Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

A multi-disciplinary approach to treating hepatitis C with interferon and ribavirin in alcohol-dependent patients with ongoing abuse

Caroline Le Lan[1,2,3], Anne Guillygomarc'h[2], Hélène Danielou[2], Gérard Le Dréau[5], Fabrice Lainé[3,4], Claude Védeilhié[6], Yves Deugnier[2,3,4,7], Pierre Brissot[2,3,7], Dominique Guyader[2,3,7], Romain Moirand[1,2,3,7,*]

[1]*CHU de Rennes, Unité d'Addictologie, F-35033 Rennes, France;* [2]*CHU de Rennes, Service des Maladies du Foie, F-35033 Rennes, France;* [3]*INSERM, UMR-991, F-35000, France;* [4]*CHU de Rennes, Centre d'Investigation Clinique, F-35033 Rennes, France;* [5]*CHBS Lorient, Service de Gastroentérologie, F-56322, France;* [6]*CHS Guillaume Régnier, Pôle Addiction Précarité, F-35703 Rennes, France;* [7]*Univ Rennes 1, Faculté de médecine, F-35043 Rennes, France*

Background & Aims: Guidelines recommend 6 months of alcohol abstinence before treating hepatitis C (HCV). Abstinence is difficult for alcohol-dependent patients to achieve. This study evaluated HCV treatment in alcoholic patients with ongoing consumption or less than 6 months of abstinence.

Methods: A multidisciplinary management model was built by a liver unit and two centers involved in the care of addict patients. Patients were included in a prospective observational study of treatment with pegylated interferon and ribavirin if they presented alcohol dependence with ongoing intoxication or abstinence of less than 6 months. Pre-therapeutic evaluation and follow-up were multidisciplinary, and addiction care was personalized to patient condition and willingness. Alcohol abstinence or reduction was encouraged but not mandatory. The primary end point was sustained virological response (SVR). Results were compared to a control group of patients matched for genotype, viral load, fibrosis stage, sex, and age.

Results: A total of 73 patients treated between 2002 and 2008 were included in the study. Intent to treat analysis showed an SVR in 48% (35/73) of patients versus 49% (36/73) of controls. Low viral load and length of abstinence during treatment were independently associated with SVR. During treatment, 20 (27%) patients were abstinent, 23 (32%) had controlled consumption, and 24 (33%) had excessive consumption. At the end of the follow-up, 22 (30%) patients were durably abstinent.

Conclusions: A multidisciplinary approach allowed HCV treatment in alcohol-dependent patients with a satisfactory SVR rate and positive effects on addiction behavior.

Keywords: Case-controlled study; Alcoholism; Hepatitis C virus.

Received 14 March 2011; received in revised form 1 May 2011; accepted 11 May 2011; available online 12 July 2011

* Corresponding author. Address: Unité d'Addictologie, Service des Maladies du Foie, CHU Pontchaillou, 35033 Rennes cedex, France. Tel.: + 33 2 99 28 42 98; fax: +33 2 99 28 41 12.

E-mail address: romain.moirand@univ-rennes1.fr (R. Moirand).

Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response; ALT, alanine amino transferase; Peg-IFN, pegylated interferon; ASI, addiction severity index; ISRs, interviewer severity ratings; OR, odds ratio; CI, confidence interval; IQ, interquartil.

Introduction

Excessive alcohol consumption frequently co-exists with hepatitis C virus (HCV) infection. HCV is detected in 1.3% to 30% of alcoholic patients, irrespective of the presence of liver disease, and most cases have a past history of intravenous drug use [1]. Patients with chronic hepatitis C also have a higher prevalence of excessive alcohol consumption than the general population. A study of 6664 HCV-infected French patients found that 15% of the whole group and 30% of the intravenous drug users had hazardous drinking habits [2]. Numerous studies have demonstrated a synergistic effect of excessive alcohol consumption and HCV infection on the progression of liver disease to cirrhosis [3]. Accordingly, patients who consume alcohol excessively should be treated with high priority before the occurrence of severe fibrosis, as currently available therapies for chronic hepatitis C achieve their best results in patients with mild fibrosis [4]. However, doctors are reluctant to treat patients with ongoing alcohol intoxication, which is reflected in current guidelines [4], but no published study has yet addressed this topic.

The aim of this study was to assess the outcome of hepatitis C treatment in a cohort of consecutive alcohol-dependent patients with ongoing consumption or who abstained for less than 6 months. The patients were followed in a multidisciplinary standardized management model in a country where the cost of treatment is fully covered by government-based insurance.

Patients and methods

This was a bi-center, prospective, observational, case-controlled study conducted in the French region of Brittany. The therapeutic program was built after the establishment of a multidisciplinary team including specialists in hepatology and addictive disease from a university hospital and a specialized addiction clinic in the same town. This program was secondarily implemented in another city.

JOURNAL OF **HEPATOLOGY**

Table 1. Pre-therapeutic characteristics of patients who initiated antiviral treatment (n = 73).

