Commentary

Withdrawal of cerivastatin from the world market

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Abstract

Cerivastatin was recently withdrawn from the market because of 52 deaths attributed to drug-related rhabdomyolysis that lead to kidney failure. The risk was found to be higher among patients who received the full dose (0.8 mg/day) and those who received gemfibrozil concomitantly. Rhabdomyolysis was 10 times more common with cerivastatin than the other five approved statins. We address three important questions raised by this withdrawal. Should we continue to approve drugs on surrogate efficacy? Are all statins interchangeable? Do the benefits outweigh the risks of statins? We conclude that decisions regarding the use of drugs should be based on direct evidence from long-term clinical outcome trials.

Keywords cerivastatin, drug safety, LDL cholesterol, rhabdomyolysis, statins

The recent withdrawal of cerivastatin (Baycol® or Lipobay®) from the world market generated substantial attention in the lay media. According to press reports, the use of cerivastatin was linked to rhabdomyolysis, which lead to kidney failure, and was responsible for 31 fatalities in the United States and a further 21 deaths worldwide. In addition, there were 385 nonfatal cases reported among the estimated 700,000 users in the United States, most of whom required hospitalization. In many of the fatal cases, patients had received the full dose of cerivastatin (0.8 mg/day) or were using gemfibrozil (Lopid®) concomitantly. This drug–drug interaction was implicated in 12 of the 31 fatalities in the United States.

The media reports caused concern among the users of all statins and triggered a large number of calls to treating clinicians. The American Heart Association and the American College of Cardiology took a stand, by issuing a statement aimed at reassuring statin users that the five remaining members of this drug grouping – lovastatin, pravastatin, simvastatin, atorvastatin, and fluvastatin – are safe, that only in extremely rare situations do they cause rhabdomyolysis, and that the health benefits clearly outweigh any risks [1].

Simultaneously, however, the German government accused Bayer of withholding vital information from its regulatory agency [2]. Other regulatory agencies in the United States and Europe, are reviewing the safety data or considering changes to the labeling for the other five statins, and United States law firms are putting advertisements in the press for victims of rhabdomyolysis. At the time of withdrawal, Baycol® had slightly less than 4% of the statin market in the United States. The statin manufacturers are obviously concerned, since worldwide sales in 2001 are projected to be US$16 billion.

This commentary will address the important clinical and public health questions, raised by the withdrawal of cerivastatin.

Should we continue to approve drugs based on surrogate efficacy?

Cerivastatin, as well as other lipid-lowering agents, received initial regulatory approval based on their effects on serum lipoproteins. Following approval, the three fermentation-derived statins – simvastatin, pravastatin, and lovastatin –

BIP = Bezafibrate Infarction Prevention; VA-HIT = Veterans Affairs HDL-Cholesterol Intervention Trial.
FDA = (United States) Food and Drug Administration; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

have been shown to reduce the risk of mortality and/or major coronary events [3]. However, the available documentation for long-term efficacy and safety for the synthetic statins – atorvastatin, fluvastatin, and cerivastatin – is weak or nonexistent.

The fibrates were also approved based on surrogate efficacy, primarily, an increase in high-density lipoprotein (HDL)-cholesterol. Subsequently, gemfibrozil was shown to reduce coronary events in the Veterans Affairs HDL-Cholesterol Intervention Trial (VA-HIT), despite only a very small, observed increase in HDL-cholesterol [4]. In contrast, bezafibrate, in the Bezafibrate Infarction Prevention (BIP) study, caused a marked increase in HDL-cholesterol but had no effect on the risk of coronary events [5].

