LETTER TO THE EDITOR

Non-alcoholic Fatty Liver Disease and Antiviral Therapy in Hepatitis C

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Sir,

I have read the excellent paper by Shifflet and Wu.1 Watanabe et al reported that several metabolic disturbances, such as obesity, insulin resistance, and hepatic steatosis, are significant risk factors for decreased sustained virologic response to interferon and ribavirin combination antiviral therapy in chronic hepatitis C patients.2

It should be noted, for completeness, the influence of non-alcoholic fatty liver disease (NAFLD) on post liver transplantation (LT) antiviral treatment. It is well known that the natural history of recurrent hepatitis C is accelerated after LT. Hepatitis C driven fibrosis response in the allograft leads to the development of graft cirrhosis in approximately 25% of recipients after a follow-up of 5–10 years. More than 10% of patients who undergo transplantation for hepatitis C cirrhosis eventually require retransplantation for hepatitis C related graft failure.3

In relation to organ shortage, Llado et al affirmed that retransplantation is not an option for recurrent hepatitis C cirrhosis after LT.4 For this reason, it is mandatory to protect in the best way the graft by treating with antiviral therapy for recurrent hepatitis C.5

In a substantial proportion of infected recipients, liver injury remains mild despite high viral burden.

Several factors have been clearly shown to be associated with fibrosis progression rate. Metabolic conditions and steatosis are emerging as independent cofactors of fibrogenesis.

Machicao et al suggested that allograft steatosis is a common occurrence after orthotopic liver transplantation (metabolic alterations, immunosuppression) and is independent of concomitant HCV infection.6

Till now, in our experience, there is evidence for the importance of parameters such as body mass index (BMI, kg/m²), cholesterol (mg/dL), triglycerides (TG, ng/mL) and hepatic percentage of steatosis in response to therapy with pegylated interferon (PEG-IFN) alfa-2b and ribavirin in patients with recurrent hepatitis C after LT.7

Response to therapy was evaluated in relation to virologic response (HCV-RNA assay was performed at 1, 3, 6, 12 and 18 months): sustained virologic response (SVR) was defined as the absence of serum HCV-RNA (virologic remission) and serum alanine aminotransferase (ALT) activity within the reference range for at least 6 months after; sustained biochemical response (SBR) was defined as a decrease in serum ALT activity to within the reference range but with reappearance or persistently detectable serum HCV-RNA; non-response (NR) was defined as persistence/relapse at the end of therapy of HCV-RNA and no decrease in ALT activity or relapse at the end of therapy.

Ten patients (31.2%) stopped therapy for side effects, SVR was observed in six cases (6/22, 27.2%), SBR in seven cases (7/22, 31.8%) and NR in nine cases (9/22, 40.9%).

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The observed distributions of BMI, cholesterol, TG and percentage of steatosis were confirmed to be normally distributed by the one-sample Kolmogorov-Smirnov Goodness of Fit test procedure. Comparison of BMI, cholesterol, TG and percentage of steatosis among NR, SVR and SBR groups were analyzed by ANOVA with a post hoc Bonferroni test and correlation between variables was tested by Pearson’s test. The univariate analysis was performed to estimate the probability of response on the basis of the above mentioned variables.

BMI, TG, and percentage of steatosis in the NR group (26.8 ± 3.3, 245.3 ± 84.4 and 26.8 ± 23.6, respectively) were higher than the values observed in the SVR group (20.4 ± 2.6, p < 0.001; 108.3 ± 48.4, p = 0.002; 5.75 ± 2.2, p = 0.027, respectively) and the SBR group (21.5 ± 1.6, p = 0.003; 132.4 ± 51.2, p = 0.008; 6.2 ± 2.4, p = 0.033, respectively). The differences between the SVR and SBR groups were not significant for the above mentioned variables. As for cholesterol, no significant differences were registered in the NR (197.6 ± 47.3), SVR (149.3 ± 37) and SBR (153.4 ± 41.5) groups.

Pearson’s correlation test (correlation coefficient > 0.7, p < 0.001 for every correlation) showed a strong correlation between BMI, cholesterol, TG and percentage of steatosis.

For patients with BMI < 25 and TG < 160, the chance of SVR was 48 times higher than that of NR. The chances of SVR and SBR for patients with percentage of steatosis < 15 were 12 times more than that with higher percentage of steatosis values.

The observed diminished response has been hypothesized to be due to decreased IFN bioavailability in overweight patients, presence of hepatic steatosis, which itself is a predictor of poor response to antiviral treatment. Moreover, increased expression of suppressor of cytokine that inhibit IFN signaling may be one mechanism by which overweight reduces the IFN response.

Some authors have postulated that the possible altered immune function in obesity may be mediated by leptin resistance. Leptin is an important modulator of the Th-1 response. It is possible that patients with steatosis resulting from insulin resistance and not virally mediated may be unable to upregulate adequately the Th-1 response via IFN because of underlying significant leptin resistance. This could lead to altered viral clearance and a decrease in SVR.

It is known that retransplantation is not an option for recurrent hepatitis C cirrhosis after LT. Therefore, our experience tells us the importance of a better histologic and internistic evaluation in order to reach the highest number of SVR in patients with recurrent hepatitis C.

We can conclude how the amount of steatosis can be noted specifically in biopsy examination reports of patients with relapsed chronic hepatitis C and how the management of dismetabolism, diet and exercise therapy can improve BMI, liver histology and, therefore, the response to antiviral therapy.

References