Chronic Hepatitis C Infection
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A 45-year-old man undergoing a routine examination for life insurance is noted to have an aspartate aminotransferase level of 80 U per milliliter (normal range, 9 to 40) and an alanine aminotransferase level of 110 U per milliliter (normal range, 7 to 52). He reports a remote history of intravenous drug use. Tests for hepatitis C antibody and hepatitis B surface antibody are positive, and tests for hepatitis A and human immunodeficiency virus (HIV) antibodies are negative. Genotyping of the hepatitis C virus (HCV) reveals genotype 1b; the viral load is 2,460,000 IU per milliliter. The complete blood count is normal; the platelet count is 220×10^9 per liter. An abdominal ultrasonogram is normal. How should this patient’s case be managed?

Infection with HCV affects an estimated 180 million people globally. It is a leading cause of chronic hepatitis, cirrhosis, and liver cancer and a primary indication for liver transplantation in the Western world.1 There are at least six major HCV genotypes whose prevalence varies geographically. Genotype 1 accounts for the majority of infections in North America, South America, and Europe.2 The predominant risk factor for HCV acquisition is injection-drug use; among U.S. adults 20 to 59 years of age with any history of illicit injection-drug use, the prevalence of HCV infection is greater than 45%.3 Other risk factors include blood transfusion before 1992, high lifetime number of sexual partners, and iatrogenic transmission, including through dialysis4,5; in large series, 15 to 30% of patients report no risk factors.

The host immune response largely determines whether HCV is eradicated spontaneously or persists (as it does in the majority of patients).6 Although the natural history of HCV infection is highly variable, an estimated 15 to 30% of patients in whom chronic infection develops have progression to cirrhosis over the ensuing three decades.7 A number of factors, but not viral level or genotype, have been consistently associated with an increased risk of fibrosis (Fig. 1).8,9 Patients with HCV-related cirrhosis warrant surveillance for complications, including hepatocellular carcinoma, which develops in 1 to 3% of such patients per year.10 For patients with clinically significant hepatic fibrosis (Metavir stage ≥2 or Ishak stage ≥3) (Fig. 2), there is widespread agreement that antiviral therapy is indicated because of the high risk of cirrhosis.2,12 Prospective data indicate that the stage of fibrosis predicts clinical outcomes; the cumulative 6-year incidence of liver transplantation or liver-related death ranges from 4% for an Ishak fibrosis score of 2 to 28% for an Ishak score of 6.11 Because of the extended interval between infection and the emergence of complications, the HCV-related disease burden is projected to increase severalfold over the next 20 years.13

The hepatitis C virus, an enveloped flavivirus, was first cloned in 198914; the
positive-stranded viral RNA (with approximately 9600 nucleotides) encodes a polyprotein precursor of approximately 3000 amino acids (Fig. 3A). After binding to the cell surface, HCV particles enter the cell by receptor-mediated endocytosis. Cytosolic recognition of specific motifs in viral products (known as pathogen-associated molecular patterns) induces the production of interferons and proinflammatory cytokines, leading to the recruitment of a signaling complex to activate transcription factors (Fig. 3B). Subsequent expression of interferon-β, interferon regulatory factor 3 (IRF-3) target genes, and probably lambda (type III) interferons induce innate immune programs and drive the maturation of adaptive immunity for the control of infection.\(^\text{15,16}\)

The coordinated activities of CD4+ T cells and cytotoxic CD8+ T cells, primed in the context of HLA class II and I alleles, respectively, on antigen-presenting cells, are critically important for the control of acute HCV infection. Mutations in viral epitopes that are targeted by cytotoxic CD8+ T cells can allow the virus to escape immune-mediated clearance. Up-regulation of inhibitory receptors on exhausted (functionally impaired) T cells is another mechanism of T-cell dysfunction during chronic infection (Fig. 3C).\(^\text{17,18}\)
Head-to-head comparison to be equivalent in efficacy and to have similar safety profiles. Among patients with genotype 1 who are treated with peginterferon at the standard weight-based dose of ribavirin (1000 or 1200 mg per day) for 48 weeks, 40 to 50% have a sustained virologic response (defined as an undetectable HCV RNA level 24 weeks after the cessation of antiviral therapy). A shorter course of treatment and a lower ribavirin dose are associated with lower rates of sustained virologic response (and higher relapse rates) among genotype 1–infected patients. In contrast, patients with genotype 2 or 3, who account for approximately one quarter of HCV-infected patients in the United States, have rates of sustained virologic response in the range of 70 to 80% after taking peginterferon and ribavirin at a reduced dose (800 mg per day) for 24 weeks. A sustained virologic response is associated with permanent cure in the vast majority of patients.

