

Early Virologic Response to Treatment With Peginterferon Alfa-2b plus Ribavirin in Patients With Chronic Hepatitis C

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Interferon-based regimens for the treatment of chronic hepatitis C have become increasingly effective and are able to eradicate virus in more than one half of cases. Early identification of patients who will not respond is desirable because treatment might be stopped, thereby avoiding the expense and inconvenience of unnecessary therapy. We examined the accuracy of different degrees of viral inhibition during the early weeks of treatment (early virologic response [EVR]) with pegylated interferon alfa-2b and ribavirin (PEG/R) in identifying patients who would not respond to therapy. The best definition of EVR was a reduction in hepatitis C virus (HCV) RNA by at least 2 logs after the first 12 weeks of treatment compared with baseline. Between 69% and 76% of patients achieved this threshold, depending on the treatment regimen, and sustained virologic response (SVR) occurred in 67% to 80% of these patients. Patients who did not reach EVR did not respond to further therapy. If treatment had been stopped in patients without EVR, drug costs would have been reduced by more than 20%. In conclusion, early confirmation of viral reduction following initiation of antiviral therapy for chronic hepatitis C is worthwhile. It provides a goal to motivate adherence during the first months of therapy and a milestone at which to reassess the need for continued treatment. Most patients who are able to complete the first 12 weeks of therapy achieve EVR and have a high probability of SVR. Patients who fail to achieve EVR will not clear virus even if an additional 9 months of therapy is received. Therapy can be confidently discontinued in those cases. (HEPATOLOGY 2003;38:645-652.)

Hepatitis C virus (HCV) replicates at a rapid rate, producing between 10^{10} and 10^{12} viral particles per day that have a half-life of only a few hours.¹ Thus, virus levels decline rapidly when a potent antiviral agent such as interferon inhibits replication. Viral kinetic studies have shown that the first phase of viral decay oc-

curs within 24 to 48 hours after a dose, is rapid, and results in HCV RNA level reductions of up to 4 logs.¹⁻⁴ Phase 1 decay represents direct inhibition of intracellular production and release of HCV by the drug, and the rate is dependent on the dose of interferon and the viral genotype.^{1,2,4,5} However, this early initial decline in HCV RNA levels correlates poorly with the eventual response to interferon-based therapy.^{2,6} Rather, treatment response correlates best with the subsequent slow, prolonged, and more variable period of viral decline referred to as phase 2 decay.^{2,6} This phase is believed to represent destruction of infected hepatocytes and is influenced much less by factors such as dose and genotype. However, the rate of phase 2 decay correlates closely with sustained virologic response (SVR) to interferon-based treatment regimens.^{2,6} Thus, it might be anticipated that changes in virus level over the first several weeks of therapy might correlate closely with the likelihood of ultimate eradication of HCV.

The aim of this study was to investigate whether early changes in HCV RNA levels during treatment with pegylated interferon and ribavirin could be used to accurately

Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response; EVR, early virologic response; PEG/R, pegylated interferon alfa-2b and ribavirin; PEG/R >10.6, pegylated interferon alfa-2b and weight-based ribavirin; IIR, standard interferon alfa-2b and ribavirin; PCR, polymerase chain reaction.

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predict treatment response. Because early discontinuation of treatment in nonresponders could avoid the expense and inconvenience of continuing unnecessary treatment, we also examined the potential cost savings of strategies that would use early virologic response (EVR) to develop early stopping rules for such patients.

