

COMPOSITION AND METHOD OF TREATING HEPATITIS C

RELATED APPLICATION

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 08/404,844 filed Jan. 24, 1994, which is a continuation of U.S. patent application Ser. No. 07/878,372 filed May 4, 1992 which in turn is a continuation in part of U.S. patent application Ser. No. 07/759,544, filed Sep. 13, 1991.

I. GOVERNMENT INTEREST

[0002] This invention described herein may be manufactured, used and licensed by or for the Government for governmental purposes without the payment to us of any royalties thereon.

III. FIELD OF INVENTION

[0003] This invention relates generally to the pharmacological treatment of hepatitis C virus infection in patients.

IV. DESCRIPTION OF THE RELATED ART

[0004] Hepatitis C virus (HCV), the putative agent in the majority of post-transfusion acquired hepatitis, has been recently defined by a new serologic assay. Kuo, G., et al., *Science*, 244:362-4 (1989). Despite improvement in the quality of the blood-donor pool and the recent implementation of testing of donated blood, the current estimated incidence of acute infection among persons receiving transfusions is 5 to 10%. Alter, H.J., in Zuckerman, A. J., ed., *Viral Hepatitis and Liver Disease*, Allen K. Liss, New York, 1988, pp. 537-42. Chronic hepatitis develops in at least half the patients with acute HCV infection (representing about 90% of patients with non-A, non-B hepatitis (NANB)), and cirrhosis develops in at least 20% of this group. Thus, of the approximately 3 zillion persons who receive transfusions in the United States each year, acute hepatitis C will develop in about 150,000. Chronic hepatitis c will develop in at least 75,000 of these, and among them cirrhosis will develop in more than 15,000. Among patients with post-transfusion hepatitis, up to about 90% are positive for the HCV antibody. Davis, G. L., et al., *New England Journal of Medicine*, 321:1501-6 (1989). Patients with sporadic NANB hepatitis (no specific risk factors) are also very likely to have the anti-HCV antibody. Kuo, et al. (1989) above. While most of the patients who contract hepatitis C will have subclinical or mild disease, approximately 50% will progress to a chronic disease state characterized by fluctuating serum transaminase abnormalities and inflammatory lesions on liver biopsy. By some estimates, cirrhosis will develop in up to about 20% of this group. Koretz, R. L., et al., *Gastroenterology*, 88:1251-4 (1985).

[0005] With the aim of halting or slowing the progression of HCV-related diseases, a variety of drugs have been evaluated in recent years. Both acyclovir and corticosteroids (which are beneficial in autoimmune chronic active hepatitis) are ineffective. Pappas, S. C., *J. Med. Virol.*, 15:1-9 (1985); Stokes, P., et al., *Gastroenterology*, 92:1783 abstract (1987).

[0006] To date, α -interferon (IFA) appears to be the most promising candidate, although not necessarily the final answer. Hoofnagle, J. H., et al., in *Viral Hepatitis: 1981*

International Symposium, Philadelphia, Franklin Institute Press, 1982, pp. 573-83; Hoofnagle, J. H., et al., *New England Journal of Medicine*, 315:1575-8 (1986); Thomson, J., *Lancet*, 1:539-41. (1987); Kiyosawa, K., et al., in Zuckerman, A., ed., *Viral Hepatitis and Liver Disease*, Allen K. Liss, New York, 1983, pp. 895-7. Hoofnagle, J. H., et al., *Sem. Liver dis.*, 9:259-263 (1985). The interferons are host proteins made in response to viral infections as well as other antigenic stimuli. They are classified by their cell or origin as well as their antigenicity. α -Interferon is made by lymphoblastoid cells, β -interferon by fibroblasts, and γ -interferon by T-cells. Subtypes in each group are based on antigenic/structural characteristics. Recombinant forms for each group have been developed and are commercially available. A pilot study utilizing IFA on ten patients with well-characterized post-transfusion NANB hepatitis was reported in 1986 by Hoofnagle et al. (Hoofnagle, J. H., et al., *New England Journal of Medicine*, 315:1575-8 (1986)). In this study, eight of ten patients improved their serum alanine transaminase (ALT) levels within one month of starting therapy. IFA therapy consisted of 5 million units (MU) daily in seven of the patients and one MU daily in three patients. In all subjects the dose was gradually reduced to 1 MU daily and then finally switched to an alternate day or every three day regimen. In three patients who had post-treatment liver biopsies, the specimen showed a marked improvement in the degree of portal inflammation and loss of parenchymal hepatocytic necrosis. Side effects were common at the 5 MU/day dose and virtually absent at 1 MU/day.

[0007] The effects of recombinant human interferon α in a prospective, randomized, double-blind, placebo-controlled trial in patients with well-documented chronic HCV infection has recently been carried out. Di Bisceglie, A. M., et al., *New England Journal of Medicine*, 321:1506-10 (1989). Forty-one patients were enrolled in the trial, 37 of whom were later found to have antibody to HCV. Twenty-one patients received interferon α (2 MU) subcutaneously three times weekly for six months, and twenty received placebo. The mean serum ALT and the histological features of the liver improved significantly in the patients treated with interferon, but not in the patients given placebo. Ten patients treated with interferon (48%) has a complete response, defined as a decline in mean serum ALT to the normal range during therapy; three others had a decrease in mean ALT of more than 50%. After treatment ended, however, serum ALT usually returned to pretreatment levels; six to twelve months after the discontinuation of interferon therapy, only two patients (10%) still had normal values. The authors concluded that interferon α therapy is beneficial in reducing disease activity in chronic hepatitis C; however, the beneficial responses are often transient and side effects are known to appear.

[0008] In another, broader study, chronic hepatitis C (NANB hepatitis) is 166 patients was treated with either 3 MU or 1 MU of recombinant human α -IFA three times weekly for 24 weeks or to no treatment. The serum ALT level became completely normal in 22 of the 26 patients (85%) who responded to treatment with 3 MU of interferon, and nine of the sixteen patients (56%) responded to treatment with 1 MU. The patients who received 3 MU of interferon had histologic improvement because of the regression of lobular and periportal inflammation. However, relapse within six months after the completion of treatment occurred in 51% of the patients treated with 3 MU of