

Treatment Issues With Chronic Hepatitis C: Special Populations and Pharmacy Strategies

*Based on a presentation by
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Abstract

Combination therapy with peginterferon alfa and ribavirin now eliminates detectable hepatitis C virus (HCV) from the blood of more than half of patients with long-term infections. However, many of those infected with HCV have low rates of response to therapy and/or are more susceptible to drug side effects that limit adherence to therapy. African Americans with HCV, for example, tend to be more difficult to cure with drug therapy. Individuals coinfect with both human immunodeficiency virus and HCV are also more difficult to treat. As managed care organizations begin offering anti-HCV therapy to a broader range of patients, special strategies for limiting medication side effects and enhancing overall clinical and economic outcomes will become more important. In particular, assessing the early virologic response to therapy at 12 weeks can help clinicians identify patients who are highly likely to be responsive at the end of the full course, while also identifying likely nonresponders—who can be taken off therapy and thereby avoid unnecessary side effects and costs. In all patients remaining on therapy, efforts to boost adherence will also enhance the overall rate of sustained virologic response. Special attention should be paid to managing depression and cytopenias with patient education and either dose reduction or use of hematopoietic growth factors. These 2 basic treatment strategies—of stopping treatment early or, alternatively, of pressing for full patient compliance over the full course of therapy—are flip sides of the same management coin that health plans and clinicians can employ to optimize results and cost effectiveness with the current standard of therapy for chronic HCV infection.

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Over the past decade, the benefits of combination therapy with pegylated interferon alfa and ribavirin have become abundantly clear. As public and private health plans have acted on this evidence, many of the ideal candidates for anti-hepatitis C virus (HCV) therapy have

already received this effective regimen. Although laudable, this concerted effort to target individuals most likely to benefit from treatment has left behind more difficult-to-treat populations of HCV-infected patients. These patient subgroups—including African Americans, human immunodeficiency virus (HIV)-infected patients, and those with contraindications or side effects to drug therapy—may require special approaches to increase the chance of virologic clearance.

Also, despite the steady improvements in HCV treatment efficacy, a large proportion of patients who are treated still do not achieve viral clearance. Because these treatments are costly and often produce their own level of morbidity,¹ the consequences of these treatment failures for health plans are significant. Fortunately, the past decade's treatment experiences with various interferon-based regimens have also provided valuable lessons about what does and does not work in achieving the best outcomes. In particular, the role of improved patient education and adherence to therapy have emerged as critical factors in maximizing the benefits of costly antiviral therapy. Adherence to long-term therapy, for example, is now known to be especially critical in patients with genotype 1 infections. Because these patients typically require 1 full year of drug therapy, the failure to quickly recognize and manage any of the common hematologic or neuropsychiatric side effects of therapy can lead directly to nonadherence or dose reduction.²

This article will explore strategies for optimizing HCV therapy in hard-to-treat patient subgroups. Special attention will be

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paid to black patients and to those coinfect- ed with HIV and HCV. The article will also review causes for poor adherence with anti- HCV therapy and then suggest practical steps for managed care organizations (MCOs) wishing to improve adherence and maximize results with the expensive combi- nation regimens. In many cases, improving adherence will be exactly the strategy that is required for a successful outcome in a potentially difficult patient. But adherence requires more than a 5-minute pep talk with the patient. A cooperative and sustained team approach is usually needed to provide the full package of screening, patient education, monitoring, and early identifi- cation of side effects. Thus, as combination therapy for HCV infection moves into its second decade, the pharmacist and a full multidisciplinary team of professionals will become even more essential in helping to eliminate the serious health threat that still resides in the hepatocytes of millions of aging Americans.

