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BRIEF ARTICLES

Evolution and predictive factors of thyroid disorder due to interferon alpha in the treatment of hepatitis C

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Abstract

AIM: To study predictive factors of thyroid dysfunction associated with interferon-alpha (IFNα) therapy in chronic hepatitis C (CHC) and to describe its long-term evolution in a large population without previous thyroid dysfunction.

METHODS: We performed a follow-up of thyroid function and detection of thyroid antibodies in 301 patients treated for CHC with IFNα from 1999 to 2004.

RESULTS: Thyroid disorder developed in 30/301 (10%) patients with a mean delay of 6 ± 3.75 mo: 13 patients had hyperthyroidism, 11 had hypothyroidism, and 6 had biphasic evolution. During a mean follow-up of 41.59 ± 15.39 mo, 9 patients with hyperthyroidism, 3 with hypothyroidism, and 4 with biphasic evolution normalized thyroid function in 7.88 ± 5.46 mo. Recovery rate of dysthyroidism was not modified by treatment discontinuation, but was better for patients with negative thyroid antibodies before antiviral treatment (P = 0.02). Women had significantly more dysthyroidism (P = 0.05). Positive thyroid peroxidase and thyroglobulin antibodies were more frequent before antiviral treatment in patients who developed dysthyroidism (P < 0.0003 and P = 0.0003, respectively). In a multivariate model, low fibrosis was found to be a predictive factor of dysthyroidism (P = 0.039).

CONCLUSION: In this monocentric population of CHC, dysthyroidism, especially hyperthyroidism, developed in 10% of patients. Low fibrosis was found to be a predictive factor of dysthyroidism. Thyroid disorder recovered in 16/30 patients (53%) and recovery was better in the non-autoimmune form.

Key words: Chronic hepatitis C; Interferon alpha; Predictive factors; Thyroid disorder

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INTRODUCTION

Three alpha interferons and two peg-interferons are currently commercially available for the treatment of chronic hepatitis C (CHC). Since 2001, peg-interferons have been used in association with ribavirin[1,2], and they have become the reference treatment for CHC since the French consensus conference in 2002[3]. In the presence or absence of ribavirin, interferon-alpha (IFNα) has a well-known side effect profile. Some side effects are common, such as pseudo-flu syndrome, headaches, myalgia, fever, wasting, leucopoenia or thrombocytopoenia. Indeed, clinicians often reduce the dose or sometimes discontinue IFNα in those patients who develop thyroid dysfunction, thus possibly compromising the therapeutic response to this treatment. In 1995, Preziati *et al*[4] reported that 9.3% of patients with CHC receiving IFNα developed thyroid dysfunction. During the treatment of CHC, IFNα-induced thyroid dysfunction appears in 3% to 15% of cases[5-9], with various clinical presentations. In previous

studies, the number of patients included was insufficient in certain cases[4,5,10,11], and other studies did not exclude patients with a past history of dysthyroidism[4,8,9,12,13]. However, the long-term course and the risk factors of thyroid disorder are not well understood[6,7,14].

In this single-center study we report on a large population of patients without previous thyroid dysfunction who underwent IFNα treatment for CHC. Our objectives were to describe the prevalence and long-term course of thyroid disorder in this population and to assess the factors that are predictive of dysthyroidism.

MATERIALS AND METHODS

Patients

We studied all patients with CHC, treated with IFNα from January, 1999 to May, 2004 at the Department of Hepatology and Gastroenterology at Bicêtre Hospital (Kremlin-Bicêtre, France). Patients with human immunodeficiency virus or hepatitis B virus co-infection, hemophiliacs and patients with a past history of thyroid disorder were systematically excluded. Before 2002, a liver biopsy was performed in each patient in order to evaluate inflammatory activity and the stage of liver fibrosis measured by the Metavir score[15]. Since 2002, liver biopsy was performed only in patients with genotype 1, 4 or 5. Patients received standard interferon alpha (2a), 3 MU subcutaneously thrice weekly, peg-interferon alpha (2b) (Viraferon peg®, Schering Plough, NJ, USA) 1.5 μg per kilogram of body weight subcutaneously once weekly or peg-interferon alpha (2a) (Pegasys®, Hoffmann-La Roche, Ltd, Switzerland) 180 μg subcutaneously once weekly, with or without 800 mg to 1200 mg of ribavirin per day. Thyroid-stimulating hormone (TSH) was measured before and every eight weeks during the antiviral treatment. Therapeutic follow-up of thyroid disorder was then performed until June, 2006. Thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb) and thyroid-stimulating hormone receptor antibodies (TSHRAb) were measured before the start of antiviral treatment and after the diagnosis of thyroid disorder as necessary.

