ORIGINAL ARTICLE

The Presence of Thyroid Auto-Antibodies is a Risk Factor for Thyroid Dysfunction in Chronic Hepatitis C Patients during Treatment with Interferon-α and Ribavirin

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ABSTRACT

Aim: To investigate the prevalence of thyroid dysfunction (TD) and thyroid peroxidase antibodies (TPO-Ab) and to determine the risk factors of TD in chronic hepatitis C patients during treatment with interferon-α and ribavirin combination therapy.
Study design: Prospective clinical trial
Place and duration of study: Lahore General Hospital from March 2011 to December 2011.
Methods: The study enrolled sixty diagnosed patients of chronic hepatitis C with normal baseline thyroid hormones (TSH, FT4). Thyroid peroxidase antibodies (TPO-Ab) were also assayed. Patients were treated with IFN-α and data was analyzed to determine the co-relation between thyroid dysfunction (TD) and presence of thyroid per-oxidase antibodies (TPO-Ab). Baseline results were compared with those obtained during and at the end of interferon combination therapy.
Results: The incidence of thyroid dysfunction (TD) was 10%, hypothyroidism (6.6%) was more common than hyperthyroidism (3.4%). The percentage of TPO-Ab positive patients was 1.7% before treatment and thyroid autoimmunity developed in 5% of patients after treatment with p-value 0.662. Analysis indicated that TPO-Ab positivity was most important risk factor for thyroid dysfunction (TD) in chronic hepatitis C patients treated with IFN-α and ribavirin .
Conclusion: Patients with chronic hepatitis C, undergoing interferon-alpha & ribavirin therapy are more prone to develop autoimmune thyroid disease. TPO-Ab positivity, either before or during treatment with IFN-α and ribavirin is a risk factor for thyroid autoimmunity and dysfunction (TD) in chronic hepatitis C patients.
Keywords: Thyroid dysfunction (TD),Thyroid-peroxidase antibodies(TPO-Ab), Interferon-alpha (IFN-α)

INTRODUCTION

Chronichepatitis C (CHC) is a common liver disease and more than 185 million peopleare infected with hepatitis C virus globally[1]. At present the treatment of chronic hepatitis C is based on the combination of Interferon-alpha and Ribavirin and the duration of therapy depends on viral genotype[2]. New treatment regimens have been recently approved for the treatment of CHC, but they are used to a limited extent because of high cost and side effects[3]. One of the most common extra-hepatic side effect of IFN-Alpha and Ribavirin combination treatment is thyroid dysfunction(TD)[4]. IFN-Alpha induced thyroid dysfunction may vary from subclinical to overt hypo or hyperthyroidism[5].The overall incidence of IFN-induced thyroid dysfunction varies between 2.5-35%[6]. Thyroid dysfunction related with IFNcombination therapy may be due to autoimmune andnon-autoimmune mechanisms[7]. The most common type of thyroid autoimmunity is the occurrenceof thyroid antibodies without the manifestations of disease[8]. These antibodies include thyroglobulin antibodies(TG-Abs), thyroid peroxidase antibodies(TPO-Abs) and TSH receptor antibodies (TSHA-Abs)[9]. The patients may carry one or more of these antibodies before treatment andtreatment with interferon alpha can promote the onset of autoimmune thyroiditis in patients who are more prone to develop thyroid disorders[10]. The presence ofauto-thyroid antibodies with normal thyroid functions is a common finding in the patients treated with IFN[11]. Interferon (IFN) treatment can lead to the stimulation of anti-thyroid peroxidase (TPO-Ab) and anti-thyroglobulin (TGA) antibodies[12]. The presence of these antibodies before treatment with IFN may forecast the later thyroid dysfunction and thyroid autoimmunity[13]. About 50% of patients who develop thyroid dysfunction during IFN therapy do not develop thyroid auto-antibodies suggesting that thyroid dysfunction might be provoked by a direct effect on thyroid cell function rather than immune mediated mechanisms[14].

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The major effect of interferon alpha on immune system is the augmentation of cell- cytotoxicity by the repression of T helper cell(th2) and increase in Th1 immune response[15].Autoimmune thyroiditis is an organ-specific autoimmune disease which is depicted by chronic lymphocytic infilteration of thyroid gland and the presence of circulating auto-antibodies such as thyroid-peroxidase(TPO-Ab) and anti-thyroglobulin(Tg-Ab)[16].Female gender is a common risk factor that guessed the development of autoimmune thyroiditis during interferon therapy[17]. The presence of thyroid antibodies is preclinical stage of interferon-induced autoimmune thyroiditis and the presence of these antibodies was a risk factor for the development of thyroid dysfunction, later on, in the patients treated with interferon alpha.[18] Different forms of interferon-induced thyroid autoimmunity have been identified, such as, Graves s' disease, subclinical hypothyroidism and thyroiditis[19]. There is a relationship between female gender, old age and genetic predilection with the development of antibodies[20].

