

Interstitial Pneumonitis after Combination Therapy with Pegylated Interferon α -2b and Ribavirin for Chronic Hepatitis C

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Pulmonary toxicity is a rare but potentially fatal side effect occurring during interferon (IFN) α treatment for chronic hepatitis C. We present a 47-year-old woman who had chronic hepatitis C and was treated with pegylated IFN α -2b in combination with ribavirin, with a good virological response by week 10 of therapy. Then the patient began to complain of dyspnea on exertion and a dry cough. A diagnosis of interstitial pneumonitis was made according to the results of chest X-rays, high resolution computed tomography and bronchoalveolar lavage analysis. Pegylated IFN α -2b has a longer absorption and elimination half-life than conventional IFN α -2b and a comparable potency to conventional IFN α -2b. Although the tolerability of pegylated IFN α is comparable to that of conventional IFN α , pulmonary toxicity may occur more frequently with long-acting pegylated IFN α therapy at an inappropriately high dose. Based on a MEDLINE search up to 2004, we believe that this is the first reported case of a patient recovering from interstitial pneumonitis associated with pegylated IFN α -2b for chronic hepatitis C. Physicians should keep in mind the possibility of this complication when treating chronic hepatitis C patients with pegylated IFN α -2b and ribavirin combinational therapy. (*Chang Gung Med J* 2007;30:92-7)

Key words: chronic hepatitis C, pegylated interferon alpha-2b, interstitial pneumonitis.

Pegylated interferon (IFN) α -2b in combination with ribavirin has become the optimal choice of therapy for chronic hepatitis C, as recommended by the American Association for the Study of Liver Diseases in 2004.⁽¹⁾ This long-acting, semi-synthetic form of IFN α -2b was developed by attaching an ethylene glycol polymer to the natural protein in order to reduce its rate of absorption, reduce renal and cellular clearance, and decrease its immunogenicity. The major limitation of conventional IFN α -2b is its rapid clearance from the blood stream, with an elimination half-life of 3 to 8 hours. In contrast, the serum elimination half-life of pegylated

IFN α -2b is approximately 40 hours and clinically significant levels persist for an entire week after administration.^(2,3) Despite its great efficacy in the treatment of hepatitis C, IFN α has a number of side effects, such as a flu-like syndrome (fever, chills, tachycardia, malaise, myalgia, headache), leukopenia, thrombocytopenia, depression, seizures, thyroid dysfunction, alopecia and activation of buccal lichen planus.⁽⁴⁾ Reported pulmonary toxicities, including sarcoidosis, bronchiolitis obliterans organizing pneumonia, pleural effusion, interstitial pneumonitis and exacerbation of bronchial asthma, occur rarely and develop after a long period of treatment.⁽⁵⁻⁷⁾ Here, we

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describe a patient with chronic hepatitis C who developed interstitial pneumonitis following pegylated IFN α -2b treatment in combination with ribavirin.

CASE REPORT

A 47 year-old woman was well up to April 2004 when she began to experience generalized malaise and fatigue. She was found to have abnormal liver function and the presence of hepatitis C virus (HCV) antibodies in June 2002. She had no history of collagen vascular disease, smoking or occupational exposure. The laboratory findings revealed: aspartate transaminase (AST) 84 units/liter, alanine transaminase (ALT) 81 units/liter, α -fetoprotein 4.58 ng/ml and total bilirubin 0.8 g/dL. Liver echo showed multiple hypoechoic nodules and liver cirrhosis. Echo-guided liver biopsy demonstrated chronic active hepatitis with minimal activity and the probability of cirrhosis. Immunohistochemical stain for HCV produced a positive result. HCV RNA determined by polymerase chain reaction (PCR) assay was positive (COBAS AMPLICOR™, Roche Diagnostics, Branchburg NJ, USA) and genotype 2b (INNO-LIPA™ HCV 2 test, Innogenetics, Belgium). All serum markers for hepatitis B virus produced negative results.