Methods

The diagnosis of CHC was based on positive hepatitis C virus antibodies assessed by a second or third generation enzyme immunoassay. Hepatitis C virus RNA was measured by polymerase chain reaction amplification of viral RNA from serum. Viral genotypes were determined using a hybridization technique (INNO-LIPA HCV, Innogenetics, Gent, Belgium). The serum levels of TSH were measured using the AutoDELFIA™ TSH Ultra assay (sensitivity 0.03 MIU/L, total analytical variation < 5%) from Wallacoy, Turku, Finland. The normal TSH range in our laboratory was 0.3-4.0 MIU/L. The serum levels of TPOAb, TgAb and TSHRAb were measured using radioimmunoassays or radioimmunometric assays. The normal ranges in our laboratory were TPOAb < 60 IU/L, TgAb < 60 IU/L and TSHRAb < 5 IU/L.

Thyroid dysfunction was diagnosed when TSH level was either < 0.3 MIU/L (hyperthyroidism) or > 4.0 MIU/L (hypothyroidism) by two successive tests. Thyroid ultrasonography or thyroid scintigraphy was performed according to the clinical judgement of the endocrinologist. We have previously found three profiles of dysthyroidism: hyperthyroidism, hypothyroidism and a short hyper-followed by long hypothyroidism classically named biphasic evolution[9,14,16].

Table 1 Characteristics of the study population

Characteristics	Total group (n = 301)
Age[1] (yr)	48.27 ± 11.79
Gender (%, M/F)	57.5/42.5
Contamination mode (%)	
Tranfusion	27.2
Drug-addict	26.9
Blood exposure accident	7.6
Others	38.2
Genotype (% with 1/2/3/4/5/ND)	35/11/18/8/2/26
Stage of fibrosis (% with stage 0/1/2/3/4/ND)	1/11/42/20/20/6
Type of treatment (%)	
With IFNα	3.3
Peg-interferon	9.0
IFNα + ribavirin	27.2
Peg-interferon + ribavirin	60.4
Duration of treatment (mo)[1]	7.91 ± 3.78
TSH before treatment (MIU/L)[1]	1.54 ± 1.25
Positive antibodies before treatment	
TPOAb	12/229
TGAb	8/227
TSHRAb	1/95

ND: Not determined. [1]mean ± SD.

Statistical analysis

The predictive values of the following factors were analyzed: patients age at onset of the antiviral treatment, gender, mode of contamination, viral load and genotype, grade of histological fibrosis, type and duration of the antiviral therapy, TSH levels and the presence of TgAb, TPOAb or TSHRAb before the antiviral treatment.

Descriptive statistics were obtained using the Kruskal-Wallis test as appropriate, followed by a multivariate logistic regression analysis. A two-tailed P value < 0.05 was considered significant. Data analysis was performed using the EPI-Info Statistical Package (version 3.2.2).

RESULTS

Characteristics of the study population

The main characteristics of the 301 studied patients are shown in Table 1. Genotype status was known in 224 (74%) of 301 patients, as it was not known for the patients treated before 2002. The stage of fibrosis based on the Metavir score was obtained for 94% of patients. Patients with genotype 2 or 3 treated after 2002 did not have systematic evaluation of fibrosis before antiviral treatment. 247 (87%) of the patients who had a biopsy, had moderate or severe fibrosis (equal to or more than F2). In the inclusion period, from 1999 to 2004, there was heterogeneity in the antiviral treatment. However, the majority (60.4%) of the study population received

Table 2 Classification of thyroid disorder and long-term normalisation of dysthyroidism (n = 30)

	Type of dysthyroidism of normalisation	Discontinued treatment	Normalisation	Mean delay (mo)
Hyperthyroidism	13	9	9	7.44 ± 7.05[1]
Silent thyroiditis	5	4	5	6.80 ± 3.70[1]
Graves' disease	4	2	1	5
NC	2	2	2	2.00 ± 1.41[1]
Triphasic evolution	2	1	1	24
Hypothyroidism	11	6	3	10.67 ± 4.04[1]
Autoimmune	10	5	2	8.50 ± 2.12[1]
NC	1	1	1	15
Biphasic evolution	6	3	4	10.75 ± 5.50[1]

NC: Not classified. [1]mean ± SD.

peg-interferon alpha and ribavirin bitherapy. The TSH level before the antiviral treatment was known for all studied patients and was within normal ranges.

