

Chronic Hepatitis C Virus Infection is Associated with More Severe Asthma

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ABSTRACT

Background: Chronic hepatitis C virus (HCV) infection causes intra- and extra-hepatic complications. The elimination of HCV has been reported to be beneficial for asthmatic patients with HCV infection. Therefore, we hypothesized that chronic HCV infection might be associated with the severity of asthma.

Methods: Asthmatic patients were prospectively enrolled from 13 outpatient settings. Hepatitis B surface (HBs) antigen and HCV-RNA were measured at the time of enrollment and evaluated along with the clinical characteristics of the patients including the age, sex, duration of asthma, atopic status, smoking history, and treatment step according to the Global Initiative for Asthma guideline.

Results: Of 1327 asthmatic patients, 1258 patients (94.8%) were treated with inhaled corticosteroids, 18 patients were positive for HBs antigen (1.4%), and 32 patients (2.4%) were positive for HCV-RNA. When compared with HCV-RNA-negative patients, HCV-RNA-positive patients required significantly more drugs for the treatment of asthma. No such relationship was observed in patients with positive HBs antigen. A multivariate logistic regression analysis showed that the male sex, a long duration of asthma, status as a current smoker, and HCV-RNA positivity were independently associated with more severe asthma.

Conclusions: These results suggest that chronic HCV infection is an independent factor that predisposes asthmatic patients to more severe asthma. The evaluation of chronic HCV infection may be helpful for the management of severe asthmatic patients without obvious factors associated with severe asthma.

KEY WORDS

Global Initiative for Asthma, hepatitis B virus, hepatitis C virus, severe asthma, severity of asthma

ABBREVIATIONS

GINA, Global Initiative for Asthma; HBs, hepatitis B surface; HCV, hepatitis C virus.

INTRODUCTION

Since the presence of eosinophilic airway inflammation is recognized as a consistent feature of naïve asthma, there is no doubt that inhaled corticosteroids

play a central role in the treatment of asthma.¹ Inhaled corticosteroids have drastically improved both the symptoms and the prognosis for this chronic inflammatory disease.¹⁻³ Most persistently asthmatic patients are well or totally controlled with inhaled cor-

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Authors' contributions: TN collected the data, analyzed it and wrote the manuscript. AY designed the study, collected the data, analyzed it and revised manuscript. HO, MY, MS, YH, SH, and HY

collected the data, reanalyzed it and revised manuscript. NH and NK reanalyzed the data and revised the manuscript. All the authors had full access to all of the data in the study. AY explicitly declares that he has had access to and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Received 1 July 2010. Accepted for publication 17 November 2010.

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ticosteroids alone, but there are some who need more drugs in addition to inhaled corticosteroid.^{4,5} Such a population, presenting persistent symptoms despite add-on therapy with a class of controllers other than inhaled corticosteroids, is defined as having severe asthma.⁶ Although the underlying factors that predispose asthmatic patients to severe asthma are not yet fully understood, multiple factors including tobacco smoking,⁷ genetic factors,⁸ a predominance of neutrophilic inflammation in the airway,⁹ increased tissue injury and remodeling,¹⁰ a molecular background including reduced histone deacetylase-2 expression,⁸ chronic stress,¹¹ and poor adherence¹² are supposed to be involved in this unfavorable phenotype.

Chronic infection with hepatitis C virus (HCV) is believed to cause intra- and extra-hepatic complications. Among the extra-hepatic complications, the lung is one major target organ.¹³ HCV infection resulted in a worsening of lung function, interstitial pneumonitis and pulmonary fibrosis in some patients. In patients with preexisting asthma, HCV infection is associated with an accelerated decline in lung function.¹⁴ Successful treatment in the elimination of HCV with interferon-gamma is associated with a prevention of declining lung function in patients with persistent asthma complicated with chronic HCV infection.^{14,15} These results suggest that infection with HCV may affect the severity of asthma and, thereby, the treatment of asthma.

