REVIEW

Optimizing the Dose and Duration of Therapy for Chronic Hepatitis C

Nipaporn Pichetshote, Erik Groessl, Helen Yee, and Samuel B. Ho

Departments of Medicine, Health Services Research and Development, VA San Diego Healthcare System, and University of California, San Diego, CA and Hepatitis C Resource Center, VA Medical Center, San Francisco, CA, USA

Recent studies indicate that antiviral treatment with pegylated interferon alfa and ribavirin for hepatitis C can be individualized based on viral and host characteristics and the pattern of virologic response during the initial months of antiviral treatment. Patients with a low initial viral load who demonstrate a rapid virologic response to antiviral therapy may be treated with a shorter duration of therapy and are less sensitive to reduced dosing of ribavirin. Patients with delayed virologic response will require a longer duration of therapy - up to 72 weeks for patients with genotype 1 - in order to optimize chances of a sustained virologic response. Patients who were nonresponders or relapsed after an acceptable course of antiviral therapy may be retreated using a more intensive regimen and/or a longer duration of therapy. Previous nonresponders to pegylated interferon alfa and ribavirin are less likely to respond to retreatment unless they demonstrate a virologic response within the first three months of retreatment, lack advanced fibrosis, and can tolerate a more intensive and/or lengthier treatment. Individualized treatment based on viral genotype, viral load, the presence of advanced fibrosis, and initial virologic response can improve therapy for some patients and save resources in others. (*Gut and Liver* 2009;3:1-13)

Key Words: Hepatitis C; Peginterferon alfa; Interferon; Ribavirin

INTRODUCTION

Current estimates indicate that as many as 175 million persons are infected with hepatitis C virus (HCV) world wide.¹ This includes 3.2 million persons, or 1.3% of the

population of the United States, with chronic HCV infection.² Estimates that include uncounted populations (nursing home residents, active military, incarcerated, homeless, and hospitalized persons) indicate that another 0.3-0.4% may be chronically infected in the U.S.³ Although the number of new cases of hepatitis C has steadily declined over the last 10 years in the U.S., the impact of disease in HCV-infected patients continues to grow because most of the health consequences of HCV emerge an average of 30 years after initial infection.² It is projected that as the duration of HCV infection increases in current patients, the proportion with cirrhosis will increase from 16% to 32% by 2020, and dramatic increases will also be seen in complications of cirrhosis: hepatic decompensation (projected increase 106%), hepatocellular carcinoma (increase 81%), and liver-related deaths (increase 180%).⁴ The increase in HCV-related morbidity and mortality from 2010 to 2019 will likely be associated with a projected increase in direct medical costs of over \$1 billion per year.⁵

In HCV-infected individuals not experiencing severe consequences, health-related quality of life is often impacted.⁶⁻⁹ Symptoms include fatigue, abdominal pain, nausea, and weight loss; and daily functioning is affected. In addition, anxiety and depression can emerge after being diagnosed with HCV, or from living with a serious, potentially lethal chronic disease.^{6,9}

Currently, the most powerful tool for clinicians seeking to diminish the impact of HCV on morbidity and mortality are combination antiviral drug regimens that can potentially eradicate the virus in more than half of treated patients.¹⁰ Approved antiviral drug regimens for HCV include several types of interferon alfa (standard interferon

Correspondence to: Samuel B. Ho

Gastroenterology 111-D, VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161, USA

Tel: +1-858-552-8585, Fax: +1-858-522-4327, E-mail: Samuel.Ho2@va.gov

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alfa-2b, consensus interferon (CIFN), and two types of pegylated interferon (PEG-IFN), alfa-2a and alfa-2b; which are given in combination with ribavirin (RBV). Recent data indicate that marked reductions in liver-related morbidity occur over time in successfully treated patients.¹¹⁻¹³ However, numerous factors result in variability in sustained virologic response (SVR) rates across patients, and create complexities when treatment decisions are being made. While SVR rates can be as high as 80% in genotype 2 or 3 patients, genotype 1 patients are much harder to treat successfully despite being treated for twice as long.¹⁴ African-Americans have much lower response rates than other racial/ethnic groups¹⁵ and insulin resistance and obesity results in lower SVR rates.¹⁶ Therefore, until a major breakthrough occurs with new pharmaceuticals that can cure higher proportions of genotype 1 patients and other hard to treat groups, most research is focusing on improving current therapies. Because the current and next generation combination therapies produce significant side effects, important areas of study include therapy duration, dose reduction, treatment adherence, and early response indicators. This article reviews recent data regarding antiviral treatment dosing and duration in individual patients to improve the efficiency and efficacy of this treatment.

