Successful Antiviral and Antituberculosis Treatment With Pegylated Interferon-alfa and Ribavirin in a Chronic Hepatitis C Patient With Pulmonary Tuberculosis

Ming-Chao Tsai,¹ Meng-Chih Lin,² Chao-Hung Hung¹ *

Pulmonary tuberculosis is a rare side effect of antiviral treatment for chronic hepatitis C. We present the case of a 55-year-old woman with chronic hepatitis C, who developed pulmonary tuberculosis after receiving 8 weeks of peginterferon alfa-2a plus ribavirin therapy. Antituberculous treatment was started and antiviral agents were given continually at adjusted doses. Her symptoms of cough with blood-tinged sputum improved 1 month after antituberculous therapy. Treatment for hepatitis C and pulmonary tuberculosis were completed after 6 months. At 6 months after antiviral therapy, a sustained virological response was achieved and follow-up chest radiography showed a marked regressive change. This is believed to be the first case report of complete remission from hepatitis C and pulmonary tuberculosis treated concurrently with antiviral and antituberculous agents. [J Formos Med Assoc 2009;108(9):746–750]

Key Words: chronic hepatitis C, peginterferon alfa-2a, pulmonary tuberculosis, sustained virological response

Chronic hepatitis C virus (HCV) infection is a major cause of chronic liver disease, which can lead to cirrhosis and hepatocellular carcinoma. Therefore, efficient antiviral treatment for HCV has long been needed. Recently, the most important advance in the treatment of hepatitis C has been the development of a long-acting interferon (IFN), or pegylated IFN, which is produced by covalent attachment of polyethylene glycol to the IFN molecule.¹ Combination therapy with pegylated IFN-alfa and ribavirin has become the optimal choice of therapy for chronic hepatitis C, as recommended by the American Association for the Study of Liver Disease in 2004.² Nevertheless, pegylated IFN-alfa and ribavirin combination therapy for chronic hepatitis C produces a number of side effects that are dominated by fatigue, influenza-like symptoms, hematological abnormalities, and neuropsychiatric symptoms.³ Pulmonary toxicity, including sarcoidosis, interstitial pneumonitis and bronchiolitis obliterans organizing pneumonia, occurs rarely and develops after a long period of treatment.⁴⁻⁶ In general, the adverse effects are dose- and duration-dependent; thus, most of them are managed safely and effectively by dose reduction.³ Management of infrequently reported events, such as tuberculosis (TB), remains controversial. However, once

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Divisions of ¹Hepatogastroenterology and ²Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

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*Correspondence to: Dr Chao-Hung Hung, Division of Hepatogastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, 123 Ta Pei Road, Kaohsiung 833, Taiwan.
E-mail: chh4366@yahoo.com.tw
a serious adverse event occurs, which has the potential to cause significant morbidity and end-organ damage, therapy should be withdrawn immediately.

Here, we report successful concurrent antiviral and antituberculous therapy in a patient with chronic hepatitis C who developed pulmonary TB during pegylated IFN alfa-2a plus ribavirin therapy, accompanied by HCV eradication and regression of pulmonary TB.

Case Report

A 55-year-old Taiwanese woman who had chronic HCV infection that lasted for several years was followed-up regularly at a local medical clinic. In April 2006, she was referred to our outpatient department because of persistent elevation of transaminases. She had a history of type 2 diabetes that was controlled by oral antidiabetic therapy. Laboratory analyses revealed the following: aspartate transaminase (AST), 112 U/L; alanine transaminase (ALT), 108 U/L; total bilirubin, 1.4 mg/dL; white blood cell count, 4500/mm³; neutrophil count, 2835/mm³; and lymphocyte count, 1305/mm³. Virological testing was positive for anti-HCV antibody, as assessed using third-generation ELISA (Ax SYM HCV 3.0; Abbott Laboratories, Chicago, IL, USA). HCV RNA determined by a standardized, qualitative reverse transcriptase polymerase chain reaction was positive (Amplicor; Roche Diagnostics, Branchburg, NJ, USA), and genotyping of HCV was 2a/2c by using reverse hybridization assay (Inno-LiPA HCV II; Innogenetics NV, Gent, Belgium). All serum markers for hepatitis B virus produced negative results. Liver echo revealed cirrhosis. Echo-guided liver biopsy demonstrated chronic active hepatitis with moderate activity and cirrhosis based on modified Knodell histology index.