Table 1 shows virus-specific and patient-specific factors that affect the likelihood of a sus-
Regardless of the infecting genotype, the likelihood of a sustained virologic response is lower among patients with a high pretreatment HCV RNA level (with a high level defined as >600,000 IU per milliliter in some studies and >800,000 IU per milliliter in others) and higher among patients with better adherence to antiviral therapy (receiving 80% of total interferon and ribavirin doses for 80% of the expected duration of therapy). Adherence can be problematic because of the plethora of side effects, including fevers, influenza-like symptoms, headache, cytopenias, fatigue, anorexia, depression, and anxiety.31

On-treatment viral kinetics have emerged as important predictors of the likelihood of response and are used to guide the duration of therapy.2 An early virologic response is defined as a decrease in the HCV RNA level of at least 2 log10 IU per milliliter or the complete absence of serum HCV RNA at week 12 of therapy.2 The lack of such a response in a patient has a very high negative predictive value for a sustained virologic response. Among patients with previously untreated genotype 1 infection, more than 97% of those who do not have an early virologic response to treatment will not have a sustained response. A rapid virologic response, defined as an undetectable HCV RNA level (<50 IU per milliliter) at week 4 of treatment, has been shown to predict a sustained virologic response, as well as to identify those patients for whom the duration of therapy can be shortened without compromising the virologic response. A recent meta-analysis of seven randomized trials has shown that genotype 1–infected patients with a low baseline HCV RNA level (<400,000 IU per milliliter) who have a rapid virologic response may discontinue therapy at 24 weeks rather than continue for the standard 48 weeks.32 A reduction of the treatment duration has the added benefits of decreased costs and side effects.2,32

Race is another important predictor of response to antiviral therapy. Black patients have significantly lower rates of sustained virologic response than white patients (28% vs. 52%).33 Although the reasons for this difference have been uncertain, recent data from genomewide association studies have indicated that single-nucleotide polymorphisms (SNPs) on chromosome 19 in or near the interleukin-28B gene (IL28B, encoding interferon lambda-3) are highly predictive of successful antiviral treatment.34 In an analysis that was adjusted for other predictors, the chance of cure was more than doubled with homozygosity for the C allele at the rs12979860 SNP, as compared with the TT genotype (78% for the CC genotype, 38% for the TC genotype, and 26% for the TT genotype). The C allele is much more frequent in white and Asian populations than in black populations. Moreover, in the Viral Resistance to Antiviral Therapy of Chronic Hepatitis C study (VIRAHEP-C; ClinicalTrials.gov number, NCT00038974), which involved patients infected with HCV genotype 1, pretreatment HCV–specific CD4+ T-cell responses were significantly
A rapid virologic response (RVR) is defined as an undetectable HCV RNA level (<25 IU per milliliter) at week 4 and week 12 of therapy. An early virologic response (EVR) is defined as a decrease in the HCV RNA level of at least 2 log₁₀ IU per milliliter or the complete absence of serum HCV RNA at week 12 of treatment.

The ADVANCE (A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with Telaprevir) trial (NCT00627926), a phase III randomized trial reported in this issue of the Journal, incorporated on-treatment response to tailor the duration of additional peginterferon–ribavirin. Telaprevir and peginterferon–ribavirin were administered for the first 12 weeks or for 8 weeks, followed by 4 weeks of placebo. Extended rapid virologic response was defined as an undetectable HCV RNA level (<25 IU per milliliter) at week 4 and week 12 of therapy; patients who did not have an extended rapid virologic response received 36 additional weeks of peginterferon–ribavirin, for a total of 48 weeks. More than half of the telaprevir-treated patients had an extended rapid virologic response, and

lower in black patients than in white patients and correlated with lower rates of a sustained virologic response. This study also showed that the expression level of the programmed death 1 (PD-1) receptor, with higher levels reflecting greater functional impairment of HCV-specific CD8+ T cells, was inversely associated with the likelihood of a sustained virologic response.

Directly Acting Antiviral Agents

The molecular characterization of the virologic features (Fig. 3A) and life cycle of HCV has led to the development of directly acting antiviral agents, with the goal of improved efficacy and fewer adverse effects as compared with interferon-based regimens. All the HCV enzymes, which are essential for HCV replication, are potential targets; the nonstructural 3 (NS3) serine protease inhibitors are the furthest along in development. In addition to ablating replication, protease inhibition blocks the ability of the NS3/4A serine protease to cleave the HCV polyprotein and interferon-β promoter stimulator 1, thus restoring innate immune signaling within hepatocytes (Fig. 3B).