There are three major limitations associated with reliance on surrogate efficacy. First, experience indicates that changes in surrogate markers are poor predictors of clinical efficacy [6,7]. Second, a drug may have multiple mechanisms of action, and reliance on one action for regulatory approval ignores the potential consequences of its other actions. Statins are pleiotropic and have known effects on nitrate oxide availability and vascular inflammation that could be of clinical relevance. Additionally, the dose-responses for these pleiotropic effects appear to differ from the dose-response for the low-density lipoprotein (LDL)-cholesterol lowering effect, at least in animal studies. This raises questions about its recommended or optimal dose. If, in humans, these pleiotropic effects do contribute to the mortality/morbidity benefit of statins, and if their dose-responses are different, then it follows that the optimal clinical dose cannot be determined from the LDL-cholesterol reduction. Large, long-term outcome trials would be required to determine recommended dose and clinical efficacy. Third, small short-term trials, designed to determine drug actions on lipoproteins, provide insufficient data on drug safety. Unfortunately, there are no surrogates for drug safety. The practice of medicine ought to rely on direct scientific evidence of both efficacy and safety, rather than on extrapolations based on surrogate efficacy.

Are all statins interchangeable?

The withdrawal of cerivastatin demonstrates that all statins are not interchangeable. Cerivastatin is at least 10 times more likely than the other statins to cause fatal rhabdomyolysis [8]. Statins may be similar in terms of clinical efficacy, but the current documentation for atorvastatin and fluvastatin is weak. However, several ongoing trials will provide important efficacy and safety information on these two agents.

In the marketing of atorvastatin and fluvastatin, it has been implied that these two synthetic statins convey the same clinical benefits as the fermentation-derived statins. This is a violation of the Federal Food, Drug, and Cosmetic Act. Accordingly, the United States Food and Drug Administration (FDA) issued letters of warning to the manufacturers of these products, regarding their false claims about existing health benefits [9,10].

The best clinical trial documentation of long-term safety and efficacy comes from large-scale trials of simvastatin and pravastatin. A recent meta-analysis based on three placebo-controlled trials with approximately 20,000 patients followed for over 5 years did not reveal any serious or unexpected adverse events [11]. None of the almost 10,000 patients receiving pravastatin was diagnosed with rhabdomyolysis. The practice of medicine ought to be based on scientific evidence for each individual drug rather than presuming that all drugs of a similar grouping are interchangeable.

Do the benefits outweigh the risks of statins?

This question can only be answered for the statins that have been properly examined in large, long-term trials. Clinicians can be certain that the known benefits clearly outweigh the known risks for simvastatin and pravastatin. Documentation for lovastatin is fairly convincing, but is still insufficient for atorvastatin and fluvastatin.

We take the position that large, long-term trials are desirable to evaluate individual drugs that are prescribed for lifelong use. Initial approval of the first member of a novel class of therapeutic agents that has potential important health care benefits, may in some cases be justified on the basis of surrogate efficacy. However, subsequent drugs with similar mechanisms of action should not be rushed through the approval process but receive careful consideration regarding their net risk–benefit ratio and optimal dose, prior to regulatory approval. The cerivastatin experience supports the position that unexpected serious adverse events may not be detected until a large number of patients have been exposed for an extended period of time.

In relative terms, it appears that cerivastatin was inferior to the other statins. In absolute terms, it is quite likely that the clinical benefit of cerivastatin, yet unproven, could outweigh the minimal risk of fatal rhabdomyolysis. Our assumption is that the regulatory agencies worldwide might have left cerivastatin on the market if it had been the only marketed statin. In the presence of other statins, in particular, simvastatin and pravastatin – cerivastatin was clearly inferior. Concerns about patient safety tipped the regulatory decision towards its withdrawal. It will be interesting to see if drug inferiority in the future will be an important factor in the regulatory decision-making process.

The issues raised in this commentary have implications, not only for the drug approval process but perhaps more importantly, for the public's faith in prescription drugs. Withdrawal of approved and widely used drugs such as cerivastatin, because of serious life-threatening side effects,

erodes public confidence in the medical care system. A lack of confidence may, in part, be responsible for the increasing reliance of the general public on alternative medical therapies. Approval of any drug for lifelong use on the basis of just a few thousand patients is risky and may not serve the public, as illustrated by the experience with cerivastatin and several other recently withdrawn drugs.

Competing interests

Curt Furberg, none declared; Bertram Pitt has been involved in trials of pravastatin, atorvastatatin, cerivastatin, and simvastatin. He has acted as a consultant for the Bayer Corp., Bristol-Meyers Squibb, Novartis, Merck, and Pfizer.

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