

## The Issue of Statin Safety Where do We Stand?

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Statins are first-line therapy for reducing low-density lipoprotein (LDL) levels in patients at high risk for atherosclerotic cardiovascular disease (ASCVD).<sup>1,2</sup> These agents are being used in millions of high-risk people worldwide. Many others receive statins for primary prevention. The total number can only be expected to rise with time. Although favorable results from a large number of controlled clinical trials underpin the benefits of statin therapy,<sup>2</sup> it is not surprising that the safety of statins has received much attention. Controlled trials and clinical practice have demonstrated that they generally are safe; in fact, the frequency of clinically significant side effects is quite low. In rare patients, nonetheless, side effects can occur and occasionally are serious. Most serious among these is severe myopathy (rhabdomyolysis), which can cause acute renal failure. In a small percentage of patients, statins elevate serum transaminases. There is little or no evidence that statins cause progressive liver disease<sup>3</sup>; nevertheless, persistent elevations in transaminases can be perplexing. Other less serious side effects may occur. One of these that was demonstrated recently is low-grade proteinuria, likely due to a statin-induced inhibition of proximal tubular reabsorption of protein.<sup>4</sup> To date, no evidence exists that this is accompanied by pathological tubular injury or progression to chronic renal failure.

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Side effects of statins tend to be dose related. Most side effects, including myopathy, disappear on withdrawal of the medication. Even with severe myopathy, most patients survive with supportive measures, although fatalities occasionally occur. For example, Omar and Wilson<sup>5</sup> reported that between November 1997 and March 2000, 871 cases of statin-associated severe myopathy were reported to the US Food and Drug Administration (FDA); among these reports, however, only 38 cases were listed as fatal.

Six statins currently are available by prescription in the United States. In order of increasing LDL-lowering potency per milligram of drug, they are fluvastatin, lovastatin=pra-

vastatin, simvastatin, atorvastatin, and rosuvastatin. Growing evidence from clinical trials supports the concept that to reduce ASCVD events in high-risk patients, "the lower, the better" applies to LDL levels.<sup>2,6</sup> To achieve very low LDL levels, higher doses of statins often are required. Pharmaceutical companies naturally promote their own statins as being superior to others. One way to do this is to be able to claim greater LDL-lowering potency, both per milligram and absolutely. Attempts to achieve greater LDL lowering with increasing doses of statin, though a goal both in the highly competitive marketplace of the "statin wars" and in the clinic, ultimately will be limited by toxicity. Historically, this has taken the form of myotoxicity.

The issue of statin safety came to the fore in 2001 after the withdrawal of cerivastatin from the market. Cerivastatin has a much greater potency per milligram than other statins. Consequently, doses a hundred times lower than those of other statins were required. For reasons not entirely understood, cerivastatin therapy with the higher approved doses resulted in multiple cases of severe myopathy and acute renal failure, even though these doses were intermediate in absolute LDL-lowering effect as compared with the other statins. After a rash of postmarketing reports of severe rhabdomyolysis, the FDA wisely advised the manufacturer of cerivastatin to remove it from the market. Unfortunately the publicity surrounding the cerivastatin withdrawal caused many high-risk patients to discontinue other, safer statins, to their disadvantage.

At that time, the American Heart Association (AHA), American College of Cardiology (ACC), and National Heart, Lung, and Blood Institute (NHLBI) issued an advisory on the safety of statins and their use in clinical practice.<sup>7</sup> Most important was the identification of certain types of patients who are at higher risk for severe myopathy. The following conditions were listed as carrying higher myopathy risk that require either avoidance of statins or their use in lower doses: advanced age (especially >80 years) (women more than men), small body frame and frailty, multisystem disease (eg, chronic renal failure, especially if caused by diabetes), perioperative periods, multiple medications (especially gemfibrozil, cyclosporine, azole antifungals, itraconazole and ketoconazole, macrolide antibiotics, erythromycin and clarithromycin, HIV protease inhibitors, the antidepressant nefazodone, and verapamil), consumption of large quantities of grapefruit juice (usually >1 quart per day), and alcohol abuse (which independently predisposes to myopathy). A number of the cited interacting drugs are, in fact, problems when taken with certain statins, and the products are now thoroughly labeled in this regard. Other drugs may be added to this list, so physicians should consult the package inserts of the drugs

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they prescribe. If these guidelines<sup>7</sup> are followed, the risk for severe myopathy accompanying statin therapy should be substantially reduced.

