CASE REPORT

Gut and Liver, Vol. 1, No. 1, June 2007, pp. 87-89

Thymosin Alpha-1 in Combination with Pegylated Interferon and Ribavirin in Chronic Hepatitis C Patients Who have Failed to Prior Pegylated Interferon and Ribavirin Treatment

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Combination therapy with inteferon-alpha and ribavirin is an approved therapy for patients with chronic hepatitis C. However, even with the use of pegylated interferon, response rates are still poor in many difficult-to-treat groups, especially with genotype 1 and high viral loads. Retreatment of these patients remains challenging. Newer combinations are being investigated to optimize chances of attaining a sustained response in these groups. Thymosin alpha 1 is a polypeptide with immunomodulatory properties that has been suggested to increase response rates in patients with chronic hepatitis C. Herein, we describe two cases of retreatment patients with chronic hepatitis C who have failed prior pegylated interferon and ribavirin therapy. They received triple combination therapies of thymosin alpha 1, pegylated interferon and ribavirin and achieved sustained virological responses. These cases support that thymosin-alpha 1 may increase the efficacy of pegylated interferon plus ribavirin in the treatment of non-responders to previous combination therapy. **(Gut and Liver 2007;1:87-89)**

Key Words: Chronic hepatitis C; Nonrespondents; Peginterferon alpha-2a; Ribavirin; Thymosin alpha 1 Introduction

INTRODUCTION

Chronic hepatitis C virus infection (HCV) is a major cause of liver cirrhosis and hepatocellular carcinoma. Current treatment of chronic hepatitis C is centered on the use of interferon-alpha in combination with ribavirin. New interferon-alpha such as pegylated-interferon with ribavirin has recently shown better treatment response than the traditional interferon plus ribavirin regimen. Sustained virological responses in patients with chronic hepatitis C with pegylated interferon in combination with ribavirin are now 56%.[1] However, there are still poor response rates in many difficult-to-treat patient groups.

Drugs that stimulate subset of helper-inducer T lymphocytes (Th 1 cells) and their associated cytokines might be useful for the treatment of chronic hepatitis C. Thymosin-alpha 1 is a synthetic 28-amino acid peptide with multiple biological activities primarily directed towards immune response enhancement.[2] The addition of thymosin-alpha 1 to pegylated interferon has demonstrated efficacy among difficult-to-treat patients with hepatitis C.[3] And 2 studies reported the effectiveness of triple therapy with thymosin-alpha, peginterferon alpha-2a and ribavirin for patients with chronic hepatitis C who failed to previous therapy around the world.[4,5]

In our country, the study of thymosin-alpha for treatment of hepatitis C has not been reported yet because of many limitations such as cost expensiveness and the relative low percentage of infected patients.

Herein, we describe two cases of successful triple combination therapy in patients with chronic hepatitis C who have failed prior pegylated interferon and ribavirin treatment.

CASE REPORT

1. Case 1

A 64-year-old male was diagnosed as hepatitis C in-

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Received on April 24, 2007. Accepted on May 13, 2007.

fected in our hospital in 1996. He was infected by HCV genotype 1b. He was lost to follow-up at our hospital until 2003 and when he revisited our hospital, he had been diagnosed with liver cirrhosis and had serum HCV RNA levels 9,000 IU/L. In February 2004, he was started on treatment that consisted of peginterferon alfa-2a at a dose of 180 ug/mL, 1 day per week and ribavirin 500 mg twice per day for 48 weeks. At that time, laboratory findings were normal. At 12 week, laboratory evaluation revealed a platelet count of 85×10^3/uL. The white and red blood cell count, alanine aminotransferase, bilirubin and prothrombin time were normal. We assessed the effectiveness for therapy with the reduction or disappearance in serum HCV-RNA after 12 weeks, end of treatment and 24 weeks after treatment. Early virological response (EVR) was achieved with negative HCV-RNA. But, he was positive for serum HCV-RNA at 20 weeks and 48 weeks. He failed to achieve virological response with standard peginterferon alfa-2a and ribavirin therapy.