Patients and Methods

Patients. Data from the recent international clinical trial reported by Manns et al.⁷ comparing pegylated interferon alfa-2b (PEG-Intron; Schering Corp., Kenilworth, NJ) plus oral ribavirin (Rebetol; Schering Corp.) with standard interferon (Intron A; Schering Corp.) and ribavirin was evaluated retrospectively to determine whether EVR could predict treatment outcome. We most closely evaluated treatment responses in the 511 subjects who were randomized to pegylated interferon alfa-2b at a dose of 1.5 $\mu\text{g}/\text{kg}$ each week and 800 mg/d of oral ribavirin (PEG/R) because this regimen was licensed by the Food and Drug Administration. However, we also examined the subgroup of patients ($n = 174$) from the above group who received pegylated interferon alfa-2b at a dose of 1.5 $\mu\text{g}/\text{kg}$ each week and a dose of ribavirin that was at least 10.6 mg/kg/d (PEG/R ≥ 10.6), the so-called weight-based dosing regimen, because this is the approved standard of care outside the United States and may represent a more optimal dosing regimen. Finally, we also looked for comparison at the 505 subjects randomized to standard interferon at a dose of 3 million units 3 times per week plus 1,000 to 1,200 mg/d of ribavirin (1,000 mg/d for a pretreatment weight <75 kg and 1,200 mg for weight ≥ 75 kg) (I/R). All subjects were treated for 48 weeks and provided informed consent for the study, and the ethics committee at each clinical site approved the study. The databases for the study were created and maintained by the study sponsor.

Histologic activity was assessed by a single pathologist blinded to the treatment regimen and timing of the liver biopsies and graded by the histologic activity index.⁸ Serum HCV RNA levels were measured before initiation of treatment and during therapy at weeks 4, 12, 24, and 48 by a quantitative polymerase chain reaction (PCR) assay with a dynamic range from 100 to 100 million copies/mL (National Genetics Institute, Los Angeles, CA).⁹ SVR was confirmed by undetectable HCV RNA at the end of treatment and again 24 weeks after completion of treatment. HCV genotype was performed with INNOLIPA HCV (Innogenetics, Zwijnaarde, Belgium) as described previously.¹⁰

To assess the effect of adherence on SVR, we used criteria that had been adopted previously in the assess-

ment of the efficacy of pharmaceutical agents, including treatment of HCV, therapy for human immunodeficiency virus, antihypertensive therapy, and orally administered oncologic therapies.^{11,12} We defined adherent subjects as those who received 80% or more of their total interferon dose, who received 80% or more of the ribavirin dose, and were treated for 80% or more of the expected duration of therapy. Nonadherent patients included those who underwent dose reduction (to $<80\%$ of either drug) or were prematurely withdrawn from treatment (treated for $<80\%$ of the prescribed duration).¹²

Defining EVR. Different degrees of HCV RNA level reduction (in half-log decrements from baseline) at various times (4, 12, and 24 weeks) during the initial weeks of treatment were assessed to determine which definition of this EVR best excluded those patients who would fail to achieve SVR. In developing such a definition, we sought to separate nonresponders and SVR as accurately as possible. This optimal EVR definition was then used to look at the effects of constructing stopping rules whereby patients who did not achieve EVR would discontinue therapy. Our goal was to design an algorithm that would avoid unnecessary treatment in as many nonresponders as possible while preventing premature discontinuation of treatment in those who would ultimately have achieved SVR if a full course of therapy had been given. Thus, we sought to develop a definition of EVR that would capture most sustained responders (highest sensitivity) while excluding the largest proportion of nonresponders (highest negative predictive value). We determined proportions of patients who would be able to stop treatment, loss of potential SVR, and potential cost savings.

Statistical Analysis. The likelihood of EVR for each definition was determined by intention to treat. To do so, missing virologic data at a particular time point was considered a lack of viral response. By contrast, comparisons of characteristics of patients with and without EVR excluded patients in whom virologic data at the time point was missing (*i.e.*, EVR could not be determined with certainty). Differences in baseline characteristics between the groups were compared by χ^2 test for dichotomous variables and the 2-sided t test for continuous variables. Response rates were compared by χ^2 analysis.

