Hepatitis C—Destined To Become An Infection Of The Past?

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ABSTRACT

The hepatitis C virus (HCV) currently infects 170 million individuals worldwide, placing them at increased risk for hepatocellular carcinoma, end-stage liver disease, liver transplants, and death. The incidence of hepatitis C has decreased dramatically since it was first identified, primarily as a result of preventive practices. Immunoassays and genotyping techniques now permit an accurate diagnosis and guide selection of therapy. Though viral control methods have improved, however, viral eradication methods have remained only partially effective, allowing the prevalence of infection to remain high. The relatively recent development of in-vitro systems for studying the molecular mechanisms of HCV infection has allowed investigators to identify potential targets for drugs that eradicate the virus or prevent its progression.

INTRODUCTION

Two decades ago, hepatitis C was the most common chronic bloodborne infection in the United States.[1] Since 1989, when the hepatitis C virus (HCV) was discovered, the incidence of this infection has decreased by almost 90%,[2] primarily as a result of preventive practices in blood banking and among high-risk individuals. Unfortunately, the burden of disease has declined much more slowly, leaving more than 3 million persons in the United States and 170 million worldwide, still chronically infected.[2] Many patients became infected during the decade-long lag time between the discovery of a "non-A, non-B" viral agent, and the discovery of its identity—HCV—and its structure. This elevated caseload is expected to persist until virus eradication becomes more effective. Fortunately, community-based prevention programs have been successful in reducing the rate of new infections, and techniques for immunoassays and genotyping can now provide an accurate diagnosis and guide the selection of therapy. The development of growth cultures for studying the molecular mechanisms of HCV infection has improved the potential for identifying targets toward which newly designed virus-eradicating drugs can be directed.

This article presents an overview of the primary issues contributing to the continued prevalence of hepatitis C and explores current treatments and recommendations for improved HCV control.

THE EPIDEMIOLOGY OF HEPATITIS C

HCV: A Brief History

In 1970, researchers discovered an agent other than HAV and HBV in an alarming number of patients with viral hepatitis. This "non-A non-B" hepatitis was initially considered benign, until researchers found that 20% of patients with this infection develop cirrhosis.[4] It took 12 years to identify the causative agent—HCV—and another 7 years to determine its structure. Meanwhile, rates of HCV infection surged, so that by 1988 it became the most common chronic bloodborne infection in the United States, and it remains highly prevalent today.[1,2] Thus far, it has been responsible for approximately 350,000 deaths,[3] and considerable morbidity. It accounts for approximately 60% of all cases of hepatocellular carcinoma, 40% of all cases of end-stage liver disease, and 30% of all liver transplants[5] in industrialized countries. End-stage liver disease and hepatocellular carcinoma from chronic infection are the most common indication for liver transplantation in the United States.

Prevalence

National surveillance programs reveal a detailed picture of the prevalence of hepatitis C and provide insight into the populations most likely to be affected (Table 1), and the individuals at greatest risk (Table 2). Unfortunately, reporting is voluntary and therefore incomplete, so the situation is likely worse than it seems. For every case of hepatitis reported to the Centers for Disease Control and Prevention, as many as 2 to 5 cases are not reported.[2] Consequently, rather than the 3.4 million known cases of HCV infection in the United States, there may be closer to 15 million cases. Given its reported prevalence in other countries (Fig. 1)[3] and current migration trends, the actual prevalence of this disease in the United States could be formidable.

TABLE 1. INCIDENCE OF HEPATITIS C IN VARIOUS AT-RISK CATEGORIES OF U.S. POPULATION.

Intravenous drug use	80%
Multiple sex partners	40%
Homeless	22%
Persons with HIV infection	20%
Incarcerated	15%
Alcohol use	11%-36%
Veterans	8%
General population	1.8%

Key Changes in Demographics

The demographics of hepatitis C have changed considerably over the last 2 decades. Although chronic infection rates remain highest among African Americans, the broad racial disparities of the past have diminished. The simple passage of time and consequent aging of the population have also had a notable effect, with infection rates under age 39 falling dramatically. Individuals with chronic infection today most likely contracted it during the 1980s, when the HCV infection rate was at its peak.[2]

TABLE 2. INDIVIDUALS AT GREATEST RISK FOR HEPATITIS C.

