Virologic factors related to interferon-α-induced thyroid dysfunction in patients with chronic hepatitis C


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Abstract

Objective: Hepatitis C virus (HCV), being reported to be associated with a high prevalence of serological markers of autoimmunity in HCV-infected patients, and possibly sharing partial sequences in amino acid segments with thyroid tissue antigens, may be associated with interferon-α (IFN-α)-induced thyroid dysfunction in chronic hepatitis C patients. We conducted this study to clarify the issue.

Design and Methods: One hundred and fifty chronic hepatitis C patients with normal baseline thyroid function were treated with IFN-α2a, 2b and n1 (3–6 million Units three times weekly for 24 weeks). Pretreatment sera were tested for HCV genotype and HCV RNA levels. Serum thyrotropin, total thyroxine and free thyroxine index were performed every 4 weeks for 24 weeks followed by every 8 weeks for another 24 weeks.

Results: Twenty-one (14.0%) patients developed early thyroid dysfunction (abnormal thyroid function during the first 3 months of therapy). Female gender, lower HCV RNA levels, IFN-αn1 and a lower IFN-α dose were significantly associated with early thyroid dysfunction. On multivariate analysis, gender, IFN-α preparation and HCV RNA levels were the significant factors associated with early thyroid dysfunction. Seven (4.7%) patients developed thyroid dysfunction during the second 3 months of IFN-α therapy. Taken together, 18.7% patients developed thyroid dysfunction. Female, mixed HCV genotype infection and lower HCV RNA levels were significantly associated with thyroid dysfunction. However, only gender remained significantly associated with IFN-α-induced thyroid dysfunction in multivariate analysis.

Conclusions: The virologic features of HCV may be associated with thyroid dysfunction in chronic hepatitis C patients treated with IFN-α. Nevertheless, gender still plays the most important role in IFN-α-induced thyroid dysfunction.

Introduction

Interferon-α (IFN-α) has been used for the treatment of various malignant diseases and chronic hepatitis C, with promising results (1, 2). However, many side-effects, including thyroid dysfunction, have been described. The frequency and clinical characteristics of thyroid dysfunction after IFN-α administration have been reported by many authors (3–10). Humoral factors, IFN-α preparation and dosage have been reported to be associated with thyroid dysfunction. Female gender and old age have been reported to be the risk factors for developing thyroid dysfunction in chronic hepatitis C patients treated with IFN-α, but others have disagreed (4, 8, 9, 11, 12).

Chronic hepatitis C patients have been reported to show signs of autoimmunity, including autoantibodies and autoimmune diseases (13, 14). It had been hypothesized that hepatitis C virus (HCV) might share partial sequences in a few amino acid segments with thyroid tissue antigens (15). The HCV is a highly heterogenous virus. This quasi-species nature may contribute to different immune environments, and leads to different influences on thyroid dysfunction induced by IFN-α. In the present study, we have investigated the relationship between virologic factors and thyroid dysfunction in a prospective trial of IFN-α treatment for patients with chronic hepatitis C.

Subjects and methods

One hundred and seventy-two chronic hepatitis C patients (86 males and 86 females) received thyroid function tests including serum thyrotropin (TSH), total
Detection/quantification of serum HCV RNA and genotyping

Nested RT-PCR was performed to detect serum HCV RNA using 5’ non coding region-specific primers (17). HCV genotypes 1a, 1b, 2a, 2b and 3a were determined by amplification of the core region using genotype-specific primers described by Okamoto et al. (18). Pretreatment serum HCV RNA levels were determined by using a branched-DNA assay (Quantiplex HCV RNA 2.0, Chiron, CA, USA), performed strictly according to the manufacturer’s instructions.

Laboratory tests

Second-generation HCV antibody was detected with commercially available enzyme-linked immunosorbent assay kits (Abbott, North Chicago, IL, USA). Serum ALT level (normal upper limit of serum ALT = 0.42 μkat/l) was measured on a multichannel autoanalyzer.

