Incidence of Statin Hepatotoxicity in Patients With Hepatitis C

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Background & Aims: Statins are considered contraindicated in patients with chronic liver disease. Our objective was to determine the risk of developing hepatotoxicity from statin therapy in hyperlipidemic patients with hepatitis C. *Methods:* Changes in liver biochemistry values within 12 months compared with baseline were determined in 3 cohorts matched for age, sex, and body mass index: (I) 166 anti–hepatitis C virus (HCV)-positive hyperlipidemic veterans who were initiated on statin therapy; (II) 332 anti–HCV-positive veterans who had not received statin therapy; and (III) 332 anti–HCV-negative hyperlipidemic veterans who were initiated on statin therapy. An increase in liver biochemistry values was defined as mild-moderate or severe as proposed in a previous study on statin hepatotoxicity in a non–hepatitis C population. *Results:* In patients with hepatitis C, statin therapy (cohort I) was associated with a higher incidence of mild-moderate liver biochemistry value increases compared with those not on statin therapy (cohort II) (22.9% vs 13.3%, respectively, $P = .009$), but a lower incidence of severe increases (1.2% vs 6.6%, respectively, $P = .015$). Among patients started on statin therapy (cohorts I and III), the incidence of mild-moderate liver biochemistry value increases (22.9% vs 16.3%, respectively, $P = .094$), severe increases (1.2% vs 1%, respectively, $P = .874$), or discontinuation of statin therapy as a result of hepatotoxicity (21.6% vs 9.2%, respectively, $P = .147$) were similar in hepatitis C–positive and hepatitis C–negative patients. *Conclusions:* Statin therapy was not associated with a higher risk of severe hepatotoxicity in patients with chronic hepatitis C and appeared safe.

Drug-induced hepatotoxicity is a well-recognized adverse reaction, and the proportion of cases of hepatic disease known to be drug related continues to increase.[1–3] In the United States, these occurrences account for more than 50% of the cases of acute liver failure.[4,5] The mechanism of action of drug-induced hepatic disease is either a result of the drug itself or a result of reactive metabolites of the drug that covalently bind to hepatocytes and result in either idiosyncratic (unpredictable), intrinsic (predictable), or immunoallergic hepatitis.[1,5,6] Most hepatotoxic drug reactions are idiosyncratic and are neither dose-dependent nor predictable.[5] Recently, genetic variations in systems of biotransformation or detoxification also were reported to contribute to drug hepatotoxicity.[6]

One of the most commonly prescribed class of medications is statins, the drugs of choice for low-density lipoprotein–lowering treatment in patients at risk for cardiovascular disease.[7] Although statins generally are well tolerated, they have been reported to lead to increases in transaminase level (.2%–2.7% of patients) and, rarely, symptomatic liver disease including fatal acute liver failure.[8,9] Liver enzyme level increases typically occur within the first 3–12 months after initiation of therapy, are asymptomatic, and are more prevalent with higher doses. Because of these reports, experts and manufacturers recommend routine monitoring of liver function test (LFT) values in patients receiving chronic statin therapy, and advise against statin therapy in patients with active or chronic liver disease.[7,10,11] These recommendations have been challenged recently because of a paucity of data supporting an increased risk of liver enzyme level abnormalities in the low-risk general population. In a recent meta-analysis, De Denus et al[8] found that pravastatin, lovastatin, and simvastatin at low-to-moderate doses were not associated with an increased risk of liver enzyme level abnormalities compared with placebo. Because of these findings, the latest clinical guidelines on the management of dyslipidemia in patients with type 2 diabetes mellitus did not recommend routine monitoring of liver function unless baseline LFTs were abnormal.[12]

The management is less clear for those with abnormal baseline liver enzyme levels or chronic liver diseases. When compared with controls with normal baseline liver

Abbreviations used in this paper: ALT, alanine transaminase; anti-HCV, antibody to hepatitis C virus; AST, aspartate transaminase; HCV, hepatitis C virus; LFT, liver function test; VA, Veterans Affairs.

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enzyme levels, patients with presumed nonalcoholic fatty liver disease and increased baseline liver enzyme levels did not have a higher incidence of severe increases in liver biochemistry values within the first 6 months after initiation of a statin.[13,14] However, the study excluded patients with chronic hepatitis C in whom the risk of hepatotoxicity largely is unknown. Currently in clinical practice, primary care physicians often are reluctant to prescribe statins to treat hyperlipidemic patients with chronic hepatitis C owing to concerns of hepatotoxicity. The objective of this study was to determine in patients with hepatitis C whether statin therapy increases the risk for developing hepatotoxicity when compared with hepatitis C–negative patients on statin therapy and with hepatitis C–positive patients not on statin therapy.

