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Research Article

Thyroid Dysfunction as Predictor of Sustained Virological Response (SVR) During HCV Treatment with PEGylated Interferon and Ribavirin

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ABSTRACT

Background: Thyroid disease (TD) is the most common endocrine disorder associated with HCV infection, especially in conjunction with interferon-α (IFN-α)-based therapy. The aim of the work was to evaluate the role of thyroid dysfunction in HCV treated patients with combination therapy of interferon and ribavirin and correlate it with fibrosis stage. Materials and Methods: A retrospective study of 850 HCV genotype 4 Egyptian patients treated with combination therapy were studied. Their thyroid function was normal before the initiation of the treatment then 218 patients developed thyroid dysfunction after starting the treatment. Liver biopsy was done for all patients and they were divided into two groups; group I: early fibrosis and group II: significant fibrosis. Thyroid profile and sustained virological response (SVR) were assessed. Results: The SVR in HCV patients who did not develop thyroid dysfunction was 55.7% while it was 88.1% in patients who developed thyroid dysfunction during treatment. There were no significant differences between both groups in body mass index (BMI), gender, liver fibrosis, level of viremia (PCR) and SVR (PCR negative). Hypothyroidism was detected in 70.6 % and thyrotoxicosis in 29.4 %. The PCR negative patients were more in group II (92.3%) and 7.7% were PCR positive, while in group I the PCR negative patients were 84.2% and 15.8% were PCR positive. Conclusion: This study nurtures the necessity to carefully observe thyroid function in patients during and following completion of interferon treatment. Our findings suggest that thyroid dysfunction can be considered an important predictive value of SVR in HCV combination therapy.

Keywords: HCV, thyroid disease, interferon, sustained virological response and liver fibrosis

INTRODUCTION

Hepatitis C virus (HCV) infection is a foremost cause of chronic liver disease. The World Health Organization (WHO) assessed that up to 180 million people are infected with HCV worldwide[1,2]. There is a large load of HCV in Egypt as it has the highest reported prevalence globally[3]. The most common endocrine disorder associated with HCV infection, especially in conjunction with interferon-α (IFN-α)-based therapy, is thyroid disease (TD)[4-6]. Approximately 40% of CHC patients develop thyroid disorders while receiving IFN-α[7,8]. However, several studies have confirmed an association of hepatitis C virus (HCV) infection with autoimmune thyroid diseases AITD both in adults and children[8,9]. The thyroid disorders perceived in patients with chronic hepatitis C (CHC) are characterized by a high risk of autoimmune thyroiditis (AT) and hypothyroidism in females and increased serum anti-thyroid antibody concentrations without thyroid dysfunction[10]. Moreover, a high incidence of papillary thyroid cancer (PTC) has been detected in HCV patients in the presence of AT[11,12]. Recent data have confirmed a strong association of thyroid disease with interferon (IFN)-α therapy in patients with CHC[13,14]. HCV and IFN-α can act in synergism to initiate AITD through immune stimulation in patients. The IFNs are cytokine proteins consistent with their name, they interfere with viral replication[9]. The association of interferon and ribavirin throughout treatment strongly stimulate the immune system in order to eradicate the virus[15]. Predictors of response to therapy help as decision implements for physicians to support distinguish patients who are likely or unlikely to attain an SVR, and to consider pre-treatment counseling in patients with a reduced likelihood of effective therapy, perhaps sparing them the side effects and cost of therapy[16]. The aim of the work is to evaluate the role of thyroid dysfunction in HCV treated patients with combination therapy of interferon and ribavirin and correlate the thyroid dysfunction in HCV patients with fibrosis stage.

MATERIALS AND METHODS

A retrospective study of 850 HCV Egyptian patients of

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Table 1: The demographic data of the patients.

		Number (%)	Range	Mean (S±D)
Age		218	21 - 57	39.94 (8.94)
BMI		218	21 - 46	29.36 (5.66)
PCR(IU/ml)		218	1156 - 2250000	464075.8 (524142.2)
Gender	Male	74 (33.9%)		
	Female	144 (66.1%)		
Fibrosis stage	Early fibrosis	114 (52.3%)		
	Significant fibrosis	104 (47.7%)		
PCR (IU/ml)	SVR	192 (88.1%)		
	Relapser	26 (11.9%)		
Thyroid	Hypothyroidism	154 (70.6%)		
	Thyrotoxicosis	64 (29.4%)		

genotype 4 were recruited from the HCV clinic at National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt were included in the study. Our patients received weekly injections of PEG-IFN-2a or -2b plus ribavirin orally for 48 weeks and followed up for 24 weeks after treatment. They had normal pre-treatment TSH levels, and thyroid functions were monitored serially at 12, 24 and 48 weeks. Patients with hepatitis B, HIV, autoimmune hepatitis, primary biliary cirrhosis, alcoholic liver disease, Wilson's disease and smokers were excluded. Of the 850 HCV patients 218 (25.6%) developed thyroid dysfunction on due course. The sustained virological response (SVR) for all patients on one hand and patients who developed thyroid dysfunction on the other hand were assessed and classified as followed:

-Patients response to treatment was classified as followed: At 72 weeks (24 weeks post-treatment):

PCR negative----------sustained virological response (SVR)

PCR positive----------relapser

-According to the Metavir system, liver fibrosis was staged on a scale from F0 to F4. The F0 and F1 were considered early fibrosis, whereas the scores F2-F4 was considered significant fibrosis[17]. Furthermore, patients were divided into two groups based on their fibrosis score: early fibrosis (group I) and significant fibrosis (group II). The study was approved by the Ethical Committee of the National Hepatology and Tropical Medicine Research Institute.

