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Ribavirin as a Key Factor in the Treatment of Hepatitis C

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Abstract

The treatment of hepatitis C has improved dramatically since the first trials of interferon monotherapy 20 years ago—first with the addition of ribavirin to interferon, then with the introduction of pegylated interferon. Although interferon plus ribavirin remains the standard treatment for hepatitis C, the past 5 years have seen refinements in the regimen with the use of weight-based ribavirin and alternative ribavirin dosing and therapy duration for difficult-to-treat patient populations. With these developments, the proportion of patients attaining a sustained virologic response has increased from 8–10% with interferon monotherapy to more than 40% with peginterferon plus weight-based ribavirin. Studies over the past several years have shown that adherence to the planned treatment regimen, particularly with respect to ribavirin, is important for maximizing response to treatment. Therefore, steps to increase adherence, including more convenient dosing, proper management of side effects, and patient education, should increase the likelihood of attaining a sustained virologic response, with the ultimate goals of reducing disease progression and preventing further liver damage.

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Utilizing Combination Therapy to Overcome Treatment Challenges in HCV Therapy

John G. McHutchison, MD

Interferon-based therapies have been used for the treatment of hepatitis C infection since the original interferon trials were reported in the late 1980s.[1,2] Interferon was initially administered as monotherapy and provided a sustained virologic response (SVR) in only a small proportion of patients—8–10% with 6 months of therapy and 15–20% with 48 weeks of therapy.[2] Ribavirin was first added to interferon therapy in the mid-1990s. Although the mechanism of action of ribavirin was unknown at the time, the agent had previously been used in children with respiratory syncytial viral infections. A randomized Italian study of 20 patients with interferon-resistant hepatitis C virus (HCV) found that interferon plus ribavirin was associated with a significantly higher response rate than interferon alone (40% vs 0%; $P<.05$).[3]

Additional trials confirmed these findings, demonstrating that the addition of ribavirin to interferon increased the likelihood of attaining negative HCV RNA, which in turn increased the end-of-treatment response rate, decreased the relapse rate, and provided a 2- to 3-fold improvement in SVR rates over interferon alone.[4-6]

Adherence as a Factor in Treatment Outcomes

The past five years have brought further refinements to the interferon/ribavirin regimen, including the use of weight-based dosing and other dosing strategies based on patient factors including ethnicity and HCV genotype. These modifications, which will be discussed in a later section, have enhanced the ability of ribavirin to increase SVR rates amongst difficult-to-treat patient populations.

Another important advancement in the treatment of patients with HCV is our increased understanding of the importance of adherence. The role of adherence has been thoroughly investigated in the field of HIV research. Numerous studies have shown that high pill burdens correlate with poor adherence and are associated with a lack of response to HIV therapy. Although early studies of interferon and ribavirin for HCV did not include complete adherence measures, several analyses have shown that adherence is important for optimal treatment outcomes. A pooled analysis of records from patients receiving interferon plus ribavirin (n=1,010) or peginterferon plus ribavirin (n=511) showed that patients receiving 80% of planned interferon doses and 80% of planned ribavirin doses for 80% of the expected treatment duration had higher SVR rates (52% and 63% with interferon and peginterferon, respectively).[7] The SVR rate among patients who did not meet this standard of adherence decreased to 34%. More detailed analyses showed that adherence to ribavirin was perhaps more important than adherence to interferon. Moreover, adherence appeared to be most important early during the course of treatment.

In another study, Reddy and colleagues evaluated the effects of ribavirin dose reductions on SVR rates in 569 patients with HCV genotype 1 who had received peginterferon alfa-2a and ribavirin in a phase III trial.[8] After full doses of ribavirin were used in Weeks 1–12, Reddy analyzed ribavirin exposure from Weeks 13–48. Sustained viral response rates declined with declining ribavirin exposure, from 67% among patients who received at least 97% of the cumulative planned dose of ribavirin to 57% among those receiving 60–80% and 33% among those receiving less than 60%.

Bronowicki and colleagues reported on the effect of ribavirin discontinuation on treatment outcomes in 516 patients with HCV genotype 1 receiving peginterferon alfa-2a plus ribavirin.[9] In their study, the 70% of patients who attained HCV RNA negativity at Week 24 were randomized to continue combination therapy or to switch to peginterferon alone for the remaining 24 weeks. SVR rates were significantly higher among patients who continued combination therapy (68.2% vs 52.8%; $P=.004$). These findings indicated that patients with HCV genotype 1 who respond to initial combination therapy should continue receiving concomitant ribavirin for the entire treatment duration to avoid viral breakthroughs during therapy and viral relapse after therapy.