In this prospective study the frequency of thyroid dysfunction and thyroid autoimmunity was assessed after treatment with interferon-alpha and ribavirin in chronic hepatitis C patients. The risk factors leading to development of thyroid autoimmunity and dysfunction were also analyzed.

PATIENTS AND METHODS

Sixty patients of chronic hepatitis C, 34 females, 26 males, median age 43 years, and with normal baseline thyroid functions were included in the study. The study was carried out in Lahore General Hospital which is affiliated with Post Graduate Medical Institute. The duration of study was nine months, from March 2011-December 2011.

Inclusion criteria: Diagnosed cases of chronic hepatitis C and none of them had history of thyroid gland dysfunction.

Exclusion criteria: Abnormal thyroid functions and co-existence of serious psychiatric or medical illness.

The study was approved by Ethical Committee of Post Graduate Institute Lahore.Written consent for participation in the study was taken from each patient. Patients were also advised to report for any undesirable effect during study.

At the study entry thyroid functions(Serum levels of TSH, ,FT4) and autoimmunity,(serum TPO-Ab)were evaluated at baseline, at 12 week and at the end of IFN combination therapy,using enzyme immunoassay test kits, catalog no. BC-1001, 1006 bio-check Inc, 323 Vintage park,for serumTSH, FT4 andimmune-metric enzyme immunoassay Kit (OrgentecDiagsotika GmbH) forthyroid peroxidase antibodies.Normal ranges are as follows: TSH, 0.4-6ul/ml, FT4 0.8-2.00pg/ml, TPO-Ab.below50 Iu/ml

Data was analyzed using SPSS 16.0. Normally distributed continuous variables were expressed as mean±S.D and non-normal distributed continuous data were expressed as median. Comparison of continuous data between pre-treatment and after-treatment groups wereperformed by student's t-test. Differences were considered significant with a two-tailed p-value<0.05.

RESULTS

In this prospective study the frequency of thyroid autoimmunity and dysfunctions were assessed before and after treatment with interferon alpha and ribavirin combination therapy. Along with this, the risk factors of developing thyroid autoimmunity in this population were analyzed. The demographics of 60 patients CHC are presented in table 1.

Table 1:

Age (Years)	Male	Female	Total
31 – 40	15(57.7%)	20(58.8%)	35(58.3%)
41 – 50	8(30.8%)	9(26.5%)	17(28.3%)
51 – 60	3(11.5%)	5(14.7%)	8(13.3%)
Mean	41.77±8.53	42.71±8.36	42.30±8.37

The study included 26 male and 34 female patients. The mean ages for males and females were 41.77±8.53 and 42.71±8.36 years respectively with overall 42.30±8.37 years. At the end of IFN-α combination therapy 54 (90%) patients were having normal thyroid functions.

Table2: Distribution of cases by TPO range at before, during and after treatment

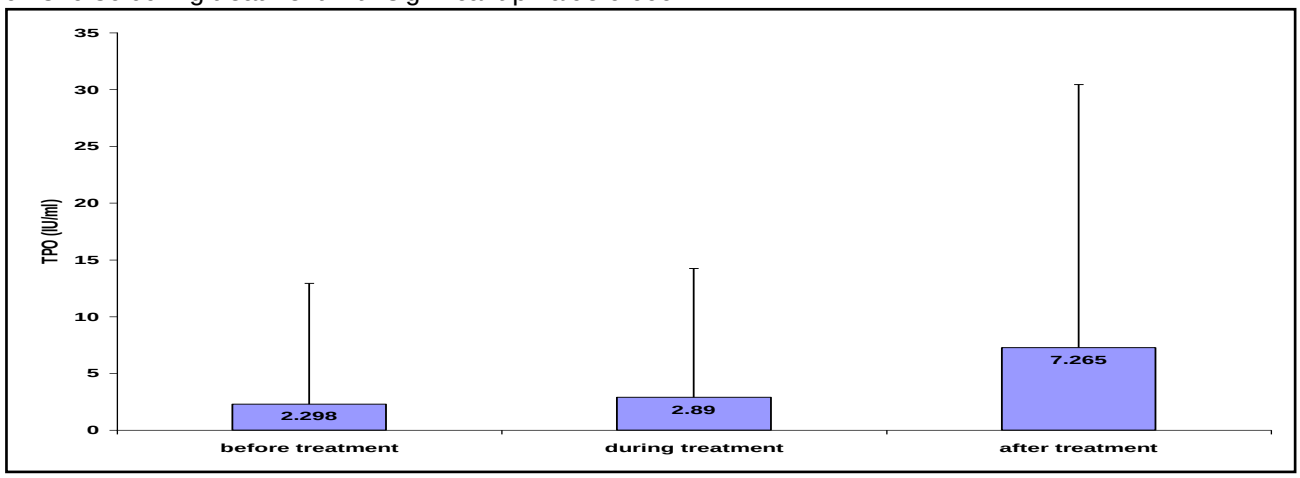
(IU/ml)	Before Treatment	During Treatment	After Treatment
Up-to 50	59(98.3%)	59(98.3%)	57(95%)
50 – 75	0	0	0
Above 75	1(1.7%)	1(1.7%)	3(5%)

