

Into the Light: Strategies for Battling Hepatitis C

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Generally, any patient with virologic or histologic signs of chronic hepatitis C virus (HCV) infection should be considered a potential treatment candidate. Whether to treat people with chronic HCV depends on the severity and ultimate treatability of liver infection, relative contraindications to treatment, and the patient's preference. To participate in treatment decisions, patients need to be educated in treatment options, the prognosis, and associated adverse effects of treatment.¹

HCV ribonucleic acid (RNA) must be detectable before treatment can be contemplated. In addition, the genotype of HCV must be known because it drives duration, dose, and monitoring decisions.²

Patients with normal serum alanine transferase (ALT) levels and milder histologic HCV changes will respond to combination antiviral therapy almost identically to those with elevated ALT levels and evidence of moderate-to-severe hepatitis. After counseling, patients with mild disease can be given the option of deferring therapy with periodic laboratory and histologic monitoring.³ The presence of cirrhosis decreases the likelihood of treatment response, but a trial is still advised in those with compensated disease. Patients with decompensated cirrhosis are not only unlikely to respond but have a high incidence of serious adverse events; therefore, treatment is not advised outside of a transplant center.

A fundamental goal of treatment is permanent eradication of the HCV.^{2,4} Antiviral therapy inhibits virus production, decreases infection of new cells, and/or accelerates clearance of cells already infected.⁴ Cure is deemed to have occurred with sustained virologic response (SVR), defined as undetectable HCV RNA 6 months after therapy stops. The reduction in viral production and the clearance of infected cells in essence eradicates the virus. In some cases, reversal of previous scar tissue also occurs. The patient benefits in terms of symptomatic relief and a general increase in level of health. Even if the virus cannot be eradicated, treatment may slow disease progression and delay the complications of chronic HCV infection.¹

About 70% to 80% of patients with genotype 2 or 3 will achieve SVR compared with only about 40% to 50% of patients with genotype 1.² The greater number of treatment failures involving the latter