Cost Analysis. The economic impact of using EVR to identify and discontinue treatment in nonresponders was estimated. To do this, we assumed treatment periods of 48 weeks for subjects with genotype 1 and 24 weeks for those with genotypes 2 or 3. We assumed that treatment would be stopped only if EVR was not achieved. Other reasons for treatment discontinuation and dose reduction were not considered. Only the cost of medication and viral testing was considered. We assumed that virus levels

Table 1. Proportion of Subjects Treated With Pegylated Interferon and Ribavirin (800 mg) Who Achieve EVR and Other Treatment Outcomes as a Function of the Different Definitions of EVR as Defined by Change in HCV RNA Level From Baseline and Time Since Starting Treatment

Change in Serum HCV RNA	Week of Therapy	Treated Reaching EVR* (%)	Treatment Outcomes (%)		SVR Who Reach EVR§ (%)
			No EVR Reached	EVR Reached	
			NR†	SVR‡	
PCR negative	4	150/511 (29.4)	221/361 (59.4)	133/150 (88.7)	133/273 (48.7)
3-log decrease or PCR negative	4	261/511 (51.1)	191/250 (74.8)	214/261 (82.0)	214/273 (78.4)
2-log decrease or PCR negative	4	320/511 (62.6)	168/191 (86.9)	250/320 (78.1)	250/273 (91.6)
1-log decrease or PCR negative	4	380/511 (74.4)	125/131 (94.8)	267/380 (70.3)	267/273 (97.8)
PCR negative	12	308/511 (60.3)	188/203 (91.2)	258/308 (83.8)	258/273 (94.5)
3-log decrease or PCR negative	12	358/511 (70.1)	147/153 (95.0)	267/358 (74.6)	267/273 (97.8)
2-log decrease or PCR negative	12	380/511 (74.4)	131/131 (100.0)	273/380 (71.8)	273/273 (100.0)
1-log decrease or PCR negative	12	417/511 (81.6)	94/94 (100.0)	273/417 (65.5)	273/273 (100.0)
PCR negative	24	329/511 (64.4)	175/182 (99.2)	267/329 (81.2)	267/273 (97.4)

*Intent-to treat. Patients without virologic data at time point are considered as "no EVR reached."

†Negative predictive value. Treatment outcomes include only patients with virologic data available at the relevant time point.

‡Positive predictive value. Treatment outcomes include only patients with virologic data available at the relevant time point.

§Sensitivity. Treatment outcomes include only patients with virologic data available at the relevant time point.

would be measured at baseline and once during therapy to determine EVR (the hypothetical control group had no viral testing). Costs resulting from laboratory tests to monitor therapy, long-term disease complications, lost productivity, and impaired quality of life were not included. Results are expressed as the proportional reduction in cost compared with a full course of treatment without treatment discontinuation in those without EVR and with the current standard of practice, which is to stop treatment if virus remains positive by PCR at 24 weeks.

Results

EVR was defined by the magnitude of decline in the virus level at specific intervals after initiation of treatment. The definitions that were studied are listed in Table 1. The proportion of treated patients who reached EVR and the treatment outcomes in those patients (SVR or not) are listed for the PEG/R group. The more rigorous the definition of EVR (*i.e.*, the greater the required decrease in HCV RNA or the shorter the time since treatment started), the fewer subjects achieved EVR. For example, the most rigorous definition of EVR tested was loss of detectable HCV RNA by PCR at week 4 of treatment. Only 29.4% of subjects treated with PEG/R achieved this milestone, whereas 74.4% showed at least a 1-log decrease in their HCV RNA level by the same time after treatment was started. Similarly, 60.3% lost detectable HCV RNA after 12 weeks compared with only 29.4% at 4 weeks.

