

# GRAVES DISEASE WITH TRANSITORY HYPOTIROIDISM DEVELOPED DURING THE THERAPY WITH PEGINTERFERON $\alpha$ 2A 180 $\mu$ g /WEEK AND RIBAVIRIN 1200 $\mu$ g/DAY IN THE TREATMENT OF THE CHRONIC ACTIVE VCH HEPATITES

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**Keywords:** Interferon alfa; chronic viral hepatitis VCH; thyroid gland; antithyroid antibodies; hypothyroidism; hyperthyroidism

**Abstract:** We present the case of a patient with active chronic hepatitis with C virus, in treatment with Peginterferon  $\alpha$  2A 180  $\mu$ g / week, whose thyroidian function was modified from hyperthyroidism initially to transitory hypothyroidism and next to hyperthyroidism. The patient of 45 years began his treatment with Peginterferon  $\alpha$  2A 180  $\mu$ g / week for chronic active hepatitis with hepatitis virus C in february 2005. The thyroid's function at the beginning of the treatment was normal, the antibodies anti-thyroid were absent. There weren't any pathological or heredo collateral personal antecedents of a thyroidal or autoimmune pathology. The patient develops hyperthyroidism at 3 months from the beginning of the therapy with Peg interferon  $\alpha$  2A, with the positivization of the antithyroid antibodies. The thyroidal scintigraphy reveals a value of 1,07% (Normal values = 0,5 – 3%). Later, the patient develops transitory hypothyroidism in 8 months from the beginning of the treatment and the intercurrance of the hyperthyroidism in January 2006. The transitory status of the hypothyroidism may be explained through two possible mechanisms: the complications induced by the destructive thyroiditis in the therapy with Peg interferon  $\alpha$  2A, respectively the variations between the levels of the anti-thyroid antibodies. A possible mechanism of passing in the phase of transitory hypothyroidism during the therapy with Peg interferon  $\alpha$  2A could be the complications in the destructive thyroiditis. The thyroid gland modifications appeared in the patient in the lack of an historical of thyroid gland pathology or positive antithyroid antibodies during the therapy with Peg interferon  $\alpha$  2A are rare. This aspect as well as the biphasic evolution of passing from hyperthyroidism in hypothyroidism and later back to hyperthyroidism represents the particularity of the presented case. Other studies will need the precise elucidation of the pathogenetic mechanism induced by the Interferon at the level of the thyroid.

**Cuvinte cheie:** Interferon alfa; hepatită cronică virală VHC; glanda tiroidă; anticorpi antitiroidieni; hipotiroidism; hipertiroidism

**Rezumat:** Prezentăm cazul unui pacient cu hepatită cronică activă cu virus hepatitic C, aflat în tratament cu Peginterferon  $\alpha$  2A 180  $\mu$ g / săptămână, a cărui funcție tiroidiană se modifică de la hipertiroidism inițial la hipotiroidism tranzitoriu și ulterior hipertiroidism. Pacientul de 45 ani a inițiat tratamentul cu Peginterferon  $\alpha$  2A 180  $\mu$ g / săptămână pentru hepatită cronică activă cu virus hepatitic C în februarie 2005. Funcția tiroidiană la inițiere a fost normală, anticorpii antitiroidieni absenți. Nu au existat antecedente personale patologice ori heredocolaterale de patologie tiroidiană sau autoimună. Pacientul dezvoltă hipertiroidism la 3 luni de la inițierea terapiei cu Peginterferon  $\alpha$  2A, cu pozitivarea anticorpilor antitiroidieni. Scintigrafia tiroidiană relevă o valoare de 1,07% (Valori normale = 0,5 – 3%). Ulterior, pacientul dezvoltă tranzitor hipotiroidism la 8 luni de la inițierea tratamentului și recurența hipertiroidismului în ianuarie 2006. Statusul tranzitor de hipotiroidism poate fi explicat prin două posibile mecanisme: complicațiile induse de tiroidita distructivă din cursul terapiei cu Peginterferon  $\alpha$  2A, respectiv variațiile între nivelurile de anticorpi antitiroidieni. Un posibil mecanism de trecere în faza de hipotiroidism tranzitoriu în cursul terapiei cu Peginterferon  $\alpha$  2A ar putea fi complicațiile din cursul tiroiditei distructive. Modificările tiroidiene apărute la pacient în absența unui istoric de patologie tiroidiană sau anticorpi antitiroidieni pozitivi în cursul terapiei cu Peginterferon  $\alpha$  2A sunt rare. Acest aspect precum și evoluția bifazică de trecere din hipertiroidism în hipotiroidism și ulterior înapoi la hipertiroidism reprezintă de altfel și particularitatea cazului prezentat. Studii ulterioare vor necesita elucidarea mai precisă a mecanismelor patogenetice induse de Interferon la nivel tiroidian.

