Rapid virological response to peginterferon alfa and ribavirin treatment of chronic hepatitis C predicts sustained virological response and relapse in genotype 1 patients

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Abstract: The treatment of chronic hepatitis C is a rapidly changing arena with new medications, new guidelines, and an evolving understanding of the virus, host factors and natural history. With the explosion of new information, the educational infrastructure to update clinicians has been outpaced; many feel uncertain if the tools they are using to care for patients are meeting the standard of practice. This review focuses on the most common genotype of the hepatitis C virus and the rules of engagement when treating with pegylated interferon and ribavirin. Viral assessment guideposts are evaluated and put into context for a clinical audience. The expected arrival of newer antiviral therapies is still years away, and maximizing the current treatment regimens is of utmost importance to eradicate virus when feasible, while minimizing toxicity.

Keywords: hepatitis C virus, pegylated interferon, ribavirin, positive predictive value, negative predictive value, rapid virologic response, early virologic response, relapse

Introduction

Pegylated interferon alfa 2a and alfa 2b (Peg IFN alfa2a and alfa2b) and ribavirin (RBV) are the accepted therapy for chronic hepatitis C (CHC). It is now accepted that CHC is curable with this therapy, even in the most difficult to eradicate genotype 1 strain. As therapy has been modified over the past decade with the pegylation of IFN and the institution of higher doses of RBV, response rates have increased. With these advances, however, medication-related adverse events have become more common, some of which are significant. Cost of therapy has also increased accordingly, and this has been a limitation in some circumstances in offering therapy to a broader patient base. Hence, predicting response or lack of response has been a focus of creating treatment paradigms to maximize efficiency. A combination of baseline and on-treatment variables has been assessed to allow physicians to predict and track responses for their patients [Lee *et al.* 2002]. Familiarization with these predictors by clinicians has been a slow process and

not uniform. As treatment algorithms become more complex, updating health care providers will become more challenging.

Baseline predictors of response

Over the past decade, a deeper understanding of predictors of response has developed. Several studies, including pivotal trials, assessed baseline host and viral predictors such as body weight, ethnicity, liver histology, genotype, and viral load [Fried *et al.* 2002; Manns *et al.* 2001]. These predictors in a recent head-to-head comparison of the two approved Peg IFN molecules yielded further insight into the relative importance of these variables. In order of descent, viral load, ethnicity, fibrosis, steatosis, diabetes mellitus, and alanine aminotransferase (ALT) were found to have significant impact on sustained virological response (SVR) in a multivariate regression analysis [Sulkowski *et al.* 2008a]. Viral load remains the most important single variable in genotype 1 patients prior to therapy,

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but one that cannot be altered. Other variables, however, may be modified prior to treatment. It is clear that metabolic factors such as elevated fasting glucose and the histologic finding of steatosis are important negative predictors. Altering these variables in the hope of a more favorable SVR is a topic of current study.

Baseline predictors are useful tools in assessing the relative difficulty of clearing hepatitis C virus (HCV). One end of the spectrum would be a low viral load, Caucasian patient without features of the metabolic syndrome, no or minimal fibrosis and elevated ALT. The more difficult-to-cure patient is an African American with metabolic syndrome features, high viral load and advanced fibrosis. The reality is that most patients fall between these two ends of the spectrum; because there are multiple variables, there is no reliable way to ascribe an odds ratio for the chance that a particular patient will respond to therapy.

Baseline predictors have limited utility for selecting which patient should be considered for therapy. A low likelihood of response based on these initial predictors will not prevent an attempt at therapy. Indeed, the patient with the poor baseline predictors is often the one that is most in need of viral eradication, since that patient is often on a more aggressive path toward end-stage liver disease. For example, diabetes and steatosis appear to accelerate hepatic scarring, shortening the timeline to cirrhosis. This population often has more advanced disease at the time of presentation, but tends to respond poorly.