The Treatment Decision

Although all patients with long-term HCV are considered potential candidates for antiviral therapy, the risks and benefits of therapy must be weighed carefully on an individual basis.^{3,4} In general, drug therapy is targeted at those patients with an in- creased risk of developing cirrhosis, such as those with a positive HCV ribonucleic acid (RNA) test result, portal or bridging fibrosis on liver biopsy, and at least moderate in- flammation and necrosis. Most but not all treated patients also have elevated alanine aminotransferase (ALT) values.³

The decision to treat becomes less clear in those with mild liver disease (eg, elevat- ed ALT, but minimal biopsy-proven liver damage), those with advanced liver disease, posttransplantation patients, active or re- covering injection drug users, active alcohol users/abusers, those with acute HCV infec- tion, the elderly, and children. In fact, the safety and efficacy data supporting combina- tion therapy are limited in these and in a variety of other patient populations.^{5,6}

In recent years, new data have emerged on 2 specific patient groups with extremely high rates of HCV infection: black patients

and patients infected with HIV. This new information sheds light on the unique viral and clinical characteristics of these infected patients and the management techniques that might improve response rates.

HCV Treatment in African Americans

The prevalence of HCV infection among black patients is approximately 3 times higher than that seen among white patients.⁷ Black patients are also more likely to be infected with the harder-to-treat genotype 1 HCV, to have a higher incidence of HCV complications, and to develop hepatocellular carcinoma at higher rates.⁸ A recent case- control study suggested that liver cancer risk was doubled among black patients with HCV and cirrhosis compared with matched white patients.⁹ Although the risk factors for infec- tion in blacks are generally the same as in the general population, the viral kinetics after treatment tend to differ¹⁰ with, for example, a reduced rate of HCV RNA decline after interferon therapy.¹¹ The mechanisms for these differences in virologic response are unclear.

Several retrospective studies also indicate that African Americans have lower rates of sustained virologic response (SVR).¹¹⁻¹³ Al- though one small, retrospective study indi- cates that black and white patients with genotype 1 infections have similar SVRs if the therapy is highly controlled (in this case, in a correctional facility), the racial differ- ence in response rate was thought to be unrelated to lack of compliance or disease severity.¹⁴ However, because black patients have been vastly underrepresented in the early prospective randomized trials of inter- feron alfa plus ribavirin, the actual causes for this apparent poor response rate have remained unknown.

In recent years, several prospective mul- ticenter trials have confirmed the significant- ly lower rates of SVR in black patients. In one trial, 100 black patients and 100 white patients with chronic HCV were treated with peginterferon alfa-2b plus ribavirin for 48 weeks.¹⁵ Each cohort had 98 patients with genotype 1 HCV. All patients received 1.5 µg of peginterferon alfa-2b per kilogram of body weight subcutaneously once weekly for 48 weeks and 1000 mg of ribavirin orally daily

Table 1. Treatment Response in Blacks and Whites: Why the Difference in SVRs?

	Blacks (%) (n = 100)	Whites (%) (n = 100)	P value
Virologic response			
Early	40	69	<.001
Sustained	19	52	<.001
Treatment responses			
Rate of discontinuation	19	21	
Dose reduction	22	24	
Adverse events			
Headache	39	43	
Fatigue	68	60	
Myalgia	40	37	
Nausea	21	26	
Fever	52	58	
Alopecia	37	31	

SVRs indicates sustained virologic responses.
Source: Reference 15.

for the first 12 weeks and then 800 mg per day for weeks 13 to 48. Eighty-one percent of black patients and 79% of white patients completed therapy. The rate of SVR, defined as a negative serum test for HCV RNA 6 months after completion of therapy, was higher among white patients than among black patients (52% vs 19%; $P < .001$). In this trial, none of the black patients lacking an early virologic response (EVR) at 12 weeks went on to have an SVR. Multivariate analysis showed that race was the only variable significantly associated with the difference in response rate. The groups had similar rates of adverse events, dose reduction, and discontinuation (Table 1).¹⁵

Another prospective, multicenter clinical trial in patients with chronic HCV infection also showed a lower rate of SVR among 78 blacks receiving combination antiviral therapy (26%) compared with 28 white patients (39%).¹⁶ This 26% SVR in blacks was higher than noted previously in retrospective trials, and 90% of these patients showed stabilization or improvement in liver fibrosis.^{8,16} Still, based on these prospective studies and other recent analyses,¹⁷ the treatment response

rates among black patients with HCV are clearly lower than those seen among white patients. The underlying cause of this difference due to race is unclear but may involve the genetics of the immune response.

