

# Patients with chronic hepatitis type C and interferon-alpha-induced hyperthyroidism in two-years clinical follow-up

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## Abstract

**OBJECTIVES:** Interferon- $\alpha$  (IFN- $\alpha$ ) is a gold standard in the therapy of viral chronic hepatitis type C (CHC). However, such treatment might lead to thyroid dysfunction. Patients usually present hypothyroidism, but rarely also hyperthyroidism may develop. The aim of the study is to present two-year clinical follow-up of patients with CHC and IFN- $\alpha$ -induced hyperthyroidism (IIH), with special regard to the methods and efficacy of the therapy.

**METHODS:** A group of 106 patients with CHC and IIH were analyzed. Subjects were divided into two groups according to etiology: group 1, with Graves' disease (GD) and group 2, with Hashitoxicosis (HT). The diagnosis of GD and HT was based on: clinical signs of hyperthyroidism, hormonal profile (TSH, fT<sub>4</sub>, fT<sub>3</sub>), level of thyroid autoantibodies (Tg-Abs, TPO-Abs, TSHRabs). Treatment of hyperthyroidism was monitored by repeated clinical assessment and laboratory tests.

**RESULTS:** 28 patients (26 with GD of which 5 exhibited mild orbitopathy and 2 with HT) were treated with radioiodine [the average dose of was 17 mCi [668 MBq]. In addition 78 out of 80 patients with HT mostly  $\beta$ -blocker therapy was successful (transient hyperthyroidism). At the end of the observation

period, in group 1 remission was achieved in 17 (65.4%) cases, 6 (23.1%) patients showed hypothyroidism and 3 (11.5%) presented recurrence of hyperthyroidism.

**CONCLUSIONS:** Most patients with IIH present Hashitoxicosis, while a minority of them develop Graves' disease. In a majority of patients with HT spontaneous remission of disease occurs. In patients with long-term hyperthyroidism, radioiodine therapy is an effective and well-tolerated.

#### Abbreviations:

|                 |   |
|-----------------|---|
| AST             | - Aspartate Aminotransferase                    |
| ALT             | - Alanine Aminotransferase                      |
| ATD             | - antithyroid drugs                             |
| CHC             | - chronic hepatitis C                           |
| fT <sub>4</sub> | - free tetraiodothyroxine                       |
| fT <sub>3</sub> | - free triiodothyronine                         |
| GD              | - Graves' disease                               |
| GT              | - Graves' hyperthyroidism                       |
| GO              | - Graves Ophthalmopathy                         |
| HT              | - Hashitoxicosis                                |
| IIH             | - Interferon- $\alpha$ -Induced Hyperthyroidism |
| RAI             | - radioiodine                                   |
| RAIU            | - radioiodine uptake                            |
| RIT             | - radioiodine therapy                           |
| TSH             | - thyrotropin                                   |
| TSHR-Abs        | - autoantibodies to the thyrotropin receptor    |
| Tg-Abs          | - thyroglobulin autoantibodies                  |
| TPO-Abs         | - thyroperoxidase autoantibodies                |

## INTRODUCTION

Interferon- $\alpha$  (IFN- $\alpha$ ) is the gold standard in therapy of type C chronic viral hepatitis (CHC). The pathophysiological mechanisms of IFN- $\alpha$  acting on the thyroid gland are concerned with immunomodulating properties of this molecule. It has been reported that the incidence of thyroid disease, hyperthyroidism and hypothyroidism, varies between 2% and 45% (Carella *et al.* 1995; Deutsch *et al.* 1997; Carella *et al.* 2004; Moncoucy *et al.* 2005; Gelu-Simeon *et al.* 2009; Tomer 2010). Autoimmune thyroiditis belongs to most common dysfunction of the thyroid gland, presenting usually frequent hypothyroidism, but rarely may develop in hyperthyroidism [Hashitoxicosis (HT) or Graves' disease (GD)] (Hsieh *et al.* 2000; Wong *et al.* 2002; Carella *et al.* 2004). Interferon- $\alpha$ -induced hyperthyroidism (IIH) is usually transient and in the majority of cases resolves spontaneously. This does not always correlate with levels of thyroid autoantibodies (TPO-Abs and Tg-Abs), which may result in: undetectable, elevated, or rise after withdrawal of IFN- $\alpha$  administration (Deutsch *et al.* 1997; Carella *et al.* 2001; Vezali *et al.* 2009). Sometimes, in certain cases when IFN- $\alpha$ -induced GD develops a dilemma exists whether to use radioiodine therapy (RIT) in cases when antithyroid drugs (ATDs) are contraindicated, such as: high levels of aminotransferases, thrombocytopenia, agranulocytosis, or to discontinue IFN- $\alpha$  therapy?