The definition of EVR that optimized capture of potential responders (where most SVR have EVR; highest sensitivity) while excluding the largest proportion of non-responders (highest negative predictive value) was at least a 1- or 2-log decrease in HCV RNA from baseline after 12 weeks of treatment (Table 1). A 2-log decrease in HCV RNA was a more efficient definition of EVR than a 1-log decrease in that all of the patients with SVR were captured by both definitions, although the former definition did so with a lower proportion of patients achieving EVR. Thus, fewer patients would need to continue therapy to achieve the optimal outcome. Most patients (74.4%) achieved a 2-log decrease in HCV RNA by 12 weeks and therefore were justified in continuing therapy (Fig. 1). If treatment had been discontinued in the other 25.6% of treated patients, no patients with SVR would have been lost by premature interruption of treatment. Furthermore, all of the subjects who failed to reach EVR were nonresponders 24 weeks after completing a full course of treatment. Looked at another way, those patients who failed to achieve EVR after 12 weeks had no chance of reaching SVR, even if they completed the additional 9 months of treatment that was originally prescribed.

Patients who failed to reach EVR did not differ by age, sex, weight, or degree of hepatic fibrosis. However, they were more likely to have genotype 1 (for PEG/R: 94% vs. 60%, $P < .001$; for PEG/R >10.6 : 90% vs. 57%, $P < .001$) and HCV RNA greater than 2 million copies/mL

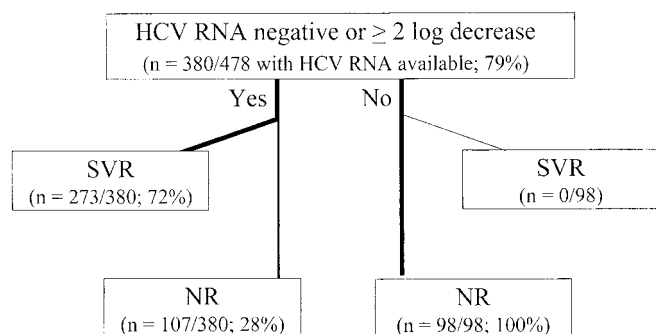


Fig. 1. Fate of patients who received pegylated interferon alfa-2b 1.5 $\mu\text{g}/\text{kg}$ once weekly plus oral ribavirin 800 mg/d according to whether or not HCV RNA levels decreased by more than 2 logs or to an undetectable level at week 12 compared with baseline (EVR).

(for PEG/R: 85% vs. 64%, $P < .001$; for PEG/R > 10.6 : 77% vs. 56%, $P < .05$). These baseline characteristics have been previously described as being associated with SVR response. Unfortunately, these are fixed characteristics that cannot be modified. In contrast, treatment adherence is often controllable and was closely associated with the likelihood of achieving EVR. Intent-to-treat analysis showed that poor adherence during the first 12 weeks of treatment had a particularly strong negative impact on EVR (Table 2). Dose reductions that resulted in receipt of less than 80% of the prescribed dose of one drug or both were common during the first 12 weeks (105 of 511 [20.5%]). Reductions of either ribavirin alone (5 of 105) or PEG alone (54 of 105) reduced the chance of EVR compared with those who received full doses (60% and 70%, respectively, vs. 80%), but the differences were not significant. However, reduction and/or discontinuation of both drugs was necessary in 46 cases and resulted in a marked reduction in EVR (33% vs. 80%; $P < .001$). It is clear that dose reductions during the first 12 weeks can reduce the chance of EVR, and this is most pronounced when the doses of both drugs are reduced.

Not all patients who had EVR ultimately achieved SVR (Fig. 1). Indeed, the positive predictive value of EVR, defined as a decline in HCV RNA by at least 2 logs or to an undetectable level after 12 weeks, was only 72%. There are several reasons for this. SVR was lower in patients who had a 2-log decrease in the HCV RNA level but remained PCR positive (15 of 72 [21%]) than in those who had both a 2-log decrease and undetectable HCV RNA by PCR after 12 weeks (258 of 308 [83%]; $P < .001$). Of the 72 subjects (19%) with EVR who still had residual virus detected by PCR at 12 weeks, repeat HCV RNA testing was available at week 24 in 67. Of those who remained PCR positive at week 24, only 1 of 24 (4%) achieved SVR compared with 14 of 43 (33%) of those who lost virus between weeks 12 and 24 ($P < .01$).