Prevalence of thyroid dysfunction during the antiviral treatment

Amongst the 301 patients with CHC, 30 (10%) developed biochemical thyroid dysfunction (TSH < 0.3 or > 4.0 MIU/L) during the antiviral treatment, 17 women and 13 men. Hyperthyroidism was seen in 13 (43%) of the 30 cases, hypothyroidism in 11 (37%) and biphasic evolution in 6 (20%). Table 2 shows the prevalence and classification of the thyroid disorders. The investigative work-up performed for each case with thyroid dysfunction, classified 11 of the 13 patients with hyperthyroidism as Graves' disease, silent thyroiditis or triphasic evolution, and 10 of the 11 patients with hypothyroidism as autoimmune hypothyroidism. Graves' disease was defined by the presence of clinical hyperthyroidism with positive TSHRAb and diffusely increased radioactive iodine intake on thyroid scintigraphy. Silent thyroiditis was defined by thyrotoxicosis, no tender goitre, and markedly decreased radioactive iodine intake on thyroid scintigraphy. Cases of "triphasic evolution" were defined as reported by Bohbot *et al* in 2006[17] (unusual evolution of silent thyroiditis to Graves' disease). Autoimmune hypothyroidism was defined by positive TgAb and/or TPOAb associated with clinical hypothyroidism.

Long-term course of dysthyroidism

Dysthyroidism occurred at an average of 6 ± 3.75 mo after the beginning of antiviral treatment. The evolution of the different profiles of dysthyroidism was described (Table 2) during a long-term follow-up (41.59 ± 15.35 mo) after the diagnosis of dysthyroidism. We observed that practitioners did not have the same attitude with respect to the evolution of dysthyroidism because the antiviral treatment was more frequently discontinued in hyperthyroidism (69%) than in hypothyroidism (55%) or biphasic evolution (50%). Four patients with hyperthyroidism did not require discontinuation of antiviral treatment. Among them, 1 patient presented with transient Graves' disease and another died before the end of follow up, 1 patient continued the antiviral treatment for only one month because hyperthyroidism occurred at the end of antiviral treatment and the type of hyperthyroidism could not be classified in 1 patient. Hypothyroidism that needed discontinuation of antiviral treatment was more frequently autoimmune hypothyroidism with TSH > 50 MIU/L except in 3 patients (1 with not classified with hypothyroidism and 2 with moderate elevation of TSH). Concerning therapeutic normalisation, no difference was observed regarding the discontinuation of antiviral treatment (56.6% *vs* 50.0%, NS). Treatment for thyroid disease was administered to 14 symptomatic patients (5 patients received carbimazole and 9 levothyroxine).

Prevalence of positive thyroid antibodies before antiviral treatment

Amongst the patients tested for TPOAb (n = 229), TgAb (n = 227) and TSHRAb (n = 94) before antiviral treatment, 12 (5%) were found to be positive for TPOAb (> 60 IU/L), 8 (3%) positive for TgAb (> 60 IU/L), and only 1 (1%) for TSHRAb (>5 IU/L). None of these patients had thyroid disorder before the introduction of IFNα. 7/12 patients with positive TPOAb and 4/8 patients with positive TgAb developed thyroid disorder during the antiviral treatment. The patients who had positive pretherapeutic TSHRAb did not develop Graves' disease. Regarding the presence of autoantibodies, IFNα induced-thyroid disease was classified as "autoimmune form" and "non-autoimmune form" similar to Mandac *et al*[18]. The autoimmune form was defined by the development of thyroid antibodies with or without clinical disease, including both autoimmune hypothyroidism and Graves' disease. The non-autoimmune form was defined by destructive thyroiditis or hypothyroidism with negative thyroid antibodies. We observed that patient recovery was significantly better in the non-autoimmune form than in the autoimmune form (33.3% *vs* 66.7%, P = 0.02).

