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The influence of interferon alpha on the induction of autoimmune thyroiditis in patients treated for chronic viral hepatitis type C

Wpływ interferonu alfa na indukcję autoimmunologicznego zapalenia tarczycy u chorych leczonych z powodu przewlekłego wirusowego zapalenia wątroby typu C

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Abstract

Background: Different forms of interferon alpha (IFN-α) have been used for several years in the treatment of chronic viral hepatitis type C (CVHC). Currently, pegylated forms of interferon alpha (PegIFN-α) in combination with ribavirin is the standard treatment. During therapy with IFN-α, side-effects occur, including thyroid diseases. The aim of this study was an evaluation of administered interferon's impact on the frequency of autoimmune thyroiditis (ATI) occurrence among patients with CVH type C treated with INF-α and an assessment as to whether the type of interferon used is significant in ATI development.

Material and methods: 149 patients aged 18–70 (mean 43.9 ± 2.3 years) with CVH type C participated in the study. The serum concentrations of thyrotrophin (TSH), free tyrosine (FT4), triiodothyronine (FT3), thyreoglobulin (Tg), antithyroid antibodies: antiperoxidase (TPOAb) and antithyreoglobulin (TgAb) were evaluated before, and after six and 12 months of treatment. Additionally, the thyroid echostructure was evaluated with ultrasonography. Sixty out of 149 patients received Peg-INF-α, and 89 patients were treated with recombinant IFN-α.

Results: ATI was confirmed in nine patients (6.04%) with CVH type C before the introduction of interferon. Seven of them underwent an exacerbation of hypothyroidsm during therapy with interferon. In 24 patients (17.14%), who did not have the signs of ATI at baseline, an elevated concentration of antithyroid antibodies was detected during therapy with interferon. The mean concentrations of TPOAb before, and after six and 12 months of treatment were, respectively: 12.4; 310.4 and 141.3 IU/ml, and the mean concentrations of TgAb were, respectively: 17.40; 108.0; and 125.6 IU/ml. After six months of treatment in this group of patients, 11 had hypothyroidsm and six had hyperthyroidsm. After 12 months of therapy, four patients had hypertthyroidsm and four showed signs and symptoms of hypothyroidsm; the remaining patients were in a euthyroid state. In ultrasound examination, reduction of echogenicity among patients with ATI before treatment was revealed in 75% of cases at baseline, in 83.3% after six months and in 100% after 12 months of treatment. In the group of patients presenting with ATI during IFN-α therapy, in which no disorders were found in initial examination, after six months of treatment a reduction of echogenicity was found in 69.2%, and after 12 months in 75%, of patients.

Conclusions: Among patients treated with interferon due to CVH type C, there is a risk of the development of ATI or the exacerbation of an existing one. There is no significant difference in ATI presentation in relation to the type of IFN-α used for treatment.

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Key words: *chronic viral hepatitis, alpha interferon, pegylated alpha interferon, autoimmune thyroiditis*

Streszczenie

Wstęp: W leczeniu przewlekłego wirusowego zapalenia wątroby typu C (PWZWC) od kilkunastu lat stosuje się różne preparaty interferonu alfa (INF-α). Aktualnie standardem leczenia jest skojarzone zastosowanie pegylowanej formy interferonu alfa (PegINF-α) i rybawiryny. W trakcie leczenia INF-α występują działania niepożądane, wśród których znajdują się choroby tarczycy. Celem pracy jest ocena częstości występowania autoimmunologicznego zapalenia tarczycy (AZT) u pacjentów z PWZW C leczonych INF-α oraz ocena, czy na rozwój AZT ma wpływ rodzaj stosowanego INF.

Materiał i metody: W badaniu uczestniczyło 149 chorych z PWZW typu C w przedziale wieku 18–70 lat (średnia 43,9 ± 2,3 roku). U chorych przed leczeniem oraz po 6 i 12 miesiącach leczenia oceniano stężenia w surowicy: tyreotropiny (TSH), wolnej tyroksyny (FT4), trijodotyroniny (FT3), tyreoglobuliny (Tg), przeciwciał przeciwtarczycowych: antyperoksydazowych (TPOAb) i antytyreoglobulinowych (TgAb). Dodatkowo oceniano echostrukturę tarczycy w USG. Wśród wszystkich 149 chorych u 60 stosowano pegylowany interferon alfa (PegINF-α), a u 89 INF-α.