CATEGORIES/DEFINITIONS OF VIROLOGIC RESPONSE TO ANTIVIRAL TREATMENT

The primary aim of antiviral therapy in patients with chronic HCV infection is a sustained virologic response (SVR). Sustained virologic response is defined as having undetectable virus for at least 6 months after completion of therapy.¹⁷ Predictors of response to PEG-IFN plus RBV therapy in randomized trials conducted in previously untreated, immunocompetent patients with compensated chronic hepatitis C include non-1 genotype, low baseline viral load, absence of cirrhosis or severe fibrosis, absence of steatosis, lighter body weight, age less than 40 years, and non-black ethnicity.¹⁴ The end of treatment response (ETR) is defined as an undetectable HCV RNA at completion of treatment.¹ Most studies measure HCV virus with both quantitative and qualitative polymerase chain reaction assays, and define viral negativity as below the lower limit of detection of a qualitative assay. The most common qualitative assay used in studies reviewed in this paper was the Cobas Amplicor HCV monitor test, v2.0 (Roche Diagnostics), with a lower limit of detection of 50 IU/mL.¹ Studies using tests with other limits of detection are indicated in Tables 1-4.

On-treatment virologic responses have been shown to

affect SVR and treatment duration, and the types of responses are listed in Fig. 1. Rapid virologic response (RVR) is defined as undetectable HCV RNA (<50 IU/mL) after the first 4 weeks of therapy.¹⁸ In a recent multivariate analysis, the independent predictors of RVR were baseline serum HCV-RNA levels <400,000 IU/mL and absence of advanced fibrosis.¹⁹ Early virologic response (EVR) is defined as a ≥ 2 -log₁₀ reduction in HCV RNA levels during the first 12 weeks of therapy (defined as partial EVR) or undetectable serum HCV RNA level at week 12 of treatment (defined as complete EVR).^{14,20} Treatment naïve patients who achieve an EVR with PEG-IFN plus RBV have a 65-76% likelihood of attaining SVR.¹ A complete EVR can be further categorized as viral negativity occurring between week 8 and 12 (cEVR₁₂) or viral negativity occurring between weeks 4 and 8 (cEVR₈). Among patients with HCV RNA first undetectable at week 8, age <45 yrs, BMI <27 kg/m², and HCV genotype 1a rather than 1b were predictors of response; in multivariate analysis response was predicted by young age.¹⁹ Slow virologic response is defined as patients who have a partial EVR and then become HCV-RNA negative between weeks 12 and 24.^{19,21} Nonresponders to treatment are patients with a decrease of less than 2 log₁₀ at week 12 of therapy, or patients with any detectable viremia after 24 weeks of treatment as compared to baseline.¹ If EVR is not achieved at week 12, patients are considered nonresponders, and discontinuation of treatment has been recommended because the likelihood of achieving SVR is very small if treatment is continued.¹ One alternative for patients not achieving an EVR is to increase the intensity of therapy (Table 5). Leevy *et al.* reported in a single center study that patients not achieving EVR were switched to daily consensus interferon 15 μ g/d $\times$ 12 weeks, decreasing to 15 μ g three times a week $\times$ 36 weeks with continued weight-based RBV, and found that 37% were able to achieve SVR.²² A relapse is defined as undetectable viremia during and/or at the end of treatment followed by detectable viremia after treatment is stopped. Patients with undetectable viremia during treatment who then develop detectable viremia while still on treatment are defined as "breakthrough" patients.