Whole population		Frequency of patients with SVR*	OR (95% CI) for patients with SVR *vs.* patients without	Frequency of patients with good compliance#	OR (95% CI) for patients with good compliance *vs.* patients without
Sociodemographic characteristics					
Sex	Male: 63 (86.3) Female: 10 (14.7)	31 (49.2) 4 (40.0)	1 0.69 (0.16-2.64)	55 (87.3) 10 (100.0)	n.s
Age at HCV treatment (yrs)	42 (37-46)	41 (35-45)	0.94 (0.87-1.02)	42 (38-46)	1.10 (0.97-1.28)
Employment	Yes: 27 (37.5) No: 45 (62.5)	12 (44.4) 22 (48.9)	1 1.20 (0.46-3.15)	25 (92.6) 39 (86.7)	1 0.52 (0.07-2.46)
Married or common law	Yes: 24 (33.3) No: 48 (66.7)	9 (37.5) 25 (52.1)	1 1.8 (0.67-5.08)	20 (83.3) 44 (91.7)	1 2.2 (0.48-10.18)
Have children	Yes: 44 (61.1) No: 28 (38.9)	21 (47.7) 13 (46.4)	1 0.95 (0.36-2.46)	39 (88.6) 25 (89.3)	1 1.06 (0.24-5.58)
Accommodation before the initiation of therapy	Yes: 67 (91.8) No: 6 (8.2)	32 (47.8) 3 (50.0)	1 1.09 (0.20-6.28)	61 (91.4) 4 (66.7)	1 0.20 (0.03-1.62)
Years of school attendance	10 (9-12)	10 (9-12)	1.04 (0.81-1.34)	10 (9-12)	1.21 (0.81-2.00)
Alcohol and drug-related characteristics					
Age at onset of addiction (yrs)	28.5 (19.75-36)	27 (18-34.75)	1.00 (0.95-1.05)	28 (19-36)	1.01 (0.93-1.10)
History of illicit drug use	Yes: 66 (90) No: 7 (10)	33 (50.0) 2 (28.6)	1 0.4 (0.05-2.00)	58 (87.9) 7 (100.0)	n.s.
Previous therapy for addiction	Yes: 49 (67.1) No: 24 (32.9)	25 (51.0) 10 (41.7)	1 0.69 (0.25-1.83)	43 (87.8) 22 (91.7)	1 1.5 (0.32-11.06)
Previous hospitalization for addiction therapy	Yes: 40 (54.8) No: 33 (45.2)	19 (47.5) 16 (48.5)	1 1.04 (0.41-2.63)	35 (89.0) 30 (90.1)	1 1.43 (0.32-7.43)
Duration of alcohol problem (yrs)	11 (8-16)	10 (6-15)	0.98 (0.91-1.04)	10.5 (8-15.7)	1.01 (0.91-1.14)
Alcohol consumption during period with maximal consumption (drinks per week)	120 (70-200)	120 (66-209)	1.0 (0.99-1.00)	120 (63-200)	0.99 (0.98-1.00)
Alcohol consumption before treatment (drinks per week)	50 (30-98)	50 (30-105)	1.0 (0.99-1.01)	50 (30-88)	0.99 (0.98-1.01)
Number of positive items for DSM-IV diagnosis of alcohol dependence	5 (4-7)	5 (4-7)	1.07 (0.27-4.30)	5 (4-6)	**0.38 (0.13-0.81)**
Dependence on other drugs					
Cannabis	Yes: 8 (11.0) No: 65 (89.0)	5 (62.5) 30 (46.2)	1 0.51 (0.10-2.27)	8 (100.0) 57 (87.7)	n.s.
Opiates	Yes: 26 (35.6) No: 47 (64.4)	15 (57.7) 20 (42.5)	1 0.54 (0.20-1.42)	23 (88.5) 42 (89.4)	1 1.09 (0.21-4.88)
ASI ISR (n = 67)					
Medical status	3 (2-5)	4 (2-6)	1.30 (0.99-1.72)	3 (2-5)	1.20 (0.78-1.98)
Employment/support status	1 (0-3)	1 (0-3)	0.94 (0.75-1.15)	1 (0-3)	0.99 (0.08-21.30)
Alcohol use	4 (3-7)	4 (3-7)	1.02 (0.81-1.27)	4 (3-7)	1.05 (0.73-1.55)
Drug use	2 (1-4)	4 (1.5-4.5)	**1.47 (1.13-1.99)**	1 (2-4)	0.80 (0.55-1.15)
Legal status	0 (0-2)	1 (0-2)	1.12 (0.79-1.60)	0 (0-1)	0.67 (0.42-1.08)
Family and social relationship	1 (0-2)	0 (0-2)	0.94 (0.71-1.22)	0.5 (0-1)	**0.67 (0.45-0.92)**
Psychiatric problems	4 (3-6)	4 (3-6)	0.99 (0.77-1.27)	4 (3-6)	0.79 (0.50-1.19)
Abstinent from alcohol at the first injection	No: 44 (62.0)	22 (50.0)	1	42 (95.5)	1
1 week to 1 month:	12 (16.9)	5 (41.7)	0.71 (0.19-2.58)	11 (91.7)	0.52 (0.05-11.87)
More than one month:	15 (21.1)	8 (53.3)	1.14 (0.35-3.79)	10 (66.7)	**0.10 (0.01-0.51)**
Addiction treatment at the initiation of antiviral therapy	No: 30 (41.1)	12 (40.0)	1	28 (93.3)	1
As an outpatient:	23 (31.5)	15 (65.2)	2.81 (0.93-9.02)	21 (91.3)	0.75 (0.08-6.66)
As an inpatient:	20 (27.4)	8 (40.0)	1.00 (0.31-3.18)	16 (80.0)	0.29 (0.04-1.63)
Patient's goal at the initiation of antiviral therapy					
Reduced alcohol consumption:	31 (42.5)	13 (41.9)	1	29 (93.6)	1
Abstinence:	42 (57.5)	22 (52.4)	1.52 (0.60-3.94)	36 (85.7)	0.41 (0.06-1.95)