The aim of this study is to present results of clinical observations of patients with CHC with IIH, during 2 years of follow-up taking into account the above choice

of treatment. Additionally, we presented the possible modification of the method of the therapy CHC patients with IIH.

## MATERIAL AND METHODS:

### Study design

In two-years period of follow-up, 106 cases were retrospectively analyzed (80 women and 26 men, aged from 21 to 58;  $x \pm SD$ :  $34.3 \pm 12.8$  years, mean: 38.9 years) with CHC and IIH. Patients with thyroid disease before therapy were excluded from the study group. The patients were divided into two groups according to etiology: group 1, with GD [radioiodine uptake (RAIU) normal and elevated], group 2, with HT, low RAIU (Table 1). The hyperthyroidism was diagnosed according to: serum levels of thyroid hormones (fT<sub>3</sub>, fT<sub>4</sub>), TSH, antibodies (TPOAbs, TgAbs and TSHRabs), thyroid ultrasound (US), thyroid scintigraphy, and RAIU at 5 and 24 hours. Additionally, patients with GD were examined by an ophthalmologist, using a new consensus of European group on Graves' orbitopathy (EUGOGO) (Bartalena *et al.* 2008). The diagnosis of destructive thyroiditis was confirmed by anti-TSH receptor antibody (TSHRab) negativity and the absence of radio-nuclide (<sup>99</sup>Tc) uptake on thyroid scintiscans. CHC was diagnosed by liver biopsy and the presence of anti-HCV antibodies detected by enzyme-linked immunosorbent assay II. The study protocol was approved by the local ethical committee. Subsequently, the patients consented to treatment and participation in the study according to the Patient's Rights and Patient's Rights Representative Act from 6 November 2008 (2009).

### Follow-up by endocrinologist

Treatment for hyperthyroidism was monitored by clinical assessments and laboratory evaluations of the serum T<sub>3</sub>, free T<sub>4</sub>, TSH, anti-TPO and anti-Tg levels as follows: at baseline, after 1, 2, 12 and 24 months in both groups. Serum TSH receptor antibodies (TSHRabs) were analyzed at baseline, 2, 6, 12, and 24 months in group 1.

### Thyroid hormones and autoantibody immunoassays

Free-triiodothyronine (fT<sub>3</sub>), free-thyroxine (fT<sub>4</sub>), and TSH were measured by a immunoradiometric method on an automated platforms: Cobas 6000 (Roche Diagnostics, Mannheim, Germany, www.Roche.com). The normal range was: 3.9–6.8 pmol/L for fT<sub>3</sub>, 11.5–21.5 pmol/L for fT<sub>4</sub>, and 0.27–4.20  $\mu$ IU/ml for TSH. The intra-assay and inter-assay coefficients of variation (CV) were 3.3 and 5.1% for fT<sub>3</sub>, 1.6 and 3.5% for fT<sub>4</sub>, and 8.6 and 8.7% for TSH, respectively. The lower limit of sensitivity was 0.26 pmol/L for fT<sub>3</sub>, 0.023 pmol/L for fT<sub>4</sub>, and 0.005  $\mu$ IU/ml for TSH. The thyroglobulin autoantibodies (Tg-Abs) and thyroid peroxidase autoantibodies (TPO-Abs) were measured using an automated Cobas electrochemiluminescence ECLIA. Tg-Abs (normal values, <115 IU/ml); TPO-Abs, TPO autoan-

tibodies (normal values, <34 IU/ml); with precision better than 7% CV for a sample of at least 21.3 IU/ml for Tg-Ab, and better than 10% for a sample of 15.3 IU/ml, respectively. The TSHRabs [TRAK RIA (Brahms AG, Hennigsdorf, Germany)] binding activity interassay precision CV were between 3.9 and 7.5% for TSHRAB 13.2–27 IU/l, and 14.1% for TRAb 1.1 IU/l, evaluation limit of 1 IU/l, and TSHRab positivity greater than 1.5 IU/l.