INITIAL VIROLOGIC RESPONSE TO ANTIVIRAL TREATMENT CAN PREDICT SUSTAINED RESPONSE

Recent studies have shown that achieving RVR is the strongest predictor of SVR.^{18,23} A retrospective analysis of genotype 1 patients receiving 48 weeks of PEG-IFN alfa-2a 180 μ g/wk+RBV 1-1.2 gm/d (n=453) by Ferenci *et*

al. demonstrated that 15% achieved RVR, 35% achieved EVR, 15% were slow virologic responders, and 20% were null responders. The longer it took for patients to become virus negative the lower the SVR rate - from 90% in RVR patients to 66% in EVR patients to 45% in slow virologic responders. Genotype 1 patients with RVR appear to at-

Fig. 1. Patterns of virologic response to therapy. Lower limit of viral detection=50 UI/mL. Adapted from references.^{19,27,33}

tain SVR with the same frequency if they were treated with PEG-IFN and RBV (91% SVR), PEG-IFN alone (93% SVR), or standard interferon and RBV (91% SVR).¹⁸ Predictors of achieving an RVR in genotype 1 patients include low baseline viremia and younger age.^{19,23}

Preliminary studies indicate that the degree of viral suppression at week 4 also predicts SVR. In a retrospective analysis of 160 patients at a single institution, a $<1 \log_{10}$, $1- <2 \log_{10}$, $2- <3 \log_{10}$ reduction at week 4, and $\geq 3 \log_{10}$ reduction but still detectable viremia at week 4 were associated with SVR rates of 3, 9, 14, and 38%, respectively.²⁴ Failure to achieve a $1 \log_{10}$ reduction in viremia at week 4 was associated with a 93% negative predictive value for SVR and was independent of genotype or viral load. A retrospective analysis of 2,054 patients in a multicenter trial treated with either PEG-IFN alfa-2b 1.5 ug/kg/wk and RBV 800-1,400 mg/d or PEG-IFN alfa-2a 180 ug/wk and RBV 1,000-1,200 mg/d categorized patients according to the week 4 virologic response. They found that patients with a $<1 \log_{10}$, $1- <2$

Table 1. Studies of Shorter Duration of Therapy for Genotype 1 Patients

Reference	Type of study	Treatment regimens	Overall SVR	SVR in patients with RVR	SVR in patients without RVR
Jensen <i>et al.</i> , 2006 ²⁸	Retrospective n=740	PEG-IFN α -2a 180 ug/wk + RBV 800 mg/d $\times$ 24 wks	29%	89%	16%
		PEG-IFN α -2a 180 ug/wk + RBV 1000-1200 mg/d $\times$ 24 wks	42%	88%	23%
		PEG-IFN α -2a 180 ug/wk + RBV 800 mg/d $\times$ 48 wks	41%	73%	35%
		PEG-IFN α -2a 180 ug/wk + RBV 1000-1200 mg/d $\times$ 48 wks	52%	91%	44%
Zeuzem <i>et al.</i> , 2006 ³⁰	Prospective n=235 low baseline viremia patients only ($<600,000$ IU/ml)	PEG-IFN α -2b 1.5 ug/kg/wk + RBV 800-1400 mg/d $\times$ 24 wks	50%	89%	20.0%*
Ferenci <i>et al.</i> , 2008 ²³	Prospective n=516 Only patients with RVR (n=150) received 24 wks treatment [†]	PEG-IFN α -2a 180 ug/wk + RBV 1000-1200 mg/d $\times$ 24 wks	NA	76.7% (gen1 74.2% gen4 86.7%)	NA
Mangia <i>et al.</i> , 2008 ¹⁹	Prospective n=696 Patients with RVR received 48 vs. 72 wks treatment	PEG-IFN (α -2a 180 ug/wk or α -2b 1.5 ug/kg/wk) + RBV 1000-1200 mg/d $\times$ 24 wks	NA	77.2%	NA
		PEG-IFN (α -2a 180 ug/wk or α -2b 1.5 ug/kg/wk) + RBV 1000-1200 mg/d $\times$ 48 wks		87.0%	

*Patients without RVR included those who were HCV-RNA negative at week 12 (SVR 25%) and HCV-RNA negative at week 24 (SVR 17%).

[†]Ferenci *et al.* studied at genotypes 1 and 4. Intention-to-treat results are shown.

NA, not applicable; SVR, sustained virologic response; RVR, rapid viral response.