Wyniki: U badanych chorych z PWZW C przed włączeniem interferonu AZT stwierdzono u 9 chorych (6,04%), wśród których u 7 nastąpiło zaostrzenie niedoczynności tarczycy w trakcie leczenia interferonem. U 24 chorych (17,14%), u których początkowo nie stwierdzano cech AZT, w trakcie leczenia INF wykazano podwyższone stężenia przeciwciał przeciwtarczycowych. Średnie stężenia TPOAb przed, po 6 i 12 miesiącach leczenia wynosiły odpowiednio: 12,4; 310,4 i 141,3 IU/ml, a średnie stężenia TgAb odpowiednio: 17,40; 108,0 i 125,6 IU/ml. W tej grupie pacjentów po 6 miesiącach stwierdzono u 11 chorych hipertyreozę, a u 6 chorych hipotyreozę. Natomiast po 12 miesiącach

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u 4 badanych odnotowano hipertyreozę i u 4 hipotyreozę; pozostali pacjenci byli w stanie eutyreozy. W badaniu USG obniżenie echogeniczności wśród pacjentów z AZT przed leczeniem stwierdzono u 75% w badaniu wstępnym, u 83,3% po 6 miesiącach oraz u 100% po 12 miesiącach leczenia. W grupie chorych z AZT w trakcie leczenia INF-α, u których w badaniu wstępnym nie wykryto żadnych zmian, po 6 miesiącach leczenia obniżenie echogeniczności stwierdzono u 69,2%, a po 12 miesiącach u 75%.
Wnioski: U chorych leczonych interferonem z powodu PWZW C istnieje ryzyko rozwoju świeżego lub nasilenia wcześniej występującego AZT. Rodzaj stosowanego INF-α nie wykazuje związku z występowaniem zaburzeń czynności gruczołu tarczowego.
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Słowa kluczowe: *przewlekłe wirusowe zapalenie wątroby, interferon alfa, pegylowany interferon alfa, autoimmunologiczne zapalenie tarczycy*

Introduction

Chronic viral hepatitis type B (CVHB) is caused by the HBV virus, while chronic viral hepatitis type C (CVHC) is caused by the HCV virus. The number of people chronically infected with the B and C viruses are respectively 350–400 million and about 170 million worldwide [1, 3]. About 500,000 people die every year due to complications of chronic HBV infection such as hepatic cirrhosis and hepatocellular carcinoma [2]. CVHC is a disease of slow progression: 20–30% of these patients within 10–20 years develop liver cirrhosis, and 5% of them will subsequently develop hepatocellular carcinoma [3–5]. The risk of hepatocellular carcinoma increases among patients with established cirrhosis [3].

The aims of CVHC treatment are the elimination of the virus and inhibition of the disease development, limitation of HCV infection spread, increase and prolongation of survival rate, and quality of life improvement [6, 7]. Currently, the standard CVHC treatment is the co-administration of PegINF-α together with ribavirin [8]. The mechanism of INF-α action is complex and based on antiviral, anti-proliferation and immunomodulatory effects [9, 10]. INF-α binds to the specific cell receptor that enhances target genes expression, which products cause: increase of class 1 major histocompatibility complex (MHC1) expression, increase of adhesive particles on effector cells count, increase of macrophages, NK cells and T lymphocytes activity and regulation of immunoglobulins production due to lymphocytes B activation [9–11]. The disadvantage of treatment with INF-α and ribavirin are frequently observed, and numerous, side effects [12]. It is assumed that INF-α is responsible for the occurrence of: fever, muscle and joint pain, sleeplessness, depression, thyroid function disorders, thrombocytopenia, leucopenia, hair loss, autoimmune haemolytic anaemia, psoriasis exacerbation and sarcoidosis development [9, 12]. Ribavirin, however, causes haemolysis, skin itching, skin rashes and cough [12].

Material and methods

The study included 149 patients aged 18–70 years, 82 men and 67 women. The average age was 43.9 ± 2.3 years. All patients were under the control of the Hepatology Outpatient Department of the Westpomeranian Provincial Hospital in Szczecin between 2003 and 2007. All patients were checked for serum level of hormones: TSH, FT3, FT4 and for serum concentrations of antithyroid antibodies: TPOAb, TgAb and thyroglobulin (Tg) to detect ATI at baseline and then after six and 12 months of treatment with INF-α.

