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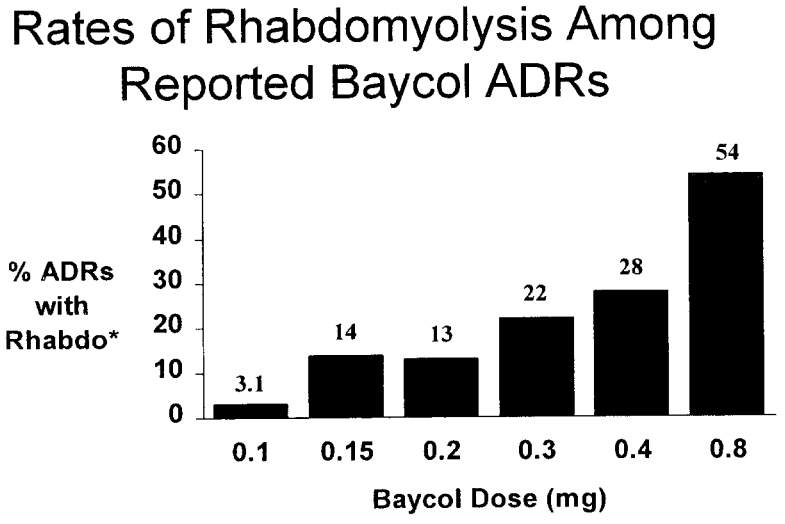
Director, Public Citizen's Health Research Group
FDA Endocrinologic and Metabolic Drugs Advisory Committee Hearing
On Rosuvastatin: July 9, 2003

As can be seen in the table below, most (68.2%) cases of rhabdomyolysis with Baycol did not occur at the 0.8 mg dose and 51.7% occurred at 0.4 mg.

BAYCOL: rhabdomyolysis % of ADRs as a function of dose

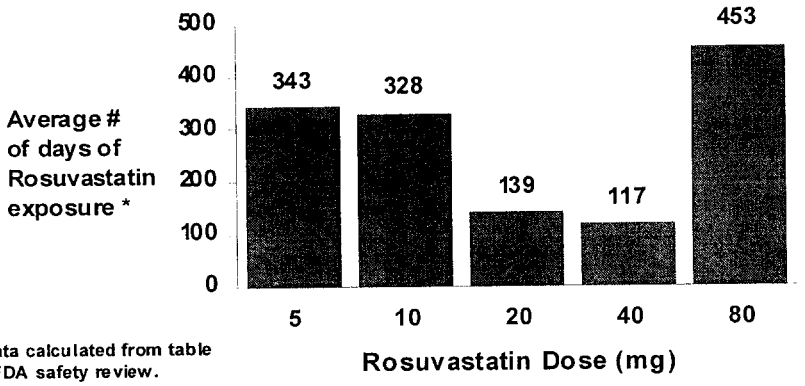
Dose (mg/day)	All Baycol ADRs	Baycol rhabdomyolysis cases	
		Number (% Of all rhabdo cases)	Per cent of all Baycol ADRs that are rhabdo
0.1	64	2 (0.2%)	3.1
0.15	81	11 (1.2%)	14
0.2	120	16 (1.7%)	13
0.3	583	126 (13.4%)	22
0.4	1703	485 (51.7%)	28
0.8	551	298 (31.8%)	54

AERS Data base: 4th quarter 1997 through the 2nd quarter of 2002



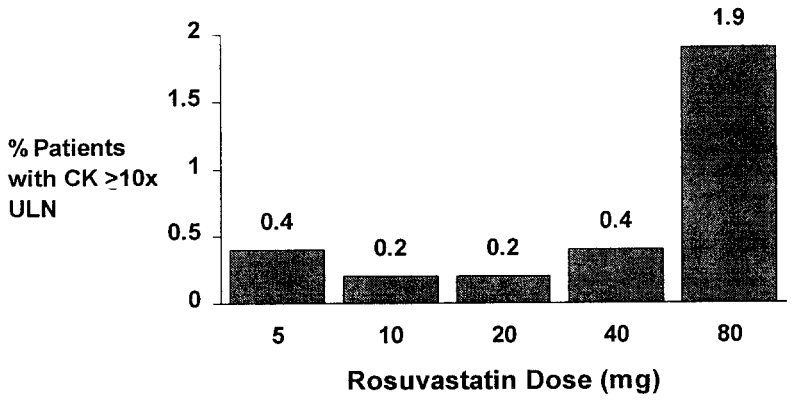
* For each dose, the number of Baycol ADRs listing rhabdomyolysis is divided by all Baycol ADRs reported to FDA from 11/97-6/03

