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CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Alcohol Use and Treatment of Hepatitis C Virus: Results of a National Multicenter Study

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Background & Aims: **Patients with hepatitis C virus (HCV) infection who use alcohol have been excluded from clinical trials; therefore, outcomes with antiviral therapy are unknown. The aim of the study was to determine the impact of alcohol use on HCV treatment outcomes.** ***Methods:*** **Subjects using alcohol were categorized as follows: no alcohol versus regular alcohol use, quantity consumed (none, <6 drinks/day, ≥6 drinks/day), CAGE score <2 or ≥2, and recent alcohol use (past 12 months). Patients were treated with interferon plus ribavirin.** ***Results:*** **A total of 4061 subjects were enrolled, and 726 (18%) received treatment. Alcohol use (past and within 12 months) reduced treatment candidacy. Past alcohol use did not affect the end-of-treatment response, sustained virologic response (SVR), and treatment discontinuation rates. However, recent alcohol use resulted in higher treatment discontinuation (40% vs 26%; *P* = .0002) and tended to reduce the SVR (14% vs 20%; *P* = .06), but when patients who discontinued treatment were excluded from analysis, the trend in favor of nondrinkers for SVR disappeared (25% vs 23%). These findings were also consistent in subgroup analyses on race and genotype.** ***Conclusions:*** **Eligibility for anti-HCV treatment was reduced in past and recent drinkers. Recent alcohol use was associated with increased treatment discontinuation and lower SVR. However, patients who use alcohol and completed the treatment had a response comparable to that of nondrinkers. Patients with a history of alcohol use should not be excluded from HCV therapy. Instead, additional support should be provided to these patients to ensure their ability to complete treatment.**

Chronic hepatitis C is a common cause of end-stage liver disease, cirrhosis, and hepatocellular carcinoma and is the leading indication for liver transplantation.[1] Left untreated, significant costs related to hepatitis C virus (HCV) infection in both direct medical care and indirect losses are projected.[2,3] At the same time, antiviral therapy continues to improve, with sustained virologic response (SVR) rates nearing 60% in randomized controlled trials.[4,5] However, as recent studies make clear, response to therapy in clinical populations is well below that seen in controlled trials.[6–8] This is likely due to several factors, including patients not fully engaging in care; the impact of comorbid psychiatric, substance use, and medical problems; and difficulties in adhering to complicated treatment regimens.[7,9] Substance use disorders, particularly alcohol use, are a common reason for excluding patients from antiviral therapy. Typically, clinicians require complete abstinence from alcohol for at least 6 months before initiating antiviral treatment. However, few data exist in patients with hepatitis C regarding the impact of alcohol use on adherence to antiviral therapy or its influence on treatment outcomes.

Alcohol abuse and HCV frequently coexist in the same patient. HCV infection is detected in 16% to more than 40% of alcoholic patients with or without liver disease.[10–13] Several studies have shown increased histologic liver damage in chronic alcoholic patients with HCV infection, in the form of higher rate of fibrosis progression and development of cirrhosis compared with HCV infection in nondrinking subjects.[14–19] However, the

Abbreviations used in this paper: CI, confidence interval; ETR, end-of-treatment response; OR, odds ratio; SVR, sustained virologic response.

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effect of any amount of alcohol use on antiviral treatment outcomes is much less clear. Several studies suggest that cumulative lifetime alcohol use worsens antiviral treatment outcomes.[20–23] In one of these studies, Ohnishi et al suggested that prolonged abstinence from alcohol improves interferon treatment outcomes.[20] In an Italian study, Loguercio et al showed that the SVR decreased as alcohol use increased.[24] These studies have several limitations, including small sample size, retrospective data analysis, and inclusion of patients treated with interferon monotherapy. None of these studies assessed the effect of alcohol use on treatment compliance and treatment outcomes with interferon and ribavirin combination therapy. The present study was performed to determine prospectively the effect of various levels of alcohol intake on treatment outcomes in patients with HCV infection.

