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Medicine

Effects of Combined Interferon Alpha and Ribavirin Therapy on Thyroid Functions in Patients with Chronic Hepatitis C, Attending Hepatitis Centre Ghulam Mohammad Medical College Hospital, Sukkur

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ABSTRACT

Objective: To determine the frequency of thyroid dysfunction in patients of chronic hepatitis C during treatment with interferon alpha-2b and ribavirin therapy.

Study Design: A cohort study.

Place and Duration of Study: Hepatitis Centre Ghulam Mohammad Mahar Medical College Hospital, Sukkur, from February 2009 to January 2010.

Materials and Methods: One hundred and sixty seven non-cirrhotic chronic hepatitis C patients were grouped into treatment group (n=107) and control group (n=60) awaiting treatment. Baseline serum(s.) Alanine Transferase (ALT) and S. Aspartate Transferase (AST) were measured by IFCC method. Serum Thyroid Stimulating Hormone (S. TSH), serum free thyroxine (S. Free T4) and serum total triiodothyronine (S.T3) level were determined by chemiluminescence. Study group patients underwent 24 weeks IFN and ribavirin therapy and were followed-up for thyroid dysfunction at weeks 0, 12 and 24. Control group patients underwent the same tests at weeks 0, 12 and 24. Statistical analysis was done on SPSS 15.

Results: Out of 107 patients of treatment group, 20 patients (18.69%) developed thyroid dysfunction. Females were at higher risk with Relative Risk (RR) of 11.25 and Attributable Risk (AR) of 91%. Hypothyroidism was more common than hyperthyroidism.

Conclusion: Interferon-alpha and ribavirin therapy induces thyroid dysfunction in chronic hepatitis C patients. Hypothyroidism was more common. Females are at a higher risk of developing thyroid dysfunction.

Key Words: Thyroid dysfunction. Chronic hepatitis C. Interferon. Ribavarin

INTRODUCTION

World Health Organization estimated that approximately 170 million individuals of the world population are diagnosed to be infected with Hepatitis C Virus (HCV).1 It is the most common blood-borne infection in USA.**2** The prevalence rate of anti-HCV antibodies in Pakistan reported mostly by hospital based studies in patients, blood donors and in general population is 0.5-25.7%.[3-9] Around 20% of persons with HCV infection experience progressive liver disease leading to cirrhosis or hepatocellular carcinoma over 20-40 years.[10] No vaccine is currently available to prevent this chronic disease. The goals of therapy are to slow the pace of disease progression, reduce the infectivity and decrease the risk of hepatocellular carcinoma. Combination therapy with INF-alpha-2b and ribavirin has resulted in two to three folds improvement in virological response to the disease. The effects of combination therapy are thought to be two folds, antiviral mechanisms and immunomodulation.[11] INF-alpha- 2b and ribavirin may trigger production of different types of non-specific and specific auto-antibodies such as antinuclear antibodies, rheumatic factor and anti-thyroid antibodies.[12] In most cases, these antibodies do not produce clinically significant diseases. Minor adverse effects have been reported with combination therapy. Thyroid dysfunction, which has been reported to occur from 3.9 – 33.33%, is the most common autoimmune disorder associated with combination therapy.[13-16] Therefore, it is necessary that thyroid functions are monitored during INF therapy and the course of thyroid disease is watched once autoimmune thyroid disorder develops during INF-alpha treatment. The objective of the study was to evaluate frequency and type of thyroid dysfunction among patients of chronic hepatitis C during treatment with combined INFalpha- 2b and ribavirin therapy at Hepatitis Centre Ghulam Muhammad Medical College Hospital, Khairpur.

MATERIALS AND METHODS

This cohort study was conducted at Hepatitis Centre Ghulam Mohammad Medical College Hospital, Sukkur from February 2009 to January 2010. One hundred and sixty seven diagnosed patients of chronic hepatitis C, age ranging 18-48 years, were included by non-probability convenience sampling technique. Before the

