Steatosis as a Predictive Factor for Treatment Response in Patients With Chronic Hepatitis C

IVÁN ANTÚNEZ, MD*; NESTOR APONTE, MD*; ALBERTO FERNÁNDEZ-CARBIA, MD FCAP MD†; FEDERICO RODRÍGUEZ-PEREZ, MD*; DORIS H. TORO, MD*

***Background*. Hepatic steatosis has been described in 31-72% of chronic hepatitis C virus (HCV) liver biopsies. Steatosis has been related to disease progression and suggested as a predictor of treatment response in chronic HCV. This study aims to evaluate the presence and degree of steatosis in liver histology of patients with chronic HCV prior to combination therapy with interferon (INF) and ribavirin (RBV), and how it influences treatment response.**

***Methods.* The medical charts of patients with chronic HCV who received treatment at the San Juan Veterans Affairs (VA) Medical Center from 1998 to 2002 were reviewed. Selected patients completed therapy, had a pre-treatment liver biopsy, genotype determination, and pre and post treatment HCV-RNA levels. Patient's age, sex and body mass index (BMI) were determined. Pre-treatment liver biopsy slides were reviewed and graded for steatosis by a hepatopathologist blinded to the treatment outcome. Steatosis was graded by the presence of fat in total biopsy area as: mild (<33%), moderate (33-66%), severe (>66%) or absent. Treatment response was defined as virological clearance measured by HCV RNA at the end of treatment and 24 weeks after completion of treatment. The presence of steatosis was compared to BMI, HCV genotype and treatment response.**

***Results*. 46 patients met the inclusion criteria. All patients were male of Hispanic origin. Mean age: 52.7 years (range: 40-68). Mean BMI: 27.5 kg/m2 (range: 21.1-35.9). HCV genotype 1 was present in 67% of patients. 82.6% (38/46) of the patients had hepatic steatosis: 29 (63%) mild, 7 (15%) moderate and 2(4%) severe. 16.6% (8/46) of the biopsies did not show steatosis. Overall, the response rate for those with steatosis was 31.6% (12/38): 10/29 (34.5%) mild, 1/7 (14.3%) moderate and 1/2 (50%) of severe. 75% (6/8) of those without steatosis responded to treatment. This difference (31.6% vs.75%) was statistically significant (p=.042). The mean BMI of both groups was similar (27.7 kg/m2 for those with steatosis and 26.6 kg/m2 for those without steatosis). This difference was not statistically significant (p=.308).**

***Conclusions*. The results of our study show a high prevalence of steatosis in the liver histology of patients with chronic HCV. The presence and degree of steatosis in our HCV patients appears to be unrelated to either genotype or BMI.**

Furthermore, the response to therapy is negatively influenced by the presence of steatosis regardless of genotype. Hepatic steatosis, mild, moderate or severe, appears to be an independent predictor of poor response to therapy.

Key words: Hepatitis C, Hepatic steatosis, Predictive value of tests

Hepatitis C virus infection affects approximately 2% of the United States population and is the leading cause of liver transplantation (1,2). Hepatic steatosis is a common histological finding in patients with chronic hepatitis C infection; however the pathophysiology of steatosis and its role in disease progression have not been established. Previous studies have reported the prevalence of hepatic steatosis to range from 31 to 72 % in patients with chronic hepatitis C (3-9). The causes underlying the fat accumulation in chronic hepatitis C patients may encompass obesity, drugs, alcohol abuse, diabetes and concomitant infections. However, even when all of these causes are carefully excluded, a significant proportion of patients chronically infected with hepatitis C virus may still have steatosis (8,10). This feature is so frequent among chronic hepatitis C patients compared with patients with other chronic hepatitis that it is

From the *Department of Medicine,Gastroenterology Section, Veterans Affairs Medical Center, San Juan, Puerto Rico and the †Laboratory of Cytology and Surgical Pathology, University Pathologists, San Juan, Puerto Rico.

