The withdrawal of cerivastatin (Baycol, Bayer) from the market for safety reasons posed a huge problem for P&T committees and all members of the health care team who uphold the safety of patients. It came in the face of a worldwide evolution to modern lifestyles that in the aggregate involve decreased exercise levels with a consequen-
tial rise in lipid levels. This rise in lipid levels puts into sharp focus the continued need to balance aggressive treatment for high lipid levels against the increased need to monitor the sometimes dire medical consequences of using this powerful class of medications. The purpose of this article is to address the proper balance between these two divergent foci.

The negative publicity surrounding cerivastatin has placed into question the safety of all 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also known as statins. The first duty of all members of the health care team is to overcome our patients’ fears about taking statins. This effort should exist across the continuum from personnel in clinical offices (nurses, nurse practitioners, physician asis-
tants, and physicians) to pharmacists and PharmD’s. This has never been more important, as the incidence of hyperlipidemia is increasing at epidemic proportions among our patients. Under the new National Cholesterol Education Program (NCEP) guidelines, it is estimated that in excess of one-third of all American adults should be placed on pharmaceutical intervention. With clinical research underway to determine secondary long-term benefits from the use of statins in Alzheimer’s disease and in osteoporosis prevention, this percentage could increase even more.

The great fear is that the type of patient who tends to over-
estimate the medical risk from taking lipid-lowering medica-
tions is the same type of patient who tends to underestimate the risk of hyperlipidemia, which is often aggravated by the patient’s lifestyle.

The challenge facing our P&T committee was that there was no precedent for our committee to readdress the safety of cerivastatin after the higher dosage was approved by the Food and Drug Administration (FDA). This problem extends even further, as there is no precedent for readdressing the safety of a medication after a new dosage has been approved. Nor is there any protocol to review new indications for previously approved medications. This is a concern for all the members of the health care team who are responsible for the safety of patients. The concern for those who manage formu-
laries is even greater, as providers often prescribe medications for non–FDA-approved indications and dosages after a new drug enters the marketplace.

We, as health care providers, must empower our patients. The patient is in a better position than the physician to control the risk of deleterious side effects of taking a statin. The well-
formed patient, for example, is more inclined to alert the provider to the presence of myalgias. This early notification allows the provider to begin a diagnostic evaluation and to alter the therapy sooner. The hope is that the earlier the change in therapy, the less likely the patient is to have long-
term negative effects from the therapy.

All patients should be educated that even a moderate change in lifestyle can have a positive effect on LDL levels, obviating the need to increase the dose and decreasing the chance for side effects. The problem with most physicians is that after they make the decision to place a patient on a statin, they have a tendency to de-emphasize non-pharmacologic cholesterol reduction. During the year or so that it takes to titrate to the proper dose, the degree of change in the patient’s lifestyle will ultimately determine the maximum dose required.

The focus should be on identifying patients with multiple risk factors for coronary artery disease (CAD). The new ATP III guidelines raise persons with diabetes without coronary heart disease (CHD) to a CHD risk equivalent. Type 2 diabetes is a fast-growing epidemic. These new guidelines use projections based on the Framingham data of 10-year absolute risk to identify patients with multiple risk factors for more intensive treatment. The guidelines also identify patients with the dys-
metabolic profile (those with abdominal obesity, low HDL, hypertriglyceridemia, hypertension, and impaired glucose tolerance) who are candidates for therapeutic lifestyle modification.