Research Article

Table 1 (*continued*)

Whole population			Frequency of patients with SVR*		OR (95% CI) for patients with SVR *vs.* patients without	Frequency of patients with good compliance#		OR (95% CI) for patients with good compliance *vs.* patients without
Hepatitis C-related characteristics								
Previous therapy for HCV								
Never:	40 (54.8)		21 (52.2)		1	36 (90.0)		1
Previously denied:	22 (30.1)		11 (50.0)		0.90 (0.32-2.58)	21 (95.5)		2.33 (0.32-47.24)
Already treated:	11 (15.1)		3 (27.3)		0.34 (0.07-1.36)	8 (72.7)		0.30 (0.05-1.74)
Initial visit								
Hepatologist:	49 (67.1)		23 (46.9)		1	44 (89.8)		1
Addictologist:	24 (32.9)		12 (50.0)		1.13 (0.42-3.03)	21 (87.5)		0.80 (0.18-4.17)
Viral load								
Low$:	30 (42.3)		23 (76.7)		**8.96 (3.14-28.43)**	28 (93.3)		1
High:	41 (57.8)		11 (26.8)		1	36 (87.8)		0.51 (0.07-2.58)
Genotype	1: 40 (54.8)		16 (40.0)	19 (39.6)	1	35 (87.5)		1
	4: 8 (10.9)		3 (37.5)			7 (87.5)		
	2: 1 (1.4)		1 (100.0)	16 (64.0)	**2.71 (1.02-7.62)**	1 (100.0)		1.64 (0.35-11.83)
	3: 24 (32.9)		15 (62.5)			22 (91.7)		
Fibrosis (n = 67§)	O: 3 (4.5)	48 (65.8)&	2 (66.7)	26 (54.2)&	0-I-II: 1	3 (100.0)	41 (85.4)&	1
	I: 21 (31.3)		10 (47.6)			16 (76.2)		
	II: 19 (28.4)		9 (47.4)			17 (89.5)		
	III: 12 (17.9)	25 (34.2)&	3 (25.0)	9 (36.0)	III-IV: 0.48 (0.17-1.27)	12 (100)	24 (96)	4.10 (0.67-78.99)
	IV: 12 (17.9)		6 (50.0)			12 (100)		
Activity (n = 66§)	1: 30 (45.5)		10 (33.3)		1	26 (86.7)		n.s.
	2: 29 (43.9)		13 (44.8)		1.62 (0.57-4.76)	26 (86.7)		
	3: 7 (10.6)		6 (85.7)		**12.00 (1.73-243.37)**	7 (100)		
Aspartate aminotransferase	71 (44.2-108.7)		73 (48.5-130.7)		1.00 (1.00-1.01)	67.5 (44.7-110.2)		1.00 (1.00-1.02)
Alanine aminotransferase	101 (67-165)		117 (74.5-202)		1.01 (1.00-1.01)	104 (66-169)		1.00 (1.00-1.02)
Gamma glutamyl transpeptidase	120 (64.7-249.7)		101 (46-154)		1.00 (0.99-1.01)	121 (65-255)		1.00 (1.00-1.01)
Body mass index	23.3 (21.1-26.0)		23.3 (21.0-26.0)		0.95 (0.81-1.11)	23.4 (21.2-26)		1.22 (0.84-2.08)

Significant results are in bold. NS: not significant, ASI: Addiction Severity Index, ISR: interviewer severity rate, SVR: sustained virological response, IQ: interquartile. *Data are presented as n (% of patients with SVR according to the variable), or median [IQ range] in patients with SVR. #Data are presented as n (% of patients with good compliance according to the variable), or median [IQ range] in patients with good compliance. $<800,000 IU/ml. §Fibrosis assessment by METAVIR score for liver biopsy. &Including fibrosis assessment by non-invasive tests.