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Address for correspondence: Doris H. Toro, MD, Chief, Gastroenterology Section (111G- OPA), Veterans Affairs Medical Center, #10 Casia St., San Juan, P.R. 00921-3201 Email: DorisToro@med.va.gov

considered of diagnostic significance (8). The pathogenesis of hepatic steatosis in patients with chronic hepatitis C is currently under investigation. Recent studies have implicated that viral factors, such as genotype, maybe a critical determinant for the development of hepatic steatosis. Patients with hepatitis C genotype 3 are more likely to develop hepatic steatosis than those with genotype 1. Furthermore, recently published study demonstrated regression of hepatic steatosis in genotype 3 patients that achieved sustained therapeutic response (11,12). *In vitro* and *in vivo* studies have shown that hepatitis C virus core protein expression in either cell culture systems or in transgenic mice directly leads to the development of steatosis in the liver (13,14). The most important concern regarding the clinical significance of hepatic steatosis in chronically infected patients is whether it influences liver disease progression or if it is solely an innocent bystander.

The morbidity and mortality associated to hepatitis C infection is related to the development of cirrhosis and its complications (17). It has been shown that the progression to cirrhosis is clearly related to the grade of inflammation and stage of fibrosis (15). Many factors have been proposed to be associated with the development of fibrosis in patients with chronic hepatitis C infection. Although the strength of association varies, these factors include male gender, advanced age, excessive alcohol use, duration of infection, hepatitis C genotype, and hepatitis C viral load (16-21). Recently, nonalcoholic fatty liver disease and its associated risk factors have also been associated with hepatic fibrosis and several studies have found that the grade of fibrosis significantly correlates with hepatic steatosis in patients with chronic hepatitis C (22-24). The stage of fibrosis has been proposed as a predictive factor of hepatitis C treatment response to interferon (25). The clinical and pathological significance of hepatic steatosis in chronic hepatitis C requires further clarification. In view of this data, this study was designed to retrospectively evaluate the response of chronic hepatitis C patients treated with the combination of interferon/ribavirin, as measured by HCV RNA PCR serum viral clearance, based on the degree or presence of hepatic steatosis found on the pre-treatment liver biopsies.

Methods

The medical charts of patients with chronic hepatitis C treated with the combination of interferon and ribavirin at the VA outpatient liver clinics were reviewed. An independent pathologist, blind to the treatment outcome, examined the pre- treatment liver biopsies and staged them for grade of steatosis and fibrosis. Histological findings were compared to the virological response to therapy at the end of the treatment period and 6 months later. The histological activity (grade) and degree of fibrosis (stage) was assessed according to the modified histological activity index (HAI) of Ishak (26). The grading of steatosis was assessed using a modified pathologic protocol previously applied to patients with pure nonalcoholic fatty liver disease (27). The extent of hepatic steatosis was graded as follows: 0: none, 1: mild <= 33%, 2: moderate (33-66%), 3:severe (>66%).

A virological clearance of the virus as measured by hepatitis C RNA - PCR quantification of <100 copies/ml was used as a definition of response to treatment. The study was submitted and approved by the San Juan VA Medical Center Institutional Review Board.

Only the medical charts with a pre-treatment liver biopsy were included in the study. The histological activity (grade) and degree of fibrosis (stage) was assessed according to the modified histological activity index (HAI) of Ishak (23). Steatosis grade was assessed using a modified pathologic protocol previously applied to patients with pure nonalcoholic fatty liver disease. The extent of hepatic steatosis was graded as follows: 0: none, 1: <=33%, 2: >= 33%. Patients were then divided into 2 groups. Group A comprised patients who responded to treatment, and group B those patients who did not respond to treatment. Response rate was also evaluated for those with and without steatosis. The degree of steatosis and fibrosis was compared with treatment response between groups. The baseline variables identified above were compared between both groups and those with significantly different prevalence were also examined with a multivariate regression analysis. Student t-test was used for the continuous variables.

