Accelerated Decline of Lung Function in COPD Patients With Chronic Hepatitis C Virus Infection*

A Preliminary Study Based on Small Numbers of Patients

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Study objectives: It has been suggested that chronic viral infection may increase the risk for development of COPD. This prospective study was designed to determine that chronic hepatitis C virus (HCV) infection is associated with accelerated decline of lung function in patients with COPD, and that antiviral therapy against HCV is effective for such patients.

Design: Prospective 5-year follow-up study.

Setting: University hospital.

Patients: Fifty-nine patients with COPD (group A, 15 HCV-negative ex-smokers; group B, 14 HCV-negative current smokers; group C, 14 HCV-positive ex-smokers; group D, 16 HCV-positive current smokers).

Interventions: After a 5-year follow-up period, 21 HCV-positive patients received interferon (IFN)-α therapy.

Measurements and results: The rate of annual decline in FEV₁ and diffusing capacity of the lung for carbon monoxide (DLCO) during the 5-year follow-up period were significantly higher in group B (ΔFEV₁, 59.7 mL/yr [SD, 17.5], p = 0.0008; ΔDLCO, 3.50%/yr [SD, 0.44], p < 0.0001) and group C (ΔFEV₁, 54.0 mL/yr [SD, 15.3], p = 0.0128; ΔDLCO, 3.36%/yr [SD, 0.28], p < 0.0001) than in group A (ΔFEV₁, 33.5 mL/yr [SD, 7.7]; ΔDLCO, 2.66%/yr [SD, 0.34]). Moreover, these parameters in group D (ΔFEV₁, 79.5 mL/yr [SD, 20.6]; DLCO, 4.5%/yr [SD, 0.40]) were also significantly higher than those in group B and group C. We evaluated the ΔFEV₁ after IFN therapy during the 3-year follow-up period in the 8 IFN responders and 13 IFN nonresponders. ΔFEV₁ in the IFN nonresponders did not significantly change during the 3-year follow-up period (before, 65.5 mL/yr [SD, 23.5]; after, 66.1 mL/yr [SD, 24.0]). However, ΔFEV₁ in the IFN responders significantly decreased (before, 68.4 mL/yr [SD, 26.2]; after, 57.3 mL/yr [SD, 23.6], p = 0.0116).

Conclusions: Our findings suggest that chronic HCV infection might accelerate decline in lung function in patients who already have COPD. (CHEST 2003; 123:596–599)

Key words: chronic HCV infection; cigarette smoking; COPD; decline of lung function

Abbreviations: CTL = cytotoxic T lymphocytes; DLCO = diffusing capacity of the lung for carbon monoxide; HCV = hepatitis C virus; IFN = interferon

One prevalent theory concerning the pathogenesis of COPD is of an abnormal balance between proteases and antiproteases in the lung.1 This theory proposes that increased numbers of neutrophils and macrophages, activated by cigarette smoke, produce large amounts of proteases and oxidants responsible for lung destruction.2 However, one study showed that patients with COPD have an increased number of T lymphocytes in central and peripheral airways, and that destruction of the lung is directly related to the number of T lymphocytes.3

Hepatitis C virus (HCV), an RNA virus first identified in 1989, is a major cause of posttransfusion and sporadic hepatitis. The most striking feature of
hepatitis C is the risk of persistent infection and progression to chronic liver disease. T lymphocytes are typically observed within the hepatic parenchyma in patients with chronic HCV hepatitis, and it has been suggested that HCV-specific cytotoxic T lymphocytes (CTL) may contribute to the pathologic consequences of HCV infection.4 Indeed, HCV-specific CTL have been shown to be an important component of the host immune response to HCV infection.5 Several reports have suggested that some HIV-seropositive persons may acquire an accelerated form of lung injury that has physiologic features, which are consistent with COPD, and that HIV-specific CTL may play an important role in the pathogenesis of COPD.6,7 Thus, the possibility that chronic viral infection may increase the risk for development of accelerated lung destruction may have broad biological relevance to the pathogenesis of COPD. Therefore, this prospective study was designed to determine that chronic HCV infection is associated with accelerated decline of lung function in patients with COPD, and that antiviral therapy against HCV is effective for such patients.

Materials and Methods

Thirty HCV-positive patients and 29 HCV-negative patients with COPD were randomly enrolled from the outpatient clinic of our institution. Anti-HCV antibody was measured with a first-generation or second-generation enzyme-linked immunosorbent assay (Ortho Diagnostics; Tokyo, Japan). Serum HCV RNA was detected by reverse transcription and nested polymerase chain reaction with primers derived from the highly conserved 5′-untranslated region of the viral genome, as described previously.8 HCV-positive patients were defined as anti-HCV and HCV RNA positive. All COPD patients had a history of former smoking (> pack-years) and an irreversible airflow limitation (reversibility < 10% of predicted FEV1 after 200 μg of inhaled salbutamol). Thus, all patients with COPD satisfied the American Thoracic Society criteria for COPD.9 Their regular medication consisted of theophylline and an inhaled anticholinergic drug, but none had received oral or inhaled corticosteroids. All patients received no medication during the 12-h period preceding the spirometric study. All study subjects gave their written informed consent for participation in this study, which was approved by the Ethics Committee of Osaka City University.

