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The Impact of Lifetime Alcohol Use on Hepatitis C Treatment Outcomes in Privately Insured Members of an Integrated Health Care Plan

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Treatment of chronic hepatitis C infection (HCV^+) has historically been shown to be less effective in patients with a heavy drinking history. The effect of moderate and heavy alcohol use on treatment with pegylated interferon-alpha and ribavirin (P/R) in an insured household population has not been previously reported. We investigated the effect of alcohol on treatment outcome in a cohort of 421 treatment-naïve HCV^+ patients, members of an integrated health care plan treated with P/R between January 2002 and June 2008. A detailed drinking history was obtained for 259 (61.5%) eligible patients. Regular drinking was reported by 93.1% of patients before HCV diagnosis, by 30.9% between HCV diagnosis and treatment, by 1.9% during treatment, and 11.6% after the end of treatment. Heavy drinking patterns were reported by 67.9%, 63.5% of patients drank more than 100 kg of ethanol before initiating HCV treatment, and 29.3% reported abstaining less than the required 6 months before treatment. Despite these reports of heavy drinking, sustained virological responses (SVRs) were obtained in 80.2% of patients with HCV genotypes 2 or 3 and 45.1% of patients with genotypes 1, 4, or 6. Pretreatment drinking patterns and total alcohol intake were both unrelated to SVR rates. Abstaining less than 6 months before treatment was related to lower SVR rates in moderate, but not heavy, drinkers. HCV treatment relapse was unrelated to drinking after treatment ended. *Conclusion:* The amount of alcohol consumed before HCV treatment did not have a negative effect on treatment outcomes in our population. A history of heavy drinking should not be considered a deterrent to HCV treatment in members of an integrated health care plan who are closely monitored. (HEPATOLOGY 2012;56:1223-1230)

Hepatitis C virus (HCV) is the most common blood-borne infection in the United States. Based on national seroprevalence data, it is estimated that over 3 million of the noninstitutionalized U.S. population are chronically infected with HCV.[1] HCV incidence rates were at their highest from 1970 to 1990, creating a cohort of chronically infected individuals that threaten to produce an epidemic of HCV-related disease.[2] A multiple cohort model has been developed to predict the effect of chronic hepatitis C infection (HCV^+) on public health.[3] The model takes into consideration known differences in disease progression related to sex and age at infection. It predicts that 24.8% of the cohort infected between 1970 and 1990 will have cirrhosis by 2010, and 44.9% will progress to cirrhosis by 2030. Eleven percent of the cohort with cirrhosis currently have hepatic decompensation, and this proportion will increase through 2030. The incidence of HCV-related hepatocellular carcinoma (HCC) is increasing and is forecast to peak in 2019.[3] The effect of these projections is already becoming evident. HCV-related ambulatory care visits more than doubled between 1997-1999 and 2003-2005.[4] Complications related to HCV

Abbreviations: ALT, serum alanine aminotransferase; AST, serum aspartate aminotransferase; CD, chemical dependency; CLDH, Cognitive Lifetime Drinking History; ETR, end-of-treatment response; GI, gastroenterology; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HCV^+, chronic hepatitis c infection; LEC, Lifetime Event Calendar; NIAAA, National Institute on Alcohol Abuse and Alcoholism; P/R, pegylated interferon alpha and ribavirin; SVR, sustained virological response.

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are already the leading cause for liver transplants, and this demand is expected to increase, exacerbating the current shortage of available organs.[5] The incidence of HCC, much of which is caused by HCV, tripled between 1975 and 2005,[6] and HCV-related mortality increased 123% between 1995 and 2004.[7]

Treatment has the potential to greatly reduce the public health effect of this epidemic. In 2010, it was estimated that based on current treatment practices (i.e., chronic hepatitis C infection [HCV^+] was diagnosed in 30% of cases; 25% were treated and 40% responded to treatment), only 1% of cirrhosis cases would be prevented.[3] Since then, more effective antiviral therapies have been approved, but more patients need to be diagnosed and treated to fully realize the potential of HCV treatment to reduce HCV-related disease. In this article, we focus on barriers to treatment, specifically findings that patients with a history of alcohol abuse are less likely to be treated,[8] and that patients who reported any drinking in the 12 months before treatment were less likely to respond to treatment.[9] The issue of how to manage HCV in patients with a history of moderate to heavy drinking is a critical one because many patients with HCV have such a history. A national seroprevalence survey found that 48% of HCV^+ participants had had five or more drinks in a single day during the previous year, and 33% had done so on at least 50 days.[1]