Results

Forty-six medical charts of patients with chronic hepatitis C met the inclusion criteria during the evaluated study period. All the patients were males of Hispanic origin. Their mean age was 52.2 years (range: 40-68) and mean BMI was 27.5 kg/m^2, ranging from 21.1 to 35.9 kg/m^2. Sixty seven percent (67%) of the study population had hepatitis C genotype 1. 82.6% (38/46) of the patients had hepatic steatosis: 29 (63%) mild, 7 (15%) moderate and 2(4%) severe. 16.6% (8/46) of the liver biopsies did not show steatosis. (Figure 1) The patients were then divided into those with steatosis of any degree (38/46) and those without it (8/46).

Genotype distribution within groups was similar; 63% of those without steatosis and 68.4% of those with any degree of steatosis had genotype 1. (Figure 2) The mean

Figure 1. Degree of Hepatic Steatosis in Liver Biopsies

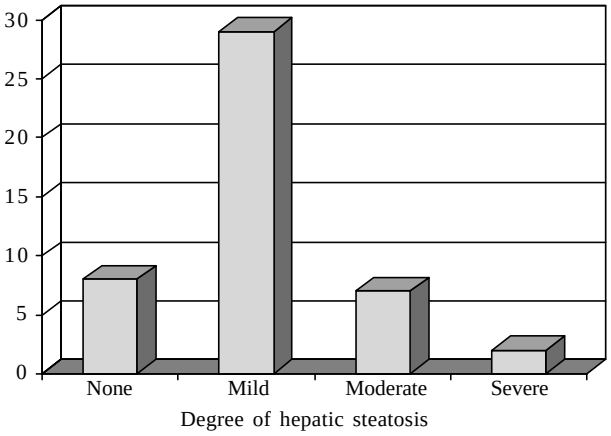
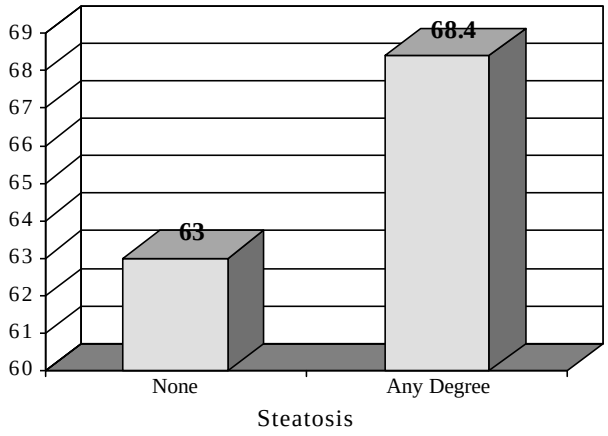


Figure 2. Hepatitis C Genotype 1 Distribution Between Groups



BMI of both groups was also similar; 26.6kg/m^2 for the no-steatosis group vs. 27.7 kg/m^2 for those with any degree of steatosis. (Figure 3) This difference was not statistically significant (p=.308). When considering the response to treatment, the overall response rate for those with steatosis was 31.6% (12/38): 10/29(34.5%) of those with mild steatosis, 1/7 (14.3%) with moderate and 1/2(50%) with severe steatosis. Those patients without steatosis had a 75% (6/8) response rate. The difference between those with any degree of steatosis vs. those without steatosis (31.6% vs.75%) was statistically significant (p=0.042). (Figure 4).

Figure 3. Body Mass Index Distribution Between Groups

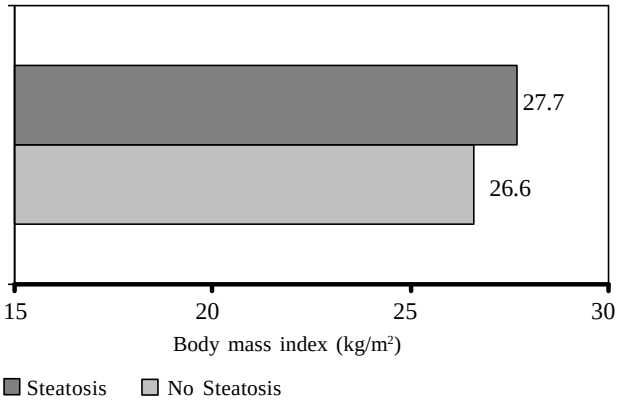
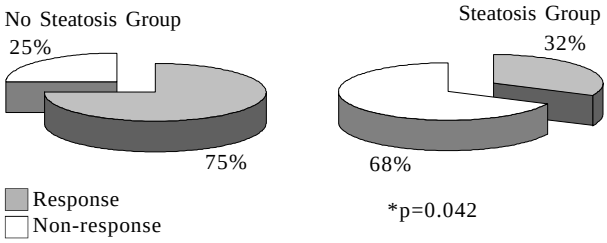


