Short communication

Treatment outcome in relation to alcohol consumption during hepatitis C therapy: An analysis of the Swiss Hepatitis C Cohort Study

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\textbf{A B S T R A C T}

\textbf{Background:} Adherence to hepatitis C treatment is influenced by alcohol as is the action of interferon; yet the clinical significance of the latter remains unclear. The aim of our study was to investigate the influence of ongoing alcohol intake on sustained viral response (SVR) rates in adherent patients receiving hepatitis C treatment.

\textbf{Methods:} A retrospective analysis of patients treated with antiviral therapy for hepatitis C infection who were enrolled in the Swiss Hepatitis C Cohort Study was completed. Patients were eligible for the study if they had their HCV RNA tested 6 months following treatment completion and at least one cohort follow-up visit during HCV therapy, documenting the consumed amount of alcohol. They were assigned to three groups according to the amount of alcohol consumption: group A without alcohol consumption, group B ≤24 g/d alcohol and group C >24 g/d alcohol.

\textbf{Results:} 554 patients were included. Patients with at least 80% of the scheduled cumulative dose and duration did not significantly differ between the three groups. SVR rates according to alcohol consumption were 60% for non-drinkers (group A), 57% in group B and 50% in group C. No significant negative influence from alcohol consumption during therapy was observed in the multiple regression analysis for treatment success.

\textbf{Conclusion:} In this evaluation, we demonstrated comparable SVR rates in non-drinkers and in patients with daily amounts of alcohol intake up to 24 g during hepatitis C therapy.

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1. Introduction

Individuals with a history of alcohol abuse have a higher prevalence of hepatitis C virus (HCV) infection than the general population (Tsuji et al., 2006; Pares et al., 1990; Nalpas et al., 1992). Alcohol and HCV infection have a synergistic effect on progression of liver fibrosis and cirrhosis and on the risk of hepatocellular carcinoma (Poynard et al., 1997; Corrao and Arico, 1998; Wiley et al., 1998; Ikeda et al., 1998). Therefore, HCV positive patients who are not able to abstain from alcohol use especially need to eradicate the virus. At present there is reluctance in clinicians and current guidelines to treat HCV positive patients with ongoing drinking problems (European Association for the Study of the Liver, 2009; National Institute of Health, 2002; Ghaney et al., 2009).

Clinicians normally require complete abstinence for at least 6 months prior to treating alcoholics for hepatitis C, in addition, major clinical trials have excluded patients with ongoing alcohol use, resulting in little available data on the effect of alcohol consumption during HCV therapy (Loguercio et al., 2000). Several authors studied the influence of recent alcohol use (abstinence for less than 6 months before starting therapy) on HCV treatment outcomes (Oshita et al., 1994; Ohnishi et al., 1996; Okazaki et al., 1994). All of these studies demonstrated a decreased effectiveness and efficacy in heavy drinkers. Past alcohol use (abstinence for at least 12 months before starting HCV therapy) had no relevant impact on achieving sustained virological response (SVR) (Anand et al., 2006).

In their large study that included more than 4000 patients, Anand et al. concluded that alcoholics who adhere to a whole course of HCV therapy have the same response rate as non-drinkers. Whether these patients consumed alcohol during therapy and the amount consumed unfortunately was not assessed in this study (Anand et al., 2006).

Alcohol increases the replication of the hepatitis C virus and inhibits the anti-HCV action of interferon by multifactorial mechanisms, as several studies have shown (McCarty et al., 2008; Safdar and Schiff, 2004). The mechanisms of alcohol influencing HCV related liver injury are not clearly understood. Several factors
have been postulated including enhanced oxidative stress (Larraea et al., 1998; Barbaro et al., 1999; Cardin et al., 2001), modification of the immune system (Szabo et al., 2001) and direct increase of intracellular HCV replication in liver cells (Romero-Gomez et al., 2001; Pessione et al., 1998). The clinical relevance of these in vitro findings remains unclear.

The aim of this study was to examine the effect of ongoing alcohol intake on SVR rates in adherent patients receiving HCV antiviral therapy. A retrospective analysis was conducted in patients treated for chronic HCV infection in the Swiss Hepatitis C Cohort Study (SCCS).

