

REVIEW ARTICLE

## Thyroid disorders associated with hepatitis C or interferon based therapies

Şener Barut, Özgür Günel

*Gaziosmanpaşa University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Tokat, Turkey*

### ABSTRACT

Several extrahepatic diseases have been associated with chronic hepatitis C virus (HCV) infection (i.e. hematologic diseases, renal disease, dermatologic conditions). It has also been shown that HCV infection is associated with increased incidence of clinical and subclinical autoimmune thyroid disorders. Moreover, interferon (IFN)- $\alpha$  therapy of chronic HCV infection is associated with subclinical or clinical thyroiditis in up to 40% of cases. Interferon induced thyroiditis (IIT) can be classified as autoimmune type and non-autoimmune type. Current studies indicate that viral load, viral genotype and therapeutic regimen do not influence development of IIT in chronic hepatitis C patients thus, and development of IIT is not a predictor of sustained viral response. However, evidence suggests that genetic factors, gender, HCV infection and positivity of thyroid antibodies may play role. *J Microbiol Infect Dis 2013; 3(3): 147-149*

**Key words:** Hepatitis C, interferon, thyroid disorders

### Hepatit C veya interferon tedavisi ile ilişkili tiroit hastalıkları

#### ÖZET

Karaciğer dışı birçok hastalık kronik hepatit C virüs (HCV) enfeksiyonu (hematolojik hastalıklar, böbrek hastalığı, dermatolojik problemler) ile ilişkilendirilmiştir. HCV enfeksiyonunun klinik ya da subklinik oto-immün tiroit hastalıklarının artmış insidansı da ilişkili olduğu gösterilmiştir. Ayrıca, kronik HCV enfeksiyonunun interferon (IFN)- $\alpha$  ile tedavisi vakaların % 40'ına kadar olan kısmında subklinik veya klinik tiroit ile ilişkilidir. İnterferon ilişkili tiroit (İİT), otoimmün tip ve otoimmün olmayan tip olarak sınıflandırılabilir. Mevcut çalışmalar viral yük, viral genotip ve tedavi rejiminin kronik hepatit C hastalarında İİT gelişimini etkilemediğini, ayrıca İİT gelişmesinin kalıcı viral yanıt (KVY) için bir gösterge olmadığını, ancak, genetik faktörler, cinsiyet, HCV enfeksiyonu ve tiroit antikor (TAB) pozitifliğinin rol oynayabileceğini göstermektedir.

**Anahtar kelimeler:** Hepatit C, interferon, tiroit hastalıkları

#### Hepatitis C infection and thyroid disorders

Several extra hepatic diseases have been associated with chronic hepatitis C (HCV) infection including hematologic diseases such as cryoglobulinemia and lymphoma, renal disease, dermatologic conditions (lichen planus and porphyria cutanea tarda).<sup>1</sup> Chronic HCV infection has also been demonstrated to be associated with clinical and subclinical autoimmune thyroiditis (i.e. the presence of thyroid antibodies in euthyroid subjects).<sup>2,3</sup> Two studies are important in this field. A large and well-controlled study showed that the prevalence of both hypothyroidism and thyroid autoimmunity were significantly higher in patients with hepatitis C compared to controls.<sup>3</sup> The other study strengthened further the evidence for this association which found that the prevalence of non-autoimmune hypothyroidism, as well as

the presence of anti-thyroglobulin antibodies, was higher in untreated children with HCV compared to children without HCV infection. This increased prevalence was not found to be related other parameters (family history of autoimmune diseases, duration of HCV infection, viral genotype, viral load or liver function) except active HCV infection.<sup>4</sup> In addition, analyzing of all published controlled studies on HCV infection and thyroid autoimmunity resulted a significant increase in the risk of thyroiditis in HCV patients. This implies that, HCV infection is the only infectious agent that is clearly associated with an increased risk for autoimmune thyroiditis.<sup>2</sup> It is possible that HCV induce thyroid autoimmunity in genetically susceptible individuals by interacting with genetic risk factors. However, the biologic mechanisms of such interactions is not known yet.<sup>6</sup>