Patients

Inclusion criteria for this study were: (i) alcohol dependence diagnosed using DSM-IV criteria; (ii) ongoing excessive alcohol consumption or abstinence for less than 6 months before the first injection of interferon; (iii) presence of HCV-RNA in the 6 previous months with increased alanine aminotransferase (ALT) at least twice in the past two months, and/or chronic hepatitis on liver biopsy; (iv) age between 18 and 70; and (v) acceptance of the study procedure by providing written informed consent. Exclusion criteria were: (i) severe liver cirrhosis with prothrombin index <60%; (ii) history of severe liver cirrhosis complications; (iii) overt alcoholic hepatitis associated with liver cirrhosis defined either on liver biopsy, when available (n = 67; 92%), or suspected by typical bioclinical features if the patient refused the liver biopsy; (iv) other etiologies of liver disease; (v) platelets <100,000/mm^3, neutrophils <1000/mm^3, or hemoglobin <12 g/dl in women and <13 g/dl in men; (vi) severe extra-hepatic diseases; (vii) pregnancy or supposed inability to maintain safe contraception; or (viii) uncontrolled psychiatric disorders, such as severe major depression with suicidal thoughts without treatment or uncontrolled psychosis.

Therapeutic program

Patients could enter the program after an initial evaluation by either a hepatologist or addictologist. In the former case, the patient was initially referred by general practitioners or sought evaluation on their own. In the latter case, patients were treated for alcohol dependence and screened for hepatitis C. In both cases, the pre-treatment evaluation had to include at least one evaluation visit with an addictologist to assess the psychosocial characteristics of the patient, including the search for psychiatric exclusion criteria for HCV treatment, and at least one evaluation visit with a hepatologist for a physical examination, biochemistry, and ultrasound examination of the liver and to receive information regarding benefits and potential side effects of antiviral treatment. Liver biopsy was recommended, but not required, unless alcoholic hepatitis associated with cirrhosis was suspected. Alcohol reduction was strongly encouraged, but was not mandatory, and treatment was not stopped in the case of relapse to excessive alcohol consumption. At the beginning of the treatment, patients attended one session of therapeutic education with a reference nurse, during which they were taught the practice of treatment and management of side effects. Ribavirin was taken daily at home. Pegylated interferon (peg-IFN) was administered either by self-injection or a nurse at home, or in the outpatient center. The planned follow-up during hepatitis C treatment comprised of a monthly visit with a hepatologist and personalized addiction therapy. Psychosocial treatment was on out- and/or in-patient basis and adapted to each patient situation and willingness, but the minimal condition was a quarterly visit. The planned follow-up after HCV treatment was a visit with a hepatologist at 3 and 6 months and the continuation of personalized addiction therapy.

Study procedure

The study was explained by the hepatologist, who obtained written informed consent from the patient. Information on the history of HCV and prior treatments were recorded. The liver histology was analyzed using the METAVIR classification [5]. For the purpose of the analysis, mild fibrosis included stages 0, 1 (periportal

fibrotic extension), and 2 (periportal septa); severe fibrosis was defined as stages 3 (porto-central septa) and 4 (cirrhosis). Viral load was measured by quantitative PCR and considered low or high using a cut-off of 800,000 IU/ml. Just before beginning the anti-HCV treatment, patients had an interview with a research assistant trained to use the Addiction Severity Index (ASI) [6]. The ASI is a multi-dimensional interview used to measure the substance use, health, and social problems of individuals with alcohol and other drug problems. It leads to the establishment of Interviewer Severity Ratings (ISRs), ranging from 0 (no problem) to 9 (severe problems), in seven different dimensions. Information was collected concerning the patient's history of dependence, previous treatments for addiction, and the consumption of other drugs; standardized questionnaires included a diagnosis for dependence according to DSM-IV criteria, the ASI, and a quantitative evaluation of alcohol consumption [7]. During follow-up visits with a hepatologist, alcohol consumption, adherence to HCV therapy, and adverse effects according to a modified version of the World Health Organization (WHO) Toxicity Grading Scale were recorded. During follow-up visits with the addictologist, the consumption of alcohol and other drugs and psychosocial situation, particularly anxious or depressive symptoms, were recorded. Abstinence referred to patients off alcohol during all the treatment and was defined on the basis of a patient's declaration and biochemistry. Low risk consumption was defined as consuming no more than 21 standard drinks (10 g of pure ethanol) in men and no more than 14 in women per week, and no more than 4 by drinking occasion, according to WHO recommendations, during the treatment period. Excessive consumption was defined as drinking more than the previous limits on at least two occasions during the treatment. Attempts were made to contact patients who did not attend a scheduled visit.

Treatment

Patients were treated with 1.5 μg/kg peg-IFN alpha2b subcutaneously once a week and 800–1200 mg ribavirin per day according to body weight for 24 (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4). At the end of the second and fourth treatment weeks, and monthly thereafter, patients underwent clinical and laboratory tests, including blood ethanol concentration. Thereafter, treatment was adjusted as recommended.

