Virus C genotype predisposes to primary hypothyroidism during interferon-α treatment for chronic hepatitis C

ABSTRACT

Objective: The treatment of the chronic hepatitis C (HCV) with α-interferon is associated with thyroid dysfunction (TD). The aim of this study was to evaluate thyroid function outcome among patients with chronic HCV under treatment with conventional interferon (IFN) or peguilated interferon (PEG-IFN) in association with ribavirin. **Patients and Methods:** We studied 293 patients with chronic HCV, submitted to drug therapy for 24 or 48 weeks. Initially, we evaluated FT4, TSH, TPOAb, TgAb, and continued to monitor FT4 and TSH every three months during therapy and six months thereafter. **Results:** At baseline, TD prevalence was 6.82% (n = 20); 6.14% hypothyroidism; 0.68% hyperthyroidism. TPOAb was present in 5.46% of euthyroid patients. Out of 273 euthyroid patients at baseline, 19% developed TD: 17.2% hypothyroidism; 1.8% hyperthyroidism; 5.1% destructive thyroiditis (DT). 90% of TPOAb-positive patients at baseline developed hypothyroidism vs 14.5% of TPOAb-negative patients ($p < 0.001$). On average, TD occurred after 25.8 ± 15.5 weeks of treatment. 87.2% of patients who developed hypothyroidism did so during the first therapeutic cycle ($p = 0.004$; OR = 3.52; 95% CI = 1.36-9.65). Patients infected with genotype 1 virus were 2.13 times more likely to develop hypothyroidism ($p = 0.036$; 95% CI = 1.04-4.38). Hypothyroid and DT patients presented higher TSH levels before-treatment than patients who had remained euthyroid ($p < 0.001$; $p = 0.002$, respectively). DT patients presented lower qALT ($p = 0.012$) than euthyroid patients. **Conclusion:** Hypothyroidism was the most frequent TD, especially during the first cycle of α-interferon. Genotype 1 virus was associated with a risk two times higher for developing the illness. There was no need to interrupt or to change HCV treatment. Therefore, approximately 34% of TD was transient.

Keywords: hypothyroidism; hepatitis C, chronic; interferon-α.

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INTRODUCTION

Hepatitis C virus (HCV) affects from 1.5% to 2.5% of the Western population, and is the most common source of infections transmitted by blood transfusions. HCV should be diagnosed as early as possible as most patients without treatment develop hepatic cirrhosis and, eventually, hepatocellular carcinoma.[1]

Interferon-α (IFN-α) is a good option for treating HCV. The antiviral action and modulatory effect of the drug on the autoimmune response may elicit a production of antinuclear, antithyroid antibodies, as well as amplification of cellular cytotoxic response. Treatment using IFN-α and ribavirin (RBV), a synthetic guanosine-nucleotide analog, increased remission rates from 20% to 40%. The therapeutic efficacy of this regimen can be explained by the immunomodulatory and anti-inflammatory additional effects of RBV. Hence, this combined treatment favors the development of systemic and organ-specific autoimmune diseases, such as autoimmune thyroid disease (ATD) and thyroid dysfunction (TD).[2-4]

Patients infected with HCV present 40-42% of detectable antithyroid autoantibody levels; whereas in patients with hepatitis B virus, the index varies from 5 to 10%.[4] The prevalence of TD in patients under IFN-α use ranges from 1 to 35%, possibly due to the lack of standardization for the routine screening of thyroid function evaluation in several studies. TD resulting from the use of

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IFN-α presents a wide spectrum of forms and intensities, such as thyrotoxicosis in 2-3% and hypothyroidism in 2.4-19% of the cases.[4-6] TD is frequently associated with the female gender and HCV-related factors.[7] There seems to be no correlation between TD and IFN-α dosage; however, the duration of treatment may interfere. Additionally, various authors have reported that 50% of patients with HCV and antithyroperoxidase antibodies detectable prior to IFN-α treatment developed ATD vs. 5.4% of patients with negative antibodies.[5,6]

Considering that ATD and TD occur frequently during HCV therapy with IFN-α and RBV, there is a recommendation of systematic evaluation for their presence during treatment and follow-up. Once TD is diagnosed, very often the treatment for HCV is unnecessarily interrupted, which drastically reduces therapeutic success.[6]

The aim of the present study was to assess thyroid function at baseline and during treatment for HCV with standard interferon-α (IFN-α) or peguilated interferon-α (PEG-IFN-α) combined with RBV.