2. Methods

2.1. Patients

SCCS collects prospective information on adults with confirmed HCV infection. These data are collected through standardized questionnaires, clinical examination and laboratory investigations, which are conducted yearly at eight centres providing specialist treatment across Switzerland (Prasad et al., 2007). Recruitment began September 1, 2000 and ended June 19, 2008, with a total of 3263 individuals enrolled in the cohort. At each follow-up visit, enrolled patients were asked about alcohol use since the previous visit. Follow-up visits took place every 6 months until 2005, and then cohort participants were followed-up yearly. Hepatitis C treatment indication was done by each centre irrespective of the cohort study. Possible alcohol interventions before or during hepatitis C therapy provided by the individual centres are not documented in the cohort database and could therefore not be evaluated in this study. In order to be eligible for enrolment in the present study, patients had to fulfil the following criteria:

- chronic hepatitis C treatment based on the combination of standard or pegylated interferon-alpha (IFN-α) and ribavirin;
- serum HCV RNA assay performed 6 months following treatment completion;
- at least one follow-up visit within 6 months before HCV treatment commencement and 6 months after the end of HCV treatment completion;
- a declaration about the amount of daily alcohol use in the above mentioned visit.

Cohort participants were allocated to three groups depending on the maximum self-reported amount of daily alcohol intake at the time of treatment. Patients refraining from alcohol use at follow-up visits during the period defined above were categorised as group A and are referred to as “non-drinkers”. Those drinking between 1 g/d and 24 g/d (up to 2 standard drinks) were assigned to “group B” and those drinking more than 24 g of alcohol a day to group C.

| Type of HCV medication used (pegylated interferon-alpha 2a/2b, standard interferon), duration of therapy (24 weeks for genotype 2/3, 48 weeks for genotype 1/4) and cumulative dose were assessed for each patient. A sufficient exposure to antiviral treatment was defined as at least 80% of the prescribed cumulative dose of each drug and at least 80% of the scheduled therapy duration. (McHutchison et al., 2002). In all patients, factors that could potentially influence therapy were recorded at the last follow-up visit before treatment started. These factors included HCV genotype, HCV viral load, treatment for depression or other psychiatric therapy, and liver cirrhosis (for detailed description of the SCCS protocol, see Prasad et al., 2007). The protocol for this study has been approved by the board of the cohort.

2.2. Statistical methods

We began by using cross-tabulations to examine the differences between the three groups in terms of their socio-demographic characteristics, HCV therapy outcomes (measured as SVR) and the above-mentioned factors potentially influencing the outcome. Chi-square coefficients were calculated and tested for two-sided statistical significance on the 0.05 alpha level (Table 1).

A multiple logistic regression model (logit model) was then calculated for predicting the probability of successful HCV therapy with SVR as a dependent variable and alcohol use during HCV therapy, HCV genotype, age, body mass index, liver cirrhosis, medication type, and adherence to therapy (30/80/80 rule, see Section 2.1) as predictor variables. To accentuate possible effects, we categorised the continuous variables alcohol during therapy (3 categories: 0 g/d, >24 g/d, >24 g/d; age (4 categories: <30 years, 30–39 y., 40–49 y., ≥50 y.) and BMI (≤18.5, <25, <30, ≥30). A dichotomous “compliance-index” was calculated in such a way that patients reaching at least 80% of the scheduled medication and therapy duration were considered compliant (value = 1), and patients not fulfilling either one of these two criteria were considered non-compliant (value = 0). For all variables in the model first categories were used as reference. This analysis comprised of 554 cases with valid data for all variables in the model. In an effort to not lose cases in the logit model due to missing data, we did not include HCV viral load and alcohol consumption before treatment. All data transformations and analysis were done with SPSSX Version 16 for Windows.

Table 1

<table>
<thead>
<tr>
<th>Study groups’ characteristics according maximum amount of daily alcohol consumption during HCV treatment*</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>Patient related</td>
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<td>Sex</td>
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<tr>
<td>Female</td>
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<td>&lt;30 y.</td>
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<tr>
<td>30–39 y.</td>
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<td>40–49 y.</td>
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<td>≥50 y.</td>
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<tr>
<td>Body Mass Index</td>
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<td>&lt;18.5</td>
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<td>≤25</td>
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<td>&gt;25</td>
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<tr>
<td>Cirrhosis</td>
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<td>Treatment for depression</td>
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<td>Treatment for other psych. disorder</td>
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<td>HCV disease related Genotype</td>
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<td>2</td>
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<tr>
<td>3</td>
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<td>4</td>
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<tr>
<td>HCV Viral load before treatment ≥2 × 10^5 IU/ml</td>
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<tr>
<td>HCV therapy related Medication type of HCV therapy</td>
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<tr>
<td>Ribavirin + P12 interferon</td>
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<tr>
<td>Ribavirin + recombinant interferon</td>
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<tr>
<td>Compliance with HCV therapy</td>
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<tr>
<td>≥80% of prescribed dosage reached</td>
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<tr>
<td>≥80% of treatment duration reached</td>
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<td>≥80% of dosage and duration reached</td>
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<td>Outcome of HCV therapy</td>
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* No significant differences on 5% α-level between values of any variable (Chi-square 2-tailed).