This suggests that patients with EVR who remain PCR positive at 12 weeks should have PCR testing repeated after 24 weeks before making any decision about discontinuing treatment. Another factor that explains the failure of patients with EVR to reach SVR is the ability to adhere to the prescribed treatment regimen. Reduction of pegylated interferon or ribavirin or both to less than 80% of the prescribed dose after EVR had been reached only reduced the chance of SVR from 72% to between 61% and 63%, but premature discontinuation or significant interruptions of treatment resulting in receipt of less than 80% of the expected duration reduced the chance of SVR to 50%. Patients who had treatment reductions in the first 12 weeks were not different from adherent patients with respect to age, sex, genotype, viral level, or presence of cirrhosis.

A 2-log decrease in HCV RNA at week 12 was the optimal definition of EVR regardless of viral genotype. Among the 348 subjects with genotype 1 infection, 12-week viral data were available in 321 (92%). Of these, 229 (71%) reached EVR and 144 (63%) resulted in SVR. Nearly all of the subjects with genotype 2 or 3 infection and a week-12 viral determination reached EVR (140 of 142 [99%]; $P < .001$ compared with genotype 1), and 121 of these (86%) achieved SVR ($P < .001$ compared with genotype 1).

Weight-Based Dosing and Standard Interferon.

The ribavirin dose chosen in the original design of this study was, in retrospect, suboptimal.^{7,12} The optimal dose of ribavirin has been proposed to be at least 10.6 mg/kg/d, a dose responding to 800 mg in a 75-kg individual; therefore, a ribavirin dose of 800 to 1,200 mg based on body weight is more appropriate.^{7,12,13} Although the post-hoc analysis showing higher responses when the ribavirin dose exceeded 10.6 mg/kg may simply reflect the lower body weight in those individuals, weight-based dosing of ribavirin is now recommended in Europe, Canada, and Australia.¹⁴ Thus, we have included analysis of the EVR in this subgroup for comparison.

Table 2. Influence of Dose Reductions During the First 12 Weeks of Treatment on the Chance of Achieving EVR

Pegylated Interferon by 12 Weeks	Ribavirin by 12 Weeks	EVR Reached (HCV RNA negative or decreased > 2 logs)	
		n	%
At least 80% received	At least 80% received	324	80
	Less than 80% received	3	60
Less than 80% received	At least 80% received	38	70
	Less than 80% received	15	33*

* $P < .001$.

Table 3. Baseline Characteristics of the 3 Reported Groups

Interferon	PEG/R	PEG/R >10.6	I/R
	PegIntron 1.5 $\mu\text{g}/\text{kg}/\text{wk}$	PegIntron 1.5 $\mu\text{g}/\text{kg}/\text{wk}$	Standard rIFN 3 MU thrice weekly
Ribavirin (mg/day)	800	>10.6 per kg	1,000-1,200
No. of subjects	511	188	505
Age (mean \pm SD; yr)	43.9 \pm 8.0	42.8 \pm 8.7	43.2 \pm 8.1
Sex (% male)	321 (63)	66 (35)	336 (67)
Weight (mean \pm SD; kg) (% >85 kg)	82.4 \pm 18.0	64.5 \pm 7.5	81.7 \pm 17.4
	216 (42)	0 (0)	204 (40)
Genotype 1 (%)	348 (68)	122 (65)	343 (68)
HCV RNA (log copies/mL) (>2 M copies/mL)	6.4 \pm 0.6	6.3 \pm 0.6	6.4 \pm 0.6
	351 (69)	115 (61)	344 (68)
Serum ALT/ULN (mean \pm SD)	2.9 \pm 1.9	2.8 \pm 1.8	3.0 \pm 2.4
Bridging fibrosis or cirrhosis (%)	136/469 (29)	44/168 (26)	132/468 (28)
SVR (%)	274 (54)	114 (61)	235 (47)

NOTE. The PEG/R >10.6 group is a subgroup of the PEG/R group that in retrospect received an optimal ribavirin dose (>10.6 mg/kg). Thus, the weight is lower and the proportion who are female is higher; the groups are otherwise not different.