This study extends previous research in three ways. One, it was conducted in a representative cohort of privately insured members of an integrated health care plan. HCV treatment outcomes have been understudied in insured patients, despite the fact that they represent a large portion of the infected population, and they are likely to have access to resources needed to obtain treatment. Two, it contributes to the limited information available on the relation of alcohol consumption to outcomes of treatment with pegylated interferon-alpha and ribavirin (P/R). Three, and most significant, it is based on an in-depth assessment of lifetime drinking patterns as they relate to the length of abstinence before initiation of antiviral therapy and four critical periods: (1) before HCV diagnosis; (2) from HCV diagnosis to initiation of antiviral therapy; (3) during HCV treatment; and (4) the 6-month period after the end of treatment. Specific aims were to (1) determine the effect of alcohol intake before HCV treatment on treatment completion and outcomes, (2) investigate the relation of pretreatment abstinence to treatment outcomes, particularly in moderate drinkers, and (3) examine the association between drinking after treatment and sustained virological response (SVR) in patients who obtained an end-of-treatment response (ETR).

Patients and Methods

Patients were members of an integrated health care system in Northern California with HCV^+, naïve to previous treatment with interferon-based antiviral therapy, who initiated treatment with P/R between January 2002 and June 2008. HCV treatment was headed by an HCV registered nurse and a hepatologist with backup from all subspecialties, including psychiatry, chemical dependency (CD), and internal medicine. Policy was to require a 6-month period of abstinence preceding treatment, and all patients referred for treatment were screened for alcohol and drug abuse. Those with active substance abuse were referred to the Chemical Dependency Recovery Program for rehabilitation and clearance before treatment.

Procedures. Patients were identified by searching electronic pharmacy records between January 2002 and June 2008 for initial ribavirin prescriptions. Their primary care physicians were sent a description of the study and were asked whether any of the identified patients should be excluded because they were too ill, did not speak English, were cognitively impaired, or otherwise thought to be ineligible. Eligible patients were sent a letter inviting them to participate in the study. It explained the aim of the study, its requirements (i.e., a 90-minute interview covering sensitive material, including questions on alcohol and drug use, and extraction of data from patients' electronic and paper medical records), its voluntary nature, and the complete confidentiality of all information provided. Participants were offered a subject fee of $75 to compensate them for their time and travel expenses. A telephone number was provided to schedule an interview appointment or to request removal from the list of eligible participants. Patients were given time to respond and were then telephoned by our project manager who offered to answer any questions patients had about the study and to schedule an interview appointment. Before the interview, patients were sent a Lifetime Event Calendar (LEC) and were asked to use it to record ages at which significant events occurred in their lives and bring it to the interview. The interview site was miles from their HCV treatment site. The interviewer obtained a signed informed consent and reviewed the LEC before administering the interview. This study was approved by institutional review boards at the Kaiser Permanente Sacramento Health Care Center (Sacramento, CA) and the Pacific Institute for Research and Evaluation (Berkeley, CA).

Sample. Of 2,315 patients with HCV^+, 608 (27.2%) initiated treatment with P/R from January 2002 to June 2008, and 421 were eligible for the present study. Reasons for exclusion included the following: not treatment naïve (n = 62); no longer members of the health care plan (n = 61); died (n = 35); post-transplant (n = 20); coinfected with HBV or human immunodeficiency virus (n = 4); primary care physicians' recommendation (n = 3); not English-speaking (n = 1), or too ill (n = 1). Data for 3 additional patients were lost as the result of a computer failure; 95 (22.6%) refused, and we were unable to contact 67 (15.9%). Interviews were completed with 259 (61.5%) of the eligible patients.