#### Ultrasonography

Thyroid US was performed with the use of a 7.5–17 MHz linear probe using an ALOKA SSD 3500 SV. The thyroid volume was measured using the elliptical shape volume formula ( $\pi/6 \times \text{length} \times \text{width} \times \text{depth}$ ) (Knudsen *et al.* 1999)

#### RAIU and scintigraphy

RAIU was measured at 5h and 24h after administration of a tracer dose (ca. 2MBq of <sup>131</sup>I). The thyroid scintiscan was performed 30 min. after i.v. administration of 150 MBq of <sup>99m</sup>Tc. Images were obtained using a Nucline gamma camera (Mediso, Hungary).

#### Treatment

Interferon- $\alpha$  (INF)

All patients received INF- $\alpha$ -2b (Roferon-A, Hoffman-LaRoche Inc., Basel, Switzerland) or PEG-INF- $\alpha$ -2b (Pegylated-INF  $\alpha$ -2b), in combination with ribavirin (Rebetol). INF was administered three times per week (3 MU subcutaneously) and ribavirin in a dose 1 000–1 200 mg/day orally.

Antithyroid drug therapy (ATD)

Methimazole (MMI) or [propylthiouracil (PTU)], or was given 5 mg three times daily for about 3 weeks, later 5 mg twice daily for 3 weeks, and finally 5 mg daily until achieving remission.

Beta-blockers

Beta-blockers were used for symptomatic treatment. Patients with destructive thyrotoxicosis in a case when tachycardia occurred and in GD as a first line or showing serious adverse reactions to ATDs.

Iodine-131

Every patient before treatment radioiodine (RAI) received clear information about his/her current health status projected results and possible consequences of these therapy. The intention was to give one dose of RAI, in cases where ATD therapy was contraindicated (agranulocytosis, thrombocytopenia, transaminasemia).

Substitution therapy

Substitution therapy with L-Thyroxine was administered to compensate for hypothyroidism during INF treatment or after RIT.

#### Statistical analysis

The data were analyzed using the program Statistica 7.1, StatSoft Inc. Results were expressed as the mean $\pm$ SD in the text for data with normal distribution. Failure rates are presented as percentages of the total within each category examined. Mann-Whitney's tests were performed for comparative purposes of the results before and after RIT. Unpaired *t* tests were used to compare continuous variables, and  $\chi^2$  tests were to compare discrete variables between groups. All statistical tests were two-sided. The *p*-value  $\leq 0.05$  was considered significant.

## RESULTS

In the period of two-years follow-up, 106 patients were treated with INF- $\alpha$ . They were divided into two groups according to etiology: group 1, with GD [26 patients, 43 $\pm$ 12 y], group 2, [80 patients, 39 $\pm$ 16 yr.] In both groups dominated females. Duration of ITH were not statistical different in both groups [ 23.7 $\pm$ 32.1 weeks in group 1 and 17.7 $\pm$ 28.1 weeks in group 2]. The levels of

**Tab. 1.** Features of the study groups at baseline.

|   | Group 1                          | Group 2                          |
|---|----------------------------------|----------------------------------|
| N   | 26                               | 80                               |
| Gender (M/F)  | 10/16                            | 16/64                            |
| Age (yr)  | 43 $\pm$ 12                      | 39 $\pm$ 16                      |
| Duration of hyperthyroidism during therapy of INF- $\alpha$ (weeks) | 23.7 $\pm$ 32.1                  | 17.7 $\pm$ 28.1                  |
| Presence of GO (n)  | 5                                | –                                |
| AST (N: 10–31 U/l)  | 48.4 $\pm$ 30.8                  | 49.6 $\pm$ 43.0                  |
| ALT (N: 10–31 U/l)  | 45.6 $\pm$ 34.2                  | 43.4 $\pm$ 35.3                  |
| TSH (N: 0.27–4.2 $\mu$ U/mL)  | 0.12 $\pm$ 0.06                  | 0.09 $\pm$ 0.07                  |
| fT <sub>4</sub> (N: 11.5 – 21.5 pmol/L)                             | 24.3 $\pm$ 3.1                   | 22.2 $\pm$ 3.9                   |
| fT <sub>3</sub> (N: 3.9–6.8 pmol/L)                                 | 4.6 $\pm$ 0.8                    | 4.5 $\pm$ 0.5                    |
| TPO-Abs (N: < 34 IU/ml)   | <b>133.5<math>\pm</math>64.0</b> | <b>90.2<math>\pm</math>59.3</b>  |
| Tg-Abs (N: 10–115 IU/ml)  | <b>178.1<math>\pm</math>99.0</b> | <b>117.7<math>\pm</math>90.2</b> |
| TSHR-Abs (N: < 2 IU/L)  | <b>4.4<math>\pm</math>3.5</b>    | <b>0.6<math>\pm</math>0.2</b>    |
| Thyroid volume (N: < 18 ml)   | 21.01 $\pm$ 8.03                 | 19.02 $\pm$ 6.03                 |
| RAIU (%)  |                                  |                                  |
| after 5 h   | <b>24.6<math>\pm</math>6.3</b>   | <b>3.5<math>\pm</math>1.7</b>    |
| after 24 h  | <b>44.2<math>\pm</math>14.4</b>  | <b>5.5<math>\pm</math>2.7</b>    |