High risk of HCV Infection is associated with:

- Any history of injection drug use
- Contaminated blood or blood products or organ transplantation before July 1990
- Incarceration
- Needlestick or sharp injuries
- Procedures (e.g. injection, vaccination, surgery, transfusion, ceremonial rituals) involving reuse or sharing of contaminated equipment in parts of the world with high HCV prevalence
- Nonsterile contaminated tattooing or body piercing equipment
- Receiving hemodialysis
- Sharing personal items contaminated with blood with an HCV-infected person (e.g., razors, nail clippers, toothbrush)
- Sharing contaminated intranasal cocaine equipment
- Hepatitis B virus infection
- HIV infection
- Children born to mothers with HCV infection
- Undiagnosed liver disease

Moderate risk of HCV Infection is associated with:

- A sexual partner with HCV
- Multiple sexual partners
- Sexually transmitted infection, including HIV and lymphogranuloma venereum
- Traumatic sex that involves the potential for mucosal tearing (sex toys, fisting)
- Vaginal sex during menstruation

Transmission of hepatitis C virus is NOT associated with:

- Coughing
- Food
- Water
- Sharing eating utensils
- Hugging or kissing
- Shaking hands
- Toilet seats
- Other casual contact
- Breastfeeding (unless nipples are cracked and bleeding)
- Oral sex (unless blood exposure is involved)

Figure 1: Estimated prevalence of HCV worldwide, by region.

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Modes of Transmission

In the United States HCV is usually transmitted parenterally – most often through use of injected drugs, especially when needle sharing is involved,[2] and less commonly through occupational exposure among healthcare workers. The next most common exposure is sexual, especially when multiple partners are involved. Transfusion is now only a rare cause because of mandatory blood screening, although many patients with chronic infections were exposed through blood products during the 1970s and 1980s, before blood screening became routine. Perinatal transmission is very uncommon, at least in the United States.[2]

THE VIRUS: A CLOSER LOOK

HCV is an RNA virus of the Hepacivirus genus of the Flaviviridae family that only infects humans. It consists of 6 major genotypes with nucleotide sequences that vary by as much as 30%, and at least 50 subtypes.[6,7] The dominant genotype varies with geographic location and changes over time. Local genotype tracking is crucial for treatment success, since treatment responses vary with genotype. The 3-dimensional structure and active sites of key enzymes involved in the infectious process have been identified; these may serve as targets for drugs that may lead to eradication of the virus and prevent acute infections from becoming chronic.

Natural History of HCV Infection

HCV begins as an acute infection, with HCV RNA levels rising rapidly within 2 weeks of exposure, then leveling off over the following 4 to 6 weeks.[8] Meanwhile, serum aminotransferase levels rise, peaking within 3 months of exposure.[4]

The first line of defense against HCV is the hepatic natural killer (NK) cell, which secretes interferon (INF)-α to inhibit HCV replication.[9] However, HCV can inhibit T-cell proliferation, which facilitates progression to a chronic infection.[4] The role of the anti-HCV antibody is unclear; spontaneous viral clearance has been observed in children with agammaglobulinemia, which suggests that HCV infection can be controlled without elevated levels of anti-HCV antibodies.[4]

Viral clearance occurs in 20% to 40% of patients with acute infection, but the remaining 60-80% develop a chronic infection, which lead to a mild chronic hepatic inflammation. In at least 20% of patients, the resulting necrosis and apoptosis may lead to progressive fibrosis accompanied by nodular regeneration, i.e. cirrhosis, 2-3 decades after the chronic infection begins. Progression to cirrhosis is slow compared with other types of liver disease, but increases with male gender, higher age at exposure, longer duration of infection, immunosuppression, chronic coinfection with hepatitis B or HIV, alcohol use, and obesity. Each year up to 5% of HCV patients with cirrhosis develop liver failure, and up to 4% develop hepatocellular carcinoma.[6]

TESTING FOR HCV

Who Should Be Tested?

The American Association for the Study of Liver Diseases (AASLD) recommends an HCV test for:

a. Anyone who has ever injected an illicit drug - even once;
b. Anyone with an illness associated with hepatitis C, eg, HIV infection or hemophilia, particularly if they received clotting factors before 1987 when viral inactivation procedures were initiated;

c. Those with a history of dialysis, transfusion, or organ transplant before July 1992, when routine blood screening was initiated;
d. Current sex partners of infected individuals, although the risk of transmission in monogamous relationships is very low.[10]
e. Children of infected mothers, preferably at about 18 months of age, although the risk of perinatal transmission is low.

Testing Strategy: An Overview

A routine test for anti-HCV often reveals chronic infection. An HCV RNA test is recommended after a positive anti-HCV test, as well as for patients with unexplained liver disease, immunosuppression, or acute HCV infection. HCV genotyping is recommended if treatment is considered, in order to determine the duration of treatment and to predict the likelihood of a response. A liver biopsy, while not essential, may be considered to assess the extent of liver involvement, to eliminate coexisting conditions, and to determine the prognosis.