Statistical analysis

Qualitative categorical variables are described by proportions and Percentages. Chi-squared test of independence is applied. Quantitative variables were described by the Mean, Standard Deviation (SD), the Range (Maximum – Minimum) Kolmogorov-Smirnova and Shapiro-Wilk tests of normality are used to test normality hypothesis of all quantitative variables. As the variables were found to be abnormally distributed Mann and Whitney U test are used for comparing the changes between the two groups. Significant level was considered at $P < 0.05$ (S); while $P < 0.01$ was considered highly significant (HS). Two Tailed tests were assumed throughout the analysis for all statistical tests.

RESULTS

The SVR in HCV patients who did not develop thyroid dysfunction was 55.7% while it was 88.1% in patients who developed thyroid dysfunction during treatment. Table (1) showed patients' characteristics, in which the age was 39.9±8.94 years and BMI was 29.36±5.66. The male to female ratio was 1:1.9; early fibrosis was present in 52.3% and significant fibrosis in 47.7% of the patients, hypothyroid in 70.6 %, thyrotoxicosis in 29.4 % and SVR (PCR negative) in 88.1% and relapse (PCR positive) in 11.9%. Table (2) showed correlation between the stage of fibrosis and other predictive factors of SVR. There were no significant differences between both groups related to BMI, gender, liver fibrosis, and the level of viremia (PCR). There was highly significant difference in the age between both groups, as patients were elder in group II. Concerning the SVR (PCR negative patients) was more in group II (92.3%) and number of relapsers (PCR positive) was (7.7%), while the SVR was 84.2% and relapsers were 15.8% in group I.

DISCUSSION

Thyroid dysfunction (TD) represents the most common autoimmune disorder observed during CHC treatment. The incidence of TD during interferon-(IFN-) plus ribavirin combination therapy has been reported to occur in 4.7% to 27.8% of patients, with a mean incidence of 12.1%. This condition may be the result of immune activation by interferon[18].

Traditional predictors of response to combination therapy of HCV identified in international studies regardless of genotype can be divided into three groups: (1) epidemiological factors including patient age, sex and race (2) viral factors, most importantly the pre-treatment viral load, rapid virologic response, and the genotype and (3) histological factors including the amount of fibrosis and steatosis and worsening of hepatic fibrosis was the best surrogate marker of disease progression[15]. In our study the SVR in HCV patients who did not develop thyroid dysfunction was 55.7% while it was 88.1% in patients who developed thyroid dysfunction during treatment. Kamal et al.,[19] reported in a previous report a SVR rate more than 50% in patients treated with pegylated interferon and ribavirin combination therapies. This can be partially explained by the presence of mild viremia, young age of the patients and the prevalence of females in our study. The

Table 2: Correlation between the stage of fibrosis and other predictive factors of SVR.

		Early fibrosis (Group I)	Significant fibrosis (Group II)	P-value
Gender	Male (%)	42 (36.8 %)	32 (30.8%)	0.504
	Female (%)	72 (63.2 %)	72 (69.2%)	
PCR(IU/ml)	SVR (%)	96 (84.2%)	96 (92.3%)	0.193
	Relapser (%)	18 (15.8%)	8 (7.7 %)	
Age	Number (mean ± SD)	114 (36.07 ± 8.19)	104 (44.17 ±7.77)	0.000001
BMI	Number (mean ± SD)	114 (29.28 ± 7.14)	104 (29.46 ±3.44)	0.0678
PCR(IU/ml)	Number (mean ± SD)	114 (403948.05 ± 441571.81)	104 (529985.03 ± 599332.06)	0.37226

P<0.05 significant; p<0.01 highly significant

higher SVR in patients who developed thyroid dysfunction during treatment suggest that thyroid dysfunction can be considered an important predictive value of SVR in HCV combination therapy. Moreover, the SVR was higher but not statistically significant in the group of significant fibrosis. Similarly, Barut et al.,[17] reported that TD patients achieved SVR (88.9%) more frequently than euthyroid (61.2%) but were non-significant. However, Tran et al.,[14] found a positive and significant association between thyroid disease and viral clearance. Furthermore, previous investigators showed that TD in their patients during treatment with pegylated interferon and ribavirin combination therapies had no correlation with SVR rate or viral kinetic[20,21]. On the contrary, EASL[22] clinical practice guidelines for management of HCV infection emphasized that the strongest baseline predictors of SVR were: HCV genotype; genetic polymorphisms located in chromosome 19 (IL28B) and the stage of liver fibrosis. However, Tran et al.,[14] explained that IFN and ribavirin have a synergistic effect in augmentation and stimulation of the immune system in order to eradicate the virus and the thyroid is one of the innocuous spectators in this accentuated response.

CONCLUSION

This study nurtures the necessity to carefully observe thyroid function in patients during and following completion of interferon treatment. Our findings suggest that thyroid dysfunction can be considered an important predictive value of SVR in HCV combination therapy. The authors declared no conflict of interest.

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