Ribavirin dosing was further investigated in the multicenter, randomized, controlled Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial, which was designed to evaluate the benefit of long-term interferon treatment. Shiffman and colleagues evaluated the effect of dose reductions in 936 patients with HCV genotype 1 receiving peginterferon alfa-2a and ribavirin who previously had not responded to standard interferon therapy with or without

ribavirin.[10] Reduction of the cumulative peginterferon dose from over 98% to 60% or under during the first 20 weeks of treatment caused the SVR rate to decline from 17% to 5%. Reduction of the cumulative ribavirin dose by the same amount did not affect SVR rates as long as ribavirin was not interrupted for more than 7 consecutive days. However, discontinuing ribavirin reduced the SVR rate to 4% or less, even if peginterferon was administered at full dose. These findings suggest that adherence to ribavirin is more important than adherence to interferon, with premature ribavirin discontinuation having a greater impact on SVR rates.

Ribavirin is also important in driving higher rates of rapid virologic response (RVR), a measure of HCV RNA negativity at Week 4 of treatment. Patients who attain an RVR are more likely to achieve SVR. Therefore, adequate adherence during the early treatment period is important for maximizing responses to HCV therapy.

Overall, the evidence indicates that adequate ribavirin is essential for optimal hepatitis C treatment outcomes. However, the threshold for the ideal dosage of ribavirin remains controversial. Although we know that discontinuing ribavirin is undesirable, the length of time that patients can be treated without ribavirin without affecting the response rate has not been determined definitively. The upper threshold of ribavirin dosing also has not been determined. Some studies have evaluated the feasibility of higher doses of ribavirin. In 2007, Shiffman and colleagues published a single-center randomized study of peginterferon plus ribavirin and epoetin alfa (EPO).[11] Patients receiving the higher-dose weight-based ribavirin (15.2 mg/kg/day) with EPO attained a significantly higher SVR than patients receiving lower-dose ribavirin, which the investigators attributed to a lower relapse rate (8% vs 38% for other patients; $P<.05$). Although this dosing is not administered routinely in clinical practice, it does provide further evidence that more ribavirin may be beneficial.

Adherence Considerations with New HCV Therapies

In the future, triple therapeutic regimens consisting of interferon, ribavirin, and a direct antiviral agent, such as a protease or polymerase inhibitor, will be more effective for the treatment of patients with HCV. Preliminary data from a number of phase II trials show that the addition of specifically targeted antiviral therapy (STAT-C) agents to peginterferon and ribavirin provides a higher SVR rate and may also shorten the duration of therapy in the difficult-to-treat genotype 1 population.[12,13] Patients who do not respond to these new targeted antivirals tend to have lower trough levels of interferon and ribavirin early during treatment. Thus, adherence will be an important issue with these new therapies in order to maximize response rates and minimize the risk of drug resistance, particularly early during the course of treatment.

Pill burden will also be a significant factor with the development of new agents for the treatment of HCV. Most patients undergoing HCV therapy today take 5–6 ribavirin pills, capsules or tablets, daily and require interferon injections. The addition of a STAT-C agent that requires dosing 2 or 3 times daily would further increase the pill burden. A higher pill burden is associated with a higher risk of poor adherence and, in turn, a higher risk of resistance and breakthrough. Thus, in the next 5–10 years, issues of adherence education, monitoring, and management will be critically important. Steps should be taken when possible to decrease pill burden, through the use of alternative ribavirin dosing or combination pills, as have been utilized in the treatment of HIV.