Patient Counseling

Infected individuals should receive counseling to prevent them from transmitting the virus. Those who inject or snort illicit drugs should of course be encouraged to stop, or at least to stop sharing or reusing syringes and other drug paraphernalia. All patients should be advised against sharing toothbrushes or shaving equipment; donating body tissues, including blood, organs, or semen;10 drinking alcohol; or taking hepatotoxic medications (acetaminophen may be taken in low doses). They should be encouraged to use condoms, to be vaccinated against hepatitis A and hepatitis B, and to receive yearly flu shots.

Diagnosis of Hepatitis C

The clinical symptoms of HCV infection vary considerably, so the diagnosis is based primarily on laboratory assessments. Since liver enzymes may not be elevated, it is necessary to perform assays specific for Hepatitis C.

Clinical manifestations. During the HCV incubation period (approximately 6-8 weeks after exposure) symptoms may include fatigue, anorexia, malaise, jaundice, a maculopapular rash, mild hepatosplenomegaly, and arthralgia.[6] These symptoms may be only mild, but they worsen with the severity and duration of the infection. Within 2 to 3 decades after exposure, approximately 20% of patients may show signs and symptoms of cirrhosis (ascites, edema, jaundice, easy bruising, variceal bleeding, encephalopathy), but until end-stage liver disease develops, most patients are asymptomatic. Coexisting extra-hepatic disorders – e.g. glomerulonephritis, mixed cryoglobulinemia, porphyria cutanea tarda, vasculitis, depression, and diabetes – are not uncommon in these patients.

Laboratory testing. Screening laboratory tests are used to find anti-HCV. HCV RNA testing should be ordered to document viremia.

Assessment assays. Enzyme immunoassays (EIAs) are used to quantify serum anti-HCV levels, and current third-generation EIAs have high anti-HCV specificity (99%). Antibodies against HCV proteins can be detected by a second-generation recombinant immunoblot assay[4] (RIBA); this increases the specificity of the EIA in low-risk populations, but is rarely necessary for diagnosis or management.

Serum HCV RNA can be quatified by the signal amplification branched DNA assay (bDNA), but is limited by relatively high upper limits of detection for HCV RNA, and lower sensitivity. More sensitive assays are preferred, including PCR-based and transcription-mediated amplification (TMA) techniques with a lower limit of detection of 50 IU/mL or less.[10,11]

Results and their interpretation. Both anti-HCV and HCV RNA are detected in most patients with chronic hepatitis C and later-phase acute hepatitis C. A positive anti-HCV and negative HCV RNA could indicate any of the following: chronic hepatitis C with very low-level viremia, a false-positive EIA, spontaneous or treatment-related HCV clearance, or a false-negative HCV RNA (if the blood is not processed immediately). A positive HCV RNA and negative anti-HCV result may indicate acute hepatitis C, immunosuppression, a false-positive HCV RNA, or a false-negative anti-HCV result. Acute infection can be verified by a positive HCV RNA result obtained 1 week after HCV exposure.[10]

Genotyping. As discussed previously, treatment response varies with HCV genotype.[11] Two genotyping tests are available for use in clinical settings: 1) Direct sequencing (Trugene HCV 5'NC, Visible Genetics, Toronto, Canada); and 2) Reverse hybridization of known

oligonucleotide probes (InnoLiPA HCV II,Innogenetics, Ghent, Belgium).

Liver biopsy. The diagnostic role of liver biopsy in chronic hepatitis C is controversial because of procedure-related risks and the availability of accurate noninvasive tests. Its primary role is to determine the severity of inflammation and the extent of fibrosis, which are used to decide whether treatment is needed.[10] A liver biopsy can also be used to find coexisting liver conditions that cannot be identified by serology, e.g. nonalcoholic fatty liver disease, medication-induced hepatitis, and granulomatous hepatitis.

TREATMENT

The decision to treat a patient with an HCV infection is based primarily on the severity of hepatic involvement, the presence of contraindications, and the patient's age, co-morbid conditions, and willingness to be treated. Genotype is also considered, because patients with genotype 2 or 3 have high response rates.

Treatment of Chronic Hepatitis C

The overall goal is a sustained virologic response (SVR), ie, the inability to detect serum HCV RNA with a sensitive assay 6 months following the end of treatment.

Standard treatment for chronic HCV infection is pegylated (covalently bonded to polyethlene glycol) Interferon and ribavirin. Interferon is usually given as IFN alfa-2a 180 μg/wk, regardless of body weight, or IFN alfa-2b 1.5 μg/kg weekly, and the dosage of ribavirin varies with weight and genotype, which also influences the duration of treatment.

