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Thymosin Alpha 1 in combination with Interferon Alpha and Ribavirin in Chronic Hepatitis C Patients who are non-responders or relapsers to Interferon Alpha plus Ribavirin

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Abstract

Objective: Interferon alpha (IFN-alpha) with or without ribavirin is an approved therapy for patients with chronic hepatitis C. However, a sustained response is achieved in less than 40% of all treated cases. Retreatment of relapsers or non-responders usually fails. Thymosin alpha 1 (Ta-1) is a polypeptide with immunomodulatory properties that has been suggested to increase response rates in patients with chronic hepatitis C. The aim of present study was to evaluate the efficacy of a novel triple regimen which includes Ta-1 for relapsers and non-responders to the combination of TA-1 and ribavirin.

Methods: In the present study, 11 patients who relapsed (n=5) or did not respond (n=6) to previous INF-alpha-based therapy were retreated with combination Ta-1, INF-alpha and ribavirin for 12 months, and followed up for a further six months.

Results: Four out of five relapsers had a sustained response. One of the non-responders cleared the HCV RNA during the post-treatment follow-up. Minor adverse effects were observed during treatment with this combination therapy and no dose reduction or discontinuations were needed.

Conclusion: This data suggests that thymosin alpha 1 may add to the efficacy of INF-alpha plus ribavirin in the retreatment of relapsers or non-responders to previous INF-alpha-based hepatitis C therapy (JPMA 54:571;2004).

Background

The combination of IFN-alpha and ribavirin is an approved treatment for chronic hepatitis C virus (HCV) infection. IFN-alpha is given in a dose of 3 million units subcutaneously three times a week for a period of six months for genotypes 2 and 3 and one year for genotypes 1 and 4.¹ A sustained response to interferon therapy however remains a difficult goal to achieve in hepatitis C patients. Current evidence suggests that only up to 15-20% of patients demonstrate a sustained response to interferon monotherapy. Combination treatment with interferon and Ribavirin increases the sustained response rate to about 40%.²⁻⁴ Therefore, therapy of chronic hepatitis C with INF-alpha and ribavirin is still less than ideal. This combination does not influence much the initial response rates so that the problem of the non-responding patients to interferon remains. Most non-responders are infected with genotype 1. A recent meta-analysis demonstrated a sustained virological response of only 13-14% with interferon plus ribavirin in non-responders to interferon monotherapy.^{5,6} In patients who have failed to respond to interferon plus ribavirin, there are no clear data to indicate that re-treatment will be beneficial.

Patients who relapse after an initial response to interferon may respond to a combination of interferon with ribavirin.⁷ However, not all relapsers respond to retreatment. Moreover, a different strategy may be needed for patients who are considered as non-responders to interferon therapy. Because of the limitations of antiviral drugs, other

ways to enhance the immune system's ability to clear HCV should be explored.

Thymosin alpha 1, a 28-amino acid peptide originally derived from the thymus gland, has been sequenced and chemically synthesized.^{8,9} It has been evaluated for its immunomodulatory activities and therapeutic potential in several diseases, including chronic hepatitis B and C. The basis for its effectiveness may be its capacity to modulate immunological responsiveness and to increase T cell differentiation and maturation.⁸ For example thymosin increases CD3 +, CD4 + and CD8 + cell proliferation and also stimulates NK cell activity. Initial trials with thymosin monotherapy for chronic hepatitis C showed mixed results. However, combination therapy have had different results as thymosin has been suggested to add to interferon in chronic hepatitis C patients. The aim of the present study was to evaluate the efficacy and safety of a triple regimen, a combination treatment with thymosin alpha 1 and interferon alfa with ribavirin in patients who have not previously responded or relapsed after treatment with interferon in combination with ribavirin.

Patients and Methods

In this open labeled study two categories of patients were included. (1) Non-responders: patients previously treated with interferon in combination with ribavirin for at least three months in case of genotype 3 infection and six months for genotype 1, and had not shown a response by normalization of their ALT levels and disappearance of

HCV RNA from serum. (2) Relapsers: patients who were HCV RNA negative at the end of the treatment with interferon and ribavirin combination but relapsed at six months post-treatment. Patients in both groups must not have received interferon alpha, ribavirin or other immunomodulatory drugs such as corticosteroids within 3 months of entering this trial. Other exclusion criteria were co-infection with either human immunodeficiency virus (HIV) or hepatitis B virus (HBV), decompensated liver disease as indicated by any of the following; serum bilirubin >2 x upper limit of normal, prothrombin time >4 seconds prolonged, serum albumin <3.5 g/dL, history of ascites, variceal hemorrhage or hepatic encephalopathy, evidence of bone marrow suppression as indicated by hemoglobin <10 gm/dL, white blood cell count $<4 \times 10^9/L$, platelet count $<100 \times 10^9/L$, serum creatinine >1.5 times upper limit of normal, serious concurrent medical illnesses such as uncontrolled diabetes and tuberculosis, history of serious adverse effects with previous interferon therapy, pregnant or breast feeding mothers, concomitant chronic use of aspirin, non-steroidal anti-inflammatory drugs, immunosuppressive drugs or concomitant chronic use of any drug known to be hepatotoxic.

