Current Views on Hepatitis C Virus Infection

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Hepatitis C virus infection affects more than 4 million people in the United States and is a leading cause of liver failure necessitating transplantation. Effective combination therapies are now available for subgroups of patients at risk for progression to cirrhosis. The benefits of therapy in immunosuppressed hosts, such as HIV-infected patients and liver transplant recipients, are less well established.

Introduction

The hepatitis C virus (HCV), a single-stranded RNA virus, was identified in 1988 [1]. Currently, HCV infection is a major cause of liver disease and liver failure throughout the world. A progressive decrease in bloodborne transmission of HCV has occurred since the screening of blood products was instituted; today, injection drug use accounts for most cases of HCV transmission in the United States [2]. Other modes of transmission include placental-fetal transmission, which is dependent on maternal viral load; exposure to multiple sexual partners; occupational exposures in patient care or clinical laboratory work; and intravenous immunoglobulin and solid-organ transplantations done before screening for HCV. Patients receiving hemodialysis and hemophiliac patients are also at increased risk secondary to repeated parenteral exposures. No definitive data implicate isolated nasal cocaine use, body piercing, tattooing, or breastfeeding in the transmission of HCV.

Currently, more than 4 million persons in the United States are infected with HCV. Most of these persons are asymptomatic and unaware of their infection. In a study of an inner-city emergency department population [3], almost one fifth of patients were infected with HCV. Approximately 40% of cases of chronic liver disease are HCV related [4••]. Furthermore, HCV infection accounts for most of the liver transplantations performed in the United States. At our institution, approximately 40% of liver transplantations are done for HCV cirrhosis. The highest prevalence of infection is in persons 20 to 39 years of age, and infection is more common in Hispanic persons and men [4••].

Diagnosis

Serologic testing remains the cornerstone of diagnosis of HCV infection. Detection of HCV antibody is done with enzyme immunoassay, which has a sensitivity of approximately 97% on third-generation assay, and recombinant immunoassay (RIBA), which is more specific. A positive RIBA result does not necessarily indicate active viremia; many patients who have recovered from acute HCV infection remain RIBA positive for years [5]. Currently, tests for HCV antigen are not commercially available. Molecular tests for HCV RNA are commercially available and are used extensively but have not yet been approved by the US Food and Drug Administration. RNA is measured qualitatively by reverse transcriptase polymerase chain reaction and quantitatively by reverse transcriptase polymerase chain reaction and branched-chain DNA techniques, and levels as low as 9000 copies/mL are detected. There are six HCV genotypes; the predominant US genotype is 1, and 1a is more common than 1b. Furthermore, although multiple serotypes have been identified, knowledge of serotypes is more useful epidemiologically than clinically. Quasispecies may play a role in drug resistance and inability to clear infection, and determination of quasispecies may be used to predict therapeutic response in the future [5,6•].

Clinical Features

Acute infection

Acute HCV infection may be asymptomatic in most persons. Approximately one third of patients with acute HCV infection develop jaundice; others may have constitutional symptoms, including anorexia, fatigue, right upper-quadrant pain, and nausea, which may persist for up to 6 months [7]. A fulminant course secondary to HCV infection is rare [8,9]. The incubation period lasts for a mean of 7 weeks, and HCV antibody develops within 8 to 9 weeks after exposure. Of persons with newly acquired infection, 90% seroconvert within 6 months [10]. A minority of patients (approximately 20%) resolve infection (resolution is defined as a positive HCV antibody test result, the absence of HCV RNA, and a normal alanine aminotransferase [ALT] level) with no long-term sequelae.

Chronic infection

Most patients with chronic HCV infection are asymptomatic. The most common symptom associated with chronic

infection is fatigue. Most patients with chronic infection have fluctuating liver transaminase abnormalities, although normal ALT levels are not uncommon. In general, elevated ALT levels do not correlate with degree of histologic inflammation, and assessment of the true extent of disease is best made by liver biopsy [7]. Liver disease is usually slowly progressive, and cirrhosis and liver failure manifest after 20 years of infection in 10% to 20% of persons [11]. However, in many persons, chronic HCV infection follows an indolent course without progression to cirrhosis and liver failure. The predictors of progression to cirrhosis include age greater than 40 years, ongoing alcohol use, male sex, immunodeficiency (*eg*, from HIV infection), and chronic active hepatitis on biopsy. Hepatocellular carcinoma occurs in 2% to 7% of patients, with an annual risk of 1% to 4% per year in patients with HCV cirrhosis. Women and persons older than 50 years of age may have an even greater risk [12].