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Academic Perspectives on Hepatitis C Treatment Adherence

Sammy Saab, MD, MPH

Weight-Based vs Flat-Dosing of Peginterferon/Ribavirin Therapy

Ribavirin has been a part of the hepatitis C treatment armamentarium for over a decade. The addition of ribavirin to interferon therapy has been shown to significantly enhance SVR rates. In the 1998 randomized Hepatitis Interventional Therapy Group trial of 912 patients with chronic HCV infection, SVR rates were significantly higher with interferon alfa-2b plus ribavirin versus interferon alfa-2b alone after 24 weeks (31% vs 6%; *P*<.001) and 48 weeks (38% vs 13%; *P*<.001).[1]

Whereas this early trial evaluated two doses of ribavirin, 1,000 and 1,200 mg daily, depending on body weight, later studies showed that a wider range of weight-based ribavirin dosing is more effective than flat dosing. In the prospective, US multicenter, open-label, WIN-R trial, 5,027 patients received peginterferon alfa-2b 1.5 µg/kg/week with either flat-dose ribavirin (800 mg/day) or weight-based ribavirin (800–1,400 mg/day).[2] SVR rates were significantly higher with weight-based versus flat-dose ribavirin (44.2% vs 40.5%; *P*=.008). The benefit of weight-based ribavirin dosing was particularly evident in the difficult-to-treat genotype 1 population, in whom the rates of SVR were 34.0% with weight-based dosing versus 28.9% with the flat dose (*P*=.005). In genotype 1 patients with a high baseline HCV RNA level, SVR rates were 31.2% and 26.7%, respectively. Patients with HCV genotypes 2 and 3 do not appear to benefit from weight-based dosing.

Another important recent study evaluating the optimal ribavirin dosing scheme was the randomized, open-label, phase IIIb IDEAL (Individualized Dosing Efficacy vs Flat Dosing to Assess Optimal Pegylated Interferon Therapy) trial, which randomized 3,070 naïve patients with genotype 1 HCV to two weight-based doses of peginterferon alfa-2b (1.0 or 1.5 µg/kg/week) plus ribavirin 800–1,400 mg/day, or flat dosing of peginterferon alfa-2a at 180 µg/week plus ribavirin 1,000–1,200 mg/day.[3] SVR rates were comparable among the treatment groups, at approximately 40% across the three arms.

Some patient populations have historically attained lower SVR rates than others with interferon-based treatment. In addition to patients with genotype 1 infection, these include obese patients and African Americans.[4,5] For these three patient populations, ribavirin appears to be a great equalizer as long as weight-based dosing is used.

Ribavirin-Associated Anemia: Laboratory Values vs Clinical Symptoms

Like any medication, ribavirin has its set of signature adverse events, including its most common, anemia. The threshold for treating anemia can be stratified based on laboratory values or clinical symptoms. The definition of clinically relevant anemia varies based on a variety of factors, including the patient's sex, age, and comorbidities. For example, anemia may not be of as great concern in a 20-year-old man compared with a 55-year-old man with a history of heart disease or pulmonary issues.

Anemia can be defined by an absolute value (eg, hemoglobin <10 g/dL for women or 11 g/dL for men) and the presence of symptoms such as fatigue and shortness of breath, or by the rate of hemoglobin decline over a period of time. Moreover, clinical judgment remains important for evaluating patients with potential anemia. For example, a patient with an initial hemoglobin level of 14 g/dL that falls to 11 g/dL within 3 weeks may not meet the definition of anemia according to many scales, but, clinically, the patient will have lost a substantial amount of blood and may be extremely symptomatic with fatigue and dyspnea. Moreover, the patient's hemoglobin levels will likely continue to fall. It may be difficult to regain adequate hemoglobin levels following such a rapid decline. Therefore, treating the anemia may be warranted in this type of situation.

Management of Ribavirin-Associated Anemia

As with many adverse effects of interferon, ribavirin-related adverse effects can be predicted, managed, and may resolve with treatment modification. One of the most common adverse effects seen with ribavirin is hemolytic anemia. Ribavirin-associated anemia can negatively affect the hepatitis C treatment course. Not only can anemia lead to

quality-of-life issues, but it is also the most common reason for ribavirin dose reductions and discontinuations that reduce treatment efficacy.[6] McHutchison and colleagues showed that adherence to interferon/ribavirin combination therapy enhances SVR rates among genotype 1 patients with chronic HCV.[7] Therefore, the management of ribavirin-associated anemia is essential to optimizing treatment outcomes.

Ribavirin-associated anemia can be addressed in a variety of ways, including the use of growth factors, ribavirin dose modifications and, in severe cases, blood transfusions. Although patient quality of life shows greater improvement when ribavirin-related anemia is treated with the addition of EPO rather than with a reduction in ribavirin dose, it is unknown whether this translates into an improved SVR.[8] Moreover, EPO is not FDA-approved in this setting, and can complicate treatment because of additional costs, potential toxicity, and the requirement for another parenterally administered drug.[6] For patients with severe symptoms or other comorbid conditions, transfusions or ribavirin dose modifications may be required. Some patients may need to discontinue ribavirin. However, the most critical issue in successful treatment is to avoid ribavirin discontinuation. The quickest way to fall below the minimal ribavirin threshold dose requirement is to discontinue ribavirin therapy, even temporarily.