Patients were divided into three groups:

— Group 1 (116 patients) — without thyroid dysfunction before and during therapy with INF-α;
— Group 2 (nine patients) — with ATI before the commencement of therapy with INF-α;
— Group 3 (24 patients) — who developed ATI during therapy with INF-α.

The type of administered interferon was analysed among all patients in whom thyroid dysfunction occurred. In 60 out of 149 patients with CVHC, PegINF- α was used, while the remaining 89 had INF- α administered. Two patients from Group 2 were treated with PegINF-α, and the remaining seven patients with INF-α, whereas in Group 3, 12 patients were on PegINF-α and the other 12 on INF-α. Commercial kits by DPC Corporation were used to assay the serum level of TSH, FT3, FT4, TPOAb and TgAb. The laboratory tests were performed with Immulite unit in the Central Laboratory of the Westpomeranian Provincial Hospital in Szczecin. The criteria of diagnosing hyperthyroidism were, apart from the typical clinical symptoms, a decrease in TSH level < 0.4 mIU/ml (normal 0.4–4.0 mIU/ml) and an increase of FT4 (normal range: 0.8–1.9 ng/dl) and/or FT3 (normal range: 1.8–4.2 pg/ml). Subclinical hyperthyroidism was diagnosed in case of a decrease in TSH level and normal concentration of free thyroid hormones (TH). Hypothyroidism was diagnosed when the increased serum concentration of TSH and a decreased level of FT4 concentration were revealed (24). In a case of increased level of TSH within the limits of 5–10 mIU/ml and normal FT4 serum level, a latent hypothyroidism was diagnosed (24). ATI was diagnosed if an increased TPOAb level (normal range: 0–35 IU/ml) and/or TgAb (normal: 0–40 IU/ml) were found. Increased concentrations of TPOAb and/or TgAb (level > 100 IU/ml) were set as a criterion of ATI diagnosis (24). Before the onset of treatment and after six and

12 months, the patients also had a thyroid ultrasound performed to evaluate its echogenicity.

In the statistical analysis of hormonal parameters, Statistica 60 Software was used. The data analysis began with verification of normal distribution hypothesis. For this purpose, the Lilliefors and Shapiro-Wilk tests were used. Hypothesis about the normal distribution was rejected because of asymmetry and too great a diversity of measurements. As a consequence, a non-parametric Kruskal-Wallis test was used for data analysis.

The protocol of the study was approved bt the Ethical Committee of the Pomeranian Medical University.

Results

Table I presents the median concentrations of thyrotrophin, thyroxin, triiodothyronin, anti-peroxidase and antithyreoglobulin antibodies and thyreoglobulin in the examined groups of patients with CVHC.

Before the onset of therapy with INF-α, patients with ATI from Group 2 had the highest median TSH serum concentration. The median TSH serum concentration in Groups 2, 1 and 3 was 2.39 mIU/ml, 1.15 mIU/ml and 1.115 mIU/ml, in that order. Within the FT3 level, the highest median was registered in Group 2, where it was 4.465 pg/ml, significantly higher than in Groups 3 and 1, where it was 4.34 and 3.5 pg/ml respectively. The examined groups did not differ in respect to the median FT4 serum level before the onset of treatment with INF-α. The results of Tg concentration show that patients from Group 2 were characterised by significantly lower median (2.595 ng/ml) compared to Group 1 (17.15 ng/ml) and Group 3 (10.29 ng/ml). Within the TGAb concentration in Group 2, the results significantly exceeded the normal range (median reaching 165 IU/ml). In the case of patients without and with thyroid function disorders after the beginning of therapy with INF-α, the baseline median value of TgAb serum concentration did not vary significantly and was within the normal range. An analogous situation was revealed in the case of TPOAb serum concentration median in the analysed groups of patients. After six months of therapy with IFN-α, a very high median TSH serum concentration was reached in Group 2 of 7.77 mIU/ml. Of the nine patients in this group, seven had hypothyroidism exacerbation. Six of them received INF-α and only one was on PegINF-α. In Group 3, 11 patients were diagnosed with hyperthyroidism; three of them were treated with PegINF-α, and the rest with INF-α. Six patients presented with hypothyroidism, of whom five received PegINF-α and one INF-α. The remaining patients were in a euthyroid state. The median of serum level of FT3 was the highest among patients in Group 3 compared to Groups 1 and 2: 3.94 pg/ml, 3.2 pg/ml and 2.735 pg/ml, in that order. In the case of FT4 serum concentration, significantly lower median values were found in Group 2 than in Groups 1 and 3: 0.82 ng/dl, 1.25 ng/dl and 1.27 ng/dl, in that order. In the range of serum Tg, the lowest median value was reached in Group 2, but the differences between the groups were not statistically significant. The most visible differences between the separate groups of patients were found in TgAb and TPOAb ranges. Significantly higher values were noted for Groups 2 and 3 compared to Group 1. In the case of TgAb, the median of concentrations for these groups were 280.5 IU/ml, 68.3 IU/ml and 20.0 IU/ml, respectively. Similarly, TPOAb values were 786.5IU/ml, 16.6 IU/ml and 10.0 IU/ml, respectively. After 12 months of therapy, the comparison examination of hormone levels still showed significantly different results for particular groups of patients. In the case of TSH, the highest value of median was reached in Group 2 (4.67 mIU/ml). In this group, six patients maintained TSH serum concentration in the range typical for hypothyroidism. Five of them had INF-α administered, and only one was on PegINF-α.