Thyroid function tests

Thyroid function tests, including serum TSH, TT4 and FT4I were performed by using commercial assay kits (Daiichi, LABSLTD, Japan). Tg-Ab and TPO-Ab were determined by using hemagglutination kits (Fuji Rebio Co, Japan). Baseline thyroid function tests were performed before IFN therapy and then every 4 weeks for 24 weeks, followed by 8 weeks for another 24 weeks. The normal range of each assay was as follows: TSH, 0.4–5.0 mU/l; TT4, 58–155 nmol/l; FT4I, 1.55–4.0; Tg-Ab and TPO-Ab, <100. The definitions of thyroid dysfunction included: (a) hyperthyroidism, TSH < 0.1 mU/l accompanied by increased FT4I; (b) hypothyroidism, TSH > 5.0 mU/l accompanied by decreased FT4I; (c) subclinical hyperthyroidism, TSH < 0.4 mU/l accompanied by normal FT4I; (d) subclinical hypothyroidism, TSH > 5.0 mU/l accompanied by normal FT4I; and (e) destructive thyroiditis, hyperthyroidism or subclinical hyperthyroidism followed by hypothyroidism or subclinical hypothyroidism.

Statistical analyses

Frequency was compared between groups using the Chi-square test and group means using the t-test. Stepwise logistic regression was used to analyze factors associated with thyroid dysfunction in chronic hepatitis C patients treated with IFN-α.

Results

Before being enrolled in the present study, all patients received thyroid function tests. One male (hypothyroidism) and four females (two with hypothyroidism, one with subclinical hypothyroidism and one with hyperthyroidism) had thyroid dysfunction. All these patients had Tg-Ab and/or TPO-Ab. Another four males and thirteen females with normal thyroid function had Tg-Ab and/or TPO-Ab. The prevalence of thyroid abnormalities was 12.8% (males 5.8%, females 19.8%). A total of twenty-two patients with thyroid abnormalities were excluded. Fifty-three of one hundred and fifty (35.3%) chronic hepatitis C patients achieved complete response to IFN-α therapy. Table 1 summarizes the findings on patients with chronic hepatitis C who developed thyroid dysfunction induced by IFN-α. During the first 3 months of IFN-α therapy, twenty-one (14%) (three males and eighteen females) had thyroid dysfunction, including hyperthyroidism in five, subclinical hyperthyroidism in eight, subclinical hypothyroidism in five and destructive thyroiditis in three. Nine patients developed thyroid dysfunction in the 8th week of IFN-α therapy and twelve patients developed thyroid dysfunction in the 12th week of IFN-α therapy. We defined these patients as having early thyroid dysfunction. The abnormal thyroid function of patients 2, 3, 6, 9, 10, 14, 15, 19 and 21 returned to normal spontaneously during IFN-α therapy. The abnormal thyroid function of other patients returned to normal spontaneously within 24 weeks after cessation of IFN-α therapy, except for the persistent hyperthyroidism in patient 13 who received anti-thyroid drug therapy.

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later. Unfortunately, this patient was diagnosed as having papillary thyroid carcinoma by cytology 6 months after cessation of IFN-α therapy and was treated by total thyroidectomy and 131I radioiodine therapy. During the second 3 months of IFN-α therapy, another seven patients (4.7%) (one male and six females) had thyroid dysfunction, including hyperthyroidism in two, subclinical hyperthyroidism in three, subclinical hypothyroidism in one and destructive thyroiditis in one. Two patients developed thyroid dysfunction in the 20th week of IFN-α therapy and five patients developed thyroid dysfunction in the 24th week of IFN-α therapy. All these patients were defined as having late thyroid dysfunction. These seven patients were all treated with 6 MU IFN-α given intramuscularly three times a week for 24 weeks. With the exception of patient 25 who developed persistent hyperthyroidism and received anti-thyroid drug therapy, all abnormal thyroid functions spontaneously returned to normal within 24 weeks after cessation of IFN-α therapy.

Table 2 shows the characteristics of early thyroid dysfunction in chronic hepatitis C patients treated with IFN-α. In univariate analysis, the rate of thyroid dysfunction in females (18/69, 26.1%) appeared to be significantly higher than that in males (3/81, 3.7%) (P < 0.001). The patients treated with lymphoblastoid IFN-α n1 (13/55, 23.6%) had a significantly higher frequency of thyroid dysfunction than those treated with the other two recombinant IFN-α (8/95, 8.4%) (P < 0.05). The patients with early thyroid dysfunction induced by IFN-α had a markedly lower pretreatment serum HCV RNA level (P < 0.001) and received a significantly lower total dose of IFN-α in the first 3 months (P < 0.05) than those without early thyroid dysfunction. Further analysis, using stepwise logistic regression, revealed that female, lymphoblastoid IFN-α n1 and lower pretreatment HCV RNA levels were significant risk factors associated with early thyroid dysfunction induced by IFN-α.