In my practice, our approach to the management of ribavirin-associated anemia depends on the patient, although we prefer to avoid dose reductions. For patients with a substantial drop in hemoglobin, we try to use growth factors in order to maintain an appropriate dose of ribavirin. However, some comorbidities, such as renal insufficiency or prior liver transplant, make patients more sensitive to ribavirin-associated anemia.[9] For these patients, we temporarily reduce the ribavirin dose while the EPO reaches a steady state in the blood stream. As soon as hemoglobin levels are restored we resume the standard ribavirin dose. Overall, between 15% and 20% of patients in our practice require ribavirin dose adjustments. These are generally only minor modifications, with patients rarely requiring temporary discontinuations.

Ribavirin Dosing Options

Ribavirin is administered twice daily, with the generic form available in 200 mg tablets. Many academic centers use tablets containing higher amounts of ribavirin, including 400 and 600 mg doses. These offer the advantage of fewer pills, and a blister dose pack that helps with adherence and compliance. According to Reddy and colleagues, higher ribavirin adherence is associated with measurable improvement in SVR.[10]

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Maximizing Hepatitis C Treatment Adherence in the Community Setting

Tuesdae R. Stainbrook, DO, MPH

Strictly defined, medication compliance or adherence refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage, and frequency of medication. Medication compliance may also be defined as the extent to which a patient acts in accordance with a prescribed interval and dose of the dosing regimen. As discussed earlier, poor compliance is an important cause of treatment failure in patients undergoing antiviral therapy for chronic HCV infection. Dose reductions and missed doses of ribavirin, particularly in the first 12 weeks, appear to negatively affect the likelihood of attaining an early virologic response and sustained virologic response.[1,2] In fact, ninety-seven percent compliance with ribavirin is associated with a 10% increase in sustained virologic response.[1] Therefore, increased compliance correlates with improved outcomes and lower healthcare costs. Understanding potential causes of poor adherence may help improve compliance and in turn maximize treatment outcomes.

Risk Factors for Nonadherence

Adherence is an age-old, complex problem that involves numerous factors. Barriers to adherence include age, education level, neurocognitive impairment, medication administration, family involvement, and severity of side effects. Although these factors all contribute to the patient's willingness to be adherent, they are not consistent predictors of nonadherence.

In 2002, Lacro and colleagues conducted a literature review and identified seven factors most consistently associated with nonadherence (Table 1).[3] Although the study focused on patients with schizophrenia, the factors are applicable to any disease state. The first factor is poor insight. Patients need to take some responsibility for their own healthcare. In order to do this, a person must have an awareness of their disease and treatment options. At our community-based office practice, we provide extensive counseling regarding the various aspects of hepatitis C, including long-term disease complications and treatment challenges, on the patient's initial visit. We review signs and symptoms of chronic hepatitis C as well as end-stage liver disease and cirrhosis. The discussion includes risk factors for progression of liver disease and the probability of different treatment outcomes. We conclude with treatment options along with common side effects. Patients then have time to ask questions and are sent home with a folder of information regarding HCV and its treatment.

The second factor consistently associated with nonadherence is negative attitudes or subjective responses to medication. Negative attitudes are often a challenge with patients who know someone who underwent treatment for hepatitis C or who have read about hepatitis C treatment on internet blogs. These patients often have an exaggerated view of the unfavorable treatment side effects. It often takes much encouragement to overcome these fears and concerns. We tell patients that although they are in charge of their success in treatment, they are not alone in the treatment.

The third factor associated with nonadherence is previous noncompliance. For patients with HCV, there may be previous nonadherence with hepatitis C treatments or with other medications. These situations are always challenging. It is important to educate patients about the concepts of rapid and early virologic responses, along with the goal of attaining a sustained virologic response. We use this information to motivate patients to prevent them from feeling overwhelmed about their extended treatment. These educational techniques aid in a successful treatment approach. At

Table 1. Factors Associated with Nonadherence

- Poor insight
- Negative attitude or subjective responses to medication
- Previous noncompliance
- Substance abuse
- Shorter illness duration or few or no symptoms of disease
- Inadequate aftercare
- Poor therapeutic alliance

Data from Lacro et al.[3]

any given point, most of our patients understand that their expected success rate depends on their viral response earlier in the course of treatment and they understand the ramifications of key decisions to withdraw, continue, extend, or even change treatment.

