ORIGINAL ARTICLE

Frequency of Thyroid Disorders During Interferon and Ribavirin Therapy in Chronic Hepatitis C Infection

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ABSTRACT

Objective: The objective of this study was to assess the frequency of thyroid dysfunction in response to combination of interferon and ribavirin therapy in chronic hepatitis C (CHC) patients and HCV outcome.

Study Design: Descriptive study.

Place and Duration of Study: This study was conducted at Outpatient Department of Liaquat University of Medical and Health Sciences, Jamshoro, Hyderabad from September 2005 to September 2007.

Patients and Methods: One hundred cases of CHC, proven by anti-HCV and HCV RNA-positive with baseline TSH, FT_4 and FT_3 within the normal reference range, who were treated with interferon alpha-2b (3 million unit subcutaneously three times per week) and oral ribavirin (1000-1200 mg per day) were included in this study. All patients were assessed for TSH, FT_4, FT_3 levels at 12 weeks and 24 weeks during therapy.

Results: Among the 100 patients, overt thyroid disease developed in 13 (13%) and sub-clinical thyroid disease in 5 (5%). Out of 13 patients of overt thyroid disorders, 11 (84.6%) had hypothyroidism and 02 (15.3%) hyperthyroidism. Four (80%) patients were of sub-clinical hypothyroidism and 01 (20%) patient was of sub-clinical hyperthyroidism. Overall, thyroid disorders developed in 18 (18%) both as overt and sub-clinical thyroid disorders. Ninety one (91%) patients became negative by HCV RNA.

Conclusion: Treatment of HCV with IFN-alpha and ribavirin can be safely continued in patients with over and sub clinical hypothyroidism because thyroid disease responds well to treatment.

Key words: *Thyroid hormone. Interferon. Ribavirin. Chronic hepatitis C. Hypothyroidism. Hyperthyroidism.*

INTRODUCTION

Thyroid disease is a frequent side-effect of interferon (IFN) therapy for Hepatitis C Virus (HCV) and other disorders. The importance of this disorder is emphasized by the fact that 1.5-2.2% of western populations are positive for HCV.[1] HCV infection is a potentially life threatening disease because 75% of the affected patients with acute infection develop chronic disease with a high risk of cirrhosis and hepatocellular carcinoma.[2]

IFNs are a family of naturally occurring, small protein molecules with molecular weight of approximately 15,000-21,000 Da.[3] They are included in three groups, IFN α, IFN β, and IFN γ with different biological effects and variable duration of activity.[2] They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. IFN was discovered almost 50 years ago by Isaacs and Lindenmann[4], who observed that virus-infected cultures produced a protein that reacted with cells, making them resistant to infection by many other viruses. IFNs have been widely used in the treatment of neoplastic, viral and autoimmune diseases.

Adverse effects of IFN treatment include systemic and organ-specific pathological changes, many of them being the consequences of immune enhancement or immune dysregulation induced by IFN itself.[5,6]

In patients treated with IFN, activation of the immune system leads to the development of thyroid disease. Furthermore, IFN has direct inhibitory effects on thyroid hormone synthesis, release and metabolism.[7] The critical point is to understand how a generalized activation of the immune system, induced by the cytokine treatment, may result in an organ-specific involvement of the thyroid gland. A genetic predisposition to thyroid autoimmune disease is probably necessary for the development of thyroid disease in patients treated with IFN.[8,9] In addition to the systemic effects, IFNs may have direct effects on the thyroid gland by modulating the aberrant expression of major histo-compatibility antigens on thyroid cells[10],

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favouring a cytokine microenvironment, which may lead to the immune mediated damage of thyroid tissue.[11] The prevalence of thyroid disease during IFN treatment is extremely variable, ranging between 1 and 35%.[12] Women are more susceptible than men to develop IFN related thyroid disease, having a relative risk 3 to 7-fold higher as reported in some,[12-15] but not in all studies.[8, 16]

It has been argued that virus-related factors especially HCV infection itself, may predispose to the development of thyroid autoimmune disease. Positive thyroid antibodies were found in 20-42%. The development of thyroid disease does not seem to be related to the dose of IFN.[17] In contrast, duration of IFN treatment has been related to the occurrence of thyroid dysfunction.[18]

