

## Original Article

# Effect of interferon- $\alpha$ on pulmonary function and airway responsiveness in patients with chronic hepatitis C

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### ABSTRACT

**Background:** Interferon (IFN)- $\alpha$  is the only approved treatment for chronic hepatitis C. Interstitial pneumonia and, rarely, exacerbation of bronchial asthma have been reported as adverse pulmonary effects of IFN- $\alpha$  treatment. The purpose of the present study was to clarify whether IFN- $\alpha$  treatment affects pulmonary function and airway responsiveness in patients with chronic hepatitis C.

**Methods:** We studied 17 patients (nine males and eight females; mean age 46 years; range 30–62 years) with chronic active hepatitis C diagnosed by serum tests and liver biopsy. Pulmonary function tests included vital capacity (VC), forced expiratory volume in 1 s (FEV<sub>1</sub>), forced expiratory flow in the middle half of the forced vital capacity (FVC<sub>25–75%</sub>), total lung capacity and carbon monoxide diffusing capacity of the lung (D<sub>LCO</sub>), which was adjusted for hemoglobin concentration. Airway responsiveness was measured by methacholine inhalation challenge and determination of the provocative concentration of methacholine causing a 20% fall in FEV<sub>1</sub> (PC<sub>20</sub>). These tests were performed before and 3 months after initiation of IFN- $\alpha$  therapy.

**Results:** No patient developed interstitial pneumonia, although there was a tendency for the hemoglobin-adjusted D<sub>LCO</sub> to decrease. Other pulmonary function

test parameters were not affected. Overall, there was no significant change in PC<sub>20</sub> (from 15.0 to 11.4 mg/mL). In three patients whose initial PC<sub>20</sub> was within the normal range, airway hyperresponsiveness was induced and one patient developed bronchial asthma after IFN- $\alpha$  therapy.

**Conclusions:** These findings suggest that IFN- $\alpha$  induces airway hyperresponsiveness to methacholine in a few patients with chronic hepatitis C.

**Key words:** airway responsiveness, carbon monoxide diffusing capacity, chronic hepatitis C, interferon- $\alpha$ , methacholine, pulmonary function.

### INTRODUCTION

Infection with hepatitis C virus (HCV) is the most common cause of chronic viral hepatitis worldwide and 20–30% of patients develop liver cirrhosis or hepatocellular carcinoma. Interferon (IFN)- $\alpha$  is widely used as the only approved therapy for chronic hepatitis C.<sup>1</sup> Although the rate of the long-term or sustained response, in which serum aminotransferase is normal and no HCV-RNA is detectable after the cessation of therapy, is only 15–25%, IFN- $\alpha$  therapy usually leads to rapid eradication of viremia. The side effects of IFN include an influenza-like reaction with fever and chills, proteinuria, bone marrow suppression, fatigue, depression, alopecia and autoimmune diseases, such as various thyroid disorders.<sup>2</sup> As an adverse pulmonary effect, a number of cases of interstitial pneumonia or pneumonitis have been reported.<sup>3–5</sup> The characteristic clinical features of interstitial pneumonia include respiratory symptoms, such as fever, dyspnea

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and cough, diffuse reticular interstitial infiltrates on chest X-rays, restrictive impairment with reduced diffusion capacity on pulmonary function testing and arterial hypoxemia. Discontinuation of IFN with occasional corticosteroid use leads to resolution in most cases. Monitoring of pulmonary function testing, especially diffusion capacity, has been used for the diagnosis of drug-induced interstitial pneumonia at an early stage. Recently, exacerbation of bronchial asthma has been reported as a new side effect of IFN- $\alpha$  therapy.<sup>6</sup> Two patients developed severe exacerbation of asthma, which resolved promptly following discontinuation of IFN and the use of corticosteroid therapy. However, it is not known whether IFN- $\alpha$  induces bronchial asthma or airway hyperresponsiveness (AHR), which is a characteristic phenomenon and mostly attributable to airway inflammation of asthma, in patients without underlying asthma.

In the present study, we investigated the effects of IFN- $\alpha$  therapy on pulmonary function and airway responsiveness in patients with chronic hepatitis C.

## METHODS

### Subjects

Seventeen patients (nine males and eight females; mean age 46 years; range 30–62 years) with chronic hepatitis C diagnosed by elevated serum aminotransferase concentrations, anti-HCV and HCV-RNA in the serum and chronic active hepatitis on liver biopsy, were enrolled in the study. There were nine smokers, three ex-smokers and five subjects who had never smoked. Two patients had seasonal rhinitis and one had diabetes mellitus, but none had bronchial asthma or chest X-ray abnormalities.