Written, informed consent was obtained from patients fulfilling the eligibility criteria. Medical history was taken and physical examination including height and weight was performed. Quantitative serum HCV RNA was determined by bDNA assay version 2.0 (Chiron, Emeryville, CA). Once patients became negative with the above assay, reverse transcription polymerase chain reaction assay (The AMPLICOR HCV Test, v2.0, Roche) with a sensitivity of 50 IU/ml was used in the follow up visits. HCV genotype was determined by the Murex HCV serotyping 1-6 assays (Murex Biotech, UK). A liver biopsy was obtained prior to therapy. Hepatic inflammation and fibrosis were assessed by the METAVIR scoring system.¹⁰ The fibrosis stage was assessed on a scale of 0-4 and activity was graded on a scale of 0-3. Abdominal ultrasound scan were obtained and alpha-fetoprotein levels were assessed to rule out focal malignant liver lesions.

Patients received thymosin alpha 1 in a dose of 1.6 mg by subcutaneous injection twice a week and interferon alfa 2b in a dose of 3 million units by subcutaneous injection 3 times a week. Ribavirin was given in a dose of 800mg/day for patients weighing <60 kg, 1000mg for patients between 60-70 kg and 1200 mg for patients with >70 kg body weight. Patients were followed up in the clinic at weeks 2 and 4 and then at monthly intervals until the end of treatment. The following evaluations were performed at each visit: physical examination, assessment of any adverse event, concomitant medications, and assessment of compliance, hematology and biochemistry. Determination

of serum HCV RNA was performed at months one, three, six and nine; at the end of treatment and at six months post treatment.

Patients who completed six months of treatment were evaluated for response to therapy which was defined as negativity of serum HCV RNA by PCR. Patients who were considered as responders continued the treatment till the end of 52 weeks. These patients were seen at 3 months and 6 months after the end of treatment to evaluate for the sustained response.

Results

Eleven patients were included in the study, eight female and three males, with a median age was 42 years (range 28-50). The liver biopsy showed grade 0-1 necro-inflammatory activity in 4 and grade 3 in 7 patients. The stage of the disease was 0-2 in 7, and 3-4 in 4 patients. HCV genotype was type 1 in five, and 3 in six patients.

Baseline median ALT was 76 IU/L (range 33 - 198) and HCV RNA was 3.17 million units per milliliter (range 0.15-10.16). There were six patients in this study who were non-responders to the previous interferon plus ribavirin therapy while five patients had relapsed after a successful end of treatment response. Two groups differed in the baseline HCV RNA which was much higher in non-responders ($5.59 \pm 3.29 \times 10^6$ IU/ml) as compared to relapsers ($1.15 \pm 1.83 \times 10^6$ IU/ml) ($p=0.022$) (Table).

Non-responders to the combination of interferon plus ribavirin therapy remained non-responders to the triple regimen of thymosin with interferon and ribavirin after six months of therapy, though improvement in ALT levels was observed during the treatment. However, one patient had a

Figure. Response to the triple therapy: ALT and HCV RNA levels in "relapsers" and "non-responders" to interferon plus ribavirin therapy.

Table. Characteristics and response to the triple regimen in relapsers and non-responders to the previous interferon plus ribavirin treatment.

	Non-responders (n = 6)	Relapsers (n = 5)	P value
Sex (M/F)	2/4	1/4	
Age (yrs.) Mean \pm S.D.	44.0 \pm 8.0	39.6 \pm 7.6	
HCV genotype			
1	3	3	
3	3	3	
Liver biopsy (grade)			
0-1	2	2	
2-3	4	3	
Stage			
0-2	4	3	
3-4	2	2	
Baseline HCV RNA ($\times 10^6$ IU/ml) mean \pm S.D.)	5.59 \pm 3.29	1.15 \pm 1.82	0.022
Baseline ALT (IU/L) (mean \pm S.D.)	74.33 \pm 23.7	102.2 \pm 80.5	0.436
HCV RNA at month six ($\times 10^6$ IU/ml) (mean \pm S.D.)	6.69 \pm 5.67	0.32 \pm 0.65	0.035
ALT (IU/L) at month six (mean \pm S.D.)	40.8 \pm 16.9	20.8 \pm 6.7	0.035
End of treatment virological response	0/6	4/5	0/015
Sustained virological response	1/6*	4/5	0.080

p values by two sided Fisher exact test and independent sample t-test.