From this point of view, we hypothesized that chronic HCV infection might be involved in the severity of asthma. To test this hypothesis, we evaluated the relationship between chronic HCV infection in asthmatic patients and the Global Initiative for Asthma (GINA) treatment step, which is associated with the severity of asthma.¹

METHODS

SUBJECTS AND DESIGN

The protocol of this multicenter, cross-sectional study was approved by the institutional review board of Hiroshima University (Ethical Review Board for Clinical Study of Hiroshima University, approved number 247), and Ehime University (Ethical Review Board for Clinical Study of Ehime University Hospital, approved number 16-54). All patients gave informed consent before any study-related procedures were performed. We prospectively recruited all chest physician-diagnosed asthmatic patients who visited 13 outpatient settings in Japan (Hiroshima University-related hospitals and clinics: Hiroshima University Hospital, Chugoku Rousai Hospital, Hiroshima Allergy and Respiratory Clinic, Hiroshima City Funairi Hospital, Hiroshima General Hospital of West Japan Railway Company, Hiroshima Prefectural Hospital, Ikuta Medical Clinic, JA Hiroshima General Hospital, Takahashi Medical Clinic and Tsuya Clinic; Ehime

University-related hospitals: Ehime University Hospital, Ehime Prefectural Imabari Hospital, and Uwajima City Hospital) between October 18, 2004, and December 12, 2004. The diagnosis of asthma was made by specialized pulmonologists according to typical asthmatic symptoms including wheezing, coughing, dyspnea, and chest tightness that are often more problematic at night.

Eligible patients were typical asthmatic patients who had been treated in an outpatient setting for at least 6 months. During the recruitment period, we included the asthmatic patients regardless of the past medical history of HCV treatment. We excluded patients who were judged as having poor adherence to the medication, who presented obvious malignancy, or who had obvious other respiratory diseases or other systemic diseases requiring oral corticosteroids (i.e., Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis). The clinical characteristics of the patients, including age, sex, duration of asthma, atopic disposition, smoking history, and medical treatment for asthma, were recorded at the time of enrollment. Based on the GINA guidelines,¹ atopic asthmatic patients are defined as those who presented positive skin-prick tests or higher levels of serum IgE specific to common environmental allergens compared to the normal range. Current smokers were defined as those having a smoking status with a greater than a 10 pack-year smoking history.¹⁶ Based on Japanese guideline produced by Japanese Society of Allergology, we defined the "more severe asthma patients" as patients who required step 4 treatment in Japanese Society of Allergology guideline, because the treatment step 4 in Japanese guideline is the most severe group. When we applied our definition into GINA guideline, treatment step 4 in Japanese guideline were equivalent of treatment step 4-5 in GINA guideline. Therefore, we defined "more severe asthma patients" as patients who required step 4-5 treatment in GINA guideline. Thus, we compared patients who required GINA treatment at steps 1-3 or steps 4-5 to control asthmatic symptoms. In the HCV-RNA positive asthmatics treated with GINA 4-5 treatment steps, the lung function data performed within 3 months during the registration period were also collected.

HEPATITIS VIRAL INFECTION

Following enrollment, the patients who participated in the study were evaluated for hepatitis B surface (HBs) antigen and anti-HCV antibody. Most patients had not been examined for HCV infection. HBs antigen was measured with a chemiluminescent enzyme immunoassay (Lumipulse II HBsAg, Fujirebio Inc., Tokyo, Japan). Anti-HCV antibody was measured with a third-generation chemiluminescent enzyme immunoassay (Lumipulse II Ortho HCV, Ortho Clinical Diagnostics, Tokyo, Japan). HCV-RNA was fur-

ther measured using reverse transcription-PCR (AmpliCap GT HCV MONITOR Test version 2.0, Roche Diagnostics, Tokyo, Japan) in patients whose HCV antibody levels were higher than the normal range.

