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Epidemiology, risk factors and prognosis of Interferon alpha induced thyroid disorders. A Prospective Clinical Study

Ocena epidemiologii, czynników ryzyka oraz rokowania u osób z chorobą tarczycy indukowaną interferonem alfa

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A Study Design
B Data Collection
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D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Introduction: Hepatitis C virus (HCV) infection is a worldwide problem and hepatitis, which is its natural unfavourable course, is still a challenge for hepatologist. At present, standards of treatment are changing from combined therapy with interferon alpha (IFN-α) and ribavirin to new antiviral drugs. The current classification divides interferon induced thyroid diseases (IITD) into two groups: autoimmune (Hashimoto disease, Graves disease, positive antithyroid autoantibodies in euthyroid patients) and non-autoimmune (destructive thyroiditis, non-autoimmune hypothyroidism). A common complication of cytokine therapy is the induction of antithyroid autoantibodies *de novo* without thyroid dysfunction. During therapeutic regimens combined with ribavirin, destructive thyroiditis with typical biphasic course is more common than in IFN-α monotherapy. Clinically, overt pathologies often have discrete symptoms, which cause diagnostic and therapeutic dilemmas.

Aims: The aim of this study was to estimate IITD occurrence, to find risk factors for IITD development.

Material & methods: The study group consisted of 66 patients treated for HCV infection. Before and during antiviral therapy, hormonal (TSH, fT4, fT3), immunological (thyroid autoantibodies), ultrasonographic and genetic (HLA-A2) parameters were evaluated.

Results: Hormonal disturbances were detected in 24.2% of patients; however, 43.9% of patients had positive thyroid autoantibodies (*de novo*) without hormonal imbalance. Multivariate analysis revealed the following: female sex, elevated TSH level, occurrence of anti-TPO autoantibodies (TPO-Ab), and increased blood velocity in thyroid arteries are risk factors for IITD development.

In conclusion: Thyroid disorders are common during IFN-α therapy. Previous epidemiological data seem to be underestimated. Important risk factors for IITD development are: female sex, elevated serum TSH concentration (≥2.5 μU/mL), positive TPO-Ab and increased blood velocity in thyroid arteries.

Key words: **hepatitis C • interferon alpha • thyroid • interferon induced thyroid disorders**

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Abbreviation list: CD – color Doppler, CMIA – chemiluminescent microparticle immunoassay, EVR – early virological response, fT3 – free triiodothyronine, fT4 – free thyroxin, HBV – hepatitis B virus, HCV – hepatitis C virus, HIV – human immunodeficiency virus, IFN-α – interferon alpha, IITD – interferon induced thyroid disease, PD – power Doppler, rTSH-Ab – anti-TSH receptor autoantibodies, SVR – sustained virological response, Tb-Ab – anti-thyroglobulin autoantibodies, TD – thyroid dysfunction, TPO-Ab – anti-TPO autoantibodies, TSH – thyreotropic hormone, V – coefficients of variation.

Introduction

Hepatitis C virus (HCV) infection is a worldwide problem. Currently there are approximately 130-170 million chronic carriers [10]. Because there is a risk of liver cirrhosis and/or liver malignancy development, precise qualification and antiviral treatment is definitely necessary. Historically, hepatitis C treatment initially consisted of interferon alpha (IFN-α) monotherapy, later combined therapy with different forms of IFN-α (natural, pegylated, combined with albumins) with ribavirin, and finally a new group of investigated antiviral drugs was introduced. In December 2013, the FDA approved the nucleotide analog inhibitor sofosbuvir for the treatment of chronic HCV infection in adults [1]. Currently, in many countries the standard treatment is still the classic therapy with IFN-α and ribavirin.

This classic therapy is related to a wide spectrum of side effects that significantly reduce the quality of life. The most common acute side effects are flu-like symptoms, while chronic side effects include hematologic, neuropsychiatric and endocrinological (mainly thyroid) complications [8].

