Review Article

Medical Progress

Hepatitis C Virus Infection

Georg M. Lauer, M.D., and Bruce D. Walker, M.D.

HEPATITIS C virus (HCV) infects an estimated 170 million persons worldwide and thus represents a viral pandemic, one that is five times as widespread as infection with the human immunodeficiency virus type 1 (HIV-1). The institution of blood-screening measures in developed countries has decreased the risk of transfusion-associated hepatitis to a negligible level, but new cases continue to occur mainly as a result of injection-drug use and, to a lesser degree, through other means of percutaneous or mucous-membrane exposure. Progression to chronic disease occurs in the majority of HCV-infected persons, and infection with the virus has become the main indication for liver transplantation. HCV infection also increases the number of complications in persons who are coinfected with HIV-1. Although research advances have been impeded by the inability to grow HCV easily in culture, there have been new insights into pathogenesis of the infection and improvements in treatment options.

EPIDEMIOLOGIC CHARACTERISTICS

The prevalence of HCV infection varies throughout the world, with the highest number of infections reported in Egypt. The use of parenteral antischistosomal therapy in Egypt is thought to have contributed to a prevalence of antibodies against HCV in various regions ranging from 6 to 28 percent (mean, 22 percent).[1] In the United States, 1.8 percent of the population is positive for HCV antibodies. Given that 3 of every 4 seropositive persons also have viremia, as assessed by currently available tests, an estimated 2.7 million people in the United States have active HCV infection.

The factors most strongly associated with infection are injection-drug use and receipt of a blood transfusion before 1990,[2] but in some cases no risk factors can be identified.[3,4] Poverty, high-risk sexual behavior, having less than 12 years of education, and having been divorced or separated are linked to an increased risk of infection, but the reasons for some of these associations remain unclear.[2] Maternal–fetal transmission occurs but is infrequent and often associated with coinfection with HIV-1 in the mother.[5,6] Sexual transmission of the virus appears to be an inefficient means, certainly less efficient than is the case for HIV-1[7]; whether this is due to the low levels of the virus in genital fluids and tissues or to a lack of appropriate target cells in the genital tract is not known. However, coinfection with HIV-1 appears to increase the risk of both sexual and maternal–fetal transmission of HCV.[5,8,9]

Virus can be recovered from the saliva of infected persons,[10] and although chimpanzees have been experimentally infected by the injection of saliva from HCV-infected persons,[11] casual household contact and contact with the saliva of infected persons also appear to be very inefficient modes of transmission.[10,12] Nosocomial transmission has been documented, such as from patient to patient by a colonoscope,[13] during dialysis,[14] and during surgery.[15,16]

Until relatively recently, blood transfusion posed a major risk of HCV infection in developed countries. The introduction in 1990 and 1992 of improved blood-screening measures based on the detection of HCV antibodies has dramatically decreased the risk of transfusion-associated HCV infection. The current risk in the United States from blood that is negative for HCV antibodies is less than 1 in 103,000 transfused units,[17] with the residual risk resulting from blood donations that occur in the interval between infection and the development of detectable antibodies (estimated to be less than 12 weeks).[18] This is about half the risk of transfusion-related infection with hepatitis B virus (HBV) (1 in 63,000) and nearly five times the estimated risk of HIV-1 infection (1 in 493,000).[17] The risk associated with blood transfusion may now be even lower, since new screening methods, such as direct screening of pooled samples by polymerase-chain-reaction (PCR) assays,[19] should decrease the window period after infection to about three weeks.

Even though the prevalence of HCV infection is not higher among health care workers than in the rest of the population,[20] needle-stick injuries in the health care setting continue to result in nosocomial transmission of the virus. The rate of transmission after a needle-stick injury involving blood known to be infected ranged from 0 to 10 percent in various studies.[21,22] A rough estimate of the comparative risks of transmission through a needle stick is provided by the rule of threes: HBV is transmitted in 30 percent of exposures, HCV in 3 percent, and HIV-1 in 0.3 per-

From the Infectious Disease Division and Partners AIDS Research Center, Massachusetts General Hospital and Harvard Medical School, Boston. Address reprint requests to Dr. Walker at the Partners AIDS Research Center, Infectious Disease Division, Massachusetts General Hospital East, 149 13th St., Charlestown, MA 02129, or at bwalker@helix.mgh.harvard.edu.

cent. These numbers are most likely influenced by the size of the inoculum, the size of the needle, and the depth of inoculation.

PATHOGENESIS

HCV is an RNA virus that belongs to the family of flaviviruses; the most closely related human viruses are hepatitis G virus, yellow fever virus, and dengue virus.[23] The natural targets of HCV are hepatocytes and, possibly, B lymphocytes.[24,25] Viral replication is extremely robust, and it is estimated that more than 10 trillion virion particles are produced per day, even in the chronic phase of infection.[26] Replication occurs through an RNA-dependent RNA polymerase that lacks a "proofreading" function, which results in the rapid evolution of diverse but related quasispecies within an infected person and presents a major challenge with respect to immune-mediated control of HCV.

Despite in vivo replication rates in excess of those observed in HIV-1 and HBV infection, efforts to grow HCV in culture have been largely unsuccessful. Injection of recombinant transcribed HCV RNA into chimpanzees has resulted in the successful propagation of virus, accompanied by clinical and histologic signs of hepatitis.[27,28] Recent genetic manipulations of the RNA of virions have resulted in high-level replication in cell lines derived from hepatocytes, offering a more tractable means to study viral RNA and protein synthesis.[29,30]

HCV encodes a single polyprotein of 3011 amino acids, which is then processed into 10 mature structural and regulatory proteins (Fig. 1). Structural components include the core and two envelope proteins. Two regions of the envelope E2 protein, designated hypervariable regions 1 and 2, have an extremely high rate of mutation, believed to be the result of selective pressure by virus-specific antibodies. E2 also contains the

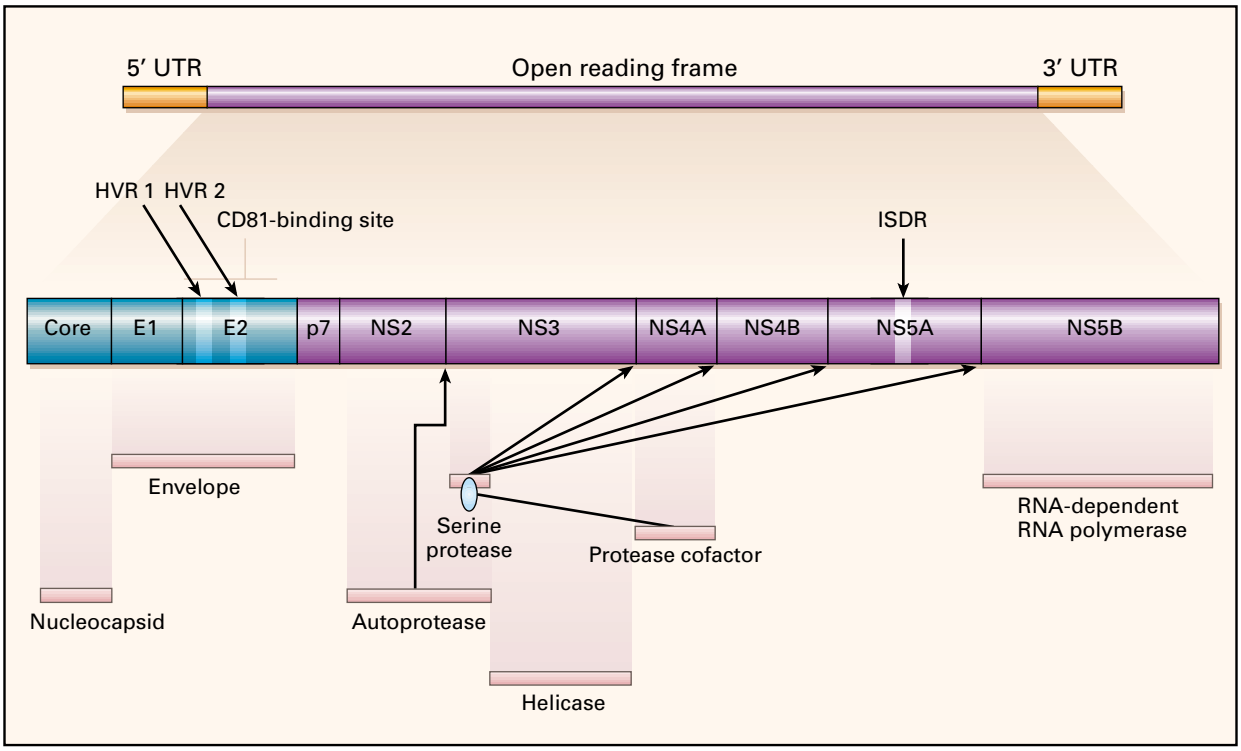

Figure 1. The HCV Genome and Expressed Polyprotein.