Interview. Lifetime drinking patterns were assessed retrospectively using a computer-assessed personal interview with good test-retest reliability, the Cognitive Lifetime Drinking History (CLDH) developed by Russell et al.,[10] to improve recall in studies relating alcohol consumption to chronic disease. The CLDH was administered to patients who had at least 12 drinks during a 12-month period and reported drinking regularly at some point in their lifetimes (e.g., at least one drink per month for 6 months). Patients were encouraged to use the LEC during the interview to help them recall their activities during different periods of their life and whether drinking was associated with these activities. Recall was also stimulated by letting patients use a comprehensive list of alcoholic beverages to identify all the different types they had drunk. We used models of beverage containers to help patients define their usual drink size for each beverage. Computer programming enabled the interview to be tailored to each respondent's drinking history, so that only relevant questions were asked (e.g., patients who only drink beer were not asked about wine and liquor). Questions on usual drink size spare patients the mental arithmetic required to translate their consumption into arbitrarily defined standard drink sizes, and the potential embarrassment of admitting their usual drink size is much bigger than the standard.

Intervals of life during which drinking patterns were either relatively homogeneous, or respondents did not drink regularly, were defined by asking patients when they began to drink regularly, when their drinking changed, whether they continued to drink regularly after it changed, and, if not, whether they ever started drinking regularly again. Drinking patterns were assessed for each of the defined intervals. For intervals during which respondents drank weekly or more often, patterns were assessed by asking how often respondents drank on Fridays during a typical month during the interval and how many drinks they usually had when they drank on a Friday during that interval. These quantity-frequency questions were repeated for Saturdays, Sundays, weekdays, and days when patients drank more than usual. For intervals during which respondents drank less often than weekly, they were simply asked about usual drinking quantity and frequency. Also assessed for each interval were the proportion of drinks represented by beverage types consumed during the period, liquor, beer (as lite/regular/malt liquor, etc.), and wines (fortified versus table wines).

The CLDH was expanded for this study to assess drinking patterns during four critical periods related to HCV diagnosis and treatment: (1) before HCV diagnosis; (2) from diagnosis to HCV treatment; (3) during HCV treatment; and (4) from end of treatment to 6-month follow-up SVR test.

Alcohol Measures. Data from the CLDH were used to generate estimates of total volumes of ethanol consumed (in kg) for three periods: (1) before HCV diagnosis; (2) from diagnosis to treatment; and (3) the sum of 1 and 2, which yielded ethanol consumed before HCV treatment. Total volumes of ethanol were divided by 14 g to calculate total numbers of standard drinks, which were divided by number of drinking days to estimate drinking intensity (i.e., drinks per drinking day) for these three periods. Total drinks were also divided by week and used together with drinks per drinking day to classify patients as heavy or less than heavy drinkers according to National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria, where heavy drinking is the consumption of more than three drinks on any day or more than seven per week for women and more than four drinks on any day or more than 14 per week for men.[11] Duration of abstention before HCV treatment was calculated by subtracting age at last drink before treatment from age at treatment initiation. Drinking during HCV treatment and during the 6 months after treatment is characterized as present or absent.

Information on CD diagnosis was extracted from an electronic database for Outpatient Services Clinical Records dating back to 2000. Primary care physicians and specialists complete an outpatient services clinical record on which they check off patients' current and ongoing medical problems, including alcohol and drug abuse, every time they see a patient. Date and type of visit to the health care plan's Chemical Dependency Recovery Program have been recorded electronically since 2000. Patients having a record of at least one group visit were considered to have a recent history of CD treatment.

HCV Treatment Measures. Information on HCV treatment was extracted from the electronic medical records and medical records kept by the gastroenterology (GI) department. Treatment records were kept by a single nurse who recorded all HCV-related laboratory and pathology findings; she completed a flow sheet summarizing adverse reactions and changes in interferon and ribavirin dose for each patient at each visit to the GI department. Visits were scheduled at weeks 1-2 and at least every 4 weeks thereafter. Study measures extracted from these records included genotype (2 and 3 versus 1, 4, and 6), pretreatment viral load (<600,000 versus >600,000 IU/mL), and Metavir stage 3 or 4 (advanced fibrosis) versus stages 0-2 (not advanced). Stage was determined by histology, but in the absence of a liver biopsy, patients were also considered to have advanced fibrosis if they had a platelet count <110,000, serum aspartate aminotransferase (AST)>ALT (serum alanine aminotransferase), and splenomegaly. Records contained data on all premature treatment discontinuations, including date and reason (i.e., adverse reactions to treatment or noncompliance). Treatment that was appropriately stopped because of early nonresponse was coded as failure to obtain an SVR, not treatment discontinuation. Also extracted were data on ETR and SVR.