Modifications of the lipid and lipoprotein classification now identify LDL cholesterol below 100 mg/dl as optimal. What is now considered to be low HDL cholesterol has changed to values below 40 mg/dl, up from the previous 35 mg/dl. The optimal triglyceride level has been determined to be less than 150 mg/dl. The new guidelines suggest a comprehensive lipoprotein panel (total, LDL-C, HDL-C, and triglycerides) as the preferred initial test, rather than the previous recommen-
iation of total cholesterol and HDL-C alone. The new guide-
lines also encourage a more rapid initiation of drug therapy,
sometimes simultaneously with lifestyle modifications.2

In the near future, newer modalities will be available to
treat hypercholesterolemia. For example, ezetimide is a new
cholesterol-absorption inhibitor being developed by Schering-
Plough that is believed to have a reduced potential for sys-
temic side effects because it is non-absorbed. It has been
used as monotherapy and in conjunction with statins.4,5 Rosuvas-
tatin is a new, more potent statin that should be available later
this year. In clinical trials, rosuvastatin has proved to be more
effective that atorvastatin.5

On January 18, 2002, Bayer announced that it was aware of
over 100 deaths linked to the use of cerivastatin.6 Studies
from the FDA have determined that the rate of fatal rhab-
domyolysis associated with cerivastatin is 16 to 80 times as
high as the rate for any other statin.7 Among patients in
whom cerivastatin was used without the concomitant use of
gemfibrozole, deaths were twice as likely to occur at the
0.8-mg dose than at the 0.4-mg dose.7 The majority of compi-
lcations and deaths occurred in elderly patients and occurred
more frequently in women.

Former cerivastatin patients can be classified as symp-
tomatic, asymptomatic, and fearful. Those that were symp-
tomatic were the easiest to identify. However, even
asymptomatic patients might be at a permanently increased
risk of liver, kidney, cardiac, and skeletal muscle damage,
especially during re-challenge to a statin or upward titration.

Those patients who are now fearful of the entire statin class
require the assistance of the health care team to educate
them on the risk/benefit ratio of statins. It is hoped that those
in need will realize that the benefits of cholesterol reduction
with statins far outweigh the risks associated with treatment.

The actual cause of statin-induced myalgia is not known.
One theory suggests that the myalgia, usually expressed and
pronounced in the calves and low back, increases with dose
and might be caused by interference with oxidative phosphory-
lization and the depletion of coenzyme Q (ubiquinone).8

In essence, former cerivastatin patients who are now on a
different statin might represent a new class of patients. The
estimated 700,000 to 800,000 former cerivastatin patients
should be treated with the same caution and monitoring as
subjects enrolled in clinical trials, and might benefit from clos-
er monitoring of their liver and muscle enzymes than is cur-
rently recommended by the manufacturers for patients
beginning therapy on a statin de novo.

We encourage the pharmaceutical industry to form a col-
laborative effort with its physician and pharmacist partners to
establish registries to track patients who have been subjected
to adverse effects of medications. One such example is the
registry that was created by GlaxoSmithKline to track patients
with irritable bowel disease who were exposed to alosetron
(Lotronex). We know of no such registry funded by Bayer’s
pharmaceutical division for cerivastatin. If the pharmaceutical
industry doesn’t participate in helping to create these reg-
istries, physicians should seek a government endowment or
other private funding.

A registry of former cerivastatin patients might reveal pat-
tterns of early indications of myalgia and rhabdomyolysis. More
importantly, we must address the question of why deaths
occurred. Were they predictable, and therefore avoidable? Were
other confounding factors, such as alcohol usage, involved? Key
questions such as these cannot be answered without the forma-
tion of registries to effectively track and monitor patients.

One irony of properly designed clinical trials is that subject
protection frequently precludes all but the healthiest patients
from participating. Therefore, we might not be getting a true
picture of how those patients who would not have met entry
criteria might respond to a given medication. Post-marketing
self-reporting by physicians remains an imperfect solution
because of physician under-reporting to the FDA.

In summary, the adverse reactions and deaths suffered by
patients exposed to cerivastatin have brought to light a whole
new series of challenges for P&T committees and all health care
providers involved in patient safety. Although the exact cause of
these adverse reactions is not known, the growing pool of
patients exposed to statins intensifies the need to better track
these patients. This situation also exposes the need for P&T
committees to have in place methods to review new dosages
and indications for medications, along with adequate monitoring
systems to track adverse reactions. ■

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