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• VIRAL HEPATITIS •

Impact of cigarette smoking on response to interferon therapy in chronic hepatitis C Egyptian patients

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Abstract

AIM: Smoking may affect adversely the response rate to interferon-α. Our objective was to verify this issue among chronic hepatitis C patients.

METHODS: Over the year 1998, 138 chronic hepatitis C male Egyptian patients presenting to Cairo Liver Center, were divided on the basis of smoking habit into: group I which comprised 38 smoker patients (>30 cigarettes/d) and group II which included 84 non-smoker patients. Irregular and mild smokers (16 patients) were excluded. Non eligible patients for interferon-α therapy were excluded from the study and comprised 3/38 (normal ALT) in group I and 22/84 in group II (normal ALT, advanced cirrhosis and thrombocytopenia). Group I was randomly allocated into 2 sub-groups: group Ia comprised 18 patients who were subjected to therapeutic phlebotomy while sub-group Ib consisted of 17 patients who had no phlebotomy. In sub-group Ia, 3 patients with normal ALT after repeated phlebotomies were excluded from the study. Interferon-α 2b 3 MU/TIW was given for 6 mo to 15 patients in group Ia, 17 patients in group Ib and 62 patients in group II. Biochemical, virological end-of- treatment and sustained responses were evaluated.

RESULTS: At the end of interferon-α treatment, ALT was normalized in 3/15 patients (20%) in group Ia and 2/17 patients (11.8%) in group Ib compared to17/62 patients (27.4%) in group II (P=0.1). Whereas 2/15 patients (13.3%) in group Ia. and 2/17 patients (11.8%) in group Ib lost viraemia compared to 13/62 patients (26%) in group II (P = 0.3). Six months later, ALT was persistently normal in 2/15 patients (13.3%) in group 1a and 1/17 patients (5.9%) in group Ib compared to 9/62 patients (14.5%) in group II (P = 0.47). Viraemia was eliminated in 1/15 patients (6.7%) in group Ia and 1/17 patients (5.9%) in group Ib compared to 7/62 patients (11.3%) in group II, but the results did not mount to statistical significance (P = 0.4).

CONCLUSION: Smokers suffering from chronic hepatitis C tend to have a lower response rate to interferon-α compared to non-smokers. Therapeutic phlebotomy improves the response rate to interferon-α therapy among this group.

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INTRODUCTION

It has been reported that cigarette smoking causes a variety of life threatening disorders such as pulmonary, cardiovascular, neoplastic, secondary polycythemia and others[1]. In addition, cigarette smoking has hepatotoxicity independent from alcoholic cirrhosis[2,3] and chronic hepatitis B virus carriers[4]. It increases the 5-year mortality rates of patients with alcoholic cirrhosis[5]. Furthermore, tobacco consumption has been associated with an increased risk of hepatocellular carcinoma (HCC) in patients with viral hepatitis[6-8]. A recent report has found that cigarette smoking was associated with increased fibrosis and histological activity in chronic hepatitis C (CHC) patients. It suggested that cigarette smoking could influence liver disease either by direct hepatotoxicity through its various constituents or secondary to erythrocytosis, immunological impact or synergistic effect with other factors such as alcohol[9].

The spectrum of liver injury in patients with CHC is broad and many factors influence the severity and progression of the lesion such as age[10], route of infection[11], genotype[12], concomitant chronic hepatitis B virus (HBV) infection[13] and others. Furthermore, many factors influence the natural history of CHC, clinical picture, and response to therapy, yet not all identified factors[12]. The adverse effects of heavy smoking particularly the response to therapy among CHC patients have been overlooked. Accordingly, we were motivated to study the impact of heavy smoking on clinical presentation, laboratory parameters and response to interferon-α (IFN-α) therapy in these patients.

MATERIALS AND METHODS

Over the year 1998, 138 CHC Egyptian male patients presenting to Cairo Liver Center for assessment of eligibility to interferon therapy were recruited. All patients met the following inclusion criteria: hepatitis C virus (HCV) antibody positive for ELISA, detectable HCV-RNA (Innolipa PCR) in serum, negative for HBsAg (Abbot ELISA), absent clinical and ultrasonographic evidence of cirrhosis, no ascites or hepatocellular carcinoma. No patient had received previous course of IFN-α therapy.

A standardized questionnaire to assess the smoking history was used[14] and accordingly all patients were divided into: smokers (group I) which consisted of 38 patients who smoked >30 cigarettes/d and non-smokers (group II) which included 84 patients who never smoked. Sixteen patients who were irregular, mild and passive smokers as well as pipe water and cigar smokers were excluded owing to difficulty in calculating smoking index. All patients in both groups were residents away from known

districts of high carbon monoxide pollution. None of the patients received drugs causing haemolysis over the preceding 6 mo period. All patients in both groups were assessed for haemoglobin, haematocrit, serum iron, and liver profile before liver biopsy. Patients who had persistently normal transaminases or had thrombocytopenia (platelet count less than 80 000/mm^3, 1 patient from group 1 and 16 patients from group 2) were considered non-eligible to interferon therapy and therefore excluded from the study.