None of the patients from Group 2 had the TSH concentration characteristic for hyperthyroidism. In the first and third groups, the TSH median values were significantly lower: 1.29 mIU/ml (Group 1) and 2.25 mIU/ml (Group 3). In Group 3, after 12 months of therapy, the number of patients suffering from thyroid dysfunction decreased to four patients with hyperthyroidism and four with hypothyroidism. Also after 12 months, the median FT3 and FT4 serum concentration values did not differ significantly in the studied groups. The median Tg serum level was significantly lower in Group 2 than in the other groups. Patients from Group 2 showed the highest TgAb and TPOAb serum concentrations, and the median of these antibodies level were 266 IU/ml and 607 IU/ml, respectively. In Group 3, the values of serum concentration were significantly higher than in Group 1 and lower than in Group 2. The median of serum TgAb and TPOAb concentrations in patients from Group 3 were 106 IU/ml and 43.9 IU/ml, respectively, and in the patients from Group 2 — 20 IU/ml and 10 IU/ml, respectively.

Table II presents the behaviour of thyroid echogenicity in the studied groups of patients before and during the treatment with interferon.

In thyroid ultrasound, decreased echogenicity in the group of patients with ATI before the therapy with INF-α was revealed in 75% of patents at baseline, in 83.3% examined after six months, and in 100% examined after 12 months of therapy. However, in the group of patients in whom ATI developed during the interferon treatment, decreased echogenicity was initially found only in 7.7% of them, while after six months of therapy the decrease of echogenicity was already diagnosed

Table I. *Median of thyrotrophin, thyroxin, triiodothyronin, anti-thyroid antibodies and thyroglobulin concentrations in examined groups of patients with CVH*

Tabela I. *Mediana stężeń w surowicy tyreotropiny, hormonów tarczycowych, przeciwciał przeciwtarczycowych i tyreoglobuliny w badanych grupach chorych z PWZW C*

