Incidence of Thyroid Dysfunction During Interferon Alfa-2b and Ribavirin Therapy in Men With Chronic Hepatitis C

A Prospective Cohort Study

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Background: Thyroid dysfunction is a known complication of interferon monotherapy in women with hepatitis C virus (HCV) infection. The aims of this study were to determine the incidence and long-term outcome of thyroid dysfunction in HCV-infected men receiving interferon and ribavirin combination therapy.

Methods: We prospectively studied 225 HCV-infected men with baseline levels of thyrotropin (TSH) within the reference range who were treated with subcutaneous interferon alfa-2b (3 million units 3 times per week) and oral ribavirin (1000-1200 mg/d) for 24 to 48 weeks. Patients underwent screening of TSH levels every 12 weeks during HCV therapy and at weeks 12 and 24 after completion of treatment. Patients with abnormal TSH levels underwent a comprehensive thyroid evaluation.

Results: Among the 225 patients, overt thyroid disease developed in 6.7% (95% confidence interval, 3.8%-10.8%), and subclinical thyroid disease was diagnosed in 4.0% (95% confidence interval, 1.8%-7.4%). In the 12 patients with overt hypothyroidism, antithyroglobulin antibodies were present in 11 and antithyroid peroxidase antibodies were present in 10, whereas thyroid-stimulating immunoglobulins were present in 2 of the 3 individuals with overt hyperthyroidism. Most of the patients with thyroid dysfunction completed HCV therapy, and thyroid disease resolved in 10 of the 12 patients with overt hypothyroidism, 2 of the 3 with overt hyperthyroidism, and all 9 with subclinical thyroid disease.

Conclusions: Men with HCV infection treated with interferon and ribavirin should undergo routine screening for thyroid disease. Treatment of HCV can be safely continued in these patients because thyroid disease responds well to treatment and is reversible in most individuals.

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HCV antibody (Ortho HCV enzyme-linked immunosorbent assay, version 3.0; Ortho-Clinical Diagnostics, Inc, Raritan, NJ), a polymerase chain reaction (COBAS Amplicor HCV Monitor Test version 2.0; Roche Diagnostics, Branchburg, NJ) finding positive for HCV RNA, findings consistent with a diagnosis of chronic HCV on results of a liver biopsy, and baseline levels of thyrotropin (TSH) within the reference range.

Patients were excluded from this study if they were co-infected with the hepatitis B virus or human immunodeficiency virus; had known thyroid disease or decompensated cirrhosis; had undergone an organ transplantation; were taking immunosuppressive medications; had neoplastic, autoimmune, or severe cardiac, pulmonary, or other comorbid diseases; had severe depression or other psychiatric disorders; or were currently using alcohol or other drugs.

STUDY DESIGN

This prospective cohort study was conducted at the Veterans Affairs New York Harbor Healthcare System in New York from January 1, 1999, through December 31, 2001. The protocol was approved by our local institutional review board, and all patients provided written informed consent.

Patients were treated with US Food and Drug Administration–approved doses of Rebetron (Schering-Plough, Kenilworth, NJ), which included subcutaneous interferon alfa-2b, 3 million units 3 times per week, and oral ribavirin, 1000 mg/d (weight, <75 kg) or 1200 mg/d (weight, ≥75 kg). Patients with genotypes 2 or 3 were treated for 24 weeks, whereas those with genotype 1 were treated for up to 48 weeks. In patients with genotype 1, therapy was stopped after 24 weeks if HCV RNA was still detectable by means of polymerase chain reaction (COBAS Amplicor HCV Monitor Test version 2.0; sensitivity, 100 copies/mL). Genotyping of HCV was performed using the Inno-LiPA HCV II assay (Innogenetics, Gent, Belgium).

Patients were followed up at weeks 2 and 4 and every 4 weeks thereafter during treatment and at 4, 8, 12, and 24 weeks after therapy. At each visit, the presence and severity of adverse events were assessed and routine laboratory testing was performed. Patients underwent screening for thyroid disease by means of TSH levels every 2 weeks during therapy and at weeks 12 and 24 after treatment.