Statistical Analyses. Relations of known host and viral risk factors and pretreatment patterns of alcohol intake to SVR were examined using chi-square statistics for cross-tabulations. Cross-tabulation analyses were also conducted to detect potentially confounding relationships between host and viral risk factors and patterns of alcohol intake. Multiple logistic regression analyses were used to determine the independent contributions of host, viral, and alcohol risk factors to SVR failure.

Results

Analyses for Bias. Comparison of eligible patients who were and were not interviewed revealed that interviewed patients tended to have somewhat higher SVR rates (60.6% versus 55.4%; $P = 0.304$) and were somewhat more likely to have a chemical dependency diagnosis mentioned in their medical record (30.9% versus 26.6%; $P = 0.357$), or a record of recent treatment for chemical dependency (7.7% versus 4.5%; $P = 0.207$), but none of these differences were statistically significant.

Cohort host, viral, and alcohol-related risk factors are characterized in Table 1 as they relate to SVR. Age and sex were not significantly related to SVR. SVR rates were significantly lower in patients with the following risk factors: a racial/ethnic background other than white non-Hispanic, pretreatment viral load ≥600,000 IU, HCV genotypes 1, 4, or 6, advanced fibrosis, or treatment discontinuation. However, no significant effect on SVR rates was associated with moderate or heavy drinking or with failure to abstain 6 months before treatment.

Analyses investigating relations between host and viral risk factors and pretreatment alcohol measures are

Table 1. Host, Viral, and Alcohol-Related Risk Factors According to HCV Treatment Outcome (SVR)

Risk Factor	N (%)	SVR (%)	*P* Value
Age, years			
<50	116 (45.1)	60.3	0.916
≥50	141 (54.9)	61.0	
Sex			
Male	154 (59.5)	59.7	0.726
Female	105 (40.5)	61.9	
Race/ethnicity			
White non-Hispanic	207 (79.9)	64.3	0.017
Other	52 (20.1)	46.2	
Pretreatment viral load, IU			
≤600,000	115 (44.4)	68.7	0.017
>600,000	144 (55.6)	54.2	
Fibrosis			
Not advanced	132 (65.3)	63.6	0.024
Advanced	70 (34.7)	47.1	
HCV genotype			
2 or 3	116 (45.0)	80.2	<0.001
1, 4, or 6	142 (55.0)	45.1	
Treatment completion			
Completed 80-80-80 dose[a]	204 (79.9)	66.7	<0.001[ac]
Dose reduced to less than 80-80-80[b]	17 (6.7)	58.8	0.531[ab]
Discontinued[c]	34 (13.4)	20.6	0.006[bc]
For adverse effects	27 (10.6)	18.5	
For noncompliance	6 (2.4)	33.3	
For unrelated illness	1 (0.4)	0	
Pretreatment alcohol drinking patterns, NIAAA physician guidelines			
Abstainer	18 (7.1)	66.7	0.702
Moderate drinker	64 (25.0)	57.1	
Heavy drinker	171 (67.9)	62.0	
Total pretreatment alcohol consumption (kg)			
<100	92 (36.5)	52.2	0.105
≥100 and <350	67 (26.6)	67.2	
≥350 and <1,000	54 (21.4)	70.4	
>1,000	39 (15.5)	59.0	
Pretreatment abstinence (excluding lifetime abstainers)			
<6 months	70 (29.3)	57.1	0.748
6 months to 2 years	31 (13.0)	67.7	
2-10 years	61 (25.5)	62.3	
10 years or more	77 (32.2)	58.4	
Chemical dependency diagnosis			
No	180 (69.5)	61.1	0.806
Yes	79 (30.5)	57.9	
Chemical dependency treatment			
No	239 (92.3)	61.9	0.157*
Yes	20 (7.7)	45.0	

*Exact significance (one-sided) = 0.107.
ac = 66.7% vs 20.6%; ab = 66.7% vs 58.8%; bc = 58.8% vs 20.6%.