Control group

In order to compare HCV treatment outcomes in our study group to those of patients who did not consume alcohol, we set up a matched control group. Controls were extracted from a local database maintained since 1992 by the Liver Unit. All consecutively referred HCV-positive patients have been included in the database (3984 patients currently). We extracted the data for all patients who began peg-IFN and ribavirin treatment in the hepatology clinic during the same period as the alcoholic patients and were classified as low risk drinkers, on the basis of their declarations, biological and histological data and the clinician's opinion. We excluded patients who were referred as non-responders from other centers. We matched a control to each patient in the study according to genotype (1 and 4 *vs.* 2 and 3), fibrosis (mild *vs.* severe), viral load (low *vs.* high), sex, and age.

Statistical analysis

The primary end point of the study was sustained virological response (SVR). SVR was evaluated in an intent-to-treat analysis. Non-response was defined as a failure to decrease HCV RNA by >2 logs after 12 weeks of therapy or to clear HCV RNA from the serum after 24 weeks of therapy. Relapse was defined as a reappearance of HCV RNA in the serum after therapy was discontinued. We also recorded premature termination due to side effects and loss to follow-up. Secondary end points were compliance with HCV therapy and the evolution of alcohol consumption. We defined "patients with good compliance" as those who had the whole course of treatment or whose treatment was stopped by inefficacy or non-psychiatric side effects. Characteristics of patients before treatment and alcohol consumption during treatment were compared between patients with and without SVR using logistic regression to calculate the crude odds ratios (ORs) and respective 95% confidence intervals (CIs) for the association of SVR with each category of variable or unit of continuous values. Independent factors associated with SVR were assessed using stepwise logistic regression. Only the most informative variables were used at this stage based on substantive knowledge and preliminary univariate analysis. p values of 0.05 and 0.15 were used for entry and removal of variables, respectively. Similar logistic regression analysis was conducted for the association between individual pre-treatment characteristics and good compliance. Data were analyzed using JMP®9 (SAS institute Inc, USA) for MacOS®10.

Results

Pre-treatment socio-demographic and substance-related characteristics

A total of 73 patients (63 males, age 42 [37–46]) who started HCV therapy between September 2002 and February 2008 were included in the study. Pre-therapeutic characteristics of the study population are presented in Table 1. Alcohol consumption the week before the first injection of interferon was excessive in 44 (62%) patients, and 24 (34%) stopped for less than 3 months. Twenty (27%) patients were hospitalized for addictive care at that time. Forty-nine (67%) patients had been previously treated for an alcohol problem and 30 (41%) were not in therapy at the proposal of the study. Forty-nine (67%) patients were seen initially by hepatologists, and the others by addictologists. The median duration of excessive alcohol consumption was 11 years, and median consumption before treatment was 50 drinks per week (interquartile (IQ) range 30–98). Most patients (66–90%) had a history of intravenous drug use and 26 (36%) were still on opiate maintenance therapy. The ASI at the beginning of treatment (Table 1) differed greatly among patients; some patients presented with moderate problems in specifically explored dimensions and others with major difficulties in most dimensions. The most marked problems were in medical, alcohol, and psychological dimensions.

Hepatitis C-related characteristics

Sixty-two (85%) patients were naive to HCV treatment, and 22 (30%) had already refrained from treatment because of ongoing alcohol consumption. Genotype 3 was observed in 25 (34%) patients, and 30 (42%) had a low viral load. A total of 25 (34%) patients had severe fibrosis.

Alcohol consumption during and after treatment

During the treatment period, 20 (30%) patients remained abstinent, 23 (34%) had constant low risk consumption, and 24 (36%) consumed alcohol excessively (Table 2). Some of the later patients alternated periods of abstinence and periods of excessive alcohol consumption; we measured the cumulative duration of abstinence during treatment (in months). Thirty-nine (53%) patients remained abstinent for at least 3 months. The type of therapy for alcohol problems during HCV treatment varied considerably from one patient to another. Twenty-nine (40%) adhered only to the minimal schema imposed by the study (one visit every three months), seven did not follow this schema, and 37 had personalized care, ranging from regular out-patient follow-up to detoxification or rehabilitation programs. Six months after the end of HCV treatment, 22 (30%) patients were durably abstinent and 47 (64%) still practiced excessive consumption; of these patients, 25 were always in treatment as out-patient and 22 were lost to follow-up by addiction teams. The duration of alcohol abstinence (in days) before the first injection was not different between patients who were abstinent

Research Article

Table 2. Alcohol consumption and management in patients (n = 73) during and after antiviral therapy.