DIAGNOSIS AND MANAGEMENT OF HYPOTHYROIDISM

Patients with elevated TSH levels underwent testing for levels of total triiodothyronine (T3), free T3 (FT3), total thyroxine (T4), and free T4 (FT4); antithyroglobulin antibody titers; and antithyroid peroxidase antibody titers. Diagnostic testing of TSH (ultrasensitive TSH assay with a reference range of 0.4–5.5 mIU/L), T3 (reference range, 88–194 ng/dL [0.9–3.0 nmol/L]), FT3 (reference range, 230–420 pg/dL [3.5–6.5 pmol/L]), T4 (reference range, 4.8–12.8 µg/dL [61.8–164.7 nmol/L]), and FT4 (reference range, 0.8–2.7 µg/dL [10.3–34.7 pmol/L]) was performed using commercially available chemiluminescence immunoassays (Bayer Diagnostics, Tarrytown, NY). Antithyroid peroxidase antibody (reference range, <2.1 IU/mL) and antithyroglobulin antibody (reference range, <2.0 IU/mL) was detected using chemiluminescence assays (Nichols Institute Diagnostics, San Clemente, Calif).

Overt hypothyroidism was defined as an elevated TSH level (>5.5 mIU/L) along with low levels of T3 (<58 ng/dL [<0.9 nmol/L]), FT3 (<230 pg/dL [3.5 pmol/L]), T4 (<4.8 µg/dL [61.8 nmol/L]), and FT4 (<0.8 µg/dL [10.3 pmol/L]), whereas subclinical hypothyroidism was defined as an elevated TSH level (>5.5 mIU/L) with reference-range levels of T3, FT3, T4, and FT4. Patients who developed overt hypothyroidism and who had not yet completed therapy for HCV were treated with levothyroxine sodium, 30 µg/d, and the dosage was increased as needed. Patients with overt hypothyroidism who completed their HCV therapy at the time thyroid disease was diagnosed and those with subclinical hypothyroidism were not treated with levothyroxine.

Levothyroxine therapy was continued for 4 weeks after HCV therapy was completed and then tapered during the next 8 weeks. Levels of TSH, FT3, and FT4 were obtained every 4 weeks during levothyroxine therapy and until resolution of hypothyroidism.

DIAGNOSIS AND MANAGEMENT OF HYPERTHYROIDISM

Patients with low TSH levels (<0.4 mIU/L) underwent testing for levels of total T3, FT3, total T4, FT4, and thyroid-stimulating immunoglobulin. A luciferase in vitro bioassay was used to determine thyroid-stimulating immunoglobulin levels (reference range, <130.0% of basal activity; Nichols Institute Diagnostics). Overt hyperthyroidism was defined as a low TSH level (<0.4 mIU/L) along with elevated levels of T3 (>194 ng/dL [3.0 mIU/L]), FT3 (>420 pg/dL [6.5 pmol/L]), T4 (>12.8 µg/dL [164.7 nmol/L]), and FT4 (>2.7 µg/dL [34.7 pmol/L]), whereas subclinical hyperthyroidism was defined as a low TSH level (<0.4 mIU/L) with reference-range levels of T3, FT3, T4, and FT4. In those with overt hyperthyroidism, an iodine 123–labeled thyroid scan (reference range, 15.0%–40.0% at 24 hours) was performed to differentiate thyroiditis from Graves disease.

Patients with overt hyperthyroidism were treated with β-blockers (atenolol, 50 mg/d) during HCV therapy, and the dosage was increased as needed. In addition, patients with Graves hyperthyroidism were treated with propylthiouracil at a dosage of 100 mg 3 times daily. Patients with subclinical hyperthyroidism were not treated with β-blockers or propylthiouracil.

Therapy for hyperthyroidism was continued for 4 weeks after HCV therapy was completed and then tapered during the next 8 weeks. Levels of TSH, FT3, and FT4 were obtained every 4 weeks during β-blocker therapy alone or in combination with propylthiouracil until resolution of hyperthyroidism.

