

Peginterferon Alfa-2b and Ribavirin in Thalassaemia/Chronic Hepatitis C Virus-Co-Infected Non-Responder to Standard Interferon-Based Therapy

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Summary

We describe a patient with HbE-beta-thalassaemia and chronic hepatitis C virus infection (genotype 1a) who was treated successfully with peginterferon alfa-2b and ribavirin, following failure to respond to standard interferon and ribavirin therapy. She had sustained virological response for nearly 24 months after completing peginterferon alfa-2b and ribavirin therapy. Transfusion requirements were significantly increased during combination therapy due to ribavirin-induced haemolysis. The adverse effects of interferon were well tolerated. Combination therapy with peginterferon alfa-2b and ribavirin maybe a feasible treatment option for a subset of thalassaemia/HCV infected non-responders to standard interferon-based therapy.

Key Words: Thalassaemia, Blood transfusion, Hepatitis C virus, Peginterferon, Ribavirin

Introduction

Thalassaemia is an important public health problem in Malaysia which has approximately 2400 transfusion dependent thalassaemics. Transfusion-related infections especially chronic hepatitis C virus (HCV) infection increases the morbidity and mortality of this condition. The seroprevalence of HCV infection amongst transfusion dependent thalassaemics in Malaysia is 22.4%. Most of them started receiving blood transfusions before local screening for hepatitis C virus in blood products became routine. Combination therapy with interferon alfa (IFN-alfa) and ribavirin is highly effective in the treatment of chronic HCV infection. HCV genotype 1 has been associated with a lower response rate to treatment when compared with genotype 2 or 3. Recent data have demonstrated that

some patients with previous nonresponse to standard interferon therapy achieved a sustained virological response (SVR) when retreated with peginterferon and ribavirin. We report here a patient with thalassaemia and chronic HCV infection who was treated successfully with peginterferon alfa-2b and ribavirin after nonresponse to standard IFN-alfa-2b therapy.

Case Report

The patient is a 23-year-old Malay lady with HbE-beta thalassaemia, who requires blood transfusion when hemoglobin level falls below < 7g/dl or when she becomes symptomatic. She was splenectomized at the age of 10 years. A screening test for anti-HCV antibodies was positive in October 2000 and the HCV-

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CASE REPORT

RNA level was 3.3×10^6 IU/mL of serum. Further analysis showed that she had HCV genotype 1a infection. The hepatitis B surface antigen and anti-HBs were negative. Liver biopsy showed changes of chronic hepatitis infection with no evidence of cirrhosis (Scheuer classification grade 1). However mild hemochromatosis changes were present. Her serum alanine aminotransferase level was 170 U/L at diagnosis with no clinical evidence of hepatic decompensation. Her serum ferritin level was 7123 $\mu\text{g/l}$ indicating suboptimal compliance to treatment. She was commenced on combination therapy with subcutaneous IFN- α -2b 3 mega units thrice weekly and oral ribavirin 1g/day in two divided doses. Six months later, the HCV-RNA was still detected at 1.1×10^4 IU/mL of serum. She had no deterioration in her liver function. She was then commenced on peginterferon α -2b 1.5 $\mu\text{g/kg}$ weekly and oral ribavirin 1g/day for one year. The HCV-RNA became undetectable 6 months later and until completion of one year of peginterferon α -2b. She had Sustained Viral Response (SVR) for nearly twenty-four months after completing therapy (Figure 1). During the standard combination therapy and peginterferon therapy, her transfusion requirements increased markedly. She received nine blood transfusions in fifteen months compared to none in two years prior to treatment and twice in one and a half years after completion of treatment (Figure 1). She also had moderate 'flu-like' symptoms, weight loss and mild depression during the initial months of combination

therapy. However, the adverse events resolved three months after commencing therapy. Her mean serum ferritin level rose to 8012.75 $\mu\text{g/l}$ during the therapy due to worsening of iron overload secondary to increased blood transfusion but later declined to 5621.03 $\mu\text{g/l}$ after the therapy. The serum alanine aminotransferase levels did not fluctuate or worsen during the therapy.

Discussion

We report a patient with thalassaemia and chronic HCV infection who was treated successfully with peginterferon α -2b and ribavirin after nonresponse to standard IFN- α -2b therapy. Combination therapy with IFN- α and ribavirin is the international standard of care for treating chronic hepatitis C in treatment-naïve or relapsed (after IFN- α monotherapy) patients with compensated liver disease. With this regimen about 40% of patients achieve a SVR and the associated potential long-term benefits. We previously reported 2 cases of transfusion dependent thalassaemia with HCV infection that achieved SVR for more than 12 months following the standard combination therapy¹.

