

## CLINICAL PRACTICE

## Chronic Hepatitis C Infection

Hugo R. Rosen, M.D.

*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**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  $220 \times 10^9$  per liter. An abdominal ultrasonogram is normal. How should this patient's case be managed?**

## THE CLINICAL PROBLEM

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.<sup>1</sup> 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.<sup>2</sup> 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%.<sup>3</sup> Other risk factors include blood transfusion before 1992, high lifetime number of sexual partners, and iatrogenic transmission, including through dialysis<sup>4,5</sup>; 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).<sup>6</sup> 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.<sup>7</sup> A number of factors, but not viral level or genotype, have been consistently associated with an increased risk of fibrosis (Fig. 1).<sup>8,9</sup> Patients with HCV-related cirrhosis warrant surveillance for complications, including hepatocellular carcinoma, which develops in 1 to 3% of such patients per year.<sup>10</sup> For patients with clinically significant hepatic fibrosis (Metavir stage  $\geq 2$  or Ishak stage  $\geq 3$ ) (Fig. 2), there is widespread agreement that antiviral therapy is indicated because of the high risk of cirrhosis.<sup>2,12</sup> 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.<sup>11</sup> 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.<sup>13</sup>

The hepatitis C virus, an enveloped flavivirus, was first cloned in 1989<sup>14</sup>; the

From the Division of Gastroenterology and Hepatology, Department of Medicine, University of Colorado School of Medicine, Aurora, and Eastern Colorado Veterans Affairs Medical Center, Denver. Address reprint requests to Dr. Rosen at the Division of Gastroenterology and Hepatology, University of Colorado, Denver, B-158 Academic Office Bldg. 1, 12631 E. 17th Ave., Rm. 7614, Aurora, CO 80045, or at hugo.rosen@ucdenver.edu.

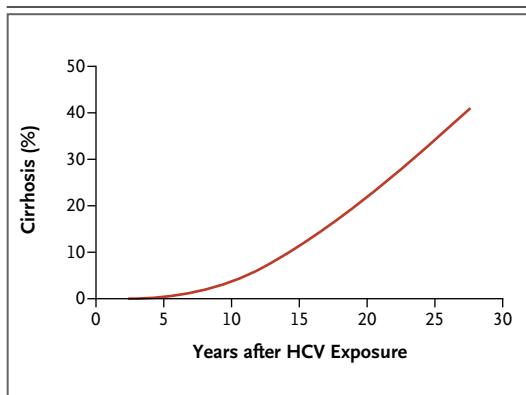
N Engl J Med 2011;364:2429-38.

Copyright © 2011 Massachusetts Medical Society.



**An audio version  
of this article  
is available at  
NEJM.org**

## STRATEGIES AND EVIDENCE



**Figure 1. Natural History of Hepatitis C Virus (HCV) Infection.**

Cumulative rates of cirrhosis are shown according to the number of years since HCV exposure. The curve is derived from Thein et al.<sup>7</sup> Factors associated with an increased rate of fibrosis development include a longer duration of infection, an older age at the time of exposure (more rapid progression in patients who acquire HCV after 40 years of age), male sex, coinfection with other viruses such as hepatitis B virus (HBV) or the human immunodeficiency virus (HIV), and daily alcohol consumption (especially >50 g per day).

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).<sup>15</sup> Subsequent expression of interferon- $\beta$ , 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.<sup>15,16</sup>

