Review

Reducing treatment duration in patients infected with hepatitis C genotype 1: any need for further studies?

Antonio Craxi[1]*

[1]Gastroenterology and Liver Unit, Di.Bi.M.I.S., University of Palermo, Palermo, Italy

*Corresponding author: e-mail: craxanto@unipa.it

The recommended treatment duration with pegylated interferon-α plus ribavirin for patients infected with hepatitis C virus (HCV) genotype 1 is 48 weeks. Interestingly, a subpopulation of genotype 1 patients experience rapid decreases in HCV RNA levels once treatment is initiated and attain rapid virological response, defined as undetectable HCV RNA at week 4 of therapy. Several studies have shown that these patients can be effectively treated for a 24-week period without any significant decreases in sustained virological response rates. The aim of this review was to consider the existing clinical evidence regarding the use of a 24-week treatment schedule among genotype 1 patients and to highlight the characteristics of patients most suitable for this shortened treatment schedule.

Introduction

The recommended treatment for patients with chronic hepatitis C (CHC) caused by hepatitis C virus (HCV) genotype 1 (G1) is pegylated interferon (PEG-IFN)-α plus ribavirin for 48 weeks [1]. Overall, 42–46% of G1 patients treated with PEG-IFN-α plus ribavirin for the recommended 48 weeks attain sustained virological response (SVR), defined as undetectable HCV RNA at 24 weeks after stopping treatment [2,3]. Although this approach has been considered optimal in this patient population, current clinical evidence suggests that many G1-infected patients are under-treated and some are over-treated with this one-size-fits-all paradigm. Paradoxically, a longer-than-needed treatment plan might ultimately reduce its effectiveness in real-life practice, acting as a deterrent to initiate therapy in some patients.

On-treatment measures of efficacy, such as early decreases in HCV RNA, can be used to optimize therapy for each patient; treatment duration is defined according to each individual's response profile. G1 patients who are slow to respond to therapy and have first undetectable HCV RNA between weeks 12 and 24 (partial early virological response) might benefit from extending treatment from 48 to 72 weeks [4]. Approximately 60% of G1 slow responders who are treated for the recommended 48 weeks experience relapse after having undetectable HCV RNA at the end of therapy. Conversely, G1 patients with first undetectable HCV RNA at week 4 of therapy (rapid virological response [RVR]) might be amenable to a shorter, 24-week treatment schedule [5]. For these patients, 48 weeks of therapy might be excessive, resulting in unnecessary health care costs and unwarranted drug-related toxicity.

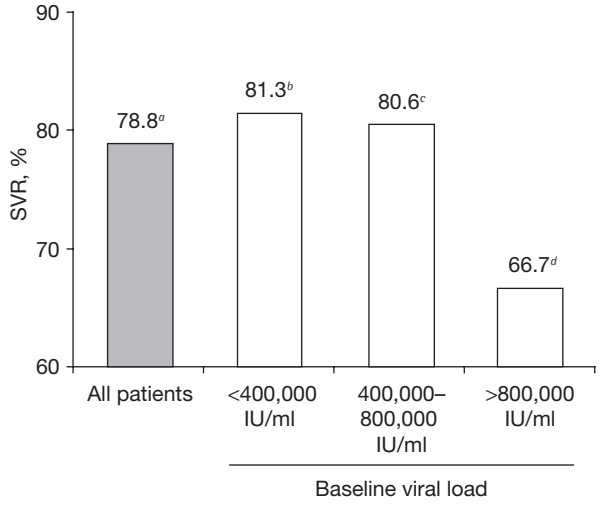
The aim of this review was to consider the strengths and weaknesses of existing clinical evidence regarding the use of a 24-week treatment schedule among G1 patients, to highlight the characteristics of patients who are most suitable for this shortened treatment schedule and to discuss how ongoing clinical trials will help to bridge these gaps.