HCV, a single-stranded RNA virus of 9.5 kb, consists of a single open reading frame and two untranslated regions (UTRs). It encodes a polyprotein of approximately 3000 amino acids, which is cleaved into single proteins by a host signal peptidase in the structural region and the HCV-encoded proteases in the nonstructural (NS) region. The structural region contains the core protein and two envelope proteins (E1 and E2). Two regions in E2, called hypervariable regions 1 and 2 (HVR 1 and HVR 2), show extreme sequence variability, which is thought to be the result of selective pressure by virus-specific antibodies. E2 also contains the binding site for CD81, the putative HCV receptor or coreceptor. The nonstructural proteins have been assigned functions as proteases (in the case of NS2, NS3, and NS4A), helicase (in the case of NS3), and RNA-dependent RNA polymerase (NS5B). Although the crystal structure of NS3 and NS5 is known,[31] the function and properties of the other proteins (such as p7) are less well characterized. A region in NS5A has been linked to the response to interferon alfa therapy and is therefore called the interferon-sensitivity–determining region (ISDR). However, the relevance and importance of this region are still unclear.

binding site for CD81, a tetraspanin expressed on hepatocytes and B lymphocytes that is thought to function as a cellular receptor or coreceptor for the virus.[32] HCV also encodes a virus-specific helicase, protease, and polymerase, and because of the critical function of these proteins in the viral life cycle, they represent attractive targets for antiviral therapy.[33] Similarly, the untranslated regions at both ends of the viral RNA may show promise as therapeutic targets, since they are highly conserved and involved in critical stages of viral replication.[34]

Six distinct but related HCV genotypes and multiple subtypes have been identified on the basis of molecular relatedness. In the United States and western Europe genotypes 1a and 1b are most common, followed by genotypes 2 and 3. The other genotypes are virtually never found in these countries but are common in other areas, such as Egypt in the case of genotype 4, South Africa in the case of genotype 5, and Southeast Asia in the case of genotype 6. Knowledge of the genotype is important because it has predictive value in terms of the response to antiviral therapy,[35,36] with better responses associated with genotypes 2 and 3 than with genotype 1. Certain strains of HCV may have enhanced virulence, although the specific molecular determinants that may confer this phenotype have not yet been identified.[37] Variability within a region of the gene for nonstructural protein 5 (*NS5A*) appears to have particular clinical significance in determining the sensitivity to interferon, as shown in isolates of Japanese subtype 1b.[38] However, European and American isolates of HCV 1b do not share this property to the same degree.[39,40]

In most persons who become infected with HCV, viremia persists, accompanied by variable degrees of hepatic inflammation and fibrosis. Earlier studies of chronic HCV infection suggested that only a small number of hepatocytes become infected, but more recent estimates suggest that 50 percent or more harbor the virus.[41]

The presence of lymphocytes within the hepatic parenchyma has been interpreted as evidence of immune-mediated damage. Recent studies of acute HCV infection in chimpanzees and humans, however, suggest that immune-mediated control of HCV may be possible. Viral clearance is associated with the development and persistence of strong, virus-specific responses by cytotoxic T lymphocytes[42-44] and helper T cells.[43] The responses of helper T cells appear to be critical, since the loss of these cells has been linked to the reemergence of viremia.[45] The finding that viral diversity is reduced in persons in whom the infection is cleared is also consistent with the occurrence of greater immune-mediated control of the virus.[46] The relatively weak response of cytotoxic T lymphocytes in persons with chronic HCV infection seems to be insufficient to contain viremia and genetic evolution of the virus, but sufficient to cause collateral damage through the elaboration of inflammatory cytokines in the liver.[47] The presence of ineffective immunity in persons with chronic HCV infection is also suggested by the occurrence of superinfection with other genotypes[48] and, in animal models, by reinfection on rechallenge with closely related strains.[49]

CLINICAL CHARACTERISTICS AND THE NATURAL COURSE OF DISEASE

HCV infection is infrequently diagnosed during the acute phase of infection. Clinical manifestations can occur, usually within 7 to 8 weeks (range, 2 to 26) after exposure to HCV, but the majority of persons have either no symptoms or only mild symptoms. Fulminant hepatitis has been described during this period, though it is very rare.[50] In cases in which symptoms of acute hepatitis have been documented, they usually consisted of jaundice, malaise, and nausea.[51] The infection becomes chronic in most cases, and chronic infection is typically characterized by a prolonged period in which there are no symptoms. An estimated 74 to 86 percent of persons will have persistent viremia,[2,52] and this range may prove to be low as more sensitive tests become available to detect viremia.

The natural history of HCV infection has been very difficult to assess, because of the usually silent onset of the acute phase as well as the frequent paucity of symptoms during the early stages of chronic infection. Since the interval between infection and the development of cirrhosis can exceed 30 years, few prospective studies have been performed. Still, the data from retrospective and prospective studies[53-58] allow several conclusions to be made. Acute infection leads to chronic infection in the majority of persons, and spontaneous clearance of viremia once chronic infection has been established is rare. Most chronic infections will lead to hepatitis and to some degree of fibrosis, which may be accompanied by relatively nonspecific symptoms such as fatigue. Severe complications and death usually occur only in persons with cirrhosis, which is estimated to develop in 15 to 20 percent of those infected.[51,59]

Two studies in women who received anti-D immune globulin contaminated by HCV in the late 1970s showed that after 17 to 20 years, more than 95 percent of those who had a liver biopsy had evidence of hepatic inflammation, but in most it was slight or moderate.[54,55] Half had fibrosis, with only 2 percent having cirrhosis and 3 to 15 percent precirrhotic bridging fibrosis. Although these findings may be generally reassuring for the majority of infected persons, the high prevalence of the disease still translates into a large number of persons with clinical sequelae of disease. In addition, these figures may be an underestimate, because of the high percentage of favorable factors in the cohorts studied and the short duration of follow-up. Furthermore, these studies concentrated on mortality and serious complications, but HCV infec-

tion can also have adverse effects on the quality of life even in the absence of severe disease.[60]

The time frame in which the various stages of liver disease develop is highly variable (Fig. 2), with serious liver disease developing in one third of persons 20 years or less after infection and no progression in another third for 30 years or longer.[61] Factors that accelerate clinical progression include alcohol intake, which has a pronounced effect on the course of the disease; coinfection with HIV-1 or HBV; male sex; and an older age at infection.[61-63] Once cirrhosis is established, the risk of hepatocellular carcinoma is approximately 1 to 4 percent per year.[64-66] Hepatocellular carcinoma can occur without cirrhosis but is rare.

In addition to hepatic disease, there are important extrahepatic manifestations of HCV infection.[67] Most of these syndromes are associated with autoimmune or lymphoproliferative states and may be related to the possibility that HCV is able to replicate in lymphoid cells.[24,25] Cryoglobulins can be found in up to half of persons with HCV infection, and the cryoprecipitates usually contain large amounts of HCV antigens and antibodies.[68] Only a small fraction of affected persons (10 to 15 percent) have symptomatic disease.[69] These symptoms are often related to vasculitis and consist of weakness, arthralgias, and purpura. The most severe cases are associated with membranoproliferative glomerulonephritis,[69] as well as involvement of the nerves and brain.[70] HCV is the chief cause of essential mixed cryoglobulinemia (type II cryoglobulinemia), with up to 90 percent of affected persons having HCV viremia. Since false negative tests for HCV antibodies are common in these persons, an HCV RNA assay should be used for diagnosis.[68] A higher incidence of non-Hodgkin's lymphoma has also been observed in HCV infection, both with and without mixed cryoglobulinemia.[71,72] This correlation is not seen in all geographic areas; whether this difference is due to viral or host factors is not known. Other diseases, including lichen planus, sicca syndrome, and porphyria cutanea tarda, have been linked to HCV infection.[73-75] However, a clear pathophysiological role of HCV has been difficult to establish.

Other clinically important syndromes include coinfections with other viruses, especially HIV-1 and other hepatitis viruses. In a large European cohort, 33 percent of HIV-1–positive patients were coinfected with HCV, and this percentage rose to 75 percent when the analysis was limited to patients with known injection-drug use. With better treatment options for HIV-1, patients who are coinfected with HCV and HIV-1 will become an especially important group, since the course of HCV infection is accelerated by coinfection with HIV-1.[76] After 15 years, the risk of cirrhosis in such patients was 25 percent, as compared with 6.5 percent in those with HCV infection alone.[62] Patients

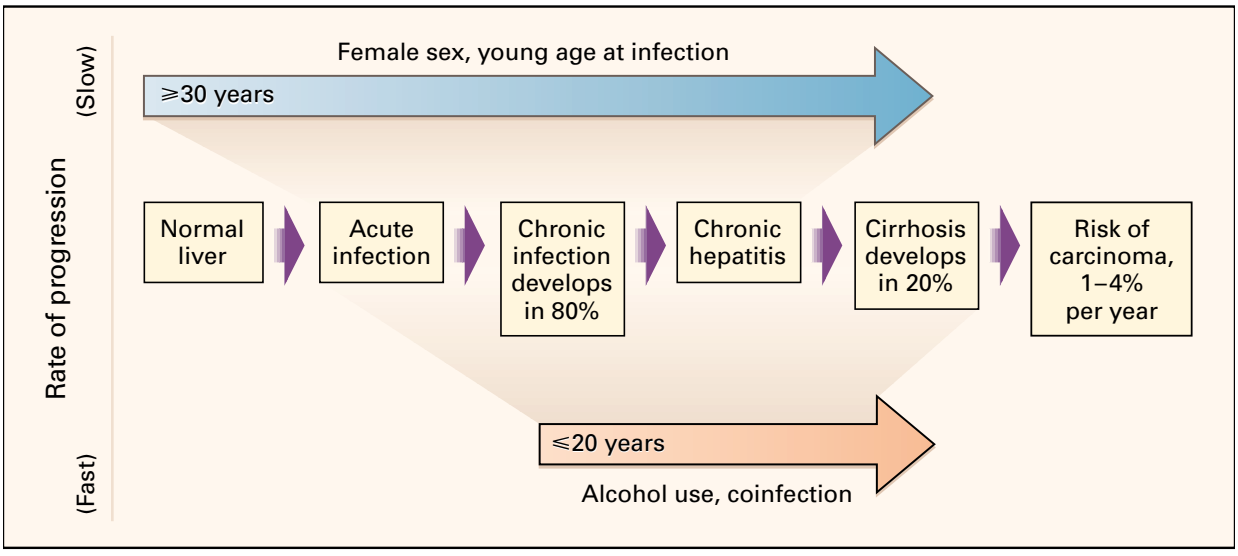

Figure 2. The Natural History of HCV Infection and Its Variability from Person to Person.