Combination therapy with pegylated IFN alfa-2a 180 μg weekly subcutaneously and ribavirin 1000 mg/day orally was initiated on May 15, 2006. She began to suffer from cough with blood-tinged phlegm in July 2006, 8 weeks after treatment.

Figure 1. (A) Screening chest radiography 2 years before antiviral treatment shows a patchy density over the right upper lobe (RUL). (B) Eight weeks after antiviral treatment, chest radiography shows a cavitary lesion with mixed alveolar and interstitial infiltration over the RUL. (C) After completion of treatment for pulmonary tuberculosis, chest radiography shows a marked regressive change over the RUL as compared with that in (B).
started. Crepitant rales were audible on auscultation over the right upper lobe of the lung. Chest radiography (Figure 1B) showed a cavitary lesion and mixed alveolar and interstitial infiltration over the right upper lobe. A review of chest radiography at a screening performed on December 2004 found a patchy density over the same pulmonary area (Figure 1A), which was highly suggestive of TB reactivation. Sputum culture was positive for *Mycobacterium tuberculosis*, which was susceptible to all tested antimicrobial agents. Anti-TB therapy with rifampicin (450 mg/day), isoniazid (300 mg/day) and ethambutol (1200 mg/day), together with pyridoxine was started on July 21, 2006. Meanwhile, pegylated IFN alfa-2a and ribavirin were given continually at adjusted doses. After 1 month of anti-TB treatment, the symptom of cough with blood-tinged sputum improved. At the end of HCV treatment, the patient achieved a biochemical and virological response (normal ALT and negative HCV RNA). The ALT levels decreased gradually and normalized 6 weeks after antiviral therapy, and were persistently normal during antituberculous treatment. At 6 months after antiviral therapy, a sustained virological response (SVR) was achieved.

In addition, the treatment for pulmonary TB was carried out for 6 months (from July 2006 to January 2007). Repeated sputum cultures for *M. tuberculosis* were negative in three consecutive samples, and follow-up chest radiography showed a marked regressive change (Figure 1C). Details of the clinical course, neutrophil and lymphocyte counts, and ALT levels are shown in Figure 2.

**Discussion**

Over the past few years, the global burden of TB has been increasing despite the availability of effective treatment. Human immunodeficiency virus (HIV) infection is considered to be the most potent risk factor for the resurgence of TB. Moreover, a recent, large, case-controlled trial demonstrated that chronic hepatitis C patients had a significantly higher prevalence of TB infection compared with control subjects (3.3% vs. 1.3%) in the United States. After excluding potentially immunocompromised patients, including those with HIV, organ transplant, and cirrhosis, HCV remained significantly associated with TB infection. In Taiwan, there has been a gradual rise in

![Figure 2](image_url)

**Figure 2.** Clinical course and laboratory data of the patient with chronic hepatitis C who developed pulmonary tuberculosis during pegylated interferon alfa-2a plus ribavirin therapy. Peg-IFN = pegylated interferon; RIF = rifampicin; INH = isoniazid; EMB = ethambutol; ALT = alanine transaminase.
the annual incidence of TB in recent decades, following a transient decrease in the 1970s; the highest incidence was in the 1950s and 1960s.9 Thus, in Taiwan, a TB endemic area, patients with chronic hepatitis C may have co-infection with TB. Careful evaluation of clinical history and control chest radiography should be taken into account before the initiation of IFN-based antiviral therapy. Our patient developed pulmonary TB after receiving 8 weeks of peginterferon alfa-2a plus ribavirin therapy. A major possibility was reactivation of pulmonary TB during antiviral therapy. However, the possibility of unrecognized reactivation of TB before antiviral therapy could not be excluded because pretreatment chest radiography was performed, although there were no obvious respiratory symptoms and signs before initiation of treatment.