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal.

The baseline characteristics of the patients in the weight-based group were similar to those in the other study groups (Table 3). When our analysis is confined to the patients who received at least 10.6 mg/kg/d of ribavirin, the results are nearly identical to the analysis of the entire study group (Table 4). A similar proportion (76%) achieve at least a 2-log decrease in HCV RNA after 12 weeks of treatment, and no patients who fail to achieve this milestone go on to obtain SVR (negative predictive value, 100%). As with the overall treatment group, the chance of reaching EVR was lower in those patients with genotype 1, high HCV RNA levels, and lower serum alanine aminotransferase levels.

Sixty-nine percent of patients treated with standard (nonpegylated) interferon and ribavirin had a 2-log or greater decline in HCV RNA level after 12 weeks of therapy (Table 4). Nearly all patients (>99%) who failed to achieve EVR also failed to clear virus (SVR, 0.6%). Thus, the 12-week quantitative assessment in patients treated with standard interferon and ribavirin is equivalent to the previously recommended 24-week assessment that used qualitative testing only.^{15,16} Although redefining EVR as a 1-log decrease in virus at week 12 in this treatment group had a slightly higher negative predictive value of 100%, the specificity was much less (0.30 vs. 0.57), indicating that many more patients would have to continue treatment without a chance of reaching SVR.

Cost Savings by Utilizing EVR. If the quantitative comparison between the baseline and 12-week virus levels was used as a measure of treatment responsiveness and determinant as to whether treatment would be stopped in those without EVR, treatment costs would have been reduced by 17.8% (PEG/R group) compared with the full course of treatment in all patients. Most of the cost sav-

ings accrued by EVR determinations was in patients with genotype 1, in which testing reduced overall treatment costs by 21.5%. In contrast, stopping treatment based on failure to reach EVR would reduce drug costs by only 0.8% in patients with genotypes 2 or 3, less than the cost of viral testing to measure EVR. Thus, EVR testing is not cost-effective in patients with genotypes 2 and 3. The reduction in treatment costs projected by using the 12-week EVR in patients with genotype 1 was only slightly better than that accrued using the standard 24-week PCR-positive stopping rule (2.7%).

Discussion

Interferon-based regimens for the treatment of chronic hepatitis C have become increasingly effective and currently are able to eradicate virus in more than one half of cases. However, treatment is complicated. First, treatment requires administration of 2 drugs by different routes and frequent dose adjustments. Second, therapy is usually associated with side effects that can require frequent physician visits, loss of work, and dose adjustments. Finally, therapy is expensive. Thus, one would like to be able to assess whether long-term response is likely as early as possible during the treatment course and have the option of treatment discontinuation in those cases in which viral clearance is not going to occur. This strategy has the potential of making a trial of treatment more appealing to patients by providing a limited "test" period of treatment before committing to a full course of therapy. It can also be a strong motivating feature for patients and physicians by providing an early goal of therapy (EVR) that, if achieved, is associated with a greater likelihood of sustained response.

Table 4. Comparison of EVR, (≥ 2 -Log Decrease in HCV RNA by Week 12) and Other Treatment Outcomes in Subjects Treated With Pegylated Interferon and Ribavirin (800 mg), the Subset That Received a Ribavirin Dose 10.6 mg/kg/day, and Those Who Received Standard Interferon and Ribavirin