MATERIAL AND METHODS

Patients

We prospectively studied 293 patients with HCV, treated with a combined regimen (IFN or PEG-IFN and RBV), and they were followed by the Infectious Disease Service between 2001 and 2007. Other etiologies of chronic hepatitis were excluded and no patients presented hepatitis B or AIDS.

Thyroid function was evaluated in patients before treatment, every three months during treatment and six months after treatment. Patients who presented TD at baseline underwent monthly reassessment; however, they were excluded from the follow-up group, comprised by euthyroid individuals. The patients were from the city Campinas and region, state of São Paulo, an iodine sufficient area.

Therapeutic plan

All patients were treated with IFN or PEG-IFN and RBV and received 1-3 therapeutic schedules. Treatment for viral genotypes 2 and 3 lasted for 24 weeks, and 48 weeks for genotypes 1 and 4. IFN was indicated for patients infected by viral genotypes 2 and 3, and PEG-IFN was the first choice for those with genotype 1 or a second option for those with genotypes 2 and 3 who had failed therapy with IFN. Patients weighing less than 75 kg used PEG-INF-α 2b (Peg-Intron®), whereas patients over 75 kg were treated with PEG-INF-α 2a (Pegasys®). Virologic response was assessed at the end of treatment and 24 weeks thereafter.

A subcutaneous IFN dose of 3 MU was administrated three times a week. A subcutaneous PEG-IFN dose of 180 mg was administrated once a week for Pegasys® and 1.5 mg/kg/week for Peg-Intron®. The RBV dose varied from 1,000 to 1,250 mg/day. IFN/PEG-IFN/RBV dose was not modified by the presence of thyroid dysfunction. The patient was referred to the Endocrinology Service when thyroid dysfunction persisted for over 30 days.

Laboratory assessment

Chronic hepatitis C diagnosis was investigated through alteration of qALT (ALT of patient/ALT maximum reference values, RV ≤ 1), through the presence of anti-HCV antibody, and was confirmed through the presence of HCV-RNA (qualitative PCR-HCV, Amplicor 2.0, Roche). Viral genotype was determined by Line Probe assay, LIPA HCV, Innogenetics, Gent, Belgium. Hepatic damage was evaluated by biopsy and classified according to the recommendations of the Brazilian Society of Pathology.

Thyroid function was assessed by serum free T_4 (FT_4, RV = 0.9-1.8 ng/dL), thyrotrophin (TSH, RV = 0.41-4.5 mIU/mL) (enzyme immunoassay kits, GenBio, San Diego, USA). ATD was verified by the detection of serum antithyroperoxidase (TPOAb, RV > 76 IU/mL) and antithyroglobulin antibodies (TgAb, RV > 120 IU/mL) (fluorimetric enzyme immunoassay, Dade Behring Inc., Miami-FL, USA).

Thyroid disorders

The following thyroid disorders were considered:

- autoimmune thyroid disease: clinical and laboratory euthyroid patients presenting elevated serum levels of TPOAb and/or TgAb;
- subclinical primary hypothyroidism: increased serum TSH levels, less than 10 mUI/mL with normal FT_4 levels;
- evident primary hypothyroidism: increased serum TSH levels with reduced FT_4 levels;
- hyperthyroidism: increased FT_4 with reduced levels of TSH;
- destructive thyroiditis: transient TD auto-limited. Initial phase of thyrotoxicosis, intermediate phase of hypothyroidism and resolution phase of euthyroidism or permanent primary hypothyroidism.

Thyroid disorders were classified as transient or definitive, depending on whether or not they returned to normal levels after hepatitis treatment withdrawal. Autoimmune etiology was based on the presence of elevated serum levels of TPOAb and/or TgAb.

