

Severe autoimmune hemolytic anemia in a patient with chronic hepatitis C during treatment with peginterferon alfa-2a and ribavirin

Peginterferon (Peg-IFN) alfa in combination with ribavirin represents the gold standard treatment for chronic hepatitis C, but is associated with various side effects, especially hematological abnormalities. We report here a case of severe autoimmune hemolytic anemia (AIHA) complicated by symptomatic myocardial ischemia in a patient with chronic hepatitis C during combination therapy. The worsening hemolysis after ribavirin withdrawal and exclusion of other causes implicated Peg-IFN alfa as the cause of AIHA. Our study demonstrates that in patients without preexisting immunological abnormalities Peg-IFN can *de novo* induce autoimmune complications that, albeit rarely, may be life-threatening.

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Peginterferon (Peg-IFN) alfa in combination with ribavirin (RBV) represents the most effective therapy for chronic hepatitis C (CHC),¹ although it is associated with various side effects.^{2,3} Hematological abnormalities are the most frequent causes of dose reduction or drug discontinuation⁴ and, albeit rarely, may be life-threatening. We report here a case of severe autoimmune hemolytic anemia (AIHA) during treatment with Peg-IFN alfa-2a plus ribavirin. A 63-year-old man with chronic hepatitis C, genotype 4, was referred to our Center in 2002; he had no history of immunologic abnormalities and, specifically, of autoimmune disorders or allergy. In May 2005, because of persistently increased alanine aminotransferase (ALT) levels and histological findings of marked portal-portal and portal-central bridging with initial nodule formation (Ishak Fibrosis Score 5), the patient was started on Peg-IFN alfa-2a (Pegasys, Roche), 180 µg/week subcutaneously, plus RBV, 1000 mg/day per os. The baseline hemoglobin (Hb) concentration was 14.9 g/dL (Figure 1). After 5 weeks, RBV was stopped because of gastrointestinal disturbances. Subsequently, RBV was reintroduced at 400 mg/day and then the dose was adjusted according to the Hb levels, as shown in Figure 1. Serum ALT significantly decreased during treatment; the patient had an early 2-log drop of serum hepatitis C virus



Figure 1. Hematological, biochemical and serological profiles of the patient during antiviral treatment and after admission for severe hemolytic anemia. The black line indicates Hb values; the blue area indicates ALT levels; the red horizontal bars indicate positive assays for serum HCV RNA by PCR; the blue horizontal bar represents the dosage and duration of treatment with Peginterferon alfa-2a (180 µg/weekly until week 29; 90 µg/weekly at week 30); the white bar indicates the duration of treatment with erythropoietin (30,000 U subcutaneous once weekly); the orange area indicates the dose of ribavirin; the yellow area indicates the dose of methylprednisolone after admission. Each arrow denotes transfusion of a single unit of packed red blood cells.

(HCV) RNA at week 2, which became undetectable by PCR at week 9. After 24 weeks of combination therapy, because of Hb reduction to 9.4 g/dL, treatment with erythropoietin was started (10,000 U thrice weekly). This notwithstanding, Hb did not increase, thus, at 29 weeks of therapy RBV was stopped and one week later the dose of Peg-IFN was reduced to 90 µg/week (Figure 1). After 3 days, the clinical conditions of the patient suddenly deteriorated, with acute attacks of high fever, chills, nausea, dizziness, pallor, tingling of the extremities and dark-red urine; Peg-IFN was withdrawn and the patient was admitted. Laboratory tests upon admission revealed: Hb 5.5 g/dL, hematocrit 15.9%, mean corpuscular volume 112 µm³, leucocytes 6.4×10⁹/L (neutrophils 3.8×10⁹/L, lymphocytes 1.7×10⁹/L), platelets 158×10⁹/L, bilirubin 3.9 mg/dL (indirect 2.5), lactic dehydrogenase (LDH), 992 U/L (normal values from 240 to 480). During the first week of admission, the reticulocyte count was only slightly increased (2.7%) most likely due to bone marrow suppression by interferon, as previously reported.⁵ Serum levels of iron, ferritin, vitamin B12 and folate were normal, while haptoglobin was reduced (<6 mg/dL, range 30-200); aspartate aminotransferase values were slightly elevated (44 U/L), while ALT was within the normal range (28 U/L). Urine examination showed hemoglobinuria. Direct Coombs test was positive for IgG and C3d; indirect Coombs test was positive for panagglutinins. Examination of bone marrow aspirate showed erythroid hyperplasia without maturation abnormalities in the myeloid series. Based on these results, a diagnosis of AIHA was made.⁶ The temporal association between antiviral therapy and the development of severe anemia, the worsening hemolysis despite RBV withdrawal, the exclusion of other causes of AIHA, such as tumors, infectious diseases, immunodeficiency, lymphoproliferative and autoimmune disorders, led us to a more specific diagnosis of Peg-IFN-induced AIHA. Corticosteroid therapy was immediately started. Because of the onset of symptomatic myocardial ischemia, transfusion of red blood cells was undertaken (Figure 1). After 2.5 months of corticosteroid therapy, the patient conditions improved; Hb and haptoglobin returned to normal levels and the direct Coombs test became negative. However, due to discontinuation of antiviral therapy, there was a biochemical and virological relapse of hepatitis C with reappearance of HCV RNA by PCR in serum after 18 days of corticosteroid treatment.

Two other cases of AIHA during treatment with Peg-IFN plus RBV for CHC have been described.^{7,8} In both, however, the patients had pre-existing signs of immunologic abnormalities. By contrast, our patient had no history of autoimmune diseases or allergy, and serum autoantibodies were all negative before treatment. Thus, our study suggests that Peg-IFN, as previously documented with standard IFN,⁹⁻¹¹ can *de novo* induce the appearance of an autoimmune disorder and not merely exacerbate a preexisting one. A significant drop of Hb levels persisting despite withdrawal of RBV therapy, associated with elevated reticulocyte counts and increased indirect bilirubin and LDH concentrations, should induce the physician to suspect an AIHA. However, in IFN-induced AIHA the diagnostic value of the reticulocyte count is limited due to the myelosuppressive effect of interferon.^{5,12} The rapid hematological and clinical deterioration seen in our patient suggest that careful medical supervision is necessary during treatment with Peg-IFN and RBV for the early detection and management of medical complications that, albeit rarely, may be life-threatening.

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