Chronic Hepatitis C: Common Questions, Practical Answers

Barak Gaster, MD, and Anne Larson, MD

Background: **The hepatitis C virus (HCV) is the most common cause of chronic liver disease in the United States. Dramatic advances have been made recently in the treatment of this potentially life-threatening infection by using a combination interferon and ribavirin therapy.**

Methods: **The most common questions regarding chronic HCV infections that occur in the course of clinical practice of primary care physicians were elicited through e-mail and telephone interviews. To answer these questions, computerized literature searches of the MEDLINE database were performed and expert opinion was sought.**

Results: **For many patients with HCV who are treated with combination therapy, there is now a greater than 30% chance of achieving long-term normalization of transaminase levels and the loss of detectable viral load. Treatment is expensive, however, and can be difficult to tolerate. The effect of treatment on the risk of progression to liver failure and hepatocellular carcinoma is promising but has not yet been determined.**

Conclusions: **Primary care physicians play an important role in the diagnosis and initial workup of patients with HCV. By understanding the correct use of HCV diagnostic testing and the risks and benefits of antiviral therapy, providers will be better equipped to screen and counsel their patients infected with HCV. (J Am Board Fam Pract 2000;13:359–63.)**

Since the discovery of hepatitis C in 1989, a growing body of evidence has established the hepatitis virus (HCV) as the most common cause of chronic liver disease in the United States and one of the most common chronic infections of any kind encountered in the primary care setting.[1,2] More than 2.7 million persons in the United States (or 1.3% of the population) are chronically infected with HCV,[3] and many of these patients will go on to develop end-stage liver disease.[4]

Rapid advances in the diagnosis and treatment of this often asymptomatic infection raise numerous questions for primary care physicians, who are responsible for diagnosing and counseling most patients with chronic HCV. This article will provide practical answers to some of these important questions.

Submitted, revised 25 October 1999.

From the Department of Medicine (BG, AL), University of Washington, Seattle. Address reprint requests to Barak Gaster, MD, Department of Medicine, Box 354760, 4245 Roosevelt Way NE, Seattle, WA 98105-6920.

Methods

In March 1999 all providers in a primary care clinic at a major medical center were surveyed by telephone and e-mail. Nine of the 24 providers who were surveyed responded. The 17 most commonly asked questions that respondents listed regarding the diagnosis and management of chronic HCV infection were tabulated. Answers to these questions were then formulated based on literature searches of the MEDLINE database using the National Library of Medicine's PubMed search engine. Expert opinion was also sought.

Results

1. Who should receive routine screening for chronic HCV infection?

Anyone with an alanine aminotransferase (ALT) level that is elevated above normal or with a history of risk factors, such as injection drug use, blood transfusion before July 1992, treatment with clotting factor concentrate before 1987, or long-term hemodialysis, should be screened for chronic HCV infection by testing for the presence of antibody to HCV.[5]

Table 1. Contraindications to Combination Interferon-Ribavirin Therapy.

Decompensated liver disease
Pre-existing psychiatric condition or history of severe psychiatric disorder
Active alcohol or injection drug abuse
Autoimmune hepatitis or a history of autoimmune disease
Immunosuppression as a result of organ transplantation
Pre-existing thyroid abnormalities not controlled by medication
Nursing of infants

2. Should a viral load be measured in all patients who are positive for anti-HVC antibody?

Most patients should have an HCV RNA level, or viral load, measured to assess whether their HCV infection is active and to help predict their odds of responding to antiviral therapy.[6,7] Viral load testing can reasonably be deferred in some patients who are positive for HCV antibody, such as patients who have an elevated ALT level indicative of active infection but who also have clear contraindications to antiviral therapy (Tables 1 and 2).[8]

3. How should an undetectable viral level be interpreted in a patient?

An undetectable viral level could be caused by (1) a very low-level of viremia, (2) a resolved HCV infection, or (3) a false-positive HCV serologic finding. A viral load measurement should be repeated in 3 to 4 months, because some patients with active infection have viral loads that are at times undetectable.[9] If the repeated viral load measurement remains at undetectable levels, the patient either has a resolved infection or a false-positive antibody test.[10] An HCV recombinant immunoblot assay (RIBA) can help differentiate between the two, but usually a reliable clinical assessment can be made based on the medical history. If the patient has risk factors for a past HCV infection, such as injection drug use, he or she is likely to have a resolved infection. If the patient has a history of an autoimmune disease, such as lupus, the initial serologic finding was more likely due to a false-positive test result.

Table 2. Conditions in Which Combination Interferon-Ribavirin Therapy Should be Given with Caution.

