HCV UPDATE: TESTING AND TREATMENT

S O BY NOW you have read the HCV Update in the March 14, 2000 *CD Summary,* and are familiar with the epidemiology of hepatitis C. For those of you anxiously awaiting the promised issue discussing HCV testing and treatment, your ship has come in.

HCV TESTING
Screening tests

Enzyme immunoassays (EIAs) measure anti-HCV antibody and are highly sensitive, but do not distinguish between acute, chronic, or resolved infections[1]. Three versions of EIAs have been developed; later versions contain multiple HCV antigens from the core and nonstructural regions and have improved sensitivity (97%) and specificity (99%)[2]. The third generation tests can detect antibody as early as 7-8 weeks after exposure. Even with these great numbers, however, false-positive results are common in low-prevalence populations, often necessitating the use of supplementary testing.

Supplemental tests

Recombinant immunoblot assays (RIBAs) use the same (and, sometimes, additional) HCV antigens as the EIAs. RIBA results are reported as positive (two or more positive antigens), indeterminate (one positive antigen), or negative. Although useful in ruling out false positive EIA results, the RIBA is not as sensitive as the EIA and should not be used as a screening test. Persons with a positive EIA result but a negative RIBA result should be considered uninfected, absent other evidence of infection (e.g., abnormal ALTs in immunocompromised individuals or in persons with no other etiology of their liver disease). Indeterminate RIBA results may indicate recent seroconversion or a false-positive result, particularly in persons without identifiable risk factors. Because most patients with HCV infection are EIA-positive, confirmation by RIBA is generally not necessary when the serum ALT is elevated and risk factors for infection are present.

Qualitative tests for HCV RNA

Detection of HCV RNA in patient serum by highly sensitive assays has become increasingly important for confirming the diagnosis of HCV and assessing the response to antiviral therapy. The reverse transcription–polymerase chain reaction (RT–PCR) can detect HCV RNA in serum or plasma within 1-2 weeks after exposure to the virus and weeks before the onset of liver enzyme elevations or the appearance of anti-HCV antibodies[3]. Several RT-PCR assays for HCV infection are commonly used in clinical practice and have a lower limit of detection of 100-1,000 viral genome copies/ml. HCV RNA testing may be used for diagnosis in the early stages of acute HCV infection (before antibody production), in immunocompromised patients (whose antibody production may be impaired) and in patients with indeterminate RIBA results. It is also useful in the serologically positive patient with normal ALTs, where it can be used to distinguish patients who have resolved their infections (i.e., HCV-RNA negative) or who are viremic (HCV-RNA positive). However, false negative RT-PCR results can occur in HCV-infected persons with low levels of virus who are intermittently viremic.

Quantitative assays for measuring the level of HCV RNA are available from commercial laboratories and have been recently approved by the FDA. All are generally less sensitive than qualitative tests, and they use different standards, so results from the different kits cannot be directly compared. Testing for the level of HCV RNA is clinically useful for predicting likelihood of response to antiviral therapy, as well as for monitoring response to therapy.

TREATMENT OF HCV
Whom to Treat

The most important point to take away from this article is that not everyone with chronic HCV infection requires treatment. The NIH consensus guidelines [4] recommend treatment only for those patients with chronic HCV infection who are at greatest risk for progression to cirrhosis, as characterized by: a) persistently elevated ALT levels; b) detectable HCV RNA; and c) a liver biopsy indicating either portal or bridging fibrosis or at least moderate degrees of inflammation and necrosis. Most patients with HCV infection and elevated ALT levels undergo a liver biopsy before undergoing treatment, although a recent decision and cost-effective analysis showed that routine liver biopsy before treatment increases the cost of managing patients without improving outcomes.

Treatment Options

First, a little jargon from the world of clinical trials of HCV therapy. The response to treatment is described as either an end-of-treatment response (ETR) or a long-term post-treatment sustained response (SR). A SR is a biochemical or virologic response (defined as a negative qualitative HCV RNA by PCR) that persists for 6 months or more after discontinuation of treatment. Virologic response is the most reliable indicator of treatment efficacy.