STUDY OUTCOMES

The primary outcome of this study was the development of overt thyroid dysfunction during interferon alfa-2b and ribavirin therapy. Secondary outcomes included development of subclinical thyroid dysfunction, symptoms at the time thyroid disease was diagnosed, prevalence of thyroid autoantibodies, response to treatment of thyroid disease, and reversibility of thyroid dysfunction after completion of HCV therapy. Follow-up was performed until June 30, 2003, and the duration of follow-up was calculated as the time since the completion of HCV therapy until the last time that the patient was seen in the outpatient clinic.

STATISTICAL ANALYSIS

Continuous variables were compared using the unpaired, 2-tailed t test or the Mann-Whitney test. Data are expressed as mean ± SD for those variables that were normally distributed, and medians and interquartile range (IQR; 25th to 75th percentiles) for those with a nongaussian distribution. Categorical variables were compared using the χ2 test with Yates correction or the Fisher exact test. A comparison of patients with and without overt thy-
roid dysfunction was performed, and we calculated odds ratios (ORs) and 95% confidence intervals (CIs) for those variables that were significantly associated with the development of overt thyroid dysfunction. We performed statistical analysis using SPSS software, version 11.5 for Windows (SPSS Inc, Chicago, Ill), and a 2-tailed P value of less than .05 was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

A total of 225 men with baseline TSH levels within the reference range were enrolled in this study. The population was racially diverse, and nearly two thirds had HCV infection from use of injected drugs (Table 1). Most patients were infected with genotype 1, and the frequency was similar to the proportion reported among HCV-infected patients in the United States.17

INCIDENCE OF THYROID DYSFUNCTION

Among the 225 patients who were treated with interferon alfa-2b and ribavirin, 188 (83.6%) completed a full course of therapy. During treatment, overt thyroid disease was diagnosed in 15 (6.7%; 95% CI, 3.8%-10.8%) of the 225 patients, including hypothyroidism in 12 (5.3%; 95% CI, 2.8%-9.1%) and hyperthyroidism in 3 (1.3%; 95% CI, 0.3%-3.8%). In addition, 9 patients (4.0%; 95% CI, 1.8%-7.4%) received a diagnosis of subclinical thyroid disease, including subclinical hypothyroidism in 6 (2.7%; 95% CI, 1.0%-5.7%) and subclinical hyperthyroidism in 3 (1.3%; 95% CI, 0.3%-3.8%). Therefore, the overall incidence of thyroid dysfunction (overt and subclinical) in our male patient population was 10.7% (95% CI, 7.0%-15.4%). New-onset diabetes also developed in 2 patients (both with overt hypothyroidism) during HCV treatment. Thyroid dysfunction did not develop in any patient during the 6-month follow-up after HCV therapy was completed.

Patients who developed overt thyroid disease were significantly more likely to self-report a family history of thyroid disease in a first-degree relative than those without thyroid dysfunction (20.0% vs 2.4%; OR = 6.8; 95% CI, 2.2-18.1). The remaining patient characteristics shown in Table 1 did not differ significantly between patients with and without overt thyroid dysfunction.

DIAGNOSIS, MANAGEMENT, AND OUTCOME OF HYPOTHYROIDISM

The characteristics of the 12 patients with overt hypothyroidism are shown in Table 2. In addition, FT₃ and FT₄ levels were low in all 12 individuals at the time of diagnosis. At least 1 thyroid autoantibody was present in all 12 patients, including antithyroglobulin antibodies in 11 and antithyroid peroxidase antibodies in 10. Fatigue (12/12 [100%]), decreased appetite (11/12 [91.7%]), depression (9/12 [75.0%]), and myalgias (9/12 [75.0%]) were common symptoms at the time of the diagnosis of hypothyroidism. In contrast, none of these individuals had thyromegaly, thyroid nodules, bradycardia, cold intolerance, or edema. Deep tendon reflexes were not assessed.

Nine (75.0%) of the 12 patients with overt hypothyroidism were treated with levothyroxine, with 100.0% having resolution or improvement of clinical symptoms and 8 (66.7%) having normalization of TSH levels during HCV therapy. All 9 patients treated with levothyroxine were able to complete a full course of HCV therapy. Three patients were not treated with levothyroxine because hypothyroidism was diagnosed at the end of HCV treatment.