Liver biopsy was performed using a true-cut needle to 37 patients from group I and 68 patients from group II scheduled for IFN-α therapy. All liver biopsy specimens were fixed in formalin, embedded in paraffin and routinely processed. The histological grade of disease activity and fibrosis was assessed using a reproducible scoring system[15] as follows: A 1 to A 3 for the degree of necroinflammatory activity (A 1 = mild, A3 = marked) and stage F0 to F4 for the degree of fibrosis (F0 = no fibrosis, F4 = cirrhosis). Two patients from group 1 and 6 patients from group 2 who had F4 (established cirrhosis) were also eliminated from IFN-α therapy. Iron staining using Perl's stain was done to non-cirrhotic specimen in both groups and scored according to percentage of iron stained hepatocyte.

Phlebotomy at a 2-wk interval till achieving low normal serum iron level was performed to 18 randomly allocated cases in group I patients (Ia), whereas 17 smoker patients had no phlebotomy and formed group Ib. Before undergoing phlebotomy all patients were instructed about its possible complications and all gave informed consent. None of the patients developed serious complications and all continued their schedule of phlebotomy. On serial ALT follow up, persistent normalization of ALT was observed in 3 patients in group Ia and therefore they were excluded from interferon therapy.

Thirty two smoker patients (15 from group1a and 17 from group 1b) and 62 non smoker patients from group II with persistent elevation of ALT received IFN-α therapy -3 MU TIW for 6 mo with serial evaluation of transaminases and test for HCV-RNA at the end of treatment and 6 mo later.

Statistical data was presented as mean±SD for the numeric variables. *t*-test was performed to compare both groups to each other. Response to therapy was categorized into responders and non-responders then presented into cross tables. χ^2 analysis was performed to assist the difference between the two groups. A *P* value of less than 0.05 was accepted as a level of significance.

RESULTS

Patients in group 1 had a significantly higher haemoglobin level ranging 16.1-19.1 g/dL with a mean of 16.9±0.54 g/dL compared to the patients in group 2 whose haemoglobin level ranged 13.5-16.3 g/dL with a mean of 15.3±0.59 g/dL. All patients in group 1 (100%) had a haemoglobin level exceeding 16 g/dL compared to 12/84 (14.3%) in patients of group 2.

The haematocrit level among group 1 patients ranged 56.1-61.4% with a mean of 56.3±0.86%, while group 2 patients had a haematocrit level ranging 45-55.9% with a mean of 54.8±1.16%, the difference was statistically significant ($P<0.005$). All patients in group 1 had a haematocrit value exceeding 55% compared to 14.3% of group 2 patients.

The mean serum iron level was significantly higher in group 1 (160.4±38.36 μg/dL) with a range of 100.3-283 μg/dL compared to group 2 (148.8±28.11 μg/dL) with a range of 90-194.3 μg/dL ($P<0.05$). Serum iron in 12 (31.5%) patients of group 1 was above normal level.

The mean serum uric acid level was 5.4±1.0 mg/dL in group 1 (range of 4-9 mg/dL) compared to 5.0±0.7 mg/dL (range of 3.8-6.9 mg/dL) in group 2, and the results were statistically significant ($P<0.01$).

Liver biopsy was performed to 37 patients from group 1 and 68 patients from group 2. Mild hepatitis was recorded in 10 (27%) patients of group 1 and 39 (57.4%) of group 2, whereas 17 patients (45.9%) of group 1 and 20 patients (29.4%) of group 2 had moderate hepatitis. Severe hepatitis was recorded in 8 patients (21.6%) of group 1 and 3 patients (4.4%) of group 2. Cirrhosis was recorded in 2 patients (5.4%) of group 1 and 6 patients (88%) of group 2. Iron staining using semiquantitative Perl's stain was positive with predominant periportal localization and associated steatosis in 3 (8.6%) patients of group 1 and 1 patient (1.5%) of group 2.

The end treatment biochemical response (ETBR) was reported in 5 patients (15.6%) of group 1 and 17 patients (27.4%) of group 2. Six months later only 3 patients (9.4%) of group 1 showed sustained normal ALT compared to 9 patients (14.5%) of group 2. The end treatment virological response (ETVR) was reported in 4 patients (12.5%) of group 1 and 3 patients (26%) of group 2. Six-months later, the sustained virological response (SVR) was reported in 2 patients (6.3%) of group 1 and 7 patients (11.3%) of group 2, but the differences did not reach statistical significance ($P>0.05$).

Among group I patients, ETBR in patients who had phlebotomy (group Ia) was recorded in 3 patients (20%) compared to 2 patients (11.8%) in those underwent no phlebotomy (group Ib). Two patients (13.3%) in group Ia had sustained biochemical response (SBR) compared to 1 patient (5.9%) in group 2b.

