Current and Future Therapies for Hepatitis C Virus Infection

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Only 20 years after the discovery of the hepatitis C virus (HCV), a cure is now likely for most people affected by this chronic infection, which carries a substantial disease burden, not only in the United States but also worldwide. The recent approval of two direct-acting antiviral agents that specifically inhibit viral replication has dramatically increased the viral clearance rate, from less than 10% with the initial regimen of interferon monotherapy to more than 70% with current therapy. Moreover, many other drugs targeting viral or host factors are in development, and some will almost certainly be approved in the coming years. The questions of who should be treated and with what regimen will be increasingly complex to address and will require careful consideration. As therapy improves, systemwide identification and care of patients who need treatment will be the next challenge. Because most infected persons are unaware of their diagnosis, the Centers for Disease Control and Prevention recently recommended screening for HCV all persons born between 1945 and 1965. It is anticipated that in the course of such a screening process, a large number of persons will be found to be infected with the virus; whether it will be possible to treat all these people is unclear. This article reviews the current therapy for HCV infection and the landscape of drug development.

MECHANISM OF ACTION OF THERAPY FOR HCV INFECTION

Basic research aimed at understanding the molecular pathways of the life cycle of the virus has been the engine that has driven the development of therapies for HCV infection over the past 20 years. HCV is a positive-strand RNA virus encoding a polyprotein that undergoes proteolytic cleavage to 10 polypeptides, each with distinct functions (Fig. 1). The structural proteins consist of two envelope glycoproteins, both of which are targets of host antibody response, and the core protein, which interacts with progeny viral genomes for assembly of the virus. The non-structural proteins NS2, NS3, NS4A, NS4B, NS5A, and NS5B form a complex with viral RNA to initiate viral replication in a cytoplasmic membranous structure. Assembly of HCV requires close interactions with lipid droplets and lipoprotein metabolism. Mature virus is released from cells as lipoviral particles. HCV infects predominantly hepatocytes and has an uncanny ability to evade the host immune response in multiple ways.

Interferon alfa is a potent inhibitor of HCV replication that acts by inducing interferon-stimulated host genes that have antiviral functions. Its pegylated form remains a mainstay of HCV therapy. By virtue of its diverse actions on HCV, interferon alfa is not associated with viral resistance. A lack of clinical response to interferon alfa is the result of chronic HCV infection that confers resistance to exogenous interferon alfa in the liver by interfering with host interferon response and interferon-stimulated gene expression. Ribavirin, a key component of the
therapeutic regimen, acts synergistically with and is used in combination with interferon alfa in the treatment of HCV infection; it probably has multiple mechanisms of action.\(^\text{13}\)

Recent efforts to develop antiviral agents for the treatment of HCV infection have focused on small-molecule inhibitors of HCV infection (Fig. 1), which can be categorized on the basis of the target of action. Some antiviral agents act directly on viral targets, whereas others target host proteins that are vital to HCV replication. The initial effort focused on two viral-encoded enzymes, the NS3/4A serine protease, which cleaves the HCV polyprotein, and the NS5B RNA-dependent RNA polymerase. The first two direct-acting antiviral agents that were approved, telaprevir and boceprevir, are inhibitors of the NS3/4A protease.\(^\text{14}\) Another target, the NS5A viral protein, has gained traction recently because of its importance in the assembly of the cytoplasmic membrane-bound replication complex and the high potency of its inhibitors as indicated by in vitro studies and studies involving humans.\(^\text{15}\) Additional viral proteins, such as core protein (which has a role in assembly of the virus), p7 (which forms ion channels involved in assembly of the virus), and NS4B (which has a role in the formation of the replication complex), are being explored as drug targets (Fig. 1).\(^\text{16-19}\)

