

The NIH Consensus Conference on the Management of Hepatitis C: 2002. Part 1

Introduction

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The National Institutes of Health convened the second Management of Hepatitis C Consensus Development Conference on June 10, 2002 in Bethesda, Maryland. The first Management of Hepatitis C Consensus Conference was held in March 1997 that established the current approaches that are utilized in the management and care of HCV. The statement that will be issued as a result of this meeting will have far reaching affects and consequences to the management, care and treatment of hepatitis C and is therefore of extreme importance to the community.

It is clear that major breakthroughs in the management and care of HCV have taken place in the years since the first conference. Some statements listed in the original consensus conference that have changed include:

- “.... persistent infection develops in perhaps as many as 85% of patients with acute hepatitis C.” We now know that the true number of people that develop chronic infection is more likely between 50-55% with a higher rate of spontaneous recovery in some groups.
- The only available treatment for HCV was various forms of interferon with “the bulk of available evidence pertains to the alpha interferons (interferon alpha).” Current HCV medications include interferon, combination of interferon and ribavirin, pegylated interferon and pegylated interferon and ribavirin.
- Treatment success was measured by normalization of biochemical markers – that is ALTs and with elimination of hepatitis C by viral load. Sustained virological response is the elimination of HCV and is now the end point of treatment.
- The sensitivity on anti HCV tests and viral load tests were questioned at the first consensus conference. Now these tests are considered very sensitive and accurate.
- At that time fibrosis was believed to be irreversible. We now know that dramatic reversal of fibrosis or scarring takes place with the elimination of HCV from successful HCV treatment and some reversal of fibrosis takes place even in people that do not clear HCV from treatment.

The first consensus conference has had many detractors in the medical field and the community. First, people with persistently normal enzymes (ALTs) were excluded from treatment except under investigational studies. We now know that approximately 20% of people with persistently normal enzymes level have moderate to severe disease progression and treatment should be evaluated under different criteria for these patients.

Secondly, people “who are drinking significant amounts of alcohol or who are actively using illicit drugs should be delayed until these habits are discontinued for at least 6 months.” This is the most controversial area that will be addressed at this conference with many advocates actively lobbying for treatment decisions on a case-by-case basis based upon the opinion of the medical provider and patient after extensive evaluation.

One of the most commonly used drugs by IDUs is heroin. Treatment for heroin addiction, which has been endorsed by a previous consensus statement, is opiate agonist therapy (methadone). However, the vast majority of medical providers will not treat this population. In addition the majority of transplant centers will not list a patient on methadone maintenance. The majority of cases of HCV are linked to active injection drug use and the current government guidelines recommend against treating active injection drug users. If methadone maintenance, the recommended treatment, is not widely accepted as a concomitant therapy during treatment for HCV then how do we give hope to the largest population infected with HCV and explain this inconsistency.

Please note that there were no major revelations in today’s presentations, but the review of the data and questions posed will provide us with many recommendations for future research.

The following are the opening session summaries for the NIH Consensus Conference on the Management of Hepatitis C: 2002.

The Course and Outcome of Hepatitis C

Jay H. Hoofnagle, M.D.

Hepatitis C is caused by a small RNA virus that belongs to the family flaviviridae and is the sole member of the genus hepacivirus. First identified in 1989, the hepatitis C virus (HCV) has a single-stranded RNA genome that is ~ 9.6 kilobases in length and encodes a single, large polyprotein of ~ 3000 amino acids. The HCV polyprotein is cleaved post-translationally into multiple structural and non-structural peptides: structural components consist of a nucleocapsid core [C] and two envelope glycoproteins [E1 & E2] and the non-structural proteins are labeled NS2 through NS5. The specific functions of the individual NS proteins have not been completely elucidated. NS3 has both helicase and protease activities and the NS5 region contains the RNA-dependent RNA polymerase activity essential for RNA viral replication. These enzymatic activities are potential targets for antiviral compounds. HCV RNA also has important and highly conserved 5’ and 3’ untranslated regions (UTRs). The 5’ UTR has an internal ribosomal entry site (IRES) essential for initiation of viral protein translation and the 3’ UTR has structured RNA elements essential for both viral replication and translation.

There are neither robust cell culture systems for propagation of HCV nor simple small animal models of the infection, so the replicative cycle of the virus has largely been deduced from that of other flaviviruses. HCV replicates in the cytoplasm of hepatocytes where it is not directly cytopathic. Persistent infection appears to rely upon rapid production of virus and continuous cell-to-cell spread along with a lack of vigorous T cell immune response to HCV antigens. The HCV RNA genome mutates frequently and circulates in serum not as a single species but as a population of quasispecies with individual viral genomes differing by 1 to 5 percent in nucleotide sequence. Six major genotypes (1 to 6) and more than 50 subtypes (e.g., 1a, 1b, 2a, 2b) have been described. Different isolates of HCV differ by 5–15 percent, subtypes by 10–30 percent, and genotypes by as much as 30–50 percent in nucleotide sequence.

Hepatitis C can cause both acute and chronic hepatitis. Knowledge of the course and outcome of infection arises largely from studies in chimpanzees and previous post-transfusion and more current post-needlestick accident cases of hepatitis C. In acute hepatitis, HCV RNA can be detected in the serum within one to two weeks after exposure, rising thereafter to levels of 10^5 to 10^7 viral genomes per ml. Serum alanine

aminotransferase (ALT) levels indicative of hepatocyte injury and necrosis start to rise 2 to 8 weeks after exposure and usually reach levels of greater than 10 times the upper limit of normal. About one-third of adults with acute HCV infection develop clinical symptoms and jaundice, the symptomatic onset ranging from 3 to 12 weeks after exposure. In self-limited acute hepatitis C, symptoms last for several weeks and subside as ALT and HCV levels fall. Acute hepatitis C can be severe and prolonged but is rarely fulminant. Antibody to HCV as detected by enzyme immunoassay (EIA) arises at the time of or shortly after onset of symptoms, so that 30 percent of patients test negative for anti-HCV at onset of symptoms, making anti-HCV testing unreliable in diagnosis. Almost all patients eventually develop anti-HCV, although titers can be low or even undetectable in patients with immune deficiencies.

Chronic hepatitis C is marked by persistence of HCV RNA for at least six months after onset of infection. The chronicity rate of hepatitis C averages 70–80 percent, but varies by age, sex, race, and immune status. During the evolution of acute to chronic infection, HCV RNA and ALT levels can fluctuate markedly, some patients having periods during which HCV RNA is undetectable and ALT levels normal. Once chronic infection is established, however, serum HCV RNA levels tend to be stable. Most patients with chronic hepatitis C have few if any symptoms, the most common being fatigue, which is typically intermittent. Right upper quadrant pain (liver ache), nausea, and poor appetite occur in some patients. Serum ALT levels are usually continuously or intermittently elevated, but the height of elevations correlates poorly with disease activity and at least one-third of infected persons have persistently normal ALT levels. In these patients, the underlying disease is usually, but not always, mild and non-progressive. Liver histology in chronic HCV infection demonstrates chronic mononuclear cell infiltration in the parenchyma and portal areas, focal hepatocyte necrosis, and variable degrees of fibrosis.

The major long-term complications of chronic hepatitis C are cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC), which develop only in a proportion of patients and only after many years or decades of infection. Progression to cirrhosis is often silent clinically and some patients are not known to have hepatitis C until they present with the complications of end-stage liver disease or HCC. Once cirrhosis is present, the ultimate prognosis is poor.