Statistical analysis

The sample profile was described by frequency tables of the categorical variables (age, gender, qALT, viral genotype, presence of cirrhosis, liver biopsy, therapeutic regimen, type of INF-α used, total treatment time, event time

during treatment, sustained virological response, demonstrating the values of absolute (n) and percentage (%) frequency. Continuous descriptive variables are presented as mean, standard deviation, minimum, maximum and median values. The association between two categorical variables was analyzed by either Chi-square or Fisher's test. The Mann-Whitney test was used to compare numerical variables between patients with and without thyroid dysfunction. The significance level was set at 5% ($p < 0.05$). Statistical analyses were performed using the SAS system for Windows (Statistical Analysis System) version 8.02. SAS Institute INC, 1999-2001, Cary, NC, USA.

RESULTS

Out of 293 patients included in the study, we verified TD prior to the use of IFN in 20 (6.82%); 18 of them presented primary hypothyroidism (prevalence = 6.14%) and two, hyperthyroidism (prevalence = 0.68%) (Table 1). Elevated serum TPOAb levels were detected in 13 (5.46%), and TgAb in five (1.68%) of 238 patients.

After excluding patients with previous TD, we studied 273 euthyroid individuals who were treated with Interferon-α and ribavirin. Table 2 describes the baseline characteristics of the euthyroid study patients prior to treatment. Under treatment, 19% (n = 52) developed TD, 18% of the men and 27% of the women (p = 0.104). TD was diagnosed 25.8 ± 15.5 weeks after treatment initiation. Hypothyroidism was verified in 17.2% (n = 47); hyperthyroidism in 1.8% (n = 5), and 5.1% (n = 14) presented destructive thyroiditis (DT).

Table 1. Baseline characteristics of patients with chronic hepatitis C and thyroid dysfunction before treatment with IFN-α

Patients (n = 20)	Hypothyroidism	Hyperthyroidism
n	18	2
Gender		
Female	6/92 (6.5%)	0
Male	12/236 (5.1%)	2
Age (years)	47.9 ± 9.6 (median = 46)	36.5
TPOAb	5/15 (33%)	0
TgAb	1/16 (6.25%)	0
Sustained virological response		
Yes	8 (44.4%)	0
No	10 (55.6%)	1/1
Virus C genotype		
1	12 (66.7%)	1
2	1 (5.5%)	0
3	5 (27.8%)	1

Table 2. Baseline characteristics of euthyroid patients with chronic hepatitis C before treatment with IFN-α

Patients (n total = 273)	
Female	74 (27.1%)
Male	199 (72.9%)
Age (years)	43.9 ± 9.7 (18-71)
qALT	2.49 ± 1.7 (0.3-13.7)
Cirrhosis	
Yes	46 (17.3%)
No	220 (82.7%)
Liver biopsy	
Structural alterations	
0/1	37 (14.6%)
2	120 (47.4%)
3	61 (24.1%)
4	35 (13.8%)
Activity	
0/1	17 (13.2%)
2	67 (51.9%)
3	45 (34.9%)
Virus C genotype	
1	151 (57.8%)
2	7 (2.7%)
3	103 (39.4%)
Number of therapeutic regimens	
1	177 (64.8%)
≥ 2	96 (35.2%)
Treatment duration	
< 48 weeks	123 (45.2%)
≥ 48 weeks	149 (54.8%)
Total treatment duration (weeks)	37.7 ± 14.0 (8-120)
Interferon used	
IFN	194
PEG	165
End of treatment response	
Yes	184 (68.4%)
No	85 (31.6%)
Sustained virological response	
Yes	144 (54.7%)
No	119 (45.2%)
Free T_4 (ng/dL)	1.21 ± 0.19
TSH (mIU/L)	1.93 ± 0.89
TPOAb > 76 IU/ml (total n =200)	8 (4.0%)
TgAb > 120 IU/mL (total n = 199)	3 (1.5%)

FT_4, RV = 0.9-1.8 ng/dL TSH, RV = 0.41–4.5 mIU/L.
TPOAb (RV ≤ 76 IU/mL) TgAb, RV ≤ 120 IU/mL.

