The Impact of Tobacco Smoking on Disease Progression and Response to Treatment in Chronic Hepatitis C

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Abstract

Smoking plays a deleterious role in progression of chronic HCV disease. The aim of the work is to assess the effect of cigarette smoking on disease progression and response to the treatment in chronic hepatitis C. 100 compensated male Chronic HCV patients were subjected to full history taking including full detailed history of tobacco smoking. Patients were divided into two groups: Chronic heavy smokers (who smoke more than 20cig/day and for more than 20 packs/year) and non-smokers groups. Full general and abdominal examination (excluding symptoms and signs of chronic liver disease), full laboratory investigations, and liver biopsy were done as a pre-enrollment for combination therapy (Peg-IFN-alpha and RBV).

The smokers were 38 (38%) while non-smokers were 62 (62%). The histological activity grades were as followed: mild 64 (64.0%), moderate 22 (22.0%) and severe 14 (14.0%). There were no fibrosis in 8 (8%) early fibrosis in 58 (58%) and advanced fibrosis was in 34 (34%). 12 (12%) out of the one hundred patients were non-responder to Peg-IFN and ribavirin combined therapy and 88 (88%) were responders. Smokers showed highly significant increase in moderate and severe necro-inflammatory versus non smokers. There was no statistically significant difference between the two groups in the early stage of liver fibrosis in spite of increase in advanced fibrosis in the smoker group. All the smokers had degree of fibrosis, while 6.5% of the non-smoker showed no fibrosis. Concerning the response rate of chronic HCV to the combined therapy of Peg-IFN and Ribavirin we did not find a significant difference between the two groups.

In Conclusion: Smoking plays a deleterious role in progression of chronic HCV disease because of enhancing the necro-inflammatory activity. Although additional work is necessary to confirm, these findings may raise the possibility that smoking could play a role in aggravating liver fibrosis. Therefore, it is highly recommended to quit smoking especially in chronic HCV patients.


Introduction

THE effect of smoking on human health is serious and in many cases, deadly. There are approximately 4000 chemicals in cigarettes, hundreds of which are toxic. The ingredients in cigarettes affect internal functioning organs and the efficiency of the immune system of the body. The effects of cigarette smoking are destructive and widespread [1].

The World Health Organization has estimated that 3% of the world population (170-200 million individuals) is infected with HCV [2]. Many of the patients with persistent infection show the medical conditions of chronic hepatitis C (CHC) [3].

Progression of chronic hepatitis is highly variable among individuals, as the result of several hosts, viral and environmental factors. The latter have been extensively investigated in order to ameliorate hepatitis C outcome, particularly in difficult-to-treat patients. In addition, recent data suggested that cigarette smoking might enhance activity grade in patients with chronic hepatitis C, thereby increasing progression of fibrosis. This assumption mostly relies on epidemiological evidences in the absence of pathogenic studies [4,5].

The only way to interfere with the progression of the disease is represented by the removal of the pathogenic agent [6]. The National Institute of Health identifies the use of PEG-IFN-alpha plus Ribavirin (RBV) as the preferred therapy for the treatment of chronic HCV infection [7].

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Although the introduction of Peg-IFN-alpha and RBV regimens for the treatment of CHC has resulted in substantial improvements in overall response rate, treatment remains a challenge, particularly for certain populations. Accurately predicting therapeutic responses is the critical issue in the management of diseases [8].

**Aim of the work:**

Our goal in this study was to assess the effect of cigarette smoking on disease progression and response to the treatment in chronic hepatitis C.

**Patients and Methods**

A total of consecutive 100 compensated male Chronic HCV patients attending the National Hepatology and Tropical Medicine Research Institute (NHTMRI) from June 2007 to April 2008. All HCV patients were subjected to full history taking including full detailed history of tobacco smoking (tobacco consumption was estimated in a standardized evaluation of smoking history) [9]. Each patient completed a questionnaire (Table 2) before starting the treatment, and was divided into two groups: chronic heavy smokers (who smoke more than 20 cig/day and for more than 20 packs/year) and non-smokers groups. Full general and abdominal examination (excluding symptoms and signs of chronic liver disease), full laboratory investigations, and liver biopsy were done as a pre-enrollment for combination therapy (Peg-IFN-alpha and RBV) and follow-up investigation was done at week 0, 1, 2,4,8,12,16,20,24.

**Laboratory investigations:**

Full Blood Count (FBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), Serum Alkaline Phosphatase, Serum Glutamyl Transferase, Serum albumin, Total protein, Coagulation profile, Serum bilirubin (total and indirect), Alpha fetoprotein, Kidney function tests, Auto antibodies screening for autoimmune hepatitis, TSH, Fasting Blood sugar, HCVab, HBsAG and HCV RNA PCR quantitative and qualitative.