Prediction of thyroid dysfunction

As shown in Table 3, we initially performed a univariate analysis using eight covariates (age, gender, contamination mode, genotype, stage of histological fibrosis, type of antiviral treatment [monotherapy with standard IFNα or peg-interferon versus combination of standard IFNα or peg-interferon with ribavirin] and duration, positive autoantibodies before the antiviral

Table 3 Features associated with dysthyroidism

	With dysthyroidism	Without dysthyroidism	*P*
Age[1] (yr)	46.20 ± 10.08	48.49 ± 11.96	0.40
Female (%)	56.9	40.9	0.05
Contamination mode (%)			0.33
Transfusion	33.3	26.6	
Drug-addict	20.0	27.7	
Blood exposure accident	13.3	7.0	
Others	33.3	38.7	
Genotype (%, 1/2/3/4/5/6/ND)	57/13/13/0/0/0/17	33/11/20/9/1/0/26	0.20
Stage of fibrosis < F2 (%)	30.0	10.3	0.009
Type of treatment (%)		0.47	
IFNα	3.3	3.3	
Peg-interferon	6.7	9.3	
IFNα + ribavirin	16.7	28.5	
Peg-interferon + ribavirin	73.3	58.9	
Duration of treatment[1] (mo)	7.73 ± 3.64	8.09 ± 3.93	0.30
Positive antibodies before treatment (%)			
TPOAb	26.9	2.5	< 0.0003
TgAb	18.5	1.5	0.0003
TSHRAb	0.0	1.3	0.42

ND: Not determined. [1]mean ± SD.

treatment: TPOAb, TgAb and TSHRAb). Four covariates were associated with dysthyroidism (gender, stage of histological fibrosis, positive TPOAb and TgAb). Secondly, in a multivariate logistic regression analysis of predictive factors of dysthyroidism using those four covariates, one predictive factor was found. The index of fibrosis was significantly less for patients with dysthyroidism than for patients without dysthyroidism. The stage of fibrosis was less than 2 units (mild fibrosis) in 30.0% of patients with dysthyroidism *vs* 10.3% of patients without dysthyroidism (OR, 0.56; 95% IC, 0.33-0.97; $P = 0.039$). There was a non significant trend towards positive TPOAb before antiviral treatment for patients with dysthyroidism. Amongst patients with positive TPOAb before antiviral treatment, 7 (26.9%) developed dysthyroidism *vs* 5 (2.5%) who did not (OR, 5.31; 95% IC, 0.80-35.16; $P = 0.083$).

DISCUSSION

The prevalence of thyroid dysfunction during IFNα therapy for CHC was 10% in our series. Amongst the 301 patients with CHC, hyperthyroidism was more frequent (13/30) than hypothyroidism or biphasic evolution. The mean follow-up of thyroid disorder in our study was 41.59 ± 15.39 mo, 53% of patients recovered from thyroid disease without a difference regarding the discontinuation of antiviral treatment. Mild fibrosis was found to be an independent predictive factor of dysthyroidism during antiviral treatment.

Our single center study included a large population of 301 patients with CHC and we performed a long term follow-up of these patients, not only during the antiviral treatment, but also after treatment, to detect dysthyroidism in patients who had no previous thyroid dysfunction. Although the patient data were retrospective, the follow-up data were partly prospective. This may explain some of the heterogeneity in the type of antiviral treatment used. In addition, the conditions under which the antiviral treatment was stopped when dysthyroidism developed were not well defined. We evaluated the presence of positive thyroid antibodies using the same methods in all patients, and an investigative work-up of the pathology was performed for each case of thyroid dysfunction.

The prevalence of hyperthyroidism found in our study (43% *vs* 37% hypothyroidism) is unusual. Previous studies have reported more hypothyroidism (two out of the three cases) than hyperthyroidism (one out of the three cases)[19] with the exception of Benelhadj *et al*[5] and Hsieh *et al*[11]. Hsieh *et al*[11] explained this difference as being related to the population's eating habits, yet our study population was not particularly exposed to an increased risk of dysthyroidism due to eating habits. Benelhadj *et al*[5] did not explain this difference as only 6 patients developed thyroid dysfunction. The discrepancy may be partly explained by the findings of several other studies including silent thyroiditis developing into hypothyroidism or biphasic evolution whereas this disease usually begins with hyperthyroidism. Furthermore, in our series, hyperthyroidism cases included 30% (4/13) with Graves' disease, which is in the same range as a previously published series[20].

In accordance with the presence of at least one thyroid antibody, we classified thyroid disorder, as autoimmune and non-autoimmune, which seemed to be predictive of the evolution of dysthyroidism. In this study we should have based the autoimmune form on at least one positive thyroid antibody rather than consider each positive antibody separately. Three of the four cases of Graves' disease developed following IFNα therapy and did not recover after the end of the antiviral therapy. This suggests that IFNα triggered the development of Graves' disease in predisposed individuals[20]. In silent thyroiditis, which is a non-autoimmune IFNα-induced thyroiditis, four patients recovered without

the addition of specific treatment when interferon was discontinued and one recovered without discontinuing antiviral treatment. This suggests that the autoimmune mechanism is more deleterious in IFNα-induced thyroid disease. Among the eleven hypothyroidism patients, therapeutic normalisation was obtained in 3 (27%) within 10.67 ± 4.04 mo. Also, the patients who developed autoimmune forms of hypothyroidism, such as autoimmune hypothyroidism, did not recover after cessation of IFNα treatment and systematically needed T4 replacement during the follow-up.

