Interferon Therapy Induces the Improvement of Lung Function by Inhaled Corticosteroid Therapy in Asthmatic Patients With Chronic Hepatitis C Virus Infection*

A Preliminary Study

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Study objectives: Several reports have suggested that subsets of asthmatic patients with chronic viral infection fail to respond to corticosteroid therapy. Therefore, this study was designed to determine that asthmatic patients with chronic hepatitis C virus (HCV) infection fail to improve lung function by inhaled corticosteroid therapy, and that interferon (IFN) therapy against HCV is effective for such patients.

Design: Prospective observational study.

Setting: University hospital.

Patients: Forty asthmatic patients with chronic HCV infection.

Interventions: After a 4-week run-in period, all asthmatic patients received therapy with inhaled beclomethasone dipropionate (BDP), 400 μg twice daily for 6 weeks. After the first study, all asthmatic patients continued to receive inhaled BDP, and 30 HCV-positive asthmatic patients received IFN-α therapy for 6 months.

Measurements and results: Prebronchodilator and postbronchodilator FEV1 values were examined after a 4-week run-in period, after 6 weeks of BDP therapy, and at 1 year from the end of IFN therapy. After the 4-week run-in period as well as after 6 weeks of BDP therapy, there were no significant differences in either prebronchodilator or postbronchodilator FEV1 values among the three groups. However, 1 year after the end of IFN therapy, the mean prebronchodilator and postbronchodilator FEV1 values were significantly higher in the IFN responder group (n = 11) [prebronchodilator FEV1, 1.93 L (SD, 0.13 L); postbronchodilator FEV1, 2.28 L (SD, 0.15 L)] than in the IFN nontreatment group (n = 10) [prebronchodilator FEV1, 1.78 L (SD, 0.10 L); p = 0.01; postbronchodilator FEV1, 2.07 L (0.13 L); p = 0.005] or the IFN nonresponder groups (n = 19) [prebronchodilator FEV1, 1.79 L (SD, 0.15 L); p = 0.006; postbronchodilator FEV1, 2.07 L (SD, 0.18 L); p = 0.002]. Moreover, prebronchodilator and postbronchodilator FEV1 values were significantly higher only in the IFN responder group at 1 year after the end of IFN therapy than after the 4-week run-in period (prebronchodilator FEV1, p = 0.028; postbronchodilator FEV1; p = 0.002) or after 6 weeks of BDP therapy (p = 0.016 and p = 0.004, respectively).

Conclusions: Our findings suggest that chronic HCV infection in asthmatic patients is associated with impaired responses to inhaled BDP therapy and that intervention with IFN reverses such responses only in the IFN responder group.

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Key words: bronchial asthma; hepatitis C virus; inhaled corticosteroid; salbutamol

Abbreviations: BDP = beclomethasone dipropionate; HCV = hepatitis C virus; IFN = interferon

Guidelines for the treatment of bronchial asthma have focused on early intervention with anti-inflammatory therapy, particularly with inhaled corticosteroids. However, a subset of asthmatic patients fails to demonstrate a satisfactory response even to systemic corticosteroid therapy. Although several types of cells are likely to be involved in patients with corticosteroid-insensitive asthma, it is thought that T cells in asthmatic airways are one of the key cell types. In this regard, corticosteroid-insensitive asthmatic patients have increased numbers of activated T cells in the airways, and the activation of T cells from these patients is not inhibited by corticosteroid therapy.

Hepatitis C virus (HCV), an RNA virus that was
first identified in 1989, is a major cause of posttransfusion and sporadic hepatitis. The most striking feature of HCV is the risk of persistent infection and progression to chronic liver disease. T cells are typically observed within the hepatic parenchyma in patients with chronic HCV hepatitis, and it has been suggested that HCV-specific cytotoxic T cells may contribute to the pathologic consequences in various organs. Moreover, several reports have suggested that subsets of asthmatic patients with chronic viral infection fail to respond to corticosteroid therapy. Therefore, this study was designed to determine whether asthmatic patients with chronic HCV infection fail to achieve improved lung function by inhaled corticosteroid therapy, and to determine that interferon (IFN)-α therapy against HCV is effective for such patients.

