Research Article

Effects of Interferone Therapy for Chronic Hepatitis C Virus Infection on Thyroid Functions in Egyptian Patients

Mohamed Helaly[*], Gamal Shiha, Mohamed Yakoot and Ibrahim Abdel Aal

Faculty of Medicine, Mansoura University, Egypt

*Corresponding author e-mail: helaly70@hotmail.com

ABSTRACT

Chronic hepatitis C virus infection (HCV) is a common health problem. Before the advent of the direct acting anti-viral treatment, the only approved treatment of HCV was the combined Interferone α (INF-α) and ribavirin. Unfortunately, INF-α had a limited success rate and many side effects including thyroid dysfunction in the form of hypothyroidism, hyperthyroidism or silent auto-antibodies production. This study was done on 60 patients (42 males and 18 females) with HCV –related chronic hepatitis receiving treatment in the form of combined pegylated Interferone and ribavirin with a mean age of 46.37 ± 12.97 years, and 24 age and sex matched healthy controls. Thyroid function tests and serum chemokine 10 (IP 10) were done for all patients before starting treatment, after 6 months and after one year. We found that IP 10 level was higher in patients than control subjects, and it progressively increasing during treatment. On the other hand, thyroid stimulating hormone (TSH) level tended to decrease during treatment.

Keywords: Chronic hepatitis C virus, Interferone, Thyroid functions

INTRODUCTION

Egypt has the highest prevalence rate of HCV infection in the world, making it the most challenging public health problem facing the country. Studies have showed that 4.7% of the Egyptian population carries HCV antibodies and 9.8% have an active infection[1]. Liver mortality in Egypt reached 40,000 per year making 10% of total mortality, and comes second after heart

diseases[2]. Thyroid dysfunction represents one of the commonest endocrine manifestations of chronic hepatitis C infection (HCV), exacerbated by Interferone based treatments. Changes in thyroid function are common side effects occurring during antiviral therapy with Interferone alpha (INF-α). In this way, the spectrum of thyroid diseases ranges from the production of isolated anti-thyroid antibodies to dysfunction such as hypothyroidism, Graves' disease (GD), and destructive thyroiditis[3]. The issue of INF-α related thyroid dysfunction has been widely investigated in patients with HCV hepatitis. Despite previous studies reporting that the risk for developing thyroid dysfunction during INF- α therapy that the risk for developing thyroid dysfunction during INF-α therapy is closely related with mixed HCV genotype infection and lower HCV RNA levels, female gender, pretreatment positivity for thyroid antibodies (particularly thyroid peroxidase (TPO) Ab) and a hypoechoic pattern of the thyroid gland at ultrasound, none of the above features has enough specificity and sensitivity to reliably predict the occurrence of thyroid dysfunction[4].

Aim of the work

Is to evaluate thyroid functions in patients with chronic hepatitis C virus (HCV) infection before, during and after combined Interferone alpha and ribavirin therapy.

Subjects and Methods

This observational, prospective and longitudinal study was carried out on 60 patients (42 males and 18 females) with HCV related chronic hepatitis receiving treatment in the form of combined pegylated Interferone and ribavirin with a mean age of 46.37 ± 12.97 years, and 24 age and sex matched healthy controls.

All patients received a course of IFN-α at doses 180 µg once weekly s.c. for one year. Patients were selected from a population of chronic HCV patients treated with combined recombinant IFN-α at the outpatient clinic of hepatology – Specialized Medical Hospital – Mansoura University.

This study was done before the advent of new direct anti-viral drugs[5]. All patients were treated according to the previous national Egyptian guidelines using approved drugs during that time including Interferone, ribavirin[6].

Exclusion criteria

We exclude patients with evident thyroid disorders before treatment, patients with HIV, hepatitis B virus co-infection, and patients with past history of thyroid disorders.

All patients were subjected to full explanation about the study design and explained to all participants, and an informed written consent was obtained at study entry and approved by Mansoura Faculty of medicine ethical committee. This study was conducted during the period between November 2013 till November 2014 with regular follow up till the end of therapy.