On therapy predictors of response

The decision to start treating a patient with CHC is not one that should be taken lightly. The adverse event profiles of IFN and RBV are such that all patients will have multiple side effects, and in some cases, significant or even irreversible injury can occur. The need to minimize adverse events and prevent futile treatment prompted the development of certain stopping rules. The first of these was at the midway point of therapy for genotype 1. The presence of any virus at the 24-week time point meant that chance of SVR would be less than 5%, and continuing beyond that was not reasonable. While this saved the patient from an additional several months of therapy, early stopping points were clearly

desirable to decrease adverse events as well as to decrease healthcare costs. As data from the pivotal Peg IFN trials was further evaluated, another time-point analysis was added. A viral load assessment at week 12 was noted to be as predictive as the 24-week mark if adequate viral clearance had not occurred. It was noted that lack of at least a 100-fold decline in baseline viral load by week 12 of therapy was associated with less than a 3% chance of response as well [Sulkowski *et al.* 2008a; Fried *et al.* 2002]. Achieving a 100-fold or 2-log₁₀ decline in virus was termed an early virologic response (EVR). Hence, both the 12 and 24-week evaluation points yielded very strong negative predictors of response, which could be used in sequence when needed to discontinue therapy if response was unlikely. Negative predictive value (NPV) is defined as the percentage of patients that do not achieve EVR (or RVR) or SVR as a proportion of the total number who do not achieve EVR (or RVR).

Stopping rules at weeks 12 and 24 were the first milestones in tailoring therapy. However, predicting who would respond to therapy was a different issue. Clinicians still did not have a reliable predictor of who would respond to therapy if the 12-week and 24-week responses were present and patient was to continue for a total of 48 weeks. Further analysis of the EVR led to a refinement of this definition [Marcellin *et al.* 2007] (Figure 1). A complete response (cEVR) is no detectable virus above a limit of quantification of 50 IU/ml whereas a partial EVR (pEVR) is at least a 100-fold decline but still detectable virus. Lack of a 2-log decline in viral load (no EVR) was associated with dismal

Figure 1. Early hepatitis C virus (HCV) kinetic responses to pegylated interferon plus ribavirin therapy.

response rates, while pEVR could predict SVR in fewer than 30% of cases. On the other hand, achieving complete viral negativity by this time point predicted over an 80% likelihood of ultimately achieving SVR with a complete course of treatment (Figure 2). This positive predictive value (PPV) is calculated as the percentage of patients who attain EVR (or RVR) and SVR divided by the number of patients that attained EVR (or RVR). This could then be used as a motivating factor for patient and health-care provider alike to continue on with confidence.

It has been a natural evolution in the care of CHC patients to minimize damage and maximize chance of response. The latter involves adjustments in dosing and duration of medications. Minimizing damage involves early recognition of adverse events and quick action when needed. It can also be achieved by further reducing exposure to drug in cases of low probability of response. Hence, NPVs of 4-week viral decline were assessed. Interestingly, lack of a 10-fold or 1-log decline of virus from baseline was almost as predictive as the lack of a 2-log decline by week 12 [Davis *et al.* 2003]. This same concept was validated in the recent head-to-head trial using three different regimens of Peg IFN and RBV (IDEAL trial). In this study, the NPV of not achieving a 1-log decline in virus by week 4 was over 95% in all three arms using Peg IFN alfa-2b of 1.5 µg/kg/week, 1.0 µg/kg/week and Peg IFN alfa-2a 180 µg/week in combination with RBV [Sulkowski *et al.* 2008b]. However, given that the NPV at week 4 is less reliable than week 12, coupled with an inherent discomfort of stopping therapy so soon into the course,

most clinicians have elected to stay with the 12-week assessment as a guidepost. The 4-week stopping rule is useful however, particularly in cases of difficult-to-treat patients or significant early toxicity. In these patients therapy can be discontinued at week 4 if there is a 'null' response and the risks of therapy outweigh the benefits.

RVR as a predictor of SVR

So while the 4-week assessment did not supplant the EVR as a stopping rule, the flip side of the coin was achieving complete viral suppression at this time point. Presence of this rapid viral response, or RVR, is highly predictive of ultimate SVR with a full treatment course of 48 weeks in genotype-1 patients. Several studies have assessed the utility of this time point and found it to be a valid indicator [Poordad *et al.* 2008].