Data correspond to the arithmetic mean  $\pm$  SD. M, Male; F, female. Underline were statistical differences between groups; *p*<0.001 (Mann-Whitney test)

AST and ALT were slightly elevated in all patients with CHC but not significant. Graves' ophthalmopathy (GO) was observed in 5 (19.2%) patients, all had only mild manifestations.

Among the 106 candidates only 28 patients consented to RIT – 26 patients had GD (group 1), and 2 patients had HT (group 2). Prior to these treatment, 7 patients (6.6%) received PTU, and 8 (7.5%) MMI (group 1). Side effects after ATDs were observed in 8 patients [1 thrombocytopenia, 5 leucopenia, 1 agranulocytosis, 4 high levels of aminotransferases]. ATDs were contraindicates as a therapy of choice due to agranulocytosis during Pegylated- $\text{INF } \alpha\text{-2b}$  therapy in 3 cases. The average dose of  $^{131}\text{I}$  was 17 mCi [(668 MBq); range, 5–22mCi (185–814 MBq)]. In group 2, (78 from 80) only  $\beta$ -blockers therapy was succesfull (withdrew from a therapeutic dose of RIT) because hyperthyroidism was transient. There were also statistical differences between RAIU in both groups ( $p=0.005$ ). The clinical characteristic of the examined patients was shown in Table 1.

Outcome of Graves' ophthalmopathy

A slight aggravation of eye disease was observed in only 5 (19.2%) patients with mild GO after RIT. Among those 5 cases, we observed two cases with a "three-stage evolution" from silent destructive thyroiditis to GO during about 5 months of  $\text{INF-}\alpha$  therapy. The CAS (Clinical Activity Score) before RIT increased insignificant from  $2.6\pm 0.3$  points at baseline,  $3.4\pm 0.2$  after 8 weeks,  $3.6\pm 0.5$  after 6 months,  $3.2\pm 0.4$  after 12 months, to  $3.1\pm 0.2$  after final observations. While in remain GD patients it was  $1.6\pm 0.2$ ,  $2.8\pm 0.3$ ,  $2.9\pm 0.2$ ,  $2.5\pm 0.6$ , and  $2.2\pm 0.2$ , respectively. Statistically significant CAS chances between GB patients were not found.

Outcome of thyroid volume and echogenicity

No statistical significant difference was observed in thyroid volume between baseline and 2, 6, 12, and 24 months and between group 1 and 2 ( $22.5\pm 5.7$  vs.  $18.4\pm 6.42$ ,  $20.6\pm 6.4$  vs.  $17.4\pm 4.34$ ,  $19.8\pm 6.82$  vs.  $17.2\pm 3.8$ ,  $19.1\pm 4.9$  vs.  $17.0\pm 3.1$ , and  $18.8\pm 6.82$  vs.  $16.1\pm 4.3$ ,  $p>0.05$ ). The baseline characteristics of US examination were typical of patients with ITH. In group 1, marked hypoechogenicity was observed in all patients after RIT. US revealed in group 2: 68 (85%) patients with definite decreased echogenicity, 12 (15%) with mild hypoechogenicity .