Other complications of chronic hepatitis C can be important and affect quality of life. The major extrahepatic manifestations of chronic HCV infection are cryoglobulinemia, glomerulonephritis, seronegative arthritis, sicca syndrome, and porphyria cutanea tarda. HCV-related cryoglobulinemia is the most common: up to 40 percent of patients with chronic hepatitis C may have low levels of cryoglobulins in serum, but only 1 percent have symptomatic cryoglobulinemia with fatigue, arthralgias, skin rash, renal disease, or neuropathy.

Thus, the course of hepatitis C is variable, the severity of illness ranging from a transient, self-limited and asymptomatic infection to a chronic, progressive liver disease that leads ultimately to cirrhosis and HCC.

References

1. Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001;345:41–52.
2. Robertson B, Myers G, Howard C, et al. Classification, nomenclature, and database development for hepatitis C virus (HCV) and related viruses: proposals for standardization. *Arch Virol* 1998;143:2393–503.
3. Farci P, Alter HJ, Wong D, et al. A long-term study of hepatitis C virus replication in non-A, non-B hepatitis. *N Engl J Med* 1991;325:98–104.
4. Alter MJ, Kniszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999;341:556–62.
5. Bellentani S, Tiribelli C. The spectrum of liver disease in the general population: lesson from the Dionysos study. *J Hepatol* 2001;35:531–7.

The Burden of Hepatitis C in the United States

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Incidence and Prevalence

Disease frequency may be measured either by the pool of existing cases (prevalence), or by the occurrence of new cases (incidence). The most widely quoted data on the prevalence of HCV in the United States are derived from the third National Health and Nutrition Examination Survey (NHANES), a national survey of a representative sample of non-institutionalized civilian Americans conducted between 1988 and 1994. Of 21,000 people tested for HCV, 380 people (1.8 percent) carried antibodies against the virus (anti-HCV), of whom 280 (74 percent) had detectable viral RNA in their serum. These numbers project to 3.9 million Americans (95 percent confidence interval (CI): 3.1–4.8 million) who have been infected with HCV, of whom 2.7 million (95 percent CI: 2.4–3.0 million) have ongoing chronic infection. Hepatitis C is the most common chronic blood-borne infection in the United States.

While HCV is a reportable infectious disease in the United States, the incidence of new HCV infection is much more difficult to estimate than its prevalence. Since the majority of acute HCV infections are not accompanied by recognizable symptoms and thus not reported, enumerating reported cases of acute hepatitis C significantly underestimates the true incidence of hepatitis C infection. Nonetheless, the Centers for Disease Control and Prevention (CDC) estimate that the annual incidence of acute HCV infection in the United States decreased from an average of approximately 230,000 new cases per year in the 1980s to 38,000 cases per year in the 1990s.

It may be expected that the reduction in new incident cases will eventually lead to a decrease in the prevalence of HCV. A report from CDC projected that, following a peak in the mid-1990s at slightly above 2.0 percent, the HCV prevalence would gradually decrease to 1.0 percent by 2030. While the prevalence of HCV infection may be decreasing, the prevalence of liver disease caused by HCV is on the rise. This is because there is a significant lag, often 20 years or longer, between the onset of infection and clinical manifestation of liver disease. CDC projects a fourfold increase in the number of persons with longstanding (20 years or longer) infection between 1990 and 2015. Furthermore, it is uncertain whether the projected decline in the HCV prevalence based on NHANES data (non-institutionalized civilians) translates to other population groups known to have very high prevalence of HCV. Examples of these groups include patients at Veterans Affairs (VA) hospitals, active intravenous drug users, and prison inmates.

Mortality from HCV

Chronic liver disease is one of the 10 most common causes of death in the United States. There has been a steady increase in the number of deaths from liver disease over time. The increase was mainly attributable to viral hepatitis and hepatic malignancies. On the other hand, the age-adjusted death rate (deaths per 100,000 living persons, adjusted to 2000 population census) from liver disease has been relatively constant.

Mortality statistics in the United States are based on the “underlying cause of death” listed on death certificates. As deaths attributable to viral hepatitis primarily result from chronic liver disease and liver failure and, in those cases, viral hepatitis may not necessarily be listed as the underlying cause of death, it is likely that deaths classified as viral hepatitis underestimate the true incidence of deaths related to viral hepatitis. Further, until 1999, when the International Classification of Disease version 10 (ICD-10) began to be used to classify causes of death, HCV was not given an independent code, making it difficult to estimate the total number of deaths attributable to HCV.

With these caveats in mind, there was a sixfold increase in the number of deaths from viral hepatitis (all types) between 1982 (n=814) and 1999 (n=4853). In 1999, the first year HCV was reported separately, the majority (77 percent, n=3759) of deaths from viral hepatitis were due to HCV. During the same period, there was a commensurate increase in the age-adjusted death rate from 0.4 to 1.8 deaths per 100,000 persons per year. To estimate the degree of under-reporting of HCV as the underlying cause of death in the mortality data, the number of in-hospital deaths from liver disease related to hepatitis C was enumerated (see below for details). In 1998, there were an estimated 4500 in-hospital deaths in the United States for liver disease related to HCV (source: Healthcare Utilization Project, AHRQ).

Morbidity and Health Care Cost from HCV

As chronic hepatitis C has a prolonged natural history and it is only a relative minority of the infected that require ongoing medical care for their hepatitis, it is difficult to estimate the magnitude of morbidity at the population level. A cost-of-illness study conducted by the American Gastroenterological Association estimated that there were 317,000 outpatient visits for the treatment of hepatitis C in the United States in 1998. The cost for outpatient physician services was projected to be \$23.9 million. During the same year, \$530 million was spent for antiviral treatment of HCV.

Patients with more advanced stage liver disease present with portal hypertension and hepatic decompensation, as manifested by ascites, hepatic encephalopathy, or gastrointestinal bleeding, which often necessitates inpatient care, including liver transplantation. End-stage liver disease and/or hepatocellular carcinoma related to HCV is already the most common indication for liver transplantation in the United States. In 1999, approximately one-third of available cadaveric livers were transplanted into recipients with HCV infection.

The nationwide impact of liver disease due to HCV has been estimated based on data derived from the Nationwide Inpatient Sample of the Healthcare Utilization Project. This database represents a 20 percent stratified sample from all non-Federal, acute-care hospitals, which account for approximately 95 percent of all hospitalizations in the nation. As liver disease from HCV may not be the main reason for all hospitalizations with a HCV diagnosis, hospitalizations were divided into three groups. These included hospitalizations in which liver disease from hepatitis C was the primary reason for hospitalization, those in which liver disease from HCV was a secondary reason, and those in which HCV was an incidental notation. Because of the uncertainty of ascertainment of HCV in the early 90s, hospitalizations for other chronic hepatitis (non-A, non-B) were also captured.

There was an almost fourfold increase during the five-year period between 1993 (n=35,700) and 1998 (n=134,200) in the total number of hospitalizations in which HCV was mentioned in the discharge diagnosis. Some of the increase was due to lack of ascertainment of HCV in the early 1990s, as there was a partially corresponding decrease in the non-A, non-B hepatitis hospitalizations (from 69,600 in 1993 to 47,800 in 1998). The number of hospitalizations in which liver disease was the principal diagnosis increased from 10,100 to 32,800 and secondary diagnosis from 6,000 to 27,100 between 1993 and 1998. As expected, the increase in hospital services for HCV-related morbidity was accompanied by a similar increase in hospital charges. Hospitalizations were given differential weight depending on the relevance of hepatitis C (principal diagnosis vs. incidental notation). After adjustment for inflation (1998 US\$), the total hospital charges for 1998 were slightly over 1 billion dollars nationwide. This represents doubling in three years (\$528M for 1995) and tripling in five years (\$348M for 1993).