Among the 13 patients presenting high TPOAb levels before using INF-α, five had a previous diagnosis of primary hypothyroidism. During the first therapeutic regimen, seven out of eight euthyroid

patients became hypothyroid. Therefore, 90% of TPOAb-positive patients before treatment developed hypothyroidism vs. 14.5% of TPOAb-negative patients ($p < 0.001$). Moreover, 10 patients were infected with genotype 1 virus (76.9%); one patient with genotype 2 virus; and one with genotype 3 (one patient did not have the genotype identified).

Table 3 lists the characteristics of patients who developed hypothyroidism under treatment. 87.2% of the patients presented hypothyroidism during the first therapeutic regimen ($p = 0.004$; OR = 3.52; 95% CI = 1.36-9.65). The logistic regression analysis related to categorical variables established that patients infected with genotype 1 virus were 2.13 times more likely to develop primary hypothyroidism ($p = 0.036$; 95% CI = 1.04-4.38) during treatment. The variables age ($p = 0.326$), gender ($p = 0.197$), presence of cirrhosis ($p = 0.984$), liver biopsy characteristics (structural alterations, $p = 0.498$ and activity, $p = 0.892$), use of IFN ($p = 0.755$) or PEG-IFN ($p = 0.153$), type of PEG-IFN used ($p = 0.766$) and sustained virological response ($p = 0.946$) were not significantly associated with TD.

Table 3. Characteristics of patients who developed primary hypothyroidism under IFN-α treatment

	Hypothyroid (n = 47)
Female	16 (34.0%)
Male	31 (66.0%)
Age (years)	44.6 ± 9.3 (25-68)
qALT	2.35 ± 1.61 (0.7-7.6)
Cirrhosis	
Yes	8 (17.0%)
No	39 (83.0%)
Liver biopsy	
Structural alterations	
0/1	4 (8.5%)
2	20 (42.5%)
3	14 (29.8%)
4	7 (14.9%)
Virus C genotype (n = 253)	
1	31 (72.1%)
2/3	12 (27.9%)
Event time under treatment (weeks)	26.52 ± 16.49 (8-96, median = 24)
Number of therapeutic regimens at the event	
1	41 (87.2%)
2	6 (12.8%)
Total treatment duration (weeks)	43.02 ± 15.64 (24-96; median = 48)
Interferon used	
IFN	14 (29.8%)
PEG	13 (27.6%)
IFN+PEG	20 (42.5%)
Final virological response	
Yes	31 (68.9%)
No	14 (31.1%)
Sustained virological response (n = 254)	
Yes	26 (57.8%)
No	19 (42.2%)
Free T4 (ng/dL)	0.79 ± 0.38 (0.04-1.6; median = 0.80)
TSH (mIU/L)	27.5 ± 30.5 (4.7-100.0; median = 9.48)

FT_4, RV = 0.9-1.8 ng% TSH, RV = 0.41–4.5 mIU/L.

Regarding patients under treatment, the euthyroid group had higher TSH serum levels before treatment (mean = 1.78 vs. 2.59; median = 1.6 vs. 2.72, $p < 0.001$) than the group that developed hypothyroidism. There was no significant difference between the two groups in relation to age ($p = 0.567$), weight ($p = 0.148$), FT_4 levels before treatment ($p = 0.126$) and qALT ($p = 0.219$). Table 4 describes the types of TD encountered in this study.

Hyperthyroidism was confirmed in a small number of patients (n = 5), allowing only for descriptive analysis (Table 5).

Table 6 describes characteristics of the 14 patients who triggered DT during treatment. Comparing to those without such complication, DT patients were not significantly different in terms of age ($p = 0.334$), weight ($p = 0.372$), gender ($p = 0.755$), presence of cirrhosis ($p = 1.000$), liver biopsy characteristics (structural alterations, $p = 0.701$ and activity, $p = 0.239$), use of IFN ($p = 0.765$) or PEG-IFN ($p = 0.147$), type of PEG-IFN used ($p = 0.510$), sustained virological response ($p = 0.823$) and viral genotype ($p = 0.082$).