ETVR was found in 2 patients (13.3%) of group Ia compared to 2 patients (11.8%) of group Ib. SVR after 6 mo obtained in 1 patient of both groups (6.7% and 5.9%) respectively. Therefore, repeated phlebotomy increased both ETBR and SBR, but had no effect on virological responses (ETVR or SVR).

In group Ia repeated phlebotomy led to a significant decrease in mean ALT level from 167±50.3 to 112±377 IU/L ($P<0.01$).

DISCUSSION

Many studies have shown that smoking is an independent factor contributing to progression of HBV induced cirrhosis[4], alcoholic cirrhosis[1] and HCC development[6-8]. A recent French study has shown similarly that smoking favors progression to cirrhosis in chronic HCV infection independent of other co-morbid conditions[9].

The impact of smoking on various liver disorders has been extrapolated from experimental studies .It has been suggested that tobacco induced liver injury is ascribed to oxidative stress associated with lipid peroxidation[16,17]. In patients with CHC, the reduction in the concentration of hepatic, plasmatic and lymphocytic glutathione could favor the hepatotoxic effect of smoking[18]. Data from experimental studies suggest that nicotine, a major component of tobacco smoke, was rapidly absorbed through the lungs and released into circulation. Thereafter, it is mainly metabolized through the liver inducing lesions characterized by steatosis and focal or confluent necrosis[19].

A recent study demonstrated that smoking was mainly related to increased inflammatory activity but not to the stage of fibrosis[20], whereas Pessione *et al*.[9] provided evidence that smoking could worsen the degree of fibrosis in CHC independent of other co-morbid conditions. Advanced fibrosis adversely affected the response to interferon therapy[21,22], but this could not explain why smokers had lower response to interferon therapy compared to non-smokers as patients in both groups had comparable histopathological affection at entry of study. Cigarette smoking could increase generation of oxygen radicals. Chronic viral hepatitis patients who were cigarette smokers tended to have lower levels of natural anti-oxidants compared to non-smokers[23].

Smoking could induce a secondary form of polycythemia.

Smoker's polycythemia was attributable to increased carbon monoxide. The latter interfered with oxygen transport and utilization[24]. Secondary polycythemia may be associated with increased red cell turnover and subsequent rise of serum iron and tissue iron. In support of this hypothesis in our study, all smoker groups had higher hemoglobin and haematocrit compared to non-smoker group. In our study all HCV smoker patients had higher serum iron compared to HCV non-smoker patients as well.

It has long been recognized that hepatic iron overload could promote hepatic fibrosis in hereditary haemochromatosis[25]. Serum iron stores were frequently increased in patients with CHC[26]. Enhanced liver fibrosis has been reported in HCV infected patients with stainable iron in liver biopsy compared with controls with no detectable liver iron[27]. The mechanism by which iron accumulates in CHC patients has not been established but might in part be the result of iron release from damaged hepatocytes[28].

Another possible mechanism is that smoker polycythemia contributes to increased serum iron by increased cell turnover.

In support of this point of view, it was found that phlebotomy ameliorated not only symptoms related to smoker's polycythemia, but also transaminase level and resulted in persistent normalization of ALT level in 3/38 smoker patients. In our study, non-smoker patients had a better-sustained virological response rate compared to smoker patients. Although, phlebotomy resulted in a slight amelioration response rate, but results did not reach statistical significance. Many reports[29,30] showed significant improvement in serum ALT levels in interferon non-responders when they underwent iron reduction by therapeutic venesection. Three prospective, randomized controlled trials showed that iron reduction could increase the response rate to interferon therapy. While another multi-center trials showed no significant improvement in response of CHC to iron reduction treatment, although, histological improvement was documented even in patients with iron therapy alone[31].

This could be explained by other possible mechanisms such as immune alterations. Cigarette smoking may induce immune impairment by increasing apoptosis of lymphocytes, and counteracting interferon effect[32]. It was shown that tobacco smoking had a suppressive effect on human immunity as a result of decreased serum concentration of immunoglobulins and lysosyme decreased absolute number of (CD16+) NK-cells and elevated population of (CD8+) T-cytotoxic lymphocytes entailing a decrease in CD4+/CD8+ ratio[33]. Cigarette smokers exhibited impaired NK cytotoxic activity and unbalanced production of pro- and anti-inflammatory cytokines[34]. Smoking could alter immune response either directly through impairment of antigen receptor mediated signal transduction pathways leading to T cell anergy[35] or indirectly through brain immune interactions[36].

In conclusion, smokers suffering from CHC tend to have lower response to IFN-α compared to non-smokers. Therapeutic phlebotomy improves the response rate to IFN-α therapy among this group. This deserves further evaluation in prospective study. Chronic hepatitis C patients should be advised to avert smoking before embarking on interferon therapy.

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