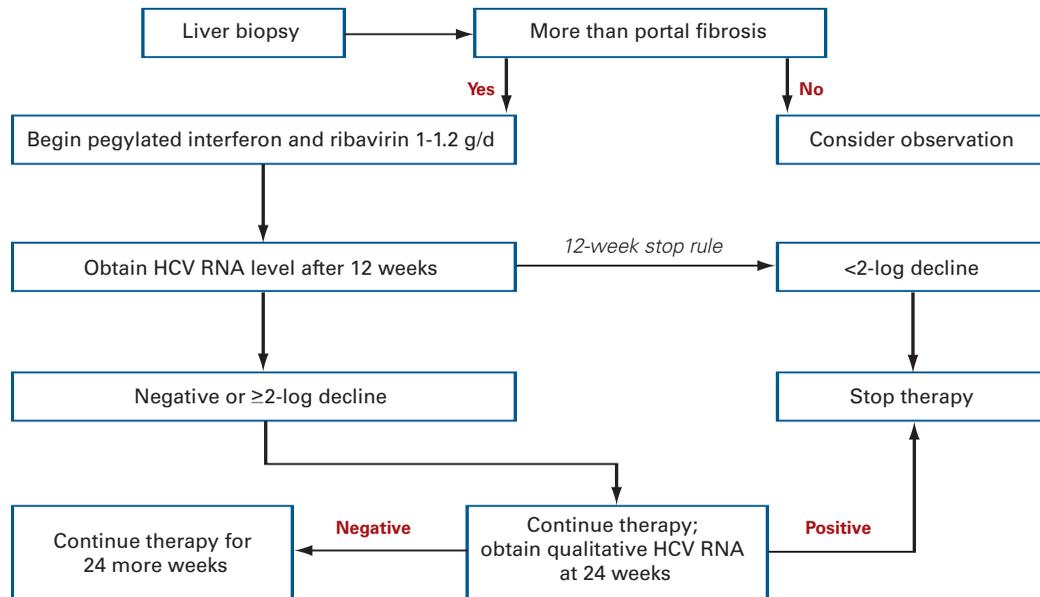
Abstract

The primary measurable goal of hepatitis C virus (HCV) therapy is permanent eradication of the virus (ie, a sustained virologic response [SVR]). Treatment decisions depend on the severity and treatability of the infection, contraindications to treatment, and patient preferences. The current standard of treatment is combination therapy with pegylated interferon (peginterferon) and ribavirin. Dosages and treatment duration vary according to viral genotype. About 70% to 80% of patients with genotype 2 or 3 will achieve SVR compared with only 40% to 50% of patients with genotype 1. Generally, those who previously failed HCV treatment with monotherapy or standard interferon plus ribavirin should be considered for re-treatment with a trial of peginterferon and ribavirin. Side effects associated with treatment include influenzalike symptoms, insomnia, neutropenia, and hemolytic anemia and should be managed aggressively to promote patient adherence to therapy. Future pharmacologic agents are currently in development for patients failing treatment or those who have relapsed.

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■ **Figure 1.** Management of HCV Genotype 1



HCV indicates hepatitis C virus; HCV RNA, hepatitis C virus ribonucleic acid.

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genotype is attributed to several factors including aspects of the virus.⁴

Treatment

The current standard of treatment is the combination of pegylated interferon (peginterferon) and ribavirin.²⁻⁴ Although investigational treatments may modify, augment, or eventually replace this standard, except for dosing variations, the standard has remained stable since 2001.

The once-weekly dose of peginterferon alfa-2a (180 mcg subcutaneously [SC]) is not contingent on body weight whereas that of peginterferon alfa-2b is weight-adjusted (1.5 mcg/kg SC). Patients with HCV genotype 1 (Figure 1) receive a high daily dose of ribavirin (1000 mg by mouth [PO] for patients weighing ≤75 kg, 1200 mg PO for patients weighing >75 kg; for all patients in 2 divided doses); patients with HCV genotype 2 or 3 (Figure 2) receive 800 mg ribavirin PO daily in 2 divided doses.² Treatment for patients with genotype 2 or 3 is usually for 24 weeks; 48 weeks is recommended for those with genotype 1. Because of the high likelihood of treatment response for those with genotype 2 or 3, on-treatment assessment of HCV RNA is not mandatory. On-treatment monitoring of HCV RNA is recommended for those with geno-

type 1. Rapid virologic response—undetectable HCV RNA by polymerase chain reaction tests after the initial 4 weeks of treatment—is an excellent positive predictor of SVR.⁵ Failure to achieve early virologic response (EVR) by 12 weeks (negative HCV RNA or a 2-log drop in viral load compared with the baseline measure^{2,5,6}) is a reliable negative predictor of response to that combination of drugs; therefore, patients who don't achieve this end point should have therapy discontinued.

For patients with genotype 1, who achieve EVR and undetectable virus at week 24, treatment should be continued for a total of 48 weeks. Patients with detectable HCV RNA at week 24 will not have SVR and treatment should be discontinued. In patients with undetectable viral loads at the end of therapy, a final test 24 weeks later will usually confirm the SVR.²

Clinical trials enrolling adequate numbers of patients with HCV of genotypes 4, 5, and 6 are not yet available.² These patients are being treated, therefore, as are those with HCV genotype 1—with the usual dose of peginterferon alfa and a high dose of ribavirin for 48 weeks.

Mechanisms of Interferon. Among the actions inherent in the natural proteins called interferons

are inducing an antiviral state in cells they target, secreting cytokines, recruiting immune cells, and encouraging cells to differentiate.⁴ When interferon alfa is given subcutaneously, it binds specifically with high-affinity receptors present on most cell surfaces, including those of hepatocytes, producing 2 separate but complementary effects:

- Establishes a nonspecific antiviral state in infected cells, inhibiting viral replication, and potentially also in noninfected cells, diminishing their chances of becoming infected; enhances the host's antiviral immune responses, possibly speeding the death of cells already infected with the virus.⁴
- Invokes a host of other effects when it binds to receptors of immune cells; activates such effector cells as macrophages, natural killer cells, and cytotoxic T lymphocytes; induces class I major histocompatibility-complex antigen expression; and interacts intricately with the cytokine cascade.⁴