Six million units natural IFN- $\alpha$  every day for 2 weeks and three times a week for 6 months was given intramuscularly. Pulmonary function and airway responsiveness were measured before and 3 months after initiation of treatment. No patients were receiving Chinese herbal medicine or any medication known to affect airway tone or responsiveness. None had respiratory complaints or findings of pulmonary infections during the 2 months prior to each testing day. If an abnormal change in each parameter was found, the parameter was followed up after 6 months treatment. Patients exhibiting a long-term or sustained response (normalization of the serum aminotransferase and undetectable HCV-RNA for at least 6 months after the cessation of IFN therapy) were identified as IFN- $\alpha$  responders.

Informed consent was obtained from all patients prior to the study.

### Pulmonary function testing

Spirometry and diffusing capacity were determined using computerized equipment (model CHESTAC-33; CHEST MI, Tokyo, Japan). The vital capacity (VC), forced expiratory volume in 1 s (FEV<sub>1</sub>), forced expiratory flow in the middle half of the forced vital capacity (FVC<sub>25–75%</sub>) and total lung capacity (TLC) were determined according to standard techniques. The carbon monoxide diffusing capacity of the lung (D<sub>LCO</sub>) was measured by the single breath method and was adjusted for hemoglobin (Hb) concentration according to the following equation of Cotes *et al.*:<sup>7</sup>

Values for pulmonary function tests are expressed as a predicted percentage.

$$\text{Hb-adjusted } D_{LCO} (\text{males}) = \frac{\text{observed } D_{LCO} (10.22 + \text{Hb})}{1.7 \text{ Hb}}$$

$$\text{Hb-adjusted } D_{LCO} (\text{females}) = \frac{\text{observed } D_{LCO} (9.38 + \text{Hb})}{1.7 \text{ Hb}}$$

### Airway responsiveness

Bronchial challenge tests to methacholine were performed with a DeVilbiss nebulizer (model 646; DeVilbiss Health Care, Somerset, PA, USA) driven by compressed air at a flow rate of 5 L/min according to the standard method proposed by the Japanese Society of Allergology in 1982.<sup>8,9</sup> Briefly, after baseline spirometry and inhalation of physiologic saline, patients inhaled aerosols from solutions of doubling doses of methacholine at concentrations of 0.078, 0.156, 0.313, 0.625, 1.25, 2.5, 5, 10 and 20 mg/mL. The aerosols were inhaled by tidal breathing for 2 min and FEV<sub>1</sub> was measured immediately after each inhalation. The tests were discontinued when FEV<sub>1</sub> decreased by more than 20% compared with the baseline value or when the highest concentration (20 mg/mL) was reached. The provocative concentration of methacholine causing a 20% fall in FEV<sub>1</sub> was calculated as PC<sub>20</sub>. A PC<sub>20</sub> value  $\leq$  10 mg/mL was defined as AHR.<sup>10,11</sup>

### Statistical analysis

Results are expressed as the mean  $\pm$  SD for VC, FEV<sub>1</sub>, FVC<sub>25–75%</sub>, TLC and Hb-adjusted D<sub>LCO</sub>. The PC<sub>20</sub> values are expressed as the geometric mean  $\pm$  SD. Statistical analysis was performed using the Wilcoxon signed ranks test.  $P < 0.05$  was considered significant.

**RESULTS**

Although all patients complained of influenza-like symptoms and fatigue after IFN- $\alpha$  therapy had been initiated, these side effects were mild and no patient developed interstitial pneumonia. Five of 17 patients (29%) were found to be IFN- $\alpha$  responders, in whom a long-term or sustained response to IFN therapy was achieved.

Table 1 shows the changes in pulmonary function tests before and during treatment. There was a tendency for the Hb-adjusted  $D_{LCO}$  ( $P = 0.07$ ) to decrease from  $118 \pm 19$  to  $108 \pm 17\%$ , although each value was within the normal range. No other pulmonary function parameters were affected.

The changes in the  $PC_{20}$  of methacholine are shown in Fig. 1. There was no significant change between before and during therapy in  $PC_{20}$  values overall ( $15.0$  vs  $11.4$  mg/mL;  $P = 0.14$ ). However, three of 17 patients (18%) with  $PC_{20} > 10$  mg/mL at baseline developed new AHR without asthma-like symptoms. Table 2 summarizes the characteristics of three patients, one male and two females, consisting of one responder and two non-responders to IFN therapy. Although patient 2 had a history of seasonal rhinitis, each methacholine challenge test was performed out of season and he was asymptomatic. Patient 2 was also a current smoker, but his smoking habit had not changed during therapy. Patients 1 and 2 still showed AHR after the cessation of IFN therapy and patient 2 developed bronchial asthma thereafter. His asthma severity was mild intermittent, requiring a short-acting inhaled  $\beta_2$ -adrenergic receptor agonist on an as-needed basis. However, the  $PC_{20}$  of patient 3 returned to normal after IFN therapy. The  $FEV_1$  values of the three patients had not changed during IFN therapy and the follow-up periods. There were no

differences between these three patients and the other 14 patients with regard to the clinical features of chronic hepatitis C, including age, duration of disease, the serum level or genotype of HCV-RNA, histologic findings and cumulative IFN dose or pattern of response to therapy. The  $PC_{20}$  value of the patient with AHR before therapy was still below the normal level during therapy, but she remained asymptomatic.