N (% of the whole population)	Frequency of patients with SVR*	OR (95% CI) for patients with SVR *vs.* patients without
Alcohol consumption during antiviral therapy		
Abstinent: 20 (29.9)	13 (65.0)	**3.71 (1.10-13.67)**
Low risk: 23 (34.3)	12 (52.2)	2.19 (0.68-7.33)
Excessive: 24 (35.8)	8 (33.3)	1
Months of abstinence during antiviral therapy		
3 (0-6)	5 (2-12)	**1.27 (1.11-1.49)**
At least three months of alcohol abstinence during treatment		
Yes: 39 (53.4)	25 (64.1)	**4.29 (1.64-11.91)**
No: 34 (46.6)	10 (29.4)	**1**
Addiction treatment during antiviral therapy		
No: 7 (9.6)	1 (14.3)	1
Minimal: 29 (39.7)	15 (51.7)	6.43 (0.93-129.52)
Reinforced: 37 (50.7)	19 (51.3)	6.33 (0.95-125.82)
Alcohol consumption at the end of antiviral therapy *vs.* initiation		
Similar: 18 (24.7)	7 (38.9)	1
Reduced: 30 (41.1)	16 (53.3)	1.80 (0.55-6.10)
Abstinence: 18 (24.7)	12 (66.7)	3.14 (0.83-13.02)
Unknown: 7 (9.5)	0 (0.0)	-
Alcohol consumption 6 months after the end of antiviral therapy		
Excessive: 47 (64.4)	18 (38.3)	1
Abstinent: 22 (30.1)	16 (72.7)	**4.30 (1.48-13.89)**
Unknown: 4 (5.5)	1 (25.0)	0.54 (0.02-4.56)

Significant results are in bold. SVR: sustained virological response, IQ: interquartile. Numerical variables are presented as median [IQ range]. *Data are presented as n (% of patients with SVR according to the variable) or median [IQ range] in patients with SVR.

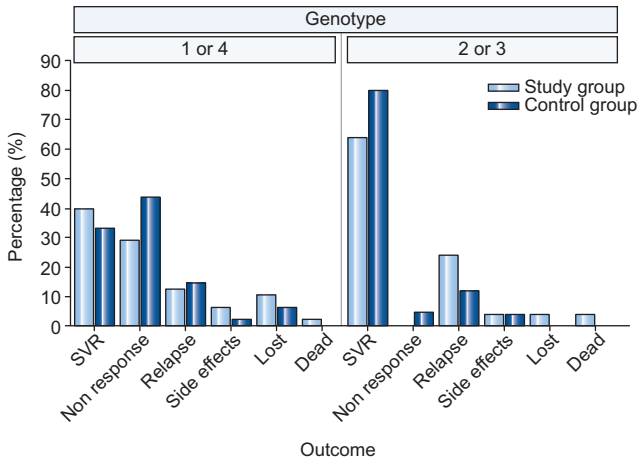

Fig. 1. Outcomes of antiviral therapy in the study group compared to the control group. Matching was perfect for genotype, viral load, and fibrosis; three alcoholic men were matched to control women (gender ratio 63/10 in subjects; 60/13 in controls). Median age was slightly greater in controls (43 [39–50]) compared to alcoholics (42 [37–46]).

6 months after the end of HCV treatment and those with excessive consumption (median 5 [0–37.5] *vs.* 0 [0–23.25]).

Treatment outcome

A SVR occurred in 35 (48%) patients versus 36 (49%) controls (Fig. 1). In univariate analysis (Table 1 and 2), variables positively associated with SVR in patients were the drug status ISR, low viral load, genotypes 2 and 3, high activity on liver biopsy, and all measures of alcohol abstinence during treatment, but not

Table 3. Sustained virological rates according to alcohol consumption during treatment and genotype.

	Frequency of patients with SVR	
Alcohol consumption during antiviral therapy	Genotype 1 or 4	Genotype 2 or 3
Abstinent	7 (53.8)	6 (85.7)
Low risk	7 (53.8)	5 (50.0)
Excessive	3 (18.7)	5 (62.5)

before treatment. A SVR occurred in 13 (65%) abstinent patients, 12 (52%) patients with low risk consumption and 8 (33%) patients with excessive consumption during treatment (Table 3). In the multivariate analysis, drug use ISR, low viral load, and duration of abstinence during antiviral therapy remained independently associated with SVR (Table 4). The duration of alcohol abstinence during antiviral therapy was significantly associated with SVR in all tested models, in those forcing known predictors of SVR, such as genotype and severe fibrosis, and restrained to patients with complete treatment (data not shown). Median alcohol abstinence during treatment was 5 [2–12] months in patients with SVR versus 0.5 [0–3.25] in patients without SVR. When considering patients with the worst prognostic factors, genotype 1 or 4, high viral load, and heavy consumption during treatment, 3/13 (23%) had SVR and 6 (46%) were non-responders.

Characteristics associated with observance

Six patients dropped out due to side effects, two of which had psychiatric symptoms due, probably, to excessive consumption. Six patients interrupted treatment by not attending the scheduled visits. We defined patients with psychiatric stops and those

JOURNAL OF HEPATOLOGY

Table 4. Adjusted OR and 95% CI for patients with sustained virological response versus patients without.