Thyroid function during follow-up

Two months after RIT in group 1 remission was observed in 17 (65.4%) and subclinical hyperthyroidism (suppressed TSH level) in 9 (34.6%) patients (Table 2). In group 2, in 70 (87.5%) cases beta-blockers were implemented achieving remission after 8 weeks. After 6 months of the study, transitory hypothyroidism was found in only 6 (7.5%) patient from group 2, and in 3 (11.5%) cases in group 1. Hyperthyroidism remain in 8 (30.8%) cases from 1 group. At 1 year period, among the group 2, 73 (91.3%) were euthyroidism and 7 (8.7%) were hypothyroidism. Similar changes were found in group 1. At the end of our observation in group 1, remission was achieved in 17 (65.4%) cases, 6 (23.1%) patients showed hypothyroidism and in 3 (11.5%) were recurrences of hyperthyroidism. In those cases ATDs were applied. In group 2, the thyroid function normalized in 78 (97.5%) patients, confirming the transient character of the thyroid gland dysfunction In two cases (after RIT) L-thyroxin was used (Table 2).

Serum thyroid hormone, TSH and autoantibodies (TgAb, TPOAb and TRAb) concentrations during follow-up

Mean serum  $\text{fT}_4$ ,  $\text{fT}_3$ , and TSH concentrations, were not statistically significant at baseline and during follow-up between two groups ( $p>0.05$ ). Serum  $\text{fT}_4$  concentrations had a similar trend in both groups during observation (Figure 1). Significant differences ( $p=0.001$ ) in level of  $\text{fT}_4$  between 6 and 24 months in group 1; similarly in group 2 (mostly without RIT) between 2, 6, and 24 months ( $p<0.001$ ) were observed. The serum level of TSH indicated a minor increase during follow-up, although not reaching statistical significance (in both groups) (Figure 2). Although, the additional decreased thyroid hormone levels occurring after RAI (group 1) and after beta-blockers therapy did not achieve significance ( $p>0.05$ ). All patients were positive for thyroid autoantibodies (Ab+), TPOAb and TgAb, and were statistically significant between two groups only et baseline ( $p<0.001$ ) (Table 1). During follow-up level of ATOAbs (IU/ml) in group 1 and 2 were  $278.42\pm 264.38$  vs.  $156.08\pm 404.29$ ,  $219.84\pm 229.34$  vs.  $145.6049\pm 352.87$ ,  $215.34\pm 169.90$  vs.  $154.60\pm 352.87$ ,  $199.00\pm 148.18$  vs.  $135.44\pm 327.66$ , respectively. The results were similar in the level of TgAb (IU/ml) [(  $311.61\pm 425.90$  vs.

**Tab. 2.** Evaluation of thyroid function during two years of follow-up in studied groups.

| Hyperthyroidism<br>n (%) |           | Euthyroidism<br>n (%) |            | Hypothyroidism<br>n (%) |         |
|--------------------------|-----------|-----------------------|------------|-------------------------|---------|
| Group 1                  | Group 2   | Group 1               | Group 2    | Group 1                 | Group 2 |
| <b>at baseline</b>       |           |                       |            |                         |         |
| 26 (100)                 | 80 (100)  | -                     | -          | -                       | -       |
| <b>after 2 months</b>    |           |                       |            |                         |         |
| 9 (34.6)                 | 10 (12.5) | 17 (65.4)             | 70 (87.5)  | -                       | -       |
| <b>after 6 months</b>    |           |                       |            |                         |         |
| 8 (30.8)                 | -         | 15 (57.7)             | 74 (92.5)  | 3 (11.5)                | 6 (7.5) |
| <b>after 12 months</b>   |           |                       |            |                         |         |
| -                        | -         | 17 (65.4)             | 73 (91.3)  | 9 (34.6)                | 7 (8.7) |
| <b>after 24 months</b>   |           |                       |            |                         |         |
| 3 (11.5)                 | -         | 17 (65.4)             | 78 (97.5%) | 6 (23.1)                | 2 (2.5) |

225.70±478.61, 266.92±386.34 vs. 204.28±442.48, 260.80±385.00 vs. 204.92±385.00, 199.00±148.18 vs. 190.64±438.98, NS)]. A majority of patients (group 1) had positive antibodies (Abs+) at the end of RIT. There were significant correlations ( $p < 0.001$ ) between TSH-RAb levels and  $fT_4$  values ( $r = 0.44$ ) and  $fT_3$  levels ( $r = 0.48$ ) in group 1, and in TSH-RAb in both groups at baseline. The changes in TSH-RAbs levels during the 2-year follow-up were presented in Figure 3.