Despite these lower response rates, and whatever the cause, combination therapy with interferon alfa and ribavirin remains the treatment of choice for blacks with chronic HCV. In counseling patients about treatment, however, a realistic appraisal of the chances of success must be conveyed. This means telling black patients that their overall chance of treatment success is likely in the range of 20% to 25% rather than 40% or 50%. Preliminary data reported at a recent meeting of the American Association for the Study of Liver Diseases (AASLD) indicate that weight-based dosing of ribavirin may improve SVRs in African Americans with genotype 1, although these results are still inferior to those typically seen in white patients.¹⁸

HIV/HCV Coinfections

Because of the shared risk factors, a significant proportion of individuals with HIV are coinfecting with HCV (Figure 1); approximately 25% of HIV-infected individuals are thought to have HCV; conversely, up to 10% of those with chronic HCV may be HIV coinfecting.^{7,19,20} Because the treatments for HIV infection have improved, patients with HIV are living longer and HCV-related liver disease is emerging as an important cause of morbidity and mortality.²¹

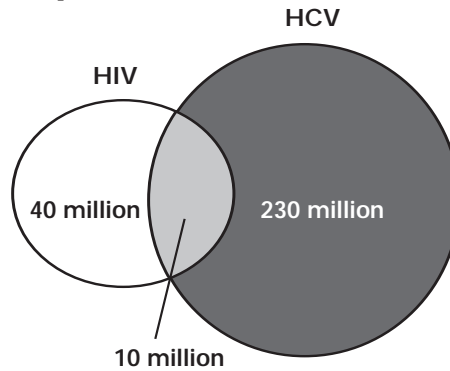
The interactions between these viruses are complex and incompletely understood (Table 2), making treatment decisions even more challenging. For example, HCV may increase the risk of HIV progression²²⁻²⁴ and highly active antiretroviral therapy may or may not also be associated with increased hepatotoxicity in HCV-infected patients.²⁵ In a prospective study of more than 3000 HIV-infected patients, 1157 (37%) of whom were seropositive for HCV, HCV coinfection was associated with increased mortality, which was possibly related to impaired CD4 cell recovery.²² Meanwhile, most studies also indicate that HIV adversely affects the natural history of HCV by increasing liver fibrosis.²⁶ In one study, the median fibrosis

progression rate in 122 patients coinfecting with HIV and HCV was 0.153 fibrosis units per year compared with a rate of 0.106 in 122 matched patients who were HIV negative and HCV positive ($P < .0001$) (Figure 2).²⁷ In the coinfecting patients, a low CD4 count, a higher alcohol consumption rate, and an earlier age of acquisition of HCV infection were associated with a higher liver fibrosis progression rate. In a more recent study of 210 HIV/HCV-coinfecting patients, advanced antiretroviral treatment did produce liver enzyme elevations in some patients but, overall, the anti-HIV therapy was not associated with advanced liver fibrosis.²⁸

Four major studies have now evaluated the safety and efficacy of combination therapy with peginterferon alfa plus ribavirin in HIV/HCV-coinfecting patients.²⁹⁻³² All of these studies showed that combination therapy involving the pegylated form of interferon was superior to combination therapy using the standard interferon or monotherapy in treating these patients. In general, response rates were lower than those seen in HCV-monoinfected patients. There were marked discrepancies in the rates of SVRs based on HCV genotypes (Figure 3). Side effects were significant in all arms of these studies, once again highlighting the need for monitoring and patient counseling to encourage adherence and chance of cure.