All patients were subjected to full history taking with stress upon symptoms related to

chronic liver disease (e.g. abdominal enlargement, jaundice, edema lower limbs) and symptoms related to thyroid dysfunction (such as sweating, weight gain or loss, palpitation.). All patients were subjected to complete clinical examination with stress upon body mass index (BMI), thyroid examination, abdominal and other systems examination. All patients were subjected to the following laboratory tests: complete blood count (CBC), liver function tests, kidney function tests, polymerase chain reaction (PCR) for HCV RNA quantitative testing via agarose gel electrophoresis, thyroid releasing hormone (TSH), and serum chemokine ligand 10 (CXCL) measurement by a quantitative sandwich immunoassay.

All participants were subjected to all these laboratory tests before starting Interferone therapy, after 6 months and at the end of therapy.

RESULTS

Data presented in Table 1 showed that was no significant difference between cases and control groups regarding age, sex distribution and BMI.

Data presented in Table 2 showed that before starting treatment with Interferone-ribavirin combination; IP-10 level was higher in cases than control subjects, while there is no statistically significant difference between them regarding TSH level.

Data presented in Table 3 showed that IP-10 level was higher after 6 and 12 months of treatment with Interferone-ribavirin combination compared with its level before starting treatment, but there is no significant

difference in its level between 6 and 12 months.

TSH tended to decrease mildly with treatment after 6 and 12 months of treatment in comparison to basal level; and its level is lower at 12 months than that at 6 months.

DISCUSSION

IFN-α based therapy for chronic HCV infection may induce thyroid changes or dysfunction in 2.5 to 20% of treated patients. Almost all side effects of IFN-α treatment are due to its effects on the immune system, and data suggest that in addition to its immunomodulatory mechanism, it also precipitates thyroiditis by direct thyrotoxicity[7].

Chemokines are a family of cytokines that induce a chemotaxis of different leucocyte subtypes, among chemokines of the CXC family, CXC chemokine ligand 10 (CXCL 10) plays an important role in several human autoimmune and non-autoimmune disease included chronic autoimmune Hashimoto's thyroiditis (HT), Grave's disease (GD) and HCV related hepatitis[8].

Because the symptoms of hypothyroidism such as fatigue, hair loss, myalgia, and weight gain may be attributable to hepatitis C or IFN-α therapy, the diagnosis of hypothyroidism in these patients may be delayed. This delay may lead to development of further complications. Thus, Interferone induced thyroiditis is a major problem for patients who receive Interferone therapy[9].

In our study IP 10 (CXCL 10) before treatment was higher in cases than control group, and its level became progressively higher after 6 months and 1 year respectively. Carella et al.[10] said that; the development of overt thyroid dysfunction in the course of IFN α therapy is associated with significantly lower serum levels of CXCL 10, both before and during the treatment. This finding seems particularly relevant as it suggests that pretreatment serum levels of CXCL10, previously proven to have a predictive value for a favorable response to IFNα, could also be useful to identify patients more prone to develop thyroid dysfunction during IFN α treatment for HCV hepatitis. The clinical importance of such finding stems from the fact that the difference in serum CXCL10 levels between patients who did or did not develop IFN α-associated thyroid dysfunction was evident before starting IFN α therapy. This would imply that serum CXCL10 measurement would allow identifying those patients in whom thyroid surveillance during IFN α therapy should be more careful. Prompt diagnosis and early treatment of IFN α associated thyroid dysfunction will be helpful to limit the necessity of stopping IFN α therapy[10]. The above findings would suggest that measurement of CXCL10 in serum of HCV patients before IFN α therapy might predict the development of an autoimmune thyroid dysfunction and amelioration of the liver disease[11].

CONCLUSION

In our study, we found a tendency towards decrease in serum TSH levels from pre-treatment with IFN α therapy, after 6 months and after one year of treatment progressively, which means a tendency to be hyperthyroid although not developing clinical manifestations of hyperthyroidism. Indeed, the previous studies gave conflicting results; some of them said that combined IFN α and ribavirinn therapy can lead to hyperthyroidism, others have suggested that it can cause hypothyroidism, while others suggest development of auto-immune antibodies without clinical disease[12,13]. However, other studies have suggested that the most common thyroid disorder during combined IFN α and ribavirinn therapy is the development of thyroid antibodies without clinical disease[14].