**Materials and Methods**

Forty-eight HCV-positive patients with a diagnosis of asthma according to the American Thoracic Society guidelines were recruited into this study. These patients were randomly selected from a region (Osaka City, Japan) with an extraordinarily high incidence of chronic HCV infection. Eight patients were lost during the follow-up period as a result of cardiovascular disease, hepatocellular carcinoma, or transfer to another hospital. 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. HCV-positive patients were defined as being anti-HCV and HCV RNA-positive. All asthmatic patients were nonsmokers, and their regular medication consisted of β2-adrenoceptor agonists, as rescue medication for the relief of acute symptoms, and theophylline. No asthmatic patients were receiving oral or inhaled corticosteroids. No medications were changed during this study. All patients had a history of mild and stable asthma, and they were aware of asthma symptoms but easily tolerated them at the start of the study. Moreover, no patients had a history of respiratory infection for at least the 4-week period preceding the study. All subjects gave their written informed consent for participation in the study, which was approved by the Ethics Committee of Osaka City University.

After the 4-week run-in period, all asthmatic patients received inhaled beclomethasone dipropionate (BDP), 400 μg twice daily for 6 weeks. Each patient was then given salbutamol, 2.5 mg, by ultrasonic nebulizer (NE-12; Omron Co; Tokyo, Japan) at maximum output. FEV1 was recorded (Chestac-25F system; Chest Co; Tokyo, Japan) thereafter at 10-min intervals for 30 min. The postbronchodilator FEV1 value was evaluated as the maximal increase in FEV1 after salbutamol administration.

After the first study, all patients continued to receive inhaled BDP, and 30 HCV-positive patients who agreed to receive therapy with IFN-α (human lymphoblastoid IFN; Sumitomo Pharmaceuticals; Osaka, Japan) received 6 MIU IFN-α by IM injection three times a week for 6 months. 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 IFN therapy and could not be detected during the follow-up period. At 1 year after the end of IFN therapy, prebronchodilator and postbronchodilator FEV1 values also were examined.

**Statistical Analysis**

All values were expressed as the mean (SD). Multiple comparisons among the groups were analyzed by one-way analysis of variance. When analysis of variance revealed a significant difference, the Bonferroni correction was applied. Statistical significance was defined as p < 0.05.

**Results**

The clinical characteristics of the 40 asthmatic patients with chronic HCV infection are shown in Table 1. The three groups were well-matched with respect to age and baseline lung function. However, increased levels of aspartate aminotransferase and alanine aminotransferase were found in all three groups. After the 4-week run-in period, there was no significant difference in either prebronchodilator or postbronchodilator FEV1 values among the three groups. After 6 weeks of BDP therapy, there was also no significant difference in either prebronchodilator or postbronchodilator FEV1 values among the three groups. Moreover, we found no significant difference in prebronchodilator and postbronchodilator FEV1 values between those measured after the 4-week run-in period and those measured after 6 weeks of BDP therapy in all three groups.

One year after the end of IFN therapy, we also evaluated prebronchodilator and postbronchodilator FEV1 values in the setting of treatment with inhaled BDP therapy. Eleven of 30 asthmatic patients with chronic HCV infection were IFN responders. Prebronchodilator and postbronchodilator FEV1 values were significantly higher in the IFN responder group (prebronchodilator FEV1, 1.93 L [SD, 0.13 L]; postbronchodilator FEV1, 2.28 L [0.15 L]) than in the IFN nontreatment group (prebronchodilator FEV1, 1.78 L [SD, 0.10 L]; p = 0.01; postbronchodilator FEV1, 2.07 L [SD, 0.13 L]; p = 0.005) or the IFN nonresponder group (prebronchodilator FEV1, 1.79 L [0.15 L]; p = 0.006; postbronchodilator FEV1, 2.07 L [SD, 0.18 L]; p = 0.002) (Fig 1, 2). Moreover, prebronchodilator and postbronchodilator FEV1 values were significantly higher only in the...
In this study, we found that inhaled BDP therapy did not significantly improve prebronchodilator and postbronchodilator FEV$_1$ values after 6 weeks of BDP therapy in patients in any of the three groups. However, previous studies have reported that the baseline value of FEV$_1$ after inhaled steroid therapy markedly improved in steroid-naive asthmatic patients. Moreover, prebronchodilator and postbronchodilator FEV$_1$ values were significantly higher 1 year after the end of IFN therapy than after 6 weeks of BDP therapy in the IFN responder group, but not in the IFN nontreatment group or the IFN nonresponder group.

**Discussion**

In this study, we found that inhaled BDP therapy did not significantly improve prebronchodilator and postbronchodilator FEV$_1$ values after 6 weeks of BDP therapy in patients in any of the three groups. However, previous studies have reported that the baseline value of FEV$_1$ after inhaled steroid therapy markedly improved in steroid-naive asthmatic patients. Moreover, prebronchodilator and postbronchodilator FEV$_1$ values were significantly higher 1 year after the end of IFN therapy than after 6 weeks of BDP therapy in the IFN responder group, but not in the IFN nontreatment group or the IFN nonresponder group.

