



Interferon-induced thyroiditis during treatment of chronic hepatitis C

Zapalenia tarczycy występujące w czasie leczenia interferonem przewlekłego zapalenia wątroby typu C

Dorota Kozielowicz, Waldemar Halota

Department of Infectious Diseases and Hepatology, L. Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland

Abstract

Thyroid function disorders affect between 5% and 15% of patients treated with IFN α and RBV for chronic hepatitis C. Women and patients with thyroid peroxidase antibodies (TPOAb) found before the treatment are at risk of developing the disorders (46.1% vs. 5.4%). The spectrum of IFN α -induced thyroiditis (IIT) includes two groups. Disorders with an autoimmune background are: presence of thyroid autoantibodies without clinical disease, Hashimoto's disease and Graves' disease. The second group comprises diseases caused by the direct toxic effect of IFN α on the thyroid gland, i.e. destructive thyroiditis and non-autoimmune hypothyroidism. Thyroid diseases are not an absolute contraindication for IFN α and RBV therapy. In patients diagnosed with thyroid dysfunction, before the antiviral therapy it is necessary to achieve euthyrosis. Thyroid function disorders may occur at any moment of the therapy. The earliest have been observed in the 4th week of treatment, and the latest 12 months after its termination. During the therapy, in order to diagnose IIT early, it is recommended to determine TSH level every 2–3 months depending on the presence of TPOAb before the treatment. The diagnosis and treatment of thyroid function disorders should be conducted in co-operation with an endocrinologist. (**Pol J Endocrinol 2012; 63 (1): 66–70**)

Key words: interferon alpha, chronic hepatitis C, interferon-induced thyroiditis, thyroid autoantibodies

Streszczenie

Zaburzenia funkcji tarczycy dotyczą 5 do 15% leczonych IFN α i RBV z powodu przewlekłego zapalenia wątroby typu C. Zagrożone ich wystąpieniem są kobiety oraz chorzy, u których stwierdzono przed leczeniem obecność przeciwciał przeciwko tyreoperoksydazie (TPOAb) (46,1% v. 5,4%). Spektrum zapaleń tarczycy wywołanych przez IFN α (IIT) obejmuje dwie grupy. Do zaburzeń o podłożu autoimmunologicznym zalicza się: obecność przeciwciał przeciw tarczycowym bez objawów klinicznych choroby tarczycy, chorobę Hashimoto i chorobę Gravesa. Drugą grupę stanowią choroby spowodowane bezpośrednim toksycznym działaniem IFN α na tarczycę, tj. destrukcyjne zapalenie tarczycy, nieautoimmunologiczna niedoczynność tarczycy. Choroby tarczycy nie są bezwzględnym przeciwwskazaniem do leczenia IFN α i RBV. U chorych z rozpoznaną przed rozpoczęciem terapii przeciwwirusowej dysfunkcją tarczycy należy uzyskać eutyrozę. Zaburzenia funkcji tarczycy mogą się pojawić w każdym momencie terapii. Najwcześniej obserwowano ich rozwój w 4. tygodniu leczenia, najpóźniej 12 miesięcy po jego zakończeniu. W czasie terapii w celu szybkiego wykrycia IIT zaleca się oznaczanie TSH co 2 lub 3 miesiące, w zależności od obecności TPOAb przed leczeniem. Diagnostyka i leczenie zaburzeń funkcji tarczycy powinny być prowadzone przy współudziale lekarza endokrynologa. (**Endokrynol Pol 2012; 63 (1): 66–70**)

Słowa kluczowe: interferon alfa, przewlekłe zapalenie wątroby typu C, zapalenie tarczycy wywołane przez interferon, przeciwciała przeciw tarczycowym

Introduction

Interferons are divided into three major types depending on their properties and ability to bind to particular kinds of receptors. Interferons α , β and ω belong to type I, and interferon γ represents type II. Interferon λ -1, undergoing the first phase of clinical trials, is classified as type III [1, 2]. There are at least 12 types of interferon alpha (IFN α). It has been used in the treatment of chronic hepatitis C since the 1990s. Initially, it was used in the recombinant form (rIFN α) and in monotherapy, and more recently in combination with ribavirin (RBV) and in pegylated form (PegIFN α). Other

forms of this cytokine, i.e. natural leukocyte interferon alpha, interferon alpha conjugated to albumin, or interferon alpha consensus-1, which is a mixture of natural and recombinant interferons, are less frequently used.

