THYROIDIAN DYSFUNCTIONS AT THE PATIENTS WITH CHRONIC ACTIVE HEPATITIS WITH HVB AND HVC PREVIOUSLY AND AFTER THE TREATMENT WITH PEG INTERFERON α 2A 180 µg

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Abstract: *The fundamental idea and the objective of this observational study were the optimisation of the treatment with Peginterferon α 2A administrated weekly to the patients with chronic active hepatitis with hepatitic virus B and C and the co-existance of thyroid dysfunctions. During the interval 1st of January 2005 - 1 January 2010 we followed 2 lotes of patients: 115 patients with chronic hepatitis with HVC, in treatment with Peginterferon α2A in a dose of 180 µg / week associated with Ribavirină in a daily dose, correlated with the weight, respectively 125 patients with chronic hepatitis with HVB in treatment with Peginterferon α2A in a dose of 180 µg / week, with the aim of establishing the frecquency of apparition of the thyroid dysfunction in the context of the specific treatment.Concomitantly, it has been pursued the establishing of age correlations, the sex correlations, the degree of activity of the disease,the possible moment of the infestation and the apparition of the clinical and paraclinical thyroid modifications.*

Cuvinte cheie: *disfuncţie tiroidiană, hepatită cronică, VHB, VHC*

Rezumat: *Ideea fundamentală şi obiectivul acestui studiu observaţional au fost de a optimiza tratamentul cu Peginterferon α 2A administrat săptămânal pacienţilor cu hepatită cronică activă cu virus hepatitic B şi C şi concomitenţă de disfuncţii tiroidiene. În intervalul 1 ianuarie 2005 - 1 ianuarie 2010 am urmărit două loturi de pacienţi: 115 pacienţi cu hepatită cronică cu VHC, aflaţi în tratament cu Peginterferon α2A în doză de 180 µg / săptămână asociat cu Ribavirină în doză zilnică, corelată la greutate, respectiv 125 de pacienţi cu hepatită cronică cu VHB aflaţi în tratament cu Peginterferon α2A în doză de 180 µg / săptămână, cu scopul de a stabili frecvenţa apariţiei disfuncţiilor tiroidiene în contextul tratamentului specific. Totodată, s-a urmărit stabilirea de corelaţii între vârstă, sex, gradul de activitate al bolii, posibilul moment infectant şi apariţia modificărilor tiroidiene clinice şi paraclinice.*

INTRODUCTION

There is an extremly complex relationship between the thyroid gland and the liver also in the healthy persons and in the different stage ill persons.The tiroxine and the triiod thyronine that regulates the methabolism of the uncountable cells and implicitely of the hepatocytes.A thyroidian dyfunction may compromise the hepatic function and vice versa a hepatic affection may influence the hormone methabolismul of the thyroid gland.

Peginterferon α determines dysfunctions of the thyroid function in 3-5% of the cases, regarding the degree of fibrosis. The development of antithyroid antibodies or a high titled are observed frecquently during the treatment with Peginterferon α, being an indicator for the existence of the imunologic mechanisms at the origin of the thyroidian dysfunction.

OBJECTIVE

The fundamental idea and the objective of this observational study were the optimisation of the treatament with Peginterferon α 2A administrated weekly to the patients with chronic active hepatitis with hepatitic virus B and C and the co-existance of thyroid dysfunctions.

MATERIAL AND METHOD

During the intervalul 1st of January 2005 - 1 January 2010 we followed 2 lotes of patients: 115 patients with chronic hepatitis with HVC, in treatment with Peginterferon α2A in a dose of 180 µg / week associated with Ribavirină in a daily dose, correlated with the weight, respectively 125 de patients with chronic hepatitis with HVB in treatment with Peginterferon α2A in a dose of 180 µg / week, with the aim of establishing the frecquency of apparition of the thyroid dysfunction in the context of the specific treatment.Concomitantly, it has been pursued the establishing of age correlations, the sex correlations,the degree of activity of the disease,the possible moment of the infestation and the apparition of the clinical and paraclinical thyroid modifications.

RESULTS

The incidence of the thyroidian pathology in patients with chronic active hepatitis with HVB, according to the majority of the studies, it isn't significantly different comparatively with the simple (healthy) population. In this context,we have evaluated the patients at the beggining of the therapy, through the determination of the antithiroid antibodies in order to identify the autoimmune thyroiditis, respectively TSH, T3 and T4 for the thyroidian dysfunctions. We have observed the presence of the antithyroid antibodies in 2 patients – one - female and another male, both patients with positive Hbe Ag. Considering the reduced number of patients,we can not establish a correlation between the existence of th Hbe Ag and the autoimmune thyroid pathology before beggining the treatment with Interferon Pegilat. We have monitored the values of TSH, T3, T4. The determination of the antithyroid antibodies T3 and T4 was done quarterly. The first determination, effectuated at 3 months of treatment revealed the existence of 9

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patients with positive antithyroid antibodies. Those 9 patients were 6 females and 3 males. 2 patients had between 18 – 35 years, 4 between 36 – 50 years and the rest of 3 patients had between 51-65 years. 6 presented positive HBe Agp and 3 negative HBe Ag.