The comparative analysis of continuous variables between the euthyroid group and the DT group of patients under treatment, demonstrated that the latter presented TSH levels significantly higher before treatment (mean = 1.78 vs. 2.55; median = 1.6 vs. 2.72, $p = 0.002$), as well as lower qALT (mean = 1.68, median = 2.10 vs. 1.35, $p = 0.012$). The comparison between the two groups regarding age ($p = 0.096$), weight ($p = 0.372$), and FT_4 levels prior to treatment ($p = 0.727$) was not significant.

Table 4. Length and intensity of thyroid dysfunction

	Hypothyroidism (n = 47)	Hyperthyroidism (n = 5)
Transient	17 (36.2%)	1 (20%)
Definitive	30 (63.8%)	4 (80%)
Subclinical	20 (42.5%)	3 (60%)
Manifest	27 (57.5%)	2 (40%)

Table 5. Patients who developed hyperthyroidism under IFN-α treatment

Hyperthyroidism (n = 5)	
Female	3 (60%)
Male	2 (40%)
Age (years)	46.4 ± 7.3 (39-56)
qALT	1.82 ± 0.94 (1.3-3.5; median = 1.4)
Cirrhosis	
Yes	1 (20%)
No	4 (80%)
Liver biopsy	
Structural alterations	
0/1	0 (0%)
2	3 (60%)
3	1 (20%)
4	1 (20%)
Virus C genotype	
1	2 (50%)
2/3	2 (50%)
Event time under treatment (weeks)	19.60 ± 8.99 (8-32, median = 18)
Number of therapeutic regimens at the event	
1	5 (100%)
Total treatment duration (weeks)	43.2 ± 10.73 (24-48; median = 48)
Interferon used	
IFN	4 (80%)
PEG	1 (20%)
Sustained virological response	
Yes	4 (80%)
No	1 (20%)
Free T4 (ng/dL)	2.57 ± 1.56 (1.36-4.46; median = 1.50)
TSH (mIU/L)	0.13 ± 0.17 (0.01-0.33; median = 0.1)

Table 6. Patients who developed destructive thyroiditis under IFN-α treatment

Patients (n = 14)	
Female	4 (28.5%)
Male	10 (71.5%)
Age (years)	40.0 ± 8.0 (30-60)
qALT	1.68 ± 1.10 (0.8-6.6; median = 1.3)
Cirrhosis	
Yes	2 (14.3%)
No	12 (87.7%)
Liver biopsy	
Structural alterations	
0/1	3 (23.0%)
2	5 (38.5%)
3	4 (30.7%)
4	1 (7.6%)
Virus C genotype	
1	11 (78.5%)*
2/3	3 (21.4%)
Event time under treatment (weeks)	19.60 ± 8.99 (8-32, median = 18)
Number of therapeutic regimens at the event	
1	13 (92.8%)
2	1 (7.4%)
Total treatment duration (weeks)	42.86 ± 10.22 (24-48; median = 48)
Interferon used	
IFN	8 (57.1%)
PEG	6 (42.8%)
Sustained virological response	
Yes	8 (57.1%)
No	6 (42.8%)
Outcome	
Hypothyroidism	10 (71.5%)
Euthyroidism	4 (28.5%)

FT_4, RV = 0.9-1.8 ng% TSH, RV = 0.41–4.5 mIU/L.

DISCUSSION

Hepatitis C virus is a hepatotropic and lymphotropic RNA virus which may be associated with chronic infectious disease.[8] Although hepatocytes are the major site of HCV replication, extrahepatic complications of HCV infection may occur, such as autoimmune diseases and lymphoproliferative disorders.[9]

HCV treatment with IFN-α and RBV can trigger adverse effects frequently leading to a reduction of the dose in over 40% of the patients or even withdrawal in approximately 14%.[8]

