

PHOENIX™ MISSION STATEMENT

To provide health care professionals with a comprehensive continuing medical education program focused on evolving concepts in the management of hepatitis C treatment failures that results in improved patient care

THE PHOENIX™ INITIATIVE

MARIA H. SJOGREN, MD, MPH

As the leading cause of hepatocellular carcinoma and the principal indication for liver transplantation in the United States, hepatitis C virus (HCV) infection represents a significant health concern. Current estimates hold the US HCV infection prevalence at 3.9 million; 2.7 million (74%) have chronic infection. The incidence of new infections is falling, yet the overall prevalence of HCV-related liver disease and associated death rate continue to climb. This growing burden is attributable to the often 20-year or greater interval between acute infection with HCV and the clinical manifestations of HCV-related liver disease.

Despite recent advances in the treatment of chronic hepatitis C infection, eradication of the virus remains quite challenging. Current standard therapy, pegylated interferon plus ribavirin, only produces an approximate 50% sustained virologic response (SVR) rate in naïve patients. Thus, half of all patients receiving treatment for HCV infection either fail to completely respond or relapse after an initial response. It is estimated that this pool of treatment failures will expand from about 150,000 in 2003 to 500,000 US patients in 2014.

New data suggest that those patients unlikely to achieve an SVR can be identified early in their course of therapy, thereby sparing them from unnecessary

exposure to costly medications that are unlikely to eventually produce an SVR, and providing an opportunity to consider options for re-treatment. Such options, including higher dose pegylated interferon, consensus interferon, and maintenance interferon, are currently under investigation in large-scale clinical trials. Educating practitioners about the emerging evidence concerning therapeutic interventions in patients failing HCV treatment will help more patients achieve viral eradication and ultimately reduce the burden of disease sequelae on our society.

Thus, a critical need for medical education has been identified with the objective of increasing therapeutic knowledge in the area of hepatitis C treatment failure. In order to fulfill the need for increased physician awareness and ultimately improved patient outcomes, an educational program entitled PHOENIX™ (Perspectives in Hepatitis C Outcomes: An Educational Network for Improving Options in TX Failures) has been developed through the support of an educational grant from InterMune®. The objectives of this initiative are to

- Evaluate current demographics and epidemiology for HCV and assess the long-term consequences of treatment failure
- Examine the scientific basis for HCV treatment failure, including predictors of response and viral kinetics

- Identify and compare therapeutic options for patients who fail initial HCV treatment
- Develop a series of healthcare professional and patient education tools designed to increase the providers' ability to successfully manage patients who initially fail HCV treatment
- Measure the impact of PHOENIX™ activities on health care provider knowledge through the gathering and analysis of objective, measurable outcome data

With these goals in mind, a Steering Committee comprised of eight healthcare professionals, with extensive experience in

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STEERING COMMITTEE MEMBERS

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AN OVERVIEW OF HEPATITIS C VIRUS INFECTION: ASSESSING EPIDEMIOLOGY, TRANSMISSION, NATURAL HISTORY, AND TREATMENT

SCOTT COTLER, MD

EPIDEMIOLOGY

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease in the United States, affecting 3 to 4 million persons, or approximately 1.8% of the population.¹ Worldwide, the prevalence is estimated to be 3% (170 million cases), with higher rates in areas such as northern Africa, parts of Asia, the Mediterranean, and the Middle East.² The highest prevalence has been identified in Egypt (17–26%).^{2,3} Most infected persons in the developing world, and many in industrialized nations, remain untreated.

The NHANES III study found that HCV is more common among non-Hispanic blacks (3.2%) and Mexican Americans (2.1%) than among non-Hispanic whites (1.5%).¹

[Figure 1] HCV is particularly prevalent among certain high-risk groups such as prison inmates, who have seropositivity rates of 30% to 40%.^{4,5} According to the Centers for Disease Control and Prevention (CDC), the prevalence of HCV is projected to continue to increase over the next decade.⁶

life compared to the general population.¹² Although HCV tends to be slowly progressive, it does lead to cirrhosis and complications of liver disease in some cases. Currently, HCV is responsible for 40% of the 25,000 deaths due to liver disease that occur annually in the US.¹³ The number of liver transplants performed in patients with HCV increased 5-fold between 1990 and 2000.¹² In fact, hepatitis C is now the leading indication for liver transplantation, accounting for nearly 40% of cases.

