Dear Colleague:

Clinical practices in the management of hepatitis C are changing rapidly. Studies of combination therapy with peginterferon alfa-2b or alfa-2a and ribavirin show that sustained virologic response (SVR) is achievable in more than half of all patients treated for chronic hepatitis C. Eighty-eight percent of The Clinician’s Companion survey respondents indicated that they have seen increases in treatment response since last year, presumably as a result of the introduction of peginterferon/ribavirin. Now, additional analyses from the pivotal peginterferon/ribavirin studies are targeting ways to further improve outcomes for more patients and are again changing patient care.

For example, the latest data show it is possible to identify nonresponders to treatment as early as week 12 using quantitative HCV RNA. Thus, physicians must now weigh the potential histologic benefits of continued treatment against exposure to side effects in patients not destined to reach SVR. Moreover, it has been determined that the likelihood of SVR increases with greater adherence to treatment. In recognition of this, physicians are seeking strategies to more aggressively promote adherence, particularly among patients with early virologic response.

This *Tx Reporter*, which discusses the importance and clinical implications of findings on early virologic response and treatment adherence, represents the second of the expanded five-part CME compendium that comprises *The Clinician’s Companion VI*. As described in Part 1, content for this series was developed at a meeting that featured expert presentations, panel discussions, case studies, and recommendations gathered via survey from a nationwide panel of leading hepatologists, gastroenterologists, and other specialists engaged in research or treatment of hepatitis C. We are pleased to bring you this second update on peginterferon/ribavirin, and hope that you find it, and the rest of *The Clinician’s Companion VI*, informative and relevant to your patient care.

Sincerely,

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Predicting Response to Peginterferon/Ribavirin

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If it were possible to accurately predict which patients are not destined to achieve SVR to peginterferon/ribavirin, it would be possible to avoid the expense and toxicity of therapy for these patients. Baseline characteristics associated with SVR have been identified, and include genotype 2 or 3 infection, lower viral burden, the absence of significant fibrosis, younger age, female gender, and body weight or surface area (with fixed doses). These factors provide an estimate of the likelihood of achieving a response. However, they are generally not helpful in accurately identifying individual patients who will respond to therapy and therefore cannot be used to exclude patients from treatment. New approaches have focused on establishing accurate criteria by which virologic nonresponders can be identified early in the course of treatment so that therapy may be discontinued.

Initial studies of treatment response indicated that the presence or absence of HCV RNA was a more accurate indicator of response than serum alanine aminotransferase values during therapy. In the past, SVR was rarely achieved by patients who remained HCV RNA positive at week 24 of treatment with interferon monotherapy or interferon/ribavirin combination therapy. Thus, determinations of response have commonly been made after 24 weeks of therapy. Recently, several smaller studies have suggested that response can be accurately predicted earlier by evaluating or quantifying reductions in viral level during therapy.

Early Virologic Response to Peginterferon/Ribavirin

Preliminary observations indicate that 97% to 100% of patients receiving peginterferon/ribavirin who fail to achieve a 2-log (100-fold) reduction in serum HCV RNA by week 12 of therapy will not achieve an SVR. Differences who do achieve a 2-log reduction by this time point have a 75% to 80% chance of achieving an SVR. Approximately 80% of patients who receive peginterferon alfa-2b/ribavirin achieve this 2-log reduction at week 12. These observations appear to hold true for patients receiving either high or low doses of peginterferon alfa-2b/ribavirin, and also hold true for standard interferon alfa-2b/ribavirin. Among 453 patients treated with peginterferon alfa-2b in combination with ribavirin, 390 (86%) had at least a 2-log decrease in HCV RNA because of the unlikelihood of reaching SVR. However, they also agreed (rating 3.7 on a scale of 1 = strongly disagree to 5 = strongly agree) that treatment could be discontinued at week 12 in the absence of a >2-log decrease in HCV RNA because of the likelihood of reaching SVR.

Similar findings were released in preliminary reports of the investigational agent peginterferon alfa-2a in combination with ribavirin. Among 453 patients treated with 180 μg QW of peginterferon alfa-2a and 1000 or 1200 mg/d ribavirin, 390 (86%) had at least a 2-log decrease in HCV RNA at week 12. The majority of these patients (n = 253) went on to achieve SVR, but over one third (n = 137) relapsed, for a positive predictive value of 65%. Only 3% of those who did not demonstrate a 2-log decrease by week 12 went on to achieve SVR, for a negative predictive value of 97%. (See Table 1.)

