A "State-of-the-Art" Conference
Hepatitis C: A Meeting Ground for the Generalist and the Specialist

Information regarding pathogenesis and appropriate management of chronic hepatitis C continues to evolve. Educational campaigns continue to increase public awareness about hepatitis C. Clinicians must be prepared to address questions about the disease, to recognize and counsel patients at risk, to perform appropriate diagnostic testing, and to treat or refer patients who have the disease.

Based on recent advances, the National Institute of Allergy and Infectious Diseases (NIAID), as part of its ongoing series, "Emerging and Re-Emerging Issues in Infectious Diseases," convened a 2-day symposium on December 8-9, 1998, to consider the current status of diagnosis and treatment for chronic hepatitis C. A second aim was to provide information to the professional and lay communities. The meeting was chaired by Leslye D. Johnson, PhD, NIAID; Willis C. Maddrey, MD, University of Texas Southwestern Medical Center at Dallas; and Stanley M. Lemon, MD, University of Texas Medical Branch at Galveston. Presentations were made by experts in the field. Key information to come from this meeting includes:

- The cost-effectiveness of screening for hepatitis C and the establishment of guidelines for screening by medical and public health organizations worldwide, including the recommendations from the Centers for Disease Control and Prevention (CDC) in the October 16, 1998 MMWR:
- The potential clinical importance of any ALT elevation, no matter how minimal;
- The detrimental effect on disease progression of even moderate alcohol consumption (1-2 drinks/day);
- The increased response rates observed with new combination treatment (interferon/ribavirin) regimens. Recently published clinical trials noted sustained response rates in up to 40% of previously untreated patients and in up to 50% of those who had relapsed following successful interferon monotherapy;
- The parallels between hepatitis C virus (HCV) and human immodeficiency virus (HIV) infection, including the importance of medical intervention and the benefit of combination antiviral therapy (interferon/ribavirin).

Hepatitis C: A Serious Public Health Problem

Hepatitis C virus infection and the liver disease associated with it are potentially serious. The infection is estimated to affect approximately 4 million Americans.

Most of the roughly 85% of persons who advance from acute to chronic infection carry the virus indefinitely. Generally, the initial infection is not associated with symptoms recognizable by either the person or the physician. Hence, the vast majority of individuals do not know that they are infected or realize that they are at risk for serious liver disease. The disease may be clinically silent for many years—the latency period before clinically evident disease is far longer than that of HIV infection. After approximately 2-3 decades, about 25% of people develop more severe liver disease and have a greater risk of progressing to cirrhosis, liver failure, and occasionally to primary hepatocellular carcinoma, ie, liver cancer. Currently there is no way to identify patients who will progress. Approximately 8,000 to 10,000 deaths occur each year in the US from these complications of hepatitis C. Without better therapies, the number of deaths is expected to triple by the year 2015—higher than the current annual death rate for AIDS.

Hepatitis C as an Infectious Disease

HCV is an RNA virus that, like HIV, is genetically diverse. It exists as 6 major genotypes and numerous subtypes, as well as closely related quasispecies that can co-exist in a single infected individual. Genotypes impact the responses to existing therapies. This marked genetic heterogeneity of HCV may allow it to escape host immune surveillance and may partially explain the variable clinical course. A number of other parallels can be drawn between HCV and HIV, including the clinical benefit of antiviral drug therapies.

Diagnosis of Hepatitis C

Early diagnosis is important for several reasons. It provides the opportunity to discuss modes of transmission and methods to curb it, to offer suggestions on minimizing disease progression and to describe methods of treatment. Reliable diagnostic testing is available. For high-risk individuals, the enzyme-linked immunosorbent assay (EIA) is sensitive and accurate, and a positive EIA establishes the diagnosis of hepatitis C. The recombinant immunoblot assay (RIBA) is added when the diagnosis is in doubt or to confirm a positive EIA in a low-risk individual (eg, blood donor with no risk factor). Ongoing infection is indicated by the presence of HCV RNA demonstrated by qualitative or quantitative reverse transcription polymerase chain reaction (RT-PCR). RT-PCR, unfortunately, is not currently licensed for use in the US, but sensitive and specific tests are available for research use. Currently, it is advisable to be consistent and use the same test and laboratory when following a patient to avoid any variability in results.