Ribavirin is a synthetic guanoside nucleoside analogue that exerts immunomodulatory effects by inducing cytokines in the immune response against HCV infection[18,19] and is frequently given with IFN in the treatment of HCV patients. Patients treated with both agents do not have an increased risk of developing thyroid autoimmunity but do have a 4.3 % relative risk to develop thyroid dysfunction, likely as a consequence of enhancement of the Th1 immune response, which induces cell-mediated cytotoxicity.[20]

In patients treated with IFN, hypothyroidism occurs in 2.4-19.0% of the patients, especially in those with pre-existing thyroid autoimmunity.[12,16, 21] Hypothyroidism is also more frequent in patients treated with both IFN and ribavirin. Severity of IFN induced hypothyroidism varies from sub-clinical, defined by elevated serum TSH and normal FT_4 concentration, to overt hypothyroidism, defined by elevated serum TSH level and decreased FT_4 concentration. Combined treatment with IFN and ribavirin seems to be associated with a higher percentage of overt hypothyroidism than monotherapy.[20]

The objective of this study was to assess the frequency of thyroid dysfunction in response to combination of interferon and ribavirin therapy in chronic hepatitis C (CHC) patients and HCV outcome.

PATIENTS AND METHODS

This study was conducted at Outpatient Department of Liaquat University of Medical and Health Sciences, Jamshoro, Hyderabad from September 2005 to September 2007. Consecutive cases of chronic hepatitis C proven by anti-HCV and PCR HCV RNA-positive, were selected for the study. A written consent was taken from all patients before the study. All patients were given interferon (3 miu subcutaneously three times a week) and oral ribavirin (1000-1200 mg per day) for 24 weeks, all patients were assessed for TSH, FT_4 and FT_3 before, at 12 weeks and after 24 weeks of therapy. TSH was assessed by the Elecsys assay employed monoclonal antibodies specifically directed against human TSH (The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and Cobase immunoassay analyzers).

In the Elecsys FT_4 and FT_3 test, the determination of free thyroxin and free triiodothyroxine is made with the aid of a specific anti-T4 and anti-T3 antibodies respectively labelled with a ruthernium complex[a] (The electrochemi-luminescence immunoassay "ECLIA" is intended for use on the Roche Elecsys 1010/2010 and MODULAR ANALYTICS E170 immunoassay analyzers). Thyroid dysfunction was defined below or above normal values of TSH at 0.72-4.2 uiu/ml, FT_4 at 0.93-1.7 ng/dL and FT_3 at 2.57-4.43 pg/ml.

Exclusion criteria were other causes of chronic hepatitis, dual B and C viral hepatitis, subject having thyroid dysfunction before the start of therapy, decompensated cirrhosis and hepatocellular carcinoma. The data was analyzed by using SPSS version 11.0. The independent sample t-test was applied to analyze the numerical data i.e. TSH, FT_4 and FT_3 with overt and sub-clinical thyroid disorder. Chi-square test was applied for gender and overt and sub-clinical thyroid disorder association. The p-value level of significance was considered at <0.05.

RESULTS

A total of 100 patients were selected for the study. Of those, 23 (23%) were male and 77 (77%) were female with the age ranging from 16-55 years (mean age and SD 35.3 $\pm$ 7.8). Thyroid profile was assessed at 12 weeks and after 24 weeks of therapy. Baseline characteristics of 100 patients are shown in Table I.

At 12 weeks, thyroid function was normal in 91 (91%) patients, whereas in 9 (9%), thyroid dysfunction was found. Out of these 9 (9%) patients, 6 (66.6%) were labelled as of hypothyroidism from which 2 (33.3%) had sub-clinical hypothyroidism and 4 (66.6%) overt hypothyroidism. Three patients had hyperthyroidism. Of these 3 (33.3%), one had overt hyperthyroidism and 2 (66.6%) sub-clinical hyperthyroidism.

Table I: Baseline characteristics of 100 patients who received combination IFN-α and RBV therapy for HCV.