Survey Findings

The Clinician's Companion VI survey respondents generally agreed (rating 3.8 on a scale of 1 = strongly disagree to 5 = strongly agree) that treatment could be discontinued at week 12 in the absence of a >2-log decrease in HCV RNA because of the likelihood of reaching SVR. However, they also agreed (rating 3.7) that it would be appropriate to continue treatment in such patients if they have F3 to F4 fibrosis, since histologic benefit has been shown even in nonresponders.

| Table I. Predicting Response to Peginterferon/Ribavirin at Week 12 of Treatment |
|---------------------------------|---------------------------------|----------------|----------------|----------------|
| Treatment Regimen | Early Response (PCR−, or PCR+ With >2-Log Decrease in HCV RNA @ Wk 12) | SVR | Ability to Predict SVR | Ability to Predict Nonresponse |
| PegIFN alfa-2b, + RBV* | Yes (n = 143) | 114 | 80% | 100% |
| 1.5 μg/kg + RBV | No (n = 31) | 0 | 100% | |
| PegIFN alfa-2b, + RBV | Yes (n = 378) | 271 | 72% | |
| 0.5 μg/kg + RBV | No (n = 98) | 0 | 100% | |
| PegIFN alfa-2b, + RBV | Yes (n = 322) | 237 | 74% | |
| 1000–1200 mg* | No (n = 157) | 0 | 99.4% | |
| IFN alfa-2b, + RBV | Yes (n = 349) | 233 | 67% | |
| 3 MU TIW + | No (n = 128) | 0 | 99.3% | |
| PegIFN alfa-2a, + RBV | Yes (n = 390) | 253 | 65% | |
| 1.5 µg/kg + RBV | No (n = 63) | 2 | 97.0% | |
| 1000–1200 mg* | No (n = 31) | 0 | 100% | |

*Off-label use of FDA-approved drugs. †FDA-approved treatment regimens. ‡Investigational regimen.
Finally, they agreed (rating 4.3) that the limitations of viral load quantification must be considered when applying early stopping rules in clinical practice. They did not widely support (rating 2.8) using HCV RNA measurements at week 4 to make determinations of response.

**Conclusion**

Most patients treated with peginterferon/ribavirin achieve an early virologic response. Among these patients, SVR is ultimately achieved by 80% of those treated with weight-based dosing of peginterferon alfa-2b/ribavirin and 65% of those treated with standard doses of peginterferon alfa-2a/ribavirin. This information should motivate patients to continue therapy and avoid unnecessary dose reduction.

In the absence of at least a 2-log reduction in HCV RNA at week 12, treatment may be discontinued, since few, if any, of such patients will achieve SVR. (See Fig. 1.) However, a number of caveats should be considered when using these data clinically. First, they do not take into account the potential histologic benefits of treatment observed in nonresponders.

Second, the limitations of HCV RNA assays in terms of their variability and precision may confound interpretation of viral load changes during therapy.

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**Promoting Adherence to Treatment**

**John G. McHutchison, MD**

Adherence to therapy is associated with enhanced sustained response rates to interferon-based combination therapy. Yet, observed rates of treatment adherence are unexpectedly low. Thus, promoting adherence to therapy is a critical component of care for patients with hepatitis C.

**Adherence Improves Response to Therapy**

A retrospective analysis of data from the pivotal interferon alfa-2b/ribavirin trials in treatment-naïve patients has demonstrated the importance of adherence. This analysis revealed that the overall SVR rate of 41% increased to 48% (P<0.001) when patients received ≥80% of their interferon dose and ≥80% of their ribavirin dose for ≥80% of the recommended duration of therapy (80+80+80). In contrast, the SVR rate was only 29% in those who met none of the 80+80+80 criteria (P<0.0001 compared with the 80+80+80 group). Importantly, nearly three quarters of patients treated with interferon/ribavirin were able to achieve the 80+80+80 adherence level, suggesting that this is a reasonable goal for adherence.

Similarly, in a retrospective review of the peginterferon alfa-2b/ribavirin trial, overall, 63% of patients who received ≥80% of expected doses of both peginterferon alfa-2b 1.5 mg/kg and ribavirin 800 mg/d for ≥80% of the recommended duration of therapy achieved an SVR (compared with 54% overall). With 80+80+80 adherence to the weight-based dosing regimen of both peginterferon (1.5 µg/kg) and ribavirin (≥10.6 mg/kg), the response rate increased from 61% overall to 72%. The impact of adherence to therapy was most notable in patients with genotype 1 infection: the SVR rate was 63% among adherent patients compared with 34% among nonadherent patients.