commencement of any therapy, they all had persistently raised serum alanine transferase (ALT) by International Federation of Clinical Chemistry (IFCC) method on Selectra, positive Hepatitis C Virus (HCV) antibodies by 3rd generation Enzyme Linked Immuno Sorbent Assay (ELISA), positive HCV Ribonucleic Acid (RNA) by Polymerase Chain Reaction (PCR), positive histopathological findings on liver biopsy depicted by Knodell Histopathological Index (in treatment group only) and normal serum thyroid functions before the commencement of treatment, depicted by Serum Thyroid Stimulating Hormone (S. TSH), serum free thyroxine (S. Free T4) and serum total triiodothyronine (S.T3) levels by chemiluminescent on immunolite 1000 at the start of treatment. Exclusion criteria were previous treatment with IFN and/or ribavirin, history of pre-existing thyroid disease, neoplastic, autoimmune, severe cardiac or pulmonary disease, those currently using immunosuppressant and/ or steroids and pregnant patients. Patients were divided into two groups, treatment group comprising of 107 patients with immediate planned treatment regimen of INF-alpha-2b and ribavirin therapy for 24 weeks and control group comprising of 60 patients who were awaiting treatment subsequently. Treatment group patients were treated with Interferon alpha 2b (INF) three million units subcutaneously three times a week and ribavirin 800-1200 mg orally daily for 24 weeks. Biochemical variables as described above were determined in treatment groups before the start of therapy, at 12 weeks during therapy and at 24 weeks at the end of IFN therapy. In treatment group, response to therapy was determined by HCV RNA by PCR test at the end of 24 weeks therapy. In control group, S. ALT, S. TSH, S. Free T4 and S. total T3 were performed at weeks 0, 12 and 24. Statistical analysis was done on SPSS 15. Mean and standard deviation of age, S. ALT, S. TSH, S. Free T4 and S. total T3 were determined. Frequency of thyroid dysfunction was also determined. Relative Risk (RR) ratio and Attributable Ratio (AR %) were calculated. Independent student's t-test was applied to S. ALT and S. AST levels. Statistical significance was set at < 0.05.[8]

RESULTS

The demographic and baseline values of liver function tests and thyroid function tests are shown in Table 1.

In the treatment group, among 107 patients of chronic hepatitis C (80 males and 27 females), having ages between 18-48 years, 24 weeks after INF-alpha-2b and ribavirin therapy, 20 patients; 10 females and 10 males (18.69%) developed thyroid dysfunction. In the control group, only one of the patients developed sub-clinical hyperthyroidism at 24 weeks. In the treatment group, frequency of hypothyroidism was 8.4%; (45% of positive cases) while that of hyperthyroidism was 7.5% (40% of positive cases), 2.8% of patients (15% of positive cases) exhibited biphasic thyroiditis i.e. transient hyperthyroidism at 12 weeks followed by hypothyroidism at 24 weeks of therapy. Thyroiditis was determined by thyroid scan in which thyroid gland showed increased radioisotope dye uptake initially, which was manifested as hyperthyroidism followed by decreased uptake of radioisotope dye, which was manifested as hypothyroidism (Table 2).

Table No.I: Demographic features and baseline values of liver function tests and thyroid function tests (n=167).

Features	Study group (n=107) Mean (SD)	Control group (n=60) Mean (SD)
Age (years)	36 (6.7)	41.39 (9.6)
Sex M/F	80/27	45/15
S. ALT (IU/L)	92.82 (62.83)	69.77 (41.36)
S. AST (IU/L)	59.65 (42.47)	55.46 (34.7)
S. T3 (nmol/l)	1.80 (0.22)	1.84 (0.21)
S. T4 (pmol/l)	14.42 (2.69)	14.37 (1.91)
S. TSH (mIU/L)	1.09 (0.63)	1.03 (0.59)

Table No.2: Frequencies of thyroid dysfunction among chronic hepatitis C patients after 12 and 24 weeks of interferon and ribavirin therapy (n=107).

Thyroid status	At 12 weeks	At 24 weeks
Euthyroid	99 (92.5%)	87 (81.3)
Hyperthyroid	4 (3.7%)	8 (7.5%)
Hypothyroid	3 (2.8)	9 (8.4%)
Biphasic thyroiditis*	1 (0.9%)	3 (2.8%)

*Biphasic thyroiditis means transient hyperthyroidism after 12 weeks of therapy followed by hypothyroidism after 24 weeks of therapy.

Table No.3: S. alaninetransferase levels in treatment group and controls at weeks 12 and 24 of therapy (n=167).

S. Alinine-transferase (ALT) (U/L)	Treatment group (n= 107) Mean (SD)	Controls (n= 60) Mean (SD)	p- value
Baseline	92.82 (62.83)	69.77 (41.36)	<0.06
At 12 weeks	38.6 (30.74)	63.68 (30.08)	<0.001
At 24 weeks	33.85 (24.02)	68.18 (54.6)	<0.001

Thyroid dysfunction was detected within 12 weeks of initiation of INF therapy in 08 patients (40% of positive cases) while in 12 patients (60% of positive cases) at the end of 24 weeks treatment. Relative risk (RR) ratio was calculated to be 11.25 and attributable risk (AR)% was 91. Among positive cases, the incidence of symptomatic thyroid disease was found to be 7.47% (40% of positive cases) and sub-clinical cases were 11.21% (60% of positive cases). Symptomatic patients

were 8 in number (40% of positive cases) out of which 3 (15% of positive cases) were hyperthyroid. They had sign and symptoms of hyperthyroidism comprising of palpitation, weight loss, anorexia, rapid pulse and tremors. All 3 patents were given anti-thyroid drug; neomercazole. All the patients completed INF therapy. Five patients (25% of positive cases) among symptomatic patients were clinically hypothyroid. They had sign and symptoms of hypothyroidism comprising of constipation, lethargy, weight gain and sleep disturbances. There were 37.03% of females as compared to 12.5% of male patients who developed thyroid dysfunction (p=0.001). Eighty four percent of chronic hepatitis C patients showed favourable response depicted by HCV RNA by PCR to combined interferon and ribavirin therapy. Eighty eight percent of them at 12 weeks and 97% of them at the end of 24 weeks treatment showed normalization of S. alaninetrans-ferase levels (Table 3).