## CASE PRESENTATION

The patient N.P., aged 45 years old, from the urban medium, was diagnosed with chronic active hepatitis with virus hepatitic C in march 2004. The patient has antecedents heredocolateral of a cardiovascular and hypertensive pathology, respectively ulcer disease, without the documentation of the thyroidian disease.

The personal pathologic antecedents document an

historic of ulcer pathology of approximately 20 years, for which follows a specific aleatory treatment. The ulcer disease is complicating in 1998 with an episode of superior digestive hemorrhage, externalized through hematemesis and melena, when the superior digestive endoscopy reveals the existence of a gastric ulcer. In this context, the patient is transfused with two units of integral blood.

The file for treatment with Peg interferon  $\alpha$  2A 180  $\mu$ g

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/ week and Ribavirin 1200 mg / day is done according to the protocol of april 2004. At this moment the hepatic biopsy is done and the result is quantificated in the score METAVIR: A1F1.

The patient receives the approval of treatment in February 2005.

The paraclinical investigations effectuated evidenciate the following:

- Hemoleucogram in normal limits (Hb = 13,8g %, Ht = 42 %, L = 7200 / UI, Neutrofiles = 54 %, Eosinophiles = 2,2 %, Basophiles = 0,4 %, Lymphocytes = 31,8 %, Monocytes = 9,2 %, Thrombocytes = 284.000 / UI);
- Minimal hepatocitolisis syndrome (TGO = 33 U/l și TGP = 58 U/l);
- Syndrom of coleastosis with FA = 170 U/l;
- Electrophoresis in normal limits (total proteins = 7,2 g/l with albumin = 3,9%);
- Syndrom hepatoprive absent;
- Coagulation in normal limit (TQ = 90 %, INR = 1,1);
- Ionogram in normal limits (Na = 137 mEq/l, K = 3,9 mEq/l);
- Viral Markers Ag HBs = negatives, Ac anti HCV = positives, ARN VHC = 1.560.000 UI/ml;
- The functional probes of the thyroid with TSH = 1,98 µg/ml, T3 = 4 µg/ml, T4 = 1,4 ng %, ATPO = negative;

At the moment of the beginning of the treatment of the patient presents values of TGP < 2 x VN, a viremi de 1.650.000 UI/ml, a normal thyroid function and the absence of the anti-thyroid antibodies.

The patient was treated according to the protocol of CNAS with Peginterferon  $\alpha$  2A 180 µg / week and Ribavirin 1200 mg / day.

Monthly, the patient was determined the HLG, TGO, TGP and TQ, TH, INR and trimestrial T3, T4, TSH, ATPO, respectively the viremia.

At three months from the beginning of the therapy, in may 2005, the patient is accusing at the re-evaluation palpitations, hot perspirations, ponderal loss and intolerance at heat.

The laboratory evaluations show us absent, normalization of the transaminases, simple leucopenia.