## DISCUSSION

INF- $\alpha$  is commonly used as an anti-viral medication for therapy of CHC infection (permanent normalization of alanine-aminotransferase and reduce virus [HCV] RNA) with varying negative effects on the thyroid gland (Braga-Basaria & Basaria 2003). This kind of deregulation, resulting from immunomodulatory effects leads most commonly to the following medical complications: hypothyroidism and hyperthyroidism, silent destructive thyroiditis and rarely Graves' hyperthyroidism (Braga-Basaria & Basaria 2003; Csaki & Blum 2000; Wong *et al.* 2002). In our observations hypothyroidism was not a serious complication, usually were requiring no specific treatment and only in certain cases demands supplementation with L-thyroxin. Even though hyperthyroidism is sometimes mild and self-limiting, the patients requires observations and cooperation between an endocrinologist and infection disease specialist.

In our observations, from among 106 examined patients, GD was diagnosed in 26 cases (25% of all our cases), including 5 cases of mild GO (group 1). Tran *et al.* (1993) reported the presence of TSHRABs in about 15% of patients with chronic HCV. According to others authors GO occurs rarely after and during INF- $\alpha$  therapy (Wong *et al.* 2002; Binaghi *et al.* 2002). We have demonstrated, for the first time so a significant number of patients in whom RAI was the only one method of treatment. However, in certain cases RIT should be considered (Czarnywojtek *et al.* 2012). In our study RAI was applied in 28 cases (26 with GD, and 2 with HT) where thyrotoxicosis was permanent and beta-blockers were ineffective, and ATDs were contraindicated due to low leukocyte levels and/or hepatic failure (increased ALT and AST levels). Additionally, similar to findings by Bohbot (2006) and Tran (2010) we observed two cases with a "three-stage evolution" from silent destructive thyroiditis to GO among group 1. Nevertheless, uncertainty remains since RIT is contraindicated in HT (beta-blockers were usually sufficient treatment), due to the very long course of the disease, over 1/2 year – phase of hyperthyroidism. RIT also does not apply in HT because of greatly reduced RAIU, however, are exceptional situations where it is particularly important for example in type 2 Amiodarone-induced thyrotoxicosis (AIT) (Czarnywojtek *et al.* 2009). In our study, the time needed for normalization

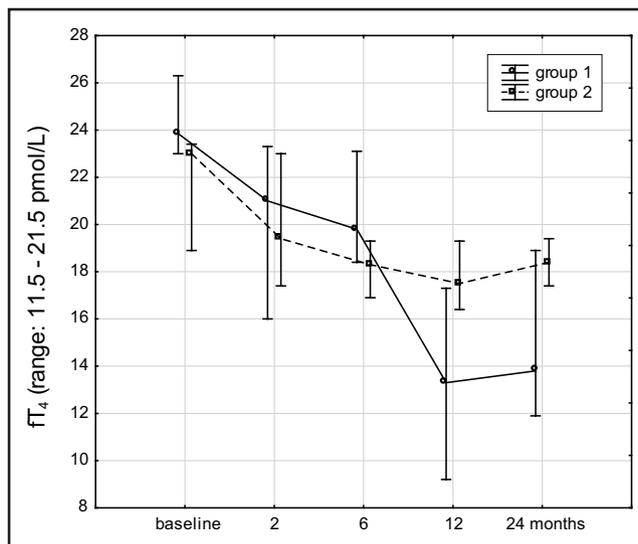


Fig. 1. Serum  $fT_4$  in patients with IH.

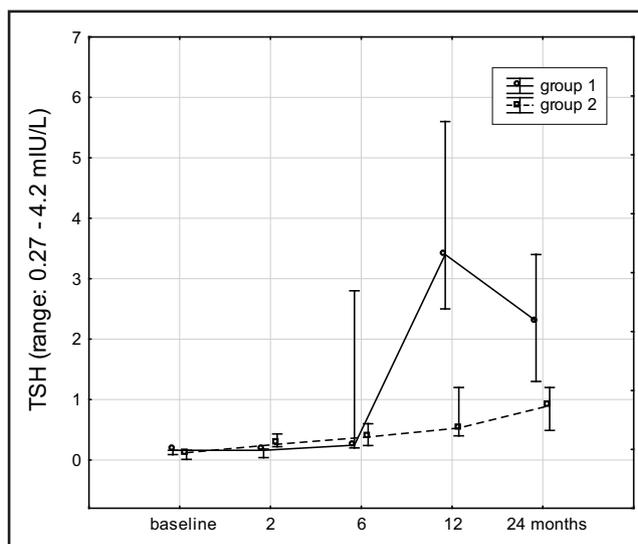


Fig. 2. Serum TSH in patients with IH.