Real occurrence of interferon alpha thyroid disorders (IITD) is hard to establish. This difficulty is related to a few unique characteristics of IITD. Firstly, IITD have usually mild symptoms, and they might be masked by IFN-α induced side effects. Moreover, hepatitis C symptomatology may mimic hypo – or hyperthyroidism. The similarity between hepatitis C, side effects of IFN-α, and thyroid function abnormalities is shown in Figure 1.

Secondly, some older clinical trials assessed thyroid hormones only when typical symptomatology of hypo – or

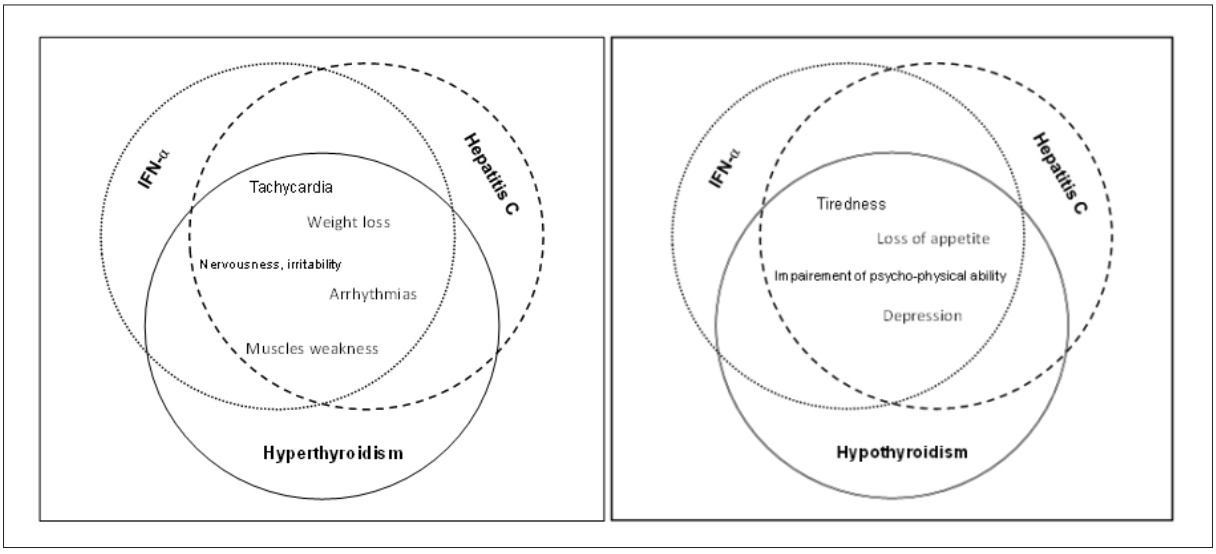

Fig. 1. Common symptomatology of hyper – and hypothyroidism, IFN-α therapy side effects and chronic hepatitis C

hyperthyroidism occurred. Because of these two factors, the real occurrence of IITD might be underestimated.

The newest classification divides IITD diseases into two groups: autoimmune (Hashimoto disease, Graves disease, positive antithyroid autoantibodies in euthyroid patients) and non-autoimmunologic (destructive thyroiditis, non-autoimmune hypothyroidism). The most common complication of cytokine therapy is induction of antithyroid autoantibodies *de novo* without thyroid dysfunction (Table 1) [20].

IITD classification
Autoimmune IITD
• Euthyreosis with positive (de novo) thyroid autoantibodies • Hashimoto disease • Graves-Basedow disease
Non-autoimmune IITD
• Destructive thyroiditis • Non-autoimmune thyroiditis

[20,24]

In 2008 we proposed a modification of Mandac's classification and the addition of a new term "undifferentiated IITD". Very often IITD have a variable course and, what is unusual in "classic" endocrinology disorders, may change from hypo – to hyperthyroidism (and the other way round) many times. In this situation, the term undifferentiated IITD helps to avoid misunderstandings, which might consequently change the diagnosis [24]. Finally, it should be emphasized that biphasic, hyper-hypothyroidism course may appear in each type of IITD.