Summary

Hepatitis C infection is common, affecting nearly 2 percent of the general population and a much higher percentage of people under special circumstances. Since the early 1990s, national statistics indicate that morbidity, mortality, and health care utilization associated with consequences of long-standing infection with hepatitis C are increasing in epidemic proportions. Future projection studies predict that the increase will continue in the foreseeable future.

References

1. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *New Eng J of Med*, 1999;341(8):556–62.
2. Anonymous. Recommendations for prevention and control of hepatitis C virus infection and HCV-related chronic disease. *MMWR* 1998, Centers for Disease Control and Prevention (CDC): Atlanta, GA. 1–9.
3. Armstrong GL, Alter MJ, McQuillan GM, Margolis HS. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology* 2000;31(3):777–82.

4. Anonymous. Compressed mortality file <<http://wonder.cdc.gov>>. 2002 (accessed on 3/10), Centers for Disease Control and Prevention.
5. Anonymous. The burden of gastrointestinal diseases. 2001, The American Gastroenterological Association: Bethesda, MD. 41–60.
6. Kim W, Gross J, Poterucha J, Locke G, Dickson E. Outcome of hospital care of liver disease associated with hepatitis C in the United States. *Hepatology* 2001;33:201–6.

Natural History of Chronic Hepatitis C

Leonard B. Seeff, M.D.

Introduction

The rationale for establishing the natural history of any disease is to inform both the patient and physician of future expectations and to assess the need for treatment. Unfortunately, the characteristics of hepatitis C—its silent onset, evolution to a generally asymptomatic and greatly prolonged chronic phase, its co-mingling with other morbid conditions, and the fact that treatment that alters the course is now almost routine—have limited the ability to accurately define its natural history. Several strategies have been used for this purpose, all of which have their drawbacks but still have provided useful information. Because of the many inherent difficulties, there is much controversy regarding the natural history of hepatitis C. The outcome of concern is increasing fibrosis progression, culminating in cirrhosis and, occasionally, advancement to hepatocellular carcinoma (HCC). Some believe this sequence to be common; others believe that serious progression is relatively limited. Both of these views may be valid, both identifying a frequency of progression that is modified by differing demographic characteristics of the population studied and by varying intrinsic and extrinsic factors. In essence, the controversy derives from the uncertainty of whether or not fibrosis progression is linear.

Advancement from Acute to Chronic Hepatitis

The natural history is a product of the outcome of the acute infection as well as the outcome of the subsequent chronic hepatitis. A problematic issue is the actual timing of evolution to chronic hepatitis. Traditionally, this has been based on persistence of virus for at least 6 months. However, viremia may persist beyond this time, although it is believed that loss of virus after one year is exceptional. Prospective study has indicated that chronic hepatitis evolves in about 85 percent of acutely infected persons. On the other hand, cross-sectional studies of large, untreated anti-HCV positive cohorts, consisting mainly of young persons, many of them female, have reported absent virus in as many as 45–50 percent of instances, implying a higher rate of spontaneous recovery in some groups. Thus, spontaneous recovery from acute hepatitis C occurs in 15–45 percent of instances.

Progression to Cirrhosis

Once chronic hepatitis has developed, the question then is: What are the long-term sequelae? Numerous efforts have been made to define the frequency and rate of progression to cirrhosis and HCC. Evident in all these studies is that clinically overt liver disease is generally not seen in the first two decades following the acute infection. This does not imply that cirrhosis does not evolve during this period, but the actual timing of its onset cannot be determined without performing serial liver biopsies. Early reports, based largely on retrospective studies, indicated that, at the end of two decades of infection, about 20 percent had developed cirrhosis, although some of the studies have reported rates of almost 50 percent. The drawbacks of retrospective studies are that evaluation is limited to those who have achieved an end point and that tracing to disease onset is hindered by the paucity of symptoms at onset. Thus, ascertainment bias may exist using this approach. Later prospective studies, mainly of HCV-infected transfusion recipients, reported a lower rate of development of cirrhosis (7–16 percent), but most of these studies were too short in duration to provide an accurate assessment of the ultimate outcome. Even lower rates of cirrhosis have been reported among several groups in whom it was possible to trace back far in the past to the time of onset or near onset. Thus,

among children infected through transfusion in the first years of life and traced 20 years later, and among young women infected through receipt of HCV-contaminated Rh immunoglobulin and traced over approximately the same time period, cirrhosis was noted to have occurred in about 2 percent. A similar rate was noted in a 45-year follow up of young HCV-positive military recruits who had been bled at the time of serving on a military base, the samples having been retained in a repository. The common theme of this lower rate of cirrhosis is that it was noted among persons infected at a young age.

Taking the numerous variety of studies into account, a group of Australian investigators who reviewed the world's literature for the rate of cirrhosis development at 20 years concluded that the studies could be divided into 4 broad categories: those performed in liver clinics, the mean cirrhosis rate being 22 percent (95 percent CI, 18–26 percent); post-transfusion hepatitis studies, with a mean of 24 percent (11–37 percent); studies of blood donors, with a mean of 4 percent (1–7 percent); and studies of community-based cohorts, with a mean of 7 percent (4–10 percent). They concluded that selection bias accounted for the two higher rates, and that the community-based cohort studies appeared more representative in estimating disease progression at a population level. These data provide useful figures for the frequency of progression to cirrhosis two decades after acute infection that appears to range between about 2–4 percent to 20–25 percent, depending on several factors, to be described below. However, many of those infected are young and are destined to live for several more decades. Therefore the question that must be posed is: What happens after the first two decades with regard to liver disease progression? Does fibrosis progression continue to increase at a linear rate? Does the rate level off and remain the same throughout life? Does fibrosis progression increase as age advances? Certainly, many chronically infected persons are known to live for a lifetime without succumbing to liver disease, whereas others are known to develop end-stage liver disease 30 to 60 years after acute infection. Thus, these questions can only be answered by conducting markedly extended studies, few of which have been accomplished for obvious reasons. Other approaches have been to model the expected outcome based on preconceived notions, models that may or may not turn out to be valid. Most important, is it possible to predict in the individual HCV-infected person what the outcome is likely to be? The answer is a qualified maybe, taking into account the many factors that might enhance progression.

Factors That May Determine Progression

The differing outcomes suggest that there are variables that may contribute to the rate of liver disease progression. These can be considered as being viral-related, host-related, or a consequence of external factors.

Viral-Related

Factors that might contribute include viral load, viral genotype, and quasispecies diversity. There is little evidence to indicate that viral load plays a role in disease progression; there are suggestions that progression is more likely following infection with genotypes 1a and 1b than genotype 2, although this has been disputed, most studies now reporting that there is no effect of genotype characteristics on disease outcome. While the degree of quasispecies diversity appears to play a role in evolution from acute to chronic hepatitis, there is no evidence that it enhances progression of already established chronic hepatitis.

Host-Related

One of the most important determinants is age at the time of infection, the relationship being an inverse one. What is not yet established is whether the relatively mild disease seen two decades after infection of young people will begin to accelerate with increasing age. This brings into account the fact of duration of infection, since it is rare although not unheard of, to identify end-stage liver disease in under one-and-a-half to two decades. Perhaps the flourishing of liver disease with time may be a consequence in part of age-related immune depression. Certainly, an immune suppressed state vigorously enhances disease progression as is noted among infected persons with hypogammaglobulinemia and, especially, HIV co-infection. Hepatitis B and schistosomal co-infection also increase disease progression perhaps through induced immune

dysfunction as well as through direct cytotoxicity. Genetic background also may be of importance. Genes of the major histocompatibility complex appear also to play a role, not so much in fibrogenesis, but in clearance of the virus. HLA class I antigens seem to be associated with viral persistence whereas class II antigens (DRB1 alleles) are identified more frequently in those who clear virus and therefore have milder disease. Inheritance of high TGF- β 1 and angiotensinogen-producing genotypes has been linked to fibrosis progression. Co-morbid conditions such as hemochromatosis and non-alcoholic steatohepatitis are also associated with advancing chronic liver disease. In addition, outcome may be influenced by gender and race. Females are reported to have a slower rate of progression, a finding that seems to be emerging also among African-Americans. Finally, the expression of the disease plays a role in outcome. HCV-infected persons with raised aminotransferase levels are far more likely to develop progressive liver disease than are those with normal serum enzymes.