The prognosis of chronic hepatitis C is determined in large measure by the presence and extent of fibrosis identified via liver biopsy. Risk factors for fibrosis include older age, male sex, and even moderate alcohol ingestion. At present, a liver biopsy is the only method available to assess the degree of fibrosis.

In October 1998, the CDC recommended routine screening of individuals with HCV risk factors including:

- Individuals who have ever, even once as an experiment, injected illegal drugs;
- Individuals with selected medical conditions who
  - had received clotting factor concentrates made before 1987,
  - have had chronic hemodialysis, or
  - have persistently abnormal ALT levels, even slightly above normal
- Individuals who
  - were notified to have received blood from an HCV-positive donor, or
  - received a blood transfusion, a blood component, or an organ transplant at any time before July 1992.

Careful, thoughtful patient histories will be helpful in identifying those with increased risk of having hepatitis C.

Alcohol and Hepatitis C

Viral titers are significantly higher and liver disease progresses more rapidly in alcohol abusers. Furthermore, recent studies indicate that even moderate alcohol consumption (>10-20 grams or only two 1-oz drinks per day) has substantial adverse effects. Liver biopsies in such individuals reveal histologic features that are predominately those of chronic hepatitis C. Because of their poor response to treatment regimens, alcoholics should not be treated until they have been alcohol-free for at least 6 months.

HCV Infection in Special Populations

Although HCV infection and disease affect individuals from all walks-of-life, there are some patient populations that need special mention. These include patients with concurrent HIV infection, hemodialysis patients, renal transplant patients, hemophiliac patients, patients with alcoholic liver disease, and inmates of correctional institutions.

- With improved therapies, patients with HIV infection are living longer and having a better quality of life. HIV infection tends to worsen hepatitis C progression. Hence, patients with stable HIV disease may benefit from treatment of their HCV infection.
- Studies in hemophiliac patients have shown that after factor replacement a liver biopsy can be as safe as it is in non-hemophiliac patients. As with non-hemophiliac patients, histologic changes are generally mild, even after 20 years of infection, unless HIV co-infected. Treatment trials are underway.

- About 20% of patients receiving long-term hemodialysis for kidney disease have chronic hepatitis C. There is limited experience with interferon therapy in this group. Small studies suggest response rates similar to those in other patient groups, but high dropout rates suggest poorer tolerability. In contrast, IFN-a therapy is not effective in renal transplant patients and may increase the rate of rejection. If treatment of HCV is desired, it should be given only before transplantation.
- Strategies to control hepatitis C in the US should include focus on the prison population due to the high prevalence of HCV infection and high rates of reentry into the community. There are wide variations in correctional healthcare, low funding, and limited access to specialty care. An additional problem is the high prevalence of underlying psychiatric disorders.

Evolution of Therapy for Chronic Hepatitis C

Three patient response terms are now in use and help patients and physicians to understand drug effectiveness. "Sustained responders" are individuals who 6 months after therapy is completed have no virus by RT-PCR and normal ALTs. "Relapsers" are those who respond to treatment but in whom virus comes back during the 6 months after therapy. "Non-responders" never lose virus, using sensitive methods. Clearly, sustained response is a primary treatment objective.