Table 2. Cohort Host and Viral Risk Factors and Abstinence According to Pretreatment Alcohol Intake

	Pretreatment Alcohol Intake					
Risk Factors	Less Than 100 (N = 93)*	100-350 (N = 67)	351-1,000 (N = 54)	Over 1,000 (N = 39)	Totals (N = 253)	*P* Value†
Age (mean ± SD)	50.2 (7.3)	49.6 (6.5)	50.2 (5.9)	49.2 (9.5)	49.9 (7.2)	NS
Gender (% male)	22.2	38.2	59.0	85.2	59.9	<0.001
Race/ethnicity (% non-Hispanic white)	76.6	89.6	79.6	71.8	79.9	0.106
Pretreatment viral load (% ≥600,000 IU/mL)	54.8	58.2	48.1	59.0	54.9	NS
Genotype (% 1, 4, or 6)	51.6	53.0	53.7	64.1	54.4	NS
Advanced fibrosis (% positive) (N = 197)	38.6	31.4	41.5	33.3	35.5	NS
Failure to meet 80-80-80 criteria (%)	11	7.7	0.0	5.1	6.9	0.086
Treatment discontinuation (overall %)	17.4	9.1	5.6	20.5	13.1	0.073
For adverse events (%)	15.2	9.1	3.7	12.8	10.8	NS
For noncompliance (%)	1.1	0.0	1.9	7.7	2.0	0.042
For unrelated illness (1%)	1.1	0.0	0.0	0.0	0.4	NS
Duration of pretreatment abstention (%)						
<6 months	25.0	35.8	35.2	15.4	28.8	0.054
6 months to 2 years	9.2	14.9	11.1	20.5	13.1	
2-10 years	22.4	22.4	22.2	41.1	25.4	
10+ years	43.4	26.9	31.5	23.2	32.6	

Abbreviations: SD, standard deviation; NS, not significant.

*Includes 18 patients who said they never drank regularly: 14 drank irregularly, and 4 never drank or had fewer than 12 drinks in a 12-month period. Duration of abstention is missing for these 18 patients.

†Probability of significantly different ages related to pretreatment alcohol intake is based on analysis of variance; elsewhere, significance levels are based on two-sided chi-square tests for categorical variables.

summarized in Tables 2 and 3. Pretreatment alcohol intake, categorized as total kg of ethanol consumed, is examined in Table 2. Sixty-three percent of patients reported drinking more than 100 kg of ethanol before HCV treatment. Pretreatment alcohol intake is strongly associated with being male, and there is a tendency for white non-Hispanics to be underrepresented in the lowest and highest alcohol intake categories. Treatment discontinuation overall tended to be higher among the heaviest drinkers, and this was significant for treatment discontinuation associated with noncompliance—7.7% in those with pretreatment alcohol intake over 1,000 kg. However, overall treatment discontinuation rates were low in our cohort, and discontinuation was related to noncompliance among only 2.0%. Pretreatment alcohol intake was associated with the length of abstinence before HCV treatment—the heaviest drinkers were more likely than others to have abstained more than 6 months, and the majority in all drinking categories abstained more than 2 years. Pretreatment abstinence is examined further in Table 3. Older patients were significantly more likely to report over 10 years of abstinence, and women tended to have abstained for longer periods than men

Table 3. Cohort Host and Viral Risk Factors According to Duration of Pretreatment Abstinence