Materials and Methods

This was a multicenter study to evaluate the epidemiology, natural history, and treatment response in unselected patients with HCV infection. The criteria for patient enrollment in the screening phase included a positive antibody to HCV serologic test and patient consent. The study was approved by the institutional review boards at each participating site.

Screening Phase

At enrollment, the patients were screened to determine whether or not they were suitable candidates for treatment with interferon and ribavirin. Additionally, patient counseling on HCV disease and risk factor assessments were performed. The inclusion criteria for treatment were male or female patients 18 years of age or older, a positive HCV RNA level by qualitative or quantitative polymerase chain reaction, and no previous HCV treatment with interferon and ribavirin combination therapy. The treatment exclusion criteria included patients with active hepatitis B virus infection and other forms of liver disease such as hemochromatosis, Wilson's disease, and α_1-antitrypsin deficiency; hemoglobinopathies; evidence of advanced liver disease or hepatocellular carcinoma; preexisting uncontrolled severe depression or other psychiatric diseases; evidence of ischemia or significant cardiac disease; or other comorbidities such as renal disease.

All patients were counseled to stop drinking and were provided with detailed counseling about the risks associated with continued use of drugs and alcohol and the factors associated with virus transmission. Patients with ongoing substance or alcohol use and those who declined to quit their substance use were not considered for treatment. Practitioners, in conjunction with patients, discussed treatment candidacy eligibility based on the risk factors, laboratory results, and standardized treatment inclusion and exclusion criteria. Patients who were determined to be treatment candidates and agreed to proceed with the recommended therapy entered the treatment phase of the protocol. In patients not selected for therapy, the caregivers were required to state why a patient was not considered a treatment candidate.

Alcohol Questionnaire

The patients completed a questionnaire on alcohol use during the screening phase of the study (see Appendix). Information collected included the type of alcoholic beverage usually used (beer, wine, mixed drinks), the highest number of drinks consumed on a regular basis, the total duration of alcohol use, and the number of drinks usually consumed during the past 12 months. In addition, the CAGE score was determined for each patient. The CAGE score is a validated screening instrument designed to assess alcohol dependence or abuse.[25] The total CAGE score ranges from 0 to 4, based on responses to the following 4 questions: have you ever felt you should cut down your drinking, have people ever annoyed you by criticizing your drinking, have you ever felt bad or guilty about your drinking, and have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (an eye opener).

Categorization of Alcohol Use

Alcohol use was categorized in 4 different ways. In category 1, the patients were divided into nondrinkers and drinkers. Nondrinkers included patients who either did not drink at all or drank only occasionally, whereas drinkers included patients who consumed alcohol on a regular basis, which was defined as at least one drink a day. In category 2, the patients were divided into 3 subgroups: nondrinkers (as defined previously), moderate drinkers ($<$6 drinks a day), and heavy drinkers ($\geq$6 drinks/day). In category 3, the patients were divided into 2 groups based on the CAGE score (CAGE score $<$2 or $\geq$2). In category 4, the patients were divided into 2 groups based on current alcohol use patterns (active drinking within the past 12 months and not actively drinking). Thus, categories 1, 2, and 3 were based on the alcohol use patterns of patients in the past (beyond 1 year), while category 4 assessed drinking status within the past 12 months at the time of baseline enrollment. All patients who were actively drinking were advised to stop alcohol use, and those who agreed were considered for therapy.

Treatment Phase

Patients selected for treatment were started on interferon alfa 2b 3 million units 3 times a day and ribavirin 1000–1200 mg/day (1000 mg for weight $\leq$75 kg and 1200 mg for weight $\geq$75 kg) for 24 weeks (genotypes 2 and 3) and 48 weeks (all other genotypes). Patients were assessed for efficacy and safety of treatment by regular follow-up visits scheduled at week 1–2 and every 4 weeks after initiation of therapy. At each follow-up visit, the patients were questioned about drug-related adverse effects, and blood tests were performed for hematologic and biochemical assessment. The study coordinator was required to fill out a form indicating compliance with therapy at weeks 12,