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3. Results

Table 1 gives a descriptive overview of the patients HCV disease and treatment related characteristics for the three study groups (A: 0 g/d, B: ≤24 g/d, C: >24 g/d alcohol during HCV therapy). Bivariate comparisons (Chi-square statistics) showed no significant differences of the value distributions for any of the included variables.

3.1. Patient characteristics potentially influencing therapy outcome

554 patients fulfilled the inclusion criteria in the present study. 447 (81%) did not drink any alcohol during HCV therapy and were allocated to group A (0 g/d alcohol), 91 (16%) had a maximum daily alcohol consumption of ≤24 g (group B) and 16 (3%) reported an alcohol intake of more than 24 g a day during antiviral therapy (group C). The maximum amount of self-reported daily alcohol intake was 100 g.

As mentioned above, the three study groups did not differ significantly according to sex, age, body mass index (BMI), treated psychiatric co morbidity, and presence of cirrhosis. However, it is notable that there was a higher proportion of males in group C (81%) compared to groups A (62%) and B (66%). Group C also had a higher proportion of above normal BMI (A: 34%, B: 36%, C: 50%). However, group A (non-drinkers) had a higher proportion of treated psychiatric disorders (other than depression) than groups B and C (A: 12%, B: 4%, C: 6%). Previous treatment for depression (A: 33%, B: 29%, C: 38%) and presence of cirrhosis (A: 20%, B: 19%, C: 19%) were quite equally distributed across the groups, affecting one-third, and one-fifth of the patients, respectively.

3.2. Alcohol intake before antiviral therapy commencement

Prior to inclusion in the SCCS, 76% of group A patients (non-drinkers) were already abstinent, another 5% had an alcohol consumption of more than 24 g a day before going on treatment, but were able to abstain during treatment. 80% of group C patients consumed more than 24 g of alcohol a day before going on HCV therapy. By starting therapy the alcohol intake was reduced from >24 g/d to ≤24 g/d in 43% and to abstinence in 31%. All in all, 75% of those drinking >24 g/d before starting their hepatitis C treatment managed to reduce their consumption during therapy, 53% of those drinking between 1 g/d and 24 g/d before therapy managed to abstain during treatment.

3.3. HCV disease related factors potentially influencing therapy outcome at baseline

Genotype 1 was the most commonly found genotype in the study population (48%), followed by genotypes 3 (35%), 2 (10%) and 4 (7%). The prognostic unfavourable genotypes, 1 and 4, were in total, present in 55% of group A (0 g/d) and B (≤24 g/d), and in 75% of group C (>24 g/d).

High viral load, defined as >2 × 10^6 IU/ml, was present in 22% of the non-drinkers, in 20% of ≤24 g group and in 13% of >24 g group. These differences did not reach statistical significance.

3.4. Type of interferon used and factors of adherence (HCV treatment related characteristics)

Patients of group C (>24 g alcohol/d) were more often treated with pegylated interferon (INF) –α 2b than the other two groups.
PEGylated INF-α 2a was part of the combination therapy in 66%, 55%, and 50% of groups A, B and C patients, respectively. Recombinant interferon was used only in a minority of the patients (A: 4%, B: 6%, C: 6%).

As far as anti-HCV drug exposure was concerned, 60% of group A patients reached 80% or more of the prescribed cumulative dose of each of the antiviral drugs, compared to 64% in group B, and 63% in group C. 83% of group A, 77% of the group B and 75% of group C reached at least 80% of the scheduled treatment duration. None of these differences were statistically significant. Overall, 58% of patients were compliant with HCV therapy in terms of dosage and duration (A: 58%, B: 59%, C: 63%). The three groups did not differ significantly. Thus, the amount of daily alcohol consumption during treatment was not linked with adherence.

3.5. HCV treatment outcome

Overall, 60% of the study patients achieved SVR. Therapy outcomes did not differ between the three groups: SVR was seen in 60% of the non-drinker group, in 57% of <24 g/d group and in 50% of those patients drinking more than 24 g/d alcohol during therapy. Alcohol consumption did not have a significant impact on SVR, neither with <24 g/d nor with >24 g/d (Table 2).

3.6. Multiple logistic regression analysis

The multiple logistic regression model (Nagelkerke R² = .387) showed that adherence to therapy (medication and duration of ≥80% scheduled), genotypes 2 and 3, age under 40, and body mass index of <18.5 positively influenced treatment outcome, whereas the pre-existence of liver cirrhosis had a negative impact on SVR rate.

Conflict of interests

P.B. and L.F. designed the study protocol. L.K. managed the literature searches and summaries of previous related work. L.F. and M.D. undertook the statistical analysis and P.B. wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.
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