Demographic	(n=100)
Mean age (years)	35.3 $\pm$ 7.8
Gender:	
Males	23 (23.0%)
Females	77 (77.0%)
Anti HCV positive	100 (100%)
PCR (HCV RNA) positive	100 (100%)
TSH	* 1.70 $\pm$ 0.80 (100%)
FT_4	* 1.38 $\pm$ 0.22 (100%)
FT_3	* 3.27 $\pm$ 0.54 (100%)

** Mean $\pm$ standard deviation.*

Out of 6 (66.6%) hypothyroidism patients, 1 (16.6%) was male and 5 (83.3%) were females, whereas out of 3 (33.3%) of hyperthyroidism, 1 (33.3%) was male and 2 (66.6%) were females. Out of 100 patients, PCR HCV RNA was negative in 81 (81%) patients and positive in 5 (5%) patients, whereas in 14 (14%) patients, PCR was not done because of non-affordability (Table II).

Table II: Thyroid dysfunctions after 12 weeks of therapy.

	Hyperthyroidism		p-value
	Overt Hyperthyroidism n=1	Sub-clinical Hyperthyroidism n=2	
Gender:			
Male	0	1 (4.3%)	0.5
Female	1 (1.3%)	1 (1.3%)	
TSH	0.05 ± 0.00	0.13 ± 0.01	0.12
FT_4	2.80 ± 0.00	1.05 ± 0.04	0.01*
FT_3	4.60 ± 0.00	3.55 ± 0.70	0.43
	Hyperthyroidism		p-value
	Overt Hyperthyroidism n=4	Sub-clinical Hyperthyroidism n=2	
Gender:			
Male	1 (25.0%)	0	0.43
Female	3 (75.0%)	2 (100%)	
TSH	6.32 ± 2.5	7.11 ± 3.7	0.77
FT_4	0.63 ± 0.31	1.17 ± 0.13	0.08
FT_3	4.69 ± 3.10	1.33 ± 0.93	0.22
PCR HCV RNA			
Positive		5 (5%)	
Negative		81 (81%)	
Nil		14 (14%)	

Mean ± standard deviation.

Out of 100 patients, 18 (18%) patients developed thyroid dysfunction at the end of 24 weeks of therapy. Of those 18 patients, 15 (83.3%) were hypothyroid and 3 (16.6%) were hyperthyroid. Out of the 15 hypothyroidism cases, 4 (26.6%) had sub-clinical and 11 (73.3%) had overt hypothyroidism. Out of the 3 hyperthyroid patients, 1 (33.3%) had sub-clinical and 2 (66.6%) had overt hyperthyroidism. While HCV RNA was negative in 91 (91%) patients and positive in 5 (5%) and in 4 (4%), PCR was not done because of non-affordability (Table III).

Table III: Thyroid dysfunctions after 24 weeks of therapy.

	Hyperthyroidism		p-value
	Overt Hyperthyroidism (n=2)	Sub-clinical Hyperthyroidism (n=1)	
Gender:			
Male	0	1(100%)	0.08
Female	2 (100%)	0	
TSH	0.08 ± 0.43	0.40 ± 0	0.10
FT_4	3.25 ± 0.49	1.50 ± 0	0.21
FT_3	5.32 ± 0.48	2.55 ± 0	0.13
	Hyperthyroidism		p-value
	Overt Hyperthyroidism (n=11)	Sub-clinical Hyperthyroidism (n=4)	
Gender:			
Males	0	2 (50%)	0.01*
Females	11 (100%)	2 (50%)	
TSH	10.77 ± 9.69	6.23 ± 2.12	0.38
FT_4	0.59 ± 0.31	1.24 ± 0.29	0.003*
FT_3	2.09 ± 0.58	2.44 ± 0.34	0.29
PCR HCV RNA			
Positive		5 (5%)	
Negative		91 (91%)	
Nil		4 (4%)	

*Mean ± standard deviation. * p-value statistically significant*

DISCUSSION

The development of thyroid dysfunction during interferon alpha monotherapy in patients with hepatitis C virus has been well-described. The incidence ranges from 25 to 34.3%[22] with a mean incidence of 6.6%.[23] These studies have shown that hypothyroidism was more common than hyperthyroidism (3.8 vs. 2.8%), and thyroid dysfunction occurred more often in females than in male patients (13.0 vs. 3.0%).[23] The strongest risk factors that were associated with an increased risk of development of thyroid disease, during interferon-alpha therapy, were female gender and the appearance of thyroid auto antibodies before the initiation of therapy.[14,21,23] Thyroid disease is less likely to develop in patients with chronic hepatitis B infection who are treated with interferon alpha than in chronic hepatitis C virus infection despite the use of higher doses of interferon alpha for the treatment of hepatitis B virus.[14] This finding suggests that hepatitis C virus and interferon alpha may have a synergistic role in inducing thyroid disease during antiviral therapy.