In January 2006, the patient was retreated with thymosin-alpha 1 1.6 mg twice weekly, peginterferon alfa-2a 180 ug weekly and ribavirin 400 mg twice a day for 6 months. Alanine aminotransferase (ALT) was 218 IU/L and aspartate aminotransferase (AST) was 116 IU/L. At 12 weeks, EVR was achieved and liver function tests showed reductions in serum ALT and AST levels. By 24 weeks, there were no dosage adjustment for thymosin-alpha 1, peginterferon alfa-2a and ribavirin without additional toxicities compared with prior combination therapy. The patients had negative serum HCV RNA and normalization of serum ALT level in July 2006. He achieved end of treatment response (ETR). After 6 months, he achieved sustained virological response (SVR) in June 2007.

2. Case 2

A 57-year-old man was diagnosed as hepatitis C infected with genotype 1b and received treatment with interferon monotherapy in 1995 and 2000. He was a non-responder to an interferon monotherapy and started a treatment with peginterferon alfa-2a 180 ug weekly and ribavirin 400 mg three times a day in May 2001. At that time, serum HCV RNA level was 480×10^3 IU/mL and ALT level was 145 IU/L. After 12 weeks, serum HCV RNA level and other laboratory finding revealed that EVR was achieved. However, ETR and SVR were not achieved because HCV RNA level was positive at 48 week and 72 week.

In July 2005, he was treated again by adding thymosin-alpha 1 1.6 mg twice weekly to peginterferon alfa-2a 180 ug weekly and ribavirin 400 mg three times a day. His serum HCV RNA level was 68×10^3 IU/mL and ALT level was 63 IU/L. At 12 week, serum HCV RNA level was negative and ALT was normal. The patient was well tolerated and no significant adverse events were observed. He continued the treatment and was monitored at 2-3 month intervals. After 24 and 48 weeks, serum HCV RNA level and other laboratory findings revealed that ETR and SVR were achieved. He is continuously monitored to assess maintenance of SVR.

DISCUSSION

Interferon and ribavirin represent the standard treatment for chronic hepatitis C infection, but approximately half of the treated patients experience a sustained response. Dissatisfaction with the efficacy and tolerability of the currently available treatments has led to the search for alternative therapies.

In hepatitis C virus infection, the immune response to the virus appears to be critical both in determining viral clearance or persistence and in contributing to liver injury. There is evidence that an efficient type 1 immune response (Th1) to viral proteins is required for viral elimination, and the recruitment of such effector cells to the liver is dependent on the local activity of specific inducible chemokines. Multiple factors determine the ability of hepatitis C virus to survive against host immune responses including an ability to alter the cytokine profile secreted by T cells and to cause resistance to the effects of antiviral cytokines such as interferon.[6-7] Therefore, the balance between Th1 and Th2 responsiveness seems to represent a key event in the evolution of HCV infection.

Thymosin-alpha 1 has been shown to enhance the differentiation of stem cells to CD4 cells,[8] to augment T-cell function as well as to stimulate the production of Th 1 cytokines.[9,10] Recently, a study demonstrated that incubation of peripheral blood mononuclear cells of patients with chronic hepatitis C infection with thymosin-alpha 1 alone resulted in a significant increase in Th1 cytokine production. In addition, thymosin-alpha 1 induced a decrease in the Th2 cytokines IL-4 and IL-10. In vitro treatment of lymphocytes obtained from HCV patients with thymosin-alpha 1 induced a significant increase in production of IL-2 and 2',5'-oligoadenylate synthetase, a protein with direct antiviral activity.[8] In addition, incubation with thymosin-alpha 1 and interferon-alpha together led to an additive or synergistic effect.[11] These findings and activities of thymosin alpha 1 give a strong rationale to include this molecule in the future strategies for the treatment of chronic hepatitis C infection in the absence of the limiting toxicity.

Several studies have demonstrated that thymosin-alpha

1 on the base of interferon-alpha had efficacy for chronic hepatitis C.[12-15] However, only one study demonstrated the efficacy of combination therapy with thymosin-alpha 1 and pegylated interferon for hepatitis C[3] and other two studies reported that the triple therapy with thymosn-alpha, pegylated interferon and ribavirin had efficacy among difficult-to-treat pateitns around the world.[4,5]

According to our experiences, two patients failed prior pegylated interferon-alpha and ribavirin combination therapy which achieved sustained virological and biochemical responses and had few additional side effects by adding thymosin-alpha 1.

In conclusion, since thymosin-alpha 1 has few side-effects and is effective in combination with pegylated interferon and ribavirin, future clinical trials should demonstrate the potential utility of thymosin-alpha 1. Optimal treatment regimen should be determined in future trials.

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