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).<sup>17,18</sup>

**DIAGNOSIS AND CLINICAL STAGING**

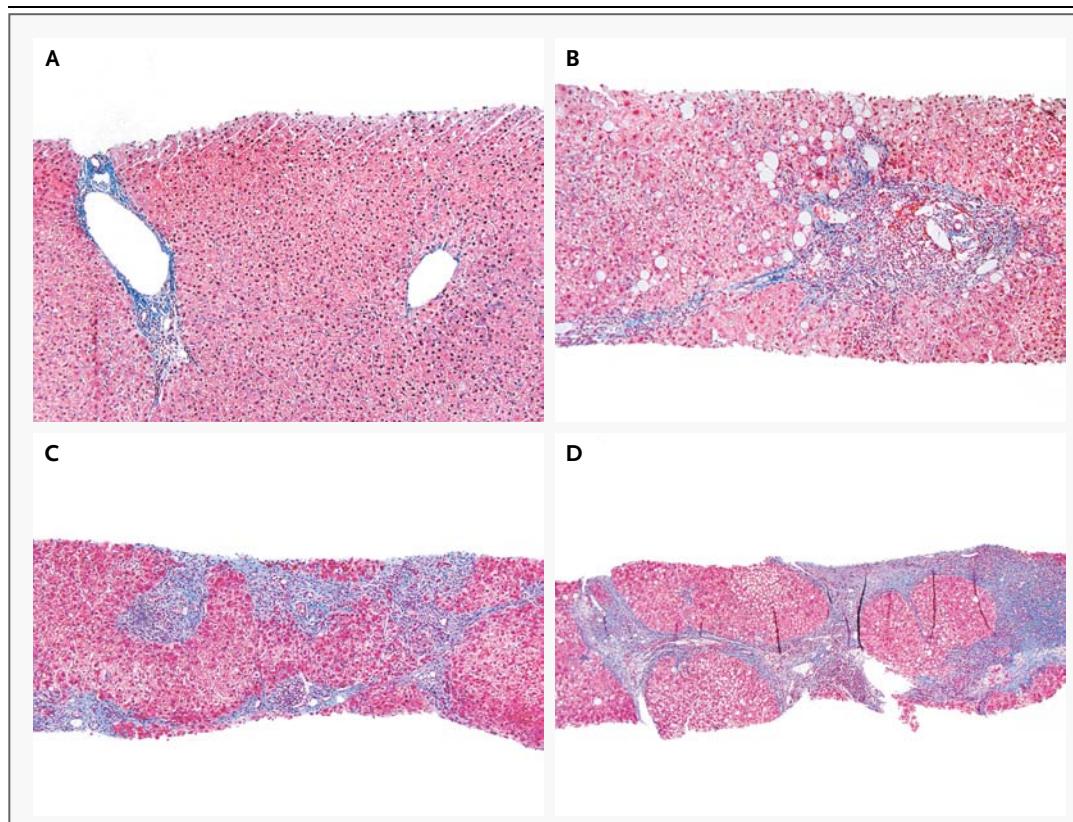
Liver biopsy remains the standard for assessment of hepatic fibrosis and is helpful for prognostication and decision making. The histologic pattern of HCV infection consists of lymphocyte infiltration of the parenchyma, lymphoid follicles in portal areas, and reactive bile-duct changes. However, liver biopsy is costly and invasive, and it carries a risk of complications (e.g., 1 to 5% of patients who undergo the procedure require hospitalization).<sup>19</sup> Additional limitations of biopsy include sampling error and interobserver variability.

Several methods have been used to quantify hepatic fibrosis, including the simple aspartate aminotransferase:platelet ratio index (APRI) and commercially available assays of some or most of the following biomarkers:  $\alpha_2$ -macroglobulin,  $\alpha_2$ -globulin,  $\gamma$ -globulin, apolipoprotein A-I,  $\gamma$ -glutamyltransferase, total bilirubin, and hyaluronic acid.<sup>19-21</sup> (For more information on APRI, see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.) The sensitivity and specificity of these assays for the detection of clinically significant fibrosis range from 41 to 94% and from 44 to 95%, respectively,<sup>21,22</sup> and the assays are typically much better at detecting advanced fibrosis and cirrhosis than mild-to-moderate fibrosis. Combining assays (e.g., APRI and FibroSURE or HepaScore) appears to increase the diagnostic accuracy and may eliminate the need for liver biopsy in more than half of patients.<sup>12,22,23</sup> Optimal cutoff values for establishing the accurate diagnosis of fibrosis may vary across populations, depending in part on the prevalence of advanced fibrosis.<sup>23</sup>