Two protease inhibitors, telaprevir and boceprevir, were recently approved by the Food and Drug Administration (FDA).

In the Protease Inhibition for Viral Evaluation 1 trial (PROVE1, NCT00336479) and PROVE2 trial (NCT00372385), which involved genotype 1–infected patients who had not previously received treatment, the rates of sustained virologic response were 61% and 69%, respectively, among those who received a 12-week course of telaprevir, an orally bioavailable inhibitor of NS3/4A, in combination with peginterferon–ribavirin, which was continued for an additional 12 weeks (total duration of antiviral therapy, 24 weeks; T12PR24 in Fig. 4). As compared with standard therapy with peginterferon–ribavirin, the addition of telaprevir resulted in a shorter median time to achieve an undetectable HCV RNA level (<30 days, vs. 113 days). Major side effects of telaprevir included rash, pruritus, anemia, and gastrointestinal symptoms. The observation that viral relapse (detectable HCV RNA level during the 24-week posttreatment period in patients with an end-of-treatment response) occurred in 48% of patients who did not receive ribavirin (T12P12 in Fig. 4) underscores the critical role of this agent in preventing relapse and the emergence of telaprevir resistance.

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Table 1. Predictors of a Favorable Response to Treatment with Peginterferon and Ribavirin.

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>Before treatment</th>
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<tbody>
<tr>
<td>HCV genotype other than 1</td>
<td>Absence of both insulin resistance and steatosis</td>
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<tr>
<td>Low baseline viral level</td>
<td>Statin use</td>
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<tr>
<td>White race</td>
<td>During treatment</td>
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<tr>
<td>Interleukin-28B genotype</td>
<td>Response during treatment (RVR or EVR);</td>
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<tr>
<td>Absence of fibrosis</td>
<td>Adherence to treatment</td>
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<tr>
<td>Body weight &lt;85 kg</td>
<td>Standard dose of ribavirin</td>
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<tr>
<td>Age &lt;40 yr</td>
<td></td>
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<tr>
<td>Female sex</td>
<td></td>
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<tr>
<td>ALT quotient ≥3</td>
<td></td>
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<tr>
<td>HCV-specific immune response</td>
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* C (vs. T) allele is advantageous for single-nucleotide polymorphism (SNP) rs12979860; T (vs. G) allele is advantageous for SNP rs8099917.
† The alanine aminotransferase (ALT) quotient is the average of the serum ALT level divided by the upper limit of the normal range.
‡ A rapid virologic response (RVR) is defined as an undetectable HCV RNA level (<50 IU per milliliter) at week 4 of treatment. An early virologic response (EVR) is defined as a decrease in the HCV RNA level of at least 2 log₁₀ IU per milliliter or the complete absence of serum HCV RNA at week 12 of treatment.

Table 1. Predictors of a Favorable Response to Treatment with Peginterferon and Ribavirin.
24 weeks of total therapy was associated with a rate of sustained virologic response that was higher than 80% among these patients. As in all the other telaprevir studies, virologic failure was more common in patients with genotype 1a than in those with genotype 1b. The REALIZE (Re-treatment of Patients with Telaprevir-based Regimen to Optimize Outcomes) study (NCT00703118), also reported in this issue of the Journal, showed that the addition of telaprevir to peginterferon–ribavirin significantly increased the rate of sustained virologic response among patients who had previously received treatment, particularly in prior relapers (patients with an undetectable HCV RNA level at the end of a prior course of peginterferon–ribavirin therapy but with a detectable HCV RNA level thereafter).44 The Serine Protease Inhibitor Therapy 1 trial (SPRINT-1, NCT00423670) and the SPRINT-2 trial (NCT00705432) have shown the efficacy of boceprevir in combination with peginterferon alfa-2b and ribavirin in genotype 1–infected patients who...
had not previously received treatment (Fig. 4); another recent report in the Journal showed the efficacy of this regimen in patients who had previously received treatment. These trials included groups with a 4-week lead-in phase of peginterferon–ribavirin before the addition of boceprevir in order to lower viral levels, theoretically reducing the risk that drug-resistant mutations would emerge. SPRINT-2 used a response-guided antiviral strategy; patients whose tests for HCV RNA were negative by week 8 and remained so up to week 24 were given 24 weeks of boceprevir with peginterferon–ribavirin after the lead-in phase. Rates of sustained virologic response were 63% and 66% among patients receiving a total of 28 or 48 weeks of therapy, respectively, with higher rates among whites than among blacks. Patients in whom the HCV RNA level decreased by less than 1.0 log10 IU per milliliter during the lead-in phase had significantly higher rates of virologic failure. Principal side effects of boceprevir included anemia (necessitating treatment with erythropoietin analogues in many patients) and dysgeusia, which appeared to be more common than previously reported with telaprevir; rash was reported less frequently than in the telaprevir trials. Mathematical modeling has projected that if the rate of response to antiviral therapy increases to 80%, which appears to be likely in the foreseeable future, treatment of half of HCV-infected persons would reduce cases of cirrhosis by 15%, cases of hepatocellular carcinoma by 30%, and deaths due to liver disease by 34% after just 10 years.