The majority of studies that have measured RVR have done so using the lower limit of quantification of 50 IU/ml. To use a more stringent cutoff would likely change the predictive values. This needs to be borne in mind when trying to compare across studies. Table 1 summarizes several genotype 1 studies where RVR was assessed in Peg IFN alfa 2a and alfa 2b. The overall predictability of SVR when RVR is achieved ranges from 72.5% to 100%. Importantly, in studies that have assessed truncating therapy to 24 weeks total duration when RVR is achieved have failed to show PPVs to be as robust as treating for a full 48 weeks. This sheds some further light on potential limitations of shortening therapy even when the virus is cleared rapidly. When shortening therapy to 24 weeks in RVR patients, the PPV ranges from 74.2% to 88.9%, whereas PPV with 48 weeks ranges from 72.5% to 100%.

Figure 2. Positive predictive value (PPV) at week 12 based on complete or partial early virologic response (EVR).

In a review of Peg IFN alfa-2a databases assessing hundreds of genotype-1 patients, roughly 16% achieved RVR. In an analysis of a large dataset which assessed 800 mg of RBV compared to 1000/1200 mg, it was noted that RVR was 16% in the lower-RBV-dosed patients and 20.3% in the higher-dosed arm [Jensen *et al.* 2006; Hadziyannis *et al.* 2004]. The PPV of achieving SVR was 72.5% in the lower dose, but 90.9% in the higher dose. It is known that higher doses of RBV increase SVR, but may also increase the chance of achieving RVR. In patients that do not achieve RVR, higher doses of RBV lead to lower NPV of achieving SVR compared with 800 mg of RBV (56.2 versus 64.9%, respectively).

Table 1. Positive and negative predictive values of rapid virologic response (RVR) and the relationship to sustained virologic response (SVR) and relapse.

Author	Zeuzem <i>et al.</i> (2006)	Jensen <i>et al.</i> (2006)	Berg <i>et al.</i> (2006)	Sanchez-Tapias <i>et al.</i> (2006)	Mangia <i>et al.</i> (2008)	Segadas-Soares <i>et al.</i> (2006)	Sulkowski <i>et al.</i> (2008a)
Therapy (Peg/RBV dose × 1000 mg)‡ Duration (weeks) RVR (%)	Peg2b/ 0.8–1.4 24/48 47*	Peg2a/ 0.8–1.2 24/48 16	Peg2a/0.8 48/72 22.2/15.6	Peg2a/0.8 48/72 21.6	Peg2a/2b/ 1–1.2 24/48 26.8/26.2	Peg2b/1–1.2 48 34	Peg2b/0.8–1.4 v Peg2a/1–1.2 48 11.4(Peg2b)/ 11.9(Peg2a) 92(Peg2b)/ 80(Peg2a)
PPV (%)	NC	72.5–90.9	84.3/77.1	NC	77.2/87.1	71	NC
NPV (%)	NC	64.9	56.4/50.5	72.5/55.6	NC	71	NC
SVR in RVR (%)	89	73–91	84	64–79	77.2–87.1	75	92(Peg2b)/ 80(Peg2a)
Relapse in RVR (%)	8	0–9	16	NC	18.8	NC	NC
SVR in non-RVR (%)	22.4	16–44	44	28–44	18–30.3	23	NC
Relapse in non-RVR (%)	NC	30–75	NC	17–53	24.3–26	NC	NC

*All patients were low viral load at baseline, ‡ Peg IFN alfa2b dose is 1.5 µg/kg/week; Peg IFN alfa2a dose is 180 µg/week, NC = not calculated. Peg, pegylated; RBV, ribavirin; v, versus.

In a European study using Peg IFN alfa2a and 800 mg of RBV, a total of 19% (86/455) had RVR [Berg *et al.* 2006]. Patients were randomized to 48 or 72 weeks of therapy prior to the first dose of Peg IFN. The overall SVR in these arms was 52% and 54%. However, the PPV of RVR was higher in the 48-week arm because the RVR was higher in this cohort. The NPV for SVR when not achieving RVR was only 6% higher in the 48-week arm. This indicates that when RVR is not achieved, there is minimal advantage to extending therapy to 72 weeks with fewer than 1 out of 10 patients benefiting. In contrast, in another study randomizing to 48 or 72 weeks of therapy based on not achieving RVR, there was a 17% benefit when therapy was extended [Sanchez-Tapias *et al.* 2006]. However, this benefit was lost when baseline viral load was over 800 000 IU/ml. In that group, fewer than 5% experienced a benefit when therapy was extended. This is an important point as the majority of genotype-1 patients have high viral load at baseline.