Identification of subjects predisposed to IITD should be crucial. The problem of HCV and thyroid is more complicated. Is seems that HCV in itself may be a risk factor of thyroid disorders. This is related to the similarity of aminoacids sequence in thyroglobulin and virus proteins. A large clinical trial by Antonelli et al. revealed that hepatitis C patients more often have positive antityreoperoxidase autoantibodies (TPO-Ab), positive anti-thyroglobulin autoantibodies (Tg-Ab) and hypothyroidism, when compared to a control group [2]. Two most commonly mentioned risk factors of IITD are sex and positive TPO-Ab before antiviral therapy [6, 17]. There are only a few reports which show that mixed HCV genotype infection, low initial level of HCV-RNA and HLA antigens may be risk factors of IITD [11-12, 16, 18, 28]. There is no evidence that early virological response (EVR), sustained virological response (SVR), serum albumin concentration, histopathological liver abnormalities, alanine aminotransferase activity are the risk factors of IITD. New IITD candidate genes are still under investigation. Nevertheless, there is no cheap, commonly available assessment tool helpful in quick IITD risk stratification.

To conclude, these above mentioned characteristics such as: likely underestimation of IITD, no new risk factors of IITD, and forthcoming end of IFN-α based hepatitis C therapy were all the reason for the prospective IITD study.

Aim of study. The study has two main aims. The first was to describe IITD epidemiology, and the second to assess the risk factors of IITD. An additional aim was to evaluate the risk factor of sustained IITD (at least 6 months after the end of antiviral therapy). Moreover, based on our study results, we want to create a practical, feasible algorithm for the treatment of thyroid disturbances.

Material and methods

Study group. It consisted of 66 consecutive patients with chronic hepatitis C before first antiviral treatment. The group consisted of 41 males (medium age 42.9 ± 10.2 years; range 23-58 years) and 25 females (medium age 42.9 ± 10.2 years; range 20-59 years).

Inclusion criteria were: chronic hepatitis C confirmed by HCV-RNA assessment and no previous IFN-α (with or without ribavirin) therapy. Exclusion criteria were: subclinical or overt thyroid disturbances; coinfection with hepatitis B virus (HBV) or/and human immunodeficiency virus (HIV), or any IFN-α treatment in the past. Patients with positive antithyroid autoantibodies with normal results of thyroid axis hormones were not excluded from the study.

Antiviral treatment. Standard therapy with pegylated interferon and rybawirin was used in every case. In 12th week of therapy HCV-RNA was assessed and depending on the EVR result, the therapy was prolonged.

Study protocol. Before antiviral therapy the patient had the following assessed: hormonal parameters (thyreotropic hormone – TSH; free thyroxin – fT4 and free triiodothyronine – fT3), autoimmunological parameters (TPO-Ab; Tg-Ab and anti-TSH receptor autoantibodies (rTSH-Ab)) and thyroid ultrasound. During antiviral therapy hormonal and autoimmunological parameters were assessed in 4th, 8th, 12th, 24th, 36th, 48th week of therapy. Ultrasounds were performed in the 24th and the 48th week of therapy. The final follow-up examination was performed 24 weeks after antiviral treatment. All the above mentioned parameters were checked.

HLA-A2 antigen was assessed once in every patient usually before therapy.

Laboratory measurements

- TSH, fT4 and fT3 were determined using Chemiluminescent Microparticle Immunoassay (CMIA) method. Commercially available kits Abbott, ARCHITECT (TSH, fT4 and fT3); Lisnamuck, Longford, Ireland and Abbott, ARCHITECT, i2000analyzer were used. The intrassay

TSH, fT4 and fT3 coefficients of variation (CV) do not exceed 5.0; 5.3 and 4.2%, respectively. Reference ranges for TSH, fT4 and fT3 were respectively 0.34 – 4.94 μU/mL; 9.01 – 19.05 pmol/L; 2.63 – 5.7 pmol/L.