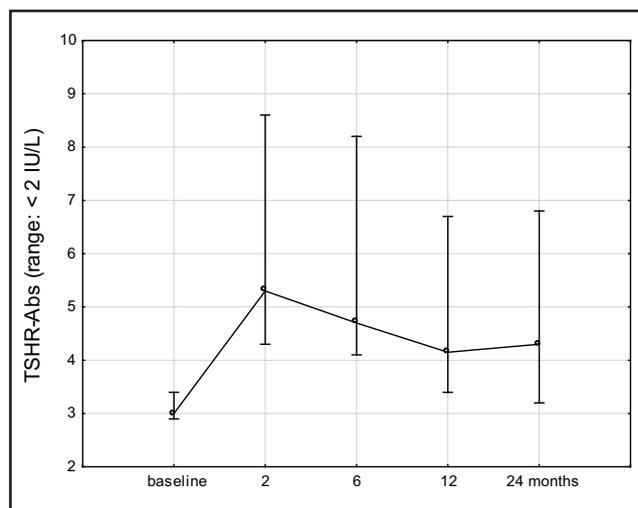


Fig. 3. Serum TSHR-Abs in CHC patients with GB disease (group 1).

**Tab. 3.** Proposed diagnostic and therapeutic algorithm of Interferon- $\alpha$ -Induced Hyperthyroidism compared with Amiodarone Induced Thyrotoxicosis.

|  | <b>Type 1, like type I Amiodarone Induced Thyrotoxicosis (AIT):</b><br>a. GT without TAO <sup>1</sup> ,<br>b. GT with TAO (mild or severe) | <b>Type 2 Destructive thyrotoxicosis, partially analogous to Type II AIT:</b><br>a. asymptomatic - silent thyroiditis,<br>b. symptomatic | <b>Type 3 Unknown etiology, partial analogy to Type III AIT - undefined or mixed</b> |
|--|--|--|--|
| <b>Diagnostic criteria</b>   |  |  |  |
| <b>Thyroid hormone</b>   | TSH↓, fT <sub>4</sub> ↑, fT <sub>3</sub> ↑   | TSH↓, fT <sub>4</sub> ↑, fT <sub>3</sub> ↑   | TSH↓,(-), ↑;fT <sub>4</sub> ↑, (-)↓; fT <sub>3</sub> ↑,(-),↓ <sup>2</sup>            |
| <b>TSHRabs</b>   | +  | (-)  | +/(-) <sup>2</sup>   |
| <b>TgAbs</b>   | ++   | ++/+/ - <sup>3</sup>   | +/(-)  |
| <b>TPOAbs</b>  | +  | +/(-)  | +/(-)  |
| <b>RAIU</b>  | ↑ or N   | ↓  | ↓↑   |
| <b>CFDS<sup>5</sup></b>  | increased vascularity  | decreased vascularity  | reduced or increased vascularity   |
| <b>Therapy for hyperthyroidism</b>   |  |  |  |
| "Wait-and-see"   | (-)  | (-)  | (-)  |
| L-thyroxin   | (-)  | (-)  | + <sup>4</sup>   |
| B-blocker drugs (tachycardia)  | +  | +  | +/(-)  |
| ATDs (when no contraindications):<br>- agranulocytosis<br>- trombocytopenia<br>- transaminasemia | +  | (-)  | +/(-)  |
| RAI*   | +  | (-)  | +/(-)  |
| Oral steroid prophylaxis after RAI   | +/(-)  | (-)  | +/(-)  |
| <b>Thyroidectomy - an existence of suspicious lesion</b>   |  |  |  |
| <b>INF-<math>\alpha</math> therapy<sup>6</sup> - continuous without interruption</b>             |  |  |  |

**Abbreviations:** <sup>1</sup>TAO - Thyroid Associated Ophthalmopathy, <sup>2</sup>during evolution - "biphasic" or "triphasic" form of thyrotoxicosis (Graves' hyperthyroidism may occur after a transient phase of destructive thyrotoxicosis or even following a period of hypothyroidism),

<sup>3</sup>thyroid autoantibodies are increased, especially thyroglobulin antibodies, <sup>4</sup>L-thyroxin used in case of hypothyroidism faze,