Study Group	Treated Reaching EVR	Treatment Outcomes		
		No EVR Reached	EVR Reached	SVR Who Reach EVR‡
		NR*	SVR†	
Pegylated interferon/ ribavirin (800 mg)	380/511 (74.4%; 0.706-0.782)	131/131 (100.0%; 0.999-1.00)	273/380 (71.8%; 0.673-0.764)	273/273 (100.0%; 0.999-1.00)
Pegylated interferon/ ribavirin (≥ 10.6 mg/kg)	143/188 (76.1%; 0.679-0.822)	45/45 (100.0%; 0.999-1.00)	114/143 (79.7%; 0.731-0.863)	114/114 (100.0%; 0.999-1.00)
Standard interferon/ ribavirin (1,000- 1,200 mg)	350/505 (69.3%; 0.651-0.731)	154/155 (99.4%; 0.977-0.998)	234/350 (66.9%; 0.618-0.717)	234/235 (99.6%; 0.984-0.999)

NOTE. Data expressed at raw number of events per study group size based on intent to treat. Patients without virologic data at time point are considered not to have EVR. Percentage and 95% confidence intervals are shown in parentheses.

Abbreviation: NR, no response.

*Negative predictive value. Treatment outcomes include only patients with virologic data available at the relevant time point.

†Positive predictive value. Treatment outcomes include only patients with virologic data available at the relevant time point.

‡Sensitivity. Treatment outcomes include only patients with virologic data available at the relevant time point.

Measurement of virus early during interferon-based treatment has been shown to be useful in determining the likelihood of response since the first studies of interferon monotherapy.¹⁷ Failure to lose detectable HCV RNA by qualitative PCR testing after 12 weeks of treatment with standard recombinant interferon alone was strongly associated with failure to respond to a full 6- or 12-month course of therapy and thus became accepted as the basis for early discontinuation of therapy. However, when the combination of standard interferon and ribavirin became available, it was apparent that some patients who remained HCV RNA positive after 12 weeks of treatment were still able to permanently clear the virus.^{15,16} Thus, the stopping rule was modified to use a 24-week assessment of HCV RNA by PCR. Although some studies suggested that quantitative HCV RNA determinations would allow earlier assessment of treatment response, these assays were not generally commercially available and were not standardized.¹⁸⁻²⁰

The current availability of reproducible quantitative HCV RNA tests makes quantitative testing more feasible as a means of assessing EVR.^{21,22} However, there are still limitations to quantitative testing. First, the current precision of most of these assays is ± 0.5 log, so decisions based on quantitative levels must consider this when marginal changes in virus level are observed. Our definition of EVR was robust to a change of 2.5 logs from baseline (data not shown), so the 2-log change is a conservative definition to use in clinical practice. The second limitation to consider is that the dynamic linear ranges of some of the tests do not allow determination of the changes we propose here without dilution of samples.²¹ Third, assays

using different methodologies are generally not comparable.^{21,22} Finally, careful sample preparation is important to prevent degradation of RNA or contamination.²³

Development of treatment decision rules based on EVR assumes that virologic response, particularly SVR after completing treatment, is required for clinical benefit. Several studies have shown that there is histologic improvement during treatment with interferon. Although this improvement is most pronounced in virologic responders, some reduction in inflammation and occasionally fibrosis is also seen in viral nonresponders.^{7,15-17,24} Histologic improvement seems to occur among those who have significant reduction in viral loads during therapy, and it remains uncertain if it provides any lasting clinical benefit to the patient.²⁵ Finally, there are reports of a lower incidence of hepatocellular carcinoma in patients with hepatitis C who have previously been treated with interferon.^{26,27} However, despite the promising retrospective reports suggesting a benefit of interferon independent of viral clearance, there are still no prospective data supporting the benefits of maintenance interferon in viral nonresponders. This question is currently being examined in several randomized, controlled prospective studies.²⁸ Until the results of those studies are available, there seems to be little justification for treating patients who do not significantly inhibit virus replication and have no chance of permanently clearing virus.