Debilitating medical conditions, particularly a history of pulmonary disease, coagulation disorders, diabetes mellitus prone to ketoacidosis, severe myelosuppression, history of cardiovascular disease
Pregnancy (potential abortifacient effects)
Age less than 18 years

4. Should patients with positive viral loads have repeated HCV-RNA testing?

In patients who are not taking antiviral medications, repeated testing is generally not helpful. Nearly all such patients remain viremic, and there is no indication that a change in their viral titer is predictive of disease progression.[6,11] The difference between the use of viral load testing in HCV infection and its use in human immunodeficiency virus (HIV) infection is considerable; in HIV infection the viral load test has been shown to be predictive of a patient's future course.[6] In HCV-positive patients who are undergoing treatment with antiviral therapy, repeated viral load testing is useful for monitoring response to therapy.

5. How should patients with chronic, active HCV infection be monitored?

Patients with chronic active HCV infection should be monitored twice yearly with laboratory studies, including measurements of serum ALT, bilirubin, albumin, and prothrombin time. Patients should be routinely questioned about their alcohol use, because it has been shown that consuming more than one drink per day is associated with a much higher risk of progression to liver failure.[12]

6. What are cost-effective indications for referral to a specialist?

Most patients who have a positive viral load and abnormal ALT levels should probably be evaluated by a specialist. Patients who might not benefit from referral are those with absolute contraindications to antiviral therapy (Tables 1 and 2).

7. What is the best approach to patients who are positive for anti-HCV antibody but who have a normal ALT?

The ALT level should be measured again after 3 to 4 months, because intermittent normal values are common.[1,2] Even with persistently normal ALT levels, these patients might still have mild signs of chronic inflammation on liver biopsy, but they are currently not considered candidates for antiviral therapy. Although some data indicate that their hepatic inflammation can be reduced with antiviral

therapy, long-term data are not yet available.[13] Patients such as these should be either monitored once or twice a year with a serum ALT measurement or referred to a research center for enrollment in a clinical trial.

8. What testing should patients receive before referral to a specialist?

A useful, cost-effective workup before referral should include a viral load measurement, HCV genotyping, and hepatitis B (HBV) serologic studies. Most specialists would recommend deferring a workup for other causes of liver disease, such as hemochromatosis, autoimmune hepatitis, or Wilson disease, because tests for these diseases can be ordered later depending on a patient's individual risk.

9. What is the importance of HCV genotype?

HCV genotype is very useful in predicting whether patients will respond to antiviral therapy. Patients infected with genotype 1 are much less likely to respond to antiviral therapy than are patients infected with genotypes 2 through 6. Approximately 70% of patients in the United States and Western Europe are infected with genotype 1.[2]

10. What is the efficacy of antiviral treatment for HCV?

Recent data from studies with the newer combination therapy, interferon alfa-2b and ribavirin, have been quite encouraging. Long-term sustained response rates, defined as continued undetectable serum HCV RNA levels 24 weeks after treatment, have been in the 30% range for patients infected with genotype 1 and in the 60% to 70% range for patients infected with genotypes 2 through 6.[14,15] The addition of ribavirin thus represents a marked improvement when compared with the 10% to 20% response rates that have been observed with interferon alone.[8,16]

The long-term benefits of antiviral therapy are less certain. Interferon has been shown to reduce fibrosis on liver biopsy in long-term responders and to improve health-related quality of life.[17,18] Observational studies also suggest that interferon has a beneficial effect on survival, liver failure, and hepatocellular carcinoma in patients who respond, but no randomized trial data are available for these end points.[19–21]

11. What are predictors of a sustained response, other than genotype?

Other primary predictors of a sustained response to antiviral therapy are a viral load of less than 2,000,000 copies/mL, a shorter duration of infection, female sex, and low body weight.[15] In addition, patients with only mild signs of inflammation and fibrosis on liver biopsy are more likely to achieve a sustained response.[22] None of these factors can predict with certainty whether a given patient will respond to therapy, however, so therapy should be considered even if none of these factors is present.[8]

12. What is the usual duration of antiviral therapy?

Combination therapy with interferon and ribavirin should be continued for 1 year in patients with genotype 1, and for 6 months in patients with other genotypes. The wholesale cost of combination therapy is more than $8000 per 6-month period.[23]

13. What are the most common side effects of antiviral therapy?

More than 50% of patients treated with interferon experience flu-like symptoms, such as fever, headache, myalgias, nausea, and diarrhea.[23] In addition, patients might develop weight loss, low white blood cell count, abdominal pain, alopecia, hyperthyroidism or hypothyroidism, irritability, anxiety, insomnia, depression, and impaired concentration. For a small group of patients, concentration difficulties can be so severe that they disable patients from working for the duration of treatment.[24] Approximately 10% of patients who take ribavirin develop hemolytic anemia. Ribavirin can also cause a chronic dry cough.