Figure 4. Treatment Response



Discussion

Our study demonstrated several important findings relevant to the medical community who is searching for predictors of treatment response for patients with chronic HCV. First, it showed a high prevalence of steatosis in the liver histology of patients with chronic HCV regardless of hepatitis C genotype. Second, it demonstrated that the presence and degree of hepatic steatosis in our HCV patients appears to be unrelated to either genotype or BMI. Furthermore it demonstrates that the response to therapy is negatively influenced by the presence of steatosis regardless of the HCV genotype. In summary, hepatic steatosis, mild, moderate or severe, appears to be an independent predictor of poor response to therapy. Future prospective studies should be done at a larger scale to further validate these findings.

Resumen

Se ha descrito la presencia de infiltración grasa en un 31-72% de las biopsias de hígado de pacientes con hepatitis C crónica. Se ha relacionado la presencia de grasa con progresión de la enfermedad hepática y se ha sugerido como un predictor de respuesta a tratamiento. Este estudio busca evaluar la presencia y gradación de la grasa en la histología hepática de pacientes con hepatitis C crónica previo a tratamiento con la terapia de combinación de interferón alfa y ribavirina y ver la influencia en la respuesta a tratamiento. Se revisaron los expedientes médicos de pacientes con hepatitis C crónica que recibieron tratamiento en el Hospital de Veteranos desde 1998 al 2002. Los pacientes incluidos completaron la terapia, tenían

biopsia previa a tratamiento, determinación de genotipo y carga viral previa y posterior a completar el tratamiento. Todas las biopsias hepáticas fueron nuevamente revisadas por un hepatopatólogo. El grado de infiltración de grasas hepática se determinó basado en la cantidad de grasa en toda el área de la biopsia como: leve (33%), moderada (33-66%), severa (>66%) o ausente. La respuesta a tratamiento se definió como la ausencia de carga viral al final de tratamiento y 24 semanas después. La presencia de grasa hepática se comparó con el índice de masa corporal (BMI), el genotipo de hepatitis C y la respuesta a tratamiento. Los cuarenta y seis expedientes cumplieron con los criterios de inclusión, todos los pacientes eran varones de origen hispano. La edad promedio fue de 52.7 años (rango: 40-68), BMI promedio 27.5 kg/m^2 (rango: 21.1-35.9). El genotipo 1 estaba presente en 67% de los pacientes. En general, el 82.6% de los pacientes tenían grasa en el hígado, 29 (63%) leve, 7 (15%) moderada y 2 (4%) severa. Por el contrario, un 16.6% de los pacientes no tenían grasa alguna en el hígado. En general, la respuesta a tratamiento para aquellos con evidencia de grasa en el hígado fue de 31.6%: 10/29 (34.5%) leve, 1/7 (14.3%) moderada y 1/2 (50%) severa. El 75% (6/8) de esos sin evidencia de grasa en el hígado respondieron a tratamiento. Esta diferencia (31.6% vs. 75%) fue estadísticamente significativa (p = .042). El promedio de índice de masa corporal fue similar entre los dos grupos (p =.308). Los resultados de este estudio demuestran una alta prevalencia de infiltración grasa en las biopsias hepáticas de pacientes con hepatitis C crónica. La presencia y la cantidad de la grasa en el hígado parece no estar relacionada con el genotipo o con el índice de masa corporal. Mas aún, la respuesta a tratamiento está negativamente influenciada por la presencia de grasa sin importar el genotipo.

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