$\log_{10}$, 2- $<3 \log_{10}$, 3- $<4 \log_{10}$, $>4 \log_{10}$ reduction, or an undetectable viral level at week 4 had corresponding SVR rates of 5%, 21-29%, 46-54%, 62%, 65-79%, and 80-92%, respectively.²⁵ These data indicate that null responders can be identified as early as 4 weeks into therapy that would be unlikely to respond to the standard dose and duration of therapy.

In genotypes 2 and 3, the number of patients achieving an RVR is much higher than genotype 1 patients. Genotype 2/3 patients treated with PEG-IFN and RBV at 800 mg/d achieved a RVR in 62-68% of patients (Table 3). In a large prospective trial of 1,469 patients, Shiffman *et al.* demonstrated that a RVR occurred in 65-68% of 1,455 patients treated with PEG-IFN alfa-2a 180 μ g/wk and RBV 800 mg/d. An additional 24% of patients achieved an EVR and 3% were considered nonresponders.²⁶ Studies that used higher weight-based dosing of RBV reported slightly higher RVR rates of 71-93% (Table 3). Achieving RVR greatly influences whether genotype 2,3 patients achieve SVR. Patients with RVR receiving a standard 24 week course of therapy achieve SVR in 80-93%, whereas non-RVR patients treated for 24 weeks achieve SVR in 55-62% (Table 3).

Hence, the extent of viral suppression after 4 and 12 weeks of treatment clearly influences the likelihood of achieving an SVR. Recent studies indicate that early and sustained suppression of HCV RNA is most important in achieving an SVR. Therefore, maintenance of exposure to full dose therapy early during the course of treatment is likely to be important in order to increase success with the usual planned duration of therapy. Early confirmation of viral reduction following initiation of antiviral therapy provides a goal to motivate adherence during the first months of therapy and a point at which to reassess the need for continued treatment.²⁷

VARIABLE DURATION OF THERAPY FOR GENOTYPE 1 PATIENTS BASED ON VIROLOGIC RESPONSE

The current standard of care for treatment of genotype 1 patients is 48 weeks of combination therapy with PEG-IFN alfa plus 1,000-1,200 mg/day of RBV. Recent studies have indicated that a shorter duration of therapy for patients with RVR may be equivalent to standard duration, and also for patients who are slow virologic responders a longer duration of therapy is important for maximizing SVR rates.

Studies comparing 24 weeks vs. 48 weeks of therapy for genotype 1 patients are indicated in Table 1. Jensen *et al.*²⁸ performed a retrospective analysis of a large trial of

patients initially reported by Hadziyannis *et al.*²⁹ and examined the factors associated with RVR and SVR in patients infected with HCV genotype 1 who were randomized to 24 weeks of treatment with PEG-IFN alfa-2a 180 μ g/wk and RBV 800-1,200 mg/d. SVR rates were higher in patients that achieved RVR than those who did not (89% vs. 19%). Multiple logistic regression analysis indicated that patients with a baseline HCV RNA of less than 200,000 IU/mL or 200,000-600,000 IU/mL were more likely to achieve a RVR than those with HCV RNA greater than 600,000 IU/mL. Interestingly, in this study HCV subtype 1b was independently associated with RVR. Both RVR and baseline HCV RNA $<200,000$ IU/mL were significant and independent predictors of SVR in patients treated for 24 weeks.²⁸ Zeuzem *et al.*³⁰ treated 235 patients with genotype 1 infection and low pretreatment viral loads ($\leq 600,000$ IU/mL) for 24 weeks with PEG-IFN alfa-2b 1.5 μ g/kg/wk and RBV 800-1,400 mg/d. The overall SVR rate was 50%; and the subset of patients with RVR achieved a 89% SVR rate, which was comparable to the 85% SVR rate in historical low viral load genotype 1 controls treated for 48 weeks reported by Manns *et al.*³¹ Patients without a RVR who became virus negative by week 12 or 24 demonstrated a 20% SVR rate. Ferenci *et al.* conducted a prospective multicenter trial treating patients with genotype 1 and 4 with PEG-IFN alfa-2a 180 μ g/wk and RBV 1,000-1,200 mg/d with RVR for 24 weeks.²³ Overall 150/516 patients (29%) had a RVR and 143 patients completed 24 weeks of treatment, with an intention to treat SVR rate of 76.7%. Among the genotype 1 patients with RVR, those with low baseline viremia ($<800,000$ IU/mL) had a higher SVR rate (81.0%) compared with patients with high baseline viremia ($>800,000$ IU/mL), (SVR=66.7%). These studies indicate that 24 weeks of therapy may be equivalent to 48 weeks in patients with genotype 1 and low baseline viremia who achieve a RVR.