The course of infection varies widely among persons. Factors that decrease the risk of progression include female sex and a younger age at infection; factors that increase the risk include alcohol intake, an older age at infection, male sex, and coinfection with other viruses. Persons with a favorable risk profile often do not have progressive liver disease until 30 or more years after infection. In contrast, 20 percent of persons with chronic hepatitis C will eventually have cirrhosis, and this can occur 20 years or less after infection, especially in those with alcohol abuse or coinfection with human immunodeficiency virus type 1 or hepatitis B virus. Once cirrhosis is established, the risk of hepatocellular carcinoma is 1 to 4 percent per year.

who are coinfected with HBV and HCV also have an accelerated course of disease.[63]

Superinfection with hepatitis A virus (HAV) in persons who are infected with HCV can result in severe acute or even fulminant hepatitis.[77] Vaccination of patients with HCV infection against HAV appears to be both safe and effective.[78] Vaccination is recommended in these patients, as it is for other patients with chronic liver disease, although this approach is not cost effective in areas with a low incidence of HAV infection.[79]

DIAGNOSTIC TESTS

Diagnostic tests for HCV infection are divided into serologic assays for antibodies and molecular tests for viral particles. Screening assays based on antibody detection have markedly reduced the risk of transfusion-related infection, and once persons seroconvert they usually remain positive for HCV antibodies. However, recent data indicate that the level of HCV antibodies decreases gradually over time in the few patients in whom infection spontaneously resolves. In a cohort with a well-documented common source and known time of infection, assays for antibodies to HCV became negative after 18 to 20 years in 18 of 43 patients with spontaneous clearance of viremia.[44] This finding may also suggest that the true incidence of acute HCV infection with spontaneous clearance has been underestimated, since not all infected persons have persistent serologic evidence of infection.

The primary serologic screening assay for HCV infection is the enzyme immunoassay, for which there have been three consecutive versions with a resultant progressive increase in sensitivity. The currently used second- and third-generation enzyme immunoassays contain core protein as well as nonstructural proteins 3 and 4 (the third-generation assay also contains nonstructural protein 5) and can detect antibodies within 4 to 10 weeks after infection. In low-risk populations, the test misses only 0.5 to 1 percent of cases.[80] It can be falsely positive, especially in persons without risk factors and without signs of liver disease, such as blood donors or health care workers, and therefore other tests must be used to confirm infection in these persons. Furthermore, false negative tests can occur in persons with immune compromise, such as HIV-1 infection[81]; patients with renal failure; and those with HCV-associated essential mixed cryoglobulinemia.[68]

The recombinant immunoblot assay has been used to confirm positive enzyme immunoassays. It uses antigens similar to those for the enzyme immunoassay but in an immunoblot format, so that responses to the individual proteins can be identified. A positive assay is defined by the detection of antibodies against two or more antigens, and an indeterminate assay by the detection of antibodies against a single antigen. The use of a recombinant immunoblot assay to confirm results is recommended only in low-risk settings such as blood banks.[59] However, with the availability of improved enzyme immunoassays and better RNA-detection assays, confirmation by recombinant immunoblot assay may become less necessary.[82]

In the past few years new assays based on the molecular detection of HCV RNA have been introduced. These tests can be categorized as qualitative and quantitative. Since viral RNA is unstable, the appropriate processing of samples is critical to minimize the risk of false negative results; samples to be tested should be separated and frozen within three hours after phlebotomy.[83] Qualitative HCV RNA tests are based on the PCR technique and have a lower limit of detection of fewer than 100 copies of HCV RNA per milliliter.[19] These are the tests of choice for the confirmation of viremia and the assessment of treatment response. A qualitative PCR assay should also be used in patients with negative results on enzyme immunoassay in whom acute infection is suspected, in patients who have hepatitis with no identifiable cause, and in those with known reasons for false negative results on antibody testing.

The viral load has been shown to be relevant to the outcome of anti-HCV therapy[35,36] but not to predicting the likelihood of disease progression. Three commercial tests are currently available to quantitate the degree of viremia: a branched-chain DNA assay (Quantiplex HCV RNA, version 2.0) and two assays involving reverse-transcription PCR (Cobas Amplicor HCV monitor, version 2.0, and HCV Superquant). All systems deliver reliable, but not easily comparable, results[84] since no standardized system of expressing the viral load has been established. They also have different dynamic ranges: the PCR-based assays are more sensitive, and the branched-chain DNA assay has a higher range and does not require dilution for the quantification of high viral loads. It is therefore advisable to use a single test system for each patient for longitudinal monitoring of the viral load.

Viral genotyping helps predict the outcome of therapy and influences the choice of the therapeutic regimen.[35,36] Different methods are available for the genotyping of HCV,[85] most of which are based on amplification with the PCR assay. Currently, the only clinically relevant distinction is between genotype 1 and genotypes 2 and 3,[35,36] and the various systems have concordant results with respect to this distinction.[86]

An important nonspecific laboratory test in HCV-infected persons is measurement of the alanine aminotransferase level, an inexpensive and readily available means of identifying hepatic disease.[51] It is the best test for monitoring HCV infection and the efficacy of therapy in the intervals between molecular testing. However, in persons with HCV infection alanine aminotransferase levels may be normal or fluctuate, and therefore, a single normal value does not rule out active infection, progressive liver disease, or even cirrho-

sis.[51] Similarly, the normalization of alanine aminotransferase levels with antiviral therapy is no proof of the success of therapy. Moreover, alanine aminotransferase levels may remain elevated for other reasons even after clearance of the virus.

Histologic evaluation of a liver-biopsy specimen (Fig. 3) remains the gold standard for determining the activity of HCV-related liver disease, and histologic staging remains the only reliable predictor of prognosis and the likelihood of disease progression.[53] A biopsy may also help to rule out other, concurrent causes of liver disease. Therefore, biopsy is generally recommended for the initial assessment of persons with chronic HCV infection.[51,59] However, a liver biopsy is not considered mandatory before the initiation of treatment, and some recommend a biopsy only if treatment does not result in sustained remission.

TREATMENT

Even before HCV was identified as the chief etiologic agent in non-A, non-B hepatitis, interferon alfa therapy was associated with normalization of alanine aminotransferase levels in some persons who were given this diagnosis.[87] In 1989, the first cases of successful treatment of documented HCV infection with interferon alfa were reported,[88,89] but the very high rates of relapse frequently necessitated retreatment, which was almost invariably unsuccessful. A number of different interferons have been used, but all appear to have similar efficacy.[51] Although the introduction of combination therapy with interferon and ribavirin has markedly improved clinical outcomes, less than half of those with HCV infection can be expected to have a favorable response to the agents that are currently available.[35,36]

The success of these therapies can be measured in terms of a biochemical response (normalization of alanine aminotransferase levels), but the introduction of new assays for the detection of viral RNA now allows the assessment of a virologic response (as defined by a negative result on a qualitative PCR assay for HCV RNA). Some clinical trials have also assessed the histologic response, but in clinical practice there is little indication for post-treatment biopsy.

Since responses to therapy may not be maintained after treatment is stopped, the success of clinical trials has been evaluated in terms of the response at the end of therapy (end-of-treatment response) and six months after the cessation of treatment (sustained treatment response). Persons with a sustained virologic response have a high probability of having a durable biochemical, virologic, and histologic response.[90]

Acute Infection

Data regarding the efficacy of the treatment of acute HCV infection are very limited, since the infection is seldom diagnosed during the acute phase. Given the high rate of progression to chronic infection and the relatively limited efficacy of therapy for chronic infection, the treatment of acute infection has been advocated,[59] but it has not yet proved to be beneficial. Furthermore, some patients with acute symptomatic HCV infection have high rates of spontaneous clearance and would therefore be treated unnecessarily.[45] However, the preliminary results of more recent studies suggest that early treatment, even with interferon alone, has a high rate of efficacy. In view of these data early therapy may be advisable, but the optimal therapeutic regimen and the best point at which to intervene have not been defined. Since the study of persons with acute HCV infection may also provide valuable information about the pathogenesis of HCV infection in general, it would be ideal to follow such patients in controlled clinical trials.

Another unanswered question is whether postexposure prophylaxis — for example, after a needle-stick injury — is beneficial, as is the case for HIV-1 infection. Currently, no prophylactic regimen has been shown to be effective and efficient, and only monitoring is recommended.