External Factors

Clearly, associated chronic alcoholism is a powerful co-factor in liver disease progression. Yet to be determined is what is the least amount of alcohol and the type of drinking pattern that plays a role in advancing chronic hepatitis C. Also of note are the data suggesting that smoking may increase disease progression. Exposure to toxic products, either in the form of administered drugs that may be hepatotoxic or as environmental contaminants, may have important effects. It is noteworthy that death associated with chronic hepatitis C in the United States is more likely to be a result of end-stage liver disease rather than HCC, whereas in Japan, virtually all deaths are attributed to HCC. It has been suggested that the difference is a consequence of a longer duration of HCV infection in Japan than in the United States, a view that may or may not be valid. Another possible explanation is that toxic environmental contaminants may play a contributory role in Japan.

Progression From Cirrhosis to HCC

HCC rarely (if ever) develops in persons with chronic hepatitis C without preceding cirrhosis or significant fibrosis. The strongest evidence for a relationship between HCV infection and HCC comes from Japan, but supporting evidence comes from many other countries including the United States, Italy, Spain, Egypt, France, and elsewhere. Recent evidence indicates that the incidence of HCC increasing in the United States is presumed to be a consequence of the mushrooming of hepatitis C infection in the 1960s and 1970s. The data in the United States indicate that once cirrhosis has developed, HCC evolves at the rate of 1–4 percent per year. The figure in Japan is even higher.

References:

1. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C infection: a perspective on long-term outcome. *Semin Liv Dis* 2000;20:17–35.
2. Poynard T, Bedossa P, Opolon P, for the OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997;349:825–32.
3. Tong MJ, El-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. *N Engl J Med* 1995;332:1463–6.
4. Kenny-Walsh E for the Irish Hepatology Research Group. Clinical outcomes after hepatitis infection from contaminated anti-globulin. *N Engl J Med* 1999;340:1228–33.
5. Vogt M, Lang T, Frosner, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery after implementation of blood-donor screening. *N Engl J Med* 1999;341:866–70.
6. Wiese M, Berr F, Lafrenz M, et al. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in Germany: a 20-year multicenter study. *Hepatology* 2000;32:91–6.
7. Thomas DL, Astemborski J, Rai, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA* 2000;284:450–6.
8. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001;34:809–16.
9. Seeff LB, Hollinger FB, Alter HJ, et al. Long-term mortality and morbidity of transfusion-associated non-A, non-B and type C hepatitis: a National Heart, Lung, and Blood Institute collaborative study. *Hepatology* 2001;33:455–63.

Fibrosis and Disease Progression

Patrick Marcellin, M.D.

Chronic infection with HCV is associated with the typical histological features of chronic hepatitis including hepatocellular necrosis and inflammation (activity or grade) and fibrosis (stage). While the activity of the chronic liver disease can fluctuate over time, the stage of fibrosis is believed to be progressive and largely irreversible. In chronic hepatitis C, the rate at which fibrosis progresses varies markedly. In some individuals, fibrosis ultimately leads to cirrhosis, which is associated with the major complications of the liver disease: portal hypertension, liver failure, and hepatocellular carcinoma. In others, fibrosis does not appear to progress even after decades of infection. For these reasons, assessment of the stage and rapidity of progression of fibrosis can be helpful in determining the prognosis and the need for therapy in the individual patient. Factors associated with fibrosis progression are not well defined and the role of necro inflammatory activity is still controversial.

Assessment of the Stage of Fibrosis

Liver biopsy remains the gold standard to assess fibrosis. Several systems for scoring liver fibrosis have been proposed, each based upon visual assessment of portal and periportal fibrosis. The more frequently used systems are the Histology Activity Index (HAI: Knodell score), the Ishak modification of the HAI score, and the METAVIR. The HAI scoring system ranges from 0 to 22 and fibrosis is staged as 0, 1, 3, and 4. This discontinuous scale was developed to allow for clear separation of mild (1+) from extensive (3+) fibrosis which has important prognostic value. The HAI system is simple and has been widely used, particularly in the large multicenter trials of interferon and ribavirin therapy of chronic hepatitis C. However, the intra- and inter-observer reproducibility of the HAI is not very good and distinction between stages 1 and 3 may be difficult. In addition, its discontinuous scale complicates statistical analysis in clinical trials.

The modification of the HAI scoring system proposed by Ishak et al. is more sensitive in assessing fibrosis. Fibrosis stage is scored continuously from 0 to 6, which permits a better assessment of the effect of therapy on fibrosis. The Ishak score is better validated and gives a more accurate assessment of fibrosis.

The METAVIR scoring system is simple; fibrosis stages are scored continuously from 0 to 4. This system has been carefully validated in large groups of patients with chronic hepatitis C and has shown good intra- and inter-observer reproducibility.

Important limitations of these scoring systems should be emphasized. Hepatic fibrosis may not be homogenous throughout the liver and the liver specimen obtained by needle biopsy may not accurately reflect the overall average degree of fibrosis. The reliability of the assessment of fibrosis stage increases with the size of the liver sample. In most studies, a minimum length of 10 mm is required. Regardless of biopsy length, however, fibrosis may be underestimated and cirrhosis missed in some patients.

Factors Associated With the Stage of Fibrosis

Most cross-sectional studies of large numbers of liver biopsies have shown that the stage of fibrosis is associated with patient age, the age at onset of infection, male sex, a history of heavy alcohol consumption, and the presence of immune deficiency, such as HIV co-infection or immunosuppressive therapy. The mechanisms by which age and sex affect the degree of fibrosis are not known. Alcohol, which by itself can cause liver disease and fibrosis, may worsen fibrosis in hepatitis C at amounts that are not injurious in non-infected persons, but the amount of alcohol beyond which the progression of fibrosis is increased is unknown.

Serum biochemical tests do not reliably predict the stage of fibrosis. Currently available, indirect serum markers of fibrosis are not reliable, particularly in discriminating between mild and moderate degrees of fibrosis. In cross-sectional studies, serum alanine and aspartate aminotransferase (ALT and AST) levels do not correlate well with fibrosis. However, patients with documented, persistently normal ALT levels usually have mild degrees of hepatitis and either no or mild stages of fibrosis. The association between fibrosis stage and the necroinflammatory activity scores on liver biopsy is controversial. Necroinflammatory activity is a dynamic process in chronic hepatitis C and may fluctuate over time. Therefore, the activity score reflects the severity of necrosis and inflammation at a given point.

Factors Associated With Progression of Fibrosis

From retrospective studies and from some prospective studies done in patients infected by blood transfusion at a relatively older age, it is estimated that 20 percent of patients with chronic hepatitis C develop cirrhosis within 20 years of onset. In contrast, studies of cohorts of women who did not drink alcohol and who were infected by Rh immune globulin at a young age indicated that fewer than 5 percent developed cirrhosis within 20 years. These natural history studies validate the importance of age, sex, and alcohol intake in progression of fibrosis.