The effects of HCV infection are not confined to the liver. Extrahepatic manifestations include glomerulonephritis, essential mixed cryoglobulinemia, polyarthritis, lichen planus, keratoconjunctivitis sicca, Sjogren's syndrome, leukocytoclastic vasculitis, and polyarteritis nodosa [13].

Prevention

Currently, no vaccine is available for the prevention of HCV infection. Immune globulin has no effect on the course of HCV infection in chimpanzees [14]. Neither postexposure prophylaxis nor administration of immune globulin to neonates born to HCV-positive mothers is recommended [4••,15]. The most effective measures for preventing HCV infection are blood and organ screening. Modification of high-risk behaviors (*eg*, cessation of intravenous drug use, use of sterile needles, and use of latex condoms by persons with multiple sexual partners) may also decrease HCV transmission.

Routine screening for HCV infection in the general population is currently not recommended; screening should be instituted only in high-risk persons: persons with a history of injection drug use, persons who received blood products before 1987, persons who received transplants before 1992, patients undergoing hemodialysis, and persons with multiple sexual partners.

Management

General measures

Alcohol use is associated with progression of hepatitis C, and the single most important recommendation for patients with HCV infection is abstinence from alcohol consumption. Furthermore, hepatotoxic drugs, including acetaminophen (>3 g/d) should be avoided. Injection drug users or others who are at risk and are not infected with the hepatitis B virus should receive hepatitis B vaccine. Hepatitis A vaccine is recommended for all persons infected with HCV [9,16]. Lifestyle modifications include not sharing toothbrushes or razors, covering any sites of bleeding, and rapidly cleaning fomites contaminated by HCV-infected blood.

In patients with HCV cirrhosis, screening for hepatocellular carcinoma with biannual α-fetoprotein determinations and ultrasonography has been shown to be cost effective on decision analysis [17].

Patient selection

The usefulness of liver biopsy in evaluating patients with HCV infection has been controversial. Liver biopsy provides objective data in determining the nature and extent of liver disease. No definitive correlation has been seen among serum transaminase abnormalities, HCV RNA levels, and extent of liver inflammation and fibrosis. Therefore, these variables are poor surrogate markers for liver histologic findings. Even patients with normal ALT levels may have advanced liver disease on histologic examination [18]. Liver biopsy provides a baseline for comparison when evaluating the effectiveness of treatment. Our practice favors obtaining liver biopsy specimens before initiating any anti-HCV therapy [19].

The benefit of treatment in patients with the greatest risk for progression to cirrhosis—those with persistently elevated ALT levels, positivity for HCV RNA, and a liver biopsy specimen showing portal or bridging fibrosis or moderate inflammation and necrosis—is clear [20••]. Treatment is also recommended for patients with acute HCV infection [2]. Definitive treatment recommendations have not been established for patients with persistently elevated ALT levels and more benign-appearing liver biopsy specimens, patients with persistently normal ALT levels, patients with compensated cirrhosis, and patients younger than 18 years of age or older than 60 years of age. It is important to recognize patients with decompensated liver disease early because waiting times on liver transplantation lists are long. Patients with Child-Turcotte-Pugh scores of 7 or more (Table 1) should be referred for transplantation evaluation [21].

Treatment

Interferon-α, initially used to treat hepatitis B, has emerged as the mainstay of therapy. Interferons are available in many forms: interferon-α2a; interferon-α2b; interferon-αcon1; consensus interferon; interferon-β; and a newer, pegylated interferon-α2a. The earlier interferons have essentially similar response rates [22]. In evaluating the results of therapy, accepted endpoints have been established. Response to treatment is evaluated at the following times: during treatment (usually 3 and 6 months after the start of treatment), and at the end of treatment. A sustained response is defined as normal ALT and absence of HCV RNA at 6 months after the end of treatment. Histologic evaluation has been a secondary endpoint in most studies [23].

Interferon-α, which has predominantly immunoregulatory and anti-inflammatory properties, has been the

Table 1. Child-Turcotte-Pugh scoring system to assess severity of liver disease

Variable	1 point	2 points	3 points
Encephalopathy	0	1 to 2	3 to 4
Ascites	Absent	Slight or moderate, controlled by diuretics	Despite diuretic treatment
Bilirubin concentration, mg/dL	<2.0	2.0 to 3.0	>3.0
Albumin concentration, g/dL	>3.5	2.8 to 3.5	2.8
Prothrombin time, INR	<1.7	1.7 to 2.3	>2.3

Adapted from Pugh *et al.* [21].
NR—international normalized ratio.

