CASE REPORT

Treatment of Chronic Hepatitis C Virus Infection with Interferon Alfa and Ribavirin: Sustained Response in Two Patients with Transfusion Dependent Thalassaemia

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Summary

We describe two cases of transfusion dependent thalassaemics with chronic hepatitis C virus infection whom were treated successfully with interferon and ribavirin, following failure of response or relapse after an initial response to interferon monotherapy. They had sustained virological response for more than twelve months after completing therapy. Transfusion requirements were significantly increased during the combination therapy, probably due to ribavirin-induced haemolysis. Serum ferritin level decreased significantly during the treatment. Combination therapy with interferon alfa and ribavirin may be a feasible treatment option for some nonresponders to prior interferon monotherapy.

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

Introduction

There are approximately 2400 patients with transfusion dependent thalassaemia in Malaysia. They are at increase risk of developing complications of iron overload and transfusion-related infections. Transfusion-related chronic hepatitis C virus infection could potentially accelerate and worsen liver damage caused by iron overload, fibrosis and cirrhosis. They are also at increased risk for hepatocellular carcinoma. The seroprevalence of hepatitis C virus infection amongst transfusion dependent thalassaemics in Malaysia is 22.4%[1]. Most of them started receiving blood transfusions before the local screening for hepatitis C virus in blood products became routine. Interferon monotherapy has given some hope to these patients, although the proportion with sustained viral response rates remained unsatisfactory. The Thalassemia International Federation recommends combination therapy in non-responders or relapsers after interferon alone, or as primary therapy in patients with poor prognostic features[2]. Combination therapy using interferon and ribavirin have shown to increase

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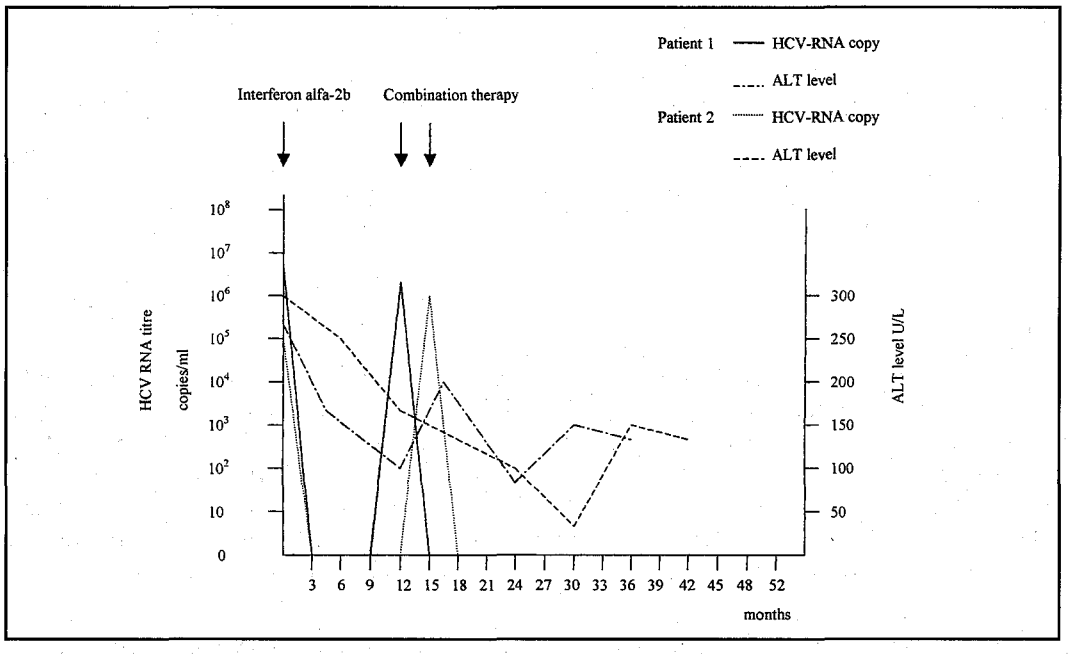
sustained response rates of up to 60%[3]. We report here two thalassaemics with hepatitis C virus infection whom were treated successfully with interferon and ribavirin.