STATISTICAL ANALYSIS

Results are shown as median values and ranges. Groups were compared using the Mann-Whitney U-test for median values and the Fisher's exact test or Chi-squared test for categorical data. Factors associated with more severe asthma (patients who required GINA treatment at steps 4-5 to control asthmatic symptoms) were evaluated using a logistic regression model. Variables with statistically significant results in the univariate analysis were included in a multivariate analysis. Differences were considered statistically significant when p -values were < 0.05 . All analyses were performed using SPSS for Windows, version 12.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

During the 8 week recruitment period, 1790 consecutive asthmatic patients were evaluated for enrollment. Two hundred eighty-five patients declined to participate, and 178 patients did not meet the enrollment criteria. Overall, 1327 asthmatic patients met the inclusion criteria and agreed to participate in the current study. The characteristics of 1327 asthmatic patients from 12 outpatient settings are shown in Table 1. Of the 1327 asthmatic patients, 1258 patients (94.8%) were treated with inhaled corticosteroids. Additionally, among these 1327 patients, there were 18 patients positive for HBs antigen (1.4%) and 67 patients positive for HCV antibody (5.0%). Among the 67 asthmatic patients who were HCV antibody-positive, 32 patients (2.4%) were also HCV-RNA-positive (Table 1). There were no subjects who had received interferon therapy, except for 1 patient, who showed both positive for HCV antibody and negative for HCV-RNA. Among 815 female subjects, 70 (8.6%) were current smokers, whereas 96 of 512 (18.8%) were current smokers among the male subjects ($P < 0.001$ by Fisher's exact test).

The frequencies of HBs antigen-positive and HCV antibody-positive patients were not different from the reported frequencies among more than a million people from the general population (i.e., blood donors) in Japan,¹⁷ when age was matched for comparison (data not shown).

When compared with HCV-RNA-negative patients, HCV-RNA-positive patients required significantly more drugs for the treatment of asthma (Fig. 1). No such relationship was observed in patients with HCV antibody or HBs antigen positivity. To identify the factors associated with more severe asthma (patients who required GINA treatment at steps 4-5 to control asthmatic symptoms), logistic multiple regression analysis was performed. The univariate analysis

Table 1 Characteristics of asthmatic patients at enrollment

Characteristics	Asthmatic patients ($n = 1327$)
Median age-yrs (range)	57.8 (15-94)
Female sex-no. (%)	815 (61.4)
Duration of asthma-yrs (range)	8.3 (1.0-71.0)
Atopic predisposition-no. (%)	693 (52.2)
Never/Ex/Current smoker-no. (%)	932 (70.2)/229 (17.2)/ 166 (12.5)
GINA treatment steps-no. (%)	
Step 1	69 (5.2)
Step 2	335 (25.2)
Step 3	443 (33.4)
Step 4	408 (30.7)
Step 5	72 (5.4)
Hepatitis virus	
HCV antibody positivity-no. (%)	67 (5.0)
HCV-RNA positivity-no. (%)	32 (2.4)
HBs antigen positivity-no. (%)	18 (1.4)

GINA, Global Initiative for Asthma; HCV, hepatitis C virus; HBs, hepatitis B surface.

showed that male sex, a long duration of asthma, current smoker status, and HCV-RNA positivity were significantly associated with more severe asthma, whereas age, atopic disposition, outpatient settings (in general hospital or clinic), HCV antibody positivity, and HBs antigen positivity were not (Table 2). The multivariate analysis showed that male sex, a long duration of asthma, current smoker status, and HCV-RNA positivity were significantly and independently associated with more severe asthma (Table 2).

To clarify the characteristics of HCV-RNA positive patients who required GINA treatment at steps 4-5 to control asthmatic symptoms, we summarized the data obtained from this group in Table 3. Among 20 HCV-RNA positive patients treated with GINA treatment at steps 4-5, lung function data were available from 12 patients (data of 5 patients were not available, and 3 could not perform lung function test accurately). As a result, airflow obstruction was observed in this category of patients in spite of more aggressive step 4-5 treatments.