**MANAGEMENT***Interferon-Based Antiviral Therapy*

Substantial progress has been made in the treatment of HCV infection. The goals of therapy are to prevent complications and death from HCV infection; regardless of the stage of fibrosis, symptomatic extrahepatic HCV (e.g., cryoglobulinemia) is an indication for therapy.<sup>2</sup> Over the past decade, on the basis of considerable data from randomized trials, pegylated interferon (peginterferon) plus ribavirin became the standard of care for all HCV genotypes.<sup>24-26</sup>

The two licensed peginterferons (Pegasys, Roche, and PegIntron, Merck) have been shown in



**Figure 2. Histologic Features of HCV Infection, According to Different Scoring Systems.**

Panel A (trichrome stain) shows the portal tract (left) and central vein (right) without substantial fibrosis. This corresponds to Batts–Ludwig stage 0, Metavir stage 0, and Ishak stage 0. Panel B (trichrome stain) shows portal fibrous expansion with periportal fibrosis. This corresponds to Batts–Ludwig stage 2, Metavir stage 2, and Ishak stage 3. Panel C (trichrome stain) shows bridging septal fibrosis with architectural distortion in the absence of regenerative nodules. This corresponds to Batts–Ludwig stage 3, Metavir stage 3, and Ishak stage 4. Panel D (trichrome stain) shows marked bridging fibrosis with numerous regenerative nodules. This corresponds to Batts–Ludwig stage 4, Metavir stage 4, and Ishak stage 6. Photographs courtesy of Maxwell Smith, M.D., Department of Pathology, University of Colorado, Denver. In the Metavir scoring system (0 to 4), stage 1 denotes minimal fibrosis, 2 scarring that extends outside the areas that contain blood vessels, 3 bridging fibrosis, and 4 cirrhosis. In the Batts–Ludwig system (0 to 4), stage 1 denotes portal fibrosis, 2 periportal or early bridging fibrosis with intact architecture, 3 fibrosis with architectural distortion, and 4 cirrhosis. In the Ishak system (0 to 6), stage 2 denotes fibrous expansion of most portal areas, 3 fibrous expansion of most portal areas with occasional portal-to-portal bridging, 4 fibrous expansion of most portal areas with marked bridging (both portal-to-portal and portal-to-central), 5 incomplete cirrhosis characterized by marked bridging and occasional nodules, and 6 probable or definite cirrhosis.<sup>11</sup>

head-to-head comparison to be equivalent in efficacy and to have similar safety profiles.<sup>27</sup> 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.<sup>24–26</sup> 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.<sup>25</sup> 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-

tained virologic response.<sup>2,24-26,28-30</sup> 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 380% of total interferon and ribavirin doses for 380% 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.<sup>31</sup>