	Duration of Pretreatment Abstinence					
Risk Factors	Less than 6 Months (N = 71)	6 Months to 2 Years (N = 31)	2-10 Years (N = 62)	Over 10 Years (N = 77)	Totals (N = 241)	*P* Value*
Age (Mean ± SD)	48.1 (8.6)	48.1 (7.3)	48.2 (7.5)	51.8 (6.1)	49.9 (7.2)	0.005
Gender (% male)	66.2	83.9	61.3	53.2	63.1	0.025
Race/ethnicity (% non-Hispanic white)	84.5	87.1	75.8	77.9	80.5	NS
Pretreatment viral load (% ≥600,000 IU/mL)	56.3	51.6	50.8	59.7	55.4	NS
Genotype (% 1, 4, or 6)	57.7	48.4	61.7	49.4	54.8	NS
Advanced fibrosis (% positive) (N = 197)	35.3	32.0	34.6	32.8	33.9	NS
Failed to meet 80-80-80 criteria (%)	2.9	6.7	8.3	2.6	4.7	NS
Treatment discontinuation (overall %)	11.4	12.9	8.3	20.8	13.9	NS
For adverse events (%)	8.6	12.9	6.7	15.6	10.9	NS
For noncompliance (%)	2.9	0.0	1.7	3.9	2.5	NS
For unrelated illness (%)	0.0	0.0	0.0	1.3	0.4	NS

Abbreviations: SD, standard deviation; NS, not significant.

*Probability of significantly different ages related to pretreatment alcohol intake is based on analysis of variance; elsewhere, significance levels are based on two-sided chi-square tests for categorical variables.

Table 4. Relation of Pretreatment Alcohol Intake to HCV Treatment Failure Adjusted for Host and Viral Risk Factors*

Risk Factors	ORs (95% CI)	*P* Values
Hispanic and/or nonwhite	2.99 (1.23-7.22)	0.016
Pretreatment viral load	2.11 (1.03-4.33)	0.042
HCV genotype (1, 4, or 6)	4.64 (2.20-9.80)	<0.001
Advanced fibrosis	1.71 (0.814-3.59)	0.157
Treatment discontinuation	9.81 (3.08-31.3)	<0.001
Pretreatment alcohol intake (kg)	1.00 (0.999-1.00)	0.303

*Multiple logistic regression, adjusted odds ratios (ORs), 95% confidence intervals (CIs), and significance levels (N = 181).

Table 5. Relation of Pretreatment Abstinence (in Months) to HCV Treatment Failure Adjusted for Host and Viral Risk Factors*

Risk Factors	ORs (95% CI)	*P* Values
Hispanic and/or nonwhite	2.31 (1.02-5.23)	0.044
Pretreatment viral load	1.98 (1.02-3.86)	0.045
HCV genotype (1, 4, or 6)	4.14 (2.07-8.27)	<0.001
Advanced fibrosis	1.81 (0.910-3.60)	0.091
Treatment discontinuation	7.29 (2.50-21.3)	<0.001
Pretreatment abstinence (months)	0.998 (0.993-1.004)	0.502

*Multiple logistic regression, adjusted odds ratios (Ors), 95% confidence intervals (CIs), and significance levels (N = 200).

before HCV treatment, but differences related to other host and viral risk factors were not statistically significant.

Findings from multiple logistic regressions examining the relation of pretreatment alcohol intake and abstention with HCV treatment outcome while controlling for host and viral risk factors are summarized in Tables 4 and 5. Race/ethnicity other than white non-Hispanic, high pretreatment viral load, HCV genotype 1, 4, or 6, and treatment discontinuation all contributed significantly to HCV treatment failure, but advanced fibrosis and pretreatment alcohol intake did not. Findings for pretreatment abstinence were similar.

More detailed analyses were conducted to examine the relation of 6-month pretreatment abstinence on SVR among moderate drinkers. One-third of moderate drinkers did not abstain for 6 months before treatment, and their SVR rates were lower than those in moderate drinkers who did abstain (42.9%, compared to 64.3%; $P = 0.105$). We conducted multiple logistic regression analyses to identify host and viral risk factors that significantly influenced SVR rates in this cohort of moderate drinkers, deleted those that were not significant, and then examined 6-month abstinence (see Table 6). After adjusting for race/ethnicity, HCV genotype, and treatment discontinuation, failure to abstain 6 months or more was associated with a significantly greater risk of treatment failure. A similar association was not observed among heavy drinkers. Although 26.9% of the heavy drinkers did not abstain 6 months, 63.0% obtained SVRs, compared to 61.6% of those who did abstain 6 months or more ($P = 0.863$). Adjusting for host and viral risk factors confirmed the lack of an effect.