In summary, large randomized trials have now documented that the combination of pegylated interferon alfa and ribavirin provides better efficacy (overall SVRs of up to 40%) and favorable risk-to-benefit ratios compared with standard regimens of interferon plus ribavirin in patients with HIV/HCV-coinfection. Although the response rates in these coinfecting patients are reduced, results still indicate that almost half of all HIV/HCV-coinfecting patients now have an opportunity for resolution of this infection that increasingly manifests as advanced liver disease in these patients. The message for patients with HIV, as for African American patients, is that treatment may provide significant benefits. The chance of success may not be as great as it is in non-HIV-infected patients, and the side effects of therapy are certainly significant, but the risks of no ther-

Figure 1. Overlapping HCV and HIV Epidemics



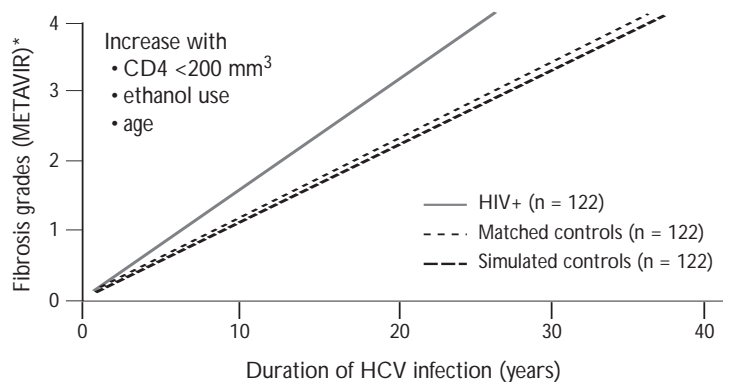
HCV indicates hepatitis C virus; HIV, human immunodeficiency virus.

Table 2. HCV and HIV Coinfection

Impact of HCV on HIV	
•	HCV may increase risk of HIV progression
•	HCV may impair reconstitution
•	HAART hepatotoxicity more common
Impact of HIV on HCV	
•	Increases HCV RNA
•	Increases fibrosis progression rates
•	Increases HCV-related morbidity and mortality
•	Increases perinatal transmission of HCV

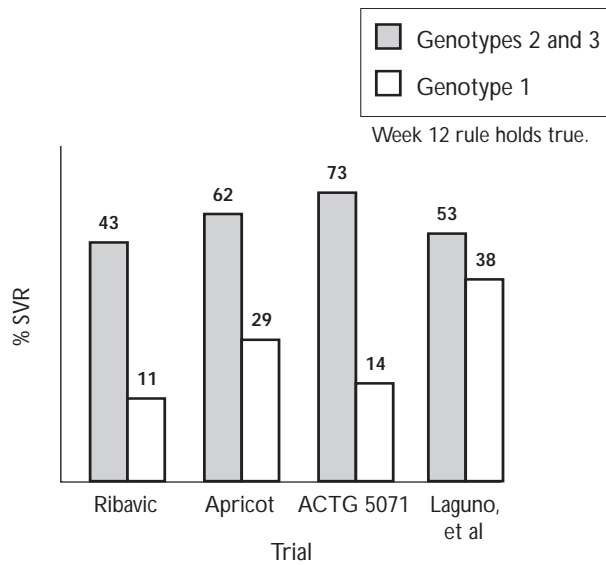
HCV indicates hepatitis C virus; HIV, human immunodeficiency virus; HAART, highly active antiretroviral treatment; RNA, ribonucleic acid.

Figure 2. Effect of HIV on Fibrosis Progression Rates



*METAVIR is a French system for scoring liver biopsies. HIV indicates human immunodeficiency virus; HCV, hepatitis C virus. Source: Reference 27.

Figure 3. HIV/HCV Coinfection According to Genotype



HIV indicates human immunodeficiency virus; HCV, hepatitis C virus; SVR, sustained virologic response; Apricot, AIDS Pegasys Ribavirin International Coinfection Trial; ACTG, AIDS Clinical Trials Group. Sources: References 29-32.

apy are in many patients no less perilous. Treatment of these coinfecting patients remains more complex than treatment of HCV-monoinfected patients, but ongoing investigations will provide valuable clues about the best strategies for patient selection, early initiation to avoid liver fibrosis, and management of antiretroviral therapy to avoid hepatotoxicity.

