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Clinical Research

October 1, 2004

Jeffrey G. Levine, M.D.
Senior Director, Clinical Research
Merck Research Labs
518 Township Line R
Blue Bell, PA 19422

Re: Issues regarding use of statins in patients with liver disease and possible prospective study

Dear Dr. Levine:

I am writing in order to summarize my thoughts of last Spring regarding the liver safety of lovastatin and, in particular, my recommendation not to perform a prospective study in patients with chronic liver disease. The essence of my thinking, then and now, is that the statins are not significant hepatotoxins and that patients with underlying liver disease are not at increased risk of statin hepatotoxicity. The specific reasons for my opinion and thus recommending not doing the prospective study are the following:

1. **Patients with underlying liver disease are not at increased risk (with very few exceptions) of hepatotoxicity.**

2. **The real life study has already been done.** The underlying incidence of liver disease (primarily fatty liver disease) in patients with hypercholesterolemia is 33% (regardless of whether or not liver enzymes are elevated). The Two Phase IV trials of lovastatin had a combined 14,850 patients meaning that at least 4900 had underlying liver disease. There would actually have been more since one of the studies enrolled patients with diabetes or obesity who have a higher incidence of fatty liver disease. Combining the two studies, 8226 patients received lovastatin and 4622 received placebo. Signals of hepatotoxicity (i.e., 10-fold

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elevation of ALT or increased incidence of 3-fold elevation of ALT or elevated ALT with hyperbilirubinemia) were evaluated in both studies. However, 3-fold elevation of ALT is not a valid tool with statins since cholesterol lowering alone causes elevation of ALT. In these two studies 6 (0.073%) patients receiving lovastatin and 3 (0.065%) patients receiving placebo had 10-fold elevations of ALT but none had evidence of liver disease. Thus there were no signals of hepatotoxicity despite the fact that a large portion had underlying liver disease.

3. **Clinical experience has not revealed a significant incidence of hepatotoxicity.** The 27.5 million patient years (33% or 9.075 million of whom would have had unrecognized liver disease) of experience have not shown an increased incidence of liver failure or hepatitis above the background incidence. In fact, the incidence is less than background suggesting that lovastatin is protective in the target population (We know that atorvastatin is therapeutic in fatty liver disease). Furthermore, it is likely that a large number of these patients had hepatitis C given that the background incidence of hepatitis C is 1.8%. Approximately half of these patients would have had normal or near normal liver enzymes. Thus in all likelihood, approximately 250,000 patients with hepatitis C have already been treated with lovastatin without evidence of significant hepatotoxicity. Furthermore, a recent prospective study by Chalasani, et al (the results of which were known to me at the time we discussed this and now published in Gastroenterology), did not detect a difference in incidence of liver chemistry abnormalities patients with liver disease treated vs not treated with statins. A subsequent study by Chalasani is in press and confirms the original observations of patients treated with lovastatin.

4. **Ethical issues.** There would be significant ethical issues with IRBs in performing a study looking for toxicity when there was no potential benefit to the people being treated. The chairman of our IRB has confirmed that such a study could not be done at our institution. Since patients with chronic liver disease typically have low cholesterol, it would be almost impossible to enroll enough patients with chronic liver disease and hypercholesterolemia, i.e., patients who could potentially benefit.

5. **A prospective study would be impractical because of the number of subjects needed.** If one assumes that 33% of the 27.5 million patient years of treatment occurred in patients with underlying liver disease, i.e., 9.075 million, there would be 22 cases of ALF in 9.075 million years or 0.24/100,000 which is the approximate background rate (or less) of ALF of 1/130,000. In order to prove that this incidence is different would obviously take millions of patients and this is simply not doable. Furthermore, if one were to use cirrhosis as an end point with either NAFLD or hepatitis C, it would take several years to demonstrate a difference given the natural history of these diseases, which is 20 plus year from detection to cirrhosis.

In summary, there is no convincing evidence of an increased incidence of hepatotoxicity with statins and in particular any reason or data to suggest an increased incidence in patients with underlying liver disease. In general, patients with liver disease do not have an increased incidence of hepatotoxicity. Furthermore, a meaningful study to prove this point would require millions of patients and is neither doable nor ethical.

Sincerely,

Keith G. Tolman, MD, FACP, FACCP
Professor of Medicine
Director of Clinical Pharmacology