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Incidence of and risk factors for thyroid dysfunction during peginterferon α and ribavirin treatment in patients with chronic hepatitis C

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Background/Aims: Thyroid dysfunction (TD) is more likely to occur in patients with chronic hepatitis C (CHC) and is particularly associated with interferon (IFN) treatment. The purpose of this study was to investigate the incidence, outcomes, and risk factors for TD during pegylated interferon (PEG-IFN) and ribavirin (RBV) combined therapy in patients with CHC.

Methods: A total of 242 euthyroid patients with CHC treated with PEG-IFN/RBV were included. Thyroid function and autoantibodies were measured at baseline, and virologic response and thyroid function were assessed every 3 months during therapy.

Results: TD developed in 67 patients (27.7%) during the PEG-IFN/RBV treatment. The types of TD were subclinical hypothyroidism (50.7%), hypothyroidism (14.9%), thyroiditis (11.9%), subclinical hyperthyroidism (10.4%), and hyperthyroidism (10.4%). Most of the patients with TD recovered spontaneously; however, seven patients (10.4%) needed thyroid treatment. The sustained virological response rate was higher in patients with TD than those without (65.7% vs. 49.1%, $p = 0.02$). Baseline thyroid stimulating hormone (TSH) concentrations (odds ratio [OR], 2.09; 95% confidence interval [CI], 1.96 to 8.77; $p < 0.001$), presence of the thyroid peroxidase antibody (OR, 8.81; 95% CI, 1.74 to 44.6; $p = 0.009$), and PEG-IFNα-2b (OR, 3.01; 95% CI, 1.43 to 6.39; $p = 0.004$) were independent risk factors for the development of TD.

Conclusions: TD developed in 27.7% of patients with CHC during PEG-IFN/RBV treatment, and 10.4% of these patients needed thyroid treatment. TD is associated with a favorable virologic response to PEG-IFN/RBV. Assessment of TSH and thyroid autoantibodies at baseline and close monitoring of thyroid function during PEG-IFN/RBV therapy are necessary for early detection and management of IFN-induced TD.

Keywords: Hepatitis C, chronic; Thyroid diseases; Interferons; Incidence; Risk factors

INTRODUCTION

Hepatitis C virus (HCV) is both a hepatotropic and a lymphotropic virus and is associated with several chronic infectious diseases [1]. Among chronically infected patients, 20% to 35% progress to cirrhosis, and they have a

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high risk of developing hepatocellular carcinoma [2,3]. The extrahepatic manifestations of HCV infection include autoimmune diseases, hematologic diseases, and rheumatic diseases [4]. Many studies have shown a high prevalence of thyroid autoimmunity and thyroid dysfunction (TD) in patients with chronic hepatitis C (CHC) [5,6]. The current treatment for CHC is a combination of pegylated interferon (PEG-IFN) α-2a or -2b and ribavirin (RBV), which leads to a sustained virologic response (SVR) rate of 54% to 80% [7]. Despite their efficacy, PEG-IFN-based therapies have various adverse effects, including flu-like symptoms, depression, anemia, and TD [5-7]. The immunostimulatory effects of PEG-IFN have been well described, and the thyroid is the most commonly affected endocrine organ. Studies have reported various incidences of TD in patients with CHC treated with PEG-IFN across countries (4.6% to 33.3%) [8-10]. PEG-IFN-related TD is associated with female sex, presence of thyroid antibodies, and Asian ethnicity [11-15]. The reversibility of TD remains controversial in terms of whether it is reversible or partially reversible [11-14].

PEG-IFN has been the drug of choice to treat CHC and is being used to eradicate HCV in Korea [3]. However, the incidence and characteristics of PEG-IFN-induced TD in patients with CHC have not been reported in Korea. The severity or reversibility of PEG-IFN-induced TD is important for making the antiviral therapy decision in the high-risk group of TD and to manage the patients. Data on clinical characteristics and outcomes of TD in Korean patients with CHC are lacking.

The purpose of this study was to assess the incidence, risk factors, and outcome of TD in patients with CHC infection who were treated with PEG-IFN and RBV combined therapy (PEG-IFN/RBV).