HCV genotype 1, high viral load at diagnosis and higher fibrosis score are amongst the factors associated with lower response rate to combination therapy. In thalassaemics, chronic HCV infection could accelerate and worsen liver damage caused by iron overload,

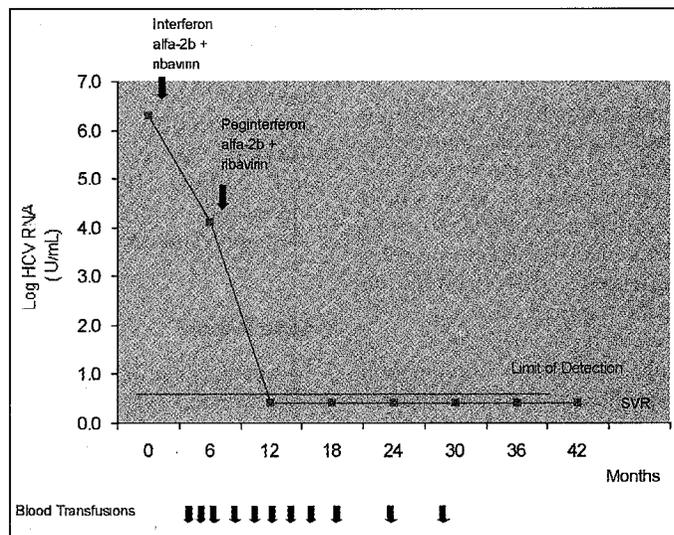


Fig. 1: Trend of HCV RNA titre at diagnosis, during and post-therapy

fibrosis and cirrhosis. Our patient had HCV infection genotype 1a, high viral load and iron overload that could explain the lower response to standard IFN-alfa-2b and ribavirin therapy. Previously, a study reported that the recommended dose of IFN-alfa (3 MIU) may not be optimal in inhibiting production of genotype 1 HCV hence a larger dose of IFN-alfa should be considered in treating genotype 1-infected patients.

Peginterferon and ribavirin therapy have been shown to induce sustained responses in about 18% of all patients with previous non-response to standard IFN-alfa therapy (with or without ribavirin)². Peginterferon alfa-2b has been shown to be more efficacious in clearing the virus because of a longer plasma half-life than with IFN-alfa-2b. Peginterferon alfa-2b at a higher dose (1.5µg/kg) plus ribavirin >10.6mg/kg has been shown to be superior in optimizing the SVR compared to low dose peginterferon alfa-2b particularly in genotype 1 patients³. We administered optimized combination therapy with peginterferon alfa-2b and ribavirin in our patient in view of nonresponse to standard IFN-alfa-2b.

During the combination therapy, our patient had increased transfusion requirements due to ribavirin-induced haemolysis. We observed the same adverse event in our patients treated with standard IFN-alfa-2b previously¹. Ribavirin has been shown to have synergistic anti-HCV effect when it is combined with peginterferon alfa, without affecting the pharmacokinetic profile of peginterferon alfa. Considering the major benefit to be gained from this

combination treatment, the risks were outweighed in our patient. The adverse events in our patient were managed appropriately with blood transfusions, patient education, and antipyretic. During the therapy, we optimized her chelation therapy to prevent worsening of iron overload. The higher level of mean serum ferritin during the therapy could be explained by worsening liver damage caused by the iron overload from the increased blood transfusion and chronic hepatitis C virus infection. It is hoped that the optimized therapy together with chelation therapy would allow regression of fibrosis or halt it completely in our patient. Regression of fibrosis appears to be most favorable in patients treated with optimized combination therapy of peginterferon alfa-2b and ribavirin. No worsening of transaminase levels and neutropenia were noted in our patient during the therapy. Normalization of serum alanine aminotransferase was not included as a response marker since these can be elevated in thalassaemics due to the iron overload, especially so in patients who are not optimally chelated.

Conclusion

Combination therapy with peginterferon alfa and ribavirin may be a feasible treatment option to achieve a SVR after non-response to standard interferon-based therapy in some patients with thalassaemia with chronic hepatitis C virus infection. Further randomized controlled trials on thalassaemics are required.

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