Chronic Infection

In principle, all patients with chronic HCV infection are candidates for antiviral therapy.[51] However, the risks and benefits of treatment must be assessed individually, particularly given the typically slow course of natural infection. Only a subgroup of infected persons will have a clear indication for therapy.[51] This is the case in patients with detectable levels of HCV RNA who have persistently elevated alanine aminotransferase levels and a liver biopsy showing fibrosis or at least moderate necrosis and inflammation. These persons have a high risk of disease progression, and treatment is strongly recommended in the absence of contraindications.[51,59] Persons with elevated alanine aminotransferase levels and only minimal or mild necrotic and inflammatory changes may also be treated. However, the risk of progressive liver disease is lower in this group, and follow-up by means of serial measurements of alanine aminotransferase and a biopsy at three to five years is considered a reasonable alternative.[51,59]

Persons with persistently normal alanine aminotransferase levels and no histologic evidence of necrotic and inflammatory changes or only minimal changes have an excellent prognosis without therapy.[91] In fact, in some such persons alanine aminotransferase levels become elevated after treatment with interferon alfa.[92] In the absence of other indications, such as extrahepatic manifestations, persons in this category are best considered for therapy only in the context of controlled clinical trials. Decreases in the quality of life of patients with detectable levels of HCV RNA, even in the absence of liver disease,[60] and an improvement in symptoms after eradication of the virus,[93] have been reported recently. Further studies of the effect of ther-

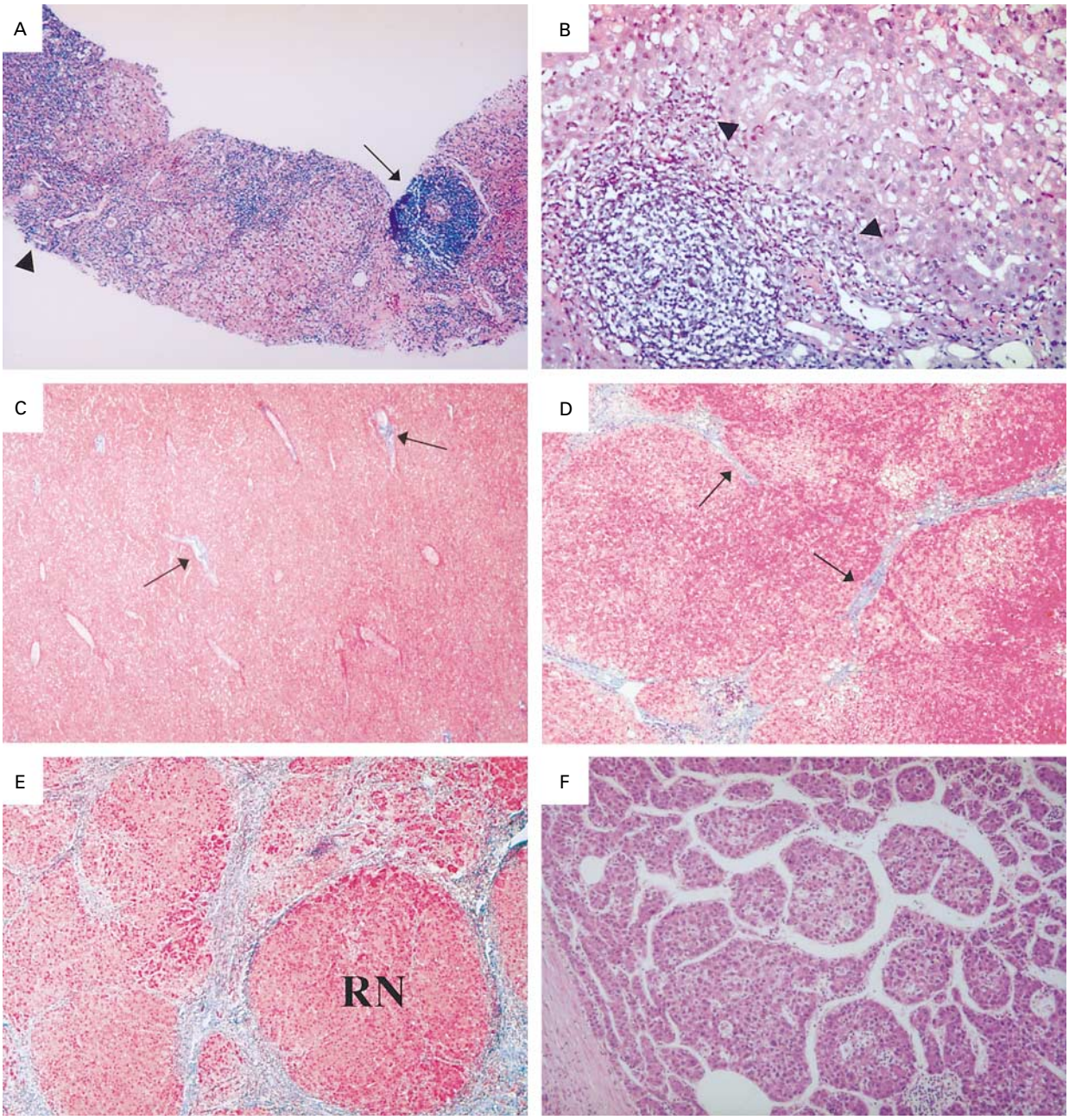

Figure 3. Histologic Stages of HCV Infection.

In Panel A, a core-biopsy specimen from a patient with chronic HCV infection shows dense portal lymphocytic infiltrates (arrow) and architectural changes (arrowhead) (hematoxylin and eosin, ×10). The lymphocytes are not limited to the portal tract but also extend into the lobules (arrowheads in Panel B) (hematoxylin and eosin, ×100). Panel C shows normal liver architecture with scant fibrous tissue (arrows) limited to the portal tracts (trichrome stain, ×20). During the progressive course of infection, the fibrotic areas expand and bridging fibrosis develops (arrows in Panel D) (trichrome stain, ×20). The final stage of cirrhosis (Panel E) is characterized by marked fibrosis and regenerative nodules (RN) (trichrome stain, ×20). Once cirrhosis has become established, hepatocellular carcinoma (Panel F) is a feared complication (hematoxylin and eosin, ×40).

apy on the quality of life are necessary before treatment for nonspecific symptoms alone can be recommended.

Persons with compensated cirrhosis are less likely to have a sustained response to monotherapy, but some studies have suggested that, even without the eradication of HCV, treated patients may have a lower risk of progression to decompensated liver disease and hepatocellular carcinoma.[94,95] Combination therapy seems to increase the rates of response in patients with cirrhosis,[35,36] but the exact benefits and optimal regimen await further study. Given the obvious need for intervention in this group of patients, combination therapy should be considered. The higher rate of side effects, especially neutropenia and thrombocytopenia, in this subgroup makes careful monitoring mandatory. Persons with decompensated cirrhosis are unlikely to have a response, and their condition may even worsen with therapy. They should not be treated with interferon alone or in combination with the nucleoside analogue ribavirin outside of controlled trials in specialized centers.

Initial Treatment Regimens

Monotherapy for HCV infection with interferon alfa was associated with initial rates of response as high as 40 percent, but the rates of sustained response are less than half this.[35,36] This is especially true in persons infected with HCV genotype 1a or 1b, the most prevalent genotypes in the United States and western Europe. Two large, prospective trials[35,36] demonstrated that the combination of interferon alfa and ribavirin significantly increases the percentage of previously untreated patients who have a sustained virologic response, from 16 percent to 40 percent. Both studies showed that in patients infected with HCV genotype 2 or 3 and in those with low viral loads before treatment, the response was maximal after 24 weeks of treatment, whereas patients infected with genotype 1 and those with a high viral load before treatment required a course of 48 weeks for an optimal outcome. This finding led to the recommendation that the duration of treatment should be based on the HCV genotype and the pretreatment viral load.[59] However, since tests for the quantification of HCV RNA are still not standardized, and since the viral load naturally fluctuates over time, the viral load is currently not routinely used for determining the treatment regimen.

The treatment of persons with chronic HCV infection is based largely on consensus guidelines.[51,59] The 1999 recommendations[59] suggest that previously untreated persons with the above-described indications and without contraindications to treatment with interferon or ribavirin (Table 1) should receive combination therapy. Treatment consists of 3 million U of interferon alfa administered subcutaneously three times a week and 1200 mg of ribavirin orally per day for patients who weigh at least 75 kg and 1000 mg of ribavirin orally per day for those weighing less than 75 kg. Usually, ribavirin is taken in divided doses, given in the morning and evening, and interferon is given before bedtime. The possible side effects of treatment are listed in Table 2.

The virologic response to combination therapy should be assessed at week 24, since elimination of the virus can occur late with this approach. Persons with a positive PCR assay for HCV RNA at week 24 should be considered to have had no response to treatment, and therapy should be discontinued. Those infected with HCV genotype 2 or 3 who have a negative PCR assay for HCV RNA can also usually stop therapy at this time, but an additional 24 weeks of treatment is suggested for patients with other genotypes and a negative PCR assay.

Often, the indication for treatment and the optimal regimen cannot be easily identified. Then, other factors, such as viral load, sex, the age of the patient, and the results of the liver biopsy, can be used to tailor therapy. Future studies should pinpoint the predictive value of such factors with respect to the response to treatment and thus allow more individualized approaches to therapy.

TABLE 1. CONTRAINDICATIONS TO TREATMENT WITH INTERFERON ALFA AND RIBAVIRIN.