Shorter average Rovustatin exposure at 20 and 40 mg doses than 80 mg



*Data calculated from table 5, FDA safety review. (Average duration of exposure of 80 mg rhabdomyolysis cases was 282 days.)

CK with Variation with Rosuvastatin Dose *



*From table 9, FDA safety presentation

In order to more accurately assess the incidence of CK elevations at each, need to have duration-adjusted data for CK elevations. For example, what was the incidence of CK>10xULN in those patients who had longer exposures to 40 or 20 mg doses. Whereas 56.8% of those getting 80 mg of rosuvastatin were exposed for longer than 48 weeks, only 6.5% of patients getting the 40 mg dose and 8.4% of those getting the 20 mg dose were exposed for more than 48

weeks. This very likely accounts for the seemingly large difference between the 80 mg cases and the 20 or 40 mg dose cases of CK elevation and for the apparent jump in rhabdomyolysis cases in patients getting 80 mg rather than 20 or 40mg. Given that the average duration of rosuvastatin exposure in the 7 patients on 80 mg who got rhabdomyolysis was 282 days, too few of the patients getting 40 or 20 milligrams took the drug long enough to accurately assess this toxicity.

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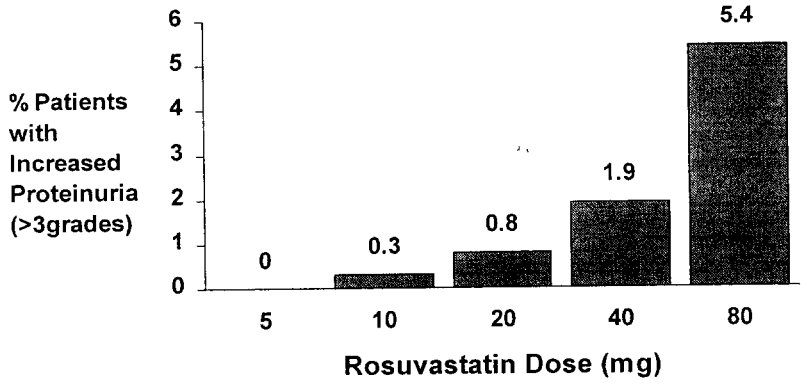
> "RHABDOMYOLYSIS in CLINICAL TRIALS with ROSUVASTATIN
> All 7 cases of rhabdomyolysis at the 80 mg dose occurred during the open-label extension trials. The average length of time on the current drug dose prior to the development of rhabdomyolysis was 282 days (9.4 months) with a standard deviation of 212 days (7 months). The median was 246 days (8.2 months) with a range of 29 to 698 days. Most patients were titrated up to the 80 mg dose so the total time on rosuvastatin at any dose was even greater at 386 days (12.9 months). Clearly these patients were able to tolerate the medication for a long time prior to the adverse event. Most hospitalizations were preceded by a 3 to 28 day prodrome suggesting a viral illness with subsequent dehydration as a possible precipitating event. Typical symptoms included loss in appetite, fatigue, malaise, muscle soreness, muscle weakness, nausea, vomiting, diarrhea and abdominal distension. None of the patients who developed rhabdomyolysis on rosuvastatin had CK elevations noted prior to the actual episode so periodic CK monitoring is unlikely to be of benefit in identifying the patients at risk for rhabdomyolysis."