During a median follow-up of 24.4 months (IQR, 19.0-32.8 months) after the completion of HCV therapy, overt hypothyroidism resolved in 10 of the 12 patients (83.3%), and 2 individuals required long-term levothyroxine treatment. Subclinical hypothyroidism resolved spontaneously in all 6 patients after completion of HCV therapy.

DIAGNOSIS, MANAGEMENT, AND OUTCOME OF HYPERTHYROIDISM

The characteristics of the 3 patients with overt hyperthyroidism are shown in Table 3. In addition, FT₃ and FT₄ levels were obtained at the time of diagnosis in all 3 patients, and the levels were elevated in all 3 individuals. Thyroid-stimulating immunoglobulins were present in 2 of the 3 patients, and both of these individuals had hyperthyroidism. In contrast, none of the patients had hypercalcemia, weight loss, heat intolerance, or a warm, moist skin. The levels of FT₃ and FT₄ were normalized in 2 of 3 patients during HCV therapy.
had increased uptake on results of the 123I thyroid scan, findings that are compatible with a diagnosis of Graves disease. Patient 3 did not have thyroid-stimulating immunoglobulin detected and had 123I thyroid scan findings compatible with a diagnosis of thyroiditis. All 3 individuals reported nervousness, irritability, fatigue, insomnia, and weight loss, and 1 patient had a resting tremor and palpitations at the time of diagnosis. In contrast, none of these individuals had thymegaly, thyroid nodules, or heat intolerance. Deep tendon reflexes were not assessed.

All 3 patients with overt hyperthyroidism were treated with β-blockers, and the 2 individuals with Graves disease were also prescribed propylthiouracil. Although all of them had resolution or improvement of clinical symptoms, none had normalization of TSH levels during HCV therapy. Two of the 3 patients were able to complete a full course of HCV therapy, whereas 1 individual with Graves disease discontinued antiviral therapy after 16 weeks because of worsening hyperthyroidism, tachycardia, and palpitations.

During a median follow-up of 22.7 months (IQR, 21.4-31.0 months) after the completion of HCV therapy, overt hyperthyroidism resolved in 2 (66.7%) of the 3 patients, and 1 patient with Graves disease required long-term therapy for thyroid disease. Subclinical hyperthyroidism resolved spontaneously in all 3 patients after completion of HCV therapy.

### Table 2. Patient Characteristics and Laboratory Data of the Patients With Overt Hypothyroidism

<table>
<thead>
<tr>
<th>Patient No./ Age, y</th>
<th>Race</th>
<th>Week of Diagnosis†</th>
<th>TSH Level, mIU/L</th>
<th>Total T3 Level, ng/dL</th>
<th>Total T4 Level, µg/dL</th>
<th>Anti-TPO Tilters, IU/mL</th>
<th>Anti-Tg Tilters, IU/mL</th>
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</thead>
<tbody>
<tr>
<td>1/60 White</td>
<td>White</td>
<td>8</td>
<td>&lt;0.01</td>
<td>651.8</td>
<td>18.2</td>
<td>465.0</td>
<td>79.6</td>
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<tr>
<td>2/59 Hispanic</td>
<td>Hispanic</td>
<td>12</td>
<td>0.04</td>
<td>439.6</td>
<td>14.9</td>
<td>310.0</td>
<td>63.2</td>
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<tr>
<td>3/51 Hispanic</td>
<td>Hispanic</td>
<td>12</td>
<td>0.09</td>
<td>277.8</td>
<td>23.1</td>
<td>ND</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Abbreviations: 123I, iodine I 123–labeled; ND, not detected; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin. SI conversion factors: To convert T3 to nanomoles per liter, multiply by 0.0154; T4 to nanomoles per liter, multiply by 12.87.

†Indicates duration of interferon alfa-2b and ribavirin treatment before diagnosis of hypothyroidism.