The incidence of hepatocellular carcinoma (HCC) has risen substantially in recent years, at least in part due to the increase in HCV cirrhosis.¹⁴ Data from the Surveillance, Epidemiology, and End Results (SEER) survey indicate that the proportion of cases of HCC related to HCV infection increased from 11% during the time period from 1993 to 1996 to 21% during the time period from 1996 to 1999.¹⁴ SEER data also showed a substantial increase in mortality from HCC.¹⁵

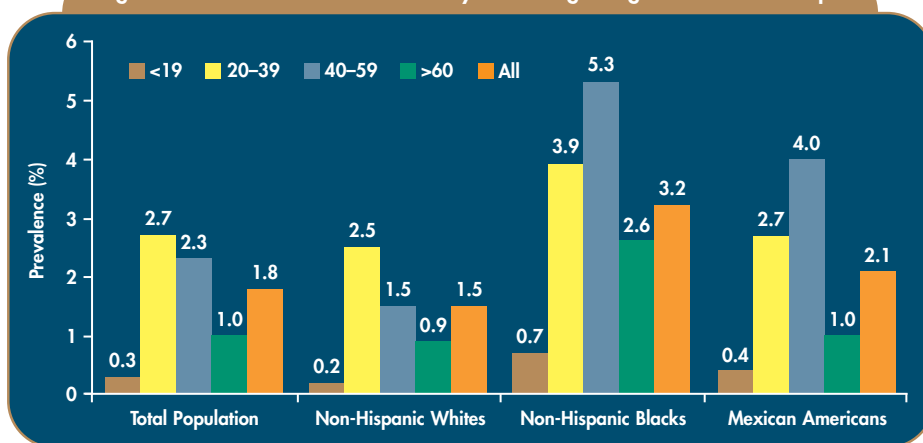
based on the high prevalence of HCV.¹³ Decreasing the burden of HCV-related liver disease will require effective primary prevention measures, identification of infected individuals, and continued advances in antiviral therapy.¹³

RISK FACTORS/TRANSMISSION

Injection drug use is the most common means of HCV transmission.⁶ Prior to the identification of HCV and screening of the blood supply, blood transfusion was also an important risk factor for infection. The risk of acquiring HCV through transfusion of a unit of blood decreased to approximately 1 in 100,000 with the institution of routine screening measures.¹⁶ Hepatitis C can be transmitted by sexual contact, although the magnitude of the risk is relatively low compared to parenteral exposure. The annual rate of acquiring HCV from an infected sexual partner was estimated to be 0–0.6% for monogamous couples and 0.5–1.8% for those with multiple sexual partners.¹⁷ In one survey, 18% of patients newly infected with HCV reported that multiple sexual partners or sexual contact with an HCV-infected individual was their only risk factor for HCV acquisition.¹⁷

Less common means of HCV transmission include vertical transmission, occupational exposure, and contact with blood in hemodialysis units. The risk of maternal to infant transmission is approximately 4% to 7% and is increased in persons with HIV co-infection.¹⁸ Tattooing, body piercing, religious scarification, exposure to a bloody object, and intranasal cocaine use might contribute to HCV transmission in small numbers of cases.¹⁹

Figure 1. Prevalence of HCV Antibody According to Age and Ethnic Group¹



Over 70% of persons with HCV in the US have genotype 1 infection.^{4,7,8} Moreover, more than one half have genotype 1 and a high viral load, defined as > 2 million copies/mL (> 800,000 IU/mL). Patients with genotype 1 and high viral load have the lowest response rates to antiviral therapy.^{9,10,11}

DISEASE BURDEN

Studies assessing health status and quality of life have found that patients with HCV experience reduced health-related quality of

Data from the Nationwide Inpatient Sample of Healthcare Utilization Project showed that HCV accounted for 2% of all hospital discharge diagnoses in 1998 and over \$1 billion in direct health care costs.¹² The number of persons at risk for complications of liver disease by virtue of having at least 20 years of HCV infection is projected to increase 4-fold between 1990 and 2015.¹² Morbidity, mortality, and use of healthcare resources associated with HCV are all expected to rise over the next 10 to 20 years

NATURAL HISTORY

Defining the natural history of HCV has been difficult because acute infection generally goes unrecognized and liver injury progresses gradually over the course of decades. Estimates of the rate of development of cirrhosis differ depending on the characteristics of the population studied. A review of 57 studies published between 1990 and 2000 divided the literature on natural history into 4 categories.²⁰ The rate of progression to cirrhosis over 20 years was estimated at 24% in longitudinal studies of

transfusion recipients, 22% in cross-sectional analyses of patients seen in liver clinics, 7% for longitudinal studies of community based cohorts, and 4% for cross-sectional series of blood donors.²⁰

Alcohol abuse, male gender, age > 40 years at time of infection, and co-infection with HIV or hepatitis B are associated with more rapid development of cirrhosis.^{6,21,22} In a study using mathematical modeling, the average time to development of cirrhosis among alcoholic men who were infected after age 40 years was estimated at 13 years, compared to 42 years for women who contracted HCV before age 40 and did not drink alcohol.²² Recent reports have implicated non-alcoholic steatohepatitis and tobacco as additional co-factors for the development of fibrosis in patients with HCV.^{23,24} In contrast, HCV viral load and genotype are not associated with disease progression.^{22,25}