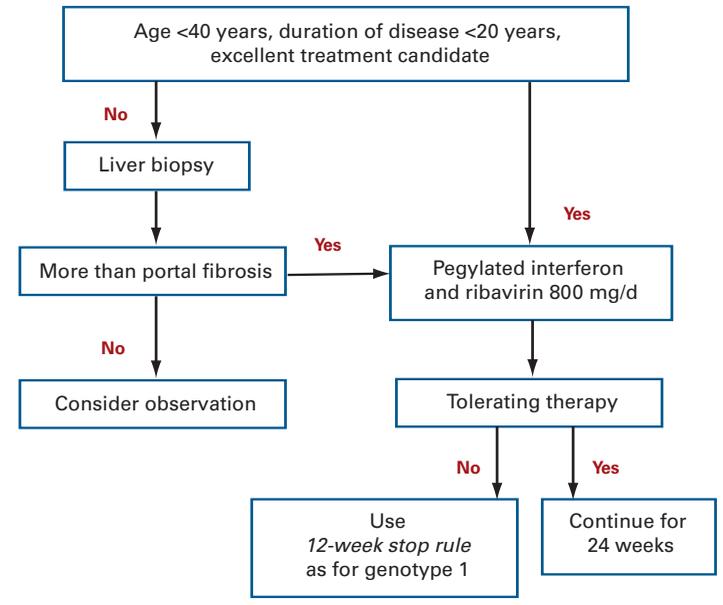
Mechanisms of Ribavirin. In vivo, ribavirin exhibits minimal antiviral action on HCV. Nevertheless, in combination with interferon alfa, ribavirin improves HCV RNA levels and enhances rates of SVR. Although the mechanism has yet to be confirmed experimentally or in large patient numbers, it appears that ribavirin prevents de novo hepatocyte infection. Ribavirin also appears to have immunomodulatory properties.⁴

Combined Interferon Alfa Plus Ribavirin. Before 1998, interferon monotherapy for HCV conferred an SVR of 16%. The introduction of ribavirin boosted that rate to 41%, the biggest increase in SVR rates in HCV therapy in almost 20 years. Then peginterferons were combined with ribavirin, and the SVR increased to between 54% and 56%.⁷

Currently, interferon is seldom used in treatment of HCV without having first been *pegylated* by attaching to it strands of the polymer polyethylene glycol. Pegylation improves efficiency of the drug by increasing its systemic retention and may enhance its binding affinity for cell receptors, which may speed absorption and alter distribution patterns.⁸

Recommended dosages and duration of treatment with peginterferon plus ribavirin vary with viral genotype.⁸ Clinical data indicate that strict observance of the recommended dose of peginterferon alfa-2b with ribavirin increases both EVR and

■ **Figure 2.** Management of HCV Genotypes 2 or 3



HCV indicates hepatitis C virus.

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SVR in genotype-1 patients.⁹ Data are not yet available to address the questions that this raises concerning effects of reducing, interrupting, or stopping either or both interferon or ribavirin dosages in anemic or otherwise treatment-impaired genotype-1 patients. However, other clinical data have shown that a cumulative ribavirin dose of less than 60% of that recommended, which generally accrued from doses missed, was accompanied by a lower rate of SVR.⁷

Managing Side Effects. Treatment for HCV can be physically draining, and side effects are more pronounced if a patient has a history of drug or alcohol abuse. The **Table** lists common side effects of treatment for HCV.³

A large percentage of people will feel influenza-like symptoms for a few days after the weekly interferon injection. These symptoms are particularly common early in the treatment course and can be managed with nonsteroidal anti-inflammatory drugs.³ Insomnia can be treated with sleep-promoting agents, and depression, which should not be underestimated, can be treated with antidepressants. Dose suppression will usually alleviate symptoms of neutropenia, and it is only in individual

