Interferon α is the mainstay of hepatitis C virus (HCV) treatment. Due to the high frequency of relapse seen with conventional interferon therapy, other treatment options have been explored, namely, pegylated interferon-αb, used alone or in combination with ribavirin.

Pegylated interferon-αb has various side effects. Interstitial pneumonitis has been previously described as a complication of interferon-α therapy but, to our knowledge, has never been reported with pegylated interferon-αb therapy following its approval by the US Food and Drug Administration in January 2001. We describe here a patient who developed interstitial pneumonitis with ARDS following two weekly doses of pegylated interferon-αb in combination with ribavirin therapy.

Case Report
A 49-year-old white man with a medical history significant for depression and HCV was evaluated by his primary care physician for HCV treatment. He had a history of IV drug abuse and heavy alcohol use. He had quit smoking 15 years ago and denied any recent alcohol or recreational drug consumption. He had no known pulmonary disease and no history of frequent respiratory infections.

The patient was started on a combination treatment consisting of pegylated interferon-αb and ribavirin. He weighed 94 kg. Both medications were appropriately prescribed (pegylated interferon-αb, 150 µg once weekly; and ribavirin, 600 mg bid).

Two weeks after the initiation of treatment, the patient presented to the emergency department of an outside hospital with cough and dyspnea. On hospital admission, a chest radiograph revealed bilateral interstitial and alveolar infiltrates that were greater on the right than on the left (Fig 1). Oxyhemoglobin saturation dropped from 93 to 87% while breathing room air, and the patient was consequently given oxygen therapy using a nasal cannula. A possible pulmonary allergic reaction to pegylated interferon-αb was suspected as the cause of his symptoms, and the patient therefore started on treatment with myeloprep-sisolone, 60 mg IV q6h. Therapy with levofloxacin, 500 mg po qd, also was initiated to cover for possible community-acquired pneumonia. On day 3 of hospital admission, the patient awoke with increased shortness of breath. His oxyhemoglobin saturation was 80% despite a 100% oxygen concentration being administered by face mask. Arterial blood gas levels were as follows: PO2, 73 mm Hg; PCO2, 42 mm Hg; and pH 7.44. The findings of the cardiac examination were normal, and the echocardiogram showed a normal left ventricular ejection fraction and no other evidence of congestive heart failure.

A CT angiogram of the chest was negative for pulmonary embolism and revealed patchy ground-glass opacities bilaterally with right lower lobe infiltrates (Fig 2). As the patient’s symptoms and oxygenation gradually improved, the myeloprep-sisolone...
The lungs together weighed 3,200 g, which is five times the normal weight. They showed diffuse alveolar damage in a more advanced fibrosing state. There was also evidence of necrotizing bronchopneumonia, acute tubular necrosis, and micronodular cirrhosis with extensive ischemic hepatic necrosis.

**DISCUSSION**

HCV is a viral pandemic. Almost 2.7 million individuals in the United States are HCV RNA (+). Pegylated interferon-α,β was approved by the US Food and Drug Administration in 2001 for the treatment of patients with chronic HCV who have compensated liver disease. The use of this agent has resulted in a significantly higher sustained virologic response than the one seen with conventional interferon-α,β therapy. Pegylation is the attachment of an inactive, nontoxic polyethylene glycol moiety to the active conventional interferon molecule. The resulting compound has sustained absorption, considerably higher serum concentration, a slower rate of clearance, and a longer half-life, allowing for more constant therapeutic concentrations.

The biological activity of pegylated interferon is derived from the interferon-α moiety. Interferons bind to specific membrane receptors on the cell surface, and trigger a cascade of intracellular events and immunomodulating activities. These include the induction of enzymes, the suppression of cell proliferation, the enhancement of macrophage phagocytic activity, and the augmentation of the specific cytotoxicity of lymphocytes for target cells.

On day 15, the patient’s pulmonary function started to improve, but he was noted to have a distended abdomen with high residual contents from the tube feedings, despite an aggressive bowel regimen to prevent opiate-induced ileus. Kidney-ureter-bladder radiographs taken in the flat and upright positions showed no evidence of obstruction. LFT results increased from baseline, as follows: ALT, 157 U/L; AST, 123 U/L. On day 17, the WBC count increased from 18,000 to 34,000 cells/μL. A CT scan of the abdomen showed pancoelitis with subcutaneous emphysema, with small pockets of intraperitoneal air with no evidence of perforation. The toxin test was positive for *Clostridium difficile*. Despite antibiotic therapy, the patient became septic from an unknown source, and required norepinephrine and vasopressin therapy to maintain a mean arterial pressure within the normal range.

