

CLINICAL DECISIONS

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Management of Incidental Hepatitis C Virus Infection

This interactive feature addresses the diagnosis or management of a clinical case. A case vignette is followed by specific clinical options, none of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. In the online version of this feature, available at NEJM.org, readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A 25-year-old black woman is referred to your clinic for management of an incidental positive result on a hepatitis C virus (HCV) antibody test. She had decided to donate blood because her mother had recently become ill and required a transfusion. Three weeks after her donation, she received a telephone call and was told that her donated blood could not be used because her HCV antibody test was positive. She was encouraged to see her primary care physician to determine whether anything further should be done.

The patient is otherwise healthy, with no medical illnesses. She does not recall ever having had hepatitis. Her only medication is oral contraceptive pills. She has no known allergies to medication. She works as an investment banker and typically runs 2 to 3 miles a day. She reports never using intravenous drugs and reports four lifetime sexual partners. She reports being a social drinker. She received the hepatitis B vaccine series in college before traveling abroad. On physical examination, she appears to be fit, with no hepatosplenomegaly and no stigmata of liver disease. Laboratory studies are requested, and she is to return to your office in 1 month's time to determine how to proceed.

The findings on the laboratory tests are as follows: alanine aminotransferase, 31 U per liter (normal range, 7 to 52); aspartate aminotransferase, 30 U per liter (normal range, 9 to 30); total bilirubin, 0.7 mg per deciliter (12.0 μ mol per liter) (normal range, 0.2 to 1.2 [3.4 to 20.5]); alkaline phosphatase, 96 U per liter (normal range, 36 to 118); albumin, 4.2 g per deciliter (normal range, 3.7 to 5.4), prothrombin time, 11.4 sec (normal range, 12.2 to 14.8); white-cell

count, 2600 per cubic milliliter (normal range, 4000 to 10,000); hemoglobin, 11.1 g per deciliter (normal range, 11.5 to 16.4); and platelet count, 175,000 per cubic milliliter (normal range, 150,000 to 450,000). The patient is found to have hepatitis B immunity, with a positive hepatitis B surface antibody, and to be seronegative for human immunodeficiency virus (HIV) and hepatitis A virus. The HCV viral load is 2.3 million IU per milliliter and is genotype 1.

When the patient returns to discuss follow-up, you administer the hepatitis A vaccine and counsel her to minimize exposure to potential hepatotoxic factors such as alcohol and excessive use of acetaminophen.

In addition, which one of the following treatment options for HCV infection, any of which could be considered correct, would you find most appropriate for this patient? Base your choice on the published literature, your own experience, recent guidelines, and other sources of information, as appropriate.

1. Expectant management with periodic assessment of liver function.
2. Liver biopsy, with treatment based on the findings.
3. HCV therapy with peginterferon and ribavirin.

To aid in your decision making, each of these approaches to treatment is defended by an expert in the management of hepatitis C infection in the following short essays. Given your knowledge of the patient's condition and the points made by the experts, which treatment approach would you choose? Make your choice at NEJM.org.



Choose an option and comment on your choice at NEJM.org

TREATMENT OPTION 1

Expectant Management with Periodic Assessment of Liver Function

Nezam H. Afdhal, M.D.

There are three clear reasons why an observational approach without either a liver biopsy or drug therapy is appropriate for this 25-year-old, healthy black woman with HCV genotype 1 infection. First, in the management of HCV infection, a liver biopsy is performed for staging of the disease and to determine whether advanced fibrosis or cirrhosis is present. The major risk factors for advanced fibrosis are obesity and diabetes, which are risk factors for steatohepatitis, the use of more than 10 g of alcohol daily, and coinfection with HIV or hepatitis B.¹ Our patient has none of these risk factors and leads a healthy and active lifestyle. All the biochemical and radiologic tests were normal, but even if the alanine aminotransferase and aspartate aminotransferase levels are within the normal range, up to 25% of patients can still have clinically significant fibrosis and inflammation.² If the patient is eager to know the stage of her liver disease, there are emerging alternatives to liver biopsy, involving noninvasive tests for fibrosis.³

