

interferon and in 44% of those treated with 1 MU. Davis, G. L., et al., *New England Journal of Medicine*, 321:1501-06 (1989). These authors concluded that a 24-week course of interferon therapy is effective in controlling disease activity in many patients with hepatitis C, although relapse after the cessation of treatment is common.

[0009] A multi-center randomized control trial of recombinant human α -IFN in patients with chronic NANB hepatitis has been reported recently. Marcellin, P., et al., *Hepatology*, 13:393-97 (1991). Patients were randomly assigned to no treatment or to 1 to 3 MU of α -interferon given three times a week for 24 weeks. Forty-five patients (75w) were positive for antibody to HCV. During the 24 week treatment period, mean serum ALT levels decreased in both treatment groups, but the decrease was statistically significant only in the 3 MU group. However, at 24 weeks, the proportion of patients with normal ALT levels was similar in the 3 MU group (39%) and the 1 MU group (45%) and both were significantly higher than in controls (0%). Repeat liver biopsy specimens showed a significant decrease in the severity of histological changes in the higher dose group but not in the lower dose group or in controls. However, after treatment, the mean ALT levels rose in both treated groups. The proportion of patients with normal ALT levels at week 48 was 28% in the 3 MU group and 20% in the 1 MU group. The authors conclude that a dose of 3 MU was superior to 1 MU of α -interferon given three times per week for 24 weeks in inducing improvements in serum ALT levels and liver histological examinations. However, relapse in disease activity occurred in approximately half of the responders when interferon was stopped. The response to α -interferon did not correlate with the source of infection or with the presence or absence of anti-HCV antibody titers in patient sera.

[0010] It is clear, therefore, that while α -interferon has a beneficial effect on the course of HCV infection, this effect is frequently only transient. therefore, new modalities are necessary in order permanently to eradicate the effects of hepatitis C virus on the patient.

[0011] Another class of polypeptide immune modifiers derived from the thymus gland, the thymosins, has been shown to trigger maturational events in lymphocytes, to augment T-cell function and to promote reconstitution of immune defects. Low, T. L. K., et al., "Thymosins: Structure, Function and Therapeutic Application", *Thymus*, 6:27-42 (1984).

[0012] Thymosin Fraction Five (TF-5), originally described by Goldstein et al. (*Proc. Nat'l Acad. Sci. (USA)*, 69:1800-1803 (1972)), is a partially purified extract of bovine thymus containing at least 40 peptide components, 20 of which have been purified to homogeneity or near homogeneity; it contains about 0.6% of Thymosin α -1 (THN α ₁). Low, 1984, above.

[0013] THN α ₁, initially isolated from TF-5, has been sequenced and chemically synthesized. Wetzel, R., et al., *Biochemistry*, 19:6096-6104 (1980). Its sequence is highly homologous in mice, calves and humans. THN α ₁ is a 28 amino acidic polypeptide with a molecular weight of 3100 that has shown activity qualitatively similar to TF-5 in modulating the immune system. Low, T. L. K., et al., *J. Biol. Chem.*, 254:981-6 (1979). THN α ₁ has potent immunologic activity, including stimulation of α - and γ -interferon pro-

duction, increasing macrophage migration inhibitory factor production, inducing expression of T-cell markers, including IL-2 receptors, and improving T-cell helper cell activity. Schulof, R. S., et al., in *The Lymphocyte*, Allen J. Liss Inc., New York, 1981, pp. 191-215; Low, T. L. K., et al., in "Thymosins: Structure, Function and Therapeutic Applications", *Thymus*, 6:27-43 (1984); Koutab, N. M., et al., *Immunopharm.*, 16:97-105 (1988). Studies in mice have demonstrated a synergistic effect of THN α ₁ and interferon on natural killer-cell activity in immunosuppressed mice. Favilli, C., et al., *Cancer Immunol. Immunother.*, 20:189-92 (1985) TF-5 and THN α ₁ can influence immunoregulatory T-cell function, promote production of interferon- α , interferon- γ and interleukin-2 by human lymphocytes and increase interleukin-2 receptor expression. Marshall, G. D., et al., *J. Immunol.*, 126:741-4 (1981); Mutchnick, M. G., et al., *Clin. Immunol. Immunopathol.*, 23:626-33 (1982); Szein, M. B., et al., *Proc. Nat's Acad. Sci. (USA)*, 83:6107-6111 (1986); Serrate, S. A., et al., *J. Immunol.*, 1939:2338-43 (1987); Bazevanis, C. N., et al., *Immunopharm.*, 13:133-41 (1987); and, Svedersky, L. P., *Eur. J. Immunol.*, 12:244-7 (1982).

[0014] Clinical trails of TF-5 and THN α ₁ as primary or adjunctive therapy in patients with immunodeficiency or cancer indicate that these agents enhance immune responsiveness and augment specific lymphocyte functions, Clinical trials of TF-5 and purified THN α ₁ have been underway for a number of years. Early trials in patients with cancer or immunodeficiency states were encouraging, though not definitive. Goldstein, A. L., et al., *Transp. Proc.*, 9:1141 (1977); Barrett, D. J., et al., *J. Pediatr.*, 97:61 (1980); and Cohen, M. H., et al., *J. Amer. Med. Assoc.*, 241:1813-5 (1979). THN α ₁ use has been described in a randomized trial of patients with nonsmall cell lung cancer. Patients were treated with THN α ₁ at a dose of 900 μ grams/m² subcutaneously twice weekly or daily for two weeks and then twice weekly after completing a course of radiotherapy. The only side effect of THN α ₁ was mild burning at the injection site in three patients. This was attributed to the drug lot and may have been due to the carrier preparation. Relapse-free survival and overall survival were greater in both THN α ₁ treatment groups than in the placebo group; some restoration of radiation-suppressed immune function was also noticed. There was no increase in T-cell numbers associated with this. Schulof, R. S., et al., *J. Biol. Response Modifiers*, 4:147-58 (1985).

[0015] Recent double-blind, randomized trials with thymosins have been performed in elderly men in an effort to increase response to influenza vaccine. Gravenstein, S., et al., *JAGS*, 37:1-8 (1989). Patients received synthetic THN α ₁ subcutaneously twice weekly starting at the time the influenza vaccine was given. At six weeks post-vaccine, those patients randomized to receive the drug had higher levels of antibody to influenza than controls. This difference was accentuated in the very elderly (ages 77-99). No clinical or biochemical toxicity was observed in drug recipients.

[0016] There are preliminary reports that thymosins may be effective against infections caused by hepatitis viruses other than HCV. In an animal model of viral hepatitis, the woodchuck infected with the Woodchuck Hepatitis Virus, THN α ₁ suppressed viral DNA replication, but produced no improvement in clinical parameters. Korba, B. E., et al., *Hepatology*, 12:Abs. 880 (1990). In a pilot clinical trial with