Parameters and time of examination			Group 1	Group 2	Group 3	Kruskal-Wallis test
TSH	At baseline	Median	1.15 *(2)	2.39 *(1.3)	1.115 *(2)	p = 0.0244
		Min–Max	0.42–3.85	0.61–12.2	0.411–3.67	
	6m	Median	1.2 *(2)	7.77 *(1.3)	0.814 *(2)	p = 0.0000
		Min–Max	0.406–4.0	3.91–75	0.002–74.6	
	12m	Median	1.29 *(2)	4.675 *(1)	2.25	p = 0.0007
		Min–Max	0.403–3.94	1.08–8.98	0.016–11	
FT3	At baseline	Median	3.5 *(2)	4.465 *(1)	4.34	p = 0.0015
		Min–Max	1.81–4.2	4.1–5.03	2.01–4.19	
	6m	Median	3.2 *(3)	2.735 *(3)	3.94 *(1.2)	p = 0.0049
		Min–Max	1.8–4.19	2.22–3.34	2.11–6.06	
	12m	Median	3.39	3.215	4.04	p = 0.1534
		Min–Max	2.11–4.19	1.99–4.07	1.31–6.64	
FT4	At baseline	Median	1.27	1.205	1.245	p = 0.6239
		Min–Max	0.83–1.85	0.8–1.43	1–1.54	
	6m	Median	1.25 *(2)	0.82 *(1.3)	1.27 *(2)	p = 0.0517
		Min–Max	0.8–1.85	0.45–1.31	0.44–2.6	
	12m	Median	1.23	1.095	1.265	p = 0.6053
		Min–Max	0.8–1.69	0.99–1.79	0.55–3.38	
Tg	At baseline	Median	17.15 *(2.3)	2.595*(1.3)	10.29 *(1.2)	p = 0.0229
		Min–Max	0.5–53.7	0.81–84.4	0.91–52.7	
	6m	Median	17.85	1.4	38.2	p = 0.0864
		Min–Max	3.8–54.7	0.5–139	0.84–349	
	12m	Median	16.5 *(2)	0.5 *(1)	16.1	p = 0.0165
		Min–Max	0.5–55	0.5–48	0.2–160	
TgAb	At baseline	Median	20 *(2.3)	165 *(1.3)	18 *(1.2)	p = 0.0000
		Min–Max	7.2–31	20–259	10–33.7	
	6m	Median	20 *(2.3)	280.5 *(1.3)	68.3 *(1.2)	p = 0.0000
		Min–Max	3.04–37.5	170–2052	18.5–873	
	12m	Median	20 *(2.3)	266 *(1.3)	106 *(1.2)	p = 0.0000
		Min–Max	12–40	37.7–1166	20–362	
TPOAb	At baseline	Median	10 *(2)	252 *(1.3)	10 *(2)	p = 0.0000
		Min–Max	5.0–34.6	51.7–468	4.2–34.3	
	6m	Median	10 *(2.3)	786.5 *(1.3)	16.6 *(1.2)	p = 0.0000
		Min–Max	2.08–32.7	40.6–2500	5–4181	
	12m	Median	10 *(2.3)	607 *(1.3)	43.9 *(1.2)	p = 0.0000
		Min–Max	5,1-35	42-1952	10-441	

Note: statistically significant results are marked with an asterisk; a group in which the statistically significant difference occurred is written in brackets.

in 69.2%, and after 12 months in 75% of patients. Decreased thyroid echostructure was also observed in Group 1, i.e. patients without ATI before and during treatment with interferon.

Table II. *Percentage of patients with a decreased thyroid echogenicity*

Tabela II. *Odsetek pacjentów z obniżoną echogenicznością tarczycy*

Time of examination	Group 1	Group 2	Group 3
At baseline	14.7%	75.0%	7.7%
After 6 months	18.0%	83.3%	69.2%
After 12 months	22.5%	100%	75.0%

Discussion

Chronic viral hepatitis type B and C are diseases that have a progressive course which may lead to liver cirrhosis and hepatocellular carcinoma [13]. About 300–400 million people are chronically infected with HBV, despite the effective prophylaxis, passive and active, that has been available for more than 25 years around the world [13]. Infection with HCV concerns about 2% of the human population, meaning that in Poland 400,000-700,000 people could be affected [13]. The HCV virus infection, because of its widespread prevalence and progressive nature, is the major cause of end-stage liver disease worldwide [8].

Currently, the standard treatment of CVHC is co-administration of alpha interferon with ribavirin [3]. During the therapy with interferon, mostly transient side effects occur, such as clinically manifested autoimmune diseases or the presence of antibodies against many tissues and organs without clinical symptoms. Usually, the autoaggressive diseases concern the thyroid gland [14]. Antithyroid antibodies production is a result of improper class II histocompatibility antigens expression on the thyreocytes surface and a direct cytotoxic action of lymphocytes T on thyroid cells [14]. In our own material, ATI was revealed in nine (6.04%) out of 149 patients with CVHC before the IFN therapy onset. A similar percentage with increased antithyroid antibodies serum concentration among patients with CVHC has been described by Pawlotsky et al. who found an increased concentration of antibodies in five out of 61 patients —7% of the studied group [15], whereas Marcellin et al. showed an increased concentration of antithyroid antibodies in only 3% out of 86 patients with CVHC [16]. The frequency of increased antithyroid antibodies concentrations without the clinical thyroid disorders among patients with CVHC depends in large measure on geographical factors, gender and age [16]. Similar results are found in patients with normal thyroid function without CVHC. Pearce et al. confirmed an elevated level of antithyroid antibodies in 10% of the general population in the United States; but in women over 60, the increased antibodies level was found in as many as 25% of the researched population [17]. In our study, of the nine patients with ATI diagnosed before IFN treatment, hypothyroiditis exacerbation was detected in seven of them. Tran et al. in a study of 72 patients, 29 women and 43 men, diagnosed an elevated concentration of antithyroid antibodies concentration in nine women (31%). In only six of them (20.7%) was the level very high, and two patients had clinical symptoms of hypothyroidism. During 12 months of therapy with INF-α, one patient had a significant increase of antibodies, while in three patients, another exacerbation of hypothyroidism occurred [18].