The second reason why observation is preferred is this patient's expected response to the standard therapy of peginterferon alfa and ribavirin. The goal of treatment for HCV infection is to achieve a sustained virologic response, defined as a negative polymerase-chain-reaction assay for HCV RNA 6 months after treatment is stopped. The rate of sustained virologic response quoted for patients infected with HCV genotype 1 is between 42 and 51% and requires 48 weeks of treatment with peginterferon alfa and ribavirin.⁴ The major predictors of a sustained virologic response are HCV genotype, race or ethnic group, viral load, and degree of liver fibrosis. In the recent Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (VIRAHEP-C) study⁵ of patients infected with HCV genotype 1 (ClinicalTrials.gov number, NCT00038974), sponsored by the National Institutes of Health, black race was associated with a sustained virologic response of 28%, as compared with 52% among whites. After black race, the second most important predictor was a high viral

load, as seen in our patient. The reason blacks respond less well than whites to drug therapy is probably multifactorial and includes a host-specific, slow viral kinetic response to peginterferon alfa. Blacks have neither an effective early reduction in viral load nor a second-phase response (rate of decline in the viral load with increasing time of treatment) to peginterferon that is adequate to produce viral clearance. The sustained virologic response is optimal when compliance with the medication regimen is 80% and there is no reduction in dose because of side effects. Side effects of peginterferon alfa and ribavirin are variable, but our patient would be at risk for both neutropenia and hemolytic anemia. Thus, drug therapy could realistically result in a 25 to 30% chance of a sustained virologic response in our patient.

The third reason why I would suggest observation of the patient is the recent data on new treatments with protease inhibitors for HCV genotype 1 infection. Bocepravir and telaprevir are inhibitors of nonstructural 3/4A (NS3/4A) HCV protease. In patients in the United States who had HCV genotype 1 infection and had not received treatment previously, therapy with bocepravir and telaprevir, in combination with peginterferon alfa and ribavirin, resulted in a sustained virologic response of 74% and 61%, respectively.^{6,7} Since protease inhibitors do not require a host immune response, we could expect that race would no longer be a major determinant of sustained virologic response.

Expectant observation would involve the evaluation of alanine aminotransferase levels every 6 months and a physical examination and discussion of risk factors with the patient every year. A persistently elevated alanine aminotransferase level or a change in the status of risk factors would be an indication for a liver biopsy to evaluate further the potential need for therapy.

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From the Division of Gastroenterology–Hepatology, Beth Israel Deaconess Medical Center, Boston.

TREATMENT OPTION 2

Liver Biopsy, with Treatment Based on the Findings

Anna S.F. Lok, M.D.

The goal of treating HCV infection is to prevent the progression of liver disease. Accordingly, the success of treatment is largely determined by the achievement of a sustained virologic response, defined as undetectable HCV RNA level in the blood at the end of the treatment period and at 6 months after treatment ends.

Current treatment for HCV infection involves the use of peginterferon alfa and ribavirin combined, which results in overall rates of sustained virologic response of 50 to 60%.⁸ Rates of sustained virologic response are lower, 40 to 50%, in patients infected with HCV genotype 1. Blacks have lower rates of response than other groups, even after correction for genotype. In the VIRAHEP-C study, 196 blacks and 205 whites infected with HCV genotype 1 received identical treatment, and the rates of sustained virologic response were 28% and 52%, respectively.⁵ Given the likelihood of achieving a sustained virologic response (<30%), the need for a long duration of treatment (48 weeks), and the frequent adverse events associated with the use of peginterferon alfa and ribavirin, treatment should not be recommended for our patient unless she has clinically significant liver disease.

The patient has no symptoms or signs of liver disease, and her blood tests revealed a normal liver panel and platelet count. These results indicate that she does not have advanced liver disease, but blood tests (particularly if performed on a single occasion) are not reliable in predicting the activity or stage of liver disease. In one study of 486 patients infected with HCV who had at least three normal alanine aminotransferase values during an 18-month period, 25% of patients had moderate-to-severe inflammation and 30% had significant fibrosis on liver biopsy.⁹ Therefore, clinically significant liver disease can be present in patients with no symptoms and with normal alanine aminotransferase levels. A variety of serum markers and imaging techniques, including elastography, have been evaluated to assess liver fibrosis. These noninvasive tests are more reliable in identifying patients with cirrhosis than in differentiating patients with moderate and those with mild fibrosis.¹⁰

Therefore, a liver biopsy is valuable in guiding treatment decisions. If liver biopsy in our patient shows clinically significant fibrosis (that with a Metavir score of 2 or more, out of 4, or an Ishak score of 3 or more, out of 6, with higher scores indicating more fibrosis), treatment should be initiated; otherwise, treatment can be deferred.

