Adverse response to pegylated interferon therapy in two patients with chronic hepatitis C

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Abstract

Pegylated interferons have recently been approved for treatment of hepatitis C. The safety of these formulations is reported to be similar to that of non-pegylated interferon. We present two patients who experienced exacerbations of their liver disease following administration of pegylated interferon alfa-2b. Vigilant monitoring of patients treated with these new agents is recommended.

Introduction

Hepatitis C virus infects almost 200 million people worldwide.[1,2] In the US, chronic hepatitis C is estimated to affect nearly four million people. Recently, the FDA has approved two formulations of pegylated interferon, pegylated interferon alfa-2b (PEG-Intron®, Schering) and pegylated interferon alfa-2a (PEGASYS®, Roche) for therapy of hepatitis C, increasing the therapeutic options available to treat this disease. Studies have shown the safety profiles of both pegylated and non-pegylated interferons to be similar.[3,4,5] Although adverse effects are common with interferon therapy, no severe adverse effects unique to the pegylated form of this drug have been described. We report two cases of adverse effects seen with the use of pegylated interferon alfa-2b.

Case 1

A 78-year-old Asian male was referred to our department for evaluation of chronic hepatitis C, genotype 1a. Prior to initiation of treatment, his laboratory tests showed the following: alanine aminotransferase (ALT) 241 U/L (normal range [NR] 0-40), aspartate aminotransferase (AST) 117 U/L (NR 0-37), total bilirubin (TB) 1.0 mg/dL (NR $\leq$1.0), hepatitis C viral load by RNA PCR testing (HCV RNA) 107,300 copies/mL, hepatitis B surface antibody (anti-Hbs) and total hepatitis A antibody (anti-HAV) positive. A biopsy of his liver showed chronic hepatitis with mild steatosis, grade 3 inflammatory changes and stage 3 fibrosis. He was started on combination therapy of interferon alfa-2b, 3 million units by subcutaneous injection three times weekly, and oral ribavirin 1000 mg daily (Rebetron®, Schering, Kenilworth, NJ).

The patient did not tolerate the combination treatment secondary to ribavirin-induced hemolytic anemia despite trials of dose adjustments and erythropoietin. Thus, the ribavirin was stopped and he was continued on monotherapy with interferon alfa-2b. Twenty-four weeks into his therapy, the patient was noted to have normal transaminases and undetectable serum HCV RNA. Following the FDA approval of pegylated interferon alfa-2b (PEG-Intron®, Schering, Kenilworth, NJ), he was switched to this product at a dose of 50 mg (1.0 μg/kg) weekly. The first dose was given two days following his last dose of non-pegylated interferon.

Laboratory evaluation after two doses of this new therapy revealed an AST of 28 U/L and an ALT of 20 U/L. After the sixth dose ALT increased to 469 U/L. Repeat testing after his seventh dose revealed an AST of 312 U/L, an ALT of 602 U/L, and HCV RNA was 351,000 copies/mL. Given these results, treatment with pegylated interferon was discontinued. During these seven weeks of pegylated interferon therapy, patient reported only other medication to be a single daily multivitamin. He denied used of other prescribed, over-the-counter, herbal medicines or health supplements.

Thirteen days after his last pegylated interferon dose, his AST had decreased to 171 U/L and ALT to 376 U/L. By 21 days, AST and ALT were 79 U/L and 204 U/L, respectively. After one month AST and ALT were 39 U/L and 64 U/L, respectively. The patient was started back on monotherapy with non-pegylated interferon alfa-2b and his transaminase levels have subsequently returned to normal limits. Repeat antinuclear antibody (ANA) and anti-smooth muscle antibody were negative. His albumin prothrombin time (PT) remained normal throughout all treatments.

Case 2

A 49-year-old Caucasian male with chronic hepatitis C, genotype 1b, who had not responded to a previous trial of combination interferon alfa-2b and ribavirin, was referred to our center for further evaluation. Liver biopsy done two years previously revealed grade 3 inflammation and stage 3 fibrosis. Treatment with 1.0 μg/kg body weight/day of subcutaneous pegylated interferon alfa-2b was started with the goal of preventing progression of fibrosis and decompensation of his liver disease. Medications prior to treatment initiation included citalopram and ranitidine. Patient denied use of other prescribed, over-the-counter, herbal medicines or health supplements immediately prior to, or following his single dose of pegylated

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interferon. Before this treatment, his laboratory values included ALT 56 U/L (NR 0-40), AST 93 U/L (NR 0-37), TB 2.4 mg/dL (NR < 1.0), alkaline phosphatase (ALP) 103 U/L (NR 38-126), PT 12.8 seconds (NR 10.4-12.7), HCV RNA >1,000,000 copies/mL. No ascites or encephalopathy was evident.