DISCUSSION

This study suggested that the existence in the bloodstream of HCV-RNA, but not of anti-HCV antibody or HBs antigen, is associated with the severity of asthma. Univariate and multivariate analyses also demonstrated that chronic HCV infection is a significant and independent factor predisposing asthmatic patients to more severe asthma. Therefore, chronic HCV, but not HBV infection, was considered an important factor for predisposing asthmatic patients to more severe asthma. In addition, we also found that both HBs antigen and HCV antibody positivity rates

	GINA treatment step					
	1	2	3	4	5	
HCV-RNA (+) <i>n</i> = 32	0 (0%)	5 (16%)	7 (22%)	17 (53%)	3 (9%)	<i>P</i> = 0.033
	12 (38%)			20 (63%)		
HCV-RNA (-) <i>n</i> = 1295	69 (5%)	330 (26%)	436 (34%)	391 (30%)	69 (5%)	<i>P</i> = 0.003
	835 (64%)			460 (36%)		
HBs antigen (+) <i>n</i> = 18	1 (6%)	5 (28%)	8 (44%)	2 (11%)	2 (11%)	<i>P</i> = 0.393
	14 (78%)			4 (22%)		
HBs antigen (-) <i>n</i> = 1309	68 (5%)	330 (25%)	435 (33%)	406 (31%)	70 (5%)	<i>P</i> = 0.321
	833 (64%)			476 (36%)		

Fig. 1 Association between medical treatment steps defined by Global Initiative for Asthma and chronic infection with hepatitis C virus (HCV) or hepatitis B virus. Asthmatic patients complicated with HCV infection required more add-on therapy with a class of controllers other than inhaled corticosteroids than did patients without HCV infection. Hepatitis B viral infection showed no effect on the treatment of asthma.

Table 2 Factors associated with more severe asthma

Variables	Odds ratio	95% confidence interval			<i>P</i> -value
		Lower	Upper		
Univariate analysis					
Age (≥65 yrs)	1.010	0.798	1.278	0.933	
Sex (male)	1.482	1.179	1.863	0.001	
Duration (≥8 yrs)	1.289	1.028	1.615	0.028	
Atopic predisposition (+)	0.893	0.714	1.117	0.321	
Smoking (current smoker)	1.770	1.275	2.456	0.001	
Outpatients settings (clinic)	1.113	0.884	1.402	0.362	
HCV antibody (+)	1.283	0.779	2.114	0.327	
HCV-RNA (+)	3.025	1.466	6.245	0.003	
HBs antigen (+)	0.500	0.164	1.528	0.224	
Multivariate analysis					
Sex (male)	1.422	1.126	1.795	0.003	
Duration (≥8 yrs)	1.319	1.049	1.658	0.018	
Smoking (current smoker)	1.679	1.201	2.346	0.002	
HCV-RNA (+)	2.997	1.443	6.223	0.003	

Logistic multiple regression analysis was performed to identify the factors associated with more severe asthma (patients who required GINA treatment at steps 4-5 to control asthmatic symptoms). HCV, hepatitis C virus; HBs, hepatitis B surface.

in asthmatic patients were not significantly different from those of the general population when adjusted for age.¹⁷ These results suggest that chronic HCV infection is related to the more severe phenotype in asthma but is not a determinant of predisposition to asthma.

We speculate that the underlying mechanism predisposing asthmatic patients with chronic HCV infection to more severe asthma may be an alteration of

Table 3 Characteristics of severe asthmatic patients with chronic HCV infection

Characteristics	
Median age-yrs (range), <i>n</i> = 20	65.0 (38-78)
Female sex-no. (%), <i>n</i> = 20	12 (60.0)
Duration of asthma-yrs (range), <i>n</i> = 20	13.5 (1.0-50.0)
Atopic predisposition-no. (%), <i>n</i> = 20	8 (40.0)
Never/Ex/Current smoker-no. (%), <i>n</i> = 20	11 (55.0)/4 (20.0)/5 (25.0)
Pack-years of smoking history (range), <i>n</i> = 9	30 (18-60)
GINA treatment steps-no. (%), <i>n</i> = 20	
Step 4	17 (85.0)
Step 5	3 (15.0)
FEV ₁ -L (range), <i>n</i> = 12	1.76 (0.80-2.96)
Percent predicted FEV ₁ -% (range), <i>n</i> = 12	67.8 (45.6-121.5)
FEV ₁ /FVC-% (range), <i>n</i> = 12	68.1 (42.9-85.0)
Serum IgE-IU/mL (range), <i>n</i> = 15	180 (13-2200)
Peripheral blood eosinophils-μL (range), <i>n</i> = 18	200 (0-1500)