	Regression coefficients	Standard errors	Adjusted OR (95% CI)	*p* value
Addiction Severity Index				
Drug use interview severity rate	0.557	0.223	1.55 (1.13-2.23)	0.009
Months of abstinence during antiviral therapy	0.235	0.096	1.31 (1.11-1.61)	0.003
Viral load				
High			1	
Low	0.963	0.381	4.56 (1.26-17.93)	0.02

lost to follow-up as "incomplete treatment due to low compliance". Pre-therapeutic variables that associated negatively with good compliance were: the number of positive items for the diagnosis of alcohol dependence on DSM-IV, the family and social status ISR, and a longer period of abstinence before antiviral therapy (Table 1). In the multivariate analysis, family and social status ISR and duration of abstinence before antiviral therapy remained independently associated with compliance.

Two patients died during HCV treatment, one suddenly from a pulmonary embolism and the other was found dead in bed. Both of the patients were responders and were not found to practice excessive consumption at the last visit. No evidence indicated that the deaths were related to treatment.

Discussion

Large randomized trials of HCV treatment have continuously excluded difficult patients, such as substance abuse or psychiatric patients. However, these patients are frequent. Regarding drug consumption, numerous studies have demonstrated that intravenous drug users can be efficiently treated for HCV [8]. Other studies have shown good results in the treatment of patients with psychiatric diseases [9]. In contrast, no study has prospectively addressed alcoholic patients with ongoing consumption. The only report was from an analysis of the Swiss Hepatitis C Cohort Study, which prospectively collected information on patient alcohol consumption during treatment: 16 patients (3% of the cohort) were reported to consume more than 24 g of alcohol per day, and their SVR rates were not different from the rest of the cohort [10]. Doctors are reluctant to treat alcoholic patients because they fear that these patients may experiment more side effects and have poor adherence and that heavy alcohol consumption may worsen antiviral treatment outcomes [11]. Current guidelines [4] recommend abstinence or minimal alcohol consumption 6 months prior to antiviral treatment. Problem drinkers without a dependence on alcohol will easily achieve the objective and, therefore, be treated [12], but achieving this objective is far more difficult for alcohol-dependent patients [13]; thus, alcohol problems represent a significant barrier against initiating HCV treatment [14]. The paradox is that alcoholic patients, who have the highest potential to progress to severe liver disease, are excluded from treatment without any published evidence. Our study is the first to address prospectively the issue of treating alcohol-dependent patients, the majority of whom have ongoing intoxication and the others experiencing a short period of abstinence, without requiring them to abstain from alcohol. We demonstrated that HCV treatment is quite efficient in these patients.

Factors associated with SVR

Apart from the usual predictors of SVR, two factors appeared to influence independently treatment efficacy. Excessive alcohol consumption during treatment was clearly associated with a failure to eradicate HCV. The effects of alcohol consumption on antiviral therapy have been a matter of debate for a long time. Earlier retrospective studies of interferon monotherapy showed decreased efficacy in patients who consumed alcohol before treatment, but alcohol abstinence at the initiation of treatment was a prerequisite [11]. In a large prospective epidemiological study, Anand *et al.* [15] showed that past alcohol use did not affect treatment outcomes, and recent alcohol use before the initiation of treatment did not result in reduced success rates in patients who completed treatment. Alcohol use during treatment was not assessed in this study. Our study is the first to systematically initiate and pursue treatment in patients with heavy consumption, and to document the duration of abstinence during the treatment period. We found a relationship between the length of abstinence during treatment and SVR. This relationship was not due to different treatment duration, because an effect was also observed after excluding patients who had failed to complete the full course of therapy. We could not exclude the possibility that patients with high consumption had decreased compliance to the daily treatment, especially ribavirin. The detrimental effect of alcohol consumption on treatment efficacy demonstrated here could be an argument against treatment without requiring abstinence. However, the proportion of patients with excessive consumption during treatment obtaining SVR was not negligible (33%). This validates the decision to treat even in case heavy consumption is maintained or relapses during treatment. The second factor was the ISR for drug status; patients with more severe drug problems before treatment were the most likely to have a SVR. This indicates that difficulties with drugs, such as pursuing injections despite substitution treatment, are not a reason to exclude patients from treatment.

Compliance

The good adherence to the course of antiviral therapy observed in this study was rather unexpected, as we initially hypothesized that more patients would stop treatment prematurely. The multidisciplinary team approach was important to achieve such an efficient performance. The close collaboration between hepatologists and addictologists allowed the matching of the modality and intensity of addiction care to the patient situation and willingness. Therefore, a patient with alcohol relapse could be managed quickly without interrupting HCV treatment. Importantly, abstinence for more than one month before starting therapy was not associated with increased retention in treatment, so

Research Article

the decision to treat a patient cannot rely on such a period of abstinence before treatment.

Alcohol consumption after treatment

One-third of the patients, half of whom were heavy drinkers at the onset of treatment, were durably abstinent at the end of follow-up. This outcome compared favorably with the usual care of addiction [16]. Notably, two-thirds of the patients were addressed by hepatologists, and 33% met an addictologist for the first time during the procedure. Thus, the treatment of HCV was an incentive for alcohol treatment, which was successful in some patients.