In the multivariate analysis, one factor was significantly correlated with the development of dysthyroidism during antiviral treatment: the stage of fibrosis below the F2 Metavir score. However, patients treated with IFNα had more severe fibrosis (82% of patients with a stage of fibrosis equal to or above F2). Perhaps this was correlated to the variability in the autoimmune response to hepatitis C virus infection, however, this predictive factor will require further study. Surprisingly, the presence of TPOAb before the introduction of antiviral treatment was not significant in the multivariate model whereas it was in the univariate analysis; this may have been due to the small number of patients with positive antibodies. Kabbaj *et al*[21], found three predictive factors for dysthyroidism in a univariate analysis: female gender, positive anti TPO antibodies before antiviral treatment and TSH before antiviral treatment (even if it was still in the normal ranges). We do not understand why the variable "stage of fibrosis under F2" is mentioned in the statistical analysis because only patients with fibrosis equal or more than F2 were treated. Kee *et al*[22], found that only female gender was predictive of dysthyroidism in a multivariate model. Thyroid microsomal antibody was found to be predictive of thyroid disease in a case-control study. There were no significant differences between thyroid dysfunction patients in the case-control study with respect to liver inflammation and fibrosis grade, however, the authors used the Knodell score which does not distinguish activity and fibrosis.

Some practical guidelines may be drawn from this study: the TPOAb state should be determined in patients before introducing IFNα and a regular follow-up of TSH every two mo or less is needed in patients with a risk of dysthyroidism (low fibrosis, female gender, positive TPOAb). Finally, two distinct mechanisms are described in the development of thyroid disorder during IFNα therapy: autoimmune and non-autoimmune-induced thyroid dysfunction. With regard to our results, the autoimmune form seems to have more severe consequences and longer evolution, which indicates the importance of early detection, in order to adapt the follow-up of thyroid function and therapy without discontinuing the antiviral treatment, since the discontinuation of antiviral treatment seems to have no predictive value on the evolution of dysthyroidism.

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COMMENTS

Background

Alpha interferons and peg-interferons have successively become the reference treatment for chronic hepatitis C with or without ribavirin. They have both induced thyroid dysfunction in 3% to 15% of cases. Indeed, clinicians often reduce the dose or sometimes discontinue interferon-alpha (IFNα) in patients who develop thyroid dysfunction, thus possibly compromising the therapeutic response to this treatment. In previous studies, the number of patients included was insufficient in certain cases, and other studies did not exclude patients with a past history of dysthyroidism. However, the long-term course and the risk factors for thyroid disorder are not well understood.

Research frontiers

Despite the role of IFNα, the pathogenesis of thyroid disease remains uncertain; also it seems to be related to an immunologic predisposition. Therefore, the authors tried to determine the risk factors which influence thyroid dysfunction.

Innovations and breakthroughs

Two distinct mechanisms are described for the development of thyroid disorder during IFNα therapy: autoimmune and non-autoimmune- induced thyroid dysfunction. With regard to our results, the autoimmune form seems to have more severe consequences and longer evolution, which indicates the importance of early detection, in order to adapt the follow-up of thyroid function and therapy without discontinuing the antiviral treatment, since the discontinuation of antiviral treatment seems to have no predictive value on the evolution of dysthyroidism. Furthermore, the stage of fibrosis below the F2 Metavir score was significantly correlated with the development of dysthyroidism during antiviral treatment. We hypothesized that low fibrosis, associated with better HCV response, was also associated with autoimmune activation, including the development of anti-thyroid autoantibodies.

Applications

Some practical guidelines may be drawn from this study: the TPOAb state in patients should be determined before introducing IFNα and a regular follow-up of TSH every two mo or less is needed in patients with a risk of dysthyroidism (low fibrosis, female gender, positive TPOAb).

Peer review

This is a fairly good written manuscript. But the authors need to deal with the issue of predictive factors for developing dysthyroidism in detail in the discussion section and make a plausible explanation about the difference from the previous papers.

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