Cross-sectional studies using mathematical modeling performed on cohorts of patients with a single liver biopsy suggest that the average rate of progression of fibrosis in chronic hepatitis C is 0.133 METAVIR points per year. Based on this rate, the estimate is that cirrhosis develops in the average patient after 30 years. The average delay to the development of cirrhosis ranges from 13 years in infected men aged 40 or more years who drink more than 50 g of alcohol to 42 years in infected women under 40 years of age who do not drink alcohol. Furthermore, the progression of fibrosis is probably not linear. For instance, the time required to progress from stage 0 to 2 may be far longer than the time required to progress from stage 3 to 4. Moreover, fibrosis progression may accelerate with age (particularly after the age of 50). Finally, fibrosis may remain mild and stable for decades and may even regress spontaneously in some patients.

The progression of fibrosis is difficult to predict in the individual patient particularly based upon assessment at one point in time. There are no good clinical, biochemical, or virological tests that predict progression of fibrosis. High serum ALT levels have been associated with more active liver disease and more rapid progression of fibrosis in some prospective studies, which supports the use of monitoring of ALT levels in assessing prognosis and need for therapy. However, the validity of this approach and the level above which the ALT elevations are predictive of more rapid progression is not known. Virological factors such as serum HCV RNA level and HCV genotype are not predictive of fibrosis. Genotype 3 is associated with more liver steatosis than other genotypes, and steatosis itself, as well as other metabolic factors (such as lipid disorders, obesity, insulin resistance, and diabetes) may also predispose to more rapid progression of fibrosis.

Repeat liver biopsy is the only reliable means of assessing the progression of fibrosis and is commonly recommended every 3 to 5 years in untreated patients. A second liver biopsy can distinguish patients with rapidly progressive fibrosis, but may also merely indicate that the initial biopsy underestimated the degree of fibrosis. Overall, the risk of progression of fibrosis of more than one point in a 3 to 5 year period is low. In patients with factors associated with a higher risk of progression such as age beyond 50 years, alcohol consumption, or high serum ALT levels, liver biopsy may be recommended more frequently (2 to 3 years); in contrast, in the younger patient with no other risk factors, liver biopsies may be performed less frequently (every 5 to 6 years).

References

1. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, et al. Histologic grading and staging of chronic hepatitis. *J Hepatol* 1995;22:696–9.
2. Bedossa P, Poinard T. The METAVIR cooperative study group. An algorithm for the grading of activity in chronic hepatitis C. *Hepatology* 1996;24:289–93.

3. Tong MJ, El-Farra NS, Reijes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. *N Engl J Med* 1995; 332:1463–6.
4. Poynard T, Bedossa P, Opolon P for the OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997;349:825–32.
5. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Sem Liver Dis* 2000;20:17–35.

Non-Invasive Monitoring of Patients With Chronic Hepatitis C

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Patients with chronic hepatitis C (CHC) are at risk of developing cirrhosis, liver failure, and hepatocellular carcinoma (HCC). However, specific symptoms and physical findings of chronic liver disease are frequently absent until patients develop hepatic decompensation. Thus, clinical examination is often unreliable in assessing the severity of liver disease in patients with CHC. Liver histology is the gold standard for establishing the severity of liver injury and fibrosis, but this procedure is associated with risks of complications, discomfort, and expense. In addition, sampling error may occur leading to erroneous staging. Nonetheless, information on the extent of hepatic fibrosis or stage of liver disease is important for prognostication as well as for decisions on treatment. As a result, practicing physicians are in need of simple, safe, inexpensive, and reliable means to non-invasively assess the severity of liver disease in patients with CHC.

The initial evaluation of patients with CHC should include a thorough history and physical examination. A PCR assay for HCV RNA is recommended to confirm the presence of viremia because up to 30 percent of individuals who test positive for HCV antibody (anti-HCV) may have resolved infection or a false positive EIA result. Quantitative HCV RNA levels and HCV genotypes do not correlate with disease severity, but these results are useful in predicting the likelihood of an antiviral treatment response. The initial evaluation should include a comprehensive metabolic panel, prothrombin time, and complete blood counts (CBC) with platelets. Serum aspartate and alanine aminotransferase (AST/ALT) levels reflect liver injury, but the correlation with histologic necroinflammatory activity as well as the severity of hepatic fibrosis is poor (1,2). Serum albumin and bilirubin levels and prothrombin time reflect hepatic function, but these values usually remain normal even in patients with compensated cirrhosis. Thus, routine blood tests cannot differentiate early (minimal fibrosis) from advanced (compensated cirrhosis) stage of liver disease. Among the routine blood tests, decreased platelet count is the earliest indicator of cirrhosis (3). Other investigators have found that as patients progress from chronic viral hepatitis to cirrhosis, there is reversal of AST/ALT ratio to >1. (4)

Ultrasound is often recommended as part of the initial evaluation of patients with CHC. Ultrasound and other imaging techniques such as CT and MRI can be used to diagnose cirrhosis based on the presence of an enlarged spleen, small nodular liver, ascites, or varices. In addition, these techniques may detect HCC. However, current imaging is unable to assess the extent of hepatic fibrosis and to diagnose early cirrhosis.

Other novel but less well-established non-invasive means of assessing disease severity in patients with compensated CHC are under development. Serum fibrosis markers that reflect the balance between fibrogenesis and fibrolysis have been proposed as a simple, non-invasive means of assessing hepatic fibrosis. (5,6) To date, none of these markers alone correlates well with hepatic fibrosis. Whether a panel of markers such as hyaluronic acid, YKL-40, and PIIINP will replace liver biopsies remains to be determined. (7,8) Contrast-enhanced ultrasound doppler has also been proposed as a simple, non-invasive means of detecting advanced hepatic fibrosis. (9) However, this method has not yet been validated and will require sophisticated instruments and operators for optimal performance. Radionuclide liver spleen scans can detect the presence of portal hypertension but are insensitive in the diagnosis of early cirrhosis. Similarly, the use of various metabolic probes to assess functional liver mass has been reported to be reliable in differentiating patients with compensated from decompensated liver disease, but these studies are cumbersome and have not been proven to be useful in distinguishing patients with various stages of hepatic fibrosis. (10)

The optimal frequency and types of tests that should be performed for monitoring CHC patients who are not on antiviral therapy have not been determined. In general, tests for CBC and platelets and a comprehensive metabolic panel should be performed every six months. As discussed above, a progressive decrease in platelet counts or a reversal of the AST/ALT ratio suggests the development of cirrhosis. Repeat testing of anti-HCV, HCV RNA level, or HCV genotype is unnecessary and does not provide any information on the stability or progression of liver disease. For patients with known cirrhosis, alfa fetoprotein testing and ultrasound should be included although the efficacy of these tests in HCC surveillance is low. Upper endoscopy should be performed in patients with cirrhosis, especially those with clinical evidence of portal hypertension, to determine the need for prophylaxis against variceal bleeding. Patients with decompensated cirrhosis may need more frequent monitoring to determine the optimal timing for transplant evaluation. Monitoring may be less frequent in patients with persistently normal aminotransferases and those with minimal hepatic fibrosis after a long duration of infection (slow progressors). Because of the variable natural course of CHC and the possibility of sampling error, many hepatologists recommend repeat liver biopsies in 4–5 years in patients who decide not to receive antiviral treatment based on the finding of early disease at initial evaluation. The availability of non-invasive tests that correlate with progression of hepatic fibrosis will obviate the need for repeat liver biopsies.