*One patient was HCV RNA positive at the end of treatment but became negative at six months and twelve months post-treatment.

significant drop of HCV RNA levels. His genotype was 1 and baseline HCV RNA 8.43×10^6 IU/ml, which decreased to 0.63×10^6 IU/ml at month six. This was considered to be an interim response and therapy was continued. This patient was still positive by reverse transcriptase PCR at month twelve when treatment was stopped and he was initially considered to be a therapeutic failure. However, HCV RNA became negative at six months and remained negative at twelve months post-treatment and he was considered to have a successful sustained response in the final analysis. The relapsers to the combination therapy showed response to triple regimen. Four out of five patients (genotype 1=2, genotype 3=2) became negative after six months of therapy and continued their treatment. Their end of treatment HCV RNA was negative and all showed sustained

virological response measured at six months post treatment. Minor adverse effects were observed during treatment with this combination therapy and these included myalgia (4), a mild form of alopecia (4), local discomfort at the injection sites (3) and weight loss (1). No serious adverse events were reported.

Discussion

Thymosin alpha 1 is an immune modulator that has been shown to increase the production of Th1 cytokines such as IL-2 in peripheral blood mononuclear cells from patients infected with HCV. Smaller increases are also seen after treatment with IFN-alpha, while thymosin alpha 1 and IFN-alpha together have a synergistic effect. Thymosin alpha 1 has also been shown to decrease the Th2 cytokines IL-4 and IL-10, whereas IFN-alpha increased these cytokines. Interestingly, a Th2 response is suggested to be associated with persistence of HCV infection.¹¹ Hence, thymosin treatment could benefit patients with hepatitis C infection by increasing the Th1 response, important for sustained clearance of hepatitis C; and by decreasing the Th2-type response, associated with persistence of viremia.

Thymosin alpha 1 may not be effective as a monotherapy in the treatment of chronic hepatitis C.¹² However, its combination with interferon effectively improves the response rate. In one randomized, double-blinded, placebo-controlled trial, end-of-treatment biochemical response was seen in 37.1% of patients treated with combination therapy of interferon and thymosin, 16.2% of patients treated with IFN alone, and 2.7% of untreated controls. Cumulative sustained biochemical responses were 14.2% and 8.1% in the IFN/TA1 and IFN arms respectively, based on an intention-to-treat model.¹³ In another study using thymosin and lymphoblastoid interferon, sustained virological response of 40% was seen, including a sustained response of 39% in patients infected with HCV genotype 1.¹⁴ Ongoing studies of combination of thymosin with pegylated interferon are expected to show further improvement in the sustained response rate.

In our study we included difficult to treat patients. These were the patients who had not responded to the previous treatment or had relapsed in the follow up period. There is still no satisfactory treatment available for these patients. In the present study, retreatment with the triple regimen was, as expected, more beneficial in relapsers than in non-responders. In addition, thymosin alpha 1 did not add toxicities to those already expected from either interferon alpha with or without ribavirin. Taken together, these data suggest that the addition of thymosin alpha 1 to interferon and ribavirin is beneficial to patients who relapsed after the end of therapy for chronic hepatitis C.

How to deal with the initial non-responders is still an unresolved dilemma. Our patients of this group did show an initial decline in the HCV RNA level. However, all of them were non-responders at month six based on the stopping rule set for this trial. Therefore, treatment was stopped in all except one who had shown significant decrease in HCV RNA level and became PCR negative after stopping treatment at month 12. This late clearance of the virus is not seen with standard therapy and may be related to sustained stimulation of the immunological mechanism eventually clearing the virus. A delayed response to thymosin alpha 1 has been consistently demonstrated in patients with chronic hepatitis B.¹⁵ It is possible that similar immune mechanisms, perhaps related to Th1 stimulation, are involved in response to thymosin alpha 1 therapy in HCV infection as well. Until more is known about the incidence of delayed, sustained response in HCV infection, we suggest that in-treatment virological response should not be used to determine whether or not to interrupt therapy that includes thymosin alpha 1.

Thymosin alpha 1 is an expensive drug. The cost of triple therapy especially in relation to those who have already received interferon and ribavirin is an important issue for patients living in a third world country. The cost would further increase if pegylated interferon replaces ordinary interferon in such triple regimens. However, not many options are available for difficult to treat patients. In summary, our data suggest that thymosin alpha 1 may be a useful addition to the treatment of relapsers and non-responders, and further studies are warranted.

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