There was no significant association between severity of the disease and development of thyroid dysfunction (p=0.81). No significant association was found between response to therapy and occurrence of thyroid disease (p=0.79). All the patients completed antiviral therapy. None of the patients had to discontinue therapy because of thyroid dysfunction or any other side effects.

DISCUSSION

INF alpha-2b and ribavirin therapy has known association with development of autoimmune thyroid disease in patients of chronic hepatitis C during treatment. Substantial research work has been carried out to determine the relationship of thyroid dysfunction and INF therapy.[12-18] In this study, the incidence of thyroid dysfunction during INF and ribavirin therapy was 18.69% among 107 patients of chronic hepatitis C, undergoing 24 weeks treatment. Previous studies have reported an incidence between 3.9–33.33%.[17-31] Present finding was consistent with most of the studies. Moreover, 8.4 % of patients (45% of positive cases) had hypothyroidism, 7.47% of patients (40% of positive cases) had hyperthyroidism while 2.8% (15 % of positive cases) had biphasic thyroiditis. Hypothyroidism was found to be more common in the study as is the case in most of the studies.[17,18,23,24,30,32,33,34] The incidence of symptomatic thyroid disease in this study was found to be 7.47% (40% of positive cases) and sub-clinical cases were 11.21% (60% of positive cases) in accordance with other studies. Bini *et al.* revealed the ratio of overt and sub-clinical thyroid disease being 6.7% and 4% (62% and 38%). In this study, 02 patients (10% of positive cases), who showed sub-clinical manifestations at 12 weeks of therapy, developed symptomatic disease at the end of treatment. Six patients (30% of positive cases) developed sub clinical picture at the end of therapy. The possibility of some of them later developing symptomatic overt disease cannot be ruled out and needs long-term follow-up of the patients.

In this study, 2.8% of total patients (15% of positive cases) showed biphasic thyroiditis in accordance with Moncoucy *et al.* who showed an incidence of 13.3% of positive cases.[17] Treatment response in this study was 84% similar to that of other local studies.**9** Eighty eight percent of them at 12 weeks and 97% at the end of 24 weeks treatment showed normalization of S. aminotransferase levels. A sustained virological response to INF and Ribavirin is associated with HCV specific and non-specific immunity.[20,30-35] It was speculated that activated nonspecific immunity may be associated with increased risk of autoimmunity, suggesting a correlation between the virological response to INF-alpha-2b and risk of developing thyroid dysfunction during treatment. Such an association has been reported in some studies in which development of hypothyroidism in patients with thyroid auto-antibodies undergoing treatment with IFNalpha-2b plus ribavirin is significantly associated with the long-term remission of the disease.[29] While other studies show that thyroid dysfunction during treatment of chronic hepatitis C with interferon-alpha has no association with either interferon dosage or efficacy of therapy.**30** However, in this study, no significantl relation was found in virological treatment response to INFalpha and ribavirin in patients with and without thyroid function. In fact, only 3 out of 20 patients (16%) revealing INF induced thyroid disease showed nonresponse to treatment while 14 patients without treatment out of 87 (13.79%) did not respond to treatment. The difference between the two was not statistically significant. One probable explanation can be that the immune mechanisms, which are involved in the pathogenesis of thyroid autoimmune phenomenon, are not the same which regulate the therapeutic response to HCV or modulate the unfavourable course of HCVrelated chronic hepatitis C.[30] The results are in accordance with the other studies, which revealed that neither severity of the disease nor the duration of therapy are related to occurrence of thyroid disease.[14] In this study, effects on thyroid function were determined, induced by 24 weeks treatment with INF. Whether prolonged therapy, as given for 48 weeks in HCV genotype 1 and 4 patients, will increase the likelihood of INF induced thyroid disease cannot be answered although international studies reveal the negative correlation between the two.[30] In most studies, the possibility of female gender being the independent predictors of INF induced thyroid disease has been determined.[17,33,36] In this study, the statistical difference between the two genders developing thyroid disease was highly significant. In fact, 37.03% of females as opposed to 12.5% of males experienced thyroid dysfunction during treatment, confirming the previous

data in literature, and difference was highly significant statistically. Whether thyroid disease, induced by INF and ribavirin, resolves spontaneously or needs long-term treatment in patients of this study can not be answered because long-term follow-up could not be done. Other studies showed that approximately 02% of patients, suffering from INF induced thyroid dysfunction, required long-term treatment for thyroid dysfunction.[31-33]

CONCLUSION

Combined INF-alpha-2b and ribavirin therapy induced thyroid dysfunction (both hyperthyroidism and hypothyroidism, later being more common) in patients of chronic hepatitis C. Females were at a higher risk to develop INF induced thyroid dysfunction.

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