**Guidelines**

The American Association for the Study of Liver Diseases and the American Gastroenterological Association have published guidelines for the assessment and management of chronic HCV infection, but these guidelines were issued before the publication of data from randomized trials of directly acting antiviral agents. Newer European guidelines take these data into account; the recommendations provided below are generally consistent with these guidelines.

**Areas of Uncertainty**

Transient elastography (FibroScan, Echosens) is a novel noninvasive technique that measures liver stiffness by assessing the velocity of a shear wave created by a transitory vibration. Thresholds for a high likelihood of clinically significant fibrosis (Metavir score ≥2) have been defined. The technique has an increased failure rate among obese patients, and it has not been approved by the FDA. Whether modifications of existing technologies (e.g., computed tomography and magnetic resonance imaging) will provide sensitive differentiation of levels of hepatic fibrosis requires further study.

Although peginterferon–ribavirin is likely to remain the backbone of antiviral therapy for the foreseeable future, options for treating HCV are expected to expand rapidly in upcoming years. The optimal combination of agents (including nucleoside and nonnucleoside polymerase inhibitors, inhibitors of NS4B and NSSA proteases, modulators of the immune response, and medications that interfere with lipid metabolism, which is essential for the assembly and maturation of HCV particles) and duration of therapy will need to be defined, in order to maximize rates of sustained virologic response while minimizing the risk that resistance will develop. A recent pilot study of a combination of directly acting antiviral agents suggests the possibility of treating HCV infection with an interferon-free, oral approach. Further study is needed in subgroups of patients with lower response rates, including black patients, patients without a response to prior treatment, liver-transplant recipients, and those who have coinfection with HIV, a high baseline viral load, advanced fibrosis, or insulin resistance.

**Conclusions and Recommendations**

The patient described in the vignette has HCV genotype 1 with a high viral load. He should be vaccinated for hepatitis A because of an increased risk of liver failure among patients with chronic hepatitis C infection; hepatitis B vaccination is also indicated in those without evidence of prior exposure. Possible contraindications to treatment (e.g., depression) should be determined, and the patient should be informed about potential side effects of antiviral therapy. Although some clinicians would administer treatment without performing a liver biopsy, I would recommend a biopsy to assess the degree of fibrosis. For a patient with clinically significant fibrosis (Metavir score ≥2),
triple antiviral therapy with peginterferon–ribavirin and an NS3/4A protease inhibitor, either telaprevir or boceprevir, should be recommended.

On the basis of data from recent randomized trials, a reasonable initial regimen would be telaprevir with peginterferon–ribavirin for 12 weeks. If tests for HCV RNA were negative at weeks 4 through 12 (indicating an extended rapid virologic response), only 12 additional weeks of peginterferon–ribavirin would be recommended, whereas if an extended rapid virologic response was not achieved, peginterferon–ribavirin would be continued for an additional 36 weeks.37 If boceprevir were used, according to new FDA guidelines, a 4-week lead-in phase of peginterferon–ribavirin would be followed by peginterferon–ribavirin and boceprevir for 24 weeks (a total of 28 weeks) if tests for HCV RNA were negative at weeks 8 through 24 of treatment. If the tests were positive between weeks 8 and 24 but negative at week 24, peginterferon–ribavirin and boceprevir would be continued for an additional 8 weeks, followed by an additional 12 weeks of peginterferon–ribavirin (a total of 48 weeks).

Alternatively, if the patient has milder fibrosis and is reluctant to receive treatment, it would be reasonable to wait and reevaluate as new therapeutic agents become available.40,47

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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REFERENCES

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