Thyroid Dysfunction During Combined Pegylated Interferon Alpha and Ribavirin Therapy in Patients of Chronic Hepatitis C-Virus Infection

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ABSTRACT

Objective: To determine frequency of thyroid dysfunction among patients of chronic hepatitis C receiving combined pegylated interferon alpha and ribavirin therapy.

Study Design: Cross sectional study.

Place and Duration of Study: Department of Medicine, Military Hospital Rawalpindi, from Jan to Jul 2017.

Methodology: One hundred and twenty patients, aged 18–60 years from both genders, with established hepatitis C were included; while the patients with decompensated liver disease, previous antiviral treatment, pre-existing thyroid, autoimmune or severe cardiopulmonary disease and on immuno-suppressants or steroids were excluded. After formal informed consent, they were prescribed 24 weeks pegylated interferon alpha-2 (3 million units subcutaneously thrice weekly) and oral ribavirin (1000–1200 mg daily) therapy. After 12 weeks, serum thyroid stimulating hormone, free thyroxine and triiodothyronine levels were determined by chemiluminescence technique.

Results: Out of 120 patients, 100 (83.33%) were males and 20 (16.67%) were females with male to female ratio of 5:1. Mean thyroid stimulating hormone levels at baseline and 12 weeks were 2.86 ± 1.03uiu/ml and 2.16 ± 0.79 uiu/ml respectively. Mean triiodothyronine levels at baseline and 12 weeks were 3.27 ± 1.31pg/ml and 2.69 ± 1.01 pg/ml respectively. Mean thyroxine levels at baseline and 12 weeks were 1.26 ± 0.38 pg/ml and 1.07 ± 0.53 pg/ml respectively. Frequency of thyroid dysfunction was found in 40 (33.33%) patients.

Conclusion: Frequency of thyroid dysfunction among hepatitis C patients receiving combined pegylated interferon alpha and ribavirin therapy is quite high.

Keywords: Chronic hepatitis C, Pegylated interferon alpha, Ribavirin, Thyroid dysfunction.

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INTRODUCTION

Hepatitis C Virus (HCV) causes disease in about seventy one million human beings worldwide, as a result of which it is a known reason of hepatic diseases, including liver failure and hepatocellular carcinoma.[1] Over 2.7 million persons have been exposed to HCV in the United States alone.[2] Prevalence of anti HCV antibodies in general population of Pakistan is 6.8%.[3] Natural history of disease reveals about 50–80% of people who have acute hepatitis due to HCV persist as HCV positive.

The risks for spread of hepatitis C infection are transfusion of blood and blood products, use of unsterilized sharp instrument or needle stick injuries and tattooing. The other routes are vertical transmission and through sexual transmission, the chance of sexual risk factor has been increasing in men, since 2012.[4] Studies have showed that repeated intravenous injections with contaminated needles were greatly linked with Hepatitis C virus detection in serum. Many of HCV antibody detected people had no data of parenteral alimentation or needle stick injuries which is the usually mentioned cause for HCV.

Commonly, HCV positive cases have chronic hepatic ailment, which may cause hepatic cirrhosis and hepatocellular carcinoma (HCC). Chronic HCV infection is one of the common reasons of chronic liver ailment. Normally patients with acute or chronic disease are asymptomatic. Proactive search and correlation for features of systemic disease is often the indicator of progressing HCV illness.[5]

HCV treatment is suggested for patients at high risk for progression of liver disease. It is postulated that hepatitis C virus particles will induce Interferon-alpha and interferon-beta in thyroid gland as a segment of individual's reaction to immunological stimuli, and it was recently reported that hepatitis C patients who developed Interferon Induced thyroiditis (IIT) showed that IIT appears in genetically prone

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individuals whose threshold for evolving thyroiditis is lowered by INF-alpha.[6,7] Combination therapy with pegylated interferon-alpha (Peg-IFN-alpha) and ribavirin has resulted in significant improvement in the disease. HCV has many genotypes among population which is an important determinant of the virological response to HCV treatment.[8] Research has been carried out in different countries to elicit relation of thyroid gland pathology and cumulative Peg-INF and Ribavirin treatment. In previous studies around 26.8% patients with chronic hepatitis C receiving combination therapy developed thyroid dysfunction.[9] While interferon induced thyroiditis has been stated in patients getting pegylated IFN-alpha for a various disorders, but many cases were reported in chronic HCV infection.

This study will help us to know the magnitude of thyroid disorder associated with HCV treatment in our society. Hence, we can know the importance of thyroid function monitoring during the combination therapy for early and prompt treatment of these disorders, which will improve patient management.

METHODOLOGY

This cross sectional study was carried out at Military Hospital Rawalpindi from January to July 2017. Formal permission was taken from "Hospital Ethical Committee" (Cert no. 8001/2/2017).

Inclusion Criteria: Patients of hepatitis C, age 18–60 years of both genders, were included in the study.