METHODS

Patient information

A retrospective cohort of patients with CHC enrolled at two tertiary referral centers from December 2005 to March 2013 was included. The diagnosis of CHC was based on an increased level of alanine aminotransferase or aspartate aminotransferase for > 6 months, anti-HCV seropositivity, and detection of serum HCV RNA. All information was retrieved from the patient database. Inclusion criteria for the study subjects were patients with CHC treated with PEG-IFN and RBV therapy for > 4 weeks and normal baseline thyroid function. Patients with the following conditions were excluded: history or presence of TD at baseline, treatment of TD, co-infection with hepatitis B virus, history of PEG-IFN therapy, noncompliance with medications (< 80% of the dose taken, except for discontinuation due to side effects). Data were available for 453 patients during the study period. Of these, 141 declined the HCV infection therapy, and 70 were excluded; the reasons for exclusion were TD at baseline (n = 58), co-infection with hepatitis B (n = 8), and history of PEG-IFN-based therapy for CHC (n = 4). Finally, 242 patients with CHC and normal thyroid function treated with PEG-IFN/RBV therapy were included in this study.

Treatment duration differed according to HCV genotype; genotype 1 infection was treated for 48 weeks, and genotype 2 and 3 infections were treated for 24 weeks. The PEG-IFNα-2a dose was 180 μg once weekly and that of PEG-IFNα-2b was 15 μg/kg once weekly. The RBV dose was 800 to 1,200 mg daily for the duration of therapy. Period and dose adjustments were made by the individual patients based on recommendations from a specialist.

Study design

A detailed history, physical examination, liver function tests, and thyroid function tests were performed before PEG-IFN/RBV therapy and every 3 months during and after the therapy in each patient. Thyroid antibodies were assessed at the beginning of therapy. HCV RNA was evaluated at baseline, 3 months, at the end of treatment, and 6 months after treatment. Patients who developed TD during and after PEG-IFN/RBV therapy were assessed and treated by an endocrinologist at each hospital.

Laboratory evaluations

Information on age, sex, biochemistry, HCV genotype, viral load, PEG-IFN type, and thyroid autoantibody status was obtained from the database. Routine biochemical and hematological tests were performed using automated techniques. Serological viral hepatitis markers were detected using an automated chemiluminescent immunoassay system (ADVIA Centaur XP, Siemens,

Erfurt, Germany). HCV viral loads were quantitatively measured by reverse transcription-polymerase chain reaction analysis using an Amplicor HCV amplification kit version 2.0 (Roche Diagnostic Systems, Basel, Switzerland). HCV genotyping was performed using an HCV Genotyping Chip kit version 2.0 (Biocore, Seoul, Korea). Total triiodothyronine (T3) and free thyroxine (fT4) levels were measured by radioimmunoassay (RIA) and thyroid stimulating hormone (TSH) levels were measured using an immunoradiometric assay (Beckman Coulter, Brea, CA, USA). The TSH reference range was 0.4 to 4.1 mIU/mL, that for T3 was 0.8 to 2.0 ng/dL, and that for fT4 was 0.8 to 1.9 ng/dL. Anti-thyroid peroxidase (anti-TPO) antibody and anti-thyroglobulin (anti-TG) antibody levels were quantified using a competitive RIA.

Definitions

TD was defined as a TSH level > 4.1 mIU/mL (hypothyroid) or < 0.4 mIU/mL (hyperthyroid). Patients who developed biochemical TD were classified into five types: (1) subclinical hypothyroidism, TSH > 4.1 mIU/mL with normal T3 and fT4; (2) hypothyroidism, TSH > 4.1 mIU/mL with decreased T3 and fT4; (3) subclinical hyperthyroidism, TSH < 0.4 mIU/mL with normal T3 and fT4; (4) hyperthyroidism, TSH < 0.4 mIU/mL with increased T3 and fT4; and (5) thyroiditis, hyperthyroidism diagnosed initially, which was converted to hypothyroidism during the follow-up [10]. SVR was defined as successful treatment for HCV infection that was confirmed by undetectable serum HCV RNA 6 months after completing treatment.

Statistical analysis

The data were analyzed using SPSS version 17.0. (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation. Comparisons between groups were performed using the chi-square test for qualitative data and the unpaired *t* test for continuous variables. A receiver operating characteristic curve analysis was used to determine sensitivities and specificities (with 95% confidence intervals [CI]) of the TSH cutoff value. Logistic regression analysis was used to identify independent factors associated with developing TD. Differences between the groups are reported with 95% CIs. Variables were compared between the two groups using analysis of variance. The *p* values < 0.05 were considered to indicate significance.