The first interferon (interferon alpha-2b) was introduced for use in hepatitis C in 1991. Since that time two other interferons (interferon alfa-2a and alfacon-1) have been introduced. The original therapeutic regimen with interferon alpha-2b was 3 MIU TIW for 6 months; the sustained response rate is quoted as 15%-20% but in practice is closer to 10%. It was later determined that a 12-18 month course of therapy resulted in a small increase in the sustained response rate. Recently published clinical trials established that interferon alfa-2b in combination with ribavirin results in almost a 40% overall sustained response rate. However, individuals with genotype 1, the major genotype in the US, have only a 28% sustained response rate compared to 66% in those with genotypes 2 and 3. For all these viral genotype groups the sustained response is roughly 3 times better than that seen with interferon alpha 2-b alone. Ribavirin does not work when used alone. Retreatment of those who relapsed after 6 months of interferon therapy with a longer duration of interferon alpha-2b therapy has minimal benefit. A new advance for relapsers is retreatment with the ribavirin/interferon combination therapy, which results in a sustained response in almost 50% of cases. Studies in interferon non-responders are underway.

With the interferon alpha-2b/ribavirin combination regimen, about 50%-60% of patients still do not achieve a sustained response. Along with the strong influence of viral genotype on response described above, high baseline viral load, stage 3-4 fibrosis, and high hepatic iron levels each decrease the likelihood of response. The recent clinical trial indicates that 24 weeks of combination therapy provides

maximal response for patients with genotypes 2 and 3 and that 48 weeks is better for genotype 1 patients.

Both ribavirin and interferon alpha 2-b have significant side effects when used as monotherapies. Some of the more minor side effects (dyspnea, pharyngitis, rash, nausea, insomnia, and anorexia) were more common when the two drugs were used in combination. Discontinuation of treatment was needed in 8%-21% of those receiving the combination. The major reason for discontinuation was emotional disturbance—mainly depression. Other side effects were headache, fatigue, and myalgia in 60%-70% of those treated. Arthralgia, musculoskeletal pain, fever, nausea, diarrhea, depression, insomnia, irritability, and alopecia occurred in 27%-40%. Specific dose reduction helped alleviate some of the side effects and did not impact the response to therapy.

Ribavirin use poses two significant safety issues. First, in animal species ribavirin is significantly teratogenic and/or embryocidal, i.e., an agent that can cause birth defects or kill embryos. Hence, males as well as females who take this drug combination must practice effective contraception both during treatment and for 6 months afterwards. Females should have a negative pregnancy test before beginning therapy. Second, ribavirin is associated with a dose-dependent, reversible hemolytic anemia that in the combination study required dose reduction in 7%-10% of patients. Multiple laboratory and clinical evaluations are needed over the course of treatment.

The Future

Left untreated, chronic hepatitis C could result in a 1.5 fold increase in cirrhosis in the next 15-20 years. The current combination regimen of interferon and ribavirin has increased sustained response rates to 40-50%. Efforts to further improve sustained response rates can take 2 paths. Additional options for interferon dosage and administration are being evaluated; these include induction dosing, more frequent administration, and new once-a-week formulations. It will be important to evaluate the safety and efficacy of the other two interferons in combination with ribavirin or other combinations of antiviral agents in well-controlled clinical trials. As with HIV therapy, the next major improvement will probably come with the use of novel small molecule antivirals (eg, helicase or protease inhibitors) in combination with interferon or interferon and ribavirin.

In the last 10 years, hepatitis C has progressed from an identified disease without a known pathogen to a disease that can now be treated with a 50% sustained response. Maximizing the benefits of treatment advances made in the last decade will require teamwork involving patients, primary care physicians, infectious disease experts, gastroenterologists and specialists in hepatology. Future therapeutic advances will surely derive from ongoing basic, applied and clinical research.

Disclosure Statement

Each of the chairpersons had significant input in the development of the program including the selection of topics and speakers. This document succinctly covers important points conveyed by the panelists. The NIH/FAES has agreed to sponsor Continuing Medical Education associated with future, more-detailed communications. SynerMed arranged for the unrestricted educational grant from Schering Oncology/Biotech, handled all the logistical arrangements, and will work with NIAID and provide support for future educational outreach efforts.

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