FDA page 12

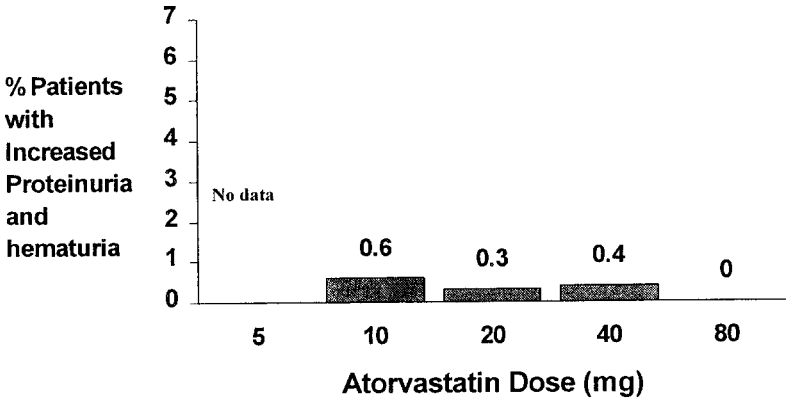
. However, because of the force-titration design of many of the trials, exposures were greatest at 5, 10 and 80 mg with fewer than 200 patients exposed to 20 or 40 mg of rosuvastatin for greater than 24 weeks and fewer than 100 patients exposed to these doses for greater than 48 weeks.

Increased Proteinuria with Increased Rosuvastatin Dose



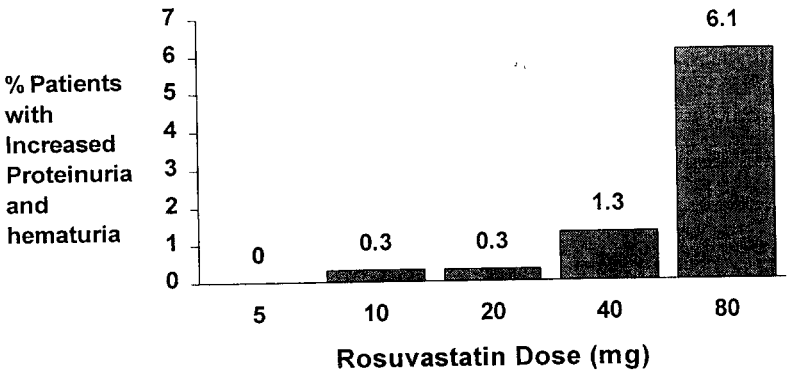
As can be seen in the above figure, taken from data in the FDA safety presentation, for renal toxicity, that can occur much more quickly after the onset of rosuvastatin therapy, there is an orderly dose-dependent increase in proteinuria. This is probably because the shorter average durations of treatment in the 20 and 40 mg dose groups did not impair the drug's ability to cause renal damage as seems to have occurred with CK elevations or rhabdomyolysis.

Proteinuria and Hematuria with Various Atorvastatin Doses



Data from Table 15, FDA presentation

Increased Proteinuria and Hematuria with Increased Rosuvastatin Dose



Data from Table 15,
FDA presentation

From page 34, FDA safety review

"These three cases of renal insufficiency of unknown etiology are of concern because they present with a clinical pattern, which is similar to the renal disease seen with rosuvastatin in these clinical trials. There is mild proteinuria associated with hematuria and the suggestion of tubular inflammation or necrosis. All cases occurred at the 80 mg dose which was also associated with the greatest number of patients with abnormal renal findings in these clinical trials. Proteinuria and hematuria could be potentially managed with regular urinalysis screening. However, if they are the signals for the potential progression to renal failure in a small number of patients, this may represent an unacceptable risk since currently approved statins do not have similar renal effects."

In summary, we strongly oppose the approval of rosuvastatin because of its unique renal toxicity. We are also seriously concerned because of the seven cases of rhabodmyolysis that were common enough to have shown up in clinical trials, unlike the pre-approval studies with all previously approved statins, including cerivastatin. The fact that so few patients on the 20 or 40 mg doses took the drug for a sufficient period of time to have had a chance to develop rhabdomyolysis seems to have imparted a false sense of security about the safety of these doses concerning muscle toxicity. The increased ability of rosuvastatin to lower LDL cholesterol is most clearly seen at the higher (20, 40 and 80mg) doses.