Exclusion Criteria: Patients with decompensate liver disease, thyroid disease, goiter, data of therapy with interferon or ribavirin, immune related diseases or significant heart or lung disorder, on immunosuppressant drugs or steroids were excluded.

A total of 120 established patients (sample size was calculated by using WHO calculator; prevalence of thyroid dysfunction during combined pegylated interferon alpha and ribavirin therapy in patients of chronic hepatitis C virus infection was 26.80%, according to study conducted by Huang *et al,*[9]) of chronic HCV disease without cirrhosis were taken through consecutive non probability sampling technique after obtaining formal informed consent. These patients were prescribed 24 weeks pegylated interferon alpha-2 (3 million units subcutaneously thrice weekly) and oral ribavirin (1–1.2 grams per day) therapy. They were told to return after twelve weeks for their thyroid function tests.

Samples were taken for serum Thyroid Stimulating Hormone (S. TSH), serum free thyroxine (S. Free T4) and serum total triiodothyronine (S.T3) using standard technique. Thyroid function was determined by chemiluminescence. Investigations were done at Armed Forces Institute of Pathology under supervision of pathologist.

Thyroid levels at start of treatment and 12 weeks after the conclusion of treatment were entered in the patient proforma. Patients with serum TSH in the range of 0.72–4.2uiu/ml, serum free T3 in the range of 2.57–4.43pg/ml and serum free T4 in the range of 0.93–1.7ng/dI were labeled as euthyroid. People having thyroid stimulating hormone levels lower than 0.72iu/ml, T3 greater than 4.43pg/ml and thyroxine levels greater than 1.7ng/dI were designated as hyper functional or thyrotoxic. People having thyroid stimulating hormone value greater than 4.2iu/ml, T3 lower than 2.57pg/ml and thyroxine lower than 0.93ng/dl categorized as hypo functional.

Statistical Package for Social Sciences (SPSS) version 22.0 was used for the data analysis. This consists of Quantitative variables which are age and Qualitative variables, such as gender and thyroid disease (functional result). Descriptive statistics such as mean and standard deviation were determined for quantitative variables including age of patient, TSH value, S. T3 and thyroxine value at start of therapy and at 12 weeks. Frequencies and percentages shown for qualitative variables such as gender and thyroid pathology linked with peg interferon alpha and ribavirin treatment. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

In total of the 120 patients, 100 (83.33%) were male and 20 (16.67%) were females. Male to female ratio was 5:1. The range of age was from twenty to sixty-years with mean age of 39.25 ± 9.23 years.

Majority of the sample 76 (63.33%) was from 18–40 years. Mean TSH levels at baseline and 12 weeks were 2.86 ± 1.03iu/ml and 2.16 ± 0.79iu/ml respectively (Table-I). Mean T3 values at the start and at twelve weeks were 3.27 ± 1.3 pg/ml and 2.69 ± 1.01 pg/ml respectively. Mean thyroxine values at the start and at twelve weeks were 1.26 ± 0.38pg/ml and 1.07 ± 0.53pg/ml respectively (Table-I).

Incidence of thyroid pathology in people with chronic Hepatic disease taking both interferon alpha and ribavirin was seen in 40 (33.33%) patients, conver-

sely there was no thyroid pathology in 80 (66.67%) patients.

Table-I: Serum thyroid profile at baseline and 12 weeks (n=120).

Parameters	Timeline	Mean ± SD
Thyroid Stimulating Hormone levels (iu/ml)	Baseline	2.86 ± 1.03
	12 weeks	2.16 ± 0.79
Triiodothyronine levels (pg/ml)	Baseline	3.27 ± 1.31
	12 weeks	2.69 ± 1.01
Thyroxine levels (pg/ml)	Baseline	1.26 ± 0.38
	12 weeks	1.07 ± 0.53

Thyroid pathology on age clusters has shown that no major deviation among various age clusters was there as shown in Table-II. Whereas thyroid pathology with regards to gender revealed no major deviation among males and females.

Table-II: Thyroid dysfunction with respect to age and gender.

Variables	Value/ Type	Thyroid Dysfunction		*p*-value
		Yes (%)	No (%)	
Age (Years)	18-40	26 (21.58)	50 (41.67)	0.789
	41-60	14 (11.62)	30 (24.9)	
Gender	Male	37 (30.71)	63 (52.29)	0.057
	Female	03 (2.49)	17 (14.11)	

DISCUSSION

Interferon alpha (IFN-a) or together with some medication has been utilized to manage HCV ailment.[10,11] Nevertheless these medications result in many adverse effects in the HCV positive people, such as flu-like features, bone marrow effects, symptoms pertaining to CNS and many endocrine disorders.[12]

Reported prevalence of thyroid diseases in hepatitis C virus positive population is more than in the normal people.[13] Thyroid disorders are suggested because of drugs such as Interferon alpha.[11]

Autoimmune thyroid dysfunction is suggested in the people during Interferon-based treatments as per literature.[14] Thyroid disease may also present like profound hyper-function, Graves's disease and reduced thyroid function. These diseases can present in the same patient as a consequence of various immune related actions of Interferon alpha treatment on the goiter a routine medicine utilized alongside Interferon alpha in management of such patients is Ribavirin.[15] Ribavirin is analogous to guanoside that stimulates the Th1 cytokines in the action for HCV treatment.