**Correspondence:** Özgür Günel,

Gaziosmanpaşa Üniv. Tıp Fakültesi, Enfeksiyon Hast. ve Klinik Mikrobiyoloji AD, Tokat, Turkey Email: ozgurgop@yahoo.com

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### Interferon based therapies and thyroid disorders

According to current medical practice, interferon (IFN)- $\alpha$  or pegylated IFN-- $\alpha$  is fundamental for chronic hepatitis C treatment.<sup>7</sup> Moreover, IFN- $\alpha$  therapy for chronic HCV infection is associated with subclinical or clinical thyroiditis in up to 40% of cases and, IFN- $\alpha$  is one of the most important environmental triggers of autoimmune thyroid disease (AITD).<sup>2</sup> Interferon induced thyroiditis (IIT) can be classified as autoimmune type and non-autoimmune type.<sup>7</sup>

i. Autoimmune IIT: The entire spectrum of AITD has been defined with the results of patients receiving IFN- $\alpha$ : Graves' disease (GD), Hashimoto's thyroiditis (HT) and the presence of thyroid antibodies (TAB's) without clinical disease.<sup>7</sup> HT is the most common clinical manifestation of autoimmune IIT whereas Grave's disease (GD) is a less common clinical manifestation.<sup>8</sup> HT develops commonly in patients having positive TAB before they receive IFN- $\alpha$ . Besides, HCV patients receiving INF- $\alpha$  may also develop HT as de novo although they did not have positive TAB prior to therapy. These data implies that genetic susceptibility may be an underlying factor for the development of AITD after receiving IFN $\alpha$ .<sup>2,7</sup> Subclinical AITD, which is characterized by production of TAB without clinical disease, may also develop during IFN- $\alpha$  therapy. De novo development of TAB is seen in approximately 10-40% of cases.<sup>7,8</sup>

ii. Non-autoimmune IIT: Non-autoimmune IIT is also common like autoimmune IIT. It can manifest as destructive thyroiditis, with early thyrotoxicosis and later hypothyroidism, or as non-autoimmune hypothyroidism. In most cases of destructive thyroiditis, subclinical thyroid dysfunction and spontaneous resolution mainly occurred. The negative TSH-receptor antibodies (TRAb) and low thyroid radioactive iodine uptake are the base for the diagnosis of destructive thyroiditis in patients receiving interferon therapy.<sup>7,8</sup> The destructive form of IIT is theorized as being secondary non-autoimmune thyroid inflammation.<sup>7</sup> Thus, this type of thyroiditis is mainly due to direct effect of IFN on thyroid gland. The differentiation of autoimmune thyroiditis from non-autoimmune IIT can be mainly based on testing thyroid auto-antibodies (anti-TPO or thyroglobulin antibodies) which are characteristics of autoimmune IIT.

### Epidemiologic studies related to IIT

Danilovic et al.<sup>9</sup> prospectively selected 26 patients with chronic HCV infections to investigate thyroid disturbances induced by IFN- $\alpha$  and ribavirin thera-

py. Of all patients, 54% had no thyroid disorders associated with the IFN- $\alpha$  therapy. Nineteen percent of the subjects had autoimmune IIT characterized by development of anti-thyroid antibodies or overt hypothyroidism. Additionally, 16% had non-autoimmune thyroiditis, which characterized by destructive thyroiditis or subclinical hypothyroidism, and 11% of patients who had TAB's prior to therapy remained in a state of euthyroidism.<sup>9</sup> In a recent study from Turkey showed that de novo incidence of thyroid dysfunction (TD) was found to be 16.8% among the 119 chronic HCV patients receiving pegylated-interferon plus ribavirin.<sup>10</sup> Similarly, a clinical study also showed that 11.5% of patients developed TD, 85.3% of these patients presented with subclinical TD, and 14.7% of them developed overt thyroiditis, at the end of the IFN- $\alpha$  based therapy. The study also showed that 67.8% of them the thyroid function spontaneously returned to normal in the six months of follow-up and only 4.4% had persistent overt TD symptoms after the 24 month follow-up period.<sup>11</sup> The likelihood of TD development during the treatment varies between 5.5% and 27.8% according to different studies.<sup>1,10,12,14</sup>