The fourth factor associated with nonadherence is substance abuse, which is certainly an issue with HCV, given that 80–90% of intravenous drug users are positive for hepatitis C.[4,5] Almost all clinicians have seen patients with hepatitis C who are still using drugs or alcohol. In our practice, we provide referrals to drug and alcohol counseling centers and we continue to monitor these patients every three months and encourage them to abstain from substance abuse. When appropriate, treatment is initiated in this challenging group.

The fifth factor associated with nonadherence is shorter illness duration or few or no symptoms of disease. Most patients with hepatitis C are asymptomatic, which makes it difficult to convince them to adhere to a 6- to 12-month regimen of difficult therapy. To counteract this, we often provide further education on preventing end-stage liver disease or cirrhosis. Having a poster or a model of the liver showing different degrees of fibrosis can be a valuable tool to use with patients when reviewing liver biopsy results and visualizing progression of disease.

The sixth factor that has been associated with nonadherence is inadequate aftercare. Managing patients with HCV requires considerable time and follow-up. Patients return to our office one month after initiating therapy and then every two months while on therapy. We encourage patients to call with any concerns or questions that may arise during treatment. Having a well-educated support staff to assist patients in answering their questions is a necessity.

The final factor identified by Lacro and colleagues as associated with nonadherence is a poor therapeutic alliance. A good patient/doctor relationship is imperative to successful treatment outcomes. Deficiencies in communication skills—the doctor's ability to listen and explain and the patient's capacity to express his or her concerns—can be overwhelming barriers to a successful course of treatment.

Strategies for Improving Adherence

Published adherence studies have shown little consistent evidence regarding the best strategies for maximizing adherence. Certainly there is a need for the development of creative strategies to increase medication adherence. With regard to patient supervision and counseling, our practice provides individual education interventions to teach patients the drug names, indications, strengths, adverse effects, and usage instructions. This process is helpful and can be beneficial in the successful treatment of chronic HCV. Education and counseling regarding the prevention of reinfection, infection with concomitant diseases, and disease complications are also essential in trying to ensure a favorable long-term outcome.

Clinicians can also use prescription refill rates to assess patient compliance, but should ask patients to bring in all missed doses for each office visit to gain greater clarity as to actual compliance. Monitoring patients' refill rates and missed doses may be useful for targeting patients with undersupplies of drugs and encouraging them to refill and take their medications as directed, particularly for patients with low income, minority status, and complicated hepatitis C infection.

Blister dose packs can be a valuable tool for increasing adherence, as they provide an easy method for counting pills and immediate awareness of medications that may have been missed. Ribavirin blister dose packs are now available in 400 and 600 mg tablets (RibaPak®) , which allows patients to simplify their regimen from up to 6 pills a day with conventional ribavirin down to just 2 pills daily. This represents a 66% reduction in the number of tablets, which practically and psychologically may help patients with adherence. In our community-based practice, all patients are encouraged to use RibaPak, and pill counts are evaluated at every office visit.

The ongoing multicenter, prospective, observational ADHERE (Accurate Dosing in Hepatitis C: Examining the RibaPak® Experience) registry is evaluating whether RibaPak could improve treatment adherence over standard ribavirin (RBV). After 4 weeks, adherence was similar with RibaPak (n=67) versus standard ribavirin (n=28), with patients reporting taking 98% and 95% of their doses, respectively.[6] However, preliminary data suggest that at 6 months, adherence is better with RibaPak (n=24) versus standard ribavirin (n=4), with patients reporting taking 96% and 66% of their doses, respectively. Data on the remaining 451 patients are forthcoming (Figures 1 and 2).

Another study evaluating dose simplification was a single-center observational study conducted by Palmer, who compared adherence, adverse effects, and quality-of-life in 92 patients with hepatitis C who had received RibaPak for longer than 12 weeks.[7] The study included treatment-experienced patients who had received standard ribavirin during a prior treatment course (n=22), treatment-naïve patients who switched to RibaPak after receiving standard ribavirin for longer than 12 weeks (n=49), and treatment-naïve patients receiving only RibaPak (n=21).