Research carried out by Huang *et al,* showed thyroid dysfunction in 26.80% patients of hepatitis C who received combined Peg INF Alpha and Ribavirin for 48 weeks whereas in our study 33.33% patients developed thyroid dysfunction after 12 weeks of treatment.[9] This study showed that female sex may put CHC patients at higher risk of developing thyroid dysfunction during peg-IFNa-2a/RBV therapy in contrary to our study which showed no association between gender and thyroid dysfunction.

Our research shows that, frequency of thyroid disease in patients of hepatitis C (HCV) disease receiving peg interferon alpha and ribavirin combination was 40 (33.33%) of the sample, conversely no thyroid disease in 80 (66.67%) of the sample at 12 weeks whereas, a research included hundred adults coming to OPD at AL-Kahera AI-Fatemya Hospital and suitable patients for Peg-Interferon and ribavirin treatment.[16] Thyroid function test (TSH, T3, T4) carried out prior to starting therapy (week 0) and then by weeks 12, 24, 48, and 72. The frequency of thyroid dysfunction was significantly seen by the conclusion of therapy (48 weeks); incidence was 35%, largely as decreased thyroid function, whereas the lowermost frequency seen by 12th week (2%), presented as increased thyroid function.

Thyroid stimulating hormone is an indicator of thyroid dysfunction in people having hepatic disease that were managed with Interferon treatment. The TSH level in plasma prior to starting Interferon treatment among people who had thyroid disturbance were greatly different from TSH levels in people that continued as having normal thyroid function. Relation among TSH levels and the thyroid disorder in normal robust people is established in studies.[17]

Interferon therapy is linked with 3 forms of thyroid disease, immune related thyroid disease, thyroid inflammation and Grave's disease. Such diseases may happen during Interferon treatment, as soon as four weeks to later as twenty months after start of therapy.[18,19]

Most of the people having hypothyroidism do have Thyroid peroxidase Ab (87%), showing the immune related process of this disorder. As per many researches hypothyroidism can be short-lived, vanishing after stopping the interferon. In a huge study at Italy, reduced thyroid function was, long-lasting in fifty-nine percent of the people.[18]

In some researches, literature pertaining to cause of hyper function of thyroid. Fattovich *et al* showed 34 people with hyper function, of which 13 had temporary hyperfunction, seemingly having thyroiditis.[18] A total of 21 patients required antithyroid therapy, sho-

wing those who had Grave's disorder. Research by Kakizaki *et al* showed 9 people with hyper function had lab proven TSH receptor Ab.[19] Wong *et al* showed 10 hyperthyroid people were seen in 321 HCV or HBV hepatic disease patients managed with interferon.[20] In 6 of such hyperthyroid patients were confirmed short of eye signs. In 3 people, a standard progression of subclinical thyroiditis took placehyper function with decreased uptake on radioactive scan, later hypothyroidism occurred. In other people, too little data was there establish a clear scenario.

The incidence of new cases of thyroid dysfunction among the patients of treatment group in a study done by El Toony *et al,* was more by the end of treatment (week 48) to be 15.5%, whereas the least incidence was detected by week 12 to be 9.1% whereas these results were not consistent with our results as our study showed thyroid dysfunction at 12 weeks as 33.33%.[21] This study also considered the effects of age, gender, BMI and pretreatment viral load on thyroid dysfunction which showed no significant effect of these variables on thyroid dysfunction which are consistent with our study in terms of age and gender.

The incidence of thyroid dysfunction among the patients of treatment group in a study done by Hwang Y *et al*, showed that thyroid dysfunction among study population was 27.7% which are in accordance with our study which showed results of 33.33%.[22]

A retrospective study by Zhou *et al,* showed that after treatment, thyroid dysfunction developed in 12.1% of patients which is not in concordance with our study.[23] In this study female gender is the risk factor of thyroid dysfunction in contrary to our study.

However, our study had certain limitations. Firstly, we followed patients only for 12 weeks contrary to other studies which followed patients for up to 48 weeks, as maximum thyroid dysfunction was seen at end of 48 weeks. Secondly, our sample included predominantly males so insignificant results in our study based on gender cannot be generalized.

It is suggested to do regular investigation for thyroid disorder in all chronic hepatitis C patients, prior to commencing interferon/ribavirin treatment.

CONCLUSION

This study concluded that the frequency of thyroid dysfunction among patients of chronic hepatitis C (HCV) infection receiving combined pegylated interferon alpha and ribavirin therapy is quite high.

Conflict of Interest: None.

Author's Contribution

MAM: Main idea, KMU: Finale approval, IA: Statisticaly analysis, KA: Data collection, QZ: Literature review, AA: Data collection

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