Studies of 24-week treatment regimens in genotype 1 patients

Low viral load at the time of treatment initiation has been recognized as a strong predictor of SVR since early investigations with interferon (IFN)-α monotherapy [6]. Studies with PEG-IFN-α plus ribavirin have identified a small subgroup of G1 patients who respond particularly well [5,7–10]. In general, these patients have low baseline viraemia and attain RVR, defined as undetectable HCV RNA at week 4 of therapy. Based on this series of clinical investigations, G1 patients who fit this response profile are considered to be effectively treated at 24 weeks, rather than the recommended 48 weeks, without discernible decreases in SVR rates.

Ferenci *et al.* [7] were among the first to note the close association between low baseline viraemia and RVR. In

Figure 1. Sustained virological response rates among genotype 1 patients with chronic hepatitis C who attained rapid virological response



All patients received pegylated interferon-α2a (180 μg/week) plus ribavirin (1,000–1,200 mg/day) for 24 weeks [9]. [a]*n*=89/113. [b]*n*=52/64. [c]*n*=25/31. [d]*n*=12/18. SVR, sustained virological response.

a retrospective analysis of the pivotal PEG-IFN-α2a trial by Ferenci *et al.* [7], RVR was attained by 22% of G1 patients who had low baseline viraemia (≤800,000 IU/ml) and who had received PEG-IFN-α2a (180 μg/week) plus ribavirin (1,000–1,200 mg/day). By contrast, only 6% of patients with baseline viraemia >800,000 IU/ml attained RVR [7]. After 48 weeks of treatment, SVR was attained by 88% of patients with low baseline viraemia who attained RVR. These data provided the first insight into the importance of low pretreatment viral load in attaining RVR and subsequently SVR.

Investigations then proceeded to determine whether treatment durations of <48 weeks were possible in G1 patients with low baseline viraemia who attain RVR. Zeuzem *et al.* [8], in a non-comparative historical control study, showed that SVR was attained by almost 90% of G1 patients with baseline viraemia ≤600,000 IU/ml who attained RVR while receiving PEG-IFN-α2b (1.5 μg/kg/day) plus ribavirin (800–1,400 mg/day). In comparison, an identical historical control cohort treated for 48 weeks attained SVR rates of 85% [8]. This study confirmed that RVR was clearly a strong predictor of SVR in G1 patients and that patients with low baseline viraemia who attain RVR can be effectively treated with a 24-week regimen without any significant decreases in SVR compared with a 48-week treatment [8].

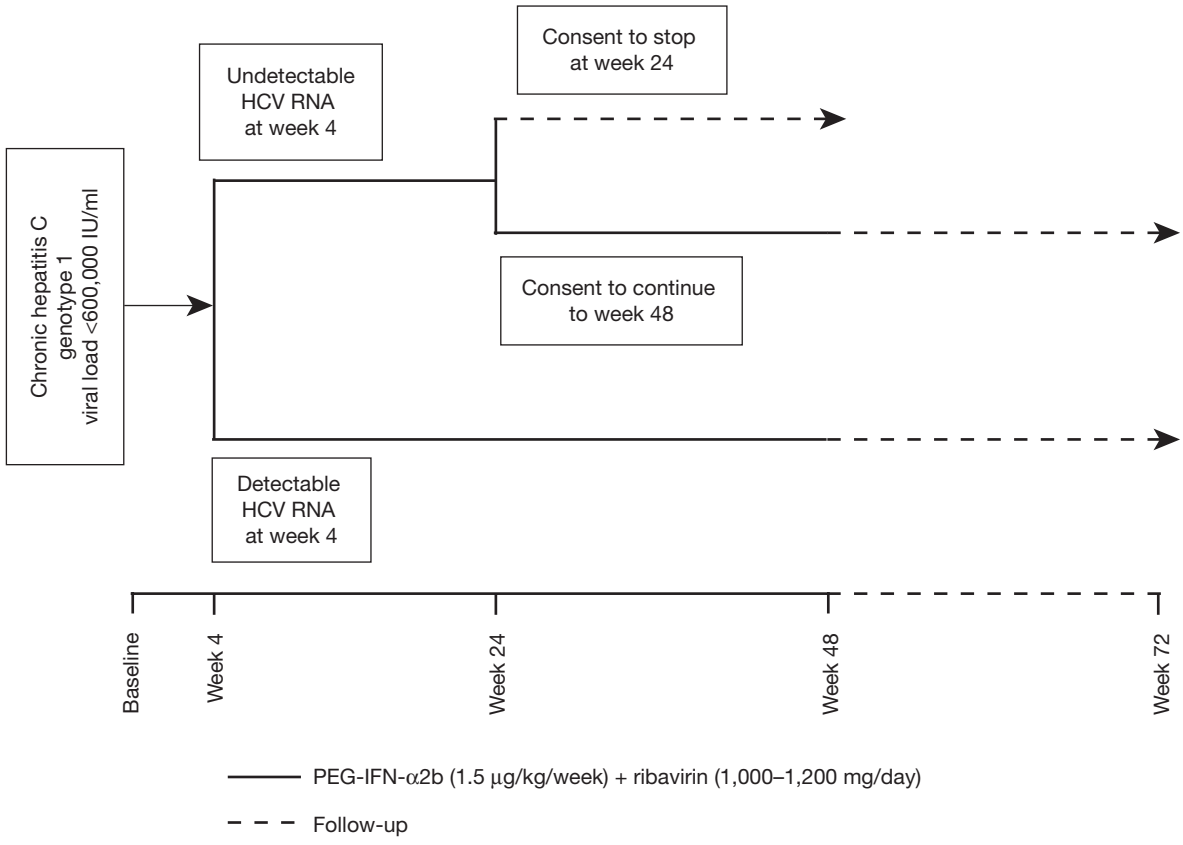
Subsequent investigations have further confirmed the results reported by Zeuzem *et al.* [8]. In a retrospective analysis [5] of data from a study originally reported by Hadziyannis *et al.* [11], SVR was attained by 88% and 91% of patients who attained RVR during treatment with PEG-IFN-α2a (180 μg/week) plus ribavirin (1,000–1,200 mg/day) for 24 and 48 weeks, respectively. Furthermore, patients with baseline viraemia <200,000 IU/ml or between 200,000 IU/ml and 600,000 IU/ml were significantly more likely to attain RVR than those with baseline viraemia >600,000 IU/ml ($P<0.0001$ and $P=0.057$, respectively).

In a more recent prospective study, Ferenci *et al.* [9] reported SVR rates of 79% among G1 patients who attained RVR while receiving PEG-IFN-α2a (180 μg/week) plus ribavirin (1,000–1,200 mg/day) for 24 weeks. In the subgroup of patients with baseline viraemia <400,000 IU/ml who attained RVR, the SVR rate was 81%. By contrast, the SVR rate was 67% (P=not significant) in patients with baseline viraemia >800,000 IU/ml (Figure 1) [9]. In this study, all patients with RVR were treated for 24 weeks; no comparator group existed to assess response if treatment had been continued for the standard 48 weeks.

Finally, Yu *et al.* [10] reported SVR rates of 96% and 100% among Taiwanese G1 patients with baseline viral load <400,000 IU/ml who attained RVR during treatment with PEG-IFN-α2a (180 μg/week) plus ribavirin (1,000–1,200 mg/day) for 24 weeks and 48 weeks, respectively. In this study, substantially higher SVR rates than generally expected of a G1 population were reported, perhaps because Taiwanese patients tend to have lower levels of HCV RNA, lower body weight and less advanced liver disease than Caucasian patients [10]; therefore, caution should be exercised when extending the results of this study to Western populations.

The findings by Mangia *et al.* [12] provide further evidence that G1 patients who attain RVR can be effectively treated with a 24-week regimen. In this study, patients received PEG-IFN-α2a (180 μg/week) or PEG-IFN-α2b (1.5 μg/kg/week) plus ribavirin (1,000–1,200 mg/day) for 48 weeks or for a variable duration, according to the time of first undetectable HCV RNA. In the variable duration arm, patients with RVR were treated for 24 weeks, patients with first undetectable HCV RNA between weeks 4 and 8 were treated for 48 weeks, and patients with first undetectable HCV RNA between weeks 8 and 12 or with ≥2 $\log_{10}$ decrease in HCV RNA at week 12 were treated for 72 weeks. Overall, SVR was attained by 45% of patients in the standard duration group and 49% of patients in the variable duration group ($P=0.37$). Importantly, among patients who attained RVR, SVR rates were similar in the standard duration (48 weeks) and variable duration (24 weeks) treatment arms (87% versus 77%; $P=0.12$) [12]. Relapse rates were also similar in the 24- and 48-week arms (19% versus 10%;

Figure 2. PREDICT study design



HCV, hepatitis C virus; PEG-IFN, pegylated interferon.

P=0.13). Furthermore, in patients with baseline viraemia <400,000 IU/ml and RVR, SVR rates were 84% in patients treated for 24 weeks and 83% in those treated for 48 weeks [12].

On the basis of the outcomes from the study by Zeuzem *et al.* [8], the European Medicines Evaluation Agency approved a 24-week treatment duration for PEG-IFN-α2b in patients with low baseline viraemia who attain RVR. However, despite the promising implications of shorter treatment durations, further data are needed [13]. Patients in the Zeuzem *et al.* [8] study were selected from a cohort from the study by Manns *et al.* [2]. These patients received optimal ribavirin dosing (>10.6 mg/kg/day) for the entire study duration and had HCV RNA samples tested at weeks 4, 12 and 24, suggesting that they were relatively lean patients, generally compliant and experienced few adverse events necessitating dose reduction [8]. The PREDICT study represents a post-approval commitment to confirm the observations of Zeuzem *et al.* [8] in a prospective, observational study.

The PREDICT study

PREDICT is an international multicentre non-interventional study in G1 patients who have pretreatment HCV RNA levels <600,000 IU/ml (Figure 2). The objective of this study is to compare clinical outcomes in these patients after 24 or 48 weeks of treatment. All patients are receiving PEG-IFN-α2b (1.5 μg/kg/week) plus weight-based ribavirin (800–1,200 mg/day). Patients who attain RVR may choose to discontinue therapy at week 24 or to continue treatment for an additional 24 weeks. By contrast, patients who do not attain RVR are treated for 48 weeks. HCV RNA assays are performed at the laboratory routinely used by each study site. Exclusion criteria in PREDICT are unrestrictive, permitting enrolment of a wide range of G1 patients. Detectable HCV RNA at week 4, previous therapy for CHC or contraindications to study medication are the only exclusion criteria. The primary end point of the study is relapse rate and the secondary end point is SVR. Because the primary concern in shortening

treatment duration is a consequent increase in relapse rates, an observational extension arm to the study has been included for patients who experience relapse after 24 weeks of therapy. In this extension arm, patients are receiving PEG-IFN-α2b plus ribavirin according to their initial regimen for a further 48 weeks. Final results of the PREDICT study are anticipated in late 2009.

Discussion

Among treatment-naive patients with CHC, those with HCV G1 infection represent the greatest unmet clinical need. Overall, <50% of G1 patients attain SVR when treated for 48 weeks [2,3], and treatment durations longer than 48 weeks are required for some of these patients to maximize treatment outcomes [4]. Still, a sizeable proportion of G1 patients respond well to treatment and would not require a full 48-week course of therapy. Several studies indicate that G1 patients with baseline viraemia ≤600,000 IU/ml (at least 20% of all HCV G1 patients in Western populations [12,14]) who attain RVR do not gain incremental benefit from treatment beyond 24 weeks [5,8,10]. However, a prospective comparison of 24- and 48-week treatment regimens conducted in a Western population with HCV infection remains elusive. To date, studies have been non-comparative [9], retrospective [5] or cannot be generalized to the population of patients with CHC caused by HCV G1 infection who are routinely present for treatment in Western countries [10]; thus, a well designed prospective study of 24 versus 48 weeks of therapy remains important to confirm the results of these studies.

The PREDICT study includes the important elements of a well designed clinical trial while having close similarities with day-to-day clinical practice. Broad enrolment criteria allow the recruitment of a broad spectrum of patients (including those with significant comorbidities and those at all stages of liver fibrosis and/or cirrhosis) who are often excluded from most clinical trials but who are frequently encountered in day-to-day clinical practice. Furthermore, because HCV RNA tests will be conducted at local laboratories, the study will closely mimic the routine day-to-day management of patients with CHC and should prove to clinicians that they can use the results of HCV RNA assays conducted at local testing facilities to reliably shorten treatment duration in G1 patients who attain RVR.

An increase in the incidence of relapse after treatment cessation is a major concern when selecting shortened treatment durations. Relapse rates approaching 20% are reported among G1 patients who attain RVR and are treated for 24 weeks (Table 1) [5,8–10,12]. For this reason, the PREDICT study design also includes an observational extension study, which provides the opportunity for retreatment of patients who experience relapse after 24 weeks of treatment using a 48-week retreatment duration.

Table 1. Clinical trials of 24-week treatment duration in genotype 1 patients with chronic hepatitis C

Treatment	Patient characteristics	Sustained virological response rate, %		Relapse rate, %		Reference
		24-Week treatment	48-Week treatment	24-Week treatment	48-Week treatment	
PEG-IFN-α2b (1.5 μg/kg/week) + RBV (800–1,400 mg/day)	≤600,000 IU/ml, RVR	89	85[a]	8	8[a]	[8]
PEG-IFN-α2a (180 μg/week) + RBV (1,000–1,200 mg/day)	RVR	All: 79, <400,000 IU/ml: 81, 400,000–800,000 IU/ml: 81, >800,000 IU/ml: 67	–	–	–	[9]
PEG-IFN-α2a (180 μg/week) + RBV (1,000–1,200 mg/day)	RVR	88	91	9	2	[5]
PEG-IFN-α2a (180 μg/week) or PEG-IFN-α2b (1.5 μg/kg/week) + RBV (1,000–1,200 mg/day)	RVR	All: 77, <400,000 IU/ml: 84, ≥400,000 IU/ml: 73	All: 87, <400,000 IU/ml: 83, ≥400,000 IU/ml: 87	19	10	[12]
PEG-IFN-α2a (180 μg/week) + RBV (1,000–1,200 mg/day)	RVR[b]	All: 89, <400,000 IU/ml: 96, ≥400,000 IU/ml: 77[c]	All: 100, <400,000 IU/ml: 100, ≥400,000 IU/ml: 100	All: 11, <400,000 IU/ml: 4, ≥400,000 IU/ml: 24[c]	All: 0, <400,000 IU/ml: 0, ≥400,000 IU/ml: 0	[10]

[a]Highly selected historical cohort. [b]Taiwanese patients are reported to have lower viraemia, body weight and fibrosis scores than Western patients. [c]Versus 48 weeks of treatment, P=0.045. G1, genotype 1; PEG-IFN, pegylated interferon; RBV, ribavirin; RVR, rapid virological response.

Whether both baseline viral load and RVR are necessary to define the patient cohort appropriate for a 24-week treatment strategy is unclear. In the studies by Mangia *et al.* [12] and Ferenci *et al.* [9] and in the analysis by Jensen *et al.* [5], RVR alone was considered sufficient to stratify patients to duration of therapy, regardless of baseline viral load. However, approximately 9% of G1 patients with a baseline viral load >600,000 IU/ml attain RVR [5]. Should these patients also be considered for a 24-week treatment regimen? Assay technology is an important component of the answer to this question. If a highly sensitive reliable assay is available, patients with high baseline viraemia who attain RVR might be considered for a 24-week treatment regimen. However, if the available assay technology is less well developed, then a cautionary approach should be considered in adhering to a 48-week regimen because of the propensity for type 2 error in using an unreliable methodology to detect a rare event. Some data indicate a trend toward lower SVR rates among G1 patients with high baseline viraemia who attain RVR compared with those who have lower baseline viraemia (Figure 1 and Table 1) [9,12]. However, the difference in SVR rates between RVR patients with high versus low baseline viraemia was not statistically significant, potentially indicative of relatively small numbers of patients within these highly selected cohorts.

In conclusion, clinical trial data indicate 24 weeks of treatment is sufficient to achieve optimal SVR rates in G1 patients with low baseline viraemia who attain RVR; however, data from further studies are required to ensure this clinical practice is prospectively evaluated. Results from ongoing studies will undoubtedly contribute prospective clinical evidence to the growing body of data that support use of a 24-week treatment regimen in G1 patients with low baseline viraemia who attain RVR.

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