CONTRAINDICATION	INTERFERON ALFA	RIBAVIRIN
Absolute	Current psychosis or a history of psychosis	Pregnancy
	Severe depression	Absence of use of a reliable form of contraception
	Neutropenia or thrombocytopenia	
	Symptomatic heart disease	End-stage renal failure
	Decompensated cirrhosis	Anemia
	Uncontrolled seizures	Hemoglobinopathies
	Organ transplantation (other than liver)	Severe heart disease
Relative	Autoimmune disorders (e.g., thyroiditis)	Uncontrolled hypertension
	Uncontrolled diabetes	Old age

Pegylated Interferons

The attachment of polyethylene glycol to interferon alfa (peginterferon alfa) extends the half-life and duration of therapeutic activity of interferon alfa. In contrast to interferon alfa, peginterferon alfa is given only once a week, and the individual dose is calculated according to the patient's weight. Treatment with peginterferon alfa results in a higher rate of response than does conventional monotherapy with interferon alfa.[96,97] Peginterferon alfa-2a has now been approved by the Food and Drug Administration for this indication. Large clinical trials are under way to evaluate the combination of peginterferon and ribavirin, and the results will determine the role of these agents in the treatment of HCV infection.

Treatment of Patients with Contraindications or Adverse Reactions to Ribavirin

Persons who cannot be treated with ribavirin (Table 1) can be treated with peginterferon alfa. This is also the therapy of choice for the 20 percent of patients who receive combination therapy and who have to discontinue such treatment as a result of ribavirin-induced anemia. The optimal peginterferon alfa regimen for various subgroups of patients has yet to be determined.

Combination Treatment in Patients Who Relapse after the Cessation of Monotherapy with Interferon Alfa

Forty-nine percent of patients who relapse after monotherapy with interferon alfa have a sustained virologic response to combination therapy with interferon and ribavirin.[98] A prolonged course of a higher dose of interferon or peginterferon alfa alone is another option,[59] mainly in patients with contraindications to ribavirin therapy. For patients who relapse after combination therapy, there are no recommended treatments. These patients should be monitored until a better treatment becomes available or enrolled in clinical studies.

Treatment of Patients with No Response to Monotherapy or Combination Therapy

No currently available treatment has been shown to be effective in patients with no response to interferon alone or in combination with ribavirin. Even with the use of combination therapy, less than 10 percent of patients with no previous response to interferon will have a sustained virologic response.[99] These patients should be treated in controlled clinical trials.

Liver Transplantation

Liver transplantation is the only available treatment option for patients with decompensated HCV-related cirrhosis and is also indicated for some patients with early stages of hepatocellular carcinoma. Reinfection of the graft with HCV is nearly inevitable, and the majority of patients will have histologic signs of hepatitis and even cirrhosis.[100] Despite these drawbacks, the one-year and five-year rates of survival of HCV-infected persons who undergo liver transplantation do not significantly differ from those of patients with other common indications for liver transplantation.[100] New therapies are necessary to improve the long-term outcome of liver transplantation, either to prevent infection of the liver transplant or to treat it effectively.

TABLE 2. SIDE EFFECTS OF TREATMENT WITH INTERFERON ALFA AND RIBAVIRIN.

FREQUENCY OF SIDE EFFECT	INTERFERON ALFA	RIBAVIRIN
>30% (very common)	Influenza-like symptoms Headache Fatigue Fever Rigors Myalgia Thrombocytopenia Induction of autoantibodies	Hemolysis Nausea
1–30% (common)	Anorexia Erythema at injection site Insomnia Alopecia Lack of motivation Inability to concentrate Irritability Emotional lability Depression Diarrhea Induction of autoimmune disease Leukocytopenia Taste perversion	Anemia Nasal congestion Pruritus
<1% (rare)	Polyneuropathy Paranoia or suicidal ideation Diabetes mellitus Retinopathy Optic neuritis Hearing impairment Seizures Loss of libido Cardiotoxicity	Gout

Treatment of Patients Coinfected with HIV-1

Patients who are coinfected with HCV and HIV-1 are at increased risk for disease progression.[62] Because of the improvements in survival associated with HIV-1–specific antiretroviral therapy, there is an increasing need to address the treatment of HCV infection in this group. Like patients with HCV infection alone, those who are coinfected with HCV and HIV-1 have poor rates of response to monotherapy with interferon alfa.[101] Combination therapy should increase the rates of response in this group of patients. Indeed, a small study[102] found that the efficacy and safety of combination therapy in these patients were similar to those in patients with HCV infection alone, and large trials are under way to clarify the role of combination therapy in this cohort.

TABLE 3. CHARACTERISTICS OF HEPATITIS A VIRUS, HEPATITIS B VIRUS, AND HEPATITIS C VIRUS.

CHARACTERISTIC	HEPATITIS A VIRUS	HEPATITIS B VIRUS	HEPATITIS C VIRUS
Type of virus	Picornavirus (RNA)	Hepadnavirus (DNA)	Flavivirus (RNA)
Mode of transmission	Fecal–oral (in some cases, parenteral)	Parenteral	Parenteral
Route of transmission	Person-to-person contact Sexual Food	Sexual Injection-drug use Perinatal (common, if mother is positive for hepatitis B early antigen)	Injection-drug use Blood products (before 1990) Sexual? Perinatal (infrequent)
Frequency of acute icteric disease	Common in adults Infrequent in children	Common in adults Infrequent in children	Uncommon
Frequency of evolution to chronic infection	Never	Infrequent in adults (<10%) Common in young children and infants	Frequent (>70%)
Estimated no. of acute infections/yr in the United States	179,000	185,000	38,000
Estimated no. of chronically infected persons in the United States	—	1,250,000	2,700,000
Estimated no. of chronically infected persons in the world	—	350,000,000	170,000,000
Treatment	None	Interferon alfa Lamivudine	Interferon alfa in combination with ribavirin
Prophylaxis	Recombinant vaccine Immune globulin (postexposure)	Recombinant vaccine Hepatitis B immune globulin (postexposure)	None

Highly active antiretroviral therapy must be initiated with caution in patients coinfected with HCV and HIV-1, since immune reconstitution associated with the treatment of HIV-1 infection may exacerbate hepatitis.[103] Hepatotoxicity is also a major problem in some of the drugs used in the regimen of highly active antiretroviral therapy, and the effect may be even more pronounced in persons with concurrent HCV infection. Therefore, it may be prudent to initiate therapy for HCV infection before highly active antiretroviral therapy is begun in patients in whom treatment for HIV-1 infection can be temporarily deferred.

CONCLUSIONS AND FUTURE DIRECTIONS

Given the present trends, HCV infection will continue to have a global impact on health in the foreseeable future. The high rates of progression to chronic infection and the lack of effective means of prevention require that HCV infection be differentiated from other causes of viral hepatitis (Table 3). Despite recent progress, efforts to develop more effective therapies must remain a high priority. Worldwide, the best hope for a solution to the epidemic of HCV infection is the development of an effective vaccine. Although the recent demonstration of apparent immunologic clearance of virus in some persons with acute infection provides hope that a vaccine may someday be developed,[43,104] it is not likely to be available soon.

For those who are already infected with HCV, new therapeutic approaches can be expected in the future. Persons who have no response to therapy and who have a high risk of imminent progression to decompensated liver disease might benefit from therapies that halt disease progression until better therapies become available. In a small study, interleukin-10 had beneficial effects on liver abnormalities.[105] This approach, as well as the long-term administration of low doses of interferon[106] or ribavirin, is currently being evaluated in large, prospective studies. With the better characterization of the replicative cycle of HCV, it should be possible to develop virus-specific inhibitors that work in a manner analogous to that of inhibitors of HIV-1 replication. Potential targets include the HCV proteases helicase and polymerase as well as the internal ribosomal entry site or the putative cell-surface receptor CD81. In the meantime, HCV infection will undoubtedly remain a clinical challenge throughout the world.

We are indebted to Gregory Y. Lauwers for the photomicrographs and to Raymond T. Chung, Margaret J. Koziel, and Markus Reiser for critical review of the manuscript.