Table 3 lists the characteristics of all thyroid dysfunction induced by IFN-α in chronic hepatitis C patients.
Twenty-eight (18.7%) (four males and twenty-four females) of 150 patients developed thyroid dysfunction induced by IFN-α. In univariate analysis, the rate of thyroid dysfunction in females (24/69, 34.8%) appeared to be significantly higher than that in males (4/81, 4.9%) ($P < 0.001$). The pretreatment HCV RNA level was significantly lower in patients who developed thyroid dysfunction than those who did not develop thyroid dysfunction ($P < 0.001$, compared by $t$-test).

**Table 2** Background of early thyroid dysfunction in chronic hepatitis C patients treated with IFN-α.

<table>
<thead>
<tr>
<th></th>
<th>Patients without early thyroid dysfunction</th>
<th>Patients with early thyroid dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>129 (86.0%)</td>
<td>21 (14.0%)</td>
</tr>
<tr>
<td>Age (years, mean ± s.d.)</td>
<td>44.8 ± 11.2</td>
<td>48.0 ± 12.2</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>78/51</td>
<td>3/18*</td>
</tr>
<tr>
<td>Liver histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>75 (58.1%)</td>
<td>10 (47.6%)</td>
</tr>
<tr>
<td>Chronic persistent hepatitis</td>
<td>30 (23.3%)</td>
<td>4 (19.1%)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>24 (18.6%)</td>
<td>7 (33.3%)</td>
</tr>
<tr>
<td>HCV genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>48 (37.2%)</td>
<td>6 (25.6%)</td>
</tr>
<tr>
<td>2a</td>
<td>43 (33.3%)</td>
<td>8 (38.1%)</td>
</tr>
<tr>
<td>2b</td>
<td>11 (8.5%)</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>17 (13.2%)</td>
<td>2 (9.5%)</td>
</tr>
<tr>
<td>Mixed infection</td>
<td>10 (7.8%)</td>
<td>4 (19.0%)</td>
</tr>
<tr>
<td>Pretreatment HCV RNA levels*</td>
<td>5.80 ± 1.27</td>
<td>4.45 ± 2.64*</td>
</tr>
<tr>
<td>IFN preparation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoblastoid IFN n1</td>
<td>42 (32.6%)</td>
<td>13 (61.9%)*</td>
</tr>
<tr>
<td>Recombinant IFN-2a</td>
<td>27 (20.9%)</td>
<td>2 (9.5%)</td>
</tr>
<tr>
<td>Recombinant IFN-2b</td>
<td>60 (46.5%)</td>
<td>6 (28.6%)</td>
</tr>
<tr>
<td>IFN total dose (MU, mean ± s.d.)</td>
<td>202.6 ± 35.7</td>
<td>180.0 ± 52.5*</td>
</tr>
</tbody>
</table>

*a$P < 0.001$, females compared with males by chi-square analysis. 
*b$P < 0.001$, compared by $t$-test. 
*c$P < 0.05$, lymphoblastoid IFN-α compared with recombinant IFN-α by chi-square analysis. 
*d$P < 0.05$, compared by $t$-test. 
*Presented as log (equivalent/ml).

**Table 3** Background of all thyroid dysfunction induced by IFN-α in chronic hepatitis C patients.

<table>
<thead>
<tr>
<th></th>
<th>Patients without thyroid dysfunction</th>
<th>Patients with thyroid dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>122 (81.3%)</td>
<td>28 (18.7%)</td>
</tr>
<tr>
<td>Age (years, mean ± s.d.)</td>
<td>45.0 ± 12.0</td>
<td>46.2 ± 11.4</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>77/45</td>
<td>4/24*</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
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<tr>
<td>Chronic active hepatitis</td>
<td>71 (58.2%)</td>
<td>14 (50.0%)</td>
</tr>
<tr>
<td>Chronic persistent hepatitis</td>
<td>28 (23.0%)</td>
<td>6 (21.4%)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>23 (18.8%)</td>
<td>8 (28.6%)</td>
</tr>
<tr>
<td>HCV genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>46 (37.7%)</td>
<td>8 (28.6%)</td>
</tr>
<tr>
<td>2a</td>
<td>41 (33.6%)</td>
<td>10 (35.7%)</td>
</tr>
<tr>
<td>2b</td>
<td>10 (8.2%)</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>17 (13.9%)</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Mixed infection</td>
<td>8 (6.6%)</td>
<td>6 (21.4%)*</td>
</tr>
<tr>
<td>Pretreatment HCV RNA levels*</td>
<td>5.78 ± 1.29</td>
<td>4.87 ± 2.42*</td>
</tr>
<tr>
<td>IFN preparation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoblastoid IFN n1</td>
<td>40 (32.8%)</td>
<td>15 (53.6%)</td>
</tr>
<tr>
<td>Recombinant IFN-2a</td>
<td>25 (20.5%)</td>
<td>4 (14.3%)</td>
</tr>
<tr>
<td>Recombinant IFN-2b</td>
<td>57 (46.7%)</td>
<td>9 (32.1%)</td>
</tr>
<tr>
<td>IFN total dose (MU, mean ± s.d.)</td>
<td>386.0 ± 77.2</td>
<td>366.4 ± 94.5</td>
</tr>
<tr>
<td>HCV response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete responders</td>
<td>44 (36.1%)</td>
<td>9 (32.1%)</td>
</tr>
<tr>
<td>Non-responders</td>
<td>78 (63.9%)</td>
<td>19 (67.9%)</td>
</tr>
</tbody>
</table>

