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Dr. Jeffrey G. Levine
OCT 01 2004
Clinical Research

Dear Dr. Levine,

I am writing to give you my thoughts regarding a prospective study of the safety of Mevacor in patients with chronic liver disease. As you know, I believe that a prospective study capable to assessing the risk to these patients would be an extremely ambitious undertaking, and probably not practically doable. I also believe such an effort is not justified based on the available data that indicate the risk is very low. Below I have highlighted three of the major issues that underlie my opinion:

1). Large sample size required: An appropriately designed prospective study would require a very large population of patients with chronic liver disease because, based on the global experience with Mevacor, we know that the risk to these patients is very low, if it exists at all. This is because a significant proportion of the adult population has asymptomatic chronic liver disease, predominantly Non-alcoholic Fatty Liver Disease (NAFLD) or viral hepatitis B or C. In patients with elevated cholesterol levels (i.e. the target population for Mevacor) the prevalence of NAFLD should be higher relative to the general adult population. A sizable proportion of people with chronic liver disease have, at least intermittently, routine liver chemistries within the established range of normal. Although precise figures are not available, it is my opinion that a conservative estimate of the prevalence among statin treated adults of patients with NAFLD or chronic hepatitis B or C and who also have unremarkable liver chemistries would be in the range of 1%. Hence, even if all patients with abnormal baseline liver chemistries were excluded from Mevacor treatment in the clinical trials and in clinical practice, it follows that more than one hundred thousand adults with chronic liver disease have been already been treated with Mevacor (given the estimated 27 million patient years of use). Moreover, since adherence to monitoring guidelines is known to be imperfect, and some patients with known abnormalities in liver chemistries are treated with statins *, it is reasonable to assume that many thousands of patients with chronic liver disease and abnormal liver chemistries have also received prolonged treatment with Mevacor. Spontaneous reports of severe liver related events, such as hepatocellular jaundice or liver failure, associated with Mevacor use have been rare and there has been no suggestion of an increased incidence in patients with chronic liver disease. Hence, I conclude that the risk of severe liver injury due to Mevacor in patients with chronic liver disease must be very low.

For arguments sake, a 1:1,000 incidence of a treatment related event would require a sample size of 3,000 (the rule of 3's) with an equal number of controls (patients with chronic liver disease but not receiving Mevacor). Thirty thousand patients in each arm would be required to appropriately power a study to detect a 1:10,000 event.

2). Prolonged treatment required: Elevations in liver chemistries would not be a suitable endpoint for a prospective study because these do not correlate well with significant liver injury with Mevacor or other statins. In addition, a recent retrospective study of patients with abnormal baseline liver chemistries was unable to detect a difference in incidence of liver chemistry abnormalities in those treated with statins vs. untreated patients. * Endpoints of hepatocellular jaundice or liver failure would require a very large sample size as discussed above. Some might argue that the most appropriate endpoint should be a Mevacor associated increase in the rate of progression of underlying chronic liver disease to clinically evident cirrhosis. However, given the very slow progression of NAFLD and chronic viral hepatitis, and the fact that such an effect has not been previously observed or suggested, the treatment duration would probably need to be very long (i.e. greater than 10 years) to detect such an effect. It would also be important in such a study to randomize the subjects to treatment vs. non-treatment based on baseline liver functional status. Unfortunately, reliable noninvasive means of assessing liver function do not exist for noncirrhotic patients, and a baseline liver biopsy would not be justifiable.

3). Potential ethical issues involved: I believe many IRBs would question the ethics of administering a drug when the end point is toxicity, unless the subjects were also clearly benefiting from therapy. Likewise, I believe IRBs would frown on denying a statin to patients in whom statins would be beneficial. The target population would therefore be people with chronic liver disease and whose LDL cholesterol was within a range considered "treatment optional". These restrictions would narrow the eligible subset of potential subjects, and might well change over the course of the study, making recruitment and retainment of large numbers difficult.

In summary, it is clear that the risk posed by Mevacor treatment in patients with chronic liver disease is very low, if a risk exists at all. Designing a meaningful prospective study to quantitate this theoretical risk would be extremely challenging due to multiple factors, including the very large sample size and treatment duration required, the inability to accurately assess baseline liver function, and the restrictions in eligibility criteria that would be necessary to address potential ethical concerns. To my knowledge, no comparable study has ever been attempted and it is my opinion that it is probably not doable. More importantly, I believe the enormous effort required by such a study is not justified since the available data indicate that the risk is very low or non-existent.

Sincerely,

Paul B. Watkins, M.D.
Verne S. Caviness Distinguished Professor of Medicine
Professor of Pharmacotherapy
Director

* "Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity". Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD Gastroenterology. 2004 May; 126(5):1287-92 .This study did not involve patients treated with Mevacor (not on the formulary

of the participating programs). However, Dr. Chalasani has recently performed a similar analysis in patients receiving Mevacor and also found no evidence of toxicity in patients with elevated baseline liver chemistries (personal communication, manuscript in press).