Several recent studies have suggested that an extended duration of therapy is beneficial for patients with genotype 1 who do not achieve RVR (Table 2). These studies cannot be directly comparable due to differences in the dose of RBV used, study design, different definitions of EVR, and in patient characteristics. Berg *et al.*³² randomized 455 genotype 1 patients to treatment with PEG-IFN alfa-2a 180 μ g/wk and RBV 800 mg/d for 48 weeks versus 72 weeks. Overall, there was no difference in SVR rates between the two groups. However, the subgroup of patients who did not achieve RVR and had any positive HCV-RNA at week 12 and achieved viral negativity by week 24 exhibited a significantly higher SVR rate when treated for 72 weeks instead of 48 weeks (29% vs. 17%,

$p=0.04$). A particular benefit was seen in patients with low level viremia ($<6,000$ IU/mL) at week 12. Patients with RVR or cEVR (HCV-RNA level <50 IU/mL) at weeks 4 or 12 achieved SVR rates ranging from 76% to 84% independent of treatment duration; and therefore did not benefit from the extended treatment.³² This study also showed an increase in discontinuation rates in patients treated for the extended duration.

Pearlman *et al.*³³ specifically evaluated patients who were “slow responders”, i.e. non RVR patients with a partial EVR at 12 weeks with >2 log drop in HCV RNA, and then became viral negative between 12 and 24 weeks (defined using a Taqman PCR assay with a detection limit of 10 IU/mL). They were randomly assigned to 48 weeks or 72 weeks of therapy with PEG-IFN alfa-2b 1.5 μ g/kg/wk and a higher dose of RBV (1,000-1,400 mg/d), and growth factors were not allowed. The patients that received 72 weeks of therapy had a significantly higher SVR rate, 38% vs. 18% ($p=0.026$), primarily due to a reduction in the relapse rate after discontinuation of therapy. There were no differences in early terminations between the two groups. Both groups noted excellent compliance; none of the discontinuations in the extended arm occurred between 48 and 72 weeks.

Sanchez-Tapias *et al.* used a different study design in the TeraViC-4 study and randomized 326 patients who had detectable viremia at week 4 of treatment (lack of RVR) to receive either 48 or 72 weeks of treatment with PEG-IFN alfa-2a 180 μ g/wk and RBV 800 mg/d, and all patients were continued regardless of subsequent viral levels on treatment. The results showed similar end of treatment response in the two arms, but the SVR rate was significantly higher in the 72 week treatment group than in the 48 week group (44% vs. 28%, $p=0.003$). Again, this was primarily due to a reduced relapse rate of 26% in the 72 week treatment group vs. 48% in the 48 week treatment group ($p=0.003$). However, those who were treated for the extended duration had a higher discontinuation rate (36% vs. 18%, $p=0.0004$). Subgroup analysis indicated that genotype 1 patients with a baseline viremia of less than 800,000 IU/mL had a significantly higher SVR rate in patients treated for 72 weeks (51%) compared with patients treated for 48 weeks (27%, $p=0.007$). This difference was not present in genotype 1 patients with baseline viremia $>800,000$ IU/mL. In addition, patients in this study who did not have at least a ≥ 2 log₁₀ drop in HCV RNA by 24 weeks rarely achieved a SVR regardless of whether they were treated for 48 or 72 weeks (6% vs. 5%, respectively). As indicated in Table 2, the Sanchez-Tapias and Berg studies used lower doses of RBV, 800 mg/day, compared with the other studies using

weight-based RBV dosing.