References

1. McCormick SE, Goodman ZD, Maydonovitch CL, Sjorgen MH. Evaluation of liver histology, ALT elevation, and HCV RNA titer in patients with chronic hepatitis C. *Am J Gastroenterol* 1996;91:1516–22.
2. Haber MM, West AB, Haber AD, Reuben A. Relationship of aminotransferases to liver histological status in chronic hepatitis C. *Am J Gastroenterol* 1995;90:1250–7.
3. Poynard T, Bedossa P, Metavir and Clinivir Cooperative Study Groups. Age and platelet: a simple index for predicting the presence of histological lesions in patients with antibodies to hepatitis C virus. *J Viral Hepat* 1997;4:199–208.
4. Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. *Gastroenterology* 1988;95:734–9.
5. Oberti F, Valsesia E, Pilette C, et al. Non-invasive diagnosis of hepatic fibrosis or cirrhosis. *Gastroenterology*. 1997;113:1609–16.
6. Wong VS, Hughes V, Trull A, et al. Serum hyaluronic acid is a useful marker of liver fibrosis in chronic hepatitis C virus infection. *J Viral Hepatitis* 1998;5:187–192.
7. Kamal SM, Turner B, Koziel MJ, Afdhal NH. YKL-40 and PIIINP correlate with the progression of fibrosis in chronic hepatitis C. *Gastroenterology (Abstract)* 2001;120:1895A.
8. Rosenberg WM, Burt A, Hubscher S, et al. Serum markers predict liver fibrosis. *Hepatology (Abstract)* 2001;34:396A.
9. Albrecht T, Blomley MJK, Cosgrove DO, et al. Non-invasive diagnosis of hepatic cirrhosis by transit-time analysis of ultrasound contrast agent. *Lancet* 1999;353:1579–83.
10. Lotterer E, Hogel J, Gaus W, et al. Quantitative liver function tests as surrogate markers for end-points in controlled Clinical Trials: A retrospective feasibility study. *Hepatology* 1997;26:1426–33.

Use and Interpretation of Virologic Tests

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Two categories of tests are used in the management of hepatitis C virus (HCV)-infected patients: (i) indirect tests that detect antibodies to HCV (anti-HCV); (ii) direct tests that detect, quantify, or characterize viral particle components, such as HCV RNA or core antigen. Direct and indirect virological tests play a crucial role in the diagnosis of infection, therapeutic choices, and assessment of the virological response to therapy.

Indirect Tests

Anti-HCV detection. Anti-HCV is typically detected using second- or third-generation enzyme immunoassays (EIAs) that detect mixtures of antibodies directed to various HCV epitopes. The specificity of currently available EIAs for anti-HCV is higher than 99 percent. Their sensitivity is more difficult to determine in the absence of a more sensitive gold standard. EIAs for anti-HCV detect antibodies in more than 99

percent of immunocompetent patients with detectable HCV RNA. EIAs are sometimes negative despite the presence of active HCV replication in hemodialysis patients or patients with profound immunodeficiencies. Immunoblot tests have been used in the past as confirmatory assays. Given the good performance of the current anti-HCV EIAs, immunoblot tests no longer have utility in the clinical virology setting. They are still useful in the blood bank setting, where the positive predictive value of a positive EIA result is significantly lower than in the diagnostic setting.

Serological determination of HCV genotype. HCV genotype can be determined by detection of type-specific antibodies using a competitive EIA (so-called “serotyping”). This assay provides interpretable results in approximately 90 percent of immunocompetent patients with chronic hepatitis C. Its sensitivity is lower in hemodialysis or immunodepressed patients. The assay identifies the type (1 to 6) but not the subtype of HCV. Concordance with molecular assays is in the order of 95 percent. Currently, no serotyping assay is FDA-approved.

Direct Tests

Available Tests

Qualitative detection of HCV RNA. Qualitative (i.e., nonquantitative) HCV RNA detection assays are useful because they are significantly more sensitive than most available quantitative assays. The qualitative assays are based on the principle of target amplification using either polymerase chain reaction (PCR) or transcription-mediated amplification (TMA). The lower detection cutoffs of the corresponding commercial assays are 50 HCV RNA international units (IU)/ml and 10 IU/ml, respectively. Their specificity is of the order of 98–99 percent. The PCR assay is FDA-approved.

Viral level quantification. HCV RNA level can be quantified by means of target amplification techniques (PCR or TMA) or signal amplification techniques (“branched DNA” assay). The lower detection cutoffs of the current assays vary between 30 IU/ml and 615 IU/ml, and the upper limit of linear quantification between 500,000 IU/ml and 7,700,000 IU/ml. Samples with a viral level higher than the upper limit of an assay should be retested after 1/10 or 1/100 dilution. Quantification is independent of the HCV genotype. The international unit, recently defined with reference to the WHO HCV RNA standard, should be used in any HCV RNA quantitative assay in order to compare results given by different assays and to apply global recommendations. Variations of less than 0.5 logs (i.e., of less than threefold) should not be taken into account as they may relate to the intrinsic variability of the assays. No HCV RNA quantification assay is approved currently in the United States, but several are likely to be in the future.

Molecular determination of HCV genotype (genotyping). The gold standard for genotyping is direct sequencing of the NS5B or E1 regions. In clinical practice, HCV genotype can be determined by direct sequence analysis, reverse hybridization onto genotype-specific oligonucleotide probes, or restriction fragment length polymorphism analysis after PCR amplification of the 5' noncoding region. Typing errors are uncommon, but subtyping errors may occur in 10–25 percent of cases. These errors may be related to the region studied (5' noncoding) rather than the technique used. Subtyping errors have few clinical consequences because only the genotype is useful for clinical decisions. No genotyping assay is currently approved in the United States.

Detection and quantification of total HCV core antigen. Total HCV core antigen can be detected and quantified by means of EIA assay. The HCV core antigen titer (in pg/ml) correlates closely with HCV RNA level, and thus can be used as an indirect marker of viral replication. However, the current version of the assay does not detect HCV core antigen when HCV RNA is below approximately 20,000 IU/ml. This assay is not FDA-approved.

Practical Use of Virological Tests

The phrase “HCV RNA detection by means of a sensitive technique” used in this presentation refers to a

technique with a lower limit of detection of 50 IU/ml or less. Furthermore, in discussing HCV RNA quantitation, it is assumed that the results are within the limits of its range of linear quantification of the assay.

Diagnosis of HCV Infection

Acute hepatitis C. During acute hepatitis of unknown origin, anti-HCV should be tested by EIA and HCV RNA by a sensitive HCV RNA technique. The presence of HCV RNA without anti-HCV is strongly indicative of acute hepatitis C, a diagnosis that can be confirmed by subsequent seroconversion. In the absence of both markers, acute hepatitis C is unlikely. In the presence of both, it is difficult to differentiate acute hepatitis C from an acute exacerbation of chronic hepatitis C or from acute hepatitis of other cause in a patient with chronic hepatitis C.

Chronic hepatitis C. In a patient with chronic liver disease, the diagnosis of chronic hepatitis C can be made based on detection of both anti-HCV and HCV RNA using a sensitive technique. The lack of anti-HCV in the presence of HCV RNA is uncommon in immunocompetent patients with chronic hepatitis C. It can occur (although rarely with the current EIAs) in hemodialysis or profoundly immunodeficient patients.

Mother-to-infant transmission. The diagnosis of HCV infection in a baby born to an HCV-infected mother should be based on the detection of HCV RNA with a sensitive technique rather than anti-HCV, because antibodies are passively transferred in utero and remain detectable for several months to more than a year after delivery regardless of whether transmission occurs. The optimal timing for HCV RNA testing for diagnosis is not known. Appropriate times are 6 to 12 months after birth.

Diagnosis of infection after an occupational exposure. HCV RNA is detectable in serum within one to two weeks after an accidental parenteral exposure. The diagnosis of acute infection should be based on detection of HCV RNA by a sensitive technique. This testing can be performed at any time after the first week after exposure, but antiviral treatment is not an emergency in this setting and can be initiated after appearance of serum aminotransferase elevations or clinical symptoms appear.