RESULTS

Incidence and types of thyroid dysfunction

The baseline clinical and laboratory characteristics of the 242 patients with CHC are presented in Table 1. The mean age of the patients was 53.7 years, and 118 were females (48.8%). All patients were treated for > 12 weeks. Positive anti-TPO and anti-TG antibodies were detected in 6.4% (12/188) and 6.9% (13/188) of 188 patients at baseline, respectively. The thyroid antibody positivity rates were 4.1% in male and 8.7% in female patients. A total of 151 patients (62.4%) completed the entire course of treatment, whereas 91 (41.2%) discontinued treatment primarily due to adverse events related to PEG-IFN (n = 70). The PEG-IFN-related adverse events were flu-like symptoms (n = 12), skin rash or urticaria (n = 11), developed TD (n = 10), depression (n = 8), alopecia (n =

Table 1. Baseline characteristics of the study population (n = 242)

Characteristic	Value
Age, yr	53.7 ± 12.4
Female sex	118 (48.8)
Body mass index, kg/m^2	24.5 ± 12.3
Cirrhosis	42 (17.8)
HCV genotype	
1	105 (43.6)
2	135 (55.6)
3	2 (0.8)
HCV viral load, $\log_{10}$ IU/mL	6.72 ± 7.39
Biochemical function tests	
Albumin, g/dL	4.28 ± 2.14
Bilirubin, mg/dL	0.83 ± 0.34
Aspartate aminotransferase, IU/L	86.14 ± 80.23
Alanine aminotransferase, IU/L	114.14 ± 131.50
Thyroid function tests	
Free thyroxine, ng/dL	1.20 ± 0.24
Thyroid stimulating hormone	1.96 ± 0.93
Anti-TPO Ab+/tested	12/188 (6.4)
Anti-TG Ab+/tested	13/188 (6.9)

Values are presented as mean ± SD or number (%).
HCV, hepatitis C virus; Anti-TPO Ab, anti-thyroid peroxidase antibody; Anti-TG Ab, anti-thyroglobulin antibody.

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5), dizziness (n = 2), neuralgia (n = 2), hematologic complications (n = 2), chest pain (n = 2), headache (n = 2), and other (n = 14). Of the 242 patients who received therapy, 67 (27.7%) developed biochemical TD during PEG-IFN/RBV therapy. The mean time to development of TD was 18 weeks after treatment. Twenty-eight patients developed TD in the first 3 months, 29 developed TD in the next 3 months, and 10 developed TD after 6 months of PEG-IFN therapy. Among the 67 patients with TD, subclinical hypothyroidism was the most frequent (50.7%), followed by hypothyroidism (14.9%), thyroiditis (11.9%), subclinical hyperthyroidism (10.4%), and hyperthyroidism (10.4%).

Table 2 shows the clinical and laboratory characteristics of the patients with CHC who developed TD during therapy compared with those of the euthyroid patients. No significant difference in sex, age, body mass index (BMI), serum HCV RNA level, or HCV genotype was observed between the groups. Data on thyroid antibody status at baseline were available for 188 patients. Positive anti-TPO antibodies were detected in 13.4% of patients with TD, and positive anti-TG antibodies in 11.9% of patients with TD, which were significantly higher values than those in euthyroid patients during treatment. Baseline TSH was higher in patients with TD (2.33 ± 0.99 mIU/mL) than that in euthyroid patients (1.82 ± 0.86 mIU/mL, $p < 0.001$).

The type of PEG-IFN therapy was significantly different between the two groups ($p = 0.045$). Of the 67 patients who developed TD, 44 (65.7%) achieved SVR, whereas 86 euthyroid patients (49.1%) achieved SVR ($p = 0.021$). However, SVR rates were comparable in patients treated with PEG-IFNα-2a and those treated with PEG-IFNα-2b (51.3% vs. 56.1%, $p = 0.451$).