LIMITATIONS OF STUDY

Is the small sample size, so we need a larger study for sub-group analysis and confirmation of our results?

REFERENCES

1. Esmat G., Hepatitis C in the eastern Mediterranean region. Eastern Med Health J 2013; 19: 7.
2. El-Sayed M., Manual, P. The new national strategy on viral hepatitis. Al-Ahram Sci Club 2014.
3. Tomer Y., Menconi F., Interferone induced thyroiditis. Best Pract Res Clin Endocrin Metab 2009; 23: 703-712.
4. Carella C., Mazziotti G., Morisco F., et al. Long-term outcome of Interferone-alpha induced thyroid autoimmunity and prognostic influence of thyroid autoantibody pattern at the end of treatment. J Clin

Endocrin Metab 2001; 86: 1925-1929.

5. Poordad F., Dieterich D., Treating hepatitis C: Current standard of care and emerging direct antiviral agents. J Viral Hepat 2012: 19: 449-464.

6. Hossam Z., Egyptian Ministry of Health announces new treatment guidelines for HCV patients: Receiving hepatic fibrosis patients of 3rd and 4th stages in 26 centers. Al-Ahram 2014.

7. Tomer Y., Blackard JT., Akeno N., Interferone alpha treatment and thyroid dysfunction. Endocrinol Metab Clin North Am 2007; 36: 1051-1066.

8. Antonelli A., Rotondi M., Fallahi P., et al. High levels of circulating CXCL 10 is associated with chronic autoimmune thyroiditis and hypothyroidism. J Clin Endocrin Metab 2004; 89: 5496-5499.

9. Russo MW., Fried MW., Side effects of therapy for chronic hepatitis C. Gastroenterol 2003; 124: 1711-1719.

10. Carella C., Mazziotti G., Amato G., Interferon-related thyroid disease: Pathophysiological, epidemiological, and clinical aspects. J Clin Endocrin Metab 2004; 89: 3656-3661.

11. Mazziotti G., Sorvillo F., Piscopo M., et al. Innate and acquired immune system in patients developing Interferone alpha related autoimmune thyroiditis: a prospective study. J Clin Endocrin Metab 2005; 90: 4138-4144.

12. Oppenheim Y., Ban Y., Tomer Y., Interferone induced autoimmune thyroid disease: A model for human autoimmunity. Autoimmun Rev 2004; 3: 388-393.

13. Weetman AP., Grave's disease. N Engl J Med 2000: 343: 1236-1248.

14. Hollowell JG., Staehling NW., Flanders WD., et al. Serum TSH, T4 and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHAHES III). J Clin Endocrin Metab 2002; 87: 489-499

Table 1: Demographic and anthropometric characteristics of study groups.

	Cases N=60	Control N=48	P-value
Age (mean ± SD)	46 ± 12.97	47.54 ± 6.8	0.69
sex	N (%)	N (%)	
female	9 (30)	11 (45.8)	0.231
male	21 (70)	13 (54.2)	
BMI (mean ± SD)	25.66 ± 2.65	25.41 ± 3.08	0.74
χ^2 =Chi Square test, P value significant<0.05, BMI: Body Mass Index			

Table 2: TSH and CXCL 10 (IP) measurement before intervention in study groups.

	Cases N=60 Median (min-max)	Control N=48 Median (min-max)	Man Whitney U test
TSH before treatment	1.125 (0.22-4.0)	1.37 (0.16-2.24)	P= 0.403
IP 10 before treatment	740 (100-1789)	300 (50-500)	P<0.001**
** High statistically significant			

Table 3: CXCL 10 (IP) and TSH changes from basal, 6 months and 12 months after treatment.

	Basal	After 6 months	After 1 year	Significance
				P1=0.001**
CXCL 10 (IP)	740	880	900	P2=0.001**
				P3=0.205
				P1=0.043*
TSH	1.125	1.2	1	P2=0.043*
				P3=0.039*
P1: Comparison between basal and 6 months after treatment, P2: Comparison between basal and 12 months after treatment, P3: Comparison between 6 and 12 months after treatment.				