Combination therapy with pegylated IFN α -2b 100 μ g/week intramuscularly and ribavirin 800 mg/day orally was initiated on the 29th April 2004. She began to suffer from dyspnea on exertion and dry cough in July 2004, eight weeks after treatment. Crepitant rales were audible on auscultation. HCV RNA by PCR assay was undetectable, and her serum AST and ALT had returned to normal. Other laboratory data showed: white blood cells (WBC) 4,600/ μ l, hemoglobin (Hb) 11.9 g/dl, platelets 8.5×10^4 / μ l, segments 65.8%, lymphocytes 16.7%, monocytes 15.4%, eosinophils 1.9%, basophils 0.2%, free T4 1.27 ng/ μ l and thyroid stimulating hormone (TSH) 0.783 μ IU/ml. Immunological examination revealed negative anti-nuclear antibody and anti-mitochondrial antibody. Chest radiography (Fig. 1) showed diffuse interstitial infiltration in both lungs. High resolution computed tomography (HRCT) (Fig. 2) revealed diffusely distributed, patchy, ground-glass opacities with mosaic patterns, and interstitial infiltration and centrilobular nodules in both lungs that were more prominent in the lower lung fields. No

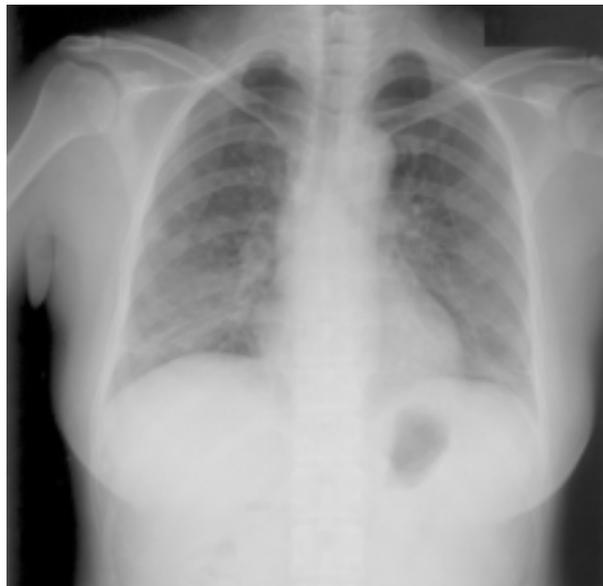


Fig. 1 Chest radiography showing bilateral interstitial opacities that are greater in both the lower lobes than in the upper lobes.

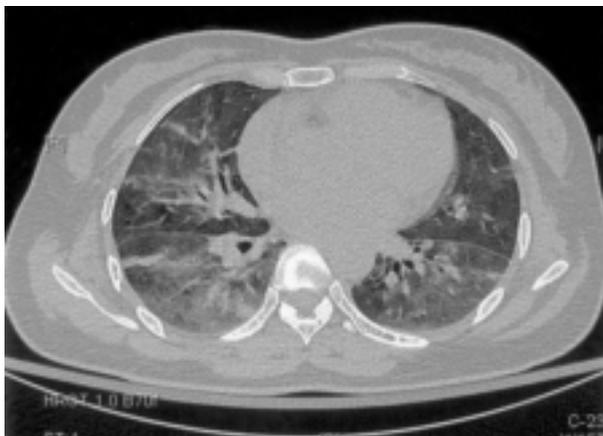


Fig. 2 High resolution computed tomography demonstrating bilateral patchy, ground-glass opacities with mosaic patterns and interstitial infiltration.

mediastinal or hilar lymphadenopathy was identified. Bronchoscopy and bronchoalveolar lavage (BAL) were performed without isolating an infectious agent causing the pulmonary condition. Specimens obtained from BAL contained: macrophages 50%, lymphocytes 44% and neutrophils 6%, with a normal T helper to T suppressor ratio of 2.3. Pulmonary function tests revealed low total lung capacity (TLC) with low diffusion capacity (TLCO) and residual

volume (RV). (First second forced expiratory volume and the forced vital capacity ratio (FEV1/FVC) 84%, FEV1 61.5%, FVC 61.3%, TLCO 45.7%, RV 71.2%, TLC 67.2%). A six-minute walking test also showed decreased walking distance (91%) and marked oxygen desaturation (87% with room air) by pulse oxymetry. Combination therapy was discontinued at week 10 because of the suspicion that the pegylated IFN α -2b had induced interstitial pneumonitis. Symptomatic improvement was noted within one month of cessation of the therapeutic regimen. Prednisolone 10 mg/day was administered for four weeks as mild dyspnea persisted after the treatment was discontinued. The patient recovered gradually and follow-up chest radiography in September 2004 showed marked regressive change. She has since led a normal life after two months of follow-up. An objective causality assessment using the Naranjo adverse drug reaction (ADR) probability scale revealed that the adverse drug reaction was probably related to pegylated IFN α -2b and ribavirin combination therapy in our patient. (The patient's score was seven.)⁽⁸⁾

