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The Development of Cold-type Autoimmune Hemolytic Anemia during Peginterferon alfa-2a plus Ribavirin Treatment in Chronic Hepatitis C Patient: a Case Report

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Abstract

Peginterferon-alfa 2a or alfa 2b plus ribavirin is the treatment of choice in chronic hepatitis C. Severe adverse effects may compromise efficacy of this regiment. There are few reports of warm autoimmune hemolytic anemia following interferon-alfa or peginterferon-alfa2b plus ribavirin treatment. This present report discusses autoimmune hemolytic anemia which developed during peginterferon alfa-2a/ribavirin treatment and caused dose cessation. The anemia was improved with discontinuation of peginterferon-alfa 2a/ribavirin and adminstration of erythropoietin stimulating agent.

Introduction

Chronic hepatitis C is still a serious health problem, with limited choice of treatment. Peg interferon based treatment combined with ribavirin is the treatment of choice. The length of treatment and their responses are well predicted by their genotype. Genotype 2 and 3 have better response rate (70%) with shorter duration of combination treatment (24 weeks), while genotype 1 and 4 have poor response rate (about 45%) and need a longer treatment duration (48 weeks). The non responder rate is still high in genotype 1 HCV infection [1].

The side effects of interferon and ribavirin limit their treatment efficacy in some cases and severe side effect may urge to stop the treatment. We report a chronic hepatitis C patient who developed cold-type autoimmune hemolytic anemia during peginterferon (Peg-IFN) alfa-2a/ribavirin combination treatment.

Case Description

A male of 64 year-old suffered from chronic hepatitis C. His pre-treatment HCV-RNA PCR was 10^7 IU/mL, with genotype 1. He was planned to get combination treatment of peginterferon (Peg-IFN) alfa-2a 180 mcg/week and 1000 mg of ribavirin/day for 48 weeks.

On the early weeks of treatment the hemoglobin level tends to decrease from 10 g/dL to 8.9 g/dL. At week-7 of treatment hemoglobin continued to fall to 8.7 g/dL that led to reduction of ribavirin dose to 600 mg/day and peg-IFN alfa-2a 135 mcg/week. Patient also received 4000 IU erythropoietin stimulating agent subcutaneously twice weekly. This treatment approach did not help much and hemoglobin level continued to fall as low as 6.6 g/dL, at week-9. Ribavirin was then discontinued and patient only received peg-interferon 135 mcg/week along with erythropoietin 4000 IU twice a week. The HCV-RNA PCR was undetected at week-12. Hemoglobin level raised to 8.2 g/dL at week-13.

At week-21 he got accident and was hospitalized for fracture of his lower left leg. His hemoglobin level was around 8 g/dL and packed red cell transfusion was given to reach 10 g/dL of hemoglobin level as preoperative requirement. Orthopaedic surgery was done successfully and ribavirin 200 mg/day was added along with peg-IFN alfa-2a 135 mcg at this time. Four days after surgery his hemoglobin level decreased to 8.7 g/dL accompanied with decreased of platelet count to 124.000/mm^3. Packed red cells transfusion was planned but the results of direct and indirect Coomb's test (direct antiglobulin test) were positive with consequence of transfusion cancelation. Reticulocyte count was 3 %. Indirect bilirubin was 2 mg/dL with peripheral blood smear showed destruction of erythrocyte cells. Serum LDH was slightly raised to 578 IU/L. Diagnosis of hemolytic anemia is made based on clinical and laboratory findings.

The 135 mcg peg-IFN alfa-2a for week-24 was injected along with erythropoietin 10.000 IU per week while ribavirin was discontinued. The hemoglobin and platelet level continued to decrease to 6.7 g/dL and 66.000 /mm^3, respectively. Screening antibody in immunohematology test revealed that he had cold type-autoimmune hemolytic anaemia (cold type-AIHA). Peg-IFN alfa-2a and ribavirin were discontinued and he only received erythropoietin. The HCV is still undetected at week-24 by HCV-RNA PCR examination even though the intensity of treatment dose was not reached.

About three months later the haemoglobin level reached 12.6 g/dL and the patient was back to normal life without continuing of peg-IFN alfa-2a and ribavirin due to the probability of these two drugs or one of them induced the development of cold-type autoimmune haemolytic anemia(AIHA). He continued the erythropoetin treatment. Twenty four weeks post treatment the patient relapsed with HCV-RNA 1.24 x 10^6IU/mL and he still use erythropoietin 10.000 UI three times a week to maintain the normal haemoglobin level.

Discussion

There is emerging evidence that hepatitis C virus may induce

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immune mediated thrombocytopenia or autoimmune hemolytic anemia [2]. Cohort from 120908 US veterans with HCV infection showed that HCV increased risk for ITP (HR=1.8; 95% CI1.4-2.3) and risk for autoimmune hemolytic anemia (HR=2.8; 95% CI 1.8-4.2) [3]. Either cold type or cold aglutinin or warm type hemolytic anemia has been reported to have association with chronic HCV infected patients [4,5].

Despite the nature of HCV in causing autoimmune disorder, its treatment may also contribute to severe cytopenia [1, 6-8]. Peginterferon alfa-2a plus ribavirin is the only available treatment for chronic hepatitis C. Flu-like syndrome, anemia, thrombocytopenia, and also psychiatric disorders are common side effects of peginterferon-alfa-2a and ribavirin combination treatment during chronic hepatitis C treatment [1].