Mangia *et al.* randomized genotype 1 patients to treatment with PEG-IFN alfa-2a 180 μ g/wk and RBV 1,000-1,200 mg/d in a standard 48 week duration group ($n=237$) or a variable duration group ($n=459$). The variable group was treated for 24, 48 or 72 weeks if they became HCV RNA negative at weeks 4, 8, or 12, respectively. This study differed from the rest in that they made a distinction between two groups of cEVR patients - those that became virus negative at week 8 (cEVR₈) and those that became virus negative at week 12 (cEVR₁₂). They found that genotype 1 patients with RVR did slightly better if treated for 48 weeks (87% SVR) compared with those treated for 24 weeks (77% SVR), although this difference was not present if patients with only low viral load were considered. Patients with cEVR₈ in both arms were treated with 48 weeks of therapy and had SVR rates of 70-72%. In contrast, patients with cEVR₁₂ had much better SVR rates if treated for 72 weeks (63%) compared with 48 weeks (38%) (19). These data raise the possibility that a distinction between cEVR₈ and cEVR₁₂ may be important for determining duration of therapy, and suggest that patients without a RVR who become virus negative by week 8 have better outcomes than those that become virus negative by week 12 in regards to the standard 48 week duration of therapy. In this study patients with a pEVR (≥ 2 log₁₀ drop at week 12 but >50 IU/mL) demonstrated 0/21 and 4/53 (7.5%) SVR rate when treated for 48 or 72 weeks, respectively. Other than small numbers of patients in these arms, it is unclear why these SVR rates were low compared with other patients with pEVR treated for 48-72 weeks listed in Table 2.

Ferenci *et al.*^{23,34} treated 517 patients with HCV genotypes 1 and 4 with PEG-IFN alfa-2a 180 μ g/wk + RBV 1,000-1,200 mg/d, and those patients who did not have a RVR but had a pEVR or cEVR at week 12 were randomized to treatment for 48 weeks ($n=139$) or 72 weeks ($n=150$). Overall SVR rates on an intention to treat basis were 51% in the 48 week group compared with 59% in the 72 week group; however, they noted the study was not powered to demonstrate a significant difference in this outcome. On the other hand, patients in the 72 week group had a significantly lower relapse rate (18.5%) compared with the 48 week group (33.6%, $p<0.025$).

In general, the studies cited above agree that HCV genotype 1 patients who become virus negative at week 4 likely do not benefit from therapy extended beyond 48 weeks, and a subgroup with low initial viremia may be effectively treated with 24 weeks. On the other hand, patients with detectable HCV viremia at week 12 and become virus negative by week 24 may benefit from a total

of 72 weeks of therapy compared with 48 weeks. As suggested by the study by Mangia *et al.*, patients without a RVR who become virus negative by week 8 may not require an extended duration of therapy and perhaps should not be included in the patients with an EVR at week 12 who may be considered for extended duration of treatment for 72 weeks.

DURATION OF THERAPY FOR GENOTYPE 2 AND 3

In patients infected with HCV genotypes 2 and 3, the standard treatment duration is 24 weeks.²⁰ Studies that have examined reduced durations of therapy for these patients are listed in Table 3. These studies differ according to the type of PEG-IFN used, the dose of RBV used, and the variations in duration of therapy. The largest randomized trial includes 1,469 patients randomized to PEG-IFN alfa-2a 180 μ g/wk and RBV 800 mg/d for either 16 or 24 weeks. Overall, patients that received 24 weeks of therapy had a significantly greater SVR (70%) compared with those receiving 16 weeks (62%, $p < 0.001$). The advantage of 24 weeks of therapy was present for patients with RVR--SVR 85% vs. 79% ($p = 0.02$) for 24 and 16 weeks of therapy, respectively--and for patients without RVR--(SVR 45% vs. 26%) for 24 and 16 weeks of therapy, respectively. However, in the subgroup of patients with low initial viral load (HCV RNA $< 400,000$ IU/mL) and RVR, there was no difference in SVR in those receiving 24 or 16 weeks of therapy (SVR 81% and 82%, respectively). Lower pretreatment HCV RNA level, lower weight, and absence of bridging fibrosis or cirrhosis were predictive of a SVR. Other studies with smaller numbers of patient also found a shorter duration of therapy in patients with RVR and low initial viral loads resulted in SVR rates similar to longer durations of therapy (Table 3). Taken together, these studies suggest that genotype 2 or 3 patients with low initial viral loads may be treated with a shorter duration of therapy, which may be enhanced by using weight-based dosing of RBV.