Prognosis of HCV-Related Disease

No virologic test (including viral load and genotype) correlates with the severity of liver injury or fibrosis, or predicts the natural course or outcome of disease or presence of extra-hepatic disease. Virologic tests are not helpful as prognostic markers.

Antiviral Treatment of HCV Infection

Decision to treat. Only patients with detectable HCV RNA should be considered for treatment. HCV genotype determination should be performed before treatment as results may help in the decision to treat as well as in determining the duration of treatment. Thus, because of the high rates of response and need for 24 weeks of therapy only in patients with HCV genotypes 2 and 3, many investigators recommend therapy to all such patients provided there are no contraindications. Because response rates are only 40–45 percent and therapy must be given for 48 weeks in patients with genotype 1, the benefits of therapy must be balanced against its risks and cost. In this context, the assessment of the natural prognosis of infection by liver biopsy examination may help in making the decision to treat. In the absence of sufficient information, the same applies to genotypes 4, 5, and 6.

Virologic followup and assessment of response. Measurement of HCV RNA levels before treatment and again at 12 weeks has been proposed as an appropriate approach to monitoring patients with chronic hepatitis C who are treated with peginterferon and ribavirin. This is particularly true for patients with genotype 1. In patients infected with genotypes 2, 3, 4, 5, and 6, monitoring of HCV RNA levels may be less important, and there is little data supporting its usefulness. The basis for this will be discussed later in this conference. In all patients, however, the virological response should be assessed by testing for HCV RNA

by a sensitive technique at the end of therapy. The presence of HCV RNA at the end of treatment is highly predictive of a relapse when therapy is stopped. The absence of HCV RNA at the end of 20 treatment indicates virological response and should lead to retesting for HCV RNA by a sensitive method 24 weeks later to document that the virological response is sustained.

Followup of Untreated Patients

Repeat virological testing is not necessary in untreated patients, as results have no prognostic value.

References

1. Thio CL, Nolt KR, Astemborski J, Vlahov D, Nelson KE, Thomas DL. Screening for hepatitis C virus in human immunodeficiency virus-infected individuals. *J Clin Microbiol.* 2000;38:575–7.
2. Pawlotsky JM, Bouvier-Alias M, Hezode C, Darthuy F, Remire J, Dhumeaux D. Standardization of hepatitis C virus RNA quantification. *Hepatology* 2000;32:654–9.
3. Pawlotsky JM, Lonjon I, Hezode C, Raynard B, Darthuy F, Remire J, Soussy CJ, Dhumeaux D. What strategy should be used for diagnosis of hepatitis C virus infection in clinical laboratories? *Hepatology* 1998;27:1700–2.
4. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958–65.
5. Fried MW, Shiffman ML, Reddy RK, Smith C, Marinos G, Goncales Jr FL, et al. Pegylated (40kDa) interferon alfa-2a (PEGASYS) in combination with ribavirin: efficacy and safety results from a phase III, randomized, actively-controlled, multicenter study. *Gastroenterology* 2001;120 (suppl. A):55.

Hepatocellular Carcinoma (HCC) and HCV in the United States

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HCC in the United States

A progressive increase in HCC-related mortality has been observed over the last 3 decades. According to the United States vital statistics, the overall age-adjusted mortality rate for HCC (ICD-9 155.0, which excludes cholangiocarcinoma and metastatic liver cancer) has risen significantly from 1.7 per 100,000 (95 percent CI, 1.7 to 1.8) during 1981–1995 to 2.4 per 100,000 (2.4 to 2.5) during 1991–1995. The recent rise in HCC mortality in the United States is a result of the rising incidence rate of HCC observed during the same time period coupled with a dismal survival rate (5 percent at 5 years). Data from the population-based SEER registries indicate that the age-adjusted incidence rate of HCC (ICD-O 8170) has increased from 1.4 per 100,000 during 1976–1980 to 3.0 per 100,000 during 1996–1998, more than a twofold increase. The latter rates probably underestimate the true incidence by approximately 30 percent as they represent only histologically confirmed HCC. During the same time, the temporal trends for hospitalizations with primary liver cancer have mirrored those of incidence and mortality. For example, data from the national VA computerized database show that the overall number of hospitalizations as well as the age-adjusted proportional hospitalization rate for HCC have increased by 42 percent from 1981–1997, reaching a hospitalization rate of 4.1 per 10,000 (3.7 to 4.5) during 1993–1997.

Demographic Risk Factors for HCC

There are significant gender, ethnicity, and geographic variations in the incidence of HCC in the United States. Caucasians are two to three times less affected than African Americans, who in turn are two to three times less affected than Asians, Pacific Islanders, or Native Americans. For all ethnic groups, men are two to three times more affected than women. Asians men have the highest age-adjusted incidence rates (up to 23 per 100,000). However, men and women of all ethnic groups have been affected by the recent increase in incidence. The reasons for these ethnic and gender variations probably relate to the prevalence and time of

acquisition of the major HCC risk factors. It is known that the prevalence of HCV, HBV, and alcoholic cirrhosis is two- to threefold higher in African-Americans and Hispanics than in whites. Native American Eskimos and recent immigrants from China, Taiwan, Korea, and Vietnam have high prevalence rates of HBV similar to those in their original countries. There are significant geographic variations within the United States in HCC (irrespective of the demographic differences between these regions): Hawaii had the highest age-adjusted incidence rate (4.6/100,000), followed by San Francisco-Oakland (3.2/100,000) and New Mexico (2.0/100,000), whereas Iowa and Utah have the lowest rates of approximately 1.0/100,000.

We used hierarchical linear multivariate analysis to examine the temporal trends in HCC incidence while controlling for age, gender, and ethnicity as well as adjusting for potential clustering of persons with similar demographic characteristics within geographic regions. This analysis has confirmed a twofold increase in HCC over a time period between 1975 and 1998 while adjusting for all the variables described above.

Concomitant with the rising rates of HCC, there has been a shift of incidence from typically elderly patients to relatively younger patients between ages 40 to 60. This shift reflects a cohort/period effect, affecting those who were born after 1920 and who seem to have been exposed to environmental agent(s) that have caused a cumulative increase in the HCC risk in all age groups of these cohorts. One plausible hypothesis is that these cohorts were infected with HCV during the 1950s–1970s, when they were in their twenties to forties, and are now presenting with HCV-related HCC. The full extent of this cohort/period effect has not been realized yet (the incidence rates have not leveled off yet).

Underlying Etiology for the Rising Incidence of HCC in the United States

Due to the essential role of cirrhosis in the development of HCC in the majority of cases, an increase in the number of persons living with cirrhosis is the likely explanation of the rising incidence of HCC. Declines in the mortality rates due to cirrhosis (partly related to improved management of esophageal varices and peritonitis) have been observed in the United States over the last 25 years. In addition, the incidence of cirrhosis related to HCV infection is rising. We carried out a population-based study in which the computerized records of hospitalized HCC patients during 1993 and 1998 (n=1,605) in all VA hospitals were searched for specific risk factors. There was a threefold increase in the age-adjusted rates for HCC associated with HCV from 2.3 per 100,000 (1.8 to 3.0) between 1993 and 1995 to 7.0 per 100,000 (5.9 to 8.1) between 1996 and 1998. HCV infection accounted for at least half of the increase in the number of HCC cases among United States veterans. During the same time periods, age-adjusted rates for HCC with either HBV (2.2 vs. 3.1 per 100,000) or alcoholic cirrhosis (8.4 vs. 9.1 per 100,000) remained stable. The rates for HCC without risk factors have also remained without a statistically significant change from 17.5 (15.8 to 19.1) between 1993 and 1995 to 19.0 per 100,000 (17.3 to 20.7) between 1996 and 1998. Thirty-eight percent of patients without specific risk factors had a diagnosis of nonspecific cirrhosis, many of whom were not tested for HCV. Similar trends have been observed from the large referral setting of M.D. Anderson Medical Center, where we recently reviewed the medical records of all patients residing in the United States who received a pathological diagnosis of HCC during 1993–1998; all patients were tested for HCV and HBV. The number of patients referred with HCC steadily increased from 143 in 1993–1995 to 216 in 1996–1998; of those, 26 patients (18 percent) and 66 patients (31 percent) were HCV positive during 1993–1995 and 1996–1998, respectively (P = 0.01). These data and a summary of all published HCC studies in the United States indicate that HCV is present in approximately 25–30 percent of cases, with more recent series reporting a greater proportion of HCV-related cirrhosis.