<sup>5</sup>CFDS - Color flow Doppler sonography pattern, <sup>6</sup> withdraw of therapy may be considered in cases of severe hyperthyroidism

**Diagnostic criteria:** "(+)" - present, "(-)" absence, "(↓)" - decrease, "(↑)" - growth

**Therapy for hyperthyroidism:** "(+)" - introduce, "(-)" - no therapy

\* RAI - in certain cases when ATDs are contraindicated

of TSH and fT<sub>4</sub> was shorter in group 1, although not significantly. RIT was a safe and effective method, and the most suitable in these clinical cases. In most it is a self-limiting disease, the effects of our treatment can not be compared with conventional RIT in typical GB not induced INF- $\alpha$ . However, while the lack of accurate data related to treatment with RIT, our results for ATDs used were consistent with previously described studies (Bohbot *et al.* 2006; Csaki & Blum 2000; Wong *et al.* 2002; Koh *et al.* 1997; Binaghi *et al.* 2002). As Bohbot *et al.* (2006) we obtained similar results in HT where the majority of cases were successfully treated with beta-block. Additionally, the problem remains whether to cease INF- $\alpha$  therapy during exacerbated hyperthyroidism; according to our observations there is no need to discontinue therapy. However, according with Carella *et al.* (1995, 2004) therapy may be discontinued for 2

to 3 months and RIT applied only in cases that involve intensification of thyrotoxicosis.

Our patients in group 2, had transient thyrotoxicosis with low RAIU and negative TSHR-Abs with spontaneous resolution of hyperthyroidism requiring only observation. The current study indicated that INF- $\alpha$  treatment can continue in the presence of destructive thyrotoxicosis controlled by beta-blockers, which was also observed by Carella (1995, 2001). Thyroid US displayed hypoechogenicity in destructive thyroiditis with reduced vascularity in color Doppler flow (Bogazzi *et al.* 1997; Schiemann *et al.* 2002; Ruchala & Szczepanek 2011; Ruchala *et al.* 2012). In our data we could not establish associations Abs(+) on thyroid disease before INF- $\alpha$  therapy because all patients had hyperthyroidism and positive titer of auto Abs(+). A review of published studies by Kohl *et al.* (1997) found that patients with

positive Topes before INF- $\alpha$  therapy were 10 times as likely to progression to thyroid dysfunction as those negative Topes patients (Carella *et al.* 1995; Deutsch *et al.* 1997; Carella *et al.* 2001). In our study, patients treated with IFN- $\alpha$  exhibit thyroid abnormalities in majority cases expressed as destructive thyrotoxicosis (80 cases) and in a minority of Graves' thyrotoxicosis (GT) with GO (26 cases). In the last cases we observed significant correlations ( $p < 0.001$ ) between TSH-RAB levels and  $fT_4$  values ( $r = 0.44$ ) and  $fT_3$  levels ( $r = 0.48$ ).

Our intention is to propose a treatment scheme for IIH that incorporates RAIU, TSHR-Abs and thyroid US vascularity, which could be implemented in the therapeutic process and would help in the choice of treatment (Table 3). This is a similar into Mandac *et al.* (2006) model and taking into account modifications according to Obołńczyk *et al.* (2007) and the scheme proposed by Carella *et al.* (1995, 2001, 2004). In addition contrasting features were previously described by Tran *et al.* (1993), but were presently modified to simplify therapeutic procedure. Additionally, in our new clinical categorization based on etiology (Table 3) we discern a certain analogy to Amiodarone-induced thyrotoxicosis (AIT) described by Bartalena *et al.* (1996). Type 1 AIT is associated with low, normal, and high 24 hour RAIU (Martino *et al.* 1987; Martino *et al.* 2001), a similar situation is observed in IIH, when there is elevated or normal levels of RAIU and TSHR-Abs in a majority of cases. Type 2 AIT patients exhibit a near zero RAIU, analogous to our cases with HT. Significantly lowered RAIU, no TSHR-Abs, and reduced vascularization in color Doppler flow can differentiate between both of types IIH.

To summarize, most patients with IIH present Hashitoxicosis, while minority of them develop Graves' disease. In a majority of patients with HT spontaneous remission of hyperthyroidism occurs. In patients with long-term hyperthyroidism, usually presenting GD, radioiodine therapy is an effective and well-tolerated treatment.

### Conflict of interest statement

The authors have no conflicts of interest, including financial and other relationships.

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