Strategies for Managing Therapy

In considering treatment in diverse patient populations, clinicians have for many years weighed individual patient factors to predict response. Based on the first wave of interferon-based therapy in the 1990s, the main predictors of positive response were determined to include genotype 2 or 3, absence of fibrosis, low viral load, younger age, female sex, and low body mass index. In recent years, many “ideal” patients with chronic HCV infection (eg, young, slim women) have been successfully treated. Now, as clinicians begin to deal with the harder-to-treat core of older patients with long-term HCV infection, a new set of predictors is emerging. Although the HCV genotype remains perhaps the key factor in

predicting therapy success, additional refined patient indicators of success include lack of steatosis, ethnicity, ribavirin dosage, early response to therapy, and adherence to therapy.³³⁻³⁶ These last 2 factors, discussed in detail below, are extremely relevant to the clinicians and pharmacists who are initiating and managing combination antiviral therapy today.

Twelve-Week Response: A Milepost for Early Reassessment. The complexity, potential side effects, and high cost of a 6- to 12-month regimen of anti-HCV therapy are hurdles to successful treatment of chronic hepatitis. One practical strategy for limiting patient exposure to side effects and reducing drug costs is to identify nonresponders early in the therapy course and stop treatment early. This early discontinuation technique is based on the evidence from the peginterferon-alfa trials in which almost all of those patients who had minimal reductions in viral load by week 12 of therapy also had no SVR at week 48 of therapy (Figure 4).^{37,38}

Based on these results, the guidelines from both the National Institutes of Health and the AASLD call for routine monitoring of patients with HCV genotype 1 (who typically require the 48-week course of therapy). Patients who fail to achieve an EVR, which is defined as a minimum 2 log (ie, 100-fold) decrease in viral load, at week 12 of treatment are deemed to have only a small chance of achieving an SVR. In these patients without EVR, clinicians can consider stopping therapy.^{3,6} For those with genotype 2 or 3, no interim viral load measurement is required, because the response rates are generally higher and treatment lasts only 24 weeks.

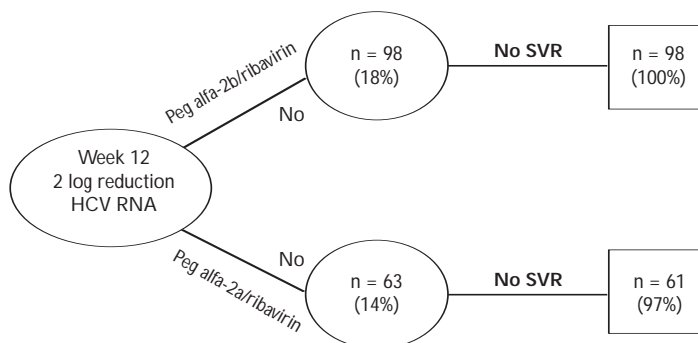
Such an early discontinuation policy not only spares the patient from unnecessary side effects, it may also reduce a health system’s drug costs.^{38,39} One estimate of the potential economic savings with application of the 12-week stopping rule found that the costs for antiviral drugs would be reduced by about 45%.³⁹ In dollar terms, the savings in patients taking peginterferon alfa plus ribavirin were about \$16 000 in treatment-naïve patients. With the introduction of

generic versions of ribavirin in 2002, the costs of combination therapy have decreased, but the savings attributable to stopping therapy at 12 weeks in a large proportion of patients are still likely significant, especially for those with genotype 1 infections who would otherwise still require the full 48-week course.

Adherence and Depression: Modifiable Predictors of Response? Just as stopping therapy early makes sense in those patients headed for treatment failure, continuing therapy for the full course makes sense in those with the best chance for HCV eradication. Adherence to therapy is, in fact, a critical part of anti-HCV success^{40,41} and it is one of the few “modifiable” predictors of response rate. The value of adherence has been quantified in data from interferon-based trials involving more than 1500 patients.^{40,41} In this analysis, those patients who received more than 80% of their total interferon and ribavirin doses for more than 80% of the duration of therapy (ie, “80+80+80”) in the initial 12 weeks had the highest EVRs (Figure 5) as well as the best eventual SVRs.⁴¹ Dose reductions or interruptions after the initial 12-week mark also reduced SVRs. Another study using this same definition of adherence recently found that both treatment-naïve patients (n = 301) and nonresponders (n = 142) who adhered to 80% or more of their intended combination treatment schedule (both dose and duration) had significantly higher response rates.⁴² Response rates in compliant and noncompliant naïve patients were 44% versus 7%, respectively; in those who had previous non-response to therapy, the corresponding response rates to retreatment were 31% and 11%, respectively.

To help patients remain adherent for up to 1 year, the provider and health system need to focus on careful patient selection; assessment for comorbidities and contraindications; and education on side effects, drug abuse, and depression. Several authors have commented on the need for early identification and management of side effects—because these are the primary reason for nonadherence.^{40,43} One alternative to reducing doses to manage a common side effect is

Figure 4. Predicting Nonresponse Early in Therapy

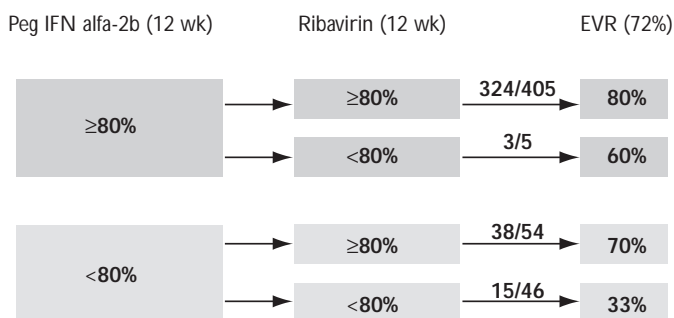


HCV indicates hepatitis C virus; RNA, ribonucleic acid; SVR, sustained virologic response.

Sources: References 37,38.

to use growth factors to treat cytopenias.^{44,45} Although not approved by the US Food and Drug Administration for use in patients being treated for HCV infection, these agents are increasingly used in this setting; a recent review of pharmacy claims at a large health benefits company found that about 9% to 17% of patients receiving pegylated interferons for anti-HCV therapy were receiving epoetin or filgrastim.⁴⁶ As discussed in the final section of this article, more research is needed to determine the impact of concomitant use of recombinant hematopoietic agents on patient quality of life, adherence, and SVRs.³

Figure 5. Adherence and Early Response



Dose reductions, especially both drugs, reduce the chance of EVR.

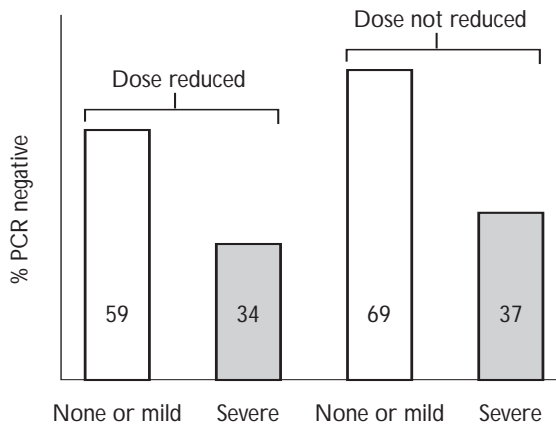
Dose reductions after EVR reduce SVR from 72% to 61%-63%.

After EVR, discontinue/discharge or long interruptions reduce SVR from 72% to 50%.

IFN indicates interferon; EVR, early virologic response; SVR, sustained virologic response.

Source: Reference 41.

Figure 6. Depression, Adherence, and Response



PCR indicates polymerase chain reaction.
 Source: Reference 49.

Severe depression and psychiatric syndromes are considered contraindications to the use of interferon alfa. In fact, a significant proportion of patients with chronic HCV infection are not started on antiviral therapy due to psychosocial factors, such as depression. In a recent study of 580 patients in a Veterans Affairs Medical Center, depression prevented 93 patients (16%) from initiating therapy.⁴⁷ A similar study found that 7% of 354 veterans were not treated due to psychiatric problems.⁴⁸

Depression is also a frequent side effect of interferon. For those patients who develop depression during the course of combination antiviral therapy, the response rate appears to be lower. One study showed that even among patients in whom the doses of interferon alfa and ribavirin are not reduced, depression remains a significant predictor of poor response to antiviral therapy (Figure 6).⁴⁹ The overall rates of HCV clearance were 34% in the 29 patients with the greatest increases in depressive symptoms, 59% in the 41 patients with moderate increases, and 69% in the 32 patients with the smallest increases ($P < .05$). These results indicate that depression is, apart from any influence it exerts on adherence or dose reduction, a predictor of treatment failure. Such results highlight the potential need to identify and treat depressive symptoms in this patient population. A small prospective study has

shown that interdisciplinary care and antidepressant treatment for psychiatric patients led to SVRs that were similar to those found in control groups.⁵⁰

Improved proactive management of depression, substance abuse, and drug-related side effects may help health plans get more patients to treatment goal with anti-HCV therapy. A number of the key patient communication issues related to these 2 key issues and others are covered in the final section of this article.

Pharmacy Considerations. In addition to the screening recommended to identify those patients who are eligible for treatment and also at high risk of developing HCV-related liver complications, the patient history should include information that will be relevant to the pharmacist and the therapy management team. As already discussed, HIV infection and depression are concomitant diseases that may impact outcomes; so are thyroid disease and diabetes. Use of alcohol and/or illicit drugs may also reduce response rates and/or raise the risk of antiviral toxicity. Medication history and allergy documentation may also be relevant to starting anti-HCV therapy; for example, an allergy to nonsteroidal anti-inflammatory drugs may preclude use of these agents to treat the side effects of peginterferon/ribavirin therapy. The patient's employment status is also a factor, because therapy may interfere with the performance of a high-risk job.

Specialty pharmacy groups are increasingly taking the lead in dispensing peginterferon and ribavirin. These groups often work in conjunction with nurses to collaborate with the physician and patient to ensure proper dispensing and patient education. At minimum, the pharmacist should schedule a counseling session with the patient after receiving the prescription. At this session (usually 45 minutes), the pharmacist can obtain the patient's weight, calculate the dose based on weight (with the injection volume rounded to 0.4 or 0.5 mL for patient ease), and then dispense the medication (a 1-month supply is normally allowed by insurers). In some cases, pharmacy consultation with the clinician will be required to review the prescription for accuracy and completeness.

Several specific points should be made to patients in terms of administration. First, ribavirin dosing should be twice daily with meals. Discussing the patient's "typical day" may help clarify how the dose spacing and consistency can be maintained, even in difficult situations, such as shift work. The dosing for peginterferon alfa is once every week on the same day, usually Friday night, so patients can manage side effects over the weekend. The patient should be reminded that this is a subcutaneous dose. Describing it as similar to the insulin dosing done by diabetic patients can help patients overcome their fear of administration.

The actual preparation and administration of pegylated interferons has become easier since the introduction of preloaded syringes or "pens." The dose is simply dialed in to these preloaded devices, obviating the need for drug vials, diluent vials, and the reconstitution procedure. The injection site, either the abdomen or the top of the thigh (where the patient must be able to "pinch an inch"), is prepared by swabbing with alcohol. The skin is pinched, the needle is inserted on an angle, and the drug is injected slowly. If blood is present when the needle is withdrawn, the site should be pressured briefly with an alcohol swab. Swabs and the used syringe/pen are disposed of in a proper needle container, which is, in turn, disposed of at a pharmacy, hospital, or doctor's office. Because the patient's blood is contagious, family members need to be protected from contact. A registration system is used to ensure adequate supplies of medication; after the patient registers, the pharmacist can procure pegylated interferon using the access number on a monthly basis. The pharmacist can track compliance and ensure a timely supply by setting up a system for drug ordering that allows for the 5 business days typically required to obtain medication.

Finally, the potential side effects of therapy with interferons and ribavirin must be clearly described. Side effects accounted for discontinuation in 10% to 14% of patients in the registration trials. Such results, even in the controlled setting of the clinical study, indicate why education of patients, their family members, and caregivers about side

effects and their management needs to be a key part of treatment.³

Hemolytic anemia is one of the major side effects of ribavirin therapy. A hemoglobin drop of 2 to 3 g/dL is normal during combination therapy, but the size of the change varies considerably from patient to patient. Some patients will have a precipitous drop in hemoglobin and develop symptoms such as fatigue, shortness of breath, palpitations, and headache. To encourage long-term treatment compliance, the patient should be informed about the role of red blood cells in oxygen transport, the hemolytic impact of ribavirin on red cells, and the likelihood of symptoms on exertion. Patients need to be reminded to comply with the laboratory tests (a "no laboratories, no drug" policy is common). Blood counts are usually measured at weeks 1, 2, and 4 and then at 4- to 8-week intervals thereafter. If the hemoglobin drops below 10 g/dL, the dose can be reduced by 200-mg increments until the level increases; if severe anemia (hemoglobin <8.5 g/dL) occurs, ribavirin therapy can be stopped.⁵¹ In selected patients with persistent anemia even after dose reductions, use of epoetin may help reduce symptoms and maintain antiviral therapy.³ However, prospective trials are still needed before support with hematopoietic growth factors can be recommended for routine or prophylactic use.^{3,6}

The potential for teratogenicity is the other major side effect risk that must be explained carefully to patients. Because ribavirin can cause birth defects, it is imperative that men and women taking the drug use 2 forms of birth control—a condom plus another form of contraception—during therapy and for 6 months after treatment completion.

Flulike symptoms, such as fever, headache, chills, and myalgia, are the most common side effects with interferon-based therapy. These usually start early in the treatment and subside somewhat with further treatment. Patient self-management techniques are important in dealing with these flulike symptoms. In particular, over-the-counter analgesics are beneficial and all patients should be encouraged to remain well hydrated (up to 8 glasses of water per day). Neuropsychiatric symptoms, such as irritabil-

ity, mood alteration, depression, and short-term memory loss, are also fairly common, as are visual changes (blurred vision, dry eyes, nystagmus, or photophobia), insomnia, photosensitivity, weight loss, alopecia, hypothyroidism or hyperthyroidism, and worsening of diabetes. Appropriate measures for such side effects should be instituted (eg, use of sunblock, nutrition or hydration therapy, caloric intake review, monitoring of glucose levels or thyroid function).

Routine testing during interferon or peginterferon therapy includes blood tests for neutrophils and platelets. The dose is adjusted downward if the absolute neutrophil count drops below 500 cells/mm³ or the platelet count drops below 30 000 cells/mm³, or if the side effects, such as fatigue or depression, become intolerable.⁵¹ Although granulocyte colony-stimulating factors have been used to counteract the side effects of interferon-based HCV therapy,⁴⁴⁻⁴⁶ there is insufficient evidence to support their routine use to counteract or ameliorate dose reductions in routine practice.⁶

For a missed dose of interferon or peginterferon, patients can inject within 24 hours and then resume the normal schedule. If more than 48 hours has passed since the missed dose, the patient should consult a clinician and perhaps modify the schedule.

To assess the end-of-treatment response, the HCV RNA level is tested by polymerase chain reaction at the end of the full therapy course. To document a long-term SVR, the patient's HCV RNA is also tested 6 months after stopping therapy. If still negative at this point, the patient has an excellent prognosis and is considered "cured."

Currently, there are few options for those patients who do not respond to therapy or who relapse. The decision to retreat or not to retreat must be individualized. In general, retreatment is more successful in patients who had monotherapy initially, who relapsed or had a partial response (vs a null response), with genotype 2 or 3, with a low serum HCV RNA level, and who had poor adherence.^{3,52}

Summary

More than half of patients treated with a full course of antiviral combination therapy

with peginterferon alfa plus ribavirin will clear the virus. Early identification of patients with chronic HCV infections will allow earlier interventions with this effective therapy and, hence, greater prevention of liver complications, such as advanced decompensated cirrhosis and the need for liver transplantation. Because it is still not possible to predict which patients with chronic hepatitis will advance to full symptomatic liver disease, all diagnosed patients are considered appropriate candidates for antiviral therapy. Two specific strategies can help MCOs manage this important but costly therapeutic opportunity. First, to limit patient exposure to side effects and maximize the cost effectiveness of drug therapy, the "12-week stopping rule" can be applied to those individuals with genotype 1 infections. And second, to maintain the highest level of institutional SVRs, programs aimed at increasing patient adherence to therapy can be supported.

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