Patients with Genotype 1

Genotype 1 is the most common genotype in the U.S., accounting for approximately 70% of infections. Treatment is not recommended for genotype 1 patients with mild lesions, except young adults before their childbearing years and persons in professions that put them at risk to transmit the virus (e.g., surgeons, nurses, dentists).

A 48-week course of pegylated IFN is recommended, along with high-dose ribavirin (1000-1200 mg/d based on weight; maximum 1600 mg/d).[11] HCV RNA should be evaluated at Week 12 and compared with baseline to identify patients who are not likely to achieve an SVR. If no change in HCV RNA is observed, treatment should be discontinued. If the HCV RNA level is still detectable at Week 12 but has decreased 102-fold from baseline, treatment should continue until Week 24. If HCV RNA is still detected at Week 24, treatment should be discontinued, because an SVR will not be achieved. In patients with undetectable virus at Week 12 or a 10^2-fold decrease in viral load at Week 12 and undetectable virus at Week 24, therapy should be continued until Week 48. Data are emerging, however, to suggest that patients with a 102-fold drop who do not achieve viral negativity at week 12 may improve the chance of an SVR with a 72-week regimen. On the other hand, patients who achieve a rapid viral response (defined as viral negative at 4 weeks) may only need 24 weeks of treatment.

These regimens give patients a 40% to 50% chance of achieving an SVR[11] and a >98% chance of long-term remission – which many hepatologists consider a cure.

Patients with Genotype 2 or 3

Most of the remaining patients have genotypes 2 or 3, which have high response rates and should be treated regardless of the severity of the liver disease. A 24-week regimen consists of pegylated IFN accompanied by low-dose ribavirin (800 mg/d, regardless of weight). HCV RNA levels are usually undetectable after Week 4; HCV RNA should be assessed 24 weeks after therapy is discontinued to determine whether an SVR has been achieved. With this regimen these patients have a 70% to 85% chance of achieving an SVR.

Patients with Genotypes 4, 5, or 6

These cases are uncommon, so limited data exist regarding the likelihood of an SVR. The current recommendation is for the same regimen as genotype 1, with assessments of virologic response at weeks 48 and 72.

Treatment of Acute Hepatitis C

When an acute infection is suspected, the physician must decide whether and when to treat the patient. The general recommendation is to wait 2 to 3 months to treat, because: 1) acute infections often resolve on their own (viral clearance can occur within 3 months of exposure); and 2) disease progression rates are low immediately after exposure. Once the decision to treat is made, the physician is faced with a dearth of firm guidelines for choosing the best treatment. In one small study, INF alfa-2b 5 MU daily for 4 weeks followed by

TABLE 3. GUIDELINES FOR HEPATITIS C VIRUS RNA TESTING.

Clinical situation	Test to use	Interpretation and comments
Acute infection suspected	Qualitative PCR or real-time PCR	Check HCV RNA and HCV antibody 4-6 wk after exposure Check HCV RNA at 8-12 wk; if positive, consider therapy Check HCV RNA and HCV antibody 4-6 mo after exposure
Chronic infection suspected† HCV antibody positive	Qualitative PCR or real-time PCR	HCV RNA positive: patient is chronically infected HCV RNA negative: patient is most likely not infected, but low-level or intermittent viremia possible. Repeat RNA testing recommended in 6-12 mo
HCV antibody negative but unexplained liver disease or immunocompromised	Qualitative PCR or real-time PCR	HCV RNA positive: patient is chronically infected, unless acute HCV infection is supported by clinical situation. HCV RNA negative: patient is most likely not infected, but low-level or intermittent viremia possible. Repeat RNA testing recommended in 6-12 mo
HCV antibody and RNA positive, eligible for treatment	Quantitative tests such as quantitative PCR, bDNA, or real-time PCR	>800 000 IU/mL is considered high, more difficult to treat Use same quantitative assay before treatment and measure 4- and 12-wk responses
Infant born to HCV positive mother; infant still antibody positive at 18 mos	Qualitative PCR or real-time PCR	HCV RNA positive: patient is chronically infected HCV RNA negative: patient is most likely not infected, but low-level or intermittent viremia possible. Repeat RNA testing recommended in 6-12 mo

Abbreviations: bDNA, branched-chain DNA; HCV, hepatitis C virus; PCR, polymerase chain reaclion.
†Most recent exposure to HCV more than 6 months prior.
(Scott JD, Gretch DR. Molecular diagnostics of hepatitis C virus infection: a systematic review. JAMA. 2007;297:724-732. Copyright © 2007, American Medical Association. All rights reserved.)

