Letter (8/8/2001)

toto (152 byte Back to Top Bacl Drug Information

FDA/Center for Drug Evaluation and Research
Last Updated: August 08, 2001
Originator: OTCOM/DLIS
HTML by MAU