Long-term outcomes of thyroid dysfunction

All 67 patients with biochemical TD underwent follow-up for thyroid function. The mean follow-up period was 24 months (range, 3 to 87). Transient TD developed in 89.6% of patients, whereas seven (10.4%) needed med-

Table 2. Comparison of the clinical and laboratory characteristics of patients with CHC with and without thyroid dysfunction during PEG-IFN/RBV treatment

Variable	Patients with TD (n = 67)	Euthyroid patients (n = 175)	*p* value
Female sex	36 (53.7)	82 (46.9)	0.338
Age, yr	52.2 ± 11.4	54.3 ± 12.8	0.271
Body mass index, kg/m^2	27.9 ± 22.9	23.3 ± 4.1	0.061
CHC with LC	9 (13.2)	33 (18.9)	0.306
HCV genotype			0.772
1	26 (38.8)	79 (45.1)	
2	41 (61.2)	94 (53.7)	
3	0	2 (1.1)	
Treatment type			0.045
PEG-IFNα-2a	25 (37.3)	94 (53.7)	
PEG-IFNα-2b	42 (62.7)	81 (46.3)	
HCV RNA, $\log_{10}$ IU/mL	6.61 ± 7.11	6.75 ± 7.44	0.645
Alanine aminotransferase, IU/L	110.4 ± 128.8	115.5 ± 132.9	0.784
Thyroid stimulating hormone, mIU/mL	2.33 ± 0.99	1.82 ± 0.86	< 0.001
Free thyroxine, ng/dL	1.21 ± 0.20	1.19 ± 0.26	0.642
Anti-TPO Ab+	9/51 (17.6)	3/137 (2.2)	< 0.001
Anti-TG Ab+	8/51 (15.7)	5/137 (3.6)	0.004
Sustained virologic response	44 (65.7)	86 (49.1)	0.021

Values are presented as number (%) or mean ± SD.
CHC, chronic hepatitis C; PEG-IFN, pegylated interferon; RBV, ribavirin; TD, thyroid dysfunction; LC, liver cirrhosis; HCV, hepatitis C virus; Anti-TPO Ab, anti-thyroid peroxidase antibody; Anti-TG Ab, anti-thyroglobulin antibody.

ical treatment (Table 3). PEG-IFN/RBV treatment was administered to most of the patients with subclinical TD, with four exceptions. They recovered spontaneously without any specific thyroid treatment. Among the 11 patients with hypothyroidism, two needed levothyroxine replacement therapy. Among the eight patients with thyroiditis, four were treated with levothyroxine during the symptomatic hypothyroid phase. Among the seven patients treated with thyroid drugs, four completed the PEG-IFN/RBV treatment. One patient with hyperthyroidism was treated with propylthiouracil, and she subsequently developed agranulocytosis due to the drug. She underwent total thyroidectomy to treat her hyperthyroidism.

Predictors of thyroid dysfunction

A univariate logistic analysis of factors associated with TD, including sex, age, HCV genotype, BMI, cirrhosis, RNA titer, type of IFN, alanine aminotransferase, TSH, and thyroid autoantibodies was performed. Baseline TSH concentrations, positive anti-TPO antibody, positive anti-TG antibody, and type of therapy were associated with the development of TD (Table 4). In the multivariate analysis, baseline TSH concentration, presence of the anti-TPO antibody, and type of therapy were independent risk factors for TD. SVR after PEG-IFN/RBV treatment was significantly associated with the development of TD during treatment.

DISSCUSSION

In this study, the incidence of TD in Korean patients with CHC who were treated with PEG-IFN/RBV was 27.7%. The incidence of IFN-induced TD in patients with CHC is 12% to 23% [8-10,16]. Our study showed a higher incidence of TD compared to those reported previously. The differences and inconsistencies in the definition of TD, ethnicity, and regional differences in iodine status among subjects of the studies may have contributed to the variation in the incidence of TD. Additionally, symptoms of TD are often subclinical and masked by the effects of IFN therapy [17].

Most patients had subclinical TD that resolved spontaneously. The most common form of TD related to PEG-IFN/RBV therapy was subclinical hypothyroidism.