Combination treatment induced-cyopenia in hepatitis C is mostly due to hemolysis, suppresion of bone marrow, or exacerbation of autoimmunity that may exist in HCV infected patients [9-11]. Either alone or in combination ribavirin and Peg-IFN alfa-2a may induce hemolysis. Peg-IFN alfa-2a itself has been reported causing autoimmune hemolytic anemia not only in HCV patients but in hematological cases as well [12].

Anemia is the most significant toxic effect as it may cause decreasing quality of life and fatigue. Worsening of fatigue is a predictor for treatment discontinuation. Based on clinical trial [13], anemia is contributing for 36% of antiviral discontinuation. Significant anemia (Hg < 10 g/dL) occurs in up to 9% to 13% patients receiving combination therapy with interferon and ribavirin. The mean maximum decrease of hemoglobin is 3.1% in non pegylated interferon and 3.7% in pegylated interferon. The hemoglobin level reached its lowest range in the first 4 weeks to 8 weeks of therapy. The lowest hemoglobin level in this patient was 6.6 g/dL at week-9 of treatment. Hemolytic anemia should be suspected and monitored in every patients with anemia during antiviral treatment. Bilirubin becomes the first indicator for hemolytic anemia during combination treatment of peg-interferon/ribavirin for HCV [14].

Interferon is a strong hematopoetic suppression as previously described by Zoumbos et al. [15]. Interferon as an anti-tiviral augments the T cell mediated cytotoxicity in bone marrow thereby causing depletion of hematopoeis. Serum eritropoetin level is increased similar with other patients with chronic inflammation but diminished production of endogenous EPO for their degree of anemia (diminished EPO response). Peg-interferon has been reported to induce hemolysis and autoimmune complication in patient without preexisting immunologic abnormalities [16]. Immunological derangement leading to this complication is poorly understood. In de novo AIHA (newly appearance AIHA) timing or onset of hemolysis is after 3 to 27 months. Based on history taking our patient did not have preexisting history of allergy, hypersensitivity, or autoimmune disease and hemolytic anemia was diagnosed at week-21 leading to hypothesis that AIHA is induced by treatment.

Ribavirin, upon oral route, will be immediately transported from the plasma to the red blood cells where it is phosphorylated into mono-, di-, tri-phosphat analogs [17]. Phosphorylated analogs are neither easily metabolized nor transported out from red blood cells. The concentration of ribavirin intracellular is much greater than extracellular, that may induce oxidative damage and extravascular death of RBC [17].

Treatment of drug induced AIHA is simply reducing or discontinuing the Peginterferon/Ribavirin dosage. Dose reduction or treatment discontinuation may adversely affect the efficacy of combination of antiviral treatment. Initiation of hematopoetic growth factor or erythropoetin stimulating agent are usefull as reported by several publication [18,19] and also cost effective compare to dose reduction strategy [20]. Endogenous erythropoetin production is suboptimal during antiviral treatment supporting use of erythropoetin stimulating agents [21] Recommended dose for erythropoetin alpha is 40,000 IU per week [13]. We use lower dose of erythropoetin for this patient. High dose purified Eicosapentaenoic acid (EPA) 1800 mg/day may attenuate hemolytic by ameliorating erythrocyte deformability [22].

The use of pegInterferon/ribavirin is not absolutely contraindicated in HCV infection with AIHA manifestation. Warm type of AIHA as an extrahepatic manifestation of HCV can also be well managed by prednison 60 mg/ day and then gradually tappered off in five months [3]. Antiviral for HCV can be instituted after stopping prednison. Some clinician use corticosteroid cautiously due to negative effect of immune suppression which exacerbate the clinical appearance of HCV infection. On the other hand, cold-type AIHA is commonly very difficult to treat even using corticosteroids,immunosuppressive drugs or splenectomy [3]. Lack of recommendation using corticosteroid in managing antiviral induced cold-AIHA make us not prescribing prednisone in this patient

To our knowledge, this was the first report of chronic hepatitis C patient developed cold type-autoimmune hemolytic anemia during treatment combination of peg-Interferon-alfa2a/ribavirin. The incidence of cold type is lower than warm type AIHA. Around 7.7% to 25% of acquired hemolytic anemias including drug induced hemolytic anemia have cold aglutinin. This cold aglutinin is best screened with serum screening procedure which can detect ability of patient's serum to aglutinate saline-suspended normal red blood cells in room temperature (20°C) after 30-60 minutes of incubation period [23]. The pathophysiology of this cold hemolytic anemia is not known; what we know is that chronic infection of hepatitis C virus can induce AIHA and may increase cold agglutinin level. The possibility of the treatment (especially, peginterferon) potentiate the "subclinical "AIHA in chronic hepatitis C infection and drive it to be "cold type" need further explanation.

In conclusion, the combination of peginterferon-alfa 2a and ribavirin treatment had possibility to induce cold type- autoimmune hemolytic anemia in chronic hepatitis C. The cold type hemolytic anemia was improved after discontinution of antiviral treatment and administration of eritropoetin-stimulating agent. Although this approach succeed in managing thehemolytic anemia, it may decrease the efficacy of antiviral treatment.

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