- TPO-Ab and Tg-Ab were determined using the immunoenzymatic method. Commercially available kits Bio Systems S.A. (TPO-Ab; Tg-Ab); Costa Brava, Barcelona, Spain) were used. The intrassay TPO-Ab and Tg-Ab CV do not exceed 4 and 7% respectively. Reference ranges for both assessments were <100 IU/mL

- rTSH-Ab were determined using the immunoenzymatic method. Commercially available kits EUROIMMUN, Medizinische Labordiagnostika AG were used. The intrassay rTSH-Ab CV was 5.5-15.5%. Reference ranges was estimated <1.8IU/L.

- Thyroid ultrasound was performed by a very experienced ultrasonographist. GE Logiq 500 with linear transducer 8-11 MHz was used. Color Doppler (CD) and Power Doppler (PD) were used to assess thyroid vascularity.

- HLA-A2 antigen was determined using Polymerase Chain Reaction with Sequence-Specific Primer (PCR-SSP) molecular technique. DynalAllSet SSP HLA-A "low resolution" (568.21) Dynal Biotech. Ltd., U.K. kits were used.

Results interpretation

Patients were classified according to laboratory results into 3 groups:

- Group 1 consisted of patients without any laboratory abnormalities (hormonal and autoimmunological).

- Group 2 consisted of patients who had positive thyroid autoantibody at least in one assessment during the treatment, and had no hormonal abnormalities. Patients with positive autoantibodies before therapy needed another positive autoantibody type to be included in this group.

- Group 3 consisted of patients with overt or subclinical thyroid dysfunctions confirmed by hormonal assessment. In this group, patients were additionally classified into subgroup 3a (hypothyroidism), 3b (hyperthyroidism) and 3c (bi-phasic hyper-hypothyroidism course).

Statistical analysis

We calculated standard descriptive statistics and studied the occurrence of IITD using survival analysis methodology. An univariate analysis was performed, which compared the Kaplan-Meier survival estimates and the log-rank test. Continuous variables were dichotomized for this analysis. A multivariate analysis was performed by fitting a discrete-time hazard model that included both time-invariant and time-varying predictors. P-values less than 0.05 were considered statistically significant. Calculations were carried out using STATA 12.0 statistical package (StataCorp LP, TX, USA).

Bioethical consideration. The entire study was approved by the Bioethical Commission of Medical University of Gdansk, Poland. There was no conflict of interests during the study.

Results

Frequency of thyroid disorders during IFN-α therapy

According to the above-mentioned classification of the entire study group (n=66), 21 patients (31.8%) did not have any thyroid abnormalities, neither hormonal nor autoimmune (group 1). Twenty-nine patients (43.9%) had elevated *de novo* thyroid autoantibodies without thyroid dysfunction. And 16 patients (24.2%) had subclinical or overt thyroid dysfunction – see Table 2.

11 subjects (16.6%) of study group had elevated concentrations of antithyroid autoantibodies before antiviral therapy. Each patient had only one type of autoantibodies elevated, e.g. 1 case with elevated TPO-Ab, 3 with Tg-Ab, and 7 with rTSH-Ab.

Group 1 consisted of 21 patients (17 males and 4 females) age from 20 to 62 years (mean age 39.2 ± 11.7). The group included 17 men and 4 women with a mean age of 41 ± 11.5 and 31 ± 10.2 years respectively.

Group 2 consisted of 29 patients age from 23 to 58 years (mean 44.6 ± 9.7). The group included 20 men and 9 women with mean age of 43.8 ± 9.5 and 46.3 ± 10.5 years respectively. We noted elevated Tg-Ab in 22, rTSH-Ab in 17 and TPO-Ab in 2 cases. The total number is not equal with the number of cases (n=29), because some of them had elevated more than one type of autoantibodies.

Group 3 consisted of 16 patients age from 30 to 56 years (mean 44.3 ± 9.9). The group included 4 males and 12 females with a mean age of 44.6 ± 10.4 and 43.2 ± 9.4 years respectively. In this group we noticed 3 types of thyroid disturbances. 7 subjects had hyperthyroidism, 4 had hypothyroidism and 5 had biphasic hyper-hypothyroidism course. An analysis of autoantibodies variety revealed elevated TPO-Ab, Tg-Ab and rTSH-Ab concentration in 7, 10 and 9 cases respectively. The total number is (similarly to group 2) not equal with the number of cases (n=16), because some of them had elevated more than one type of autoantibodies.

Univariate analysis

The overall cumulative incidence of overt thyroid dysfunction (TD) over 48 weeks of IFN-α therapy was 24.2% (95% CI: 15.2-36.3). The cumulative incidence stratified

Table 2. Cumulative incidence of thyroid dysfunction in 66 patients on IFN during 48 weeks, stratified by demographics and baseline laboratory results

Factor	Category	Number in category	Number with TD	C.Incidence % (95%CI)	RR (95% CI)
All patients	-	66	16	24.2 (15.2-36.3)	-
Gender	Male a	41	4	9.8 (3.6-23.9)	4.9 (1.8-13.6)
	Female	25	12	48 (29.0-67.6)	
Age	<45 years a	34	9	26.5 (14.1-44.2)	0.8 (0.3-2.0)
	≥45 years	32	7	21.9 (10.5-40)	
Baseline TSH	<2.5 µU/ml a	61	12	19 (11.3-31.9)	4.1 (2.1-7.9)
	≥2.5 µU/ml	5	4	80 (24.8-98.0)	
Baseline thyroid volume	<16 ml a	29	7	24.1 (11.6-43.5)	1.0 (0.4-2.4)
	≥16 ml	37	9	24.3 (12.9-41.1)	
Baseline Vmean in thyroid artery	<4.95 ml/min a	33	8	24.2 (12.3-42.2)	1.0 (0.4-2.3)
	≥4.95 ml/min	33	8	24.2 (12.3-42.2)	
HLA-A1 haplotype	Absent a	35	9	22.6 (10.9-41.1)	1.1 (0.5-2.7)
	Present	31	7	25.7 (13.7-43.1)	
Baseline TPO-Ab	Normal a	64	15	23.4 (14.5-35.7)	4.2 (2.7-6.6)
	Elevated	1	1	100	
Baseline Tg-Ab	Normal a	62	14	22.6 (13.7-35.0)	3.0 (1.2-7.4)
	Elevated	3	1	66.7 (9.1-97.6)	
Baseline rTSH-Ab	Normal a	60	14	23.3 (14.1-36.0)	1.7 (0.5-5.5)
	Elevated	5	2	40.0 (8.0-83.7)	

[a] reference category

by demographic and baseline laboratory results and the relative risks of TD are presented in Table 2. We found that women were at a higher risk for developing TD with the RR of 4.9 (95% CI: 1.8-13.6). Patients with initial TSH≥2.5 uU/ml had increased risk of TD with RR=4.1 (95%CI 2.1-7.9). The RR for abnormal baseline TPO-Ab and Tg-Ab were also significantly increased; however, the number of patients was small. The incidence of TD was not influenced by age, baseline thyroid volume, thyroid artery blood flow, presence of HLA-A1 haplotype and elevated rTSH-Ab.

Multivariate analysis

The results of multivariate analysis are summarized in Table 3. Female sex, baseline TSH≥2.5µU/mL, thyroid artery blood flow and elevated TPO-Ab were associated with significantly higher odds for developing TD during

the study. The odds for women were 5.76 times higher compared to men when the value of the remaining factors in the model were held constant (p=0.024). Initial TSH ≥2.5 μU/mL increased risk of TD 7.3 times compared to subjects with <2.5 μU/mL (p=0.036). Increased thyroid artery velocity (at any study point) by 1 ml/min increased risk of TD 1.3 times (p=0.014). Elevated TPO-Ab increased risk of TD 9.9 times (p=0.034). The remaining factors did not significantly increase the risk of TD.

Discussion

Table 3. Results of multivariate analysis

	OR	95% CI		p
Female sex	5,76	1,25	26,49	0,024
Age	1,00	0,94	1,08	0,795
Initial TSH ≥2.5 μU/ml	7,30	1,14	46,63	0,036
Thyroid volume	1,03	0,95	1,12	0,443
Thyroid artery velocity	1,29	1,05	1,58	0,014
TPO-Ab	9,87	1,18	82,20	0,034
Tg-Ab	1,43	3,38	6,03	0,628
rTSH-Ab	1,46	0,26	8,23	0,666
HLA-A2	0,51	0,09	2,78	0,436

OD – odds ratio; CI – confidence interval.

Interferons are widely used in medicine. They are commonly used in the treatment of various infectious disorders (e.g. HCV infection) and different malignancies (e.g. carcinoid). Because of decreasing cost of treatment, mild to medium side effects (comparing to classic chemotherapy) and relative contraindication during pregnancy (category C) interferons will be interesting therapeutic options for many years.

Epidemiology of IITD is not precise and data from medical literature is inconsistent. This condition is probably related to different methodologies of studies. Retrospective studies assessed only thyroid hormones, so in these situations only overt pathologies were detected. It markedly underestimated the real number of IITD cases. We may divide prospective studies into three groups. First one – thyroid hormones were assessed only when classic symptomatology of thyroid dysfunction appeared. Second one – thyroid hormones were assessed at regular periods, but thyroid autoantibodies were assessed only when hyper – or hypothyroidism appeared. Third one – thyroid hormones and autoantibodies were followed up at regular periods. According to Madac's classification, only in the third group will the epidemiology be the closest to a real one.

In our study the frequency of overt IITD (group 3 – see material and methods) and any IITD (group 2 and 3 together) was 24.2 and 43.9% respectively. In other recent studies, the frequency of overt IITD were estimated from 3.8 to 22.3% [,4,5,6,7,14,15,17,19,21,22,23,26,27]. Orsaqova et al. estimated the frequency of IITD during IFN-alpha in 25% of patients, but the study group consisted of HCV and HBV positive patients together [25]. Our results suggest that the frequency of IITD is higher than usually described. This is probably an effect of frequent blood sampling and the assessment of rTSH-Ab, which had never been performed routinely.

Risk factors of IITD. The first suggested risk factor of thyroid dysfunction was HCV *per se*; however, recent studies suggest that the coincidence of HCV and mixed cryoglobulinemia may be additional risk factors for the development of thyroid disturbance [7]. Risk factors of IITD are summarized in Table 4 [3,4,5,6,7,13,14,15,17,19, 21,22,23,26,27].

Risk factors of IITD
Highly likely
• female sex
• positive TPO-Ab before therapy
• high normal TSH concentration
Likely
• pegylated forms of IFN-α
• Asian race
• ultrasound picture suggesting AITD
Unknown significance
• polymorphism of genes: HLA-DR, CTLA-4, PTPN22, FOXP3, thyroglobulin and receptor for TSH, CD40
• positive Tg-Ab before therapy
• induction of Tg-Ab during therapy
• effect of ribavirin
• enlarge volume of thyroid gland
• mixed cryoglobulinemia
Not likely
• EVR, SVR
• genotype HCV
• initial level HCV-RNA
• AIAT activity
• albumin concentration

Similarly to other observations, univariate analysis revealed that female gender and high normal TSH (≥2.5 μU/ml) predispose to IITD. Multivariate analysis brought some new information to light. Firstly, we are convinced that HLA-A2 antigen is not a risk factor for IITD in the Caucasian race. Secondly, positive rTSH-Ab commonly observed in our study are also not a risk factor for overt TD, so the diagnosis of Graves disease cannot be established solely on the result of positive rTSH-Ab.

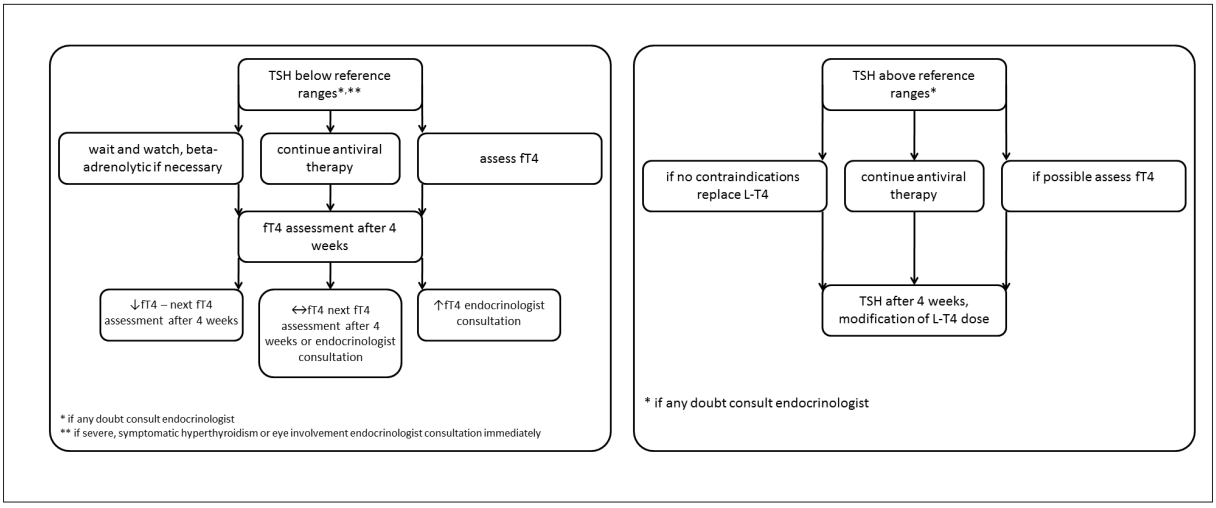

Fig. 2. Algorithm of management of IFN-α induced hyper – and hypothyroidism

Apart from the well-known factors like female sex, elevated TPO-Ab and high normal TSH, we suggest that thyroid artery velocity might be a new risk factor for IITD. In medical literature there are only a few articles describing the role of ultrasound in IITD [9]. We believe that such a fast, safe and relatively cheap procedure should be performed routinely at least before antiviral therapy.

Treatment of IITD

There is no doubt that treatment with IFN-α induces hypothyroidism. In most cases, L-thyroxine replacement therapy should be administered. However, what is still problematic is the diagnosis of primary hypothyroidism and what level of TSH is "too high". Upper reference range of TSH varies depending on the country (wide reference ranges are 0.3-5.0 μU/ml). But it is necessary to emphasize that most endocrinologists agree that TSH above 2.5-3 μU/ml should be at least followed up. A significantly more difficult problem is the treatment of hyperthyroidism. Antithyroid drugs are hepatotoxic, and so they may lead to agranulocytosis. IFN-α induced hyperthyroidism is commonly a result of destructive (self-limiting) thyroiditis, and hyperthyroidism is usually mild. In such a situation the administration of antithyroid treatment is usually not necessary immediately, and symptomatic treatment with beta-adrenolytics (e.g. propranolol) might be sufficient. We absolutely do not agree that antiviral therapy should be stopped when hyperthyroidism appears. The algorithm of management of hypo – and hyperthyroidism for hepatologistsis is presented in Figure 2.

Conclusions

Thyroid disorders are common during IFN-α therapy. Previous epidemiological data seem to be misinterpreted. Important risk factors for IITD development are: female sex, elevated serum TSH concentration (≥2.5 μU/mL), occurrence of TPO-Ab and increased blood velocity in thyroid arteries.

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