14. How effective is liver transplantation for patients with cirrhosis caused by HCV?

Patients with HCV tend to do very well after liver transplantation.[25] They typically have a much better prognosis after transplant than patients with HBV-related cirrhosis.[26] Once patients with HCV develop signs of liver decompensation, such as low albumin levels, low platelet count, prolonged prothrombin time, encephalopathy, ascites, or gastrointestinal bleeding, they should promptly be referred to a transplant center. Most centers require that patients be free of alcohol or illicit drug use for 6 months before being placed on a waiting list for a transplant.[27] Although 95% of HCV-infected pa-

tients have evidence of recurrent viremia after a liver transplant, most develop only mild to moderate hepatitis and so have a low incidence of graft failure.[28,29]

15. What precautions should HCV-infected patients take to avoid spreading the infection to others?

HCV-infected patients should be strongly encouraged to stop using illicit drugs or not reuse or share their injection paraphernalia if they are unable to quit.[30] The risk of sexual transmission of HCV appears to be minimal.[31–33] Although the available data suggest that transmission can occur, the risk appears to be very small and is much less than it is for other common blood-borne infections, such as hepatitis B and HIV. The rate of transmission among discordant couples who are not using condoms is so low that HCV-positive patients who are in a mutually monogamous relationship can be reassured that they do not need to change their sexual practices, although their partners should be encouraged to be tested for HCV.[34] Routine household exposures do not pose a serious risk of transmission of HCV.[35]

16. What is the current risk of contracting chronic HCV infection from a blood transfusion?

Before 1990 the risk of acquiring HCV from a blood transfusion was substantial (approximately 10%).[36] Blood donor screening for anti-HCV with first-generation enzyme immunoassays began in 1990, succeeded by second- and third-generation tests in 1992 and 1996, respectively.[37,38] Now that anti-HCV antibody can be detected easily, the current risk of acquiring chronic HCV infection from a blood transfusion is estimated at 0.01% to 0.001% per unit transfused (approximately 1 in 103,000 units).[36]

17. What are promising future treatment options for chronic HCV infection?

Because the current therapeutic strategies for treating HCV infection are inadequate, the search for novel treatments is an area of intensive research. Investigators have designated several promising targets for drug development, including inhibition of the protease,[39] helicase,[40] or RNA-polymerase[41] enzymes and the insertion of antisense oligonucleotides to prevent RNA replication.[42] Unfortunately, no drugs using these strategies have moved beyond the laboratory to be tested in human trials. The possibility that more effective, better tolerated drugs will eventually be found, however, leads some patients to forgo interferon-ribavirin therapy, especially as the long-term prognosis of HCV infection is still uncertain.

Conclusion

Many recent advances have been made in the monitoring and care of patients with chronic HCV infection. Primary care physicians play an important role in the diagnosis of HCV infection and in the initial workup of patients with this common and sometimes life-threatening condition. By understanding the correct use of HCV diagnostic testing and the risks and benefits of antiviral therapy, primary care physicians will be better equipped to screen and counsel their many patients who could be infected with HCV and will be able to make more appropriate referrals to liver specialists.

References

1. Alter MJ, Margolis HS, Krawczynski K, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. N Engl J Med 1992;327:1899–905.
2. Heintges T, Wands JR. Hepatitis C virus: epidemiology and transmission. Hepatology 1997;26:521–6.
3. 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.
4. Seeff LB. Natural history of viral hepatitis, type C. Semin Gastrointest Dis 1995;6:20–7.
5. Lapane KL, Jakiche AF, Sugano D, Weng CS, Carey WD. Hepatitis C infection risk analysis: who should be screened? Comparison of multiple screening strategies based on the National Hepatitis Surveillance Program. Am J Gastroenterol 1998;93:591–6.
6. Berger A, Braner J, Doerr HW, Weber B. Quantification of viral load: clinical relevance for human immunodeficiency virus, hepatitis B virus and hepatitis C virus infection. Intervirology 1998;41:24–34.
7. Lau JY, Davis GL, Kniffen J, et al. Significance of serum hepatitis C virus RNA levels in chronic hepatitis C. Lancet 1993;341:1501–4.
8. National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. Hepatology 1997;26(3 Suppl 1):2S–10S.
9. Hashimoto E, Noguchi S, Taniai M, Hayashi N. Characteristics of patients sero-positive for hepatitis C virus (HCV) antibodies but negative for HCV-RNA by polymerase chain reaction. J Hepatol 1998; 29:856–7.