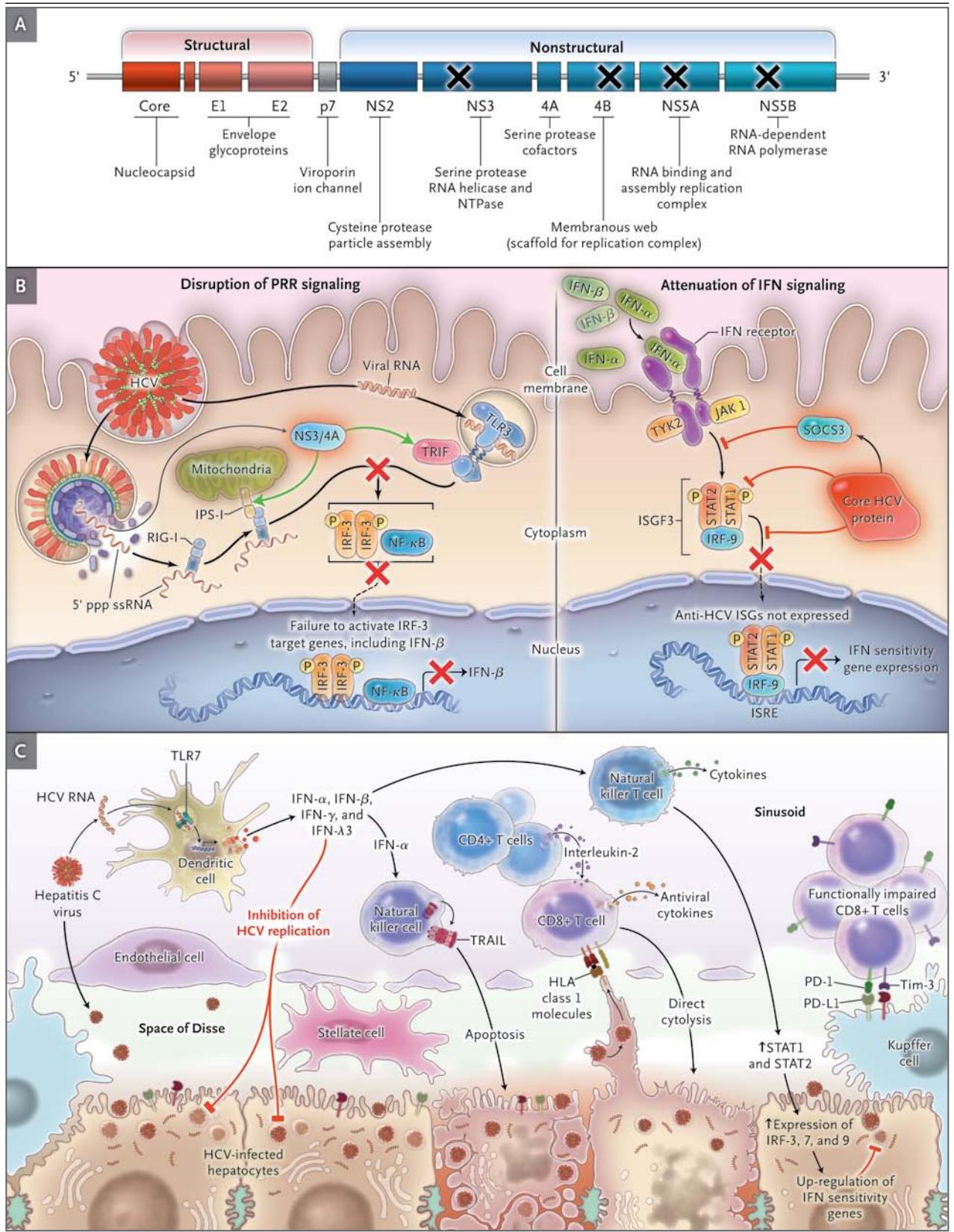
On-treatment viral kinetics have emerged as important predictors of the likelihood of response and are used to guide the duration of therapy.<sup>2</sup> An early virologic response is defined as a decrease in the HCV RNA level of at least 2 log<sub>10</sub> IU per milliliter or the complete absence of serum HCV RNA at week 12 of therapy.<sup>2</sup> 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.<sup>32</sup> A reduction of the treatment duration has the added benefits of decreased costs and side effects.<sup>2,32</sup>

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%).<sup>33</sup> 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 predic-

**Figure 3 (facing page). Hepatitis C Virology, Intracellular Innate Immune Response and Evasion Tactics, and Hepatic Immune Lymphocyte Response to Infection.**

Panel A shows the genomic structure of the hepatitis C virus (HCV). The cleavage of the polyprotein by viral and host-cell proteases yields structural viral proteins (core protein and envelope proteins E1 and E2) and nonstructural viral proteins (NS2 through NS5B), with a number of putative activities and functions. Targets of anti-HCV drugs currently in development are marked with an X. Panel B shows the mechanisms that HCV has developed to evade the host immune response within hepatocytes. Proteins known as pattern-recognition receptors (PRR) typically recognize viral motifs, but HCV can cleave adaptor proteins and disrupt PRR signaling; moreover, the HCV core protein can inhibit the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway and interferon (IFN) signaling. The inhibition or blockage of a pathway is indicated by a red X. Panel C shows the multicellular immune response to HCV infection, including cells involved in the innate immune response (dendritic cells, natural killer cells, and Kupffer cells) and adaptive immunity (CD4+ and CD8+ T cells). The orchestration and function of these cells largely mediate the outcome of infection. For technical descriptions of the mechanisms, see the Supplementary Appendix. IPS-1 denotes interferon- $\beta$  promoter stimulator 1, IRF interferon regulatory factor, ISG interferon-stimulated gene, ISGF3 interferon-stimulated gene factor 3, ISRE interferon-stimulated response element, JAK1 Janus kinase 1, NF- $\kappa$ B nuclear factor  $\kappa$ B, NS3/4A nonstructural 3/4A serine protease, NTPase nucleotide triphosphatase, PD-1 programmed death 1, PD-L1 programmed death ligand 1, 5' ppp ssRNA cytoplasmic single-stranded RNA containing a 5' triphosphate, RIG-I retinoic acid-inducible gene I protein, SOCS3 suppressor of cytokine signaling 3, STAT1 signal transducer and activator of transcription 1, STAT2 signal transducer and activator of transcription 2, Tim-3 mucin domain-containing molecule 3, TLR3 toll-like receptor 3, TLR7 toll-like receptor 7, TRAIL tumor necrosis factor-related apoptosis-inducing ligand, TRIF toll-like receptor-adaptor molecule, and TYK2 tyrosine kinase 2.

tive of successful antiviral treatment.<sup>34</sup> 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



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

HCV genotype other than 1

Low baseline viral level

White race

Interleukin-28B genotype\*

Absence of fibrosis

Body weight &lt;85 kg

Age &lt;40 yr

Female sex

ALT quotient  $\geq 3$ †

HCV-specific immune response

**Before treatment**

Absence of both insulin resistance and steatosis

Statin use

**During treatment**

Response during treatment (RVR or EVR)‡

Adherence to treatment

Standard dose of ribavirin

\* C (vs. T) allele is advantageous for single-nucleotide polymorphism (SNP) rs129789860; 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 log<sub>10</sub> IU per milliliter or the complete absence of serum HCV RNA at week 12 of treatment.

lower in black patients than in white patients and correlated with lower rates of a sustained virologic response.<sup>35</sup> 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.<sup>36</sup>

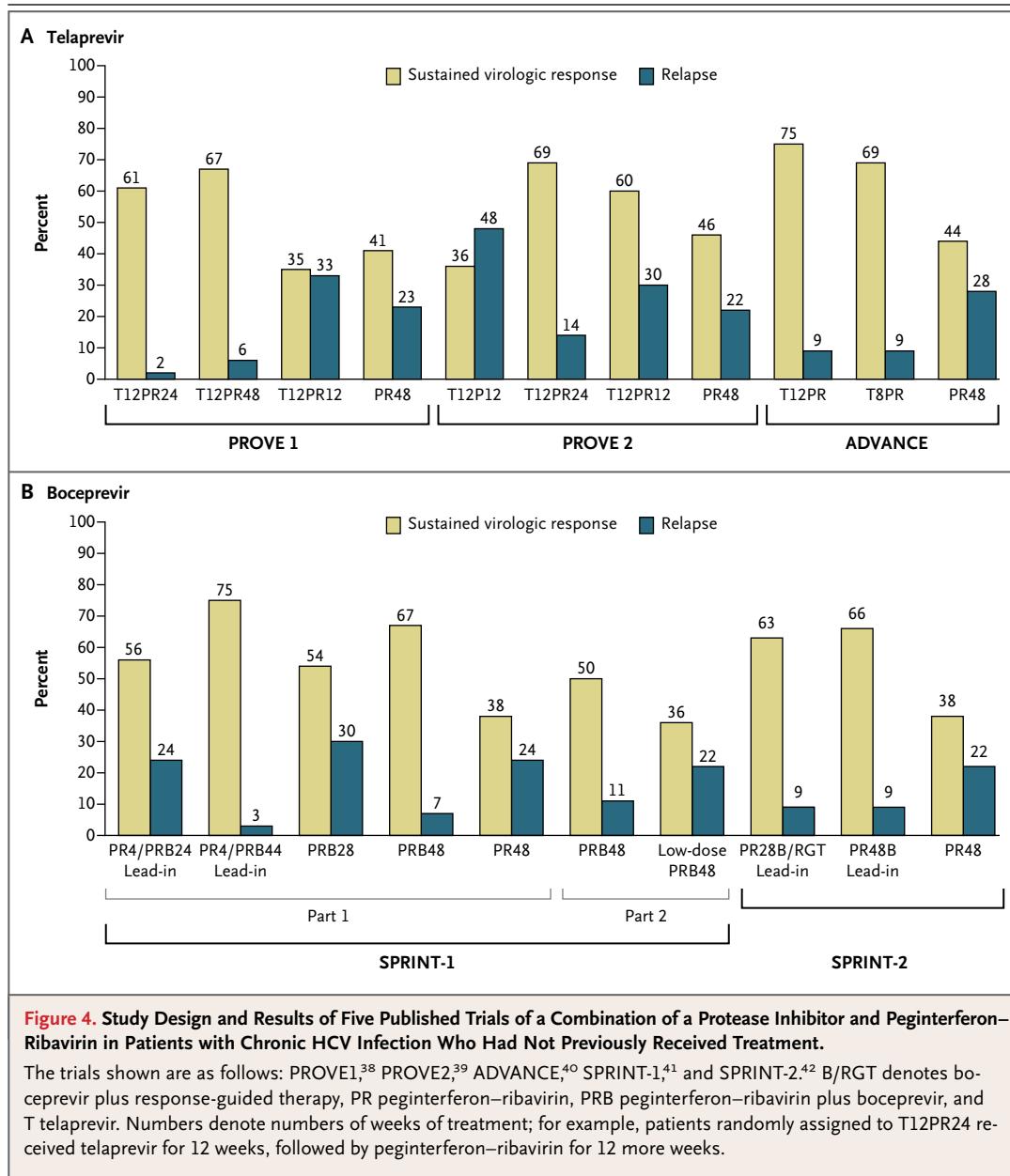
*Directly Acting Antiviral Agents*

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.<sup>37</sup> 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- $\beta$  promoter stimulator 1, thus restoring innate immune signaling within hepatocytes (Fig. 3B).<sup>15</sup> 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)<sup>38</sup> and PROVE2 trial (NCT00372385),<sup>39</sup> 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,<sup>38</sup> 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).<sup>39</sup> 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.<sup>39,43</sup>

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.<sup>40</sup> 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<sup>37</sup>; 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



**Figure 4. Study Design and Results of Five Published Trials of a Combination of a Protease Inhibitor and Peginterferon-Ribavirin in Patients with Chronic HCV Infection Who Had Not Previously Received Treatment.**

The trials shown are as follows: PROVE1,<sup>38</sup> PROVE2,<sup>39</sup> ADVANCE,<sup>40</sup> SPRINT-1,<sup>41</sup> and SPRINT-2.<sup>42</sup> B/RGT denotes boceprevir plus response-guided therapy, PR peginterferon-ribavirin, PRB peginterferon-ribavirin plus boceprevir, and T telaprevir. Numbers denote numbers of weeks of treatment; for example, patients randomly assigned to T12PR24 received telaprevir for 12 weeks, followed by peginterferon-ribavirin for 12 more weeks.

