



THYROID DYSFUNCTION; DURING COMBINED PEG-INTERFERON ALPHA-2A AND RIBAVIRIN THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C

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ABSTRACT... Hepatitis C is a burning issue. Prevalence of hepatitis C virus reported in Pakistan is 5% with areas of high infection in different cities and subsets of population. **Objectives:** To find out the frequency of thyroid related dysfunctions in chronic hepatitis C patients on Peg-Interferon Alpha-2a and Ribavirin therapy. **Study Design:** A prospective cohort study. **Place and Duration of Study:** Hepatitis Center DHQ teaching hospital Sahiwal from July 2013 to June 2014. **Material and Methods:** We studied 100 patients of chronic HCV infection with baseline level of TSH, T3 and T4. Baseline serum ALT and serum AST were also measured. Patients were put on Peg-Interferon Alpha-2a (180 ug) weekly and Ribavirin (800 to 1000 mg/d) for 24 weeks. All patients were followed up for thyroid dysfunction at weeks 0, 12, 18 and 24. **Result:** Out of 100 treated patients 65 were female and 35 were male. Fifteen (15%) patients developed thyroid dysfunction and out of these 15 patients (11 female [73.3%] and 4 male [26.7%]). Ten (66.6%) out of 15 patients developed hypothyroidism and 5 (33.3%) out of 15 patients developed hyperthyroidism. Seven (70%) out of 10 patients who developed hypothyroidism needed levothyroxine therapy. Two (40%) out of 5 patients who developed hyperthyroidism needed carbimazol therapy for their symptoms and disease control. All patients completed hepatitis C treatment with combined Peg-Interferon Alpha-2a and Ribavirin therapy.

Key words: Interferon Alpha-2a, Ribavirin, Chronic Hepatitis C, Thyroid dysfunction.

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INTRODUCTION

Hepatitis C is a burning issue. Prevalence of hepatitis C virus reported in Pakistan is 5% with areas of high infection in different cities and subsets of population¹. Hepatitis C is treated with conventional/ pegylated Interferon plus Ribavirin. The most commonly used regimen is combination of pegylated Interferon and Ribavirin therapy. Currently oral therapy is also available. Peg-Interferon Alpha-2a(180 ug)/ Alpha-2b(1.5 ug per kg body weight) is given once weekly subcutaneously and the dose of Ribavirin varies from 800 to 1200 mg per day depending upon the weight of the patient. Treatment is carried out for 24 to 48 weeks depending upon viral genotype.

Many side effects are associated with the treatment of the peg-interferon plus Ribavirin therapy such as, influenza like symptoms, fever, headache, chills and muscle aches and pains²⁻⁶.

Hair loss, weakness, fatigability, anorexia

and weight loss may occur later. Suicidal tendencies, depression and irritability have also been reported. Neuro-retinitis is rare but very serious complication and its occurrence calls for immediate discontinuation of therapy⁶. Hematological side effects like anemia, neutropenia and thrombocytopenia are common and needs dose adjustment of the drugs plus supportive therapy.

Hepatitis C infection treated with combined Peg-interferon alpha-2a and Ribavirin therapy results in many endocrinological disorders, of which thyroid dysfunction is most common⁷. Thyroid dysfunction has also been described as an extrahepatic manifestation of chronic HCV infection. This disorder can also be precipitated or exacerbated by interferon-alpha, especially in women⁸⁻¹¹. Several studies have reported the development of hypothyroidism and hyperthyroidism in patients treated with interferon monotherapy, there is a paucity of literature describing the frequency of

thyroid dysfunction during peg-interferon-alpha and ribavirin combination therapy. Therefore, we conducted a prospective cohort study to determine the frequency, clinical presentation and long term outcome of thyroid dysfunction in patients with chronic HCV infection who were treated with a combination of peg-interferon alpha-2a and ribavirin. Thyroid function tests T3, T4 and TSH were measured at 0, 12, 18 and 24 weeks of therapy. Many studies measured thyroid parameters in different schedules. Kee et al¹², and Dalgard et al¹³. Measured thyroid function test every 3 months; Moncoucy et al¹⁴. every 2 or 3 months and Hsieh et al. every 4 week for 24 weeks, followed by 8 weeks for another 24 weeks¹⁵. Minelli et al¹⁶ evaluated thyroid function at 1, 2, 3 and 6 months after diagnosis.

MATERIAL AND METHOD

One hundred chronic hepatitis C patients presented at DHQ teaching hospital Sahiwal during July 2013 to June 2014 were registered for the treatment of chronic hepatitis C with combination Peg-Interferon Alpha-2a and Ribavirin therapy. Informed consent was taken for participation in this study. All patients were assessed for thyroid disease clinically and bio-chemically using T3, T4 and TSH assays. The baseline T3 (58-194ng/dL[0.9-3.0 nmol/L]), T4(4.8-12.8ug/dL[61.8-164.7 nmol/L]) and TSH(0.4-5.5 mIU/L) levels were within the normal range in all patients. Patients were treated with Peg-Interferon Alpha-2a (180 ug) weekly and Ribavirin (800 to 1000 mg/d) for 24 weeks. All patients were followed up for thyroid dysfunction at weeks 0,12,18 and 24. The data were entered in SPSS-11 and analyzed.

Overt hypothyroidism was defined as an elevated TSH level(>5.5mIU/L) along with low levels of T3(<58ng/dL[<0.9 nmol/L]) and T4(<4.8 ug/dL[<61.8 nmol/L]). Overt hyperthyroidism was defined as a low TSH level(<0.4mIU/L) along with elevated levels of T3(>194ng/dL[>3.0 nmol/L]) and T4(>12.8ug/dL[>164.7 nmol/L]).

RESULTS

A total of 100 patients with baseline T3, T4 and TSH levels within the reference range were enrolled in

this study. Out of 100 patients, 65 were female and 35 were male. Most patients were infected with genotype 3. During treatment with combination of Peg-interferon alpha-2a and Ribavirin therapy, a total of 15 patients, 11 female (73.3%) and 4 male (26.7%) developed overt thyroid disease and were diagnosed clinically and biochemically suffering from thyroid dysfunction. Ten (66.6%) of the 15 patients suffered from overt hypothyroidism and 5(33.3%) developed hyperthyroidism.

The biochemical features of 10 patients with overt hypothyroidism were low T3 and T4 and high TSH at the time of diagnosis. Fatigue (10/10[100%]), decreased appetite (9/10[90%]), depression (7/10[70%]) and myalgias (7/10[70%]) were important symptoms in patients with hypothyroidism. On the other hand, none of these patients had bradycardia, cold intolerance, edema and thyroid enlargement.

Seven (70%) of the 10 patients having hypothyroidism were managed with levothyroxine and they responded well to the treatment clinically and biochemically and 6(60%) had normal levels of TSH during treatment of chronic HCV. All 7 patients on levothyroxine completed HCV therapy. Levothyroxine therapy was continued during HCV treatment and it was tapered in the next 2 months.

The biochemical assay of the 5 patients having overt hyperthyroidism were high T3, T4 levels with low TSH obtained at the time of diagnosis. All 5 patients reported fatigue and weight loss, irritability and nervousness, and 2 of the 5 patients also had palpitations and resting tremors in hands at the time of diagnosis. Heat intolerance and thyroid enlargement was not reported by any patient with hyperthyroidism.

All 5 patients having hyperthyroid symptoms were put on beta blockers like propranolol. 2 out of 5 hyperthyroid patients (40%) required carbimazole for their symptoms and disease control. Although clinical symptoms resolved in all subjects but no one attained normal levels of TSH during HCV treatment. Treatment for hyperthyroidism was continued for one month after HCV treatment completion and was tapered in the next 2 months.

DISCUSSION

The development of thyroid dysfunction with interferon mono-therapy in patients infected with chronic hepatitis C is well described, and the prevalence ranges from 2.5% to 30%¹⁷⁻²², with the mean prevalence of 6.6%¹⁸. Hypothyroidism (3.8%) was more commonly seen as compared to hyperthyroidism (2.8%), in these studies. Thyroid related disorders were more often seen in female patients than male (13% vs 3%)¹⁸. Female gender and thyroid auto-antibodies were the major contributors that were related with an enhanced risk of thyroid disease with interferon alpha therapy¹⁸⁻²². Despite higher doses of interferon alpha used in the treatment of patients of chronic hepatitis B infection²², thyroid disease seems to develop less in patients with chronic hepatitis B infection as compared with hepatitis C treated patients. It can be concluded that interferon therapy and HCV infection may have synergistic effect in the causation of thyroid disease. Interferon, also results in the activation and proliferation of many cells like dendritic and memory T cells etc and prevent T cell apoptosis²³. Thyroid auto-antibodies will rise ultimately leading to destruction of thyroid gland. These may cause this destruction after interaction with hepatitis C virus particle present in it²⁴. The addition of interferon alpha further causes destruction of inflamed gland. Furthermore, interferon therapy may have direct toxic effect on thyroid cells, ultimately leading to release of thyroid hormones²⁵. These patho-physiologic changes lead to biphasic thyroid response in the form of hypo and hyperthyroidism.

Many studies have reported that this combination therapy results in thyroid dysfunction. Ribavirin is a nucleoside analogue which has activity against many RNA and DNA viruses²⁶. This drug is considered to have destructive effect on thyroid gland via immune-modulation²⁶. Thyroid dysfunction with this therapy has been reported in 4.7% to 27.8% of patients, with the mean frequency of 12.1%²⁷⁻³¹ and it is low in the patients treated with interferon alone which is 6.6%¹⁸. Many studies have reported hypothyroidism more than hyperthyroidism (8.1% vs 3.8%) with this combination therapy, in contrast to our study

(10% vs 5%). Thyroid dysfunction occurs more often in females as compared to males (17.7% vs 8.3%)²⁷⁻³¹, in contrast to our study (11% vs 4%). The results of our study show that with this combination therapy thyroid related disorders was 15%. The thyroid related disorders of 15% in our study patients was higher as compared to 3% frequency mentioned in those treated with interferon monotherapy¹⁸ and was higher to the mean frequency of 8.3% with combination therapy²⁷⁻³¹.

Fatigue, myalgias and depression were common in our study cases with hypothyroidism, whereas nervousness, irritability, insomnia, fatigue were present in patients with hyperthyroidism. To overcome this problem thyroid function test should be routinely performed in patients on this combination therapy^{28,29,32,33,34}.

These have been supported by other investigators as well that this combination therapy can be continued, even in those who develop overt thyroid disease^{15,20,22}. Most thyroid disorders did not require long term therapy and mostly return to normal but few may need long term management^{17,21,29}. Coh et al¹⁸ have reported that interferon alpha induced thyroid related disorders were reversible in 61.2% of cases, these included 55.8% cases of hypothyroidism and 69.7% cases of hyperthyroidism. Longer follow up may be required to see the complete resolution of thyroid dysfunction. Patients on this therapy should be informed about the risk of thyroid related disorders.

CONCLUSIONS

This study demonstrates that 15% of HCV patients on treatment with peg-interferon alpha-2a and ribavirin combination therapy suffered from overt thyroid dysfunction. Based on these findings, it is suggested that one should have baseline thyroid function tests especially those having family history of thyroid disease. Treatment can safely be continued in these patients, however optimal methods and timing and frequency of thyroid function test need to be evaluated.

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PREVIOUS RELATED STUDY

Abdelmula M. Abdella, Gad Allah Modawe. THYROID DYSFUNCTION; SERUM LIPID PROFILE IN SUDANESE PATIENT (Original) Prof Med Jour 18(3) 436-439 Jul, Aug, Sep 2011.

AUTHORSHIP DECLARATION

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