Table 3. Clinical outcomes of the patients with thyroid disease who needed thyroid treatment

No.	Sex	Age	Genotype	Type of PEG-IFNα	Duration of tx., wk	Onset of TD, wk	Type of TD	Anti-TPO Ab	Anti-TG Ab	Follow-up duration, mon	Treatment	Outcome	SVR
1	F	40	1b	2b	48	14	Thyroiditis	Neg	Neg	35	Levothyroxine	Normalised	Y
2	F	71	2a	2a	24	24	Hypothyroidism	139	Neg	17	Levothyroxine	Normalised	N
3	F	63	2a	2b	24	24	Hyperthyroidism	Neg	283	25	Propylthiouracil	Total thyroidectomy[a]	Y
4	F	56	2a	2a	15	15	Thyroiditis	410	283	23	Levothyroxine	Normalised	Y
5	F	58	2a	2b	12	12	Thyroiditis	167	Neg	19	Levothyroxine	Hypothyroidism	Y
6	M	48	2a	2b	24	12	Thyroiditis	679	509	13	Levothyroxine	Hypothyroidism	Y
7	F	60	1b	2a	28	12	Hypo thyroidism	97	136	78	Levothyroxine	Normalised	N

PEG-IFN, pegylated interferon; tx., pegylated interferon and ribavirin treatment; TD, thyroid dysfunction; Anti-TPO Ab, anti-thyroid peroxidase antibody; Anti-TG Ab, anti-thyroglobulin antibody; SVR, sustained virologic response; Neg, negative.
[a]Patient underwent surgery because she developed agranulocytosis due to the adverse effect of propylthiouracil.

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Table 4. Logistic analysis of the risk factors for thyroid dysfunction

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Female sex	1.317	0.749–2.316	0.339			
Age	0.985	0.963–1.007	0.186			
Body mass index	1.052	0.953–1.161	0.319			
Liver cirrhosis	0.660	0.297–1.468	0.309			
Type of therapy						
PEG-IFNα-2a	Reference			Reference		
PEG-IFNα-2b	1.950	1.094–3.473	0.023	3.019	1.426–6.390	0.004
Thyroid stimulating hormone[a]	3.025	1.685–5.428	< 0.001	2.088	1.961–8.767	< 0.001
Anti-TPO Ab+	9.571	2.477–36.989	0.001	8.812	1.742–44.577	0.009
Anti-TG Ab+	4.912	1.528–15.812	0.008	2.389	0.564–10.124	0.237

OR, odds ratio; CI, confidence interval; PEG-IFN, pegylated interferon; Anti-TPO Ab, anti-thyroid peroxidase antibody; Anti-TG Ab, anti-thyroglobulin antibody.
[a]≤ 2.03 mIU/mL vs. > 2.03 mIU/mL.

Seven patients (2.9%) with TD required thyroid or anti thyroid medication. Most of the patients recovered after treatment; however, long-term medication was needed to maintain euthyroid status. Two patients completed the PEG-IFN/RBV treatment with thyroid medication maintenance. The outcome of patients with TD in previous studies was controversial in terms of whether TD is reversible or partially reversible. In recent reports, TD has been partially reversible at the end of a long-term follow-up period [8,18,19]. Most of our patients with TD recovered spontaneously or after receiving thyroid medication. However, one patient with hyperthyroidism developed agranulocytosis due to the antithyroid drug, and a thyroidectomy was inevitable. The patient recovered from agranulocytosis after medical management; however, she needed lifelong thyroid replacement therapy. Therefore, PEG-IFN-induced TD may decrease quality of life and cause unnecessary medical expenses. Our results indicate that the TD clinical course developing during PEG-IFN/RBV treatment was not always favorable due to the prolonged thyroid treatment or the risk of adverse events from antithyroid drugs. Patient status should be carefully monitored by means of laboratory data during PEG-IFN/RBV therapy after the development of TD.

We evaluated risk factors for the development of TD during PEG-IFN/RBV therapy in patients with CHC. Generally, thyroid diseases are prevalent in females, and the female sex is predictive of TD during PEG-IFN/RBV treatment [12,15]. In our study, more females than males tended to develop TD, but the difference was not significant. The relatively small number of patients in our study could have been the reason for the lack of an association between female sex and the development of TD.

The prevalence of thyroid autoantibodies in patients with CHC is 20% to 30%, and the presence of anti-TPO or anti-TG antibodies is strongly associated with IFN-induced TD [10,18,19]. These findings support the immunological basis for TD development during PEG-IFN-based therapy. HCV itself has been hypothesized to induce production of thyroid autoantibodies [20,21]. In addition to its direct effects on thyrocytes, IFN activates lymphocytes, leading to increased cytokine production and induction of thyroid antibodies [9]. In this study, anti-TG and anti-TPO antibodies were significantly related to the development of TD in a univariate analysis, but only anti-TPO antibodies were a significant factor in the multivariate analysis. These results suggest that assessing pretreatment thyroid autoantibodies in patients with CHC would facilitate prediction of the occurrence of IFN-induced TD. However, the thyroid autoantibody positivity rate was quite low, and most patients with TD were negative for thyroid autoantibody at baseline. The clinical impact of thyroid autoantibody positivity on predicting the development of TD and the cost-effectiveness of measuring thyroid antibodies at baseline

should be evaluated.