At the start of this study, the 59 patients with COPD were classified into four groups (group A, 15 HCV-negative ex-smokers; group B, 14 HCV-negative current smokers; group C, 14 HCV-positive ex-smokers; group D, 16 HCV-positive current smokers). Smoking status was monitored by a self-questionnaire at visits. Measurements of spirometric data were scheduled every 4 months and taken as the best from at least three satisfactory spirometric tracings. Spirometry was performed with a Chestac-25F system (Chest; Tokyo, Japan) by the same technician using the same spirometer. The diffusing capacity of the lung for carbon monoxide (DLCO) was measured by the single-breath carbon monoxide method at least twice. The 10-s breath-holding time was uniform over the follow-up period and between subjects. The rate of annual decline in FEV1 (milliliters per year) and DLCO (percentage per year) during the 5-year follow-up period was calculated for each subject. Briefly, we performed linear regression for each patient’s 5-year data. The decline in lung function appeared to be linear based on the degree of correlation determined by linear regression analyses. Linear regression analyses were performed using StatView-J 5.0 (SAS Institute; Cary, NC).

After the 5-year follow-up period, 21 HCV-positive patients who agreed to interferon (IFN-α)-therapy received 6 mIU of IFN-α (human lymphoblastoid IFN; Sumitomo Pharmaceuticals; Osaka, Japan) by IM injection three times a week for 24 weeks. We defined a response as the disappearance of HCV RNA from serum. We judged therapy to be effective if HCV RNA disappeared by the end of therapy and could not be detected during the 3-year follow-up period. We also evaluated the ΔFEV1 during the 3-year follow-up period after the end of IFN therapy in these patients.

Results

Clinical characteristics for all patients with COPD at the start of this study are shown in Table 1. Baseline spirometry revealed obstructive changes in all of the patients. The four groups were well matched with respect to age and number of pack-years. However, baseline values of FEV1 and DLCO were significantly lower in group B and group D than in group A. During the 5-year follow-up period, the amounts of cigarette smoking in group B and group D were comparable.

The rate of annual decline in FEV1 and DLCO during the 5-year follow-up period were significantly higher in group B (ΔFEV1, 59.7 mL/yr [SD, 17.5], p = 0.0008; ΔDLCO, 3.50%/yr [SD, 0.44], p < 0.0001) and group C (ΔFEV1, 54.0 mL/yr [SD, 15.3], p = 0.0128; ΔDLCO, 3.36%/yr [SD, 0.28], p < 0.0001) than in group A (ΔFEV1, 33.5 mL/yr [SD, 7.7]; ΔDLCO, 2.66% [SD, 0.34]; Fig 1). Moreover, these parameters in group D (ΔFEV1, 79.5 mL/yr [SD, 20.6]; ΔDLCO, 4.5%/yr [SD, 0.40]) were also significantly higher than those in group B and group C.

Eight of 21 HCV-positive patients who received IFN therapy were defined the IFN responders. We evaluated ΔFEV1 during the 3-year follow-up period.
Table 1—Clinical Characteristics of Study Subjects With COPD*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HCV Negative</th>
<th>HCV Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A (Ex-smoker)</td>
<td>Group B (Current Smoker)</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>12/3</td>
<td>12/2</td>
</tr>
<tr>
<td>Age, yr</td>
<td>59.5 (6.2)</td>
<td>56.9 (6.4)</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>59.6 (10.5)</td>
<td>50.0 (9.1)†</td>
</tr>
<tr>
<td>DLCO, %</td>
<td>62.0 (12.2)</td>
<td>49.8 (8.4)‡</td>
</tr>
<tr>
<td>Smoking history, pack-years</td>
<td>34.3 (6.5)</td>
<td>32.5 (7.2)</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>19.4 (9.3)</td>
<td>18.8 (6.6)‡</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>18.9 (8.8)</td>
<td>17.3 (7.6)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD) unless otherwise indicated. AST = aspartate aminotransferase; ALT = alanine aminotransferase.
†p < 0.05 compared with group A.
‡p < 0.01 compared with group A.
§p < 0.01 compared with group B.