REFERENCES

1. Frank C, Mohamed MK, Strickland GT, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet 2000;355:887-91.

2. Alter MJ, Kruszon-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.

3. Alter MJ, Margolis HS, Krawczynski K, et al. The natural history of community-acquired hepatitis C in the United States. N Engl J Med 1992; 327:1899-905.
4. Roudot-Thoraval F, Bastie A, Pawlotsky JM, Dhumeaux D. Epidemiological factors affecting the severity of hepatitis C virus-related liver disease: a French survey of 6,664 patients. Hepatology 1997;26:485-90.
5. Thomas DL, Villano SA, Riester KA, et al. Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers: Women and Infants Transmission Study. J Infect Dis 1998;177: 1480-8.
6. Ohto H, Terazawa S, Sasaki N, et al. Transmission of hepatitis C virus from mothers to infants. N Engl J Med 1994;330:744-50.
7. Wyld R, Robertson JR, Brettle RP, Mellor J, Prescott L, Simmonds P. Absence of hepatitis C virus transmission but frequent transmission of HIV-1 from sexual contact with doubly-infected individuals. J Infect 1997; 35:163-6.
8. Eyster ME, Alter HJ, Aledort LM, Quan S, Hatzakis A, Goedert JJ. Heterosexual co-transmission of hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Ann Intern Med 1991;115:764-8.
9. Soto B, Rodrigo L, Garcia-Bengoechea M, et al. Heterosexual transmission of hepatitis C virus and the possible role of coexistent human immunodeficiency virus infection in the index case: a multicentre study of 423 pairings. J Intern Med 1994;236:515-9.
10. Couzigou P, Richard L, Dumas F, Schouler L, Fleury H. Detection of HCV-RNA in saliva of patients with chronic hepatitis C. Gut 1993;34: Suppl:S59-S60.
11. Abe K, Kurata T, Shikata T, Sugitani M, Oda T. Experimental transmission of non-A, non-B hepatitis by saliva. J Infect Dis 1987;155:1078-9.
12. Sagnelli E, Gaeta GB, Felaco FM, et al. Hepatitis C virus infection in households of anti-HCV chronic carriers in Italy: a multicentre case-control study. Infection 1997;25:346-9.
13. Bronowicki J-P, Venard V, Botté C, et al. Patient-to-patient transmission of hepatitis C virus during colonoscopy. N Engl J Med 1997;337:237-40.
14. Katsoulidou A, Paraskevis D, Kalapothaki V, et al. Molecular epidemiology of a hepatitis C virus outbreak in a haemodialysis unit: Multicentre Haemodialysis Cohort Study on Viral Hepatitis. Nephrol Dial Transplant 1999;14:1188-94.
15. Esteban JI, Gómez J, Martell M, et al. Transmission of hepatitis C virus by a cardiac surgeon. N Engl J Med 1996;334:555-60.
16. Ross RS, Viazov S, Gross T, Hofmann F, Seipp H-M, Roggendorf M. Transmission of hepatitis C virus from a patient to an anesthesiology assistant to five patients. N Engl J Med 2000;343:1851-4.
17. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. N Engl J Med 1996;334:1685-90.
18. Legler TJ, Riggert J, Simson G, et al. Testing of individual blood donations for HCV RNA reduces the residual risk of transfusion-transmitted HCV infection. Transfusion 2000;40:1192-7.
19. Beld M, Habibuw MR, Rebers SP, Boom R, Reesink HW. Evaluation of automated RNA-extraction technology and a qualitative HCV assay for sensitivity and detection of HCV RNA in pool-screening systems. Transfusion 2000;40:575-9.
20. Thomas DL, Factor SH, Kelen GD, Washington AS, Taylor E Jr, Quinn TC. Viral hepatitis in health care personnel at the Johns Hopkins Hospital: the seroprevalence of and risk factors for hepatitis B virus and hepatitis C virus infection. Arch Intern Med 1993;153:1705-12.
21. Mitsui T, Iwano K, Masuko K, et al. Hepatitis C virus infection in medical personnel after needlestick accident. Hepatology 1992;16:1109-14.
22. Hernandez ME, Bruguera M, Puyuelo T, Barrera JM, Sanchez Tapias JM, Rodes J. Risk of needle-stick injuries in the transmission of hepatitis C virus in hospital personnel. J Hepatol 1992;16:56-8.
23. 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;143:2493-503.
24. Okuda M, Hino K, Korenaga M, Yamaguchi Y, Katoh Y, Okita K. Differences in hypervariable region 1 quasispecies of hepatitis C virus in human serum, peripheral blood mononuclear cells, and liver. Hepatology 1999;29:217-22.
25. Zignego AL, De Carli M, Monti M, et al. Hepatitis C virus infection of mononuclear cells from peripheral blood and liver infiltrates in chronically infected patients. J Med Virol 1995;47:58-64.
26. Neumann AU, Lam NP, Dahari H, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science 1998; 282:103-7.
27. Kolykhalov AA, Agapov EV, Blight KJ, Mihalik K, Feinstone SM, Rice CM. Transmission of hepatitis C by intrahepatic inoculation with transcribed RNA. Science 1997;277:570-4.
28. Yanagi M, Purcell RH, Emerson SU, Bukh J. Transcripts from a single full-length cDNA clone of hepatitis C virus are infectious when directly transfected into the liver of a chimpanzee. Proc Natl Acad Sci U S A 1997; 94:8738-43.
29. Lohmann V, Korner F, Koch J, Herian U, Theilmann L, Bartenschlager R. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. Science 1999;285:110-3.
30. Blight KJ, Kolykhalov AA, Rice CM. Efficient initiation of HCV RNA replication in cell culture. Science 2000;290:1972-4.
31. Love RA, Parge HE, Wickersham JA, et al. The crystal structure of hepatitis C virus NS3 proteinase reveals a trypsin-like fold and a structural zinc binding site. Cell 1996;87:331-42.
32. Pileri P, Uematsu Y, Campagnoli S, et al. Binding of hepatitis C virus to CD81. Science 1998;282:938-41.
33. Kolykhalov AA, Mihalik K, Feinstone SM, Rice CM. Hepatitis C virus-encoded enzymatic activities and conserved RNA elements in the 3′ nontranslated region are essential for virus replication in vivo. J Virol 2000; 74:2046-51.
34. Tang S, Collier AJ, Elliott RM. Alterations to both the primary and predicted secondary structure of stem-loop IIIc of the hepatitis C virus 1b 5′ untranslated region (5′UTR) lead to mutants severely defective in translation which cannot be complemented in trans by the wild-type 5′UTR sequence. J Virol 1999;73:2359-64.
35. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998;352:1426-32.
36. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initital treatment for chronic hepatitis C. N Engl J Med 1998;339:1485-92.
37. Farci P, Munoz SJ, Shimoda A, et al. Experimental transmission of hepatitis C virus-associated fulminant hepatitis to a chimpanzee. J Infect Dis 1999;179:1007-11.
38. Enomoto N, Sakuma I, Asahina Y, et al. Mutation in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. N Engl J Med 1996;334:77-81.
39. Chung RT, Monto A, Dienstag JL, Kaplan LM. Mutations in the NS5A region do not predict interferon-responsiveness in American patients infected with genotype 1b hepatitis C virus. J Med Virol 1999;58:353-8.
40. Zeuzem S, Lee JH, Roth WK. Mutations in the nonstructural 5A gene of European hepatitis C virus isolates and response to interferon alfa. Hepatology 1997;25:740-4.
41. Agnello V, Abel G, Knight GB, Muchmore E. Detection of widespread hepatocyte infection in chronic hepatitis C. Hepatology 1998;28:573-84.
42. Cooper S, Erickson AL, Adams EJ, et al. Analysis of a successful immune response against hepatitis C virus. Immunity 1999;10:439-49.
43. Lechner F, Wong DK, Dunbar PR, et al. Analysis of successful immune responses in persons infected with hepatitis C virus. J Exp Med 2000;191:1499-512.
44. Takaki A, Wiese M, Maertens G, et al. Cellular immune responses persist and humoral responses decrease two decades after recovery from a single-source outbreak of hepatitis C. Nat Med 2000;6:578-82.
45. Gerlach JT, Diepolder HM, Jung MC, et al. Recurrence of hepatitis C virus after loss of virus-specific CD4(+) T-cell response in acute hepatitis C. Gastroenterology 1999;117:933-41.
46. Farci P, Shimoda A, Coiana A, et al. The outcome of acute hepatitis C predicted by the evolution of the viral quasispecies. Science 2000;288: 339-44.
47. Koziel MJ, Dudley D, Afdhal N, et al. HLA class I-restricted cytotoxic T lymphocytes specific for hepatitis C virus: identification of multiple epitopes and characterization of patterns of cytokine release. J Clin Invest 1995;96:2311-21.
48. Kao JH, Chen PJ, Wang JT, et al. Superinfection by homotypic virus in hepatitis C virus carriers: studies on patients with post-transfusion hepatitis. J Med Virol 1996;50:303-8.
49. Wyatt CA, Andrus L, Brotman B, Huang F, Lee DH, Prince AM. Immunity in chimpanzees chronically infected with hepatitis C virus: role of minor quasispecies in reinfection. J Virol 1998;72:1725-30.
50. Farci P, Alter HJ, Shimoda A, et al. Hepatitis C virus–associated fulminant hepatic failure. N Engl J Med 1996;335:631-4.
51. National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. Hepatology 1997;26:Suppl 1:2S-10S.
52. Conry-Cantilena C, VanRaden M, Gibble J, et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. N Engl J Med 1996;334:1691-6.
53. Yano M, Kumada H, Kage M, et al. The long-term pathological evolution of chronic hepatitis C. Hepatology 1996;23:1334-40.
54. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. N Engl J Med 1999;340:1228-33.

55. Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. 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.
56. Niederau C, Lange S, Heintges T, et al. Prognosis of chronic hepatitis C: results of a large, prospective cohort study. Hepatology 1998;28:1687-95.
57. Seeff LB, Buskell-Bales Z, Wright EC, et al. Long-term mortality after transfusion-associated non-A, non-B hepatitis. N Engl J Med 1992;327:1906-11.
58. Seeff LB, Miller RN, Rabkin CS, et al. 45-Year follow-up of hepatitis C virus infection in healthy young adults. Ann Intern Med 2000;132:105-11.
59. EASL International Consensus Conference on Hepatitis C: Paris, 26-28, February 1999, consensus statement. J Hepatol 1999;30:956-61.
60. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. Hepatology 1998;27:209-12.
61. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet 1997;349:825-32.
62. Sanchez-Quijano A, Andreu J, Gavilan F, et al. Influence of human immunodeficiency virus type 1 infection on the natural course of chronic parenterally acquired hepatitis C. Eur J Clin Microbiol Infect Dis 1995;14:949-53.
63. Zarski JP, Bohn B, Bastie A, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. J Hepatol 1998;28:27-33.
64. Ikeda K, Saitoh S, Koida I, et al. A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis. Hepatology 1993;18:47-53.
65. Tsukuma H, Hiyama T, Tanaka S, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993;328:1797-801.
66. Colombo M, de Franchis R, Del Ninno E, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med 1991;325:675-80.
67. Zignego AL, Brechot C. Extrahepatic manifestations of HCV infection: facts and controversies. J Hepatol 1999;31:369-76.
68. Agnello V, Chung RT, Kaplan LM. A role for hepatitis C virus infection in type II cryoglobulinemia. N Engl J Med 1992;327:1490-5.
69. Horcajada JP, Garcia-Bengoechea M, Cilla G, Etxaniz P, Cuadrado E, Arenas JI. Mixed cryoglobulinaemia in patients with chronic hepatitis C infection: prevalence, significance and relationship with different viral genotypes. Ann Med 1999;31:352-8.
70. Heckmann JG, Kayser C, Heuss D, Manger B, Blum HE, Neundorfer B. Neurological manifestations of chronic hepatitis C. J Neurol 1999;246:486-91.
71. Silvestri F, Pipan C, Barillari G, et al. Prevalence of hepatitis C virus infection in patients with lymphoproliferative disorders. Blood 1996;87:4296-301.
72. Zuckerman E, Zuckerman T, Levine AM, et al. Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. Ann Intern Med 1997;127:423-8.
73. Fargion S, Piperno A, Cappellini MD, et al. Hepatitis C virus and porphyria cutanea tarda: evidence of a strong association. Hepatology 1992;16:1322-6.
74. Haddad J, Deny P, Munz-Gotheil C, et al. Lymphocytic sialadenitis of Sjogren's syndrome associated with chronic hepatitis C virus liver disease. Lancet 1992;339:321-3.
75. Tanei R, Watanabe K, Nishiyama S. Clinical and histopathologic analysis of the relationship between lichen planus and chronic hepatitis C. J Dermatol 1995;22:316-23.
76. Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol 1997;26:1-5.
77. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med 1998;338:286-90.
78. Keeffe EB, Iwarson S, McMahon BJ, et al. Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. Hepatology 1998;27:881-6.
79. Myers RP, Gregor JC, Marotta PJ. The cost-effectiveness of hepatitis A vaccination in patients with chronic hepatitis C. Hepatology 2000;31:834-9.
80. Vrielink H, Reesink HW, van den Burg PJ, et al. Performance of three generations of anti-hepatitis C virus enzyme-linked immunosorbent assays in donors and patients. Transfusion 1997;37:845-9.
81. Cribier B, Rey D, Schmitt C, Lang JM, Kirn A, Stoll-Keller F. High hepatitis C viraemia and impaired antibody response in patients coinfected with HIV. AIDS 1995;9:1131-6.
82. Pawlotsky JM, Lonjon I, Hezode C, et al. What strategy should be used for diagnosis of hepatitis C virus infection in clinical laboratories? Hepatology 1998;27:1700-2.
83. Busch MP, Wilber JC, Johnson P, Tobler L, Evans CS. Impact of specimen handling and storage on detection of hepatitis C virus RNA. Transfusion 1992;32:420-5.
84. Martinot-Peignoux M, Boyer N, Le Breton V, et al. A new step toward standardization of serum hepatitis C virus-RNA quantification in patients with chronic hepatitis C. Hepatology 2000;31:726-9.
85. Pawlotsky JM. Diagnostic tests for hepatitis C. J Hepatol 1999;31:Suppl 1:71-9.
86. Lau JY, Mizokami M, Kolberg JA, et al. Application of six hepatitis C virus genotyping systems to sera from chronic hepatitis C patients in the United States. J Infect Dis 1995;171:281-9.
87. Hoofnagle JH, Mullen KD, Jones DB, et al. Treatment of chronic non-A,non-B hepatitis with recombinant human alpha interferon: a preliminary report. N Engl J Med 1986;315:1575-8.
88. Di Bisceglie AM, Martin P, Kassianides C, et al. Recombinant interferon alfa therapy for chronic hepatitis C: a randomized, double-blind, placebo-controlled trial. N Engl J Med 1989;321:1506-10.
89. Davis GL, Balart LA, Schiff ER, et al. Treatment of chronic hepatitis C with recombinant interferon alfa: a multicenter randomized, controlled trial. N Engl J Med 1989;321:1501-6.
90. Reichard O, Glaumann H, Fryden A, Norkrans G, Wejstal R, Weiland O. Long-term follow-up of chronic hepatitis C patients with sustained virological response to alpha-interferon. J Hepatol 1999;30:783-7.
91. Mathurin P, Moussalli J, Cadranel JF, et al. Slow progression rate of fibrosis in hepatitis C virus patients with persistently normal alanine transaminase activity. Hepatology 1998;27:868-72.
92. Sangiovanni A, Morales R, Spinzi G, et al. Interferon alfa treatment of HCV RNA carriers with persistently normal transaminase levels: a pilot randomized controlled study. Hepatology 1998;27:853-6.
93. Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. Hepatology 1999;29:264-70.
94. Serfaty L, Aumaitre H, Chazouilleres O, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998;27:1435-40.
95. Nishiguchi S, Kuroki T, Nakatani S, et al. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 1995;346:1051-5.
96. Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 2000;343:1666-72.
97. Heathcote EJ, Shiffman ML, Cooksley WGE, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000;343:1673-80.
98. Davis GL, Esteban-Mur R, Rustgi V, et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. N Engl J Med 1998;339:1493-9.
99. Pol S, Couzigou P, Bourliere M, et al. A randomized trial of ribavirin and interferon-alpha vs. interferon-alpha alone in patients with chronic hepatitis C who were nonresponders to a previous treatment. J Hepatol 1999;31:1-7.
100. Feray C, Caccamo L, Alexander GJ, et al. European collaborative study on factors influencing outcome after liver transplantation for hepatitis C. Gastroenterology 1999;117:619-25.
101. Soriano V, Garcia-Samaniego J, Bravo R, et al. Interferon alpha for the treatment of chronic hepatitis C in patients infected with human immunodeficiency virus. Clin Infect Dis 1996;23:585-91.
102. Landau A, Batisse D, Van Huyen JP, et al. Efficacy and safety of combination therapy with interferon-alpha2b and ribavirin for chronic hepatitis C in HIV-infected patients. AIDS 2000;14:839-44.
103. John M, Flexman J, French MA. Hepatitis C virus-associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? AIDS 1998;12:2289-93.
104. Gruner NH, Gerlach TJ, Jung MC, et al. Association of hepatitis C virus-specific CD8+ T cells with viral clearance in acute hepatitis C. J Infect Dis 2000;181:1528-36.
105. Nelson DR, Lauwers GY, Lau JY, Davis GL. Interleukin 10 treatment reduces fibrosis in patients with chronic hepatitis C: a pilot trial of interferon nonresponders. Gastroenterology 2000;118:655-60.
106. Shiffman M, Pockros PJ, Reddy RK, et al. A controlled, randomized, multicenter, descending dose phase II trial of pegylated interferon alfa-2A (PEG) vs standard interferon alfa-2a (IFN) for treatment of chronic hepatitis C. Gastroenterology 1999;116:A1275.

CORRECTION

Hepatitis C Virus Infection

To the Editor: In their article on hepatitis C virus (HCV) infection (July 5 issue),[1] Lauer and Walker note that the pegylated interferon peginterferon alfa-2a has been approved by the Food and Drug Administration (FDA), when in fact it is peginterferon alfa-2b that has received FDA approval. Large studies in the United States and Europe of the use of either brand of pegylated interferon plus ribavirin have been completed and found sustained virologic response rates of 56 percent and 61 percent.[2,3] The combination of peginterferon alfa-2b plus ribavirin has been approved in Europe and is expected to be approved soon in the United States.

The comments about the lack of value of retreatment in patients with no response to interferon monotherapy are inaccurate; numerous studies have found sustained virologic response rates of 20 to 30 percent among such patients.[4] Approximately 30 percent of patients with chronic HCV infection have normal alanine aminotransferase levels.[4,5] Studies have shown that the sustained virologic response rates for either interferon monotherapy or combination therapy are equivalent to those among patients with elevated alanine aminotransferase levels. Although it is recognized that cirrhosis develops in only a small percentage of patients with normal alanine aminotransferase levels, as many as 20 percent of such patients will have stage 3 or stage 4 fibrosis. It is important to direct therapy to prevent progressive liver disease, but given the improvements in antiviral therapy and the opportunity to eradicate virus in an increasing number of patients, most hepatologists believe that patients with mild disease should also be treated.

Bruce R. Bacon, M.D.
Adrian M. Di Bisceglie, M.D.
Saint Louis University
St. Louis, MO 63110-0250
baconbr@slu.edu

Editor's note: Drs. Bacon and Di Bisceglie receive research support from and have consulting relationships with Schering-Plough and Roche Laboratories.

References

1. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345:41-52.
2. Fried MW, Shiffman ML, Reddy RK, et al. Pegylated (40 kDa) 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 1:A-55.
3. Manns MP, McHutchinson JG, Gordon S, et al. Peginterferon alfa-2b plus ribavirin compared to interferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C: 24 week treatment analysis of a multicenter, multinational phase III randomized controlled trial. Hepatology 2000;32:297A-297A.
4. Di Bisceglie AM, Thompson J, Smith-Wilkaitis N, Brunt EM, Bacon BR. Combination of interferon and ribavirin in chronic hepatitis C: re-treatment of nonresponders to interferon. Hepatology 2001;33:704-707.
5. Di Bisceglie AM. Chronic hepatitis C viral infection in patients with normal serum alanine aminotransferases. Am J Med 1999;107:53S-55S.

To the Editor: Lauer and Walker did not answer the following question: Do persons with HCV infection and normal liver-function results need a liver biopsy?