10. Schroter M, Feucht HH, Schafer P, Zollner B, Polywka S, Laufs R. Definition of false-positive reactions in screening for hepatitis C virus antibodies. J Clin Microbiol 1999;37:233–4.
11. Puoti C, Stati T, Magrini A. Serum HCV RNA titer does not predict the severity of liver damage in HCV carriers with normal aminotransferase levels. Liver 1999;19:104–9.
12. Schiff ER. Hepatitis C and alcohol. Hepatology 1997;26(3 Suppl 1):39S–42S.
13. Van Thiel DH, Colantoni A, De Maria N. Treatment of HCV positive individuals with normal serum ALT levels. Hepatogastroenterology 1998;45: 321–4.
14. Reichard O, Norkrans G, Fryden A, Braconier JH, Sonnerborg A, Weiland O. Randomised, double-blind, placebo-controlled trial of interferon alpha-2b with and without ribavirin for chronic hepatitis C. The Swedish Study Group. Lancet 1998;351:83–7.
15. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 1998;339:1485–92.
16. Poynard T, Leroy V, Cohard M, et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 1996;24:778–89.
17. Marcellin P, Boyer N, Degott C, et al. Long-term histologic and viral changes in patients with chronic hepatitis C who responded to alpha interferon. Liver 1994;14:302–7.
18. Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. The Consensus Interferon Study Group. Hepatology 1999;29: 264–70.
19. Lau DTY, Kleiner DE, Ghany MG, Park Y, Schmid P, Hoofnagle JH. 10-Year follow-up after interferon-alpha therapy for chronic hepatitis C. Hepatology 1998;28:1121–7.
20. 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.
21. Liang TJ. Combination therapy for hepatitis C infection. N Engl J Med 1998;339:1549–50.
22. Kaserer K, Fiedler R, Steindl P, Muller CH, Wrba F, Ferenci P. Liver biopsy is a useful predictor of response to interferon therapy in chronic hepatitis C. Histopathology 1998;32:454–61.
23. Interferon plus ribavirin for chronic hepatitis C. Med Lett Drugs Ther 1999;41:53–4.
24. Yates WR, Gleason O. Hepatitis C and depression. Depress Anxiety 1998;7:188–93.
25. Berenguer M, Wright TL. Hepatitis C and liver transplantation. Gut 1999;45:159–63.
26. Poterucha JJ, Wiesner RH. Liver transplantation and hepatitis B. Ann Intern Med 1997;126:805–7.
27. Krom RA. Liver transplantation and alcohol: who should get transplants? Hepatology 1994;20(1 Pt 2): 28S–32S.
28. Charlton M, Seaberg E, Wiesner R, et al. Predictors of patient and graft survival following liver transplantation for hepatitis C. Hepatology 1998;28:823–30.
29. Everhart JE, Wei Y, Eng H, et al. Recurrent and new hepatitis C virus infection after liver transplantation. Hepatology 1999;29:1220–6.
30. Wodak A, Crofts N. Once more unto the breach: controlling hepatitis C in injecting drug users. Addiction 1996;91:181–4.
31. Dienstag JL. Sexual and perinatal transmission of hepatitis C. Hepatology 1997;26(3 Suppl 1):66S–70S.
32. Rooney G, Gilson RJ. Sexual transmission of hepatitis C virus infection. Sex Transm Infect 1998;74: 399–404.
33. Bresters D, Mauser-Bunschoten EP, Reesink HW, et al. Sexual transmission of hepatitis C virus. Lancet 1993;342:210–1.
34. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Morb Mortal Wkly Rep 1998;47:1–39.
35. Diago M, Zapater R, Tuset C, et al. Intrafamily transmission of hepatitis C virus: sexual and non-sexual contacts. J Hepatol 1996;25:125–8.
36. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. N Engl J Med 1996;334:1685–90.
37. Alter HJ, Conry-Cantilena C, Melpolder J, et al. Hepatitis C in asymptomatic blood donors. Hepatology 1997;26(3 Suppl 1):29S–33S.
38. Huang YY, Yang SS, Wu CH, et al. Impact of screening blood donors for hepatitis C antibody on posttransfusion hepatitis: a prospective study with a second-generation anti-hepatitis C virus assay. Transfusion 1994;34:661–5.
39. 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.
40. Yao N, Hesson T, Cable M, et al. Structure of the hepatitis C virus RNA helicase domain. Nat Struct Biol 1997;4:463–7.
41. Behrens SE, Tomei L, De Francesco R. Identification and properties of the RNA-dependent RNA polymerase of hepatitis C virus. EMBO J 1996;15: 12–22.
42. Davis GL, Nelson DR, Reyes GR. Future options for the management of hepatitis C. Semin Liver Dis 1999;19(Suppl 1):103–12.