TSH is a predictor of TD development in patients with HCV infection who were treated with IFN-based therapy. The mean serum TSH concentration before PEG-IFN/RBV therapy in patients who developed TD and in those who developed hypothyroidism were significantly different from the mean serum TSH values in patients who remained euthyroid. A correlation between TSH concentration and the development of TD in healthy individuals has been reported [10]. A 20-year follow-up survey of 2,779 subjects showed an increased probability of developing overt disease in women with serum TSH > 2 mU/L, and the risk increased further in the presence of anti-thyroid antibodies prior to therapy [22]. In a follow-up study of 437 healthy females, serum TSH concentrations in the upper part of the normal range appeared to have predictive value [23]. In our study, a high TSH concentration was an independent predictor for the development of TD, particularly hypothyroidism.

In our study, PEG-IFNα-2b therapy was significantly associated with TD compared to PEG-IFNα-2a therapy. Exposure to two different forms of PEG-IFN therapy may have confounded the elicitation of TD. These two PEG-IFNs differ in their pegylation characteristics, which may have translated into differences in their pharmacokinetic and biological activities. However, pharmacological (dosage and type of PEG-IFN) parameters are not related to the development of TD [13,20]. Our sample size was too small to confirm this finding; hence, further large-scale studies are needed to clarify the relationship between PEG-IFN type and TD.

In our results, SVR was higher in the TD group regardless of how many discontinued treatment. A few published reports have assessed the development of TD in relation to SVR. Vezali et al. [20] reported no relationship between TD and SVR in patients with CHC receiving PEG-IFN/RBV therapy. Other studies demonstrated a positive association between thyroid disease and viral clearance, despite lacking supportive evidence from a meta-analysis [24]. However, the association between SVR and TD remains controversial. The mechanism of the relationship between SVR and TD in patients with CHC is unclear. The presence of TD may indicate a strong immune response, which increases the likelihood of eradicating the virus. It has been suggested that C-X-C motif chemokine 10 levels are associated with the development of autoimmune TD and the virologic response during PEG-IFN/RBV therapy [25]. Further study using a cohort with a different race and sex composition is needed to clarify this issue.

Our results provide valuable information on the incidence of TD and outcomes from longitudinal observations. The clinical relevance of TD in the prognosis of patients with CHC is important to start and maintain PEG-IFN therapy in these patients. However, this study had several limitations. First, this was a retrospective study with observational data. Second, thyroid antibodies were not measured in the whole study population. Therefore, a further prospective study on TD in patients with CHC is needed to demonstrate the clinical significance and the underlying mechanisms.

Taken together, our data suggest that the incidence of TD in patients with CHC during PEG-IFN/RBV therapy was 27.7%. The majority of patients with TD showed subclinical thyroid disease and recovered spontaneously without specific treatment. However, prolonged thyroid medication was needed in patients with clinically relevant TD. Based on our experience, the risk of serious adverse events due to an antithyroid drug should be considered. Baseline TSH concentrations, anti-TPO antibody status, and type of PEG-IFN therapy were independent predictors of the development of TD. Consequently, close monitoring of baseline thyroid autoantibody levels and serial thyroid functioning during PEG-IFN/RBV treatment are needed for early detection and proper management of IFN-induced TD in patients with CHC.

KEY MESSAGE

1. Thyroid diseases are not uncommon in chronic hepatitis C patients during or after treatment with pegylated interferon and ribavirin.
2. The thyroid diseases are mostly subclinical; however, thyroid treatments are required in patients who develop clinically evident thyroid dysfunction.
3. The thyroid adverse events during the pegylated interferon and ribavirin therapy are strongly associated with baseline thyroid characteristics. Therefore, close monitoring of thyroid antibodies and thyroid function at baseline and during the treatment for better patients' outcome.

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KJIM

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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