We haven't considered useful the correlation between viremia and the presence of the antithyroid antibodies, since the monitorization protocole doesn't include the determination at 3 months, regarding the answer of the virus to the therapy with Interferon different from the hepatitis C virus. At the end of the therapy we have observed the existence of 12 cases with positive antithyroid antibodies, at 3 more patients in contrast with the previous situation at three months.

In what regards the thyroid dysfunctions, at the beggining of the treatment there weren't any modifycations of the thyroid function. In 3 months from the begging of the treatment the thyroid dysfunction was present at only one patient –a female, from the age range 51 – 65 years, whose rapid evolution to severe hypothyroidism with mixedem and coma neccessitated the interrupting of the treatment.

At the end of the therapy, we have revealed the existence of a patient with simple to moderate hyperthyroidism that didn't neccessitate the therapeutical intervention.

We couldn't find any similar studies from the specialty literature from România, because of the insufficient bibliographic sources. In consequence, we prefered to retrospect to studies from the international specialty literature, with all the variations given by the different ehtnice groups and by the genomical distribution of the hepatitis virus B at a global level.

There have been reported varied modifications of the thyroidian dysfunctions during therapy with products such as Interferon in patients with chronic active hepatitis with HVC.Among those hypothyroidism appears more frequently, followed by the autoimmune thyroiditis and by Graves disease. The mechanisms of action through whitch the Interferon induces thyroidian dysfunctions remains incompletely known and understood, but the most important role seems to attributed to the autoimmune component.

The first studies where were observated this kind of modifications were done since the introduction of the Interferonului α2A, respectively α2B in the treatment of the chronic active hepatitis with HVC, especially from the end of 80's, to the beggining of the 90's. The results were often contradictory in comparative studies, but we have to mention the fact that the therapy evoluated relatively quickly, as a dosage and rithm of administration, where from appeared differences.

It followed the introduction in the therapeutic phase of the Interferon Pegilat, with its main advantage, the effect on long term and the prolonging of the half life to 15 – 40 hours.

In addition to the superior therapeutic effect towards the one in the therapy with simple Interferon, appeared new preocupations regarding the possible autoimmune residual effects among the therapy.

The resultats were concludent from the point of view of the incidence of the thyroid modifications, although meaningfully different in size in the varied geographical area. There existed even studies that have done the passage from the therapy with clasic Interferon to the one with Peginterferon. Thus, Nasser, 2004, in a study effectuated on a lote with 245 patients, part of which treated with Interferon α2A, 9 MUI x 3 / week and the rest with Peginterferon α2A, 180 μg / week, report a cummulated percentage of 15,9 % thyroidian dysfunctions, with the mention that in the lote treated with Peginterferon α2A their percentage rises to 25 %.

In our study, we have followed the evolution of 115 patients with chronic active hepatitis with HVC, in treatment with Peginterferon α2A, 180 μg /week and Ribavirină in a dose adaptated to the weight.

For a better homogenize of the results,we haven't taken in the study the patients treated with Peginterferon α2B, those being the only forms of Interferon Pegilat existent on the market in România at present.

We have remarked since the begging the bigger incidence (statistically meaningful) before the inception of the therapy of the antithyroid antibodies in the studied lote in contrast with the population without viral hepatic pathology.

Thus,11 patients presented at the begging antithyroid antibodies, representing 9,6 %. Among them, 8 were females and 3 males.

Ulteriorly, during treatment, the number of the patients that had antithyroid antibodies increased progresivelly, being 18 patients in 3 months, respectivelly 21 patients at the end of the treatament. It has been noticed that the majority of the patients that have developed autoimmune chronic thyroiditis at the end of the treatment had antithyroid antibodies present in the first 3 months. Also, it was observed a predominance of the cases in females (14 din 18).

The last determination of the antithyroid antibodies was effectuated at the end of the therapy. The monitorization post treatment is in progress, so we cannot appreciate yet the extension in time of the autoimmune chronic thyroiditis.

Concomitantly, the evaluation of the TSH, T3 and T4 at the beggining of the treatment distinguished the existence of a number of 2 patients with hypothyroidism and the absence of the hyperthyroidism. Both patients with hypothyroidism were females.

During treatment, the number of patients with hypothyroidism increased, as at the final of the therapy a number of 9 cases were numbered, among which 6 females and 3 men.

Once again was remarked the prevalence of the females. The majority of the cases were of medium and simple hypothyroidism.

There has been a case of female, aged 48 years, patient with antithyroid antibodies present at the beggining of the treatment, also with simple hypothyroidism, whose evolution under the treatment with Peginterferon α2A was to a mixedem coma, the patient necessitating specialty treatment in the unit of intensive care.