5 MU 3 times weekly for 20 weeks resulted in an SVR rate of 98%.[4] Pegylated INF alfa-2b 1.5 μg/kg weekly for 12 weeks resulted in SVR rates of 95%, 92%, and 76%, depending on whether INF therapy was initiated at Week 8, 12, or 20, respectively.[12] Guidelines for HCV RNA testing appear in Table 3.[13]

TREATMENT-RELATED ADVERSE EFFECTS

The adverse effects (AEs) of IFN and ribavirin are responsible for 10% to 20% of patients withdrawing from therapy and 20% to 30% of patients requiring a reduced dose. IFN is associated with bone marrow depression, neuropsychiatric effects, autoimmune disorders, and flu-like symptoms; ribavirin is associated mainly with hemolytic anemia and rash (Table 4).[14] Each AE is managed as it would be as a primary condition. Autoimmune disorders (especially thyroiditis) may continue after therapy has ended. Their development warrants immediate discontinuation of therapy. In patients with hemolytic anemia, ribavirin dosing often has to be reduced dose or stopped. These patients may respond to erythropoietin, but this drug is expensive and not universally reimbursed. Fertile men and women must use 2 methods of birth control during treatment, because ribavirin is teratogenic. Neuropsychiatric side effects (depression, anxiety, and agitation) are often the most difficult effects to manage and have been associated with relapse to alcohol and drug use.

FUTURE DEVELOPMENTS

HCV polymerase has emerged as a key target for drug development. Three types of inhibitors have been identified: nucleoside analogs (which prevent polymerase elongation), nonnucleoside analogs (which disrupt the initiation of polymerization),[15] and pyrophosphate mimics (which block the polymerase active site).[16] The in vitro efficacy of the nucleoside inhibitors (e.g. valopicitabine) and nonnucleoside inhibitors (e.g., benzothiazidines) appears to be influenced by genotype.[17] Although the nucleoside valopicitabine, NM283 (Idenix) has already demonstrated anti-HCV activity in phase 1 and phase 2 trials, further development of this drug has been halted because of gastro-intestinal toxicity. Additional trials are currently in development[17] using the nucleoside R1626 which showed significant antiviral activity in a phase IIa study.[18]

TABLE 4. ADVERSE EFFECTS OF HEPATITIS C THERAPIES INTERFERON.

Common (≥10%)

- Mild bone marrow suppression (anemia, leukopenia, thrombocytopenia)
- Depression
- Insomnia
- Fatigue and irritability
- Weight loss, anorexia
- Fever, myalgia, headaches and flu-like symptoms
- Alopecia
- Skin irritation at injection site
- Nausea, vomiting and diarrhea

Occasional (2%-9%)

- Retinopathy (usually not clinically significant)
- Exacerbation of autoimmune condition (e.g., autoimmune hepatitis, autoimmune thyroiditis, rheumatoid arthritis, psoriasis)
- Congestive heart failure and arrhythmias

Rare (≤1%)

- Severe bone marrow suppression
- Seizures
- Tinnitus and hearing loss
- Hyperglycemia
- Renal failure
- Pneumonitis

Ribavirin

Common (≥10%)

- Hemolytic anemia (dose dependent)
- Fatigue
- Rash and pruritis
- Nasal stuffiness
- Cough

Small interfering RNAs and antisense oligonucleotides are also being investigated for their efficacy against HCV. These may require delivery directly into the liver with molecular vehicles currently under investigation. These include lentiviral vectors, which allow their "passengers" to be integrated into the host genome, and vectors from nonhuman sources.[19]

Protease inhibitors (PIs) are the most promising new therapeutic agents. Since early clinical trials revealed that viral mutants emerge after short courses of PIs alone, current phase 2 and phase 3 trials use them with INF, plus or minus ribavirin. In the phase II trials (PROVE 1 and PROVE 2) presented at the 2007 meeting of the AASLD, telaprevir in combination with interferon and ribavirin achieved higher rates of rapid viral response and a lower risk of relapse (which suggests higher rates of SVR) even with shorter treatment lengths.[20,21]

Buceprevir is another oral protease inhibitor that has completed phase II trials and is heading into phase III trials. This drug is well tolerated and displays significant antiviral activity.[22] Results of the phase II trial were presented at Digestive Diseases Week in May 2008.

SUMMARY

Over the last 2 decades, significant progress has been made in the control of hepatitis C. Despite the lack of an anti-HCV vaccine, the incidence of this disease has decreased, though its prevalence remains high. Recent investigations into its molecular nature have already revealed potential targets for antiviral pharmaco-therapeutic strategies, and may someday eliminate hepatitis C as a primary cause of liver disease.

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