Table 2. Studies evaluating interferon monotherapy and combined therapy (interferon plus ribavirin) and relative response

Study	Interferon dosage and duration of interferon therapy	Subjects, *n*	End treatment response by HCV RNA, %	Sustained response by HCV RNA, %
Reichard *et al.* [25]	3 MU 3 times/wk for 24 wks	50	52	18
	3 MU 3 times/wk plus ribavirin, 1 to 1.2 g, for 24 wks	50	52	36
Poynard *et al.* [26]	3 MU 3 times/wk for 48 wks	281	33	19
	3 MU 3 times/wk plus ribavirin, 1 to 1.2 g, for 24 wks	281	57	35
	3 MU 3 times/wk plus ribavirin, 1 to 1.2 g, for 48 weeks	278	52	43
McHutchison *et al.* [20••]	3 MU 3 times/wk for 24 wks	231	29	6
	3 MU 3 times/wk for 48 wks	225	24	13
	3 MU 3 times/wk plus ribavirin, 1 to 1.2 g, for 24 wks	228	53	31
	3 MU 3 times/wk plus ribavirin, 1 to 1.2 g, for 48 wks	228	50	38
Davis *et al.* [27]	3 MU 3 times/wk for 24 wks	172	40	5
	3 MU 3 times/wk plus ribavirin, 1 to 1.2 g, for 24 wks	173	77	47
Barbaro *et al.* [28]	6 MU 3 times/wk for 24 wks	151	24	8
	3 MU 3 times/wk plus ribavirin, 1 to 1.2 g, for 24 wks	152	40	18
Lai *et al.* [29]*	3 MU 3 times/wk for 24 wks	19	32	6
	3 MU 3 times/wk plus ribavirin, 1.2 g, for 24 wks	21	76	43

*Interferon-α2a, 96-week follow-up sustained response.
HCV—hepatitis C virus.

mainstay of treatment for HCV infection [24]. As noted in Table 2, interferon-α monotherapy has limited efficacy in chronic HCV infection. Multiple pilot studies have shown improved efficacy with the combination of interferon-α and oral ribavirin [25,26,27••,28,29]. Ribavirin not only has viracidal properties but also has an anti-inflammatory effect. Specifically, it inhibits induction of macrophage pro-inflammatory cytokines and Th2 cytokines while preserving Th1 cytokines [30•]. Pegylated interferon-α2a, a chemically modified interferon with an increased half life, is currently undergoing further clinical trials and is not approved by the US Food and Drug Administration. This form of interferon may avoid the disadvantages associated with the peaks and troughs of serum interferon levels noted with three-times-weekly dosing regimens and may have increased efficacy and improved patient tolerance [31].

Our clinical practice is to offer combination therapy to both treatment-naive and previously treated persons with acute or chronic HCV infection. When possible, patients are encouraged to enroll in ongoing multicenter clinical trials. They are offered combination therapy with interferon-α2a (3 MU three times/wk) with ribavirin (1000 mg/d for body weight <75 kg or 1200 mg/d for body weight >75 kg). Our initial aim is to treat patients for 12 months. We do not routinely tailor treatment according to HCV genotype. Approximately 70% of HCV infection in the United States is due to genotype 1, and the rate of response of this genotype to monotherapy and combination therapy is lower than response in other genotypes [20••]. However,

current trials have shown that combination therapy is more effective than interferon monotherapy, regardless of HCV genotype.

At the initial screening, we exclude patients with coronary artery disease, pregnancy, significant psychiatric disease (*eg*, untreated depression), ongoing alcohol or other substance abuse, bone marrow suppression, thrombocytopenia, significant thyroid dysfunction, or autoimmune disease (*eg*, psoriasis). Patients are monitored with complete blood count with differential every week for the first month, then every 2 weeks for the second month, and then monthly throughout treatment. Liver function tests are done every month throughout treatment. To fully assess treatment response, we measure HCV RNA levels every 3 months throughout treatment. Six months after treatment, liver function tests are performed and HCV RNA levels are measured.

Patients are counseled about side effects of interferon-α therapy. Common side effects include influenza-like symptoms, neuropsychiatric-type symptoms (*eg*, mood changes, insomnia, and irritability), and modest laboratory abnormalities (*eg*, thrombocytopenia and leukopenia). These side effects usually do not require dose modification. Serious adverse effects mandating cessation of therapy or dose modification include severe depression with suicidal tendency and bone marrow depression with neutropenia and thrombocytopenia. Other uncommon adverse effects that may require dose modification are symptomatic thyroid disease, systemic autoimmune diseases, diabetes mellitus, immune-mediated dermatologic disease, psychosis, peripheral neuropathy, hemolytic anemia, cardiovascular disease, and seizures [32].