The risk of HCC in HCV:

Cirrhosis is present in virtually all cases of HCV-related HCC. Once cirrhosis is established, HCC develops at an annual rate of 1 percent to 5 percent. The more important figure, the incidence of cirrhosis in HCV-infected patients, is more difficult to determine. We have examined the natural history of HCV (i.e., non-treated) in a systematic review of the literature among all subjects at risk for chronic HCV infection (excluding studies in which cohorts were selected from patients with chronic liver disease and those where the onset time of infection could not be identified). The incidence rates of cirrhosis and HCC were

determined in 21 studies. Even within this selected groups of studies, large variations were found in the estimates of cirrhosis (0–33 percent) and HCC (0–2.8 percent), time to cirrhosis (13–23 yrs), and time to HCC (17–31 yrs). Short duration of follow-up, small sample size, incomplete documentation of risk factors (e.g., alcohol), and incomplete screening for cirrhosis/HCC explain some of these variations. Due to the significant heterogeneity in these results, pooled estimates from studies are unlikely to be valid. Nevertheless, in studies with the best-documented onset of infection, there is an average incidence of cirrhosis of 1 percent per year and of HCC of 0.05 percent per year (20 percent and 1 percent at 20 years, respectively) in patients with chronic HCV infection. The mode of HCV acquisition appears to affect the progression of HCV; studies of community-acquired or Anti-D IgG related HCV infection had more benign course than that associated with transfusion or hemophilia. A graphic presentation of the incidence rates of cirrhosis or HCC vs. the sample size/duration of followup suggests the presence of publication bias and that the true estimates could be significantly higher or lower than those described above.

Host related factors seem to be more important than viral factors in determining the progression of HCV infection to cirrhosis and HCC. These factors include older age of HCV acquisition, male gender (x2–3), heavy alcohol intake > 50 gm/day (x5–50), HBV (x 5–15) or HIV co-infection, and possibly increased hepatic iron. Most important of all seems to be time elapsed since acquiring HCV infection with a median time of 30 years being the time frame when most HCC starts appearing. All HCV genotypes have been implicated in HCV-related HCC. Diabetes and obesity are also emerging risk factors; in a large case-control study among veterans (823 patients with HCC and 3,459 controls), we found diabetes to be associated with a 1.5-fold increase in the risk of HCC in the presence of other major HCC risk factors such as HCV, HBV, and alcoholic cirrhosis. Obesity has been shown to increase the risk of hepatic steatosis and fibrosis in HCV-infected patients, and diabetes is a known risk for NASH, which could progress to cirrhosis.

Due to the large pool of HCV-infected persons, it is likely that the rising incidence of HCC will continue over the next several years. Despite having a current HCV prevalence similar to that of Japan 20–30 years earlier, extrapolating the current Japanese HCC trends (10 times that of the current United States rates) to future trends in the United States may be inappropriate. (For example, <40 percent in the United States is HCV-related vs. 90 percent of HCC in Japan; also, most patients with end-stage liver disease in the United States die from non-HCC cirrhosis related complications, whereas in Japan, decompensated liver disease is unusual.)

References:

1. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999;340:745–50.
2. El-Serag HB, Mason AC. Risk factors for the rising rates of primary liver cancer in the United States. *Arch Intern Med* 2000;160:3227–30.
3. El-Serag HB, Mason AC, Key CR. Temporal trends in survival of patients with hepatocellular carcinoma in the US. *Hepatology* 2001;33:62–5.
4. El-Serag HB. Global Epidemiology of Hepatocellular Carcinoma. *Clin Liver Dis* 2001;5:87–107, vi.
5. El-Serag HB, Everhart JE. Improved survival following variceal hemorrhage over an 11-year period in the Department of Veteran Affairs. *Am J Gastroenterol* 2000;95:3566–73.
6. El-Serag HB, Richardson P, Everhart JE. The role of diabetes in hepatocellular carcinoma among veterans: A case-control study. *Am J Gastroenterol* 2001;96:2462–7.
7. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. *Hepatology* 1997;26:34s–8s.

Screening for Hepatocellular Carcinoma (HCC): A Systematic Review

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Introduction

Hepatocellular carcinoma (HCC) is one of the most serious complications of chronic hepatitis C. For patients with chronic hepatitis C, practices of screening for HCC vary widely, largely because of uncertainty about the efficacy of screening tests in this population.

Objective

We conducted a systematic review of the literature to determine: (1) the performance characteristics of screening tests for HCC in patients with chronic hepatitis C (e.g., sensitivity, specificity); and (2) whether use of screening tests for HCC in patients with chronic hepatitis C can improve outcomes.

Methods

Literature Sources: Seven electronic databases were searched through DIALOG for the period from January 1996 to March 2002. Additional articles were identified by searching references in pertinent articles, hand searching relevant journals, and querying technical experts.

Eligibility Criteria: Exclusion criteria for review included: non-English language, articles limited to basic science or non-human data, previously reported data, and meeting abstracts. Inclusion criteria for review were: study designed to address our key question, information pertinent to management of hepatitis C, and 30 or more study subjects with hepatitis C. In addition, we required histologic confirmation of at least 50 percent of the HCC cases for studies on performance characteristics of screening tests, and at least six months of follow-up for studies evaluating use of screening tests to improve outcomes.

Assessment of Study Quality: Each eligible article was reviewed by a pair of reviewers, including at least one team member with relevant clinical training and/or one with training in epidemiology and research methods. Paired reviewers independently rated the quality of each study in terms of the following categories: representativeness of study subjects (5 items); bias and confounding (4 items); description of therapy (4 items); outcomes and followup (5 items); statistical quality and interpretation (4 items). Reviewers assigned each response level a score of 0 (criterion not met), 1 (criterion partially met), or 2 (criterion fully met) to each relevant item on the quality form. The score for each category of study quality was the percentage of the total 26 points available in each category and therefore could range from 0–100 percent. The overall quality score was the average of the five categorical scores. We also documented source of funding.

Extraction of Data: The paired reviewers also abstracted data on type of study and geographical location; study groups; specific aims; inclusion and exclusion criteria; screening regimen; demographic, social, and clinical characteristics of subjects; and results. Differences between the two reviewers in either quality or content abstraction were resolved by consensus.

Synthesis

Results of Literature Search: We identified 3,104 potentially relevant citations, and 1,731 of these were eligible for abstract review. Through the abstract review process we identified 39 articles that could contain data on one of our key questions about screening for HCC in patients with chronic hepatitis C. After reviewing these 39 articles, we found 17 studies that answered question 1 regarding performance characteristics of the screening tests and one study that answered question 2 regarding outcomes with screening for HCC. Data from these eligible studies will be presented in a series of evidence tables and figures highlighting their distinguishing characteristics, methodological strengths and limitations, and key findings.