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 (Retreatment 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 sus-

tained virologic response among patients who had previously received treatment, particularly in prior relapsers (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).<sup>44</sup>

The Serine Protease Inhibitor Therapy 1 trial (SPRINT-1, NCT00423670)<sup>41</sup> and the SPRINT-2 trial (NCT00705432)<sup>42</sup> 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.<sup>45</sup> 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.<sup>42,45,46</sup> 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 log<sub>10</sub> 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.<sup>37</sup>

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,<sup>13</sup> 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.<sup>13</sup>

#### 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.<sup>23</sup> Thresholds for a high likelihood of clinically significant fibrosis (Metavir score  $\geq 2$ ) 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 NS5A 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.<sup>46,47</sup> 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.<sup>48</sup> 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.

#### GUIDELINES

The American Association for the Study of Liver Diseases<sup>2</sup> and the American Gastroenterological Association<sup>49</sup> 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<sup>50</sup>; the recommendations provided below are generally consistent with these guidelines.

#### 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.<sup>2</sup> Possible contraindications to treatment (e.g., depression) should be determined, and the patient should be informed about potential side effects of antiviral therapy.<sup>31,37-39,41,42</sup> Although some clinicians would administer treatment without performing a liver biopsy, I would recommend a biopsy to assess the degree of fibrosis.<sup>31</sup> For a patient with clinically significant fibrosis (Metavir score  $\geq 2$ ),

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 were not achieved, peginterferon–ribavirin would be continued for an additional 36 weeks.<sup>37</sup> 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.<sup>46,47</sup>

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.

I thank Greg Everson, M.D., and Jean-Michel Pawlotsky, M.D., Ph.D., for discussions and review of an earlier version of the manuscript.

## REFERENCES

- Davis GL, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl* 2003;9:331-8.
- Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009;49:1335-74.
- Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006;144:705-14.
- Wang CC, Krantz E, Klarquist J, et al. Acute hepatitis C in a contemporary US cohort: modes of acquisition and factors influencing viral clearance. *J Infect Dis* 2007;196:1474-82.
- 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.
- Bowen DG, Walker CM. Mutational escape from CD8+ T cell immunity: HCV evolution, from chimpanzees to man. *J Exp Med* 2005;201:1709-14.
- Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008;48:418-31.
- Afdhal NH. The natural history of hepatitis C. *Semin Liver Dis* 2004;24:Suppl 2:3-8.
- Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997;349:825-32.
- Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463-72.
- Everhart JE, Wright EC, Goodman ZD, et al. Prognostic value of Ishak fibrosis stage: findings from the hepatitis C antiviral long-term treatment against cirrhosis trial. *Hepatology* 2010;51:585-94.
- Sebastiani G, Vario A, Guido M, et al. Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. *J Hepatol* 2006;44:686-93.
- Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010;138(2):521.e1-521.e6.
- Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989;244:359-62.
- Horner SM, Gale M Jr. Intracellular innate immune cascades and interferon defenses that control hepatitis C virus. *J Interferon Cytokine Res* 2009;29:489-98.
- Thio CL, Thomas DL. Interleukin-28b: a key piece of the hepatitis C virus recovery puzzle. *Gastroenterology* 2010;138:1240-3.
- Virgin HW, Wherry EJ, Ahmed R. Redefining chronic viral infection. *Cell* 2009;138:30-50.
- McMahan RH, Golden-Mason L, Nishimura MI, et al. Tim-3 expression on PD-1+ HCV-specific human CTLs is associated with viral persistence, and its blockade restores hepatocyte-directed in vitro cytotoxicity. *J Clin Invest* 2010;120:4546-57. [Erratum, *J Clin Invest* 2011;121:821.]
- Manning DS, Afdhal NH. Diagnosis and quantitation of fibrosis. *Gastroenterology* 2008;134:1670-81.
- Becker L, Salameh W, Sferruzza A, et al. Validation of hepascor, compared with simple indices of fibrosis, in patients with chronic hepatitis C virus infection in United States. *Clin Gastroenterol Hepatol* 2009;7:696-701.
- Pinzani M. Non-invasive evaluation of hepatic fibrosis: don't count your chickens before they're hatched. *Gut* 2006;55:310-2.
- Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology* 2004;127:1704-13.
- Castéra L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005;128:343-50.
- Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-82.
- Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:346-55.
- Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958-65.
- McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361:580-93.
- Foster GR, Fried MW, Hadziyannis SJ, Messinger D, Freivogel K, Weiland O. Prediction of sustained virological response in chronic hepatitis C patients treated