In a randomized trial by Yu and colleagues, 48 weeks of therapy with Peg IFN alfa2a 180 µg and RBV 1–1.2 g/day was superior to 24 weeks even when RVR was achieved [Yu *et al.* 2008]. This finding differs from other studies showing that RVR is a predictor that truncated therapy is a viable option in genotype 1. This study is unusual in that 45% of patients achieved RVR, which is more than double that found in any other trial. Furthermore, an astounding 79% achieved SVR when treated for 48 weeks

compared to 59% treated for 24 weeks. In those that achieved RVR, 100% achieved SVR when treated for 48 weeks, compared with 89% when treated for 24 weeks. Based on this paper, there was a 29% difference in the NPV of not achieving RVR when comparing the two arms. It is difficult to reconcile these findings with other trials, including the remarkably high response rates.

Perhaps the most rigorous study to prospectively assess RVR, SVR and relapse is the 3000-patient IDEAL trial. Using the standard doses of Peg IFN alfa-2a and alfa-2b, roughly 11% achieved RVR. However, relapse was significantly different between these regimens, leading to a 12% difference in PPV of RVR in predicting SVR. The PPV of over 90% is the highest in a study of this size, and demonstrates the importance of assessing early viral response as a predictor of SVR.

Although there are few studies in the HIV/HCV co-infected population assessing RVR, the concepts appear to apply equally well [Crespo *et al.* 2007; Payan *et al.* 2007; Torriani *et al.* 2004]. In a study of genotype-1 and -4 patients, RVR was achieved in 24.2% (16/66) of cases when treated with Peg IFN alfa2b and RBV 800 mg [Crespo *et al.* 2007]. The PPV of achieving SVR in that group was 81.3% (13/16). Conversely, of those not achieving RVR, the NPV of failing therapy was 84% (42/50). These values were similar (PPV 97.5, NPV 81.3%) in a smaller study using Peg IFN alfa2b or alfa2b with 800 mg RBV (Table 2).

Table 2. Mean and range of positive and negative predictive values of studies in Table 1.

	PPV	NPV
Genotype 1	81.3% [71–92]	61.8% [50.5–72.5]
HIV/HCV genotype 1	86.9% [81.3–97.5]	82.7% [81.3–84]

HCV, hepatitis C virus; HIV, human immunodeficiency virus; NPV, negative predictive value; PPV, positive predictive value.

Relapse

Relapse remains an unexplained phenomenon in the treatment of HCV. It is not clear if it is a reflection of inadequate duration of therapy, insufficient dosing, or simply a reflection of pockets of virus not exposed to medication. If relapse is a reflection of duration, then relapse should be lower in longer treatment courses. The question is how does RVR affect relapse and does achieving RVR eliminate the effect of duration or dose of therapy?

One of the first papers to address RVR and relapse was the Zeuzem *et al.* [2006] study assessing RVR and 24-week treatment duration in low-viral-load G1 patients. Compared with a historical, cohort-matched control, patients achieving RVR had the same SVR and relapse rates (8%) when treated with Peg IFN alfa2b and RBV 800–1400 mg/day. The *post hoc* analysis of a large Peg IFN alfa2a study corroborated this data, with relapse rates below 10% when RVR was attained, regardless of 24 or 48 weeks of therapy [Jensen *et al.* 2006]. Interestingly, dosing of 800 mg *versus* 1000/1200 mg RBV had no effect on relapse when RVR was achieved. In other words, when RVR was achieved, the low-dose RBV/24-week duration arm had similar relapse to the higher dose RBV/48-week arm. Hence, duration and dose of medication were not significant matters when RVR was achieved. This is not to suggest that low dose RBV should be used in genotype 1 patients with low viral load, since it is not clear at baseline which of them will achieve RVR. However, once RVR is achieved, modest RBV dose reductions for side-effects will likely not impact SVR.