On day 24, the patient underwent a total colectomy, cholecystectomy, and ileostomy for acalculus cholecystitis and for removal of a potential abdominal source of sepsis. The exploratory laparotomy with cholangiogram showed asceses, a cirrhotic liver, an inflamed distended gallbladder, and no evidence of cholangitis. On day 25, the patient developed severe metabolic acidosis with worsening renal function requiring continuous venovenous hemofiltration. His condition deteriorated rapidly with worsening ARDS and multisystem organ failure, despite maximal life-sustaining therapy. At that time, LFTs revealed an AST level of 1,408 U/L and an ALT level of 2,195 U/L. Arterial blood gas levels when the patient had a 100% fraction of inspired oxygen were as follows: Pco₂, 57 mm Hg; Po₂, 47 mm Hg; and pH 7.17.

On day 26, blood culture results came back positive for methicillin-resistant *Staphylococcus aureus* and *Candida albicans*. Sputum culture results also were positive for methicillin-resistant *S aureus*. The patient died on day 26, and an autopsy was performed.

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immune diseases, dyspnea, and cough, with influenza-like symptoms being the most commonly reported.\textsuperscript{8–10} Pulmonary infiltrates and pneumonitis with pegylated interferon-\(\alpha\) have been reported only during premarketing studies.\textsuperscript{9}

Ribavirin is a synthetic nucleoside analog that appears to enhance the anti-HCV activity of both conventional interferon-\(\alpha\) and pegylated interferon-\(\alpha\), leading to a higher sustained virologic response.\textsuperscript{8,11,12} To this date, ribavirin alone has never been reported as the cause for interstitial pneumonitis.

The lack of significant improvement despite antibiotic therapy, and negative findings on BAL specimen studies, blood cultures, and viral antibody tests are consistent with a noninfectious process. The pathology findings for a lung biopsy sample are one way of discovering the presence of
pulmonary disease that may be related to drugs. The histology is unusual in that hyaline membranes that are characteristic of diffuse alveolar damage were not present. However, fibroblast infiltrates, hyperplastic pneumocytes, and thrombosed blood vessel were present, as is commonly seen in diffuse alveolar damage.

Moreover, we know that medications can be a possible etiology of ARDS. Aspirin, opiates, tricyclic antidepressants, carbamazepine, amiodarone, protransine, radiologic contrast media, and certain antineoplastic agents have been reported to precipitate this syndrome. Therefore, since the patient experienced ARDS, one cannot exclude pegylated interferon from the potential etiologies.

Severe pulmonary toxicity from therapy with interferon-αb and pegylated interferon-αb is rare (1 to 5%). But with increased prescribing for various clinical conditions (eg, neoplasms, multiple sclerosis, and HCV), there is growing evidence for interferon-α-induced pulmonary toxicities, which have been captured in a number of case reports, as follows: pneumonitis, sarcoidosis, asthma exacerbation, pleural effusion, and bronchiolitis obliterans–organizing pneumonia.

Although the mechanism of interferon-α-induced pulmonary toxicity has never been clearly defined, the immunomodulating activities of this agent are one plausible explanation. However, as suggested in previous reports, this reaction may be due to an immune-mediated response in the lungs, with pegylated interferon, acting as an immunostimulant, triggering underlying but quiescent autoimmune disease in this patient. This mechanism has been reported previously to be associated with thyroid disease in patients who have been treated with interferon-α.

Pharmacokinetic studies comparing conventional interferon-αb to pegylated interferon-αb have shown that the mean area under the curve and the mean duration of measurable serum concentration following a single dose of 0.5 μg/kg pegylated interferon-αb are 13 times and 11 times greater, respectively, than the one observed with a dose of 3 million IU conventional interferon-αb. These findings are the expected results of pegylation. However, it remains speculative whether these findings are linked to an increased toxicity of pegylated interferon-αb and its rapid onset in this patient.

In clinical trials, the reported incidence of dyspnea and cough in patients who have been treated with pegylated interferon-α combination therapy with ribavirin was higher than the one observed with interferon-α monotherapy. However, whether ribavirin was a synergistic cause of the development of interstitial pneumonitis in this patient remains theoretical.

Although the clinical and pathologic findings suggest that the interstitial pneumonitis in this patient may have been caused by pegylated interferon/ribavirin therapy, one cannot prove that a definite causal relationship actually exists, as this is only a single case report. We believe, however, that the patient’s course and lack of other etiologies for ARDS make the relationship between interferon and ARDS suggestive.

We believe that the immediate cause of death for this patient was sepsis and multisystem organ failure. However, because these occurred as complications of pegylated interferon-αb-induced lung disease, this patient’s death should be considered a drug-related mortality.

Since interferon-αb is the active moiety in pegylated interferon-αb, interstitial pneumonitis is also likely to occur with this newer agent. Patients receiving pegylated interferon-αb monotherapy or combination therapy with ribavirin should be made aware of this complication and should be advised to watch for pulmonary symptoms. In the instance in which these symptoms occur, pegylated interferon-αb/ribavirin-induced interstitial pneumonitis should be considered in the differential diagnosis and therapy must be withheld.

While this manuscript was being reviewed for submission, a case of interstitial pneumonitis induced by pegylated interferon-αa and ribavirin therapy was reported.

REFERENCES


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