TREATMENT OPTIONS FOR NAÏVE AND NONRESPONDER PATIENTS

Approved agents for the treatment of HCV are listed in Table 1.²⁶ Pegylated interferon plus ribavirin is considered the standard of care for treatment naïve patients, achieving sustained virologic response (SVR) rates > 50% overall.^{9,10} Response rates vary from 42%–46% in patients with genotype 1 infection to 76%–82% in those with genotype 2 or 3. Patients with genotype 1 HCV require 48 weeks of therapy and ribavirin doses of 1000 mg/day for weight < 75 kg and 1200 mg/day for weight ≥ 75 kg.²⁷ In contrast, patients with genotype 2 or 3 achieve optimal response rates with only 24 weeks of treatment and a ribavirin dose of 800 mg per day.

treatment response.⁹ Therapy is generally discontinued in patients with genotype 1 infection who do not achieve an EVR because they have a negligible chance of achieving an SVR with continued treatment. It is not cost effective to evaluate EVR in patients with genotype 2 and 3 infection because 99% reach this endpoint.²⁸

Nonresponders to antiviral therapy provide the greatest treatment challenge. The number of nonresponders was estimated at 150,000 in 2003 and is growing at a rate of up to 50,000 per year.²⁹ Retreatment of patients with bridging fibrosis or cirrhosis with pegylated interferon and ribavirin yielded a SVR rate of 28% in previous nonresponders to unmodified interferon alone, and an SVR rate of 12% in nonresponders to unmodified interferon and ribavirin.³⁰ In preliminary reports, retreatment of nonresponders to unmodified interferon plus ribavirin with daily doses of interferon alfacon-1 and ribavirin was associated with SVR rates of 27% to 42%.^{31,32} Further data presented in abstract form showed SVR rates of 23%–37% for retreatment of nonresponders to pegylated interferon and ribavirin with daily, high dose interferon alfacon-1 plus ribavirin.^{33,34} Prospective studies of pegylated interferon maintenance therapy for the management of nonresponders with advanced fibrosis are underway.

SUMMARY

Hepatitis C is highly prevalent in the US and worldwide. Complications of HCV including decompensated cirrhosis, hepatocellular carcinoma, and the need for liver transplantation lead to significant morbidity,

treatment of HCV. Further efforts are needed to identify persons with undiagnosed HCV who could benefit from therapy and to investigate treatment options for the growing number of nonresponder patients. Recent results show promise in the retreatment of previous nonresponders.

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Table 1. Approved agents for treatment of chronic hepatitis C²⁶

Generic Name	Trade Name (Manufacturer)	Dosing
IFN alfa-2a	Roferon® (Roche)	3 MIU SC TIW
IFN alfa-2b	Intron-A® (Schering-Plough)	3 MIU SC TIW
IFN alfacon-1	Infergen™ (InterMune)	9 µg SC TIW 1.5 µg SC TIW*
Peginterferon alfa 2-a	Pegasys® (Roche)	180 µg SC QW
Peginterferon alfa 2-b	Peg-Intron® (Schering-Plough)	1.0–1.5 µg/kg SC QW
Ribavirin**	Copegus® (Roche)	0.8–1.2 g/day orally†
Ribavirin**	Rebetol® (Schering-Plough)	0.8–1.2 g/day orally†
Ribavirin**	Ribasphere™ (Three Rivers)	0.8–1.2 g/day orally†

IFN = interferon; QW = once weekly; SC = subcutaneous; TIW = three times weekly;
*Interferon relapsers and nonresponders; **Ribavirin is not approved for monotherapy, but as part of combination with interferon alpha; †Depending on HCV genotype and patient body weight

Measurement of early virologic response (EVR), defined as undetectable HCV RNA or ≥ 2-log decrease in viral load by week 12 of therapy, provides an interim assessment of

mortality and health care costs and are projected to increase over the next decade. The use of pegylated interferon and ribavirin has provided a substantial advance in the

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the field of hepatitis C, has been assembled to direct the development of a series of educational materials. The Steering Committee will function under the direction of predefined roles and responsibilities, with the ultimate goal of developing educational content and materials that support the PHOENIX™ initiative.

The principal educational tool in the PHOENIX™ program will be a three-section slide kit, with each section developed by a separate work group of hepatitis C experts. The slide kit will include an overview of hepatitis C, a segment on the potential scientific basis for hepatitis C treatment failure, and a detailed overview of re-treatment options for patients failing hepatitis C therapy. In addition, the program compendium will include clinical tools for health care professionals treating hepatitis C and resources for hepatitis C patient management and education.

Interactive patient cases, a written case report, quarterly newsletters, local dinner programs and a Web site (www.PHOENIXCME.ORG) comprise the remaining key elements of this initiative. The Web site will be created to help in the dissemination of the educational materials to the medical community involved in the management of hepatitis C and will host content developed for the PHOENIX™ educational programs.

The PHOENIX™ initiative will play a key role in providing the medical community with a compilation of highly effective educational materials that will support the overall goals of increasing knowledge surrounding hepatitis C treatment failure and improving the care of patients with this chronic and challenging disease.

On behalf of the Steering Committee, I invite you to participate in this important educational endeavor.

For more information about the PHOENIX™ initiative,
call toll free at **866-227-6411** or visit us at www.PHOENIXCME.ORG