THYROID DYSFUNCTION IN PATIENTS WITH CHRONIC HEPATITIS B PRIOR AND AFTER THE THERAPY WITH PEGINTERFERON α 2A 180 µg

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Keywords: *Interferon-alfa; thyroid; chronic hepatitis B*

Abstract: *Objectives of the study: 1. Monitoring the evolution of 125 patients with chronic hepatitis B treated with Peginterferon α 2A, 180 µg/week, in order to establish the occurrence of thyroid disfunctions in the course of this particular treatment; 2. Finding correlations between patients' clinical and epidemiological parameters (age, gender, level of disease activity, the potential moment of infection and the occurrence of clinical and biological modification of the thyroid). Methods: The prospective clinical study was conducted on a sample of 125 patients with chronic hepatitis B, aged 18-65 years old. Study period: 6 years. Patient monitoring was performed by determining antithyroid antibodies to identify autoimmune thyroiditis, or TSH, T3 and T4, at the beginning of the therapy, and then quarterly. Results: Of 125 patients with chronic active hepatitis with HBV included in the study, 9.6% of patients had positive antithyroid antibodies at the end of therapy, 7.2% had changes of hypothyroidism and 1.6% hyperthyroidism change. Patients with hypothyroidism at the end of therapy had late positive antithyroid antibodies. Dose reduction of Peginterferon during therapy in the context of iatrogenic haematological changes in patients with positive antithyroid antibodies led to their disappearance. Regarding HBV chronic active hepatitis, there were no significant differences in thyroid dysfunction secondary to a weekly treatment with Interferon α therapy 2A 9 MIU x 3 / week. Patients should be monitored at least 6 months after treatment to prevent worsening of thyroid dysfunction. No significant differences were found on the occurrence of thyroid changes in HBeAg-positive to HBeAg-negative ones. Conclusion: The incidence of thyroid dysfunction in patients with chronic hepatitis B, in most studies, does not differ considerably from the native population.*

Cuvinte cheie: *Interferon alfa, tiroidă, hepatită cronică B*

Rezumat: *Obiectivele studiului: 1. Urmărirea evoluţiei pacienţilor cu hepatită cronică activă cu VHB, aflaţi în tratament cu Peginterferon α2A, 180 µg/săptămână, cu scopul de a stabili frecvenţa apariţiei disfuncţiilor tiroidiene în contextul tratamentului specific; 2. Stabilirea de corelaţii între parametrii clinici şi epidemiologici ai pacienţilor (vârstă, sex, gradul de activitate al bolii, posibilul moment infectant şi apariţia modificărilor tiroidiene clinice şi paraclinice). Metodologie: Am realizat un studiu observaţional prospectiv pe un lot de 125 pacienţi cu vârste cuprinse între 18–65 ani, diagnosticaţi cu hepatită cronică activă cu VHB. Pacienţii au provenit din clinica şi ambulatorul Spitalului Clinic de Urgenţă Sibiu. Durata studiului: 6 ani. Monitorizarea pacienţilor s-a realizat prin determinarea anticorpilor antitiroidieni în vederea identificării tiroiditei autoimune, respectiv TSH, T3 şi T4 pentru cea a disfuncţiilor tiroidiene în momentul iniţierii terapiei, apoi trimestrial. Rezultate: Din cei 125 de pacienţi cu hepatită cronică activă cu VHB incluşi în studiu, 9,6% din pacienţi au prezentat anticorpi antitiroidieni pozitivi la sfârşitul terapiei; 7,2% au prezentat modificări de hipotiroidism şi 1,6% modificări de hipertiroidism. Pacienţii cu hipotiroidism la finalul terapiei au avut pozitivări tardive ale anticorpilor antitiroidieni. Scăderea dozei de Peginterferon în cursul terapiei, în contextul modificărilor hematologice iatrogene la pacienţii cu anticorpi antitiroidieni pozitivi, nu au condus la dispariţia acestora. În ce priveşte hepatita cronică activă cu VHB, nu există diferenţe semnificative ale disfuncţiilor tiroidiene secundar tratamentului în administrare săptămânală faţă de terapia cu Interferon α 2A, 9 MUI x 3 / săptămână. Se impune monitorizarea pacienţilor după tratament minim 6 luni pentru prevenirea agravării disfuncţiei tiroidiene. Nu s-au constatat diferenţe importante privind apariţia modificărilor tiroidiene la pacienţii cu AgHBe pozitiv faţă de cei cu AgHBe negativ. Concluzii: Incidenţa patologiei tiroidiene la pacienţii cu hepatită cronică activă cu VHB, conform majorităţii studiilor, nu diferă în mod semnificativ faţă de populaţia nativă.*