Recent analysis has shown a clear continuum from low response rates with low rates of adherence to high response rates with high rates of adherence. Patients who were adherent during the first 12 weeks of therapy, but not adherent thereafter, also had lower rates of SVR than those who were adherent throughout treatment (51% versus 62%), although SVR rates were lower among those who were not adherent during either period (34%).

There appears to be a direct relationship between levels of adherence and the likelihood of sustained response.

Although the trend between early adherence and SVR is suggestive, none of the differences observed reached statistical significance. Too few patients (n = 4) were nonadherent in the first 12 weeks and then adherent during the remainder of therapy to allow for meaningful assessment of the importance of early versus late adherence. Adherence also affected SVR rates among patients who showed early virologic response to peginterferon alfa-2a/ribavirin. Of 390 patients who had either undetectable HCV RNA or at least a 2-log decrease in HCV RNA at week 12, 65% went on to achieve SVR. However, in the subgroup of these patients with >80% adherence, 75% had an SVR, compared with only 48% of those with <80% adherence (see Fig. 2).

**Strategies to Promote Adherence**

To help improve adherence rates, healthcare providers should take time to educate patients and discuss their concerns, determine patients’ level of commitment to treatment, explain side effects, and handle psychiatric issues (see Table 2). Patient education should include information about the disease and its possible consequences, the benefits and risks of treatment, the consequences of nonadherence, and available resources for support.

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**Figure 2. Peginterferon alfa-2a/Ribavirin: Effect of Adherence on Response in Week-12 Responders.**

Patients with lower levels of adherence have lower response rates; patients with higher levels of adherence have higher response rates.
The treatment regimen should be tailored to the patient’s lifestyle (e.g., administering peginterferon at the start of a weekend if the patient is concerned about the impact of side effects on his or her ability to function at work). Adherence and any side effects the patient may be experiencing should be discussed at each visit, and providers should quickly address any side effects that occur, making use of adjuvant therapies (e.g., epoetin, granulocyte colony-stimulating factor, antidepressants, topical corticosteroids, appetite stimulants) as warranted. Pill organizers, reminders (e.g., phone calls, beepers), directly observed therapy, and easily accessible refills may also help with adherence.

### Table 2. Ways to Improve Compliance

- Don’t rush
- Educate the patient
- Address psychiatric issues
- Talk to your patient
- Understand the commitment
- Explain side effects before therapy
- Address side effects quickly

### Survey Findings

On a scale of 1 = strongly disagree to 5 = strongly agree, The Clinician’s Companion VI survey respondents agreed (rating 4.5) that level of adherence correlates with likelihood of achieving SVR. They estimated that about 77% of their patients treated for HCV infection maintained 80%+80%+80% adherence, but also agreed (rating 4.0) that doctors tend to overestimate patient compliance/adherence.

Factors that have the greatest effect on adherence include:

- Patient motivation (rating 4.8 on 5-point scale)
- Patient belief in benefits of treatment (rating 4.6)
- Staff support (rating 4.5)
- Physician ability to manage side effects (rating 4.5)
- Patient education (rating 4.4)
- Psychiatric adverse effects (rating 4.4)
- Provider experience (rating 4.4)
- Active injection drug or alcohol use (rating 4.3)
- Side effects that decrease comfort (rating 4.3)
- Family/social support (rating 4.2)
- Cost of treatment (rating 3.8)
- Exacerbation of pre-existing disease (rating 3.8)

### Conclusions

Patients who can be maintained on ≥80% of their peginterferon dose and ≥80% of their ribavirin dose for ≥80% of the recommended duration of therapy may have an enhanced SVR rate. Nearly three quarters of patients with 80%+80%+80% adherence to a prescribed regimen of 1.5 µg/kg peginterferon alfa-2b and >10.6 mg/kg ribavirin for 48 weeks can achieve an SVR. Patients infected with HCV genotype 1—the most difficult to treat—stand to benefit the most from 80%+80%+80% adherence. At least 70% of patients achieve 80%+80%+80% adherence in clinical trials, but adherence levels may be lower in clinical practices. However, with appropriate support from healthcare personnel, a majority of patients can succeed in reaching 80%+80%+80% adherence.

### References