DISCUSSION

The effects of IFN α include antiviral activity, growth regulation, inhibition of angiogenesis, regulation of cell differentiation, enhancement of major histocompatibility complex antigen expression, and enhancement of the activity of natural killer cells and cytotoxic T lymphocytes.⁽²⁾ Interstitial pneumonitis is a rare side effect of IFN α therapy, with an incidence of around 0.4% in a past series report.⁽⁷⁾ Although the precise mechanism is not clear, immunomodulatory reactions, such as enhanced cytotoxic T-cell action, and induction of soluble interleukin-2 receptor, interleukin-18 binding protein, platelet-derived growth factor and tumor growth factor- β , may help explain some of the observed effects.⁽⁹⁾ Typically, cell-mediated pneumonitis has a strong relationship with accumulated dosage and a high degree of reversibility. In addition, HCV itself may play a cooperative role in the pathogenesis of interstitial pneumonitis,⁽¹⁰⁾ but no such case has been reported among hepatitis B patients treated with IFN α .

Pegylated IFN α -2b has a longer absorption and elimination half-life than conventional IFN α -2b, and a comparable potency to conventional IFN α -

2b.⁽²⁾ Although the tolerability of pegylated IFN α is comparable to that of conventional IFN α ,⁽²⁾ IFN toxicity is generally dose- and duration-dependent.⁽⁵⁾ For example, Glue et al. reported that pegylated IFN α -2b produced a dose-related reduction in WBC, neutrophils and platelets, and a dose-related increase in oral temperature, serum neopterin and serum 2'5'-oligoadenylate synthetase activity.⁽¹¹⁾ This leads us to speculate that pulmonary toxicity may occur more frequently with long-acting pegylated IFN α therapy at an inappropriately high dose. In a phase 3 randomized control trial performed by Manns et al., a significantly higher sustained virological response rate was demonstrated when comparing a 1.5 μ g/Kg/week dose to a lower dose of pegylated IFN α -2b and the conventional IFN α -2b therapy.⁽¹²⁾ On the other hand, Buti et al. reported that a higher dose of pegylated IFN α -2b (3 μ g/Kg/week) had no additional benefit with respect to reducing HCV RNA levels or increasing virological response rates.⁽¹³⁾ Furthermore, the lower dose of pegylated IFN α -2b (0.5 μ g/Kg/week) without the higher dose (1 μ g/Kg/week) was associated with a better quality of life compared to conventional IFN α -2b therapy. These findings indicate that a higher dose may induce various toxicities more frequently in a dose-dependent manner without additional benefits.

In a review of English literature through an online MEDLINE search up to 2004, we found 17 cases of interstitial pneumonitis associated with various types of IFN α treatment for chronic hepatitis C.^(6,7,9,14-19) Natural IFN α was used in six cases, conventional IFN α -2b in nine, pegylated IFN α -2a in one and pegylated IFN α -2b in one. Our case is the 18th case associated with any type of IFN, and the first case associated with pegylated IFN α -2b and complete recovery. The only limit of the present case is lack of transbronchial biopsy, which was not done because of patient hesitation. However, no mediastinal lymphadenopathy on the CT scan could exclude sarcoidosis and support our diagnosis. The total accumulated dose of conventional IFN α -2b in the 9 cases varied from 36 MU to 700 MU, with a median of 324 MU. The duration of treatment in the 17 reported cases varied from 2 weeks to 24 weeks, with a median of 6 weeks. In nine cases, recovery was achieved only after steroids were administered due to persisting symptoms. In six cases, recovery was achieved with discontinuation of the therapy.

Another two cases developed progressive dyspnea with worsening condition despite steroids use,^(17,19) and one of them developed acute respiratory distress syndrome and died from multiple organ failure.⁽¹⁹⁾ With regard to combination drugs, herbal drugs were administered in four cases, ribavirin in another four cases and no herbal drug treatment in the other nine cases.