Treatment timing

Treating alcoholic patients was feasible and led to viral eradication and durable alcohol cessation in a number of them. Another question is why we should treat these patients early, without requiring a long period of abstinence before treatment. Dependent patients are known to pursue their consumption despite knowledge of its deleterious consequences. According to Miller and Rollnick [17], three important conditions cause someone to change: willingness to change, confidence in his capacity (self-efficacy), and readiness (this is the moment to do it now). When a patient consults with the willingness to obtain a treatment for hepatitis C, there is a risk that asking for 6 months of abstinence will discourage the patient, and clinical experience and studies have shown that a number of patients are lost to follow-up in this situation [14,18]. Patients may ask for another consult perhaps years later, but delaying the onset of treatment can lead to an increase in the severity of liver disease and occurrence of cirrhosis.

Study limitations

The non-randomized design of this study is a limitation. However, enrolling alcohol-dependent patients in such studies is difficult, and they have been excluded from all of the large multisite registration trials designed to assess the efficacy of antiviral therapy. The French "Agence Nationale de Recherche sur le SIDA", which is in charge of HCV studies, attempted to launch a prospective, randomized multisite study specifically for alcohol-dependent patients in 2009, but it ended up prematurely because of a lack of inclusions. Alternatively, we tried to build the best possible control group. The other limitation is the number of patients.

In conclusion, this study showed that alcohol dependent patients with ongoing excessive alcohol consumption or a short period of abstinence can be treated with peg-IFN and ribavirin with virological results similar to a matched control group when managed in a multidisciplinary setting. Furthermore, the antiviral course of therapy results in an improvement in the addictive behavior in one third of the subjects. We think that a motivated patient asking for treatment should be offered this possibility, even if alcohol consumption is still present, along with psychosocial care.

Financial support

This work was supported by the Association Fer et Foie, Rennes, France.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Some authors have been remunerated by Scherring Plough or Roche laboratories as occasional speakers, or have been sponsored for congress attendance.

The Association Fer et Foie has received unrestricted research grants from Scherring Plough or Roche laboratories.

References

[1] Rosman AS, Waraich A, Galvin K, Casiano J, Paronetto F, Lieber CS. Alcoholism is associated with hepatitis C but not hepatitis B in an urban population. Am J Gastroenterol 1996;91:498–505.
[2] Roudot-Thoraval F, Bastie A, Pawlotsky JM, Dhumeaux D. Epidemiological factors affecting the severity of hepatitis C virus-related liver disease: a French survey of 6, 664 patients. The Study Group for the Prevalence and the Epidemiology of Hepatitis C Virus. Hepatology 1997;26:485–490.
[3] Bellentani S, Pozzato G, Saccoccio G, Crovatto M, Croce LS, Mazzoran L, et al. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. Gut 1999;44:874–880.
[4] Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335–1374.
[5] Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24:289–293.
[6] McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, et al. The fifth edition of the addiction severity index. J Subst Abuse Treat 1992;9:199–213.
[7] Lainé F, Bendavid C, Moirand R, Tessier S, Perrin M, Guillygomarc'h A, et al. Prediction of liver fibrosis in alcoholic and nonalcoholic patients with features of the metabolic syndrome. Hepatology 2004;39:1639–1646.
[8] Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clinical Infectious Diseases 2009;49:561–573.
[9] Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, Schindlbeck N, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. Hepatology 2003;37:443–451.
[10] Bruggmann P, Dampz M, Gerlach T, Kravecz L, Falcato L. Treatment outcome in relation to alcohol consumption during hepatitis C therapy: an analysis of the Swiss Hepatitis C Cohort Study. Drug and Alcohol Dependence 2010;110:167–171.
[11] Mathurin P, Canva V, Dharancy S, Paris JC. Traitement de l'hépatite chronique virale C et consommation d'alcool. Gastroenterol Clin Biol 2002;26:B248–251.
[12] Nalpas B, Martin S, Fontaine H, Fabbro-Peray P, Brechot C, Pol S. Impact of medical recommendations on alcohol consumption in HCV positive patients. J Hepatol 2001;35:312–313.
[13] Cromie SL, Jenkins PJ, Bowden DS, Dudley FJ. Chronic hepatitis C: effect of alcohol on hepatitic activity and viral titre. J Hepatol 1996;25:821–826.
[14] Moirand R, Bilodeau M, Brissette S, Bruneau J. Determinants of antiviral treatment initiation in a hepatitis C-infected population benefiting from universal health care coverage. Can J Gastroenterol 2007;21:355–361.
[15] Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, et al. Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. Gastroenterology 2006;130:1607–1616.
[16] Dawson DA. Correlates of past-year status among treated and untreated persons with former alcohol dependence: United States, 1992. Alcohol Clin Exp Res 1996;20:771–779.
[17] Miller WR, Rollnick S. Motivational interviewing: preparing people for change. New York: The Guilford Press; 2002.
[18] Bini EJ, Brau N, Currie S, Shen H, Anand BS, Hu KQ, et al. Prospective multicenter study of eligibility for antiviral therapy among 4, 084 US veterans with chronic hepatitis C virus infection. Am J Gastroenterol 2005;100:1772–1779.