An examination of regular drinking during critical periods defined by HCV diagnosis and treatment revealed that over 93% of the patients were drinking regularly before receiving their HCV diagnosis, after which the number of regular drinkers decreased to only 30.9%. Regular drinking fell to less than 2% during HCV treatment and increased to 11.6% after treatment ended. When SVR rates were examined with respect to fibrosis grade and regular drinking during critical periods (Table 7), SVR was higher only among patients who did not drink regularly prior to HCV diagnosis and had lower grade fibrosis. Thirty-four patients relapsed after being clear of virus at the end of treatment; 14.7% reported drinking after treatment ended, compared with 10.7% among patients who did not relapse ($P = 0.453$).

Discussion

Early studies of alcohol consumption and outcomes of HCV treatment with interferon monotherapy in Japan[12-14] and Italy[15,16] consistently indicated that heavy drinking was associated with significantly poorer SVR rates. These studies were limited by small sample sizes, failure to control for adherence to antiviral therapy, and use of crude alcohol measures. Nonetheless, they provided a rationale for excluding patients with a history of alcohol abuse from clinical trials of new antiviral therapy. Accordingly, few studies relating alcohol consumption to HCV treatment outcomes with combination interferon and ribavirin therapy have been conducted. Anand et al.[9] reported data from a multicenter study involving a select group of 726 veterans treated three times weekly with interferon-alpha and ribavirin. They found that drinking in the 12 months before treatment was significantly associated with failure to complete treatment (40% versus 26%; $P = 0.0002$) and a reduced SVR rate (14% versus

Table 6. Failure to Abstain 6 Months and HCV Treatment Failure Among Moderate Drinkers (Multiple Logistic Regression Adjusted for Host and Viral Risk Factors)*

Risk Factors	ORs (95% CI)	*P* Values
Hispanic and/or non-white	8.11 (1.35-48.7)	0.022
HCV genotype (1, 4, or 6)	3.70 (0.986-13.9)	0.053
Treatment discontinuation	25.6 (3.50-187.5)	0.001
Pretreatment abstention (<6 months)	5.26 (1.25-22.2)	0.024

*Adjusted odds ratios (ORs), 95% confidence intervals (CIs), and significance levels (N = 63).

Table 7. SVR Rates According to Fibrosis Grade and Regular Drinking During Critical Time Periods (N = 202)

	Lower Grade Fibrosis					Higher Grade Fibrosis				
	Drank Regularly		Did Not Drink Regularly			Drank Regularly		Did Not Drink Regularly		
Critical Periods	N	% SVR	N	% SVR	*P* Value	N	% SVR	N	% SVR	*P* Value
1	125	61.6	7	100.0	0.040	62	48.4	8	37.5	0.562
2	42	57.1	90	66.7	0.289	21	42.9	49	49.0	0.638
3	2	100.0	130	63.1	0.281	2	50.0	68	47.1	0.935
4	17	70.6	115	62.6	0.523	9	33.3	61	49.2	0.374

20%; $P = 0.06$). In a per-protocol analysis of patients who completed treatment, the negative effect of recent drinking on SVR rates disappeared (25% versus 23%). A study of patients treated with P/R in a university-affiliated outpatient clinic serving an inner city population found that a past history of consuming more than 30 g/day of ethanol was associated with significantly lower SVR rates.[17] This finding was based on an intention-to-treat analysis, which included patients who discontinued treatment early for reasons other than lack of an early virological response; it was noted that 46% of the sample (53 of 115) failed to complete treatment, and that past alcohol intake was not significantly related to outcome in patients who completed treatment.