Determination of EVR can be extremely helpful in the management of patients with chronic hepatitis C who receive treatment with pegylated interferon and ribavirin. It provides patients and treating physicians with an early goal and motivates them to adhere to treatment recom-

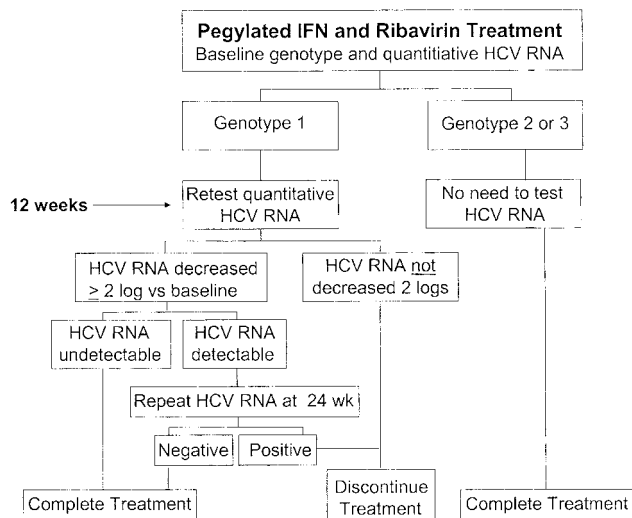


Fig. 2. Algorithm for viral testing to identify patients with EVR. Quantitative HCV RNA testing is recommended at baseline and at week 12 of therapy in patients with genotype 1. EVR (decrease in HCV RNA ≥ 2 logs compared with baseline or undetectable by PCR at week 12 of therapy) is associated with a high chance of response and justifies continuation of treatment. Those who have at least a 2-log decrease in HCV RNA but remain HCV RNA positive by PCR should have HCV RNA retested by PCR at 24 weeks. Because no patient without at least a 2-log decrease in HCV RNA at 12 weeks subsequently achieved SVR, the lack of EVR usually justifies discontinuation of therapy. Patients with genotypes 2 or 3 have a high chance of achieving EVR and SVR; retesting of HCV RNA during treatment is not cost-effective in these cases.

mentations. Adherence to the prescribed treatment regimen seems to be critically important during the first 12 weeks of treatment, and significant reductions in either drug but especially ribavirin appear to dramatically reduce the chance of responding to therapy. Future trials need to determine whether more conservative dose reductions than currently recommended or growth factors to reverse cytopenia could facilitate early treatment adherence. Assessment of EVR also provides the patient and physician with a better idea of the likelihood of a long-lasting treatment response. EVR motivates the patient to complete the prescribed course of treatment. Discontinuation of therapy in the minority who fail to achieve EVR reduces treatment costs and avoids the morbidity of therapy in those with no chance of viral clearance.

The National Institutes of Health Consensus Development Conference Statement on Hepatitis C recently recommended utilization of quantitative HCV RNA testing to assess EVR.²⁹ Based on our results, we propose a viral testing and management algorithm for patients receiving treatment with pegylated interferon and ribavirin (Fig. 2). Although the algorithm is based on the data presented here for pegylated interferon alfa-2b, similar results have been reported for another pegylated interferon preparation.^{30,31} The algorithm applies equally well to patients

treated with pegylated interferon with either fixed or weight-based ribavirin dosing as well as to those still treated with standard interferon and ribavirin. Assessment of EVR is most helpful in patients infected with genotype 1. Testing for EVR can significantly reduce the cost of therapy for these patients. On the other hand, EVR testing is of little benefit in patients with genotypes 2 and 3 because almost all achieve EVR, SVR occurs in most cases, and there is no cost savings.

In conclusion, early confirmation of viral reduction following initiation of antiviral therapy for chronic hepatitis C is worthwhile. It provides a goal to motivate adherence during the first months of therapy and a milestone at which to reassess the need for continued treatment. Most patients who are able to complete the first 12 weeks of therapy achieve EVR and have a high probability of SVR if the remainder of the treatment course can be completed. The minority of patients who fail to achieve EVR will not clear virus even if an additional 9 months of therapy is received. Therapy can be confidently discontinued in those cases.

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