Reports

■ **Table. Side Effects of Antiviral Therapy**

Related to interferon
Influenzalike symptoms
Marrow suppression (especially leukopenia and thrombocytopenia)
Emotional effects (irritability, difficulty concentrating, memory disturbances, depression)
Autoimmune disorders (especially thyroiditis)
Hair loss
Rash
Diarrhea
Sleep disorders
Visual disorders (rarely retinal hemorrhages, especially in diabetic patients and hypertensive patients)
Weight loss
Seizures
Hearing loss
Pancreatitis
Interstitial pneumonitis
Injection site reactions
Related to ribavirin
Hemolytic anemia
Chest congestion, dry cough, and dyspnea
Pruritus
Sinus disorders
Rash
Gout
Nausea
Diarrhea
Teratogenicity

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cases of severe need that a granulocyte colony-stimulating factor may be required.

A major side effect of ribavirin is hemolytic anemia. Activated to ribavirin triphosphate in red blood cells (RBCs), this drug sharply decreases RBC adenosine triphosphate (ATP), and, as RBCs lack enzymes to hydrolyze ribavirin triphosphate, there it accumulates. Deficiency of ATP causes oxidative membrane damage, and RBCs are then prematurely removed from circulation. The myelosuppressive effects of peginterferon exacerbate the anemia seen in ribavirin-treated patients.⁷

Options for management of anemia include ribavirin dose reduction, addition of erythropoietin, and/or transfusion. Although erythropoietin admin-

istration has been demonstrated to allow maintenance of ribavirin dosing, it has not yet been shown to enhance SVR compared with reduction in ribavirin dose.

Special Populations

While the combination of peginterferon alfa and ribavirin has demonstrated its efficacy in the general population, special populations with generally poor response or problems arising from comorbid conditions are more difficult to treat. These patients may have cirrhosis or steatosis, be human immunodeficiency virus (HIV) positive, be of African American ethnicity, have shown poor response to prior therapy, or have received liver transplants.¹⁰

Relapsers and Nonresponders. Relapsers are patients in whom HCV RNA is negative at the end of therapy but later becomes positive.³ If such patients receive a course of the same therapy, the same result is probable; however, the chance of SVR will increase if re-treatment is pursued with better treatment. If the initial treatment was monotherapy, for example, then combination therapy should be used to re-treat; if the initial therapy was with interferon and ribavirin, a trial with peginterferon and ribavirin should be considered.

Generally, for those who previously failed to respond to HCV treatment, re-treatment with peginterferon and ribavirin may increase the frequency of response to 10% in previous nonresponders to standard interferon plus ribavirin, and to 20% in nonresponders to interferon monotherapy.³ Re-treatment is less likely to help, or will improve responsiveness to a lesser extent, in patients with HCV genotype 1, high baseline HCV RNA levels, cirrhosis, and black ethnicity.

One predictor of nonresponse with fixed doses of ribavirin is obesity (body mass index >30 kg/m²).⁷ Weight-based dosing of ribavirin eliminates obesity as a predictor of nonresponse, but it is accompanied by higher rates of anemia regardless of weight. Higher plasma concentrations of ribavirin, which are contingent on renal function, will increase risk of anemia, however. Weight-based dosing requires careful monitoring of blood levels for all patients.

African Americans. HCV infection in blacks is about 3 times more prevalent than in whites. Blacks

are also less likely than other groups to achieve SVR. Studies have ruled out such other explanations for poor response among blacks as lack of adherence, low tolerance to treatment, or low baseline levels of neutrophils. No modifications to the standard combination therapy with interferon alfa and ribavirin are recommended for HCV-infected blacks. Although it has not been specifically studied in this population, blacks may benefit, as do certain other nonresponders and relapsers, from higher doses or longer therapy once the virus is adequately suppressed.¹⁰

Liver Disease and Transplantation. When treatment can be tolerated, patients with compensated cirrhosis can undergo antiviral therapy.³ Standard combination therapy can produce SVR, but anemia must be closely monitored. A considerable population of patients has a predisposition to developing anemia or complications of anemia when treated with ribavirin.⁷ Patients with cirrhosis are at greatest risk of morbidity and mortality should HCV progress, and many of these patients, for numerous reasons, are already anemic. Thus, when cirrhosis is decompensated, referral for liver transplantation may be the best option.