It can be argued that, given the patient's young age, treatment should be initiated regardless of her current liver disease, to prevent further progression. However, not all patients with HCV infection will have progression to cirrhosis. Our patient has several factors in her favor. She is a woman, was most likely infected at a young age, exercises vigorously (and thus is probably not obese, with no insulin resistance and no hepatic steatosis), and drinks only socially (which is unlikely to hasten disease progression). Furthermore, many specifically targeted antiviral therapies, notably HCV protease and polymerase inhibitors, are currently in phase 2–3 clinical trials. Available data suggest that the use of these drugs in combination with peginterferon and ribavirin is associated with higher rates of sustained virologic response among not only whites but possibly also blacks.¹¹ Therefore, it would be worth waiting for newer therapies that have an increased likelihood of benefit if, on biopsy, this patient has mild liver disease only.

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TREATMENT OPTION 3

HCV Therapy with Peginterferon and Ribavirin

Adrian M. Di Bisceglie, M.D.

The young woman described in the vignette has HCV infection, as evidenced by the anti-HCV antibodies and HCV RNA in the serum, and the infection is presumably chronic, since she is asymptomatic and has had no recent sources of exposure. It is not at all unusual for HCV infection to be discovered incidentally in asymptomatic persons, even when they have advanced chronic hepatitis or cirrhosis.

Antiviral therapy should be considered for this

patient because, if left unchecked, chronic HCV infection may result in chronic hepatitis, cirrhosis, and end-stage liver disease and hepatocellular carcinoma. Once chronic HCV infection is established, cirrhosis develops in approximately 20% of patients after a period of approximately 10 to 20 years.¹² A recent study showed that, among patients with cirrhosis, complications of liver disease or features of decompensation developed in about 30% over a period of approximately 4 years.¹³ Our patient's serum alanine and aspartate aminotransferase levels are within the normal range. This fact does not preclude the possibility of her already having, or having in the future, clinically significant liver disease,¹⁴ since liver-biopsy studies have shown that a substantial proportion of patients with HCV infection and normal serum aminotransferase levels will have advanced fibrosis or even cirrhosis. They may also have a significantly reduced health-related quality of life as compared with persons not infected with HCV.

The goal of antiviral therapy in this patient would be to eliminate the HCV infection. Such elimination is usually determined by the undetectability of HCV RNA in the serum at the end of therapy and 6 months after stopping treatment and is referred to as a sustained virologic response. The greatest therapeutic benefit of treatment has been seen in patients in whom a sustained virologic response is achieved. Antiviral treatment with the combination of peginterferon and ribavirin has been established as the standard of care for patients with chronic HCV infection.⁴ This combination is given for 48 weeks in patients infected with HCV genotype 1. Early testing for an improvement in the circulating HCV viral load is recommended, since treatment could be discontinued if the patient does not have an adequate response by week 12 of therapy, thus minimizing the risk of adverse effects. Both peginterferon and ribavirin are associated with side effects, such as influenza-like symptoms initially and fatigue and depression later; however, these side effects are generally tolerable in most patients and should not be considered a barrier to treatment.

Among patients with a sustained virologic response, studies involving long-term follow-up have shown a reduced rate of clinically important outcomes. For example, in two recent studies of patients with HCV infection and cirrhosis who were undergoing antiviral treatment with peginterferon, with or without ribavirin, those with a sustained

virologic response had a significantly lower rate of clinical outcomes, including liver-related death, ascites, and hepatic encephalopathy, than those without such a response. In one of the studies, approximately 20% of patients were shown to have biopsy-confirmed regression of cirrhosis — with most of the 20% having a sustained virologic response; clinical outcomes were very rare in this subgroup.¹⁵ In the other study, clinical events occurred in only 2.8% of patients who had a sustained virologic response, as compared with 24.6% of those without a sustained virologic response.¹⁶ Given the potentially severe health consequences of chronic HCV infection, treatment of our patient to induce a sustained virologic response should be strongly considered at this time.

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