**Other investigations:**

Abdominal ultrasound, Electrocardiography and fundus examination. Upper GI endoscopy (if needed).

**Follow-up investigations:**

FBC, ALT, AST, Serum bilirubin (total and indirect), Serum creatinine, HCV RNA PCR (quantitative) at week 12 for early virological response (if 2 log down or less) and qualitative PCR-sero-negative of HCV RNA at week 24 (as a predictor of end-of-treatment virological response).

**Liver biopsy methodology:**

After taking informed consent, liver biopsy was performed for the 100 patients using 16-gauge true-cut needles and was scored using Metavir scoring system for both inflammation and fibrosis. The scoring consists of using a grading and a staging system. The grade gives an indication of the activity or amount of inflammation, and the stage represents the amount of fibrosis or scarring. The grade is scored from 0 to 3 (0= no activity, 1= mild, 2= moderate, and 3= severe activity). The degree of inflammation is important because it is considered a precursor to fibrosis. The fibrosis score is also assigned to a number from 0 to 4; (0=no scarring, 1=minimal scarring corresponding to stellate enlargement of portal tracts without septae formation, 2=enlargement of portal tracts with rare septae formation, 3=numerous septae without fibrosis, 4=cirrhosis or advanced scarring of the liver). Patients graded =A2 and/or =F2 were considered to have significant pathology [10].

**Statistical analysis:**

Data was analyzed using SPSS win statistical package version 15. Numerical data were expressed as mean ± SD. Qualitative data were expressed as frequency and percentage. Chi-square test (or Fisher’s exact test) was used to examine the relation between qualitative variables. McNemar test was used to examine the change of repeated qualitative variables. For quantitative data, comparison between two groups was done using Mann-Whitney test. p-value less than 0.05 were considered significant.

**Results**

Baseline characteristics were shown in Table (1): All patients were males with mean age 41.4 (10.9), BMI 26.1 (4.1) and HCV viremia of 1445290 (5081127) IU/Ml. The smokers were 38 (38%) while non-smokers were 62 (62%). The histological activity grades were as followed: Mild 64 (64.0%), moderate 22 (22.0%) and severe 14 (14.0%). There were no fibrosis in 8 (8%), early fibrosis in 58 (58%) and advanced fibrosis was in 34 (34%). 12 (12%) out of the one hundred patients were non-responder to PegIFN and ribavirin combined therapy and 88 (88%) were responders. Checklist for Smoking history was shown in Table (2). Table (3) shows the necro-inflammatory activity grades in smokers and non-smokers. In the non-smokers group, the activity was 48 (77.4%), 8 (12.9%) and 6 (9.7%) in mild, moderate and severe respectively. While the activity in smokers group
was mild in 16 (42.1%), moderate in 14 (36.8%) and severe in 8 (21.1%). It was obvious that A2-A3 is highly significant in the smoker group \((p<0.02)\) (Fig. 1). The difference in liver fibrosis stages between the two groups was shown in Table (4). The non-smoker group had no fibrosis in 8 (12.9%), early fibrosis in 36 (58.1%) and advanced fibrosis in 18 (29.0%). The smoker group showed no fibrosis in 0 (0%), early fibrosis in 22 (57.9%) and advanced fibrosis in 16 (42.1%). It is clear that there was no statistically significant difference between the two groups in the early stage of liver fibrosis in spite of increase in advanced fibrosis in the smoker group (Fig. 2). All the smokers had degree of fibrosis, while 6.5% of the non-smoker showed no fibrosis. Table (5) shows the treatment response in the chronic HCV patients (in non-smokers and smokers) with combined therapy (Peginterferon and Ribavirin). It revealed 8 (12.9%) of non-smokers were non-responders while 54 (87.1%) were responders. Almost the same results were noticed in the smoker group as 4 (10.5%) and 34 (89.5%) were non-responders and responders respectively.

