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(54) Title: INTERFERON DRUG THERAPY FOR THE TREATMENT OF VIRAL DISEASES AND LIVER FIBROSIS

(57) Abstract: The present invention provides methods of reducing liver fibrosis; methods of increasing liver function in an individual suffering from liver fibrosis; methods of reducing the incidence of complications associated with HCV and cirrhosis of the liver; methods of reducing viral load in a patient suffering from HCV infection; methods of treating an HCV infection; methods of treating West Nile infection; and methods of treating alphaviral infection. The methods generally involve administering a therapeutically effective amount of IFN-a; and IFN-y; concurrently.

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INTERFERON DRUG THERAPY FOR THE TREATMENT OF VIRAL DISEASES AND LIVER FIBROSIS

FIELD OF THE INVENTION

This invention is in the field of flaviviral infection, particularly West Nile viral infection and hepatitis C viral infection, and in the field of liver fibrosis.

BACKGROUND OF THE INVENTION

The United States is currently experiencing an increase in the number of West Nile viral infections. West Nile virus is a member of the alpha-like Flaviviridae, as is hepatitis C virus. Most alpha-like viruses, including hepatitis C virus and poliovirus, are highly sensitive to type I interferon treatment. It appears that West Nile virus will become endemic in the United States because it has an avian reservoir and is transmitted by mosquitoes. West Nile virus can cause a harsh, self-limiting fever, body aches, brain swelling, coma, paralysis, and death. Although it is generally accepted that West Nile viral disease results in death in only one out of 40,000 cases, the death rate in the U.S. appears to be higher. In particular, 5 deaths were reported recently in the State of Louisiana. It is possible that the U.S. strain is more virulent or that the U.S. population is genetically predisposed to more severe clinical courses. In middle eastern countries, West Nile virus has been endemic for centuries, which may have allowed natural selection to create populations with resistance to the virus. There is no effective treatment for the disease.

Hepatitis C virus (HCV) infection is the most common chronic blood borne infection in the United States. Although the numbers of new infections have declined, the burden of chronic infection is substantial, with Centers for Disease Control estimates of 3.9 million (1.8%) infected persons in the United States. Chronic liver disease is the tenth leading cause of death among adults in the United States, and accounts for approximately 25,000 deaths annually, or approximately 1% of all deaths. Studies indicate that 40% of chronic liver disease is HCV-related, resulting in an estimated 8,000-10,000 deaths each year. HCV-associated end-stage liver disease is the most frequent indication for liver transplantation among adults.

Antiviral therapy of chronic hepatitis C has evolved rapidly over the last decade, with significant improvements seen in the efficacy of treatment. Nevertheless, even with combination therapy using pegylated IFN-α plus ribavirin, 40% to 50% of patients fail therapy, i.e., are nonresponders or relapsers. These patients currently have no effective

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therapeutic alternative. In particular, patients who have advanced fibrosis or cirrhosis on liver biopsy are at significant risk of developing complications of advanced liver disease, including ascites, jaundice, variceal bleeding, encephalopathy, and progressive liver failure, as well as a markedly increased risk of hepatocellular carcinoma.

The high prevalence of chronic HCV infection has important public health implications for the future burden of chronic liver disease in the United States. Data derived from the National Health and Nutrition Examination Survey (NHANES III) indicate that a large increase in the rate of new HCV infections occurred from the late 1960s to the early 1980s, particularly among persons between 20 to 40 years of age. It is estimated that the number of persons with long-standing HCV infection of 20 years or longer could more than quadruple from 1990 to 2015, from 750,000 to over 3 million. The proportional increase in persons infected for 30 or 40 years would be even greater. Since the risk of HCV-related chronic liver disease is related to the duration of infection, with the risk of cirrhosis progressively increasing for persons infected for longer than 20 years, this will result in a substantial increase in cirrhosis-related morbidity and mortality among patients infected between the years of 1965-1985.

Fibrosis occurs as a result of a chronic toxic insult to the liver, such as chronic hepatitis C virus (HCV) infection, autoimmune injury, and chronic exposure to toxins such as alcohol. Chronic toxic insult leads to repeated cycles of hepatocyte injury and repair accompanied by chronic inflammation. Over a variable period of time, abnormal extracellular matrix progressively accumulates as a consequence of the host's wound repair response. Left unchecked, this leads to increasing deposition of fibrous material until liver architecture becomes distorted and the liver's regenerative ability is compromised. The progressive accumulation of scar tissue within the liver finally results in the histopathologic picture of cirrhosis, defined as the formation of fibrous septae throughout the liver with the formation of micronodules.

There is a need in the art for improved methods for treating flaviviral infections, e.g. West Nile viral infection and hepatitis C viral infection, and for treating liver fibrosis. The present invention addresses this need.

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SUMMARY OF THE INVENTION

The present invention provides methods of treating alphavirus infection; methods of treating hepatitis C virus (HCV) infection; methods of treating West Nile virus infection; methods of reducing liver fibrosis; methods of increasing liver function in an individual suffering from liver fibrosis; methods of reducing the incidence of complications associated with HCV and cirrhosis of the liver; and methods of reducing viral load, or reducing the time to viral clearance, or reducing morbidity or mortality in the clinical outcomes, in patients suffering from viral infection. The methods generally involve administering a

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therapeutically effective amount of a Type I or Type III interferon receptor agonist and IFN-γ for the treatment of viral infection or liver fibrosis.

FEATURES OF THE INVENTION

The invention features a method of treating alphaviral infection, generally involving administering to an individual IFN-γ and a Type I or Type III interferon receptor agonist concurrently, in an amount effective to ameliorate the clinical course of the disease. The invention also features a method of treating alphavirus infection by administering to an individual IFN-γ and a Type I or Type III interferon receptor agonist in a synergistically effective amount to ameliorate the clinical course of the disease.

The invention features a method of treating West Nile viral infection, generally involving administering to an individual a Type I or Type III interferon receptor agonist, IFN-γ, or IFN-γ and a Type I or Type III interferon receptor agonist concurrently, in an amount effective to reduce the time to viral clearance or to reduce morbidity or mortality in clinical outcomes. The invention also features a method of treating West Nile viral infection by administering to an individual IFN-γ and a Type I or Type III interferon receptor agonist in a synergistically effective amount to reduce the time to viral clearance or to reduce morbidity or mortality in clinical outcomes.

The invention features a method of treating hepatitis C virus (HCV) infection, generally involving administering to an individual IFN-γ and a Type I or Type III interferon receptor agonist concurrently, in an amount effective to achieve a sustained viral response. The invention also features a method of treating HCV infection by administering to an individual IFN-γ and a Type I or Type III interferon receptor agonist in a synergistically effective amount to achieve a sustained viral response.

The invention features a method of reducing liver fibrosis in an individual, generally involving administering a Type I or Type III interferon receptor agonist and IFN-γ concurrently, in an amount effective to reduce liver fibrosis. Optionally, the method of the invention provides for administering to the patient the combination of a Type I or Type III interferon receptor agonist and IFN-γ along with an amount of pirfenidone or a pirfenidone analog effective to enhance the anti-fibrotic effect or the reduction of liver fibrosis achieved by the a Type I or Type III interferon receptor agonist and/or IFN-γ therapy. The invention also features a method of reducing liver fibrosis in an individual by administering a Type I or Type III interferon receptor agonist and IFN-γ in a synergistically effective amount to reduce liver fibrosis, optionally including co-administering to the patient an amount of

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