Data indicate SVR rates are lower in patients with genotype 3 infection than those with genotype 2 infection (SVR 66-79% vs. 80-93%, respectively) (1). In genotype 3 patients with high level of viremia ($> 600,000$ IU/mL) and steatosis or advanced fibrosis on liver biopsy, a high relapse rate has been demonstrated following 24 weeks of treatment with PEG-IFN and RBV (800 mg).¹ Therefore, perhaps patients with genotypes 2 and 3 who have poor prognostic factors and who do not attain RVR should be treated with longer duration of therapy than the standard 24 weeks. Currently there are no published randomized

controlled trials that specifically test this. A retrospective analysis by Willems *et al.* examined genotype 2 and 3 patients who did not achieve RVR and found that patients who received 48 weeks of therapy with a higher weight-based RBV dose (1,000-1,200 mg/d) had the lowest relapse rates compared with patients treated for 24 weeks and/or lower RBV doses (Table 4).

EFFECT OF RBV DOSE REDUCTIONS ON SVR

RBV appears to enhance SVR by both maintaining a virologic response to interferon and in reducing a relapse. The importance of RBV for preventing relapse was illustrated by a recent study by Bronowicki *et al.*³⁵ They studied 516 patients with HCV genotype 1 who were treated with PEG-IFN alfa-2a 180 μ g/week and RBV 800 mg/d. At week 24, 69% were HCV-RNA negative and were randomized to either continue PEG-IFN and RBV or to discontinue RBV and remain on PEG-IFN monotherapy through treatment week 48. At the end of follow-up, SVR was significantly greater in patients who remained on combination therapy (68% vs. 53%, $p = 0.004$). The decline in SVR of patients who discontinued RBV was the result of breakthrough or relapse. It was noted that half of the patients who discontinued RBV still achieved SVR, and these tended to be patients that had achieved a RVR and who had a low baseline viremia prior to treatment.³⁵

Early studies of overall attainment of the total projected IFN, PEG-IFN, and RBV dosage throughout an entire 48 week treatment period have indicated that patients that receive $\geq 80\%$ of the intended RBV dose, $\geq 80\%$ of the intended PEG-IFN dose, $\geq 80\%$ of the projected duration of therapy will have the best chance of SVR. Dose reduction in the first 12 weeks of therapy influences SVR more than dose reduction at greater than 12 weeks into therapy.³⁶ In terms of RBV dosing, practitioners should calculate what 80% of the projected total RBV dose is for each patient, and then calculate whether dose reductions will cause the total achieved dose to fall under 80%. For example, the total projected dose for RBV at 1,200 mg/d for 48 weeks is 268,800 mg. In general, it is possible to achieve $< 80\%$ of the total projected dose only by non-compliance resulting in missing doses, early discontinuation of dosing, or if the original dose is reduced early in the course of therapy and then never increased again once the adverse event or symptoms have been ameliorated.

Reddy *et al.* performed a retrospective review of 589 HCV genotype 1 patients enrolled in two phase III trials of PEG-IFN alfa-2a and RBV and determined the impact of RBV dose reductions.³⁷ Patients that achieved RVR had very high SVR rates if they achieved $\geq 80\%$ of the pro-

jected RBV dosing, however, in these patients those that achieved 60-80% and 60% or less of RBV dosing also had respectable SVR rates of 71 and 67%, respectively. In contrast, patients that did not have a RVR were markedly affected by RBV dose reductions below 60% of projected after week 4 of treatment. Patients without RVR that achieved $\geq 80\%$ and 60-80% of total RBV dosing had SVR rates of 58 and 55%, respectively, compared with a SVR rate of 29% in patients achieving $<60\%$ of total planned RBV dose.³⁷ Again, in this study SVR reduction resulting from a reduced RBV dose was primarily associated with prolonged periods of dose reduction, temporary interruptions of dosing, or premature cessation of RBV.