Coinfection with HIV. Patients who have HIV should be screened for hepatitis C. Those who are coinfecting should be evaluated, including biopsy of the liver, for antiviral therapy candidacy. If at all possible, the HIV infection should be well controlled before initiation of HCV treatment. In these coinfecting patients, HCV treatment, if tolerated, runs for 48 weeks, regardless of genotype. HIV treatment regimens that include didanosine should be altered, if possible, before starting combination HCV therapy because of potential drug–drug interactions. If didanosine is integral to the HIV regimen, ribavirin must be omitted from the HCV treatment.³

For a variety of reasons, patients with HIV are at risk for anemia even without ribavirin treatment. SVR rates with peginterferon and ribavirin in patients coinfecting with HIV and HCV are lower than in patients infected with HCV only.⁸ The 12-week stop rule based on virologic response, or lack thereof, also applies to those infected with both HCV and HIV.

Renal Disease. People in renal failure are no longer excluded from receiving treatment, but for this patient population, even small doses of ribavirin can cause severe anemia because of delayed clearance of the drug.⁷ Any HCV treatment should be done by experienced clinicians. If at all possible, patients with end-stage renal disease should be treated for HCV, with the risk of hemolytic anemia clearly in mind, before they undergo renal transplantation because, at any time posttransplant, interferon increases the rejection rate. Advanced hepatic fibrosis in HCV patients who are kidney transplantation candidates is associated with reduced graft and patient survival.³ Thus, for people with advanced renal disease and renal transplants, a more complicated question of risk versus benefit must be addressed. Combined liver and kidney transplantation should be considered for patients with cirrhosis and end-stage renal disease.

Hematologic Disorders. Although data determining the safety and efficacy of ribavirin at any dose in people with hematologic disorders are limited (many trials of combination antiviral therapy specifically excluded them), chronic HCV in patients with many hematologic disorders can be treated with peginterferon plus ribavirin.³ Although peginterferon plus ribavirin therapy may be contraindicated in patients with thalassemia and other hemoglobinopathies who have HCV from blood transfusions, researchers in a small pilot study recommended combination therapy for this population.⁷ There was a greater need for transfusions during therapy, probably because of ribavirin-related anemia. In patients who have a genetic predisposition to anemia, ribavirin-associated hemolysis and transfusion requirements are likely to be more drastic. Elderly patients, especially those with coronary artery disease, are often less able to tolerate anemia, and treatment should be given only with caution.⁷ Patients with hemophilia and HCV are treated the same as the general population although biopsy may be deferred.³

Interestingly, a group in a recent press release reports that the course of chronic infection with HCV appears to be less severe in people with hemophilia than in nonhemophiliacs.¹¹ This difference may be related to the role of thrombosis and vascular factors in the progression of cirrhosis. Patients

with hemophilia had significantly lower histological activity and fibrosis scores. None of those with hemophilia showed evidence of advanced disease with bridging fibrosis or cirrhosis compared with 30% of controls. If these findings can be verified, the researchers predict the possible inclusion of anticoagulants or antiplatelet agents in long-term treatment of chronic HCV.