Thus, it is unlikely that IFN administration directly influenced the baseline value of FEV$_1$ apart from any effect on HCV-induced airway responses. These findings suggest that chronic HCV infection is associated with impaired responses to inhaled BDP therapy and that IFN therapy reversed such responses only in the IFN responder group.

Although the cellular mechanisms predisposing asthmatic patients with chronic HCV infection to steroid resistance are unclear, three potential mechanisms may be relevant to understanding steroid resistance in these patients. One possible mechanism is related to HCV-induced cytotoxic T cells. One report has suggested that latent adenoviral infection can induce steroid resistance in an allergen-induced inflammatory response. Latent adenoviral infection increased the number of CD8$^+$ cells in the airways, which is consistent with the expected cytotoxic T-cell response to viral infection. Therefore, it seems likely that cytotoxic T cells induced by chronic HCV infection contribute to the development of airway inflammation in asthmatic airways. Indeed, a previous study reported that the numbers of lymphocytes in BAL fluid are increased in patients with chronic HCV infection, suggesting that HCV infection might be a trigger for the development of airway inflammation. Another possible mechanism hypothesized in another report is that latent viral infections may be an important cofactor in the development of airway inflammation. For example, adenoviral proteins, which are latently expressed in host epithelial cells, appear to amplify airway inflammation when exposed to allergens. The third possible mechanism is that abnormal liver function in HCV-positive asthmatic patients might have important effects on the metabolism of and responses to anti-inflammatory drugs. However, since in the present study all asthmatic patients received inhaled

![Figure 1. Change in prebronchodilator FEV$_1$ after the 4-week run-in period, after 6 weeks of BDP therapy, and at 1 year after the end of IFN therapy in the IFN nontreatment group, the IFN nonresponder group, and the IFN responder group.](Image)

![Figure 2. Change in postbronchodilator FEV$_1$ values after the 4-week run-in period, after 6 weeks of BDP therapy, and at 1 year after the end of IFN therapy in the IFN nontreatment group, the IFN nonresponder group, and the IFN responder group.](Image)

Table 1—Clinical Characteristics of Study Subjects*

<table>
<thead>
<tr>
<th>Subjects, No. (M/F)</th>
<th>IFN Nontreatment Group</th>
<th>IFN Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Age, yr</td>
<td>51.9 (4.5)</td>
<td>50.7 (6.0)</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>72.5 (24.5)</td>
<td>77.1 (26.8)</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>69.8 (18.5)</td>
<td>72.3 (21.8)</td>
</tr>
<tr>
<td>FEV$_1$, % predicted</td>
<td>87.4 (6.3)</td>
<td>85.5 (5.5)</td>
</tr>
<tr>
<td>FEV$_1$/FVC, %</td>
<td>65.3 (7.2)</td>
<td>64.4 (7.0)</td>
</tr>
<tr>
<td>FEV$_1$, L</td>
<td>1.80 (0.11)</td>
<td>1.80 (0.17)</td>
</tr>
</tbody>
</table>

*Values given as mean (SD), unless otherwise indicated. AST = aspartate aminotransferase; ALT = alanine aminotransferase.

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BDP, but not systemic corticosteroids, and since serum theophylline concentrations did not differ significantly among the three groups, this possibility does not appear to be operative.

HCV has been associated with several other syndromes, including cardiomyopathy\(^ {16} \) and proliferative glomerulonephritis.\(^ {17} \) These findings suggest that HCV may infect cells other than hepatocytes. Indeed, a 1996 study\(^ {18} \) has determined 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 asthmatic patients with chronic HCV infection. In this study, we have shown clearly that prebronchodilator and postbronchodilator FEV\(_1\) values were significantly increased only in the IFN responder group. However, further study using a larger sample size will be required to confirm this finding.

There are many bias factors and methodological limitations in the present study. The evidence provided to support our hypothesis that chronic HCV infection may affect airway inflammation and play a role in resistance to inhaled steroid therapy in asthmatic patients requires further examination. For example, a comparison of inflammatory markers and immunological patterns between HCV-negative and HCV-positive asthmatic patients should be performed. In addition, levels of cytokines and mediators such as interleukin-5 and eosinophil cationic protein, and preferably some sputum data, should be obtained before and after IFN therapy in future studies. In conclusion, our results suggest that chronic HCV infection is associated with impaired responses to inhaled BDP therapy in asthmatic patients and that intervention with IFN reverses such responses to inhaled BDP only in IFN responders.

REFERENCES


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