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### Table (1): Baseline characteristics of the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.4 (10.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 (4.1)</td>
</tr>
<tr>
<td>HCV (PCR) viremia IU/MI:</td>
<td>1445290 (5081127)</td>
</tr>
<tr>
<td>Smokers (n [%])</td>
<td>38 (38%)</td>
</tr>
<tr>
<td>Non-smokers (n [%])</td>
<td>62 (62%)</td>
</tr>
</tbody>
</table>

### Table (2): Checklist for Smoking history [9].

- Age when the patient started to smoke
- How old was the patient when he became a regular smoker?
- Duration of smoking
- Were there periods when the patient stopped smoking?
- Is the patient currently smoke?
- At what age did the patient stop smoking?
- Amount smoked
- Average life time number of cigarettes smoked per day
- Average life time number of cigar smoked per day
- Average life time amount of pipe tobacco smoked per day
- Packs-years of cigarettes smoked (average packs/day x number of years as smoker)

### Table (3): Necro-inflammatory activity and smoking.

<table>
<thead>
<tr>
<th>Necro-inflammatory Activity</th>
<th>Smoking</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>48 (77.4%)</td>
<td>16 (42.1%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>8 (12.9%)</td>
<td>14 (36.8%)</td>
</tr>
<tr>
<td>Severe</td>
<td>6 (9.7%)</td>
<td>8 (21.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>38</td>
</tr>
</tbody>
</table>

Moderate and severe groups \(p<0.02\) (significant).

### Table (4): Liver fibrosis in both groups.

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>Smoking</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8 (12.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Early</td>
<td>36 (58.1%)</td>
<td>22 (57.9%)</td>
</tr>
<tr>
<td>Advanced</td>
<td>18 (29.0%)</td>
<td>16 (42.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>38</td>
</tr>
</tbody>
</table>

\(p=0.218\) (insignificant).
Table (5): Response rate to the treatment.

<table>
<thead>
<tr>
<th>Response</th>
<th>Non smoker</th>
<th>Smoker</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>8 (12.9%)</td>
<td>4 (10.5)</td>
<td>12</td>
</tr>
<tr>
<td>Yes</td>
<td>54 (87.1%)</td>
<td>34 (89.5)</td>
<td>88</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>38</td>
<td>100</td>
</tr>
</tbody>
</table>

Discussion

Given the importance of smoking in disease progression in HCV patients, it is of interest to investigate the potential impact of smoking on histologic progression among patients with chronic hepatitis C. Our study provides evidence for a significant increase in the necro-inflammatory activity in HCV patients who consumed tobacco heavily than non-smokers. Previous studies [9,11,12] found a clear relationship between the necro-inflammatory activity and tobacco consumption. On the contrary, nearly no differences in the early stages of fibrosis were noticed between both groups. Hezode, et al. [9] observed no relationship between degree of fibrosis and both daily and lifetime tobacco consumption. While Pessione, et al. and Dev, et al. [12,13] indicated significant relationship between tobacco consumption and fibrosis. In addition, interestingly all chronic HCV patients in our smoker group had degree of fibrosis and they had increase in advanced fibrosis versus non smokers. Their studies were retrospective and their patients were alcohol consumers as an independent co-factor of fibrosis. In comparison, our study was prospective and all our patients denied any alcohol consumption. Furthermore, smoking may have rapid and reversible hepatotoxic effect that accelerates the histologic activity grades and alcohol could have synergist effect in fibrosis progression [14].

Nicotine, a major component of tobacco smoking, is rapidly absorbed through the lungs and released into the circulation. Consequently, it is mainly metabolized in the liver. The effect of nicotine on the liver was studied on rats, which developed significant liver lesions characterized by steatosis and focal or confluent necrosis [15]. Therefore, a precautionary advice of reducing or stopping tobacco smoking could be valuable to patients with HCV infection, also because of the well-known burden of disease caused by tobacco [16].

Another explanation was reported by Swati, et al. [17] who admitted that acrolein (environmental pollutant) ,which is found in smokers 4-folds more than in non-smokers, is contributing to smoking induced inflammation and hepatic injury.

Concerning the response rate of chronic HCV to the combined therapy of PegIFN and Ribavirin we did not find a significant difference between the two groups. However, EL-Zayadi [18] reported that cigarette smoking might adversely influence HCV treatment outcome, because smokers suffering from chronic HCV have lower response rate to IFN compared to non-smokers. Moreover, they hypothesised that smokers who smoke more than 30 cigarette a day had a response rate of only (12.5%). On the other hand, the viral and host factors have both been linked to the response to IFN treatment among patients with chronic HCV and their relative importance and potential interaction are unclear [19]. These findings raise the question of whether smoking might rapid fibrosis progression, which merits confirmation in prospective studies.

Conclusion:

Smoking plays a deleterious role in progression of chronic HCV disease because of enhancing the necro-inflammatory activity. Although additional work is necessary to confirm, these findings may raise the possibility that smoking could play a role in aggravating liver fibrosis. Therefore, it is highly recommended to quit smoking especially in chronic HCV patients.

References

6- DAVIDE F., LODATO F., MAZZELLA G. and COLECCHIA A.: Effects of combined IFN-alpha/ribavirin treat-