- with peginterferon alfa-2a (40KD) and ribavirin. *Scand J Gastroenterol* 2007;42:247-55.
29. Harrison SA, Rossaro L, Hu KQ, et al. Serum cholesterol and statin use predict virological response to peginterferon and ribavirin therapy. *Hepatology* 2010;52:864-74.
30. Ferenci P. Predictors of response to therapy for chronic hepatitis C. *Semin Liver Dis* 2004;24:Suppl 2:25-31.
31. Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. *N Engl J Med* 2006;355:2444-51.
32. Moreno C, Deltenre P, Pawlotsky JM, Henrion J, Adler M, Mathurin P. Shortened treatment duration in treatment-naive genotype 1 HCV patients with rapid virological response: a meta-analysis. *J Hepatol* 2010;52:25-31.
33. Conjeevaram HS, Fried MW, Jeffers LJ, et al. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology* 2006;131:470-7.
34. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009;461:399-401.
35. Rosen HR, Weston SJ, Im K, et al. Selective decrease in hepatitis C virus-specific immunity among African Americans and outcome of antiviral therapy. *Hepatology* 2007;46:350-8.
36. Golden-Mason L, Klarquist J, Wahed AS, Rosen HR. Cutting edge: programmed death-1 expression is increased on immunocytes in chronic hepatitis C virus and predicts failure of response to antiviral therapy: race-dependent differences. *J Immunol* 2008;180:3637-41.
37. Pawlotsky JM. The results of Phase III clinical trials with telaprevir and boceprevir presented at the Liver Meeting 2010: a new standard of care for hepatitis C virus genotype 1 infection, but with issues still pending. *Gastroenterology* 2011;140:746-54.
38. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009;360:1827-38. [Erratum, *N Engl J Med* 2009;361:1516.]
39. Hézode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009;360:1839-50.
40. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;364:2405-16.
41. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2010;376:705-16.
42. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1195-206.
43. Hoofnagle JH. A step forward in therapy for hepatitis C. *N Engl J Med* 2009;360:1899-901.
44. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011;364:2417-28.
45. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1207-17.
46. Gelman MA, Glenn JS. Mixing the right hepatitis C inhibitor cocktail. *Trends Mol Med* 2010 November 22 (Epub ahead of print).
47. Lemon SM, McKeating JA, Pietschmann T, et al. Development of novel therapies for hepatitis C. *Antiviral Res* 2010;86:79-92.
48. Gane EJ, Roberts SK, Stedman CA, et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. *Lancet* 2010;376:1467-75.
49. Dienstag JL, McHutchison JG. American Gastroenterological Association medical position statement on the management of hepatitis C. *Gastroenterology* 2006;130:225-30. [Errata, *Gastroenterology* 2006;130:1018, 2006;131:979.]
50. Craxi A. EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol* 2011 February 28 (Epub ahead of print).

Copyright © 2011 Massachusetts Medical Society.

#### SPECIALTIES AND TOPICS AT NEJM.ORG

Specialty pages at the *Journal's* Web site ([NEJM.org](http://NEJM.org)) feature articles in cardiology, endocrinology, genetics, infectious disease, nephrology, pediatrics, and many other medical specialties. These pages, along with collections of articles on clinical and nonclinical topics, offer links to interactive and multimedia content and feature recently published articles as well as material from the NEJM archive (1812–1989).