INTRODUCTION

The correlation between liver pathology induced by hepatic viruses and autoimmune thyroid pathology is relatively well documented in the international literature. However, most of this literature correlates the effect of hepatitis C virus within the context of thyroid autoimmune modifications followed or not by thyroid dysfunctions. Thus, if we were to quote some of these studies, they demonstrated well enough these correlations in varying proportions, depending on the ethnic specificity.(1,3,6,10,11,12,13)

The situation is different in the case of the B virus, with few studies and uncorrelated with the antibody-antigen

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complex. There are also few studies comparing the two types of viruses involved - B and C - with thyroid pathology.(5,6,12)

The study of the increased incidence of autoimmune thyroiditis and thyroid dysfunctions in patients with chronic active hepatitis B treated with Peginterferon α2A, 180 mg / week was also of great interest.

PURPOSE

Within the study, I followed up 125 patients with chronic active hepatitis with HBV treated with Peginterferon α2A, 180 mg / week.

Study objectives were the following:

1. Assessment of the incidence of thyroid dysfunctions in the patients with chronic active hepatitis with HBV treated with Peginterferon α 2A 180 mg.
2. Correlation of the incidence of thyroid phenomena with hepatocytolisis, viremia and HBeAg-Ac antiHBe complex.
3. Assessing the gravity of thyroid changes and their influence on the therapy with Peginterferon α 2A 180 mg.

METHODS

Between 1 January 2005 and 1 January 2010, I conducted a prospective clinical study in a group 125 patients with chronic active hepatitis with HBV treated with Peginterferon α2A, 180 mg / week. The inclusion and exclusion criteria coincide with the inclusion criteria in the treatment with Peginterferon α 2A 180 mg.

Gender distribution of the study group revealed a sex ratio of 1.7 (60 women, respectively 48% of the group and 65 men, respectively 52% of the batch).

Age limits were between 18 and 65 years old, among which we identified 3 sub-groups: 18-35 years old, 36-50 years old, 51-65 years old. Most of the patients (43.2%) belonged to the sub-group of 36-50 years old. These age limits were imposed by the current treatment criteria of the National Commission for the treatment of chronic active hepatitis. The patients were monitored upon the initiation of the treatment by determining the baseline transaminases, complete blood count, coagulation and the TSH, T3, and T4 levels. It was also documented the presence/absence of antithyroid antibodies. Identification test in serum of HBs antigen was made through ELISA method. The HBeAg-Ac antiHBe complex was determined with a view to specify the stage of disease activity and the presence of the mutant virus that does not synthesize HBeAg.

The determination of viremia was achieved by real-time PCR method. The criteria in the case of viremia were those of inclusion in the treatment, according to the Health Insurance House protocol. Liver biopsy followed the necroinflammatory activity. The onset of symptoms was noted down, as well as the time of diagnosis, the way of detecting the viral infection, epidemiological investigation and the establishment of the possible infection moment. Every three months, the level of transaminases was determined, as well as the antityroid antibodies, TSH, T3, T4. The diagnosis of thyroiditis was based on clinical data, laboratory investigations, namely the presence of thyroid antiperoxidase antibody. The diagnosis of hypothyroidism, respectively of hyperthyroidism was established by correlating the clinical data with the hormonal dosages (T3, T4, TSH).

For each patient, a clinical case presentation has been performed, highlighting diagnostic features, evolution and treatment.