James R. Korb, M.D.
Southern California Permanente Medical Group
Los Angeles, CA 90034
james.r.korb@kp.org

To the Editor: Drs. Lauer and Walker overestimate the importance of HCV as a cause of chronic liver disease by concentrating on review articles, consensus statements, and retrospective studies while ignoring the prospective studies. Currently there are four large, long-term, retrospective–prospective studies involving patients who have received transfusions. These studies demonstrate a rather favorable outcome of HCV-associated liver disease.[1,2,3,4] In contrast to the consensus statement the authors cite indicating that liver cirrhosis develops in 20 to 30 percent of patients with HCV, much lower rates of cirrhosis have been documented in the four prospective studies.[1,2,3,4]

Hans L. Tillmann, M.D.
Stolze Str. 41
30171 Hannover, Germany
hansltillmann@web.de

References

1. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. N Engl J Med 1999;340:1228-1233.
2. Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in Germany: a 20-year multicenter study. Hepatology 2000;32:91-96.
3. Rodger AJ, Roberts S, Lanigan A, Bowden S, Brown T, Crofts N. Assessment of long-term outcomes of community-acquired hepatitis C infection in a cohort with sera stored from 1971 to 1975. Hepatology 2000;32:582-587.

4. Seeff LB, Miller RN, Rabkin CS, et al. 45-year follow-up of hepatitis C virus infection in healthy young adults. Ann Intern Med 2000;132:105-111.

To the Editor: Drs. Lauer and Walker do not discuss the association between HCV infection and diabetes mellitus. This association was described in 1995 and has been supported by more recent cross-sectional studies in which patients with HCV infection were matched according to age, sex, and severity of cirrhosis. In one study, the prevalence of diabetes mellitus was 23.6 percent among patients with HCV infection but 9.4 percent among those infected with hepatitis B virus, and the prevalence was associated with the Child–Pugh score among patients with cirrhosis.[1] A similar prevalence has been found in other studies and in the experience at our institution.[2] Persons older than 40 years of age with HCV infection have a risk of diabetes that is three times that of those without HCV infection.[3] Furthermore, HCV-related cirrhosis was found to be a predictor of the development of diabetes after liver transplantation.[2]

Kevan C. Herold, M.D.
Columbia University
New York, NY 10032
kh318@columbia.edu

References

1. Caronia S, Taylor K, Pagliaro L, et al. Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;30:1059-1063.

2. Bigam DL, Pennington JJ, Carpentier A, et al. Hepatitis C-related cirrhosis: a predictor of diabetes after liver transplantation. Hepatology 2000;32:87-90.

3. Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. Ann Intern Med 2000;133:592-599.

To the Editor: Lauer and Walker report that current psychosis or a history of psychosis is an absolute contraindication to treatment with interferon alfa and ribavirin in persons who are infected with HCV. To support this conclusion, the authors cite the consensus statement on hepatitis C from the European Association for the Study of the Liver.[1] Yet a clear justification for such a conclusion is lacking. The 1997 consensus statement from the National Institutes of Health on the management of hepatitis C[2] does not include psychosis as a contraindication to treatment with interferon alfa. In fact, a survey of 11,241 patients with chronic viral hepatitis treated with interferon alfa reported only 10 adverse events relating to psychosis.[3] None of these events were considered life-threatening, and all remitted with the discontinuation of interferon or with treatment with appropriate psychiatric medication.

Seth Himelhoch, M.D.
Johns Hopkins University
Baltimore, MD 21287-6220
shimelh1@jhmi.edu

References

1. EASL International Consensus Conference on Hepatitis C: Paris, 26-28, February 1999, consensus statement. J Hepatol 1999;30:956-961.

2. National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. Hepatology 1997;26:Suppl 1:2S-10S.

3. Fattovich G, Giustina G, Favarato S, Ruol A. A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol 1996;24:38-47.

To the Editor: The review on HCV infection indicates that hemoglobinopathies are considered absolute contraindications to treatment with ribavirin. We think that patients with hemoglobinopathies can tolerate ribavirin, but they require close monitoring.

Hemoglobinopathies are the most common autosomal recessive diseases. The high prevalence of positivity for HCV antibodies among patients with hemoglobinopathies is related to increased requirements for blood transfusion,[1] and the increased iron stores might accelerate the progression of the disease. Therefore, antiviral therapy in patients with HCV infection and concomitant hemoglobinopathy is warranted.

A study from the United Kingdom demonstrated the feasibility of combination therapy with interferon and ribavirin in patients with thalassemia.[2] Five of 11 patients had a sustained virologic response. Transfusion requirements were increased during therapy. We also successfully treated two patients with β-thalassemia; both had a sustained virologic response. With regard to antiviral treatment in patients with HCV infection and sickle cell disease, a single successful case report is available.[3] Thus, interferon and ribavirin therapy appears feasible and should be considered in patients with HCV infection and hemoglobinopathy.

Robert J. de Knegt, M.D.
Arie P. van den Berg, M.D.
Groningen University Hospital
9700 RB Groningen, the Netherlands
r.j.de.knegt@int.azg.nl

References

1. Erer B, Angelucci E, Lucarelli G, et al. Hepatitis C virus infection in thalassemia patients undergoing allogeneic bone marrow transplantation. Bone Marrow Transplant 1994;14:369-372.

2. Swaim MW, Agarwal S, Rosse WF. Successful treatment of hepatitis C in sickle-cell disease. Ann Intern Med 2000;133:750-751.

3. Telfer PT, Garson JA, Whitby K, et al. Combination therapy with interferon alpha and ribavirin for chronic hepatitis C virus infection in thalassaemic patients. Br J Haematol 1997;98:850-855.

To the Editor: In the article on HCV infection, hepatitis A vaccine is incorrectly described as a recombinant vaccine. Both hepatitis A vaccines licensed by the FDA and available in the United States are inactivated vaccines, prepared by propagating cell-culture–adapted virus in human fibroblasts and inactivating the purified product with formalin.[1,2] To my knowledge, there are no recombinant hepatitis A vaccines available anywhere in the world.

Beth P. Bell, M.D., M.P.H.
Centers for Disease Control and Prevention
Atlanta, GA 30333

References

1. Peetermans J. Production, quality control and characterization of an inactivated hepatitis A vaccine. Vaccine 1992;10:Suppl 1:S99-S101.

2. Armstrong ME, Giesa PA, Davide JP, et al. Development of the formalin-inactivated hepatitis A vaccine, VAQTA from the live attenuated virus strain CR326F. J Hepatol 1993;18:Suppl 2:S20-S26.

The authors reply:

To the Editor: We agree with Bacon and Di Bisceglie that preliminary abstracts of studies in which pegylated interferons plus ribavirin are being used are promising, but final recommendations should await peer review. We also agree that their own study revealed relatively good results (a sustained virological response rate of 30 percent) after retreatment in patients who had no response to interferon. However, three other studies[1,2,3] have shown a sustained virologic response to combination therapy in only 4 to 14 percent of patients who previously had no response to interferon alone.

The issue of which patients require a biopsy was raised by Korb, and the question of whom to treat was raised by Bacon and Di Bisceglie. We recommend a liver biopsy for patients with viremia who have persistently normal aminotransferase levels, since the results of a biopsy can greatly influence decisions regarding treatment. We recommend treatment for those with a biopsy specimen showing liver disease,[4] but we believe that close observation is an option that can be discussed with those whose biopsy specimens show very mild disease activity. We do not recommend therapy outside of controlled clinical trials for patients with viremia who have normal liver-function results and normal liver histology.

In response to Tillmann: we indeed discussed prospective studies and their limitations in the review. We did not state that cirrhosis develops in 20 to 30 percent of patients; the numbers we gave were 15 to 20 percent. These are still estimates but are in agreement with more recent reports.[5]

We appreciate the comments by Herold about the possible association of HCV infection with diabetes mellitus. Because of space limitations, we were not able to discuss this interesting issue.

We agree with Himelhoch and de Knegt and van den Berg that some contraindications to interferon and ribavirin should be addressed again in the future, especially since groups of patients that are currently excluded from therapy may have a high prevalence of HCV infection. Our review was intended for a general audience, and pending additional studies, we would not recommend treating patients with a history of psychosis or with hemoglobinopathies except in specialized centers.

We apologize for the errors that were noted. Indeed, peginterferon alfa-2b, not peginterferon alfa-2a, has been approved by the FDA. Although the dose of ribavirin must be reduced for a substantial number of patients, less than 1 percent, not 20 percent, have to discontinue ribavirin therapy because of drug-induced anemia. As Bell correctly notes, hepatitis A vaccine is an inactivated vaccine.

Bruce D. Walker, M.D.
Georg M. Lauer, M.D.
Massachusetts General Hospital
Charlestown, MA 02129-2000
bwalker@helix.mgh.harvard.edu

References

1. Cavalletto L, Chemello L, Donada C, et al. The pattern of response to interferon alpha (alpha-IFN) predicts sustained response to a 6-month alpha-IFN and ribavirin retreatment for chronic hepatitis C. J Hepatol 2000;33:128-134.

2. Pol S, Couzigou P, Bourliere M, et al. A randomized trial of ribavirin and interferon-alpha vs. interferon-alpha alone in patients with chronic hepatitis C who were non-responders to a previous treatment. J Hepatol 1999;31:1-7.

3. Spadaro A, Freni MA, Ajello A, et al. Interferon retreatment of patients with chronic hepatitis C: a long-term follow-up. Hepatogastroenterology 1999;46:3229-3233.

4. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345:41-52.

5. 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;33:455-463.