GINA, Global Initiative for Asthma; HCV, hepatitis C virus.

airway inflammation caused by HCV. Kanazawa *et al.* reported that airway CD8⁺ T cells are increased in asthmatic patients complicated with chronic HCV infection when compared with asthmatic patients without HCV infection.¹⁸ They also found that successful treatment of HCV infection with interferon therapy in asthmatic patients resulted in a reduction of CD8⁺ T cells in the airway. On the other hand, Moorman *et*

al. discovered that HCV core protein directly induces interleukin-8 expression and production from human lung fibroblasts.¹⁹ Because interleukin-8 is a key inflammatory mediator that contributes to neutrophilic inflammation and bronchoconstriction, they concluded that a direct pro-inflammatory role of HCV core protein may injure the airway in HCV-infected patients. Our findings are consistent with these suggested notions, and HCV may worsen the severity of asthma via the alteration of airway inflammation. The altered airway inflammation in HCV-RNA positive asthmatics may result in remodeling of the airway and airflow obstruction as shown in Table 3. In addition, it should be noted that the HCV-RNA positivity rate in HCV antibody positive patients (47.8%) was not high in the current study, suggesting half of patients had experienced a transient HCV infection.

Our results also demonstrated that a long duration of asthma, male sex, and current smoker status were independent factors involved in the severity of asthma. A recent review suggested that a longer duration of asthma is associated with more severe disease and irreversible airflow limitation, which was thought to be caused by airway remodeling.¹⁰ The association between a long duration of asthma and more severe asthma observed in the current study is consistent with this notion. Similarly, tobacco smoking in asthmatic patients is regarded as an important factor of severe asthma.⁷ In the current study, an association between current smoker status and more severe asthma was also observed. In addition, we found that male sex is associated with more severe asthma, a finding that may not be consistent with previous notions. Though there are several controversial reports, severe asthma seems to be more common in women than in men.^{4,5}

There are several limitations in the current study. First, detailed information regarding asthma control and lung function was not available. However, we believe that the GINA treatment step evaluation reflected the severity of disease in this large scale population. Second, the diagnosis of asthma was physician-based. All of the physicians who participated in the current study were pulmonologists, helping to explain the extremely high adoption rate of inhaled corticosteroids (94.8%). Therefore, we believe that the diagnosis is likely accurate. Finally, the adherence of patients to the therapy was also physician-evaluated. Though we excluded patients who were judged as having poor adherence, the process may not be sufficiently rigorous. Recently, Gamble *et al.* tried to distinguish non-adherence to both inhaled and oral corticosteroid therapy in asthmatic patients by assessing prescription records and blood exams.¹² Because non-adherence to medication is one of the important factors that predisposes asthmatic patients to false severe asthma, in future studies it will be necessary to precisely evaluate the adherence to medica-

tion regimens in asthmatic patients complicated with chronic HCV infection.¹²

In conclusion, this study demonstrated that chronic HCV infection is one of the independent factors predisposing asthmatic patients to more severe asthma. Although asthmatic patients complicated with chronic HCV infection account for just a fraction of asthmatic patients, we also conclude that the evaluation of chronic HCV infection should be considered to manage severe asthmatic patients without obvious factors associated with severe asthma.

ACKNOWLEDGEMENTS

We thank Drs. Naoko Deguchi, Masamoto Funaki, Hironobu Hamada, Ryoji Ito, Takaho Ikuta, Toru Kadowaki, Yoshihiro Kitahara, Kimiko Tsuji, Jun Takahashi, Takafumi Tsuya, and Jitsuro Yanagida for their assistance in the data collection.

This study was supported in partially by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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