Since the cerivastatin withdrawal, the FDA approved a new statin, rosuvastatin. In Phase III studies, the highest dose, 80 mg, was associated with an unacceptably high number of cases of severe myopathy. For this reason, the FDA informed the manufacturer that the 80-mg dose was not acceptable and further testing at lower doses was required. With the experience of cerivastatin as a guide, and given the need to establish beyond doubt that the risk of myopathy per LDL-lowering effect of rosuvastatin was similar to that of other marketed statins (and not like that of cerivastatin), the FDA required an additional 11 000 patients at doses of 10 to 40 mg. An FDA review of results at these lower doses did not show an excess of severe myopathy as compared with other statins. For this reason, rosuvastatin was approved up to a dose of 40 mg.

In March 2004, Dr Sidney M. Wolfe, Director of the Health Research Group of Public Citizen, filed a petition with the FDA to remove rosuvastatin from the market because of his group's contention that the drug at approved doses carries too high a risk for severe myopathy with kidney failure and other types of kidney damage. In March 2005, the FDA denied this request but only after an exhaustive reexamination of the existing data. The FDA response to Dr Wolfe is a 36-page document that is posted on the FDA Web site.<sup>8</sup> All readers interested in the question of the toxicity profile of rosuvastatin should carefully review this letter before drawing conclusions one way or another. The FDA concluded that "all of the available evidence (including preclinical data, premarketing clinical studies, Phase 4 clinical studies, and postmarketing adverse event reports) indicates that Crestor (rosuvastatin) does not pose a risk of muscle toxicity greater than that of other approved statins. With respect to renal toxicity, there is no convincing evidence that Crestor poses a risk of serious renal injury." The following summarizes the major findings of the FDA in response to Dr Wolfe:

1. Before approval of rosuvastatin, 12 000 patients were treated with 5 to 80 mg. More than 4000 of these patients received the highest marketed dose, 40 mg. Among 11 000 patients treated with 10- to 40-mg doses, only a single case of severe myopathy occurred. This rate is lower than observed in other major trials, such as with the use of simvastatin as in the Heart Protection Study.<sup>9</sup> The premarketing clinical experience with rosuvastatin dwarfs that of any other statin approved to date, and premarketing testing showed no signal for excess myotoxicity at comparable LDL-lowering potency. A summary of the information provided to the FDA from a multinational Phase 2/3 program with rosuvastatin has also been published by Shepherd et al.<sup>10</sup>
2. In postmarketing (Phase 4) studies, only 2 of 17 800 patients treated with 5 to 40 mg rosuvastatin experienced severe myopathy. This rate of 0.01% is in the range observed for other statins. Again, no unique signal for rosuvastatin toxicity was noted.
3. Adverse event reports of severe myopathy are collected by the FDA. During the first 6 months after approval there were 2 cases of severe myopathy reported with rosuvastatin, which was concomitant with an estimated 763 000 prescriptions. This corresponds to a rate of 0.3 per 100 000 prescriptions, which is slightly higher than the 0.06 reported for atorvastatin in the same interval but much less than the 15.2/100 000 observed for cerivastatin 0.8 mg. Although the risk ratio of myopathy per prescription was numerically higher for rosuvastatin than for atorvastatin, the small number of reported cases makes the difference in reporting rates essentially meaningless. Subsequent reports in larger populations suggested a rate of 0.43 per 100 000 prescriptions for rosuvastatin. Because the absolute rates of adverse event reports for all the statins are so low, even if the ratio of rates for rosuvastatin compared with other statins was somewhat higher, the FDA contends that any differences in ratios do not constitute a substantial or clinically significant difference in myopathy risk with rosuvastatin as compared with other statins. The FDA noted several limitations of the Adverse Event Reporting System (AERS) reporting rates when applied to considerations of comparative statin safety. These were:
  - Uncertainties about the actual number of events and the extent of population exposures make reporting rates "soft" numbers and undermine the accuracy of comparisons of reporting rates across different drugs. AERS reporting rates cannot be said to "capture" incident events. Moreover, there is an unknown relationship between prescriptions and numbers of patients treated and duration of treatment.
  - Variation in level of reported detail makes it difficult to conclude causality, yet limited review of the individual cases supplied with adverse event reports indicated that reported cases with rosuvastatin and other statins commonly had conditions that were identified as constituting a high risk for severe myopathy according to the AHA/ACC/NHLBI advisory.<sup>7</sup>
  - With the AERS, there is no control group with similar underlying disease or risks for toxicity.
  - A potential for reporting bias existed because of heightened awareness of rosuvastatin safety concerns due to product labeling, FDA nonapproval of the 80-mg dose of rosuvastatin, and the Wolfe petition and news about it. Furthermore, publicity surrounding the removal of cerivastatin likely increased awareness of statin toxicity.
  - The presence of confounding factors (drugs, risk factors, and intercurrent illness) is poorly reported.
4. The issue of rosuvastatin-associated renal failure was raised by Dr Sidney Wolfe. In response, the FDA distinguished between acute renal failure associated with severe myopathy and the presence of proteinuria, apparently transient or intermittent in most instances, secondary to rosuvastatin therapy. No evidence from either clinical trials or postmarketing reports suggests that rosuvastatin caused acute renal failure independently of severe myopathy. Furthermore, no indication exists that the tubular proteinuria associated with rosuvastatin or other statins leads to renal damage and chronic renal failure. Until and unless further evidence to the contrary is obtained, statin-induced tubular proteinuria is considered by the FDA to be a benign condition. It must be noted that renal disease occurs commonly in populations targeted for statins. Conclusions about causality must be drawn carefully in any patient treated with a statin. In a review of available cases, the FDA found no evidence of a rosuvastatin renal "syndrome."