Promising host targets include cyclophilin A and miR122. Cyclophilin A is a crucial component of the viral replication complex.\(^\text{8}\) Cyclosporin A, a cyclophilin A inhibitor, is a potent inhibitor of HCV replication in cell culture. Its derivatives, such as alisporivir, NIM811, and SCY-635, which lack immunosuppressive properties, are being tested in clinical trials.\(^\text{20}\) MiR122 is a microRNA that is expressed abundantly in the liver and binds to viral RNA to facilitate replication.\(^\text{21}\) A nucleic acid inhibitor of miR122 (miravirsen) potently inhibits HCV replication in the chimpanzee model and in humans.\(^\text{22,23}\) Entry factors are other potential host targets; inhibitors of these factors block the access of HCV into cells (Fig. 1).\(^\text{4}\) Inhibitors of viral entry may be particularly important for the treatment of patients undergoing liver transplantation, because patients with HCV infection are invariably reinfected after transplantation, and post-transplantation hepatitis C remains a major challenge to manage and treat.\(^\text{24}\)
The boceprevir-based regimen and the telaprevir-based regimen differ in several aspects: first, with respect to the specific therapeutic regimen for each type of patient (those who have not received prior therapy vs. those who have received prior therapy, including patients with a relapse after an initial response, those with a partial response, and those with no response); second, with respect to the schedule and duration of the combination therapy; and third, with respect to the points at which therapy is changed, depending on the patient’s response, and the points at which therapy is stopped. Typically, telaprevir is given together with peginterferon and ribavirin (peginterferon alfa-2a, 180 μg per week, or peginterferon alfa-2b, 1.5 μg per kilogram of body weight per week, in combination with ribavirin, 1000 mg daily for a patient with a body weight of ≤75 kg and 1200 mg daily for a patient with a body weight of >75 kg) during the first 12 weeks of therapy; peginterferon and ribavirin are then continued without the protease inhibitor for a total of either 24 or 48 weeks, depending on the virologic response to the triple therapy (response-guided therapy). In contrast, boceprevir is administered starting 4 weeks after the initiation of peginterferon and ribavirin (at the same doses as above) and is continued with the protease inhibitor for a total of either 24 or 48 weeks, again depending on the virologic response. In general, with both regimens, patients with cirrhosis should receive the same treatment as patients who have not had a response to previous therapy. The stopping rules were as follows: for the telaprevir-based regimen, patients with an HCV RNA level greater than 1000 IU/ml at week 4 or week 12 should discontinue all three drugs; for the boceprevir-based regimen, patients with an HCV RNA level greater than or equal to 100 IU/ml at week 12 should discontinue all three drugs. For both regimens, patients with detectable HCV RNA at week 24 should discontinue therapy. Boc denotes boceprevir, PIFN peginterferon alfa, R ribavirin, and Tpv telaprevir.

**Figure 2. Boceprevir- and Telaprevir-Based Regimens for Treatment of HCV Infection.**

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in similar response rates but differ greatly with respect to the timing of administration (both when they should be administered and for how long) (Fig. 2). Neither boceprevir nor telaprevir should be used alone, nor should the dose of either drug be reduced, because drug-resistant
variants can emerge rapidly.35,36 Similarly, one agent should not be substituted for the other because they have very different treatment schedules and similar drug-resistant mutations. They are not approved for use in patients who have HCV infection with genotypes other than genotype 1. Either peginterferon-alfa-2a or peginterferon-alfa-2b may be used in the regimen.37

**CHALLENGES OF TRIPLE-THERAPY REGIMENS**

Although the approved triple-therapy regimens are more efficacious than a regimen of peginterferon and ribavirin without a protease inhibitor, they have additional side effects and are quite complex to adhere to because patients must take an increased number of pills and the schedule requires pills to be taken every 8 hours. The most common side effects with boceprevir are anemia, neutropenia, and dysgeusia (altered taste sensation),30,31 and the most common side effects with telaprevir are anemia, rash, and anorectal discomfort.32,33 Anemia (a hemoglobin level of <10 g per deciliter) occurs in 36 to 50% of cases and is the most challenging complication to manage.30,32 Erythrocyte-stimulating agents have been used with some success to manage the anemia, but these agents have serious side effects, are costly, and are not approved for routine use in patients with chronic hepatitis C.30,38 Studies have shown that a reduction in the dose of ribavirin, even as early as week 2 and to a level as low as 600 mg per day, is an effective strategy for managing anemia and is the recommended first approach.38,39