### Table 3. Patient Characteristics and Laboratory Data of the Patients With Overt Hyperthyroidism

<table>
<thead>
<tr>
<th>Patient No./ Age, y</th>
<th>Race</th>
<th>Week of Diagnosis†</th>
<th>TSH Level, mIU/L</th>
<th>Total T3 Level, ng/dL</th>
<th>Total T4 Level, µg/dL</th>
<th>TSI, %</th>
<th>Uptake on 123I Scan, %</th>
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<tr>
<td>1/60 White</td>
<td>White</td>
<td>24</td>
<td>74.5</td>
<td>21.6</td>
<td>1.6</td>
<td>104.0</td>
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<td>68.3</td>
<td>15.7</td>
<td>0.9</td>
<td>91.3</td>
<td>83.5</td>
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<tr>
<td>3/40 African American</td>
<td>African American</td>
<td>12</td>
<td>59.2</td>
<td>11.3</td>
<td>0.7</td>
<td>ND</td>
<td>112.0</td>
</tr>
<tr>
<td>4/62 White</td>
<td>White</td>
<td>24</td>
<td>55.1</td>
<td>22.6</td>
<td>2.3</td>
<td>65.9</td>
<td>55.8</td>
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<tr>
<td>5/60 Hispanic</td>
<td>Hispanic</td>
<td>36</td>
<td>84.2</td>
<td>14.7</td>
<td>1.8</td>
<td>77.2</td>
<td>84.2</td>
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<tr>
<td>6/40 Hispanic</td>
<td>Hispanic</td>
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<td>46.8</td>
<td>18.3</td>
<td>3.3</td>
<td>76.6</td>
<td>ND</td>
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<tr>
<td>7/40 Hispanic</td>
<td>Hispanic</td>
<td>36</td>
<td>51.3</td>
<td>26.5</td>
<td>0.8</td>
<td>148.1</td>
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<tr>
<td>8/41 African American</td>
<td>African American</td>
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<td>89.9</td>
<td>13.2</td>
<td>0.4</td>
<td>72.9</td>
<td>65.5</td>
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<tr>
<td>9/41 African American</td>
<td>African American</td>
<td>36</td>
<td>63.5</td>
<td>21.5</td>
<td>2.1</td>
<td>ND</td>
<td>59.8</td>
</tr>
<tr>
<td>10/42 Other</td>
<td>Other</td>
<td>48</td>
<td>47.3</td>
<td>19.6</td>
<td>0.3</td>
<td>88.1</td>
<td>86.7</td>
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<tr>
<td>11/42 African American</td>
<td>African American</td>
<td>36</td>
<td>39.5</td>
<td>27.8</td>
<td>2.2</td>
<td>65.3</td>
<td>60.3</td>
</tr>
<tr>
<td>12/42 African American</td>
<td>African American</td>
<td>36</td>
<td>31.1</td>
<td>31.4</td>
<td>2.5</td>
<td>68.4</td>
<td>49.7</td>
</tr>
</tbody>
</table>

Abbreviations: 123I, iodine I 123–labeled; ND, not detected; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin; TSI, thyroid-stimulating immunoglobulins. SI conversion factors: To convert T3 to nanomoles per liter, multiply by 0.0154; T4 to nanomoles per liter, multiply by 12.87.

†Indicates duration of interferon alfa-2b and ribavirin treatment before diagnosis of hyperthyroidism.

The development of thyroid dysfunction during interferon alfa monotherapy in patients with HCV has been well described, and the incidence ranges from 2.5% to 34.3%,18-41 with a mean incidence of 6.6%.52 These studies have shown that hypothyroidism was more common than hyperthyroidism (3.8% vs 2.8%), and thyroid dysfunction occurred more often in female than in male patients (13.0% vs 3.0%).52 The strongest risk factors that were associated with an increased risk of development of thyroid disease during interferon alfa therapy were female sex and the presence of thyroid autoantibodies (particularly antithyroid peroxidase antibodies) before the initiation of therapy.21,26,31,35,42 Thyroid disease is less likely to develop in patients with chronic hepatitis B infection who are treated with interferon alfa than in those with chronic HCV infection, despite the use of higher doses of interferon alfa for the treatment of hepatitis B virus.35 This finding suggests that HCV and interferon alfa may
have a synergistic role in inducing thyroid disease during antiviral therapy.