After the end of IFN therapy in the 8 IFN responders and 13 IFN nonresponders, ΔFEV1 in the IFN nonresponders did not significantly change during the 3-year follow-up period (before, 65.5 mL/yr [SD, 23.5]; after, 66.1 mL/yr [SD, 24.0]; Fig 2). However, ΔFEV1 in the IFN responders significantly decreased (before, 68.4 mL/yr [SD, 26.2]; after, 57.3 mL/yr [SD, 23.6], p = 0.0116).

**Discussion**

Among COPD patients, ΔFEV1 and ΔDLCO in current smokers and ex-smokers were significantly higher in HCV-positive patients than in HCV-negative patients. Moreover, these parameters with or without chronic HCV infection were significantly higher in current smokers than in ex-smokers. These findings suggest that chronic HCV infection is associated with accelerated decline of lung function in patients with COPD, and that cigarette smoking augments the decline of lung function in COPD patients with chronic HCV infection.

The cellular mechanisms predisposing those with chronic HCV infection to decline of lung function are unclear. However, three potential mechanisms may be relevant to understanding the accelerated decline of lung function induced by chronic HCV infection. One is mediated by HCV-specific T lymphocytes. Although prevailing theories of the pathogenesis of COPD have focused on smoking-induced production of proteolytic enzymes by neutrophils and macrophages, recent morphometric analyses of lung biopsy sections from smokers have demonstrated a high correlation between number of cytotoxic T lymphocytes and the presence of lung destruction.10 A previous study reported that numbers of lymphocytes in BAL fluid are increased in patients with chronic HCV infection, suggesting that HCV infection might be a trigger of the development of lymphocyte alveolitis.11 These findings suggest that cytotoxic T lymphocytes induced by chronic HCV infection may contribute to the development of parenchymal lung destruction. This hypothesis would be strengthened if HCV-specific cytotoxic T lymphocytes could be found in the lungs of COPD patients with chronic HCV infection. Another potential mechanism recently hypothesized is that latent viral infections may be an important cofactor in the development of COPD.

![Figure 1](image1.png)

**Figure 1.** The rate of annual decline in FEV1 and DLCO during the 5-year follow-up period in each group with COPD.

![Figure 2](image2.png)

**Figure 2.** Comparison of the rate of annual decline in FEV1 between before (PRE) and after (POST) IFN therapy in the 8 IFN responders and 13 IFN nonresponders. O = ex-smokers, ● = current smokers, N.S. = not significant.
Adenoviral proteins, latently expressed in host epithelial cells, appear to amplify airway inflammation when exposed to cigarette smoke. A recent study suggested that cigarette smoke-induced lung inflammation was amplified in severe emphysema and that latent viral infection influenced this amplification process. Thus, chronic HCV infection may be a cofactor in smoking-induced decline of lung function. The third possible mechanism is that chronic liver disorder decreases glutathione synthesis in the liver, and an inadequate supply of glutathione in the lung would render the lung vulnerable to oxidative damage. We speculated that chronic HCV infection might increase susceptibility to lung injury through alteration of pulmonary glutathione homeostasis. However, since patients with chronic, even severe, HCV infection do not commonly have pulmonary symptoms, this may not be the case.

Chronic hepatitis C has been associated with several other syndromes, including cardiomyopathy and proliferative glomerulonephritis. This finding suggests that HCV may infect cells other than hepatocytes. Indeed, one study found that HCV may replicate in the heart, and that HCV infection may play a role in the development of dilated and hypertrophic cardiomyopathy. However, it is unknown whether IFN therapy is effective in treating patients with cardiomyopathy who have chronic HCV infection. These findings emphasize the need for studies to determine whether IFN therapy is effective in treating COPD patients with chronic HCV infection. In this study, we have clearly shown that IFN therapy is effective in preventing annual decline in FEV1 in COPD patients with chronic HCV infection. However, further studies will be required to confirm the localization and replication of HCV in lung tissues.

There are many biasing factors and methodologic limitations in the present study. Indeed, there are numerous opportunities for bias in many variables other than HCV infection that could affect the natural history of COPD. For example, amounts of inhaled toxic particles, exposure to passive smoke, respiratory infections, etc, may differ between patients. However, these other variables cannot be controlled in a long-term follow-up study. Moreover, the inflammatory profiles and immunologic characteristics of lung in COPD patients with chronic HCV infection and the change in number of T lymphocytes or in T-lymphocyte proportion in lung after IFN therapy should be examined in future studies. In conclusion, since this study had a limited sample size and the relatively low number of participants could allow confounders to influence the results, follow-up studies using larger numbers of COPD patients with chronic HCV infection need to be carried out. However, this prospective study determined that chronic HCV infection may accelerate decline in lung function in patients who already have COPD, and that cigarette smoking augmented the decline in lung function in these patients. Our results may have potentially important implications for understanding of the pathogenesis of and future treatment trials for COPD in conjunction with HCV.

REFERENCES

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