The thyroid function shows thyrotoxicosis phenomenon (T4 = 33 ng %, T3 = 8,4 pg %, TSH < 0,03 µg/ml, ATPO positive).

The thyroid ecography evidenciate an homogenous aspect, the increasing in volume of the thyroid gland with 24% in contrast with the obtained values at the initiation of the therapy, accentuated gland vascularisation.

Correlating the clinical and paraclinical data, the diagnosis of Graves disease is established.

The thyroid scintigraphy effectuated at a week after the diagnosis reveals a degree of captation of 1,08 %.

The patient was treated with Propranolol 40 mg / day since may 2005.

The patient symptomatology remits after approximately one month from the treatment with Propranolol, the patient needn't treatment with synthesis antithyroid .

From the 7-th month of treatment, the Peginterferon  $\alpha$  2A dose was reduced to 135 µg / week, due to the adverse effects at the hematopoietic system.

The patient suddenly developed a hypothyroidian status in october 2005, when the thyroid tests showed the TSH of 48,7 µg/ml and levels of T3 and T4 of 2,2 pg/ml respectively 0,78 ng/dl. ATPO maintained positive.

In January 2006, the patient's evolution is acquainted a

hyperthyroid intercurrance. The functional thyroid tests show a level of TSH < 0,03 µg /ml and high levels of T3 – 8,5 pg/ml and T4 – 3,03 ng%, ATPO positive.

**Table no. 1. The evolution of the thyroid function during therapy was the following**

Data	TSH	T3	T4	ATPO
February 2005	1,98	4	1,4	Negative
May 2005	< 0,03	6	2,86	Positive
June 2005	< 0,09	8,4	3,31	Positive
July 2005				Positive
August 2005	15,12	2,2	0,79	Positive
September 2005				Positive
October 2005	48,7	2,2	0,78	Positive
November 2005	18,21	3,0	1,04	Positive
December 2005		8,5		Positive
January 2006	< 0,03	8,5	3,03	Positive

At this moment the patient is treated with Metimazol 15 mg/day, since February 2006 until may 2006. Ulterior, the dose was reduced to 10 mg/day.

The values of TSH, T3, T4 are normalized in June 2006, when the dose of Metimazol was reduced to 5 mg.

The therapy with antithyroid hormones of synthesis was interrupted in September 2005, when the patient's status was era euthyroid, but kept the ATPO positive.

## DISCUSSIONS

The thyroid modifications appear in patients with chronic active hepatitis with HCV in treatment with Peg Interferon.

The mechanism of production of the thyroid modifications remains incompletely elucidated, but the mechanism auto immune is considerate to be main. Interferonul  $\alpha$  stimulates the expression of the antigens of the first class in the major histocompatibility complex, that activates functionally the cytotoxic cells T.

The damage of the activity of the major group of histocompatibility complex at the cellular surface in association with the cellular antigens may be sufficient for the antibodies induction. The cytokines such as TNF- $\alpha$  and IL- $\beta$  induced by the IFN  $\alpha$  may affect directly or indirectly the thyroid functions.

In the case we have presented, the euthyroid patient at the beginning of the therapy, passes next from the hyperthyroid status appeared at 3 months of therapy in the status of transitory hypothyroidism in the 10<sup>th</sup> month of therapy and ulterior, at the end of the therapy at the status of hyperthyroidism.

ATPO were positive from the third month of treatment with an increased tited increased in the periods of hyperthyroidism and moderately increased during the hypothyroidism phase.

More studies have shown a destructive thyroiditis secondary the therapy with Peg Interferon  $\alpha$  2A.

The particularity of the presented case consists of the thyroidal modifications appeared at a patient without any historical of thyroidal pathology or antithyroid antibodies positive during the therapy with cu Peg Interferon  $\alpha$ , also the biphasic evolution from passing from hyperthyroidism in hypothyroidism and ulterior back to hyperthyroidism.

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## CLINICAL ASPECTS

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