### Factors associated with IIT

There are various factors that predisposed patients with HCV to IIT. There is a genetic susceptibility to IIT.<sup>2,7</sup> A specific pretreatment risk factor, presence of TPO-Ab, has also been shown to be a statistically significant risk factor for developing thyroid disease in patients treated with IFN.<sup>8,10</sup> Watanabe et al.<sup>15</sup> reported that the incidence of thyroid diseases in patients with baseline positive TPO-Ab was much higher than that of patients with negative TPO-Ab levels (60% vs. 3.3). Roti et al.<sup>16</sup> demonstrated that elevated TPO antibodies before IFN- $\alpha$  therapy had a positive predictive value of 67% for the development of clinical autoimmune IIT. We also found that anti-TPO positivity was the only significant predictor of thyroid disorder during IFN based therapy of chronic hepatitis C in logistic regression analysis in our previous clinical study.<sup>10</sup> Similarly a study performed among the 592 Chinese patients who received IFN- $\alpha$  based therapy for chronic HCV infection demonstrated that gender and pretreatment TPO-Ab were the independent factors related to the incidence of TD.<sup>11</sup> Therefore, it is recommended that patients with baseline TAB's should be followed more closely for thyroid dysfunction while on IFN- $\alpha$  therapy.<sup>7</sup>

Various risk factors for IIT have been evaluated. Although a recent study reported a positive and significant association between thyroid disease and

viral clearance, our previous study together with the study of Vezali et al.<sup>13</sup> demonstrated that virological factors such as early virologic response or sustained viral response (SVR) as well as the type of IFN- $\alpha$  were not associated with IFN induced thyroid dysfunction in chronic HCV patients receiving pegylated-IFN plus ribavirin.<sup>10,17</sup> Vezali and coworkers<sup>13</sup> evaluated the 94 chronic HCV patients (61 patients treated with pegylated-IFN- $\alpha$  plus ribavirin vs. 33 untreated chronic HCV patients) in long time period for TD. The control group patients remained euthyroid ( $P < 0.001$ ) and 13 (21.3%) out of 61 treatment group patients experienced TD. Eleven of this 13 patients were diagnosed with hypothyroidism and 2 of them with hyperthyroidism that later converted to hypothyroidism. The incidence of TD in women (9 of 13, 69.2%) was higher than the incidence of TD in men (4 of 13, 30.8%), however the difference was not statistically significant ( $P = 0.122$ ). Moreover, 10 (16.4%) of 61 treated patients developed at least one and more autoimmune disease during the course of therapy (4 psoriasis, 2 mixed cryoglobulinemia, 2 rheumatoid arthritis-like syndrome, 1 lichen planus and 1 idiopathic-thrombocytopenia). The authors noted that 13 independent variables were potentially associated with TD including sex, age, body mass index, HCV genotype, pretreatment viral load, treatment regimen and duration, total dose of pegylated-IFN- $\alpha$  and ribavirin, and SVR. However TD could not be predicted with any of these. The only correlation declared by that study was the relationship between TD development and the onset of other autoimmune disorders during combination therapy ( $P = 0.003$ ).<sup>13</sup>

In conclusion, both HCV itself and IFN- $\alpha$  therapy have been found to be inducing thyroid disorders in patients with HCV infection. Autoimmune or non-autoimmune thyroiditis can occur during IFN- $\alpha$  based treatment. Studies indicate that viral load, viral genotype and therapeutic regimen do not influence development of IIT in chronic HCV patients thus, and development of IIT is not a predictor of SVR. However, evidence suggests that genetic factors, gender, HCV infection and positivity of TAB's may play a role. Thyroid function tests and TAB's should be screened before treatment and also thyroid function tests should be monitored during therapy regularly.

**Conflict of interest:** The authors report no conflict of interest.

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