The next question is does dose or duration of therapy affect relapse in patients that do not achieve RVR, and which is more important? In the same analysis, Jensen *et al.* [2006] found that without RVR, more than two-thirds of patients relapse when treated for only 24 weeks,

regardless of RBV dose. However, even without RVR, only one out of three patients relapse when treated for 48 weeks, regardless of RBV dose. Hence, duration of therapy beyond 24 weeks appears to be more relevant than RBV dosing in terms of decreasing relapse rates when RVR is not achieved.

Treatment duration beyond 48 weeks may affect relapse, but this is not entirely clear. Extended therapy to 72 weeks led to 9% lower relapse, but overall SVR was similar between the two groups (44% *versus* 49%) [Berg *et al.* 2006]. The Sanchez-Tapias *et al.* [2006] paper found that relapse was significantly lower in non-RVR patients treated for 72 weeks. However, as SVR was only different in those with low baseline viral load, this effect on relapse was not likely to be of significance in those with high viral load. Other studies have not shown the same effect of duration of therapy. Mangia *et al.* [2008] found no difference in relapse with 72 weeks therapy in non-RVR patients treated with Peg IFN and 1000/1200 mg RBV.

There is data to support the use of pEVR as an indicator of extending therapy beyond 48 weeks. [Mangia *et al.* 2008; Pearlman *et al.* 2007; Berg *et al.* 2006]. Extension of therapy in that setting has been associated with improved SVR. This has not been validated with enough rigor as of yet, since these trials have variable designs and dosing regimens. However, many clinicians in practice have adopted an extended therapy protocol for selected patients (Figure 3). What is clear is that lack of RVR is not an indication to extend therapy to 72 weeks, as roughly 39% of patients will achieve SVR with the usual 48-week course of therapy, compared with roughly 47% treated for 72 weeks. This does not justify the added expense and risk of prolonging therapy based on lack of RVR.

Conclusion

The use of on-treatment viral kinetic assessments in addition to baseline predictors of response has given more structure to the care of the CHC patient. With genotype-1 patients, this is particularly relevant given that this is the most common genotype, requires the longest duration of therapy and has the lowest response rates. The stopping guidelines are now clear. Lack of a 100-fold viral decline at week 12 or any residual measurable virus at week 24 denotes less than a 5%

Figure 3. Proposed algorithm for use of rapid virologic response (RVR) and early virologic response (EVR) in genotype 1 patients with chronic hepatitis C.

chance of achieving SVR, a number that most clinicians and patients feel does not warrant further therapy.

The use of the 4-week viral load assessment as a negative predictor has not been reliable. Nor has it been an accurate gauge as to when to extend therapy. However, the use of RVR or viral negativity at that time point is a very robust indicator of high likelihood of SVR, and low likelihood of relapse. This is a valuable tool for clinicians and patients, and a powerful motivator for both to continue with therapy. The concept of RVR and its relationship to SVR and relapse holds true for both Peg IFNs when combined with RBV, although relapse rates may vary somewhat across studies. The underlying mechanisms of how relapse occurs are only partially understood. Rapid viral clearance mitigates relapse but does not completely eliminate it. Other factors are at play and will deserve further study.

One of the limitations of studies assessing response-guided therapies is the retrospective nature of many of the findings, as well as differences in treatment regimens. In particular, RBV dosing often varies, as does the method of dose modification. This can greatly impact viral kinetics, relapse and SVR, making it difficult to compare across studies. Interestingly, the European Union has elected to use data from these studies to change the Peg IFN alfa-2b prescribing label for low-viral-load genotype-1 rapid

responders to receive only 24 weeks of IFN with weight-based RBV. More data will be required before such a change in practice is officially adopted in the US.

As the treatment landscape of HCV promises to change with the arrival of small molecule therapies combined with Peg IFN and RBV, the rules of the game will likely evolve as well. The concept of rapid clearance at perhaps even earlier time points is the next logical step in this evolution. With what has been learned from these aforementioned trials to date, the advantage lies in prospectively studying and fine-tuning the concepts in future trials.

The current standard of practice is now to assess baseline, 4-week, 12-week, 24-week, end-of-treatment, and 24-week follow-up viral levels in the treatment of HCV genotype 1. Adhering to this will allow a more uniform approach and standardization of care for this complex viral disease.

Conflict of interest statement

Fred Poordad: Schering Plough (Research support, consultant, speaker's bureau), Roche (Research support, consultant, speaker's bureau).

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