Substance Abuse. Recovered intravenous drug users, even those on methadone maintenance, can be treated with combination antiviral therapy. Active drug users need evaluation on a case-by-case basis; a concurrent drug treatment program is a factor that favors treatment. Results of more trials are needed to determine optimal HCV treatment regimens; likely side effects, including depression; how antiviral therapy might alter methadone requirements; and how to encourage compliance and decrease recidivism.³

In alcoholic patients, abstinence is necessary before and during treatment. Alcohol abuse treatment can be linked to HCV treatment in alcoholic patients. No safe level of alcohol intake in HCV patients has been established.³

Other Categories. Pregnant patients should not be treated.³ The risk of transmission of hepatitis C to an infant is less than 5%. Patients with highest levels of HCV RNA, such as those with HIV, are at highest risk of vertical transmission. In people with uncontrolled or severe psychiatric diseases—clinical depression or schizophrenia—treatment is contraindicated because of the neuropsychiatric side effects of interferon. Other contraindications include advanced cardiac or pulmonary disease, severe cytopenias, retinopathy, seizure disorders, poorly controlled diabetes, or other comorbid conditions inadequately controlled. Children older than 3 years of age can be treated using the same general principles of management that are applied to adults.

Treatment Adaptations in Special Populations. There are 2 adaptations to standard HCV therapy that show promise of success in special populations:

Longer Treatment. Kinetic studies in patients who slowly approach HCV RNA negativity suggest potential value for longer intervals of standard

treatment, particularly in those infected with genotype 1.¹⁰ Preliminary results of one study indicate that either 6 or 12 months of treatment (depending on genotype) subsequent to standard 4-week treatment obtained SVR in 92% of patients who were HCV RNA–negative at week 4 and SVR of 35% and 50%, respectively, in those who were HCV RNA–positive at week 4. Extending therapy for 72 weeks has also been proposed for those patients who have a greater than 2-log drop in HCV RNA level at 12 weeks but do not become HCV RNA–negative until 24 weeks. Further study is needed before these recommendations can be broadly applied.

Stronger Treatment. Early results suggest that higher doses of peginterferons or consensus interferons for 12 weeks followed by either continued high doses or reversion to standard treatment regimens may improve SVR in previously nonresponsive and relapsed patients who had very low SVR rates.¹⁰ Again, these promising reports need to be reproduced before such regimens should be clinically applied.

The Treatment Enigma

A great number of patients are cured (ie, undetectable HCV RNA 6 months after treatment ends) after treatment with peginterferon alfa and ribavirin, with 80% of patients with HCV genotype 2 obtaining SVR. However, in patients carrying genotypes other than 2 and 3, treatment fails to eradicate HCV more commonly—as much as 60% of the time in patients with genotype 1.⁵ Although peginterferon alfa and weight-based ribavirin in combination comprise all known necessities for cure of HCV, in a substantial proportion of compliant patients, HCV is not cleared. In addition to factors related to the host, treatment regimen and HCV itself have roles in the outcomes of treatment.

Treatment Factors. Although the drug combination used to treat HCV has not changed since introduction of ribavirin, cure rates have increased through optimizing steady-state levels of interferon alfa and ribavirin.⁴ The side effects of ribavirin, however, remain problematic, particularly hemolytic anemia; weight-based dosing of ribavirin

ameliorates this effect, but does not solve the problem.⁷

There are ways that clinicians can directly enhance treatment success in their patients. Strategies include counseling and support for patients to promote adherence, scrupulous management of side effects, and early response evaluation to guide treatment decisions.^{6,12}

Virus-related Factors. Because the antiviral activity of interferon alfa is not thoroughly mapped, it is not known why the antiviral action of interferon alfa is more effective in HCV genotypes 2 and 3 than in the other genotypes.⁴ In addition, subtypes within each genotype vary in sensitivity to interferon alfa. It is encouraging to note, however, that treatment with neither interferon alfa nor ribavirin appears to promote viral resistance.

Investigational Treatments

HCV infection is a complex disease. Because of its great intrastrain variability and its inherent mutability, permanent eradication of HCV will require creative and multipronged measures. Treatments that have thus far failed to show sufficient promise in clinical trials include phlebotomy, amantadine, interferon gamma, interleukin-10, and thymosin alfa-1.³

Drugs now being developed for patients who have failed or relapsed after treatment with peginterferon and ribavirin include specifically targeted antiviral therapy (STAT) drugs for HCV (STAT-C), new interferons and inducers of interferon, ribavirin alternatives, and immunomodulatory agents.^{4,5}

STAT-C. The STAT-C regimens, akin to anti-retroviral therapies for HIV infection, are considered by some to be among the most promising of the investigational therapies. These drugs target enzymes that are crucial to HCV replication,⁵ such as NS3-4A protease and NS5B polymerase. The HCV protease and polymerase inhibitors, most of which were developed over the past 5 years, are being tested in phase 1 and phase 2 trials. Although protease inhibitors are promising, they do have a short half-life and so require dosing every 8 hours. However, evidence indicates that, used as monotherapy, protease inhibitors can attain a greater than 2.5-log

reduction in serum HCV RNA levels within 14 days. Polymerase inhibitors, used in the same way for the same duration, achieve a more modest 1-log reduction in viral load. Phase 2 clinical trials are now assessing the efficacy of these STAT-C drugs using double- or triple-combination therapy regimens.

Protease inhibitors and polymerase inhibitors, both taken orally, disrupt viral replication by inhibiting their nominal enzymes.^{12,13} These drugs, when used alone for short intervals, have impressively reduced HCV levels, and are under evaluation in clinical trials, used in combination with peginterferon and ribavirin. Other stages in HCV replication can be confounded with drugs that block production of HCV antigens from RNA (internal ribosome entry site inhibitors), prevent normal handling of HCV proteins (glycosylation inhibitors), or prevent HCV from entering cells by competitive antagonism. Ribozymes might be produced to break down particular viral RNA molecules. Complementary segments of deoxyribonucleic acid (DNA) that bind to viral RNA and inhibit its replication (antisense oligonucleotides) are also being developed.

Interferon Improvers/Alternatives. Several paths appear to have potential for improving the antiviral activity of interferon. Some changes to the primary amino acid sequence of interferon types and subtypes significantly increase antiviral activity, at least in vitro. Consensus interferon alfa is an example of this approach.⁴ Although interferon beta confers no advantage over interferon alfa for treating HCV and is not approved for that purpose, peginterferon beta as well as consensus peginterferon alfa are now being clinically tested.⁴ Interferon has also been fused with human serum albumin.^{4,12} This combination enhances its kinetic and dynamic properties in the patient and, therefore, its long-term effectiveness. Conveniently, this product is administered every 2 weeks rather than weekly. Other interferons are also under investigation. When coadministered with interferon alfa, interferon lambda appears to enhance its effect and is being tested in clinical trials; also being tested in a phase 2 trial is interferon omega. New ways to deliver interferon are under development, including infusion pumps, controlled-release injectables, and oral and inhaled formulations.⁴

Ribavirin Improvers/Alternatives. Although the antiviral mechanisms of ribavirin are largely unknown, it does appear to make the produced copies of the virus less infectious.⁴ In some patients, however, the anemia induced by ribavirin is dose-limiting.^{4,7} Viramidine is a new ribavirin analogue that lowers the risk of anemia. A prodrug, it preferentially targets the liver where, once absorbed, it is converted to ribavirin. It causes less anemia because, compared with ribavirin, there is less uptake and accumulation in RBCs.^{4,7}

Immunity Enhancers. An immune system activator that invokes and sustains high levels of endogenous interferon alfa is soon to undergo phase 1 testing in patients with chronic HCV infection, as reported at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy. In preclinical trials in human immune cell cultures and in monkeys, the drug stimulated more broadly based antiviral activity with high concentrations of chemokines and cytokines, including the full range of natural isoforms of interferon alfa, which persisted and which, in rat and monkey studies, did not interfere with ribavirin. Researchers surmise that this broader immune response might translate into an adaptive, more permanent immune response that might be useful against other types of infection as well.¹⁴

Although many new products are promising, reliable results will take time. Many questions are as yet unanswered about optimal drug combinations, treatment durations, and avoiding and controlling toxicity.⁵ Development of new drugs will increase costs, at least temporarily. Future treatment of chronic hepatitis C may well involve 1 or more of these investigational products, probably in combination with the currently well-known and well-respected standard treatments, peginterferon and ribavirin.¹²

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