After his first and only dose, his ALT and AST increased to 71 U/L and 133 U/L, respectively, and his TB doubled in value. Treatment was stopped after this first dose and repeat testing two weeks later revealed ALT 84 U/L, AST 124 U/L, and TB 7.4 mg/dL. These abnormalities peaked one month after treatment at ALT 207 U/L, AST 156 U/L, TB 8.0 mg/dL, and PT 13.2 seconds. The patient's only complaint was severe pruritis throughout this time period. No ascites or encephalopathy was evident. Treatment with ursodiol 600 mg orally twice daily was started with subsequent rapid improvement in symptoms and liver test abnormalities. Three weeks after initiation his laboratory results revealed ALT 91 U/L, AST 102 U/L, TB 2.8 mg/dL, and PT 12.4 seconds. Evaluation for other causes of acute hepatitis was unrevealing: hepatitis B surface antigen (HbsAg) nonreactive, anti-HAV IgM negative, hepatitis B core (anti-HBc) IgM negative, ANA negative, monospot negative, anti-smooth muscle antibody nonreactive, and anti-CMV IgM negative. No abnormalities of his serum albumin or ALP were noted during the course of his disease and right upper quadrant ultrasound done during bilirubin elevation was unremarkable.

Discussion

Two formulations of pegylated interferon are now available for the therapy of chronic hepatitis C, PEG-Intron®, a covalent conjugate of recombinant interferon alfa-2b with a 12 kilodalton (kd) polyethylene glycol (PEG) moiety, PEGASYS®, a conjugate of interferon alfa-2a and a branched 40 kd PEG chain.[3] Interferon is believed to work by binding to cell surface receptors and initiating a sequence of intracellular events which result in suppression of cell proliferation, inhibition of viral replication in virus-infected cells, and enhancement of the phagocytic activity of macrophages and the cytotoxicity of lymphocytes for target cells. Pegylation of interferon results in decreased clearance and thus an increase in mean half-life compared to non-pegylated drug, allowing once-weekly dosing without the prolonged serum troughs seen with non-pegylated drug. The sustained levels obtained with pegylated drug likely account for the greater efficacy of these compounds. Adverse effects of once-weekly dosed pegylated interferons have been similar to those of thrice-weekly non-pegylated drug. Common adverse effects include "flu"-like symptoms - fatigue, headache, myalgias, rigors, pyrexia, and nausea. Laboratory abnormalities occur less frequently, the most common being neutropenia, followed by thrombocytopenia and anemia. Other important adverse effects include anorexia, neuropsychiatric symptoms including insomnia, irritability, and depression, and alopecia. Adverse effects or laboratory abnormalities severe enough to warrant cessation of drug occurred in 6-11% of subjects in two of the largest trials of pegylated versus non-pegylated interferon.[4,5] The only adverse effect seen more frequently with pegylated drug appears to be injection site inflammation. Elevation of ALT of 2-5 times above baseline was seen in 10% of patients treated with PEG-Intron® in pre-marketing trials.[6] These elevations were transient and were not associated with deterioration of other liver functions. Hyperbilirubinemia was reported in 10-14% of those patients receiving combined therapy with interferon alfa-2b and ribavirin.

Case 1 may be the first case in the literature of severe worsening of hepatitis following the initiation of pegylated interferon. His ALT, while only 2.5 times his pretreatment level, rose 30 times that of the level seen on non-pegylated interferon therapy. The marked elevation in ALT and loss of HCV RNA suppression after starting PEG-Intron® indicates liver injury and uncontrolled replication of the virus. The cause of this severe worsening on change of interferon therapy is unclear but could possibly be due to an autoimmune mechanism, or less likely to another infection or intoxication we did not identify.

Case 2 demonstrates acute cholestasis following administration of PEG-Intron® as manifest by the increase in both ALT and serum bilirubin. These indices trended toward the normal range after the prompt removal of the drug and treatment with ursodiol. The marked improvement with ursodiol treatment was surprising and encouraging. Further studies are needed to evaluate the role of this medication in patients with acute hepatic injury due to pegylated interferon. No other cause for the acute abnormalities in this person was identified. These cases represent the first report of severe adverse liver reactions to the pegylated interferon, PEG-Intron® in its use in the treatment of hepatitis C. Other likely causes of exacerbation were ruled out in these cases leaving the only obvious variable in each case the introduction of this new drug. These results call for vigilant monitoring of patients treated with pegylated interferons, especially PEG-Intron® and prompt withdrawal of these drug in patients who demonstrate an acute increase in ALT.

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