RESULTS

Of 125 patients, 29 (23.20%) had HBeAg. Of these, 13 patients were males and 16 females. The 96 (76.80%) patients who showed no HBeAg 44 were females and 52 males. There was a predominance of HBeAg-negative cases.

Regarding the SGPT value, most patients, respectively 60.80% had values between 2-5 x normal value, 21.6% had normal values and 17.6% had values greater than 5 x normal value.

The above-mentioned percentage has a practical component part, the patients with chronic active hepatitis with HBV included in treatment having the SGPT level 2 times greater than the normal value. The patients with normal SGPT values presented on liver biopsy increased necroinflammatory score that allowed the inclusion in the treatment.

Viremia was of < 100.000 children / ml in 48 (38,4 %) patients and of > 100.000 children / ml in 77 (61,6 %) patients.

Antithyroid antibodies were present upon the initiation of the treatment in only 6 (4.8%) patients, only one female with HBeAg-positive, while the majority of patients, that is in 119 (95.2%) patients, these were absent. Given the small number of patients, we cannot establish a correlation between the existence of HBeAg and the autoimmune thyroid pathology before starting the treatment with Pegylated interferon.

Regarding the antithyroid antibody measurements, performed every three months, these were present in 9 (7.2%) patients and absent in a number of 116 (92.8%) patients. Of these 9 patients, 5 were females and 4 males. 3 patients were between 36-50 years old and the remaining 6 patients were between 51-65 years old.

After treatment, antithyroid antibodies continued to be absent in most patients, respectively 113 (90.4%) and present in only 12 (9.6%) patients, with 3 patients more than three months ago.

I considered useful the correlation between viremia and the presence of antithyroid antibodies, whereas monitoring protocol no longer considers appropriate the three-month measurement, taking into account the different response of the virus to interferon therapy against hepatitis C. At the end of therapy, I have documented the existence of 12 cases with positive antithyroid antibodies.

Upon the initiation of treatment, only 3 (2.4%) patients experienced hypothyroidism, the remaining 122 (97.6%) patients did not present thyroid hypofunction.

After the treatment, the number of patients with hypothyroidism increased from 3-9, of which 6 female patients and 3 males, meaning an increase in the percentage of 4.8%, the proportion of patients without hypothyroidism decreasing from 97.6 % to 92.8%.

When initiating the treatment, no patient had thyroid hyperfunction.

After treatment, hyperthyroidism was present in 2 (1.6%) patients, of which one male and one female in the age group of 18-35 years old and 51-65 years old, the evolution of one patient was towards severe hypothyroidism with myxedema and coma requiring the discontinuation of the treatment. In the case of the second patient, hyperthyroidism had an easy to moderate form and did not require therapeutic intervention.

I could not make references to similar data in the Romanian literature because of the poor bibliographic data. As a result, I preferred to make references to the international literature with all the variations given by the different ethic groups and the genomic distributions of hepatitis B virus at global level.

CONCLUSIONS

1. Of 125 patients with chronic active hepatitis with HBV included in the study, 12 (9.6%) had positive antithyroid antibodies (ATPO) at the end of therapy.

2. Of 125 patients with chronic active hepatitis with HBV, at the end of the therapy 9 patients (7.2%) had changes of hypothyroidism and 2 (1.6%) changes in hyperthyroidism.
3. The patients with hypothyroidism at the end of therapy had late positive antithyroid antibody (the last 6 months of treatment).
4. Dose reduction of Peginterferon α 2A during therapy in the context of iatrogenic hematological changes in the patients with positive antithyroid antibodies did not lead to their disappearance.
5. Regarding HBV chronic active hepatitis, there were no significant differences in thyroid dysfunction secondary to the treatment with Peginterferon α 2A 180 mg on weekly administration against Interferon α 2A 9 MIU x 3 / week.
6. Patients should be monitored at least 6 months after treatment to prevent worsening of thyroid dysfunction.
7. There were no statistically significant differences on the occurrence of thyroid changes in the patients with chronic active hepatitis with HBV and HBeAg-positive as against those with HBeAg-negative.

General conclusions: The incidence of thyroid pathology in patients with chronic active hepatitis with HBV, according to most studies, does not differ significantly from the native population.

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