In our study group, in 24 patients (17.14%) who initially did not demonstrate any features of autoimmune process, an increased level of antithyroid antibodies was found during the therapy with interferon. In this group after six months of treatment, hyperthyroidism was diagnosed in 11 patients, whereas six of them had hypothyroidism. After 12 months of therapy with interferon in this group, four patients had hyperthyroidism (in one of them it was a newly developed abnormality), one patient moved from hypothyroidism into hyperthyroidism, in two patients there was a continuation of hyperthyroidism, four patients continued with hypothyreosis and the remaining patients were in a euthyreoid state. In the study by Watanabe et al [9], nine out of 106 patients with normal thyroid function before treatment with INF-α (six women and three men) developed thyroid function disorders during the treatment. In six of them, hyperthyroidism was revealed after 16–30 weeks of therapy, and in the remaining three, hypothyroidism occurred 8–23 weeks after the therapy with INF-α had begun. In another study by Marazuela et al. [19], 14.8% of women and only 1% of men without ATI features before the therapy with INF-α, showed thyroid function disorders during the therapy. After six months of treatment with INF-α, one patient underwent a clinical transition from hypothyreoidism into hyperthyreoidism and the return of euthyreoidism after the end of therapy. The reports concerning the occurrence of thyroid dysfunctions during INF-α are inconclusive. According to Monzani et al. [20], such thyroid gland function disorders are confirmed in 6.2% of patients, more often hypothyroidism than hyperthyroidism (3.9% and 2.3%, respectively), while symptoms of hyperthyroidism develop earlier than symptoms of hypothyroidism during the therapy with interferon. Other research has concluded that 12–15% of patients suffer from thyroid functions disorders during the therapy [21, 23], and an increased level of antithyroid antibodies can be found in as many as 17–40% of patients treated with interferon [22, 23]. For autoimmune thyroid diseases, the hypoechogenic thyroid image in ultra-

sound examination is characteristic. Decreased echogenicity of thyroid gland is found in 80% of patients suffering from Graves disease and in 18–77% with Hashimoto's disease [24].

In our study, the echogenicity decrease among patients with ATI before interferon treatment was found in 75% in initial examination, in 83.3% in the examination after six months, and in 100% in the examination after 12 months, whereas in the group of patients who developed ATI during interferon treatment, 53.8% showed no alterations in the initial examination, after six months of treatment decreased echogenicity was revealed in 69.2%, and after 12 months in 75% of patients. Similarly, other authors have found changes in echogenicity during treatment with interferon, especially at significantly increased concentrations of serum antithyroid antibodies [23].

Conclusions

Therapy with interferon alpha in patients with chronic viral hepatitis bears a risk of autoimmune thyroiditis development or the exacerbation of a pre-existing inflammation in the thyroid gland, with the clinical presentation of hyperthyroidism as well as of hypothyroidism.

Patients with chronic viral hepatitis subjected to therapy with interferon should have their serum levels of thyrotrophin, thyroxin, triiodothyronin and antithyroid antibodies measured at baseline and regularly monitored during therapy. Those with pre-existing ATI should be checked more frequently because hyperthyroidism as well as hypothyroidism may develop, and one dysfunction can transit into the other.

The type of interferon administered is not associated with the frequency or the pattern of thyroid gland function.

Ultrasound thyroid examination in patients with chronic viral hepatitis is helpful in recognising and monitoring autoimmune thyroiditis during therapy with interferon.

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