Fig 1: Trends of HCV-RNA copy number and serum alanine aminostransferase (ALT) levels at diagnosis, during and post-therapy



Case 1

This is a 21-year-old Malay man who receives monthly transfusion and is on iron chelation therapy. His mean serum ferritin level was 14138 µg/l, indicating suboptimal compliance to treatment. A screening test for anti-HCV antibodies was positive in December 1997 and the HCV-RNA level was 5 x 10^6 copies/ml of serum. Liver biopsy result was consistent with chronic hepatitis infection. His serum alanine aminotranferase level was 260 U/L at diagnosis with no clinical evidence of hepatic decompensation. He was treated with subcutaneous interferon alfa-2b 3 mega units thrice weekly for one year. The HCV RNA became undetectable 3 months after commencing therapy. However his viral response was not sustained and he was commenced on a combination treatment using oral ribavirin, 1g/d, in two divided doses and subcutaneous interferon alfa-2b, 3 mega units thrice weekly for another year. There were no neutropenia, thrombocytopenia, hyperuricaemia, serological evidence of active hepatitis B virus infection or human immunodeficiency virus infection or renal impairment prior to the combination therapy. The pre-transfusion hemoglobin level was maintained above 8g/dl, with more frequent transfusions if required, during the treatment period. He attained a virological response after 3 months of therapy and the HCV-RNA remained undetectable 12 months after stopping therapy (Figure 1). During the combination therapy, his transfusion requirement increased and he experienced interferon-related 'flu-like' symptoms. No other complications

occurred. His mean serum ferritin level decreased to 6792 µg/l during the combination therapy. However, his serum alanine aminotransferase levels fluctuated during and after the therapy (Figure 1).

Case 2

This is a 17-year-old Chinese girl who receives monthly blood transfusion and is on iron chelation therapy. Her mean serum ferritin level was 4701 µg/l. She was diagnosed with hepatitis C in August 1998 with an HCV-RNA level of 3 x 10^5 copies/ml. Liver biopsy showed changes of hepatitis C infection with early cirrhosis. Her serum alanine aminotranferase level at diagnosis was 283 U/L with no clinical evidence of hepatic decompensation. She was commenced on subcutaneous interferon alfa-2b 3 mega units thrice weekly for one year. The HCV-RNA became undetectable 3 months later and until completion of one year of interferon. The HCV-RNA was detectable at 1 x 10^6 copies/ml after 3 months of stopping therapy and she was commenced on a combination therapy with oral ribavirin, 1g/d, in two divided doses and subcutaneous interferon alfa-2b 3 mega units thrice weekly for one year. Her pre-transfusion hemoglobin level was maintained above 8g/dl. She attained a virological response after 3 months of therapy and the HCV-RNA is still undetectable after 12 months of stopping therapy (Figure 1). During the combination therapy, her transfusion requirements have increased by 33.3% and she also had intermittent 'flu-like' symptoms. No other complications occurred. Her mean serum ferritin level decreased to 2736 µg/l during the therapy. Her serum alanine aminotransferase levels also fluctuated during and after the therapy (Figure 1).

Discussion

In patients with transfusion dependent thalassaemia, the risks of liver damage by the hepatitis C virus is further compounded by the ongoing iron overload especially so in patients who are poorly chelated. Hence, the current recommendation is that treatment be given for thalassaemics with chronic hepatitis C infection. Combination therapy with interferon alfa and oral ribavirin, is currently applied in many centers treating thalassaemics and non-thalassaemics with hepatitis C virus infection. One of the important side effect of oral ribavirin is increased haemolysis, due to accumulation of the drug within the erythrocyte, causing possible competition with adenosine nucleotides and brings about a deficiency of intracellular ATP with consequent reduced red cell survival. This causes significant increased in transfusion requirement during the treatment phase which may be carried over into the initial post treatment period. Our patients had increased transfusion requirement during the therapy phase. However, considering the major benefit to be gained from the combination treatment, the risks are outweighed. Both of our patients achieved sustained virologic response, although the liver enzymes didn't normalized during and after the therapy. We didn't include normalization of serum alanine aminotransferase levels as the criteria of treatment response, since these can be elevated in thalassaemics due to the iron overload, especially so in patients who are not optimally chelated. The mean serum ferritin levels decreased in both of our patients during the treatment phase as compared to pre treatment phase. Patients with persistent negativity of HCV RNA 6 months post interferon alfa therapy are unlikely to have later relapse with reappearance of HCV RNA. However, late relapsers after combination therapy have not been addressed in many studies.

Conclusion

Combination therapy with interferon alfa and ribavirin may be a feasible treatment option to achieve a sustained virological response after

failure of monotherapy with interferon alone in some cases with thalassaemia major with hepatitis C virus infection who are at additional increased risk of liver cirrhosis due to iron overload. To our knowledge, these were the first two patients with thalassaemia and chronic hepatitis C virus infection in Malaysia who have been treated successfully with the combination therapy. Further randomized controlled trials on thalassaemic patients are required.

References

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