Therapy with IFN α causes various undesirable effects. Some of them, such as fever, muscle and joint pain, and haematological disorders, occur in the initial period of the therapy. Other effects, such as mood disorders and hair loss take place later. From 5% to 15% of patients treated with IFN α for chronic hepatitis C may develop thyroid function disorders, and in 40% of the patients thyroid autoantibodies (TAb) may appear without clinical disease [3–5]. The relationship between the



cytokine and thyroid dysfunction was first described in 1985 in patients treated because of neoplasms i.e. breast cancer [6, 7].

Factors predisposing to development of thyroid function disorders

The risk of developing thyroid function disorders concerns women (they have a four times higher risk than men) and patients with thyroid peroxidase antibodies found before the treatment (46.1% vs. 5.4%) [5, 8]. Patients undergoing interferon and ribavirin combination therapy develop autoimmune hypothyroidism more often than patients receiving interferon monotherapy [9]. Destructive thyroiditis occurs more frequently in patients treated with interferon alpha consensus-1 than in patients treated with rIFN α . This fact is related to a strong, direct, cytotoxic effect of the first interferon on thyrocytes. However, there is no difference between rIFN α and PegIFN α [10]. Some research has suggested that higher doses of IFN α and longer therapy create favourable conditions for the occurrence of thyroid dysfunction [8], but analyses of other research results do not confirm this suggestion [11–13].

Data concerning the relationship between HCV infection and thyroid function disorders also diverges. Fernandez-Soto showed that 20–42% of HCV infected patients had TABs, compared to 5–10% of those infected with HBV. According to the author, this proves that such a relationship exists [14]. In their study, Marazuela et al. estimated the incidence of TPOAb in HCV infected patients to be 14.7%, which is similar to that in the healthy population [15].

Clinical spectrum of IFN α -induced thyroid function disorders

Autoimmune interferon induced thyroiditis (autoimmune IIT)

Presence of thyroid autoantibodies without clinical manifestations of thyroid disease

Patients treated with IFN α are most often found positive for TABs, mainly thyroid peroxidase antibodies and/or thyroglobulin antibodies (TgAb) without clinical disease. It is commonly believed that their presence, and that of TPOAb in particular, indicates the presymptomatic phase of autoimmune thyroiditis. The titre of antibodies may rise during IFN α therapy if they are found before the treatment [3, 4]. The risk of developing clinically apparent disease, particularly in women with goitre and antibodies, amounts to 5% per year [16, 17]. Thyroid autoantibodies can be produced during IFN α de novo therapy in 1.9–40% of patients [3, 4, 13, 18]. The

phenomenon is more frequently observed in women than in men (14.8% vs. 1%) and is also associated with increasing age [13]. In most patients, TABs are detected after the termination of IFN α therapy [19].

Hashimoto's thyroiditis (HT)

Hashimoto's thyroiditis is the commonest clinical manifestation of autoimmune IIT and occurs in 2.4% to 19% of patients treated with IFN α . A factor increasing the risk of HT development is the presence of TPOAb before IFN α therapy [4, 8, 13, 18]. TPOAb titre often increases during the therapy [4]. The disease manifests itself through subclinical hypothyroidism (elevated TSH level, normal fT4 level) or clinically apparent hypothyroidism (elevated TSH, low fT4). Goitre occurs in some patients. The disease is diagnosed on the basis of hypothyroidism symptoms and the presence of TPOAb and/or TgAb. Supplementation of thyroid hormones is used in the treatment. Hashimoto's thyroiditis rarely becomes the reason for premature termination of therapy with IFN α and RBV.

Graves' disease (GD)

IFN α leads to the development of GD in people predisposed to it (immunogenetic background) [3, 20]. Its rare occurrence during IFN α therapy is explained by the suppressive effects of IFN α on the immune response dependent on Th2 lymphocytes. In patients with Graves' disease, they stimulate B lymphocytes to produce TSH receptor antibodies (TRAb). The antibodies stimulate the activity of follicular cells, which results in thyroid hormone secretion. IFN α inhibits this signal transduction pathway [16]. Physical examination shows hyperthyroidism symptoms and goitre. Graves' ophthalmopathy develops rarely, and may lead to half-closed eyes during sleep and keratitis or optic nerve compression causing visual impairments [21, 22]. Laboratory tests show a characteristic decrease in TSH level, increase in fT4 and fT3 levels, and the presence of TRAb. Iodine uptake is normal or increased. Most GD cases do not undergo remission after completion of IFN α therapy.