**DISCUSSION**

The present study shows that AHR to methacholine was induced in three of 17 patients (18%) with chronic hepatitis C but without asthma or other respiratory disease

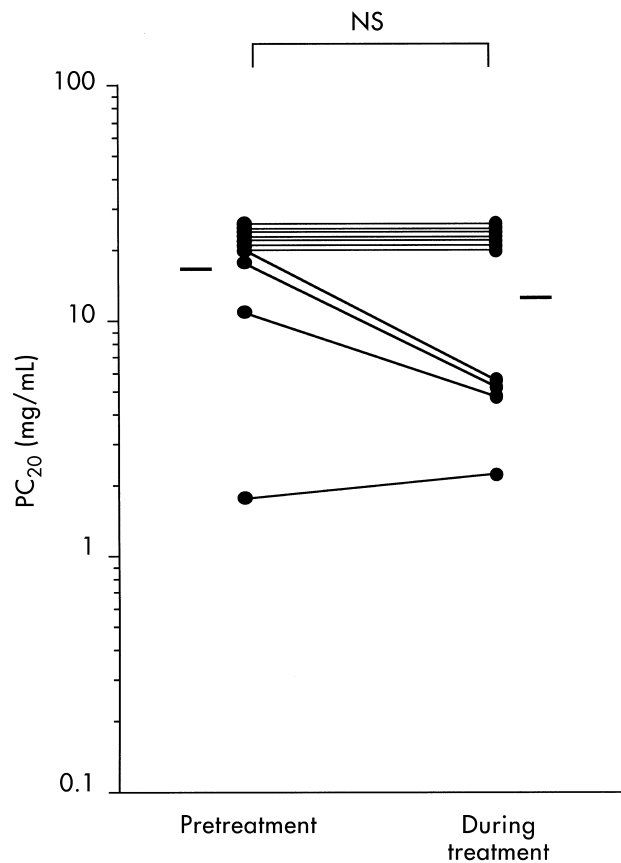
**Table 1** Changes in pulmonary function tests before and during interferon treatment

	Pretreatment	During treatment	P
VC	106 $\pm$ 12	105 $\pm$ 16	0.60
FEV <sub>1</sub>	102 $\pm$ 12	98 $\pm$ 13	0.13
FEF <sub>25-75%</sub>	96 $\pm$ 20	92 $\pm$ 20	0.34
TLC	112 $\pm$ 10	109 $\pm$ 9	0.45
$D_{LCO}$ *	118 $\pm$ 19	108 $\pm$ 17	0.07

Data are the mean  $\pm$  SD of the predicted percentage.

\*Adjusted for hemoglobin concentration.

VC, vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; FEF, forced expiratory flow in the middle half of the forced vital capacity; TLC, total lung capacity;  $D_{LCO}$ , carbon monoxide diffusing capacity of the lung.



**Fig. 1** Changes in  $PC_{20}$  of methacholine (mg/mL) before and during interferon (IFN)- $\alpha$  treatment. Although there was no significant change overall, a decrease from the normal to the abnormal range in  $PC_{20}$  was found in three patients. One patient with seasonal rhinitis had airway hyperresponsiveness before treatment, but no change was observed during treatment.

**Table 2** Characteristics of three patients who acquired new airway hyperresponsiveness

	Patient		
	1	2	3
Age (years)	45	59	62
Gender	Female	Male	Female
Response to the IFN- $\alpha$ therapy	Responder	Non-responder	Non-responder
Smoking habit	Never smokee	Current smoker	Ex-smoker
Coexisting disease	–	Seasonal rhinitis	–
Allergic status	Non-atopic	Atopic	Non-atopic
WBC (/ $\mu$ L)	6700	5100	5500
% Eosinophils	0	0	4
Total IgE (U/mL)	< 5	2300	210
Specific IgE to common inhalant allergens	Negative	Timothy, Ragweed	Negative
PC <sub>20</sub> (mg/mL)			
Before therapy	17.8	11.0	> 20.0
After initiation of therapy	5.2	4.8	5.6
1 year follow up	4.0	3.4	12.0
FEV <sub>1</sub> (L)			
Before therapy	2.30	2.07	1.70
After initiation of therapy	2.30	2.06	1.72
1 year follow up	2.26	2.00	1.78
Subsequent development of asthma	–	+	–

IFN, interferon; WBC, white blood cells; FEV<sub>1</sub>, forced expiratory volume in 1 s.