Standard or PEG-IFN-α may lead to influenza-like symptoms at the onset of treatment, as well as psychiatric, hematologic (neutropenia and thrombocytopenia)[10,11] and thyroid dysfunction.[12] As referred by Sachithanandan et al.,[13] thyropathies affect 26.3% of HCV treated patients. The association with RBV usually induces hemolytic anemia, with no additional risk of thyropathy.[10]

Generally, SVR is achieved in approximately 60% of the patients, 40% among patients of viral genotype 1 and 76% among those with viral genotypes 2 and 3. Other SVR predictive factors include: age less than 40 years, weight lower than 75 kg, female gender, Caucasian race, low viral load before treatment, and absence of liver cirrhosis.[10] In our study, HCV patients obtained 53.9% as response rate of IFN-α therapy, in accordance to the literature. The study population showed a predominance of Caucasoid male patients infected by virus C of genotypes 1 and 3.

Based on the literature,[2] standard IFN was indicated for patients infected with virus of genotypes 2 and 3, and PEG-IFN was the first choice for genotype 1. Non-responding patients with genotypes 2 and 3 could then be treated with PEG-IFN. More than one therapeutic regimen was prescribed to 35.2% of the patients, and 54.8% of them were treated for 48 weeks. PEG-IFN was administrated to 165 patients: those who weighed less than 75 kg used PEG–IFN-α 2b and those with more than 75 kg, PEG–IFN-α 2a.

Firstly, Pateron et al.[14] reported a prevalence of 14% of antithyroid autoantibodies in HCV patients. A review of published controlled studies[15] observed that most reports confirmed a higher prevalence of autoimmune thyroid disease and hypothyroidism in chronic HCV-infected patients.

Several studies found that female gender and the presence of TPOAb were considered major risk factors for the development of hypothyroidism.[16-19] Our data demonstrated that TPOAb-positive patients had a higher chance of developing hypothyroidism; however, females were not more prone, similarly to the findings reported by Muratori et al.[20] and Stefanova-Petrova et al.[21]

The prevalence of hypothyroidism in HCV patients is approximately 9% (0-13%) vs. 3% (0.5-4%) in healthy subjects.[19,22-24] Thyroid autoimmunity was demonstrated in 15% (5-28%) of the HCV patients and in 12% (0-11%) of healthy subjects, indicating a slight though significantly higher risk.[15] In our study, we verified that the prevalence of hypothyroidism (6.1%) and thyroid autoimmunity (5.5%) found in HCV patients before treatment was similar to the literature reports, in spite of the differences existing in geographical distribution, genetic variability, iodine intake or other infectious agents.[25,26] Moreover, the prevalence of hyperthyroidism before IFN-α treatment (0.68%) found in our study population was not significantly different in HCV-infected patients, as described in the literature.[15]

After IFN-α therapy, 19% presented thyroid dysfunction: hypothyroidism in 17.2%, hyperthyroidism in 1.8% and destructive thyroiditis in 5.1% – very similar values were found by Sachithanandan et al.[13] (26.3%), higher than those described by Moncoucy et al.[27] (7%) and Tran et al.[16] (6.7%).

The rates of thyroid dysfunction triggered by the two types of IFN-α, standard and peguilated, were similar, as also found by Moncoucy et al.[27] Moreover, thyroid dysfunction was not associated with sustained virological response of chronic hepatitis C to IFN-α therapy, as also demonstrated by Hsieh et al.[28] and in contrast to previous reports.[29-31] In our patients, the presence of thyroid dysfunction did not lead to changes in the dose or therapy withdrawal.

After IFN-α plus RBV treatment 17.2% developed primary hypothyroidism. However, this rate has varied in several studies.[16,27] Among risk factors evaluated: age, gender, presence of cirrhosis, qALT and FT_4 levels before treatment, type and commercial presentation of IFN-α used, and SVR, we found no association with primary hypothyroidism. In contrast, the likelihood of developing primary hypothyroidism increased in the presence of TPOAb, genotype 1, to be on the first therapeutic regimen, and having higher TSH levels before treatment. This last finding was also observed by Antonelli et al.[19]