To date, only a few studies have evaluated the incidence of thyroid dysfunction in HCV-infected patients treated with interferon alfa and ribavirin combination therapy. Ribavirin is a nucleoside analogue with a broad spectrum of activity against several RNA and DNA viruses. This drug is known to have immunomodulatory effects, and it is possible that ribavirin may stimulate the immune system alone or synergistically with interferon alfa to cause thyroid disease via an autoimmune mechanism.

The development of thyroid dysfunction during interferon alfa and ribavirin combination therapy has been reported to occur in 4.7% to 27.8% of patients, with a mean incidence of 12.1%. Therefore, the mean incidence of thyroid dysfunction in patients treated with interferon alfa and ribavirin combination therapy (12.1%) is higher than in those treated with interferon alone (6.6%). Similar to the published data on thyroid dysfunction in patients treated with interferon alone, these combination therapy studies have shown that hypothyroidism was more common than hyperthyroidism (8.1% vs 3.8%) and that thyroid dysfunction occurred more often in female than in male patients (17.7% vs 8.3%).

Our study found that the incidence of overt thyroid dysfunction during combination antiviral therapy in 225 male patients was 6.7% and was even higher (10.7%) if patients with subclinical disease were included. The incidence of thyroid dysfunction in our patients was higher than the 3.0% incidence reported in male patients treated with interferon monotherapy, but was similar to the mean incidence of 8.3% in male patients treated with interferon and ribavirin combination therapy.

Fatigue, decreased appetite, depression, and myalgias were common in our patients with overt hypothyroidism, whereas nervousness, irritability, fatigue, insomnia, and weight loss were prevalent in those with overt hyperthyroidism. Although these symptoms are common in patients with thyroid disease, they could easily be mistaken for adverse effects of HCV therapy, and thyroid dysfunction could have remained undiagnosed if the patients did not undergo routine periodic screening of TSH levels. Therefore, it is recommended that screening for thyroid disease be routinely performed in all patients with HCV infection who are treated with interferon alone or in combination with ribavirin. However, the optimal diagnostic strategy and frequency of testing are not known.

Despite the development of thyroid disease, all 12 of our patients with overt hypothyroidism and 2 of the 3 with overt hyperthyroidism were able to complete a full course of HCV treatment. This finding has also been noted by other investigators, but a reduction in the dose of antiviral therapy may be necessary in some patients. Although these findings suggest that antiviral therapy can be continued despite the development of thyroid disease, the impact of continuing interferon alfa and ribavirin therapy on the quality of life during treatment and long-term sequelae after therapy remain to be determined.

During long-term follow-up, 10 of the 12 patients with overt hypothyroidism and 2 of the 3 individuals with overt hyperthyroidism had resolution of their thyroid dysfunction and did not require long-term therapy. In addition, thyroid disease resolved spontaneously after completion of HCV therapy in all 9 patients with subclinical thyroid disease. These findings have been noted by other investigators and suggest that combination therapy for HCV can be continued, even in those who develop overt thyroid disease. However, thyroid disease may persist in some patients, thus necessitating long-term treatment.

In a review of the literature, Koh et al reported that interferon alfa–induced thyroid dysfunction was reversible in 61.2% of patients, including 55.8% of patients with hypothyroidism and 69.7% of those with thyrotoxicosis. Although the median follow-up was longer than 20 months in our patients with thyroid dysfunction, it is possible that longer follow-up may be needed to confidently establish resolution of thyroid disease. Patients who are treated with interferon alfa and ribavirin therapy should be informed about the risks of development of thyroid dysfunction and the possibility of the need for long-term treatment of their thyroid disease.

CONCLUSIONS

Our study demonstrates that overt thyroid dysfunction occurs in 6.7% of HCV-infected men treated with combined interferon alfa-2b and ribavirin. Based on our findings, we recommend that HCV-infected men undergo screening for thyroid disease before and during interferon alfa and ribavirin treatment, especially those with a family history of thyroid disease. Treatment of HCV can be safely continued in men who develop thyroid dysfunction, because thyroid disease responds well to treatment and is reversible in most individuals. Future studies to determine the optimal method and frequency of screening for thyroid dysfunction during HCV therapy and to evaluate the incidence and outcome of thyroid disease in HCV-infected patients treated with pegylated interferon in combination with ribavirin are needed.

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REFERENCES