Drug–drug interactions constitute another concern. Boceprevir is metabolized by the aldo-keto–reductase and Cyp3A4/5 pathways and telaprevir by the Cyp3A pathway.40,41 Both molecules are inhibitors of Cyp3A4 and P-glycoprotein transporter.42 Cyp3A enzymes are abundant in the liver and are involved in the metabolism of many drugs. The activities of these enzymes can also be reduced in advanced liver disease. Therefore, when these agents are administered, one should consider not only the effects of coadministered drugs on boceprevir and telaprevir levels but also the effects of boceprevir and telaprevir on the levels of other drugs. A number of medications, such as certain statins, antidepressants, anticonvulsants, analgesics, and sedatives, are contraindicated with these agents.41,43 All prescribers of boceprevir and telaprevir are strongly advised to check for the effects of drug–drug interactions before administering these agents. Important information can be obtained from a number of useful websites, from the prescribing information disseminated with the drugs, and from review articles.41-43

Antiviral resistance is another major concern and may develop as early as 4 days after initiation of the drug when these agents are used as monotherapy.35,36 The various drugs in the class of protease inhibitors have a similar pattern of drug-resistant mutations, which means that if resistance-associated variants emerge when one agent is used, another agent in the same class would not be effective. Therefore, patients who no longer have a response to one of the approved regimens should not be treated with the other. Once the drug is stopped, resistance-associated variants disappear over time, probably because they do not replicate as efficiently as does the wild-type virus. Certain mutations may persist in the viral population in a given patient for 3 years or longer after discontinuation of therapy.44,45 Adherence to the prescribed regimen and dietary considerations (to maximize absorption of the drug) should be reinforced with patients to limit the development of antiviral resistance.

There are scant data on the efficacy of these approved regimens in difficult-to-treat populations that traditionally have lower response rates to peginterferon and ribavirin, such as patients with cirrhosis or human immunodeficiency virus (HIV) coinfecion and patients who have undergone liver transplantation. In phase 3 trials of boceprevir and telaprevir, patients with cirrhosis, accounting for only approximately 10% of the populations studied, had lower rates of sustained virologic response than did patients without cirrhosis. Although the numbers of patients with cirrhosis were small, there was a trend toward lower response rates with response-guided regimens, and patients with cirrhosis should therefore receive 48 weeks of therapy.30-33 In preliminary studies, the response rate among patients with HIV coinfection was similar to that among patients without HIV coinfection, but the approved regimens are problematic in patients who have undergone liver transplantation because of drug–drug interactions and serious side effects.46-48

