AREA OF FOCUS #4

Hepatitis C Virus and Liver Disease

Liver disease ranks as the 10th most common cause of death in the United States and disproportionately affects minority populations.

The leading causes of end-stage liver disease in the United States are alcoholic liver disease and hepatitis C.

Hepatitis C affects 1.5 percent of the U.S. population and is twofold to threefold more common among African-Americans and Hispanic Americans than among Caucasians.

Therapy for hepatitis C is evolving; current recommended regimens are effective in only 40 percent of patients. The response rate in African-Americans is lower than in Caucasians.

The only therapy for end-stage liver disease is liver transplantation. At present, approximately 4,000 liver transplants are done yearly, but waiting lists are lengthening, and a shortage of organs has caused an increase in deaths among patients awaiting transplantation.

Although end-stage liver disease is more common in minority individuals, those individuals are less likely to undergo liver transplantation. Furthermore, the survival rate after liver transplantation appears to be lower for African-Americans than for Caucasians.

Current Activities

Chronic Hepatitis C in African-Americans: Study of Resistance to Antiviral Therapy in Chronic Hepatitis C

Background

The hepatitis C virus (HCV) is probably the major cause of cirrhosis and end-stage liver disease in the United States, accounting for 8,000 to 10,000 deaths per year and at least 30 percent of all liver transplants done in adults in the United States. Hepatitis C is two to three times more common among African-Americans than non-Hispanic Caucasians. The current optimal therapy of chronic hepatitis C is a combination of alpha interferon and ribavirin given for 24 to 48 weeks. Retrospective analyses of studies of antiviral therapy have shown that response rates are two to three times less among African-American patients than among non-Hispanic Caucasians with hepatitis C. The reasons for this difference are not clear but may be due to viral strain or genotype, immunological factors, or genetic differences in interferon signaling and response pathways. Unfortunately, studies of antiviral therapy have included too few African-American patients to provide reliable estimates of the response rates to current therapies or to analyze the factors responsible for a lack of effect of therapy. Better information is needed to help improve response rates among African-Americans as well as to provide valid clinical recommendations for treatment.

A Request for Applications (RFA) was released in September 2000 for an interlocking set of cooperative agreements to design and implement a study of the frequency, pattern, nature, and cause of antiviral resistance in chronic hepatitis C, focusing on a cohort of African-Americans, among whom such resistance is common.

Research Goals and Scope

The proposed study includes a cooperative agreement that will call for applications for eight clinical centers, four ancillary research studies, and a data-coordinating center. The investigators will develop a detailed clinical protocol and strategies for analysis of the mechanism of antiviral effect and resistance to alpha interferon in patients with chronic hepatitis C. During the study, each clinical center will enroll and treat 50 patients (25 African-Americans and 25 non-Hispanic Caucasians) with chronic hepatitis C using the optimal regimen of therapy. Samples will be collected for the ancillary investigations of virological, cell signaling, immunological, and genetic factors that may play a role in antiviral resistance in hepatitis C. The research goals will be to address five research questions: (1) Are there differences in sustained virological response rates among African-Americans and non-Hispanic Caucasians? (2) What factors predict a response in both groups, and are they different? (3) Do the early viral kinetics predict the ultimate outcome of therapy? (4) Can a simple, clinically useful algorithm be developed to guide clinical decision-making in therapy for both African-American and non-Hispanic Caucasians? (5) What are the virological, immunological, genetic, and pharmacokinetic causes of viral resistance to combination therapy in patients with chronic hepatitis C?

Performance Measures

The performance measures to demonstrate that the objectives have been met will include the total number of grants awarded, the quality of proposals funded, the number of patients successfully recruited, and the funding level.

Outcome Measure

The outcome measure will be the extent to which the results alter clinical practice, including the diagnosis and treatment of hepatitis C in African-Americans.

Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial: Enhanced Minority Recruitment

Background

Therapy for hepatitis C, although improving, is ineffective in "curing" the infection (eradicating HCV) in about 70 percent of treated individuals. Among African-Americans, response to treatment is even more dismal, since 90 to 95 percent fail to respond. The reason(s) for the poor response rate among African-Americans is unclear. Recent treatment studies suggest that interferon may have both an antiviral and antifibrotic action. Studies from both Japan and the United States have suggested that interferon treatment reduces progression to cirrhosis, end-stage liver disease, and hepatocellular carcinoma even if it does not eradicate the virus.

NIDDK plans to enhance minority recruitment in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis clinical trial, a 7-year study of therapy for hepatitis C focusing on patients with advanced disease (with severe fibrosis or cirrhosis) who have not responded to conventional therapy and for whom there are no other practical options available. Patients are randomly assigned to receive long-term treatment with pegylated interferon (a once weekly injection) or no therapy. Patients will be intensively studied for both beneficial and adverse effects, supplemented by 10 separately funded ancillary studies. This trial enrolled more than 1,200 patients.

Research Goals and Scope

The purpose of this project is to determine the following: (1) if 4 years of interferon therapy will prevent the progression of advanced fibrosis to cirrhosis in patients with chronic hepatitis C who failed previous interferon therapy; (2) if 4 years of interferon therapy in patients with cirrhosis secondary to chronic hepatitis C who failed previous interferon therapy will reduce the risk of developing hepatic decompensation, reduce the need for hepatic transplantation, and reduce the risk of developing hepatocellular carcinoma; and (3) if 4 years of interferon therapy will improve the quality of life in patients with advanced fibrosis secondary to chronic hepatitis C who failed previous interferon therapy.

Performance Measures

The performance measures to demonstrate that the objectives have been met will include the total number of grants awarded, the quality of proposals funded, the number of minority enrollments, and the funding level.

Outcome Measure

The outcome measure will be the extent to which the results alter clinical practice, including the diagnosis and treatment of hepatitis C in African-Americans.

Clinical Research Network in Nonalcoholic Steatohepatitis

Background

Nonalcoholic steatohepatitis (NASH) is a common but poorly understood liver disease characterized by the accumulation of fat in the liver (steatosis), accompanied by inflammation, cell injury, and fibrosis (hepatitis) that closely resembles alcoholic liver disease but occurs in patients who drink little or no alcohol. NASH is most common in adults above age 40 who are overweight or have diabetes, insulin resistance, or hyperlipidemia. However, the disease also occurs in children and in persons who are not obese or diabetic. Currently, there are no effective therapies for NASH, and its natural history and prognosis are not well understood.

An RFA was released on February 12, 2001, to form an interlocking network of cooperative agreements to design and implement a database and clinical research network to study the etiology, contributing factors, natural history, complications, and therapy of NASH. Cooperative agreements will be awarded to six clinical centers and a data-coordinating center to establish a large clinical cohort of patients with NASH who will be followed in a natural history study and will undergo clinical investigations as to the etiology and contributing factors for the development and worsening of this disease. The network is intended to provide a mechanism that will facilitate and perform clinical, epidemiological, and therapeutic research in NASH.

Research Goals and Scope

Six clinical centers and a data-coordinating center will form the NASH Clinical Research Network. The initial focus will be the development of a clinical database of patients with NASH and the development of common definitions, nomenclature, and terms for the clinical diagnosis and staging of NASH. The database will be designed to address specific questions and to provide appropriate reagents or patient populations for clinical or laboratory investigation. The NASH Clinical Research Network is intended to provide the preliminary data and background for further investigator-initiated research and is expected to interact with basic and laboratory research investigators with an interest in these types of diseases by providing reagents, specimens, or opportunities to assess hypotheses on the pathogenesis, prevention, or treatment of the disease. The NASH Clinical Research

Network will also establish pilot studies of promising therapeutic approaches and, when appropriate, full-scale clinical trials of therapies for NASH.

Performance Measures

The performance measures will include the total number of grants awarded, the quality of the proposals, the number of patients successfully recruited, and the funding level.

Outcome Measure

The outcome measure will be the extent to which the results alter clinical practice, including the diagnosis, prevention, and treatment of NASH.