In what regards the cases of hyperthyroidism, absent at the begging of the treatment, we had 2 cases at the end of the treatment, a female patient and a male one.

In conclusion, the thyroidian events manifestated on the whole with an incidence of 9,5% in the case of our study (thyroiditis, hypo – and hyperthyroidism), situating us in percentage between the limits of the studies performed at an european level. Unfortunately, there aren't any new data in the romanian specialty literature that allowes us to effectuate comparations on the same populational lote.

Thyroid dysfunctions induse by Interferon are known cunoscute since 1985 (Fentiman et al 1985.) and they count among the most frequent complications determined of the Interferon treatment.

DISCUSSIONS

Based on the epidemiological characteristics of the thyroiditei determined by the Interferon, we have considered useful the classification of the thyroiditis in the thyroiditis determined by the Interferon in the autoimmune context and the thyroiditis determined by the Interferon in non-autoimmune context. The autoimmune one may manifest as Graves disease, Hashimoto thyroiditis or as a production of antithyroid

antibodies without any clinical manifestations, while the thyroiditis determined by Interferon non-autoimmune may manifest as a destructive thyroiditis or as a non-autoimmune hypothyroidism.

The thyroiditis determined by the Interferon in autoimmune context presents the Hashimoto thyroiditis being the most common clinical manifestation.

The presence of the antithyroid antibodies at the begging of the therapy with Interferon is a risk factor for the developing of a thyroiditis determined by Interferon in an autoimmune context, manifestated as a Hashimoto thyroiditis. Roti and the colaborators proved high levels of antithyroid antibodies before the therapy with Interferon have a predictive positive index of 67% for developing an clinical manifest autoimmune pathology. This fact suggests a genetically predisposition for developping an autoimmune thyroiditis induced by Interferon.

Because the immune mechanisms plays an important role in developping the thyroiditis determined by the Interferon, the predilection for the thyroid gland and the non-autoimmune manifestation of the thyroiditis determined by Interferon suggests that the direct effect of Interferon α on the thyroid plays a major role in the ethiology of the thyroiditis induced by Interferon.

The predilection of the autoimmune effects of the Interferon on the thyroid and the apparition at approximativelly 50% of the cases of the thyroiditis induced by Interferon non-autoimmune suggests fermly that Interferon exerts direct effect on the thyroid.

Few studies investigated the direct effect of the Interferon on the thyroidian cell. It has been demonstrated that Interferon inhibits the genic expression of the thyreoglobulin induced by TSH in the crop of human thyroidian cells.

More than that,it has been proven an increasing of the thyroidian cells death induced by the Interferon α. Combinated, these data proves a toxic effect directly of the Interferon on the thyroidian follicular cells. This effect may explain the non-autoimmune manifestations of the thyroiditis induced by the Interferon.

So long the thyroiditis induced by Interferon may produce severe forms of hypo- or hyperthyroidism at present is recommended that all patients in therapy with Interferon α to have determined the level of the TSH at the begging of the therapy and repeating it at regular time interval.

If the level of the TSH is normal and the antithyroid antibodies are negative, the levels of the TSH must be monitorized quarterly untill finishing the therapy with Interferon. If the TSH levels are normal but the levels of the antithyroid antibodies are positive, we recommend the monitorization of the TSH monthly, taking in consideration the higher probability of developping a clinical manifested thyroidian pathology. Currently, there are no tests that may predict the developping of the thyroiditis induced by Interferon.

In conclusion, we can say that the infection with C hepatitic virus is more probably a factor of risk for thyroiditis, autoimmune but also non-autoimmune.

The Interferon may determine thyroiditis through at least 2 mechanisms:

- Imunological disorder, consisting in the activation of the T cells, which at the individuals with genetic predispozition will unleash autoimmune thyroidian pathology
- Direct thyroidian toxic effect, with the consequence the inflammatory thyroidian reaction, that at the fellows with a genetical predispozition may determine autoimmune thyroidian pathology.

CONCLUSIONS

There is a meaningful statistically diference between the apparition of the antithyroid antibodies after the therapy with Peginterferon α2A, 180 µg in weekly administration, associated with Ribavirină, in patients with chronic active hepatitis with HCV (21 cases from 115 pursued cases) patients with chronic active hepatitis with HBV treatated with Peginterferon α2A, 180 µg in weekly administration (18 cases from 125 pursued cases).

As a consequence of the study's results, the recommendation is of monitorization of the ATPO, TSH, T3, T4 at the patients with chronic active hepatitis with HCV at the begging of the therapy, periodically, preferably at 3 months.

Also it is useful the monitorization of the anti HCV antibodies in patients diagnosed with chronic autoimmune thyroiditis.

The monitorization of the patients is necessary post treatment, minimal for 6 months, for preventing the aggravation of the thyroidian dysfunction.

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