Materials and Methods

Study Design

This study was approved by the Institutional Review Board of Stanford University. All patients were veterans receiving care from the Veterans Affairs (VA) Palo Alto Health Care System, which is a multicampus tertiary referral teaching hospital affiliated with Stanford University. The VA Palo Alto Health Care System consists of 3 major divisions and multiple outpatient clinics in northern California. The hospital uses an elaborate electronic medical record system that includes clinic visit notes, diagnostic codes of the clinic encounter, all prescriptions, and laboratory data in a searchable form. Potential study patients were identified initially using the VA pharmacy and laboratory database. Three cohorts of patients, 1 case study group (cohort I) and 2 control groups (cohorts II and III), were identified retrospectively. Cohort I included all patients who tested positive for antibody to hepatitis C virus (anti-HCV) by third generation enzyme immunoassay (EIA III; Abbott Laboratories, Abbott Park, IL) between October 1, 2002 and September 30, 2003 and were started on a statin after the diagnosis of HCV. Cohort II consisted of a matched sample of anti-HCV–positive patients tested between October 1, 2002 and September 30, 2003 who had not received statin therapy. Cohort III included a matched sample of anti-HCV–negative patients who started statin therapy between October 1, 2002 and September 30, 2003. Patients from cohorts II and III were matched to those in cohort I based on age, sex, and body mass index. In cohorts I and III, patients who did not have LFTs within 1 year before and after initiation of the statin therapy were excluded. Similarly, patients in cohort II who did not have LFTs within 1 year before and after HCV diagnosis were excluded.

Data Collection

By using the hospital computer database, pertinent demographic data such as age, sex, height, weight, and ethnicity were collected. In addition, data on laboratory values (eg, LFTs and lipid panel), name of statin prescribed, and medication fill dates also were collected. Information regarding an active alcohol problem was obtained from patients' administrative files. An active alcohol problem was defined in this study as the inclusion of an alcohol-related diagnosis (International Classification of Diseases Version 9 codes 571.1, 303, 303.01, 303.02, 303.9, 303.91, 303.92, 305, 305.01, and 305.02) in any clinic or hospital encounter during the study period. Concomitant use of potentially hepatotoxic medications within the study period was determined from pharmacy and medical records. The LFTs consisted of aspartate transaminase (AST), alanine transaminase (ALT), and serum bilirubin values. For the purpose of this study, baseline values were defined as LFTs obtained within 1 year before the initiation of a statin (cohorts I and III) or the date of hepatitis C diagnosis (cohort II). The LFTs obtained within 1 year after the initiation of the statin in cohorts I and III were used to determine the hepatotoxic effect of the statin. In cohort II, LFTs within 1 year after HCV diagnosis were used to determine the fluctuation of liver enzyme levels over time. Statin therapy was considered as discontinued when the medication status was changed from active to discontinued in the prescription database. This was confirmed further by reviewing physician progress notes to include only those in whom the statin was discontinued owing to LFT increases.

Definition of Hepatotoxicity

The normal ranges in our laboratory were 0–45 U/L for ALT and 0–41 U/L for AST. Values above the upper limit of normal (ie, ALT $>$ 45 U/L, AST $>$ 41 U/L) were considered abnormal. For ease of comparison with published data, hepatotoxicity was defined in the same way as proposed by Chalasani et al.[13] The severity of increase was defined according to the degree of abnormality of the follow-up LFTs as compared with the baseline values. Mild-moderate increases were defined as an AST or ALT increase up to 10 times the upper limit of normal (for those with normal baseline values), or from the baseline level if patients had increased transaminase values at study entry. Severe increases were defined as serum bilirubin value greater than 3 mg/dL (regardless of AST or ALT values) or an increase in the AST or ALT value of more than 10 times the upper limit of normal (or of baseline level if patients had increased baseline transaminase values). For patients who had multiple LFTs performed within the study period, the highest value was used for comparison.

Statistical Analysis

For the data that was not distributed normally, results are presented as medians and 25th to 75th percentiles. Nonparametric statistic tests were used where applicable. Patient demographic data were analyzed using the Mann–Whitney rank-sum test for interval data and the χ^2 test with Yates correction for nominal data comparisons between the case and each control group. To compare the change in liver enzyme values between the groups, the Mann–Whitney rank-sum test was used. The χ^2 test with Yates correction was used to compare the percentage of patients with increases in liver

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