Because ribavirin has teratogenic effects, men and women planning pregnancies and women who are pregnant are excluded from ribavirin therapy. The use of effective birth control is emphasized before therapy is initiated. Most side effects related to interferon therapy are not exacerbated by the addition of ribavirin [28]. Ribavirin may cause reversible, normochromic, normocytic hemolytic anemia in up to 20% of patients treated. The implementation of strict dose-modification guidelines reduces most serious adverse events of combination therapy. These guidelines include 1) halving the ribavirin dose if the hemoglobin concentration decreases by 2 g/dL after therapy is started or decreases to less than 10 g/dL at any time during therapy, and 2) stopping therapy if the hemoglobin concentration remains less than 12 g/dL after 4 weeks of dose reduction or decreases to less than 8.5 g/dL at any time. The interferon dose is halved if the leukocyte count is less than 1.5×10^9 cells/L, the neutrophil count is less than 0.75×10^9 cells/L, or the platelet count is less than 50 x 103/L. Combination therapy should be discontinued if the leukocyte count is less than 1×10^9 cells/L, the neutrophil count is less than 0.5×10^9 cells/L, or the platelet count is less than 25×10^3/L [33].

Special Cases

Hepatitis C virus infection in HIV

Hepatitis C has been increasingly identified in persons with HIV infection, and it is estimated that 400,000 persons in the United States are coinfected [34]. Persons with HIV infection who are at particular risk for HCV infection are those with intravenous drug use experience or hemophilia; 50% to 90% of these patients are coinfected [35]. Risk for vertical transmission of HCV is increased almost threefold in women coinfected with HIV [36•], and some evidence suggests that HCV transmission is increased in homosexual men with HIV infection [37].

Persons with HIV and HCV infection differ in several ways from persons with HCV infection alone. The ability to detect HCV infection is diminished in persons with HIV infection. Whereas first-generation enzyme-linked immunosorbent assays (ELISAs) for antibodies to HCV had a high false-positive rate in persons with HIV infection, subsequent generations of ELISA and RIBA fail to identify 10% to 30% of HIV-infected persons with HCV infection because these persons lack HCV antibody production [38]. Thus, measurement of HCV RNA should be used to determine HCV viremia in persons with HIV infection and suspected HCV infection, despite a negative HCV antibody test result.

Infection with HIV increases the level of HCV viremia, and the increase is more marked with immunosuppression [39]. Coinfection is also associated with a faster rate of progression of hepatic inflammation, fibrosis, and decompensated liver disease. In a study by Soto *et al.* [40] of intravenous drug users with HCV infection, 15% of those with HIV infection compared with 2.6% of those without HIV infection developed cirrhosis within 10 years. Progression to cirrhosis, hepatic decompensation, and death is more common in those with low CD4 cell counts and AIDS [41]. Decompensated liver disease or death was seen in 9% to 11% of dually infected patients 10 to 20 years after estimated acquisition of HCV [42].

Response to interferon-α therapy, particularly a sustained virologic response, is decreased in persons with HIV infection, although higher CD4 cell counts predict improved response [43]. A multicenter trial of combination therapy (interferon-α and ribavirin) for HCV infection in patients with HIV infection is underway [43]. Because patients with combined infections are at higher risk for drug-induced hepatotoxicity, combination therapy for HCV infection may prove to be less well tolerated in this subgroup [43,44].

Hepatitis C virus infection after liver transplantation

The recurrence of HCV infection after liver transplantation can result in graft rejection, cirrhosis, and liver failure. More than 50% of liver transplant recipients develop chronic active hepatitis within 2 years of transplantation [45]. No effective prophylactic or therapeutic measures are currently available to reverse such sequelae. Immunosup-

pression is probably a major contributing factor. However, many liver transplant recipients have no apparent deterioration in hepatic function despite high HCV RNA levels.

Consequently, multiple studies have evaluated the efficacy of antiviral therapy to prevent recurrent infection after transplantation. Ribavirin monotherapy was shown to produce only a transient response; it did not affect HCV RNA levels, but it reduced ALT levels in 60% of patients because of its immunomodulatory effect [46]. Data on interferon-α monotherapy are conflicting. Singh *et al.* [47] found no decrease in the incidence or severity of HCV hepatitis after 6 months of treatment with interferon-α (3 MU three times/wk) immediately after liver transplantation. In another study, Sheiner *et al.* [48] showed a lower incidence of recurrent hepatitis after transplantation with prophylactic interferon-α2b (3 MU three times/wk) for 1 year. In contrast, combination treatment with ribavirin and interferon-α has been shown to minimize hepatocellular injury in recurrent infection, and maintenance therapy with ribavirin has been shown to maintain a therapeutic response [49]. Bone marrow suppression may be more marked with this therapy in these already immunosuppressed hosts, and interferon-α use has been associated with episodes of rejection in some patients.

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