The clinical data of the three cases associated with pegylated IFN α therapy is shown in Table 1. In case 1,⁽⁶⁾ interstitial pneumonitis had occurred one year previous to this event, when the patient received combination therapy with conventional IFN α -2b and ribavirin. The second course of combination therapy with pegylated IFN α -2a and ribavirin was initiated as repeat PCR testing for HCV RNA reverted to positive results. The optimal dose of pegylated IFN α -2a (180 μ g/week) was used. In both case 2⁽²⁰⁾ and in our case, pegylated IFN α -2b was administered at a dose greater than 1.5 μ g/Kg/week in combination with ribavirin. Interestingly, the HCV genotype was 2b in both case 1 and in our case.

The development of interstitial pneumonitis during treatment of chronic HCV with pegylated IFN α -2b and ribavirin can be attributed to several factors. First, higher doses of pegylated IFN α -2b (> 1.5 to 2.0 μ g/Kg/week) may be associated with more pulmonary toxicity because of its longer half-life and sustained action.^(12,13) Second, for patients with HCV genotype 2 or 3 and a lower HCV RNA titer (\leq 2 million copies/ml), the optimal dose of pegylated IFN α -2b is lower, since less is required to achieve a sustained virological response.⁽²⁰⁾ Finally, combination drugs may also have an additive effect. Ishizaki et al. reported that Sho-Saiko-To, a Chinese herbal drug, can induce interstitial pneumonitis through

immunomodulatory reactions.⁽⁹⁾ In contrast, ribavirin inhibits replication of RNA and DNA virus directly. Although cough and dyspnea may develop, there has never been a case reported of interstitial pneumonitis with ribavirin use alone.^(4,5)

In conclusion, the dosage of pegylated IFN α -2b should be adjusted according to the patient's weight, genotype of HCV and level of HCV RNA titer, as well as clinical symptoms and virological response. Once evidence of pulmonary injury is demonstrated, therapy must be withdrawn immediately and steroids can be administered if symptoms persist.

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Table 1. Clinical Data of the Three Reported Patients with Interstitial Pneumonitis during Pegylated IFN α Therapy for Chronic Hepatitis C

Reference and year	Case no/ age(yr)/sex	Type of FN α	Dose of IFN α	Duration of treatment	Symptoms	Outcome	HCV genotype
Kumar et al. 2002 ⁽⁶⁾	1/48/F	Pegylated IFN α -2a	180 μ g/week	6 weeks	Dry cough and fever	Recovered with steroids	2b
Abi-Nassif et al. 2003 ⁽²⁰⁾	2/49/M	Pegylated IFN α -2b	150 μ g/week	2 weeks	Cough and dyspnea	Died despite steroid use	NA
Present case	3/48/F	Pegylated IFN α -2b	100 μ g/week	10 weeks	Dyspnea and dry cough	Recovered with steroids	2b

Abbreviations: F: female; M: male; IFN: interferon; NA: not available.

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慢性 C 型肝炎以 pegylated 干擾素 α -2b 及 ribavirin 治療後 併發間質性肺炎

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肺部毒性是以 pegylated 干擾素 α -2b 及 ribavirin 治療慢性 C 型肝炎時少見的副作用，我們報告一位 47 歲慢性 C 型肝炎的女性病患以 pegylated 干擾素 α -2b 及 ribavirin 治療後 10 週，得到良好的反應。然後，她開始出現用力時呼吸短促及乾咳，根據胸部 X-光，高解析度電腦斷層攝影及支氣管肺泡沖洗液分析的結果，診斷為間質性肺炎。Pegylated 干擾素 α -2b 比傳統的干擾素 α -2b 有較長的吸收和清除半衰期，但效力相當，雖然 pegylated 干擾素 α 的耐受性和傳統的干擾素 α 相當，但是以不適當高劑量的長效性 pegylated 干擾素 α 治療時可能較容易產生肺毒性，依據 MEDLINE 直到 2004 年的搜尋，我們相信這是第一個慢性 C 型肝炎以 pegylated 干擾素 α -2b 及 ribavirin 治療後產生間質性肺炎而能復原的病例。臨床醫師以 pegylated 干擾素 α -2b 及 ribavirin 治療慢性 C 型肝炎應對這種併發症有高度的警覺性。(長庚醫誌 2007;30:92-7)

關鍵詞：間質性肺炎，慢性 C 型肝炎，pegylated 干擾素 α -2b。

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