*a$P < 0.001$, females compared with males by chi-square analysis. 
*b$P < 0.05$, mixed infection compared with single type infection by chi-square analysis. 
*c$P < 0.01$, compared by $t$-test. 
*Presented as log (equivalent/ml).
dysfunction ($P < 0.01$). Six of fourteen patients (42.6%) with an HCV mixed subtype infection developed thyroid dysfunction induced by IFN-$\alpha$. The frequency was significantly higher than that of patients with a single subtype infection (22/136, 16.2%) ($P < 0.05$). Further analysis, using stepwise logistic regression, revealed that only female gender remained as the significant risk factor associated with thyroid dysfunction induced by IFN-$\alpha$ therapy.

**Discussion**

The response rate of IFN-$\alpha$ therapy in chronic hepatitis C patients was 35.3% in the present study. It was as high as in those conducted by Toyoda et al. (19) and Kasahara et al. (20) with similar regimens. However, the response rate was much lower in the study conducted by Shiratori et al. (21) with the same dose and duration of IFN-$\alpha$ therapy. The regimen of IFN-$\alpha$ therapy is suggested to be one of the most important factors associated with HCV response. Many factors might contribute to the difference in response rate to similar regimens of IFN-$\alpha$ therapy, such as the distribution of HCV genotype, patient age and the duration of disease. Since genotype non-1b HCV was shown to have a better response to IFN therapy (22, 23), the higher rate of HCV genotype non-1b infection in our patients might be responsible for the higher response rate to IFN therapy. However, further studies are necessary to find out any other important factors.

In the present study, 28 (18.7%) of 150 Taiwanese chronic hepatitis C patients developed thyroid dysfunction induced during IFN-$\alpha$ therapy in Taiwan. The incidence of thyroid dysfunction in previous individual studies has varied from 0% (24) to 34% (3). In our study, thyroid dysfunction included hyperthyroidism (4.7%), subclinical hyperthyroidism (7.3%), subclinical hypothyroidism (4.0%) and destructive thyroiditis (2.7%). These statistics are different from previous reports which revealed that the most common type of thyroid dysfunction induced by IFN was hypothyroidism (5, 8, 25). The reason why we did not find hypothyroidism induced by IFN-$\alpha$ therapy in this study may be due to ethnic differences. Thyroid dysfunction induced by IFN-$\alpha$ therapy was usually reversible in most patients after the cessation of IFN-$\alpha$ therapy (26 of 28 patients, 92.9%) except for two patients who developed persistent hyperthyroidism and received anti-thyroid drug therapy. One patient was diagnosed as having thyroid papillary carcinoma, which might not be associated with IFN-$\alpha$ therapy.

To determine the relation of the virologic characteristics of HCV to IFN-$\alpha$-induced thyroid dysfunction, HCV genotype and quantified serum HCV RNA levels before IFN-$\alpha$ therapy were determined. Whether by using univariate or multivariate analysis, pretreatment HCV RNA levels were significantly associated with thyroid dysfunction induced by IFN-$\alpha$, especially early thyroid dysfunction. Chronic hepatitis C patients with lower HCV RNA levels have been shown to have higher cluster of differentiation (CD)4 counts and different immune environments (26, 27), suggesting that a higher frequency of IFN-induced thyroid dysfunction may occur among this population. Another important finding in the present study was that the total frequency of IFN-$\alpha$-induced thyroid dysfunction was higher in patients with mixed HCV subtype infection than in those with single HCV subtype infection. HCV, exiting high genomic variation, could be divided into different genotypes. The mixed subtype infection has been reported to be with a different immune environment from the single type infection (28). The hypothesis has emerged that HCV may infect the thyroid tissue and lead to a change in the structure and immune reaction of the thyroid gland. However, the HCV genotype-specific difference in IFN-$\alpha$-induced thyroid dysfunction did not exist after controlling the confounding factors by using multivariate analysis in the present study. However, the association of HCV genotypes with IFN-$\alpha$-induced thyroid dysfunction might be masked by strong factors, such as female gender in the present study. Further larger scale studies are needed to clarify the relation between HCV genotypes and IFN-$\alpha$-induced thyroid dysfunction.

It has been reported that HCV might share a partial sequence in a few amino acid segments with thyroid tissue antigens (15). Using the Jotun–Hein method (Lasergene; DNASTAR, Inc. Madison, WI, USA), we compared the amino acid sequence of thyroglobulin (No. U93033) and microsome (No. E15820), with HCV type 1 (No. D10749), type 2 (No. D10750) and type 3 (No. D00944). The amino acid sequence 647–653 of thyroglobulin shared six amino acids with the amino acid sequence 3047–3053 of HCV type 1. The amino acid sequence 1047–1054 of thyroglobulin shared six amino acids with the amino acid sequence 2647–2654 of HCV type 2. The amino acid sequence 471–476 of microsome and the amino acid sequence 471–476 of HCV type 3 were the same. Since HCV shared a partial sequence in a few amino acid segments with thyroglobulin and microsome, chronic hepatitis C patients might be more susceptible to autoimmune thyroid diseases.

The thyroid dysfunction induced by IFN-$\alpha$ may become apparent at any time during IFN-$\alpha$ therapy. The time of thyroid dysfunction induced by IFN-$\alpha$ seemed to be separated into two different parts, including early thyroid dysfunction (8–12 weeks after IFN-$\alpha$ therapy) and late thyroid dysfunction (20–24 weeks after IFN-$\alpha$ therapy). Previous studies have reported that thyroid dysfunction could develop from a few weeks to a few months after the start of IFN-$\alpha$ therapy and after the cessation of IFN-$\alpha$ therapy (6, 7, 9, 29). The mechanism by which IFN-$\alpha$ therapy induced thyroid dysfunction is unclear. IFN-$\alpha$ may act as an immunomodulatory agent leading to thyroid dysfunction in susceptible patients (6, 8, 30–32). In addition, IFN could directly affect both...
thyroid hormone synthesis and secretion in vitro (33). In
the present study, lymphoblastoid IFN-α n1 was found to
induce a higher frequency of early thyroid dysfunction than recombinant IFN-α. One previous study has
revealed that trace amounts of contaminated IFN-γ in
natural IFN-α were believed to be a cause of INF-
induced autoimmunity (4). Differences in the structures
of lymphoblastoid IFN-α n1 and recombinant IFN-α
day be another possibility. All seven patients who
developed late thyroid dysfunction induced by IFN-α
received a high dose of IFN-α (6 MU three times a week
for 24 weeks). These findings suggest that a cumulative
dose of IFN might also play a contributing role. Further
study is needed to clarify the dose-dependent thyroid
dysfunction.

Thyroid dysfunction was not associated with the
response of chronic hepatitis C to IFN-α therapy in the
present study: in contrast, a positive relationship
between the appearance of thyroid dysfunction and
the response to IFN-α therapy was observed in previous
studies (7, 34, 35). However, all those previous studies
did not evaluate the pretreatment serum HCV RNA
levels. The pretreatment HCV RNA level is one of the
factors influencing the outcome of IFN-α treatment (19,
36, 37) and may, in fact, be the single most important
determinant. Thus, the viral load-related thyroid
dysfunction might mimic the relation between the
response of chronic hepatitis C to IFN-α therapy and
thyroid dysfunction.

In conclusion, 18.7% of chronic hepatitis C patients
developed thyroid dysfunction during IFN therapy in
the present study. Most of the IFN-α-induced thyroid
dysfunction was reversible (92.9%). Gender (female) is a
strong risk factor for thyroid dysfunction induced by
IFN-α. However, the virologic features of HCV may be
associated with thyroid dysfunction in chronic hepatitis
C patients treated with IFN-α.

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