Detection of TPOAb before therapy was associated with a risk 3.5 times greater of becoming hypothyroid on IFN-α use; 90% of such patients in our study developed the dysfunction vs. 14.5% of TPOAb-negative, corroborating Prummel and Laurberg,[7] who found a relative risk of 3.9. Elevated endogenous interferon in response to viral diseases could possibly be associated with the development of IFN-α induced thyroiditis by in genetically predisposed individuals.[17,27,32-34]

Prummel and Laurberg[7] have demonstrated that the female gender has a relative risk of 4.4 for developing autoimmune thyroiditis. This strong preponderance may perhaps be due to the effects of estrogen or secondary to X chromosome susceptibility genes.[35,36] This fact was not corroborated by our study, as well as by Muratori et al.[20] and Stefanova-Petrova et al.[21] It is important to highlight that thyroid dysfunction could result from a direct effect of IFN-α on thyroid cell function.[28,37,38]

The higher prevalence of virus C genotype 1 in patients who developed hypothyroidism is not a consensus in the literature. Sachithanandan et al.[13] have detected elevated TPOAb levels before and during therapy only in genotype 1 patients. Conversely, Huang et al.[34] observed higher prevalence of genotype 1b/2b in women with hepatitis C and detectable TPOAb, but with no correlation with hypothyroidism. Viral replication results in the production of a heterogeneous viral population within an infected individual.[39] Some authors suggested that a portion of the HCV genome could share a partial sequence homology in a few amino acid segments with thyroglobulin and microsome, rendering HCV patients susceptible to autoimmune thyroid diseases.[28] This hypothesis could explain the relation between viral genotype and the predisposition to develop thyroid diseases in patients infected by virus C genotype 1, as verified in our patient population.

In the present study, patients had a relative risk of 3.5 for developing hypothyroidism during the first treatment course; however, Moncoucy et al.[27] found no difference in thyroid dysfunction rate between first and second courses of treatment. Previous studies have reported that thyroid dysfunction induced by IFN-α could develop in the first week or after a few months, during and after therapy, with a possible contribution of cumulative dose.[17,29,32] Nevertheless, the underlying mechanism remains unclear. The immunomodulatory action of IFN-α in susceptible patients[38,40-42] could affect the thyroid hormone syn-

thesis and secretion *in vitro*.[43] Our data did not suggest a cumulative dose-effect, as only a few patients did not present thyroid dysfunction during the first treatment. Interestingly, after drug withdrawal, 64% of the patients remained hypothyroid, requiring L-thyroxin replacement therapy, and the other patients presented the subclinical form of the disease.

Hyperthyroidism seems a rare event during IFN-α therapy and was verified in 1.8% of the patients. Several studies found even lower prevalence of hyperthyroidism, ranging from 0.9% to 1.1%.[16,27,29,44]

Destructive thyroiditis occurred in 5.1% of our patients and approximately 70% developed permanent hypothyroidism. Almost 50% of non-autoimmune IFN-α-induced thyroiditis manifests such a destructive thyroiditis, a self-limited inflammatory disorder characterized by three phases of six to eight weeks each: thyrotoxicosis, hypothyroidism and resolution to euthyroidism or definitive hypothyroidism in less than 5% of the cases. The symptoms are usually mild, probably leading to a lower diagnostic rate; however, atrial fibrillation may occur.[8,45] We observed that TSH levels before treatment were higher and qALT was lower in patients who developed destructive thyroiditis under IFN-α. This finding has not been previously reported in the literature. Some authors found recurrent thyroiditis during retreatment;[46] however, in our study, 98% of the patients developed destructive thyroiditis only during the first treatment.

We concluded that in the screening for predictive factors of thyroid dysfunction in HCV patients before treatment with IFN-α it is especially important to evaluate TSH levels, as well as antithyroid antibodies and viral genotype. Moreover, the first contact with IFN-α holds substantial risk to develop thyroid dysfunction. Special care is essential when there are laboratory alterations indicating thyrotoxicosis, which may be signaling an initial phase of destructive thyroiditis, a benign and self-limited disturbance. We emphasize that a significant part of the dysfunction was transient or subclinical, not requiring treatment.

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