Six(6) patients developed thyroid dysfunction, two(2) of them also developed thyroid autoimmunity. Positive levels of TPO-Ab were found in 5% of patients after treatment as compared to 1.7% before treatment. Thyroid gland dysfunction was more common in females.At the end of treatment three patients (5%) developed thyroid autoimmunity while one of them was TPO-Ab positive before IFN-alpha combination therapy.The average TPO-Ab values raised from baseline 2.298±10.63 to 7.265±23.17 at the end of treatment with p-value 0.662. All three patients were females, their age ranging from 45-60 years with TSH value above 6ul/ml and FT4 below0.1.(Table 3, Fig 1)

Table 3: Thyroid function tests of the patients showing thyroid dysfunction

Age (yrs)	Gender	TSH		FT4		TPO-Ab	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
50	Female	2.4	6.8	0.94	0.41	10.6	85.47
52	Female	2.69	8.35	0.96	0.22	0.79	15.70
58	Female	2.84	10.41	0.83	0.29	5.58	125.62
57	Female	2.65	8.32	0.87	0.295	8.30	15.40
54	Female	0.42	0.99	1.87	3.37	80.59	92.50
45	Male	0.85	0.32	1.15	3.92	17.58	23.22

Fig. 1: Trend of TPO-Ab from the start of treatment to the end of treatment TSH level raised by 0.51±1.06 during treatment and 1.19±1.52 after treatment with significantly higher p-value <0.001. FT4 level declined by 0.13±0.36 during treatment with significant p-value 0.006.



DISCUSSION

Treatment of chronic hepatitis C with IFN-α is associated with many side effects. Thyroid dysfunction (TD) and thyroid autoimmunity is a common adverse effect and has been reported to be more common in females having thyroid per-oxidase (TPO-Ab) or other types of thyroid auto-antibodies before treatment with interferon-alpha and ribavirin.In present study baseline thyroid functions were normal in all sixty enrolled patients. The results were compared with those obtained at 12and 24 weeks of treatment with interferon combination therapy.In this study 10% of CHC patients displayed thyroid dysfunction. The frequency of hypothyroidism was higher than hyperthyroidism. Increased TPO-Ab levels were more commonly found in female patients. Recent studies suggested that female patients carried a higher risk of TPO-Ab than males and the risk increases with age.[21]Thyroid peroxidase antibodies(TPO-Ab) were present in one female patient(1.7%) before treatment with interferon-alpha & ribavirin.Ngane et al showed that thyroid autoimmunity was also linked to HCV infection and not to interferon-alpha therapy alone because anti-thyroid antibodies were present in both treated and those without treament with interferon-alpha[22]. Present study has proved this as one patient was positive for TPO-Ab before treatment. and this patient, female, developed thyroid dysfunction after treatment with interferon-alpha and ribavirin. Four other patients also developed thyroid per-oxidase antibodies during the course of treatment, further strengthening the fact that interferon-alpha treatment is associated with the appearance of anti-thyroid antibodies in Chronic hepatitis C patients. The pathogenesis of thyroid autoimmunity is not clear but it has been reported that interferon-alpha can affect the thyroid functions by regulating T-cell and B-cell antibody responses[23].Biochemical thyroid dysfunction developed in 6 patients(10%). The majority of thyroid dysfunction (TD) events occurred in females, 5 cases (%). The frequency of hypothyroidism and hyperthyroidism was 6.6% and 3.4% respectively. Two patients, a male and a female, developed hyperthyroidism while four patients, all females, their age ranging from 45-60 years, developed hypothyroidism. All hypothyroid patients were negative for TPO-Ab before treatment and in most of these patients thyroid dysfunction and autoimmunity occurred during the early course of treatment.

Interferon-alpha induces rush of immune reactions in the body, the mechanism of which could

to be related to immuno-modulatory properties of interferon which provoke non-organ specific antibodies causing thyroid dysfunction and autoimmunity. These findings suggest that female patients with chronic hepatitis C undergoing IFN-α therapy are more prone todevelop thyroid autoimmunity.

CONCLUSION

In conclusion, the presence of thyroid auto-antibodies before treatment with IFN-Alpha and ribavirin is a risk factor for the development of thyroid autoimmunity and thyroid dysfunction in patients of Chronic hepatitis C. Women are more prone to develop interferon-alpha related thyroid diseasethan men. Interferon can induce different signs and symptoms of thyroid disease including clinical autoimmune thyroiditis (Hashimoto's thyroiditis and grave's disease). Permanent hypothyroidism which is usually treated by hormone replacement therapy is most common thyroid disorder among these patients. Thyroid functions should be checked before starting interferon-alpha therapy and frequently during treatment and at least once in six months after interferon-alpha and ribavirin treatment.

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