AREA OF FOCUS #5

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 two-to-three-fold more common among African Americans and Hispanic Americans than 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 while 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.

Research Goal 1

To improve our understanding of the hepatitis C virus and the disease that it causes

Current Activities

Basic and clinical research into the transmission, host immune response, pathogenesis, and natural history of hepatitis C viral infection in collaboration with other Institutes and Centers has been encouraged by several initiatives: RFA DK-98-017, Hepatitis C: Natural History, Pathogenesis, Therapy and Prevention; RFA AI-99-007, Hepatitis C Cooperative Research Centers; the NIDDK-supported clinical study of hepatitis C and long-term therapy with interferon aimed at preventing cirrhosis and hepatocellular cancer (HALT-C trial); and a surveillance study in cooperation with CDC on the incidence of chronic liver disease in the population.

Another initiative, PA-98-086, Liver and Biliary Diseases Among Women and Minorities, which was issued in collaboration with the NIH Office of Research on Women's Health (ORWH) and NCMHD, the National Institute on Drug Abuse (NIDA), and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), solicits R03 and R01 grants for both clinical and basic research in these areas.

Potential Initiative

Determine how the hepatitis C virus (HCV) is transmitted and what factors contribute to its pathogenesis.

Expected Outcome

Definition of the viral, host, and environmental factors contributing to the transmission and pathogenesis of HCV and the role of racial/ethnic and gender differences in the susceptibility to and outcomes of infection.

Action Plan

Mechanism of funding will be by a PA entitled "Pathogenesis and Therapy of Hepatitis C in Special Populations" for R01s and pilot and feasibility grants (R21s).

Research Goal 2

To improve the therapy for hepatitis C, particularly for African Americans

Current Activities

NIDDK convened a conference entitled "Hepatitis C in African Americans" held December 2, 1999, on the NIH campus. The workshop participants reviewed information on the prevalence, clinical course, complications, and therapy of hepatitis C among African-Americans and focused on comparisons of epidemiology and spread, serological and virological markers, disease severity and outcome, and treat-ment responses and complications between African-American and Caucasian populations. A central aim of that meeting was to plan future research directions.

In addition, the recently funded Hepatitis C Antiviral Long-term Therapy to prevent Cirrhosis (HALT-C) Trial is designed to determine the ability of long-term treatment with interferon to prevent the development of cirrhosis and hepatocellular cancer. The trial will also provide information on the natural history of HCV. As the largest and longest study of HCV, this trial should provide answers concerning disease management and provide clinical criteria for grading, staging, and assessing the prognosis of people infected with HCV. This trial will include an emphasis on recruitment of minority individuals.

Potential Initiative

Initiate a large clinical trial of combination therapy for HCV that will enroll similar numbers of African American and Caucasian patients and provide intensive investigation of viral, cell biologic, and genomic resources for laboratory investigation of viral resistance and response in HCV infection.

Expected Outcome

Characterization of the poor response rates of African Americans to current anti-HCV therapies. This characterization of resistance to interferon is key to developing effective therapy for all patients with this disease.

Action Plan

RFA for Cooperative Agreements (U01s) for clinical centers as well as a central data management, specimen bank center, and a specialized virology testing center will be issued.

Research Goal 3

To improve the availability and efficacy of liver transplantation for all groups of Americans

Current Activities

NIDDK continues to fund a long-term study on outcomes of liver transplantation. With the advent of technical advances for living donor liver transplantation, this modality of transplant has increased significantly.

Potential New Initiative

Foster discussion and collaborations on the technical, clinical, and research needs in the field.

Expected Outcome
Stimulation and development of clinical investigation and research on optimizing donor and patient selection, surgical techniques, safety, and improvement in survival of liver transplantation.

Action Plan
Organized and sponsored a clinical and research workshop on living donor liver transplantation in the Winter of 2000, to bring together clinicians and researchers to discuss the technical, clinical, and research advances in the field.

Research Goal 4

To prevent infection with hepatitis C through vaccine development

Current Activities

NIDDK's intramural investigators have taken two complementary approaches to study the development of HCV vaccine. First, in collaboration with investigators at the Southwest Foundation for Biomedical Research, an NIH Regional Primate Center, the group is conducting studies on chimpanzees, the only nonhuman primate model for HCV infection. The investigators have developed methods of synthesizing and purifying large quantities of non-infectious hepatitis C virus-like particles (HCV-LP) and have demonstrated that HCV-LP are capable of eliciting a strong humoral immune response broadly directed against various regions of HCV structural proteins in mice and rabbits. In addition, the HCV-LP is capable of inducing a cytotoxic T-cell response, which has been shown to be pivotal in controlling HCV infection. The other project involves detailed molecular, virologic, and immunologic analyses of chimpanzees infected either acutely or chronically with HCV to dissect the viral factors and host immune responses (both cellular and humoral) in viral clearance and disease progression.

Potential New Initiative

In the next 5 years, the plan is to expand along the same lines as the research program in progress. The investigators will begin testing the immunogenicity and efficacy of the HCV-like particles and other modalities in the chimpanzee model.

Expected Outcome

Given the higher prevalence of HCV infection (two-fold), increased incidence of liver cancer (three-fold), and poorer response to treatment among African Americans (<50 percent), the impact of an effective HCV vaccine will be particularly relevant on the affected minority populations. These disparities could ultimately dissipate if the infection can be prevented.

Action Plan

The proposed studies in chimpanzees will be conducted in collaboration with the Southwest Foundation for Biomedical Research. A contract has been developed with the support of NHLBI and NIDDK to perform these studies. In addition, the NIDDK investigators are also collaborating with academic investigators in extramural institutions on several NIAID-funded program projects and center grants on the immunology and vaccine development of hepatitis C.

Public Information and Outreach Goal

To increase awareness of hepatitis C among African American and Hispanic/Latino American audiences

Current Activities

NIDDK publishes a series of "easy-to-read" booklets on hepatitis through its National Digestive Diseases Information Clearinghouse (NDDIC). The series is available in the Spanish language. NIDDK also sponsored a conference entitled, "Hepatitis C in African Americans" at NIH in December 1999. CDC also publishes information for the lay public on all types of hepatitis.

Potential New Initiative

Establish a coordinated information program about hepatitis C in African Americans and Hispanic/Latino Americans.

Action Plan

Work with CDC and public and private partners representing African Americans and Hispanic/Latino Americans to identify additional needs of patients, families, and physicians. Plan and develop messages and materials. Publicize clinical trial recruitment and the results of research.