3 months after IFN- $\alpha$  therapy had been initiated. Although the cumulative dose or duration of IFN therapy and having no asthmatic symptoms were common among the three patients, it is unlikely that the induction of AHR was associated with the patients' characteristics, the serum level or genotype of HCV-RNA or the response to IFN therapy. Furthermore, the follow-up study revealed the diversity of prognosis of the three patients who acquired AHR; two still had AHR after the cessation of IFN therapy, one of whom developed mild intermittent asthma thereafter and one remained asymptomatic, while the other patient's airway responsiveness returned to normal.

When interpreting PC<sub>20</sub> results for an individual patient, several factors that will worsen or improve AHR should be taken into consideration. Concerning the quality of the patient's spirometry maneuvers, there were no changes in FEV<sub>1</sub> when testing each PC<sub>20</sub> value in all three patients. Short-term within-subject repeatability studies when patients are in a stable clinical state show that the 95% confidence intervals for repeat determinations of methacholine PC<sub>20</sub> lie within  $\pm 1.5$  doubling doses.<sup>12</sup> However, in the three patients in the present study, the changes in PC<sub>20</sub> exceeded 1.5 doubling doses either during the IFN therapy or during the follow-up

periods compared with baseline PC<sub>20</sub> values. Atopy is also an important factor for AHR. Because methacholine challenges were performed out of season in patient 2, who had a history of seasonal rhinitis, the effect of recent antigen exposure was suggested to be excluded. Furthermore, although patient 2 was a current smoker, it was unlikely that his smoking habit induced new AHR after only a 3 month interval because he showed no baseline airway obstruction and his airway caliber, measured as the FEV<sub>1</sub>, had not changed. Therefore, we cannot explain the induction of AHR in our patients by the known factors that affect the PC<sub>20</sub> value of methacholine as stated above. It is suggested that new AHR was induced by IFN therapy.

The interpretation of the induction of AHR within non-asthmatic patients is complex because of the lack of information and it must be undertaken with caution. Kennedy *et al.* reported a significant increase in AHR during a 2 year follow up among apprentices exposed to metalworking fluids.<sup>13</sup> In the study of Kennedy *et al.*,<sup>13</sup> new AHR (baseline PC<sub>20</sub> > 8 mg/mL and follow-up PC<sub>20</sub>  $\leq$  8 mg/mL methacholine) was induced in four of 157 control subjects (3%), some of whom had atopy or a smoking habit, but no underlying asthma. Compared with the incidence rate of new AHR in that study, the rate

in the present study of three of 17 patients (18%) is higher, although there are several differences between the two studies and a simple comparison is difficult.

Possible explanations for the normalization of PC<sub>20</sub> in patient 3 after the cessation of IFN therapy may be as follows. One is that the effect of IFN on her airway responsiveness may be limited to only during therapy, in contrast with the two other patients, who acquired a long-lasting effect on their airway responsiveness, suggesting a diversity of each patient's response to IFN. Another explanation is that her decrease in PC<sub>20</sub> during the IFN therapy may be false positive due to errors such as diluting methacholine solutions. Indeed, this false positive result may have occurred, but the change in PC<sub>20</sub> in patient 3 during IFN therapy increased beyond the repeatability range of  $\pm 1.5$  doubling doses, as reported previously.<sup>12</sup> Therefore, the former explanation is suggested as more possible.

The present study also showed that the Hb-adjusted D<sub>LCO</sub> tended to decrease 3 months after IFN- $\alpha$  therapy had been initiated. It has been reported that interstitial pneumonia induced by IFN- $\alpha$  typically occurs between 8 and 12 weeks after the initiation of therapy,<sup>2</sup> suggesting the possibility that IFN- $\alpha$  therapy may induce subclinical changes, leading to the onset of interstitial pneumonia. However, those changes were within the normal range and actually no patients developed interstitial pneumonia in the present study. No other parameters were affected during therapy, as reported previously.<sup>14</sup> The incidence rate of interstitial pneumonia is estimated to be 0.1%<sup>15</sup> and that of exacerbation of bronchial asthma is extremely low. As long as IFN therapy remains effective and useful, it should be elucidated what predisposing factors cause these adverse pulmonary effects to occur in such a small proportion of susceptible patients with chronic hepatitis C.

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