The causative role of IFN-based antiviral therapy in exacerbating TB infection remains controversial, and the possible mechanisms are as yet unclear. IFN-alfa is a cytokine with immunomodulatory actions, which is produced by many cell types including T cells, B cells, fibroblasts, macrophages and endothelial cells.1 Its effect includes antiviral activity, growth regulation, regulation of cell differentiation, and enhancement of the activity of natural killer cells and cytotoxic T lymphocytes. It is likely that IFN-alfa prompts the reactivation of latent TB or other opportunistic infections because of the frequent side effect of leukopenia–neutropenia.3,10,11 In particular, a decline in CD4 count in patients treated with IFN-alfa leads to reactivation of latent infection rather than the development of primary infection.10,11 Previous reports have demonstrated that infection such as herpes simplex, upper respiratory tract infection, bronchitis, oral candidiasis, skin infection, pneumonia, otitis externa, and endocarditis may occur during IFN or pegylated IFN plus ribavirin therapy for chronic hepatitis C.12,13 On the contrary, other clinical findings have shown a possible protective effect of IFN-alfa on TB exacerbation. In a report by Nahon et al, a patient undergoing treatment for hepatitis C experienced TB exacerbation after completing antiviral therapy.14 Although onset of symptoms (fever, cough and radiological chest abnormalities) had occurred during treatment, the clinical progression became apparent 1 month after treatment completion.

A review of English-language publications on MEDLINE up to 2007 shows that three cases of reactivated TB have been documented to be associated with pegylated IFN alfa plus ribavirin therapy for chronic hepatitis C.10,11,15 One report described a patient coinfected with HCV and HIV, who was diagnosed with TB adenositis after receiving 12 weeks of pegylated IFN-alfa plus ribavirin therapy.11 The other two patients developed pulmonary TB after 6 weeks and 7 months of pegylated IFN-alfa plus ribavirin therapy, respectively. Among the three cases, TB was treated successfully without complications.10,15 However, two patients discontinued the antiviral therapy at 6 and 12 weeks, respectively, and the other one completed the provisional period of 12 months without mentioning whether a SVR was achieved. Unlike the three previously reported cases, our patient achieved an SVR when developing pulmonary TB during pegylated-IFN plus ribavirin therapy for chronic hepatitis C. Concurrent anti-TB therapy resulted in complete remission of pulmonary TB. However, our case was genotype 2a/2c, which was easily eradicated, and a 24-week course of pegylated-IFN plus ribavirin therapy achieved an 80–90% SVR.16

Drug-induced hepatotoxicity associated with first-line antituberculous drugs such as isoniazid, rifampin and pyrazinamide is a well-known adverse effect and may limit their use. Although chronic liver disease is known to increase the risk of drug-induced hepatotoxicity, the relative risks for the various etiologies of chronic liver disease resulting from development of drug-induced hepatotoxicity remain unclear. In a study by Kwon et al,17 22 HCV-seropositive patients (41%) and 19 control subjects (20%) exhibited elevated liver enzyme levels during anti-TB treatment (p = 0.005). In our case, ALT levels normalized 6 weeks after antiviral therapy and were persistently normal during antituberculous treatment. However,
careful monitoring of liver function tests is still necessary in patients who receive combined antiviral and anti-TB therapy.

In conclusion, physicians should keep in mind the possibility of this rare complication when treating chronic hepatitis C patients with pegylated IFN-alfa plus ribavirin therapy. Our case showed successful treatment of reactivation of pulmonary TB during pegylated IFN-alfa plus ribavirin therapy for chronic hepatitis C.

References