To-date, only a few studies have evaluated the incidence of thyroid dysfunction in HCV infected patients treated with interferon alpha and ribavirin combination therapy. The development of thyroid dysfunction during interferon alpha and ribavirin combination therapy has been reported to occur in 4.7 to 27.8% of patients, with a mean incidence of 12.1%.[24] Therefore, the mean incidence of thyroid dysfunction in patients treated with interferon alpha and ribavirin combination therapy (12.1%) is higher than in those treated with interferon alone (6.6%).[23] Similar to the published data on thyroid dysfunction in patients treated with interferon alone, these combination therapy studies have shown that hypothyroidism was more common than hyperthyroidism (8.1 vs. 3.8%). Thyroid dysfunction also occurred more often in female than in male patients (17.7 vs. 8.3%).[24]

In this study, out of 100 patients, 77 (77%) were females and 23 (23%) were males with a mean age 35.3 ± 7.8 years. The frequency of overt thyroid dysfunction during combination of interferon and ribavirin therapy was 13% and was even higher (18%) if patients with sub-clinical thyroid dysfunction were included. These figures are quite comparable to other studies. Dalgard and his

team[17] found thyroid dysfunction in 11.8%, whereas Kee *et al.*[25], found thyroid dysfunction in 12.6% of patients. Another study by Foldes *et al.*[26], found thyroid dysfunction in 21.7% of patients of chronic hepatitis C, treated with interferon alpha, whereas Bini *et al.*[27] found thyroid dysfunction in 6.7% (95% CI, 3.8-10.8%) and sub-clinical thyroid dysfunction in 4.0% (95% CI, 1.8-7.4%) in chronic hepatitis C patients on interferon alpha and ribavirin therapy.

In this study, predominant thyroid disorder was hypothyroidism 83.3%, whereas hyperthyroidism was found in 16.6%. These results are identical to the study by Huy A Tran *et al.*[28] who found thyroid dysfunction in 6.7% out of 272 patients, out of whom, 83.3% were hypothyroid and 16.6% were hyperthyroid. Thyroid dysfunction was found to be higher in females. In this study, thyroid dysfunction was also found to be more frequent in females (83.3%) than in males (16.6%), which is comparable to similar studies.[17, 20, 24] Watanabe *et al.* did not find a correlation of gender with thyroid dysfunction.[16]

Fatigue, decreased appetite, depression and myalgias were common in patients with overt hypothyroidism, whereas nervousness, irritability, fatigue, insomnia and weight loss were common in patients with overt hyperthyroidism. Although these symptoms are common in patients with thyroid disease[29], they could easily be mistaken for adverse effects of HCV therapy, and thyroid dysfunction could have remained undiagnosed, if the patients did not undergo routine periodic screening of TSH level.[17,30] Therefore, it is recommended that screening for thyroid disease be routinely performed in all patients with HCV infection, who are treated with interferon alone or in combination with ribavirin.[31]

Patients who developed overt hypothyroidism during therapy were treated with Levothyroxin and hyperthyroidism with Propranolol, while patients with sub-clinical thyroid disorders were not given any treatment.

Despite the development of thyroid disorders, overt and sub-clinical, (patients were able to complete a full course of hepatitis C virus treatment). Although these findings suggests that antiviral therapy can be continued despite the development of thyroid disorder, the impact of continuing interferon alpha and ribavirin therapy on the quality of life during treatment of long-term sequelae and after therapy remain to be determined.

Because of limitation of follow-up, the authors cannot exactly comment on the reversibility of thyroid dysfunction after completion of interferon and ribavirin therapy in hepatitis C virus patients but in most patients thyroid dysfunction was reversible. It needs a larger scale of study to clarify this issue.

CONCLUSION

Thyroid dysfunction occurred in 18% of patients treated for chronic hepatitis C with IFN-alpha and ribavirin for 24 weeks, of whom, 15% were of hypothyroidism and 3% were hyperthyroidism. Eighty-two percent patients had intact thyroid function at the end of treatment. Treatment of HCV can be safely continued in these patients because thyroid disease responds well to treatment.

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