5. The FDA response indicated that postmarketing studies of rosuvastatin kinetics observed that Asian Americans experience blood levels of the drug twice as high as non-Asians. This higher blood level could predispose to severe myopathy. For this reason, the FDA advises that rosuvastatin be used only in low doses in Asian Americans.

The report of Alsheikh-Ali<sup>11</sup> in the present issue of *Circulation* reexamines adverse event reports obtained by the FDA and provides a different interpretation of their significance. In spite of the limitations of the AERS, the authors nonetheless are concerned by a "trend" toward more cases of severe myopathy compared with other statins and possibly by a greater frequency of proteinuria. By combining all adverse event reports into a composite end point that includes myopathy, renal failure, and proteinuria, they found that rosuvastatin is accompanied by significantly more "adverse events" than are other statins. Several questions can be raised about this study.<sup>11</sup> For example, is it appropriate to employ a composite end point in which severe myopathy is combined with an apparently benign form of proteinuria? Do the limitations of the available adverse event reports justify using them alone for making clinical decisions independently of data obtained under more controlled conditions (ie, premarketing and postmarketing testing in a large number of patients)? Are the apparent differences in frequency of very rare adverse events clinically significant even when they are "statistically" significant? Have the authors raised concerns about rosuvastatin to a level beyond that justified by analysis of available adverse event reports alone? And on the basis of the limitations of the AERS, is it sufficient to conclude that other statins are preferable to rosuvastatin? It is important to point out that in spite of the note of caution, the authors do not call for removal of rosuvastatin from the market.

Perhaps the critical issue raised by Alsheikh-Ali<sup>11</sup> is whether AERS data alone should override other lines of evidence for choosing a statin when absolute rates of adverse event reports for all the statins are very low. The limitations of the AERS are outlined in the FDA letter to Dr Wolfe. Adverse event reports can be useful for identifying signals of drug toxicity. They are much less useful for quantifying relative risk of different drugs of the same class. Particularly problematic is the pooling of different end points, which compounds the limitations of the AERS. On the basis of other kinds of data (premarketing trials and postmarketing surveys), the FDA did not note an alarming signal for rosuvastatin toxicity.

In the present editorial, several points can be made about this dispute. First, rosuvastatin toxicity is far below that of cerivastatin. Second, the absolute rate of severe myopathy is very low with rosuvastatin, just as it is with other statins. Third, when severe myopathy occurs, it often occurs in the setting of conditions that pose a high risk for myopathy. It is likely that severe myopathy could largely be eliminated by adherence to the AHA/ACC/NHLBI advisory.<sup>6</sup> Fourth, the choice of a particular statin and the dose to use should depend on several factors, including the degree of LDL lowering required to achieve the recommended goal, the cost to the payer, and the possibility of drug interaction as indicated by

FDA labeling. Fifth, physicians have the responsibility to know and understand the side effect profile of any drug they use in clinical practice so that choices of particular drugs and their doses can be made such that benefits and risks are appropriately balanced. Sixth, the doses of statins should not exceed those required to achieve current goals of therapy.<sup>1,2</sup> For persons at increased risk for myopathy, consideration can be given to using combinations of cholesterol-lowering drugs at lower doses.<sup>12</sup>

Finally, when cerivastatin was removed from the market, many patients taking other statins discontinued them because of fear of side effects. This is unfortunate because they put themselves at greater risk of heart attack. How then should patients taking statins view the study of Alsheikh-Ali et al<sup>11</sup>? It would first be prudent for anyone who takes a statin to review the FDA's letter to Dr Wolfe<sup>8</sup> before drawing conclusions. This author is impressed with the care and thoroughness of the FDA analysis and with the limitations of AERS reporting discussed in the FDA letter. It also would be appropriate to consult with one's physician before making any decision about changing medication. Informing one's physician of the FDA position on rosuvastatin would seem wise; the physician may not be aware of it. One must keep in mind that statins generally are safe and that they substantially reduce risk for coronary events in higher-risk patients. Nonetheless, statins, like all drugs, can have side effects, and care must be taken in their use in persons with predisposing conditions. Moreover, it seems unwise to use statins outside current cholesterol-management guidelines.<sup>1,2</sup>

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