Given the relatively high SVR rates obtained in our cohort, we expected moderate drinking patterns to predominate in our patients. Therefore, it came as a surprise to find that over 60% had a pretreatment alcohol intake over 100 kg, an amount above which rates of alcoholic liver disease begin to increase,[18] and over 15% reported drinking more than 10 times this amount. A key difference between our patients and those previously studied is that only 14% discontinued treatment, and discontinuation was related to pretreatment alcohol intake only in noncompliant patients, who made up less than 2% of the cohort and were mainly limited to patients whose pretreatment alcohol intake was over 1,000 kg. Thus, our findings are consistent with previous reports that past alcohol history[17] and drinking during the 12 months before treatment[9] did not influence treatment outcome in patients who completed treatment.

Failure to observe a relationship between alcohol consumption and advanced fibrosis may reflect the fact that these factors are likely to have influenced entry into HCV treatment. Patients with advanced fibrosis would have been encouraged to seek treatment, whereas heavy drinkers may have been unwilling or too ill to commit to treatment.

Integrated care and aggressive follow-up by phone and in the clinic may have contributed to the high treatment completion rates and SVR achieved in this cohort, but adherence may also have been, in part, the result of the patients' stable life circumstances and support of the family. In addition to stable insurance coverage, over 60% were married and 80% were either employed or retired. We did not assess the prevalence or severity of alcohol dependence in this study, but it seems likely that both are lower in privately insured cohorts with high marriage and employment rates than among the inner-city clinic patients and veterans studied by Chang et al.[17] and Anand et al.,[9] respectively. Socioeconomic stability and less-severe alcohol dependence may have contributed, in part, to the rapid drop in regular drinking observed in response to HCV diagnosis and the further decrease once HCV treatment was initiated. We do not believe that these findings were obtained because our cohort was unique. An increasing percentage of the U.S. population is enrolled in integrated health care plans. Except for extremes of income, membership of the Kaiser Sacramento Health Care Plan is representative of the total area's population,[19] and demographics of the Sacramento area are similar to those for the United States as a whole. This is important, because, although HCV^+ rates are relatively low among individuals who are privately insured or on Medicare, this is such a large population that it accounts for 46% of the HCV^+ patients in the U.S. household population (Third National Health and Nutrition Survey, National Center for Health Statistics, 1994, unpublished data).

Our finding that failure to abstain for 6 months before HCV treatment was related to significantly higher risk of treatment failure in moderate, but not heavy, drinkers was also unexpected. This finding is counterintuitive and is based on a relatively small sample. Therefore, it needs to be replicated in a larger sample to determine whether or not it may have occurred by chance. Meanwhile, the fact that pretreatment abstinence was not associated with treatment outcome in the cohort as a whole suggests that requiring 6 months of abstinence before treatment is less critical to outcome than ensuring that patients are committed to treatment and providing close monitoring and ancillary care.

A potential limitation of these findings concerns the validity of retrospective measures of lifetime drinking patterns. Prospective ascertainment of alcohol intake poses fewer problems concerning memory than retrospective ascertainment, but this advantage is offset by the problems involved in long-term studies of rare chronic diseases. In addition, several studies have found that heavy drinkers report higher alcohol intakes retrospectively than prospectively,[20-22] which suggests that people are more comfortable reporting past heavy drinking than current heavy drinking. Because intense pressure on patients to reduce their alcohol intake before HCV treatment seemed likely to foster denial, we chose to study patients who had already been treated to reduce denial, and we emphasized that patients' data would be kept confidential, even from their care providers. Test-retest reliability of the CLDH was not reexamined in this study, but internal validity was good. Patients with a CD diagnosis or CD treatment reported consuming approximately twice as much alcohol before HCV treatment as patients without CD records. It is possible that patients who did not obtain an SVR might have minimized their alcohol intake if they thought it might jeopardize their future treatment. However, successfully treated patients had little reason to exaggerate their drinking, and the high alcohol intakes reported both by patients who did and did not recover suggests that denial did not influence these findings.

In conclusion, excellent P/R treatment completion rates and outcomes were not impaired by high pretreatment alcohol intakes or failure to abstain 6 months before treatment in patients of an integrated health care plan who were aggressively supported and closely monitored. These findings suggest that past heavy drinking and recent drinking represent low treatment risk in these patients. The fact that over 60% of patients stopped drinking when HCV^+ was diagnosed documents the potential for immediate health benefits associated with case finding in this population.

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