Monotherapy with interferon—there are four on the market, and the NIH consensus guidelines say they are equally efficacious—for 6 months achieves a sustained biochemical and virological response with histological improvement in 7-20% of patients[5]. Predictors of an improved response to interferon (IFN) include a low serum quantitative HCV RNA level, HCV genotypes 2 or 3,* and the absence of advanced fibrosis or cirrhosis on biopsy. The current recommendation is to measure the ALT and qualitative HCV RNA levels after 12 weeks of therapy. Those patients who are nonresponders are unlikely to clear the virus with continued therapy, and should discontinue. For those patients who demonstrate a response, it is currently recommended that the total duration of therapy be 12-24 months, to achieve a sustained response rate of 20% to 30%. More than 90% of patients with a SR for 6 months after finishing treatment will maintain that response over the long term and demonstrate significant histologic improvement.

Although ribavirin alone has not been shown to be effective in treating HCV infection, the use of ribavirin in combination with IFN for 6 months doubles the rate of sustained

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*HCV is a heterogeneous family of viruses, with at least 6 different genotypes and numerous subtypes. Distribution of genotypes varies by geography, with types 1a and 1b being the most prevalent in the US, followed by types 2 and 3

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response in previously untreated patients with chronic HCV infection [6]. The main predictor of response to combined therapy is viral genotype: the SR rate to 6 months of combination therapy among patients with viral genotype 1 range from 16% to 26%, while the response among patients with viral genotypes 2 and 3 is 50% to 69%. In studies comparing duration of treatment, extending therapy from 6 months to 12 months improved the SR rate in patients with viral genotype 1 from 16%-18% to 28%-31%, but had little effect on patients with genotypes 2 and 3. Unlike IFN monotherapy, pretreatment HCV RNA level and the presence of fibrosis or cirrhosis have less influence on outcome of therapy with combined treatment. Combination therapy also appears to be effective in patients who initially responded to IFN but relapsed (pooled results from 4 controlled studies found that 80% of those who received combination therapy had a SR compared to 47% in those re-treated with IFN alone). However, studies of combination therapy in interferon non-responders have been less promising.

Several new treatments for HCV are on the horizon. Studies using pegylated interferon (PEG-IFN), a slow-release, long-acting formulation administered subcutaneously once a week, have demonstrated histologic improvement [7]. Controlled studies of triple therapy with IFN, ribavirin and oral amantadine in IFN non-responders have also been promising [8]. Novel antiviral agents in development include inhibitors of HCV replicative enzymes, such as protease, helicase and polymerase, as well as several genetic approaches, such as ribozymes and antisense oligonucleotides.

Adverse effects

Patients on IFN usually experience influenza-like symptoms during the first several weeks of treatment; later in therapy, fatigue and neuropsychiatric side effects, such as

TEST	OBJECT OF TEST	CLINICAL RELEVANCE
EIA, ELISA	Detects antibody to HCV	High-risk patients: high sensitivity and specificy. Low-risk patients: false positives likely
RIBA	Measures antibody to HCV antigens	Confirms or excludes EIA results Less sensitive than EIA
PCR Qualitative	Determines presence of HCV RNA	Indicates active infection with HCV Very sensitive. Useful in immunosuppressed patients
Quantitative	Measures RNA level	Useful in predicting likelihood of response to antiviral therapy. Used to assess response to viral therapy

confusion, inability to concentrate, impairment of memory and irritability, are more common. IFN may precipitate or exacerbate symptoms of depression. Patients who have a history of depression should be closely followed during IFN therapy or may elect not to be treated. Less frequent late side effects include reversible alopecia, rash, and hypo- or hyperthyroidism. The major side effect of ribavirin is a dose-dependent hemolytic-anemia, which is reversible and usually stabilizes after 5-6 weeks of treatment. If severe anemia develops, treatment must be discontinued. Ribavirin is also a known teratogen, and both male and female patients need to be counseled to use reliable contraception both during treatment and for 6 months afterward. Other common, albeit mild symptoms of ribavirin use include respiratory tract symptoms (cough and dyspnea), skin disorders (rash, pruritus, and dry skin), neuropsychiatric symptoms (depression, insomnia, anxiety and irritability) and gastrointestinal problems (anorexia and dyspepsia).

For more information, patients can be referred to CDC's Hepatitis website, *http://www.cdc.gov/hepatitis,* and toll-free information line, 888/4HEPCDC (888/443-7232). Health departments, hospitals, doctors' offices, community-based organizations and other health-related service organizations are

encouraged to contact CDC's Hepatitis Branch directly (404/371-5910) with any questions or to request materials. Health care professionals are also encouraged to log on to the hepatitis homepage above and click on "What's New" to get to "Hepatitis C: What Clinicians and Other Health Care Professionals Need to Know." The web-based course offers CME, CNE, and CEU credits.

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