Non-autoimmune IIT

TABs do not occur in around 50% of patients with thyroid function disorders during IFN α therapy. This fact indicates the direct toxic effect of IFN α on thyroid cells, without the participation of immunological factors [3, 20, 23]. There are two recognised clinical forms of non-autoimmune thyroiditis.

Destructive thyroiditis (DT)

Destructive thyroiditis is diagnosed in over half of the patients developing hyperthyroidism during IFN α therapy [3, 4, 23]. It is a self-limited inflammatory

Table I. Main diagnostic criteria for thyroid dysfunction associated with IFN α and RBV treatment**Tabela I. Diagnostyka zaburzeń funkcji tarczycy występujących podczas terapii IFN α i RBV**

Tests	Autoimmune interferon-induced thyroiditis		Non-autoimmune interferon-induced thyroiditis	
	Hashimoto's thyroiditis	Graves' disease	Destructive thyroiditis	Non-autoimmune hypothyroidism
TSH level	↑	↓	1st phase ↓ 2nd phase ↑ 3rd phase normal	↑
fT4 level	Normal or ↓	Normal or ↑	1st phase normal or ↑ 2nd phase normal or ↓ 3rd phase normal	Normal or ↓
TPOAb	(+)	(-) or (+)	(-)	(-)
TgAb	(+) or (-)	(-)	(-)	(-)
TRAb	(-)	(+)	(-)	(-)
Goitre present	Yes or no	Yes	Yes or no	No
Thyroid ultrasound/ /scintigraphy	Decreased echogenicity/ /lack of clinical practice	Decreased echogenicity/ /increased or normal uptake of J ¹³¹ on thyroid scan	Diffuse echogenicity/ /reduced uptake of J ¹³¹ on thyroid scan	–

disease of the thyroid gland which has three phases. The first phase is characterised by sudden onset and hyperthyroidism symptoms, sometimes accompanied by fever and neck tenderness. After several days or weeks, hypothyroidism develops, which is characteristic for the second phase of the disease. Over the following weeks and months, the thyroid gland restores its normal function (the third phase). Fewer than 5% of patients develop long-term hypothyroidism [24]. Sometimes the course of the disease is very mild and its symptoms remain unnoticed or are interpreted as undesirable effects of interferon. In many cases, spontaneous recovery takes place. Diagnosis of DT in IFN α treated patients is based on the lack of TRAb, TPOAb and low radioactive iodine uptake [3, 20].

Non-autoimmune hypothyroidism

This is a transient subclinical or clinically apparent hypothyroidism running its course without the presence of TABs. If the disease lasts longer, thyroid autoantibodies appear, which indicates the secondary role of immunological factors [3, 15, 20].

The criteria for a diagnosis of thyroid function disorders developed during IFN α and RBV therapy are presented in Table I.

Assessment of suitability of chronic hepatitis C patients for IFN α and RBV treatment

Assessment of suitability for the treatment should include:

- thorough patient interview (thyroid diseases in the patient and his/her close relatives) and physical examination (symptoms of hyperthyroidism or hypothyroidism);
- determination of TSH, fT4, TABs: TPOAb, TgAb, and also TRAb and fT3 in the case of thyrotoxicosis.

The aim is to identify patients with subclinical hypothyroidism or hyperthyroidism, apparent thyroid disease and a heightened risk of developing thyroid function disorders during the therapy. Thyroid diseases are not absolute contraindications for IFN α and RBV treatment. Patients previously diagnosed with thyroid dysfunction must be in euthyresis before the treatment begins.

Principles of monitoring and early diagnosis of thyroid dysfunction during IFN α and RBV treatment

Thyroid function disorders can occur at any moment of the therapy. The earliest have been observed in the 4th week of treatment, and the latest 12 months after its termination (in the case of a 48-week therapy) [25, 26]. During the treatment, TSH level should be determined every 2–3 months depending on the presence of TABs before the treatment [3, 13, 21]. Details are shown in Figure 1. Clinicians should routinely examine for signs of thyroid dysfunction such as tachycardia or bradycardia, heat or cold intolerance, and unexpected weight change. If the patient develops abnormal thyroid functions while on IFN α , a full work-up needs to be completed.

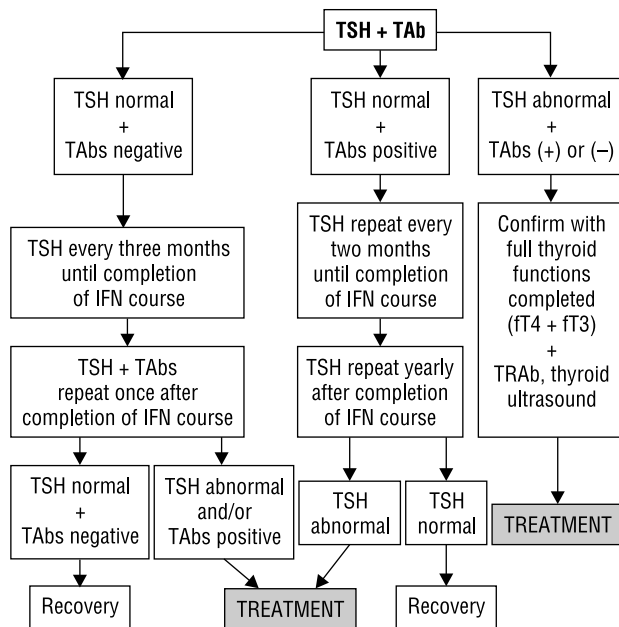


Figure 1. Guidelines for the early recognition of thyroid dysfunction

Rycina 1. Kryteria wczesnego wykrywania zaburzeń funkcji tarczycy

Treatment of thyroid function disorders

The treatment of thyroid disease should be conducted in co-operation with an endocrinologist. Endocrine consultation is recommended for all patients diagnosed with thyroid dysfunction.

Hyperthyroidism occurs less frequently than hypothyroidism [26]. Anti-thyroid drugs (ATD) used in therapy can intensify IFN α -induced neutropenia or cause agranulocytosis. One should also remember the hepatotoxic effects of the drugs. Derivatives of both imidazole and thiouracyl can cause drug-induced liver injuries. Thiamazole mainly induces dose-dependent cholestasis, while propylthiouracyl induces dose-independent hepatitis.

Due to these undesirable effects, some authors do not recommend the administration of these drugs to patients with IFN α -induced Graves' disease [27]. In a case of continuation of antiviral therapy, the patient must be kept under close observation. If it is necessary to use other methods of treatment (e.g. radioactive iodine J¹³¹, strumectomy), IFN α and RBV therapy must be discontinued [20, 21].

When destructive thyroiditis is suspected, it is recommended to administer beta blockers and perform TSH and fT₄ tests frequently. It is not advised to use ATD in the first phase of the disease, because its second phase is hypothyroidism.

In the treatment of **hypothyroidism**, thyroid hormone supplementation is used according to commonly accepted principles. Treatment tolerance is usually good. Hypothyroidism rarely becomes the reason for premature termination of antiviral therapy. During the treatment, TSH and fT₄ levels should be determined every two months [13, 20].

A decision to use **glucocorticosteroids** in IFN α -induced thyroid diseases must be taken individually. The period of time when the steroids are used should be as short as possible, as they intensify HCV replication [20].

An absolute indication to **discontinue treatment** is a life-threatening condition such as hypermetabolic crisis, myxoedema coma, or agranulocytosis. In other cases, the decision to terminate therapy should be taken jointly by the doctor treating the chronic hepatitis C patient and the endocrinologist.

Conclusions

Thyroid function disorders are not frequent complications of therapy with interferon alpha and ribavirin. They may, however, sometimes be the reason for its premature termination. The possibility of the disorder's occurrence must be taken into account, particularly when weight loss and/or hair loss are observed in the patient and he/she reports touchiness, emotional imbalance, memory disorders, general weakness, or decreased exercise tolerance. These complaints, often associated with the effects of IFN α and RBV, are in fact early symptoms of thyroid disease.

Thyroid function disorders are not an absolute contraindication for antiviral treatment, but euthyrosis should be achieved before beginning the therapy. Special attention should be paid to patients with TPOAb present before the treatment. Due to a higher risk of developing thyroid dysfunction, patients require close monitoring during the therapy. Only sound co-operation between the doctor conducting the antiviral therapy and an endocrinologist can ensure proper preparation of the patient with thyroid pathology for therapy, and its safe course.

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