**INDICATIONS FOR TRIPLE THERAPY**

The indications for the approved triple therapy remain the same as those for peginterferon and
A treatment algorithm is shown for patients who have not received prior therapy and for those who have received prior therapy, including patients with a relapse after an initial response and those with no response. Special pretreatment assessment refers to special considerations, such as genetic testing (for interleukin-28B genotype), liver biopsy, or noninvasive testing to determine the stage of liver fibrosis. Partial response is defined as an early virologic response (>2 log_{10} reduction in the HCV RNA level or undetectable HCV RNA at week 12) but detectable HCV RNA at the end of treatment, and no response is defined as the lack of an early virologic response to standard therapy with peginterferon and ribavirin. Treatment for HCV genotype 2 or 3 infection is peginterferon-alfa-2a, 180 μg per week, or peginterferon-alfa-2b, 1.5 μg per kilogram of body weight per week, in combination with ribavirin, 800 mg daily, for 24 weeks; for genotype 4, 5, or 6 infection, the treatment is the same combination with weight-based ribavirin dosing (1000 mg daily for a patient with a body weight of ≤75 kg and 1200 mg daily for a patient with a body weight of >75 kg) for 48 weeks. For patients with HCV genotype 2 infection who do not have cirrhosis and who have a low viral level and a rapid virologic response (undetectable HCV RNA at week 4 of therapy), a shorter duration of therapy with weight-based ribavirin for 12 to 16 weeks may be equally effective. A newer, all-oral regimen, for which phase 3 studies have now been completed, shows promise in the treatment of patients with genotype 2 or 3 infection who have not received prior treatment and those who have not had a response to prior treatment with interferon. SVR denotes sustained virologic response.

The patient must have documented viremia, no contraindications to therapy, and no serious coexisting illness. It is particularly important to consider initiating treatment promptly in patients with an advanced stage of fibrosis (Ishak fibrosis score of 4, 5, or 6 on liver biopsy [with scores ranging from 0 to 6 and higher scores indicating greater degrees of fibrosis]) (see the Supplementary Appendix, available with the full text of this article at NEJM.org) because these patients are at the greatest risk for disease progression. The benefits of a sustained virologic response — lower rates of hepatic decompensation, amelioration of symptoms, and a reduction in the risk of liver-related death — particularly among patients with advanced liver disease, have been firmly established. The availability of boceprevir and telaprevir has not significantly changed the risk–benefit ratio of therapy for a number of reasons. First, the side effects of triple
therapy are worse than those of peginterferon and ribavirin. Second, response rates among the patients who stand to benefit the most from treatment — those with cirrhosis — remain relatively low. Third, antiviral resistance develops in most patients who have not had a response to treatment.\textsuperscript{30,32} Better, and presumably safer, interferon-free regimens will probably be available in the not-too-distant future.

Which patients with HCV genotype 1 infection should be considered for therapy with the currently approved regimens? Previously untreated patients without cirrhosis and patients with an initial response to treatment who subsequently had a relapse after stopping therapy — the two populations in which high rates of response have been reported — are good candidates for therapy (Fig. 3).\textsuperscript{30-33} However, patients with mild disease who have not received prior treatment can probably defer therapy and wait for more effective and safer regimens to become available. Patients with cirrhosis and those who have not had a response to prior therapy stand to benefit the most from triple therapy but have the lowest response rates.\textsuperscript{30-33} An individualized approach is recommended for all patients, once the benefits of therapy, the likelihood of a response, and the potential side effects of treatment have been discussed. The efficacy of the two approved triple regimens is similar, although they have not been directly compared. Factors such as the patient’s preference, the duration of protease-inhibitor administration, the side-effect profile, and the cost should be considered in selecting a regimen.

### Therapy for HCV Infection, Genotypes 2 Through 6

The combination of peginterferon and ribavirin remains the recommended therapy for HCV genotypes 2, 3, 4, 5, and 6 infection (Fig. 3).\textsuperscript{25} Preliminary results of a study of a polymerase inhibitor (sofosbuvir) in combination with ribavirin, administered for 12 weeks, showed a 100% rate of sustained virologic response among patients with HCV genotype 2 or 3 infection.\textsuperscript{53} As reported in this issue of the Journal, two phase 3 trials of the same oral combination showed similar response rates among patients with genotype 2 infection (93% and 97% in the two studies) but much lower response rates among patients with
genotype 3 infection (56% and 61% in the two studies),\textsuperscript{51,52} indicating that better oral regimens are still needed for patients with genotype 3 infection. Activities of various direct-acting antiviral agents against other genotypes are also being investigated.

\section*{THERAPIES IN CLINICAL DEVELOPMENT}

\section*{DIRECT-ACTING ANTIVIRAL AGENTS}

The major drawback of boceprevir and telaprevir is their limited antiviral efficacy in patients with HCV infections other than genotype 1 and their low genetic barrier to resistance (Table 1). There are about a dozen second-generation protease inhibitors in phase 2–3 development that are better than the first-generation agents.\textsuperscript{54} Two classes of NS5B polymerase inhibitors — nucleoside and nonnucleoside analogue inhibitors — are being developed. The nucleoside inhibitors target the conserved nucleotide-binding pocket of the enzyme and function as chain terminators. The nonnucleoside inhibitors bind to other regions of NS5B and act as allosteric inhibitors. There are about eight NS5A inhibitors and more than a dozen NS5B inhibitors in phase 2–3 studies. The properties of these newer agents are summarized in Table 1. All the above agents are being tested in clinical trials in various combinations, with or without ribavirin or peginterferon. NS4B and p7 viral proteins are also being explored as alternative targets of direct-acting antiviral agents (Table 1). In general, the drugs targeting NS4B and p7 are not as potent as those that target NS3/4A, NS5A, and NS5B and have a relatively narrow genotypic coverage.\textsuperscript{18,55}

\section*{HOST-TARGETING ANTIVIRAL AGENTS}

Inhibitors of cyclophilin A and of miR122 are promising host-targeting antiviral agents that have advanced to phase 2 or 3 clinical trials (Fig. 1 and Table 1). Alisporivir, an inhibitor of cyclophilin A with broad genotypic coverage, has shown reasonable potency in a 14-day monotherapy trial (approximately a 3 log\textsubscript{10} reduction in HCV levels).\textsuperscript{56} Related compounds such as SCY-635 and NIM811 are being tested in clinical trials.\textsuperscript{57,58} Mutations conferring viral resistance to this class of compounds can emerge in the NS5A protein but occur less frequently than with direct-acting antiviral agents.\textsuperscript{56} A combination of alisporivir with peginterferon and ribavirin has shown improved efficacy over peginterferon and ribavirin alone, both in patients who have received prior treatment and in those who have not.\textsuperscript{59} The drug is currently on hold at the Food and Drug Administration because of several cases of severe pancreatitis that may have been associated with it. In a phase 2a trial, miravirsen, a drug that targets miR122 and is administered subcutaneously once a week, has led to a modest reduction in HCV levels (<3 log\textsubscript{10}) after 5 weeks of monotherapy.\textsuperscript{23} The effects appear to last for several weeks after the last dose, and no resistant mutations have been identified.

\section*{INTERFERON-FREE REGIMENS}

For a number of reasons, an interferon-free regimen would be advantageous for the treatment of chronic hepatitis C. Considerable progress has been made in this regard with the use of various combinations of direct-acting antiviral agents with or without ribavirin. Combining drugs that have different targets of action should result in an additive or synergistic antiviral effect while lessening the chance of antiviral resistance. The challenge is to identify the right combination of drugs with the highest potency and barrier to resistance and the best side-effect profile. What the final regimen will be remains to be determined. Currently, many combinations of protease, NS5A, and polymerase inhibitors, with or without ribavirin, are being evaluated. In a proof-of-concept study, patients with chronic hepatitis C, both those who had received prior treatment and those who had not, were treated with an interferon-free and ribavirin-free regimen consisting of the polymerase inhibitor RG7128 (a nucleoside inhibitor) and the protease inhibitor danoprevir, administered for 13 days, followed by peginterferon and ribavirin.\textsuperscript{59} A substantial proportion of patients who received the highest doses had undetectable HCV RNA levels after only 13 days, indicating that viral clearance could be achieved without the use of interferon or ribavirin.\textsuperscript{59}

Several trials of other combinations of direct-acting antiviral agents have resulted in viral clearance in patients undergoing therapy.\textsuperscript{60,61} A study of the protease inhibitor asunaprevir in combination with the NS5A inhibitor daclatasvir, administered for 24 weeks in patients with genotype 1a or 1b infection who had not had a response to previous therapy, showed eradica-
tion of the virus in 4 of 11 patients (36%).

Another study, which used the same regimen but only in patients with genotype 1b infection who had not had a response to previous therapy, showed a 90% rate of sustained virologic response. These latter studies highlight the effect of HCV subtype on the response to a regimen that consists entirely of direct-acting antiviral agents. The combination of a direct-acting antiviral agent with a host-targeting antiviral agent may circumvent the issue of the difference in response according to genotype. Two recent studies also showed high rates of sustained virologic response (80 to 90%) with other oral combinations among patients with HCV genotype 1 infection. For a discussion of other therapeutic approaches, see the Supplementary Appendix.

PRECISION MEDICINE IN HCV THERAPY

Advances in biomarker and genomic medicine have provided a unique opportunity to personalize the approach to treatment for patients with hepatitis C. Various clinical traits (e.g., the presence of cirrhosis) and virologic traits (e.g., genotype 1 vs. genotype 2 or 3) have already been incorporated into current regimens as the standard of care. In addition, monitoring the virologic response during treatment often determines the duration of therapy (response-guided therapy) (Fig. 2). Demographic and other factors that have previously been found to correlate with a response to peginterferon and ribavirin are also important determinants of a response to the approved direct-acting antiviral regimens; these factors include younger age (<45 years), non-black race, lower body-mass index, no history of diabetes, absence of cirrhosis on liver biopsy, low baseline viral load (<800,000 IU per milliliter), and HCV subtype 1b.

New biomarkers (e.g., serum IP10 levels) and genetic tests (e.g., to determine polymorphisms in the IL28B gene) appear to have strong predictive value with respect to interferon-based therapy. Polymorphisms in the inosine triphosphatase gene were recently identified as pharmacogenomic markers of ribavirin-induced anemia; however, the polymorphisms conferring protection are rare in the general population, and screening for those polymorphisms is therefore not useful. Recent cost–benefit analyses of data from a study in which a treatment regimen was chosen on the basis of the IL28B genotype suggest that patients with a favorable IL28B genotype, a subgroup in which the rate of a sustained virologic response approaches 80%, could receive peginterferon and ribavirin first, with the approved direct-acting antiviral regimen provided subsequently if the initial treatment failed. Although testing for the IL28B genotype has not been formally approved as a standard of care, such testing may be helpful if the patient or provider desires additional information on the probability of a response to treatment (Fig. 3). However, since more potent anti-HCV drugs and interferon-free regimens are being developed, these markers may no longer be relevant.

Studies of the natural history of chronic HCV infection have shown that the majority of HCV-infected persons have an indolent course of liver disease that rarely progresses to life-threatening complications. Another personalized approach to treating patients with HCV infection may be to treat only those in whom severe disease is likely to develop. However, the clinical and genetic markers that have been identified in such patients do not have strong predictive power, and better predictive markers need to be identified.

CONCLUSIONS

If the past is a harbinger of the future, therapy for HCV infection will probably continue to advance at a brisk pace. Many additional potent agents are in the clinical pipeline, and interferon-free regimens are likely to dominate the HCV therapeutic landscape within the next 5 years. If a simple treatment regimen becomes a reality, a robust health care infrastructure will be needed to identify, triage, and treat the millions of HCV-infected patients who are unaware of their status. The infrastructure in the current U.S. health care system is woefully inadequate. The rate of death from HCV infection has already outpaced the rate of death from HIV infection in the United States. Successful treatment of HCV infection has undeniable long-term benefits with respect to reducing morbidity and mortality. Perhaps the most challenging issue is not whether there will be medical tools to effectively manage and treat HCV infection, but rather whether the economic resources and societal commit-
ment will be adequate to embark on an ambitious agenda to eliminate this global public health problem.

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