Palmer reported that RibaPak was associated with fewer adverse events than standard ribavirin. Among patients switching from standard ribavirin to RibaPak, 27–32% reported a decrease in nausea, 16–27% reported a decrease in loss of appetite, 27–29% reported a decrease in dyspepsia, 20–23% reported a decrease in weight loss, and 6–9% reported a decrease in diarrhea. Patients tak-

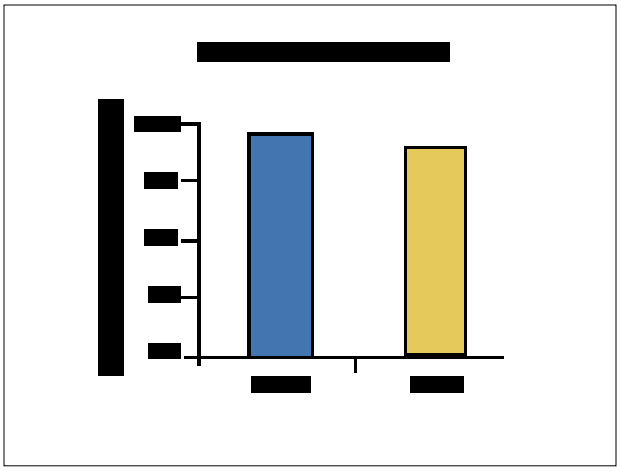

Figure 1. Percent of prescribed RibaPak® (RBP) or standard ribavirin (RBV) doses taken by 4 weeks. At 4 weeks, RBP (n=67) and RBV (n=28) patients had taken an average of 98% and 95%, respectively, of their prescribed dose.

Data from Rustgi et al.[6]

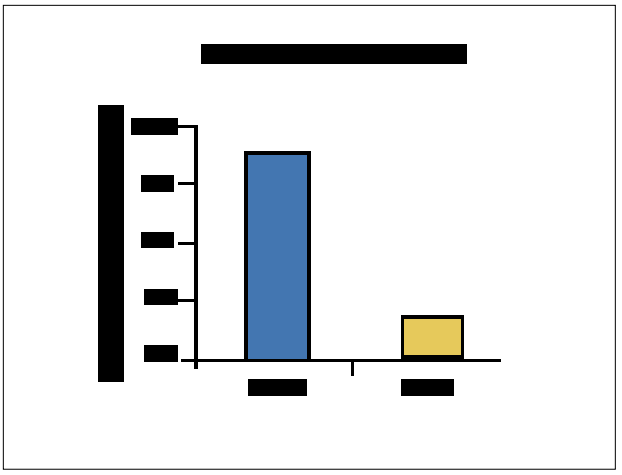

Figure 2. Percent of prescribed RibaPak® (RBP) or standard ribavirin (RBV) doses taken by 6 months. At 6 months, RBP (n=24) and standard RBV (n=4) patients had taken an average of 96% and 66%, respectively, of their prescribed dose.

Data from Rustgi et al.[6]

ing RibaPak also missed fewer pills and had quality-of-life improvements versus standard ribavirin. The majority of patients switching from standard ribavirin—68% of treatment-experienced patients and 82% of treatment-naïve patients—reportedly preferred RibaPak over standard ribavirin. Finally, a comparison of the 21 treatment-naïve patients taking RibaPak against 21 consecutive matched patients taking standard ribavirin showed a trend toward a higher SVR rate with RibaPak versus standard ribavirin (66.7% vs 57.1%). Palmer suggested that this improvement in efficacy was most likely secondary to increased adherence.

Although ribavirin blister dose packs are one example of a mechanism for increasing adherence, the most effective strategies for improving adherence have been multicomponent interventions that include cognitive and behavioral characteristics. For example, a strategy may include patient education and counseling along with the use of a more convenient medication delivery, such as blister dose packs. One study illustrating the effect of a multifaceted program designed to improve adherence was the prospective, single-center Federal Study of Adherence to Medications in the Elderly (FAME).[8] The study randomized 200 community-based patients aged 65 years or older taking at least four long-term medications to usual care or an intervention consisting of standardized medication education, regular follow-up by pharmacists, and the use of blister packs. Mean adherence in the study increased from 61.2% at baseline to 96.9% after 6 months of the pharmacy care program. Clearly, such approaches could help improve adherence, leading to improved treatment outcomes and maximizing the cost-effectiveness of treatment.

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Notes


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