RBV dosing is also of lesser importance for preventing relapse in some patients with genotype 2 or 3 that achieve a RVR. Andriulli *et al.*³⁸ randomized genotype 2 and 3 patients who achieved a RVR to PEG-IFN alfa-2a (180 $\mu\text{g}/\text{wk}$) and RBV (1,000-12,000 mg/d) to continued treatment with PEG-IFN alfa-2a monotherapy vs. continued treatment with both drugs for 12 weeks. Overall SVR rates were 54% in the monotherapy group and 82% in the combined therapy group ($p < 0.001$). This difference was due to patients with high viral loads, since patients with low ($< 300,000$ IU/mL) or intermediate (300,000-700,000 IU/mL) baseline viral loads had similar SVR rates in the monotherapy group (86 and 70%, respectively) vs. the combined therapy group (81 and 71%, respectively).³⁸

Shiffman *et al.* examined the impact of reducing PEG-IFN alfa-2a and RBV dose during retreatment of patients with hepatitis C with advanced fibrosis enrolled in the HALT-C trial.³⁹ They found that reducing the dose of RBV from full dose to $\leq 60\%$ did not affect either week 20 virologic response or SVR as long as RBV dosing was not interrupted for more than 7 consecutive days. In contrast, reducing the total cumulative dose of PEG-IFN received during the first 20 weeks of treatment from full dose to $\leq 60\%$ reduced the week 20 virologic response from 35% to 12% and the SVR from 17% to 5%. These data indicated that compliance with PEG-IFN has more effect than RBV compliance in these difficult to treat patients as long as RBV is not discontinued prematurely.

RE-TREATMENT OF PRIOR ANTIVIRAL THERAPY RELAPSE AND NONRESPONDERS

Patients who relapse or are considered nonresponders to antiviral therapy can be considered for re-treatment (Table 5). Approximately 20% of patients infected with HCV genotype 1 treatment-naïve patients are nonresponders to standard PEG-IFN and RBV treatment (< 2

$\log_{10}$ decrease in baseline HCV RNA by week 12 or any HCV RNA positive at week 24). The decision to re-treat should include the following factors: prior drug regimen, previous response achieved, stage of fibrosis, previous adherence to treatment, tolerability and side effects of prior therapy, infecting genotype, pretreatment viral load, and patient motivation.¹ In general, re-treatment outcomes are better in prior relapsers compared to nonresponders, genotype non-1 patients, and noncirrhotics.²

Relapsers to standard IFN should be strongly considered for re-treatment with PEG-IFN and RBV. If re-treatment is pursued using PEG-IFN at standard doses and RBV 800-1,200 mg/day for 48 weeks, the chance of achieving an SVR may be as high as 40-50% in prior interferon relapsers whereas SVR occurs in up to 30-40% of prior IFN nonresponders and in only 5-12% of prior IFN and RBV nonresponders.⁴⁰⁻⁴⁶ In prior IFN and RBV nonresponders, up to 18% achieved SVR with re-treatment using RBV 800-1,400 mg/day combined with PEG-IFN alfa-2b at standard doses for 48 weeks.⁴⁶ SVR with re-treatment was lower in patients with genotype 1 infection compared to genotype 2 or 3 infection (SVR 13% and 49%, respectively) and lower in cirrhotics compared to noncirrhotics (SVR 7% versus 16-18% with genotype 1 infection, respectively; SVR 18% versus 38-56% with genotype 2 or 3 infection, respectively).⁴⁶

Over 50% of treatment-naïve patients are unable to achieve SVR with PEG-IFN and RBV therapy. These patients represent the most difficult population to re-treat given that there are currently no FDA-approved therapies for PEG-IFN and RBV treatment failures. PEG-IFN and RBV nonresponders rarely benefit from re-treatment with the same agents unless treatment doses or adherence can be improved. If re-treatment is undertaken in patients previously intolerant of RBV or PEG-IFN due to cytopenias, adjunctive therapy with erythropoiesis stimulating agents or granulocyte colony stimulating factors may be considered.

Several management approaches in patients failing prior PEG-IFN and RBV treatment have been undertaken including re-treatment with PEG-IFN using induction or high doses combined with RBV up to 1,400 mg/day , extending the treatment duration to 72 weeks or switching to more intensive therapy with consensus interferon (CIFN) and RBV (Table 5). Note that many of these studies are preliminary reports only and should be interpreted with caution. In a study with prior PEG-IFN and RBV failures involving re-treatment using PEG-IFN alfa-2b at standard doses and RBV 800-1,400 mg/day , overall SVR occurred in 6-7% of prior PEG-IFN and RBV nonresponders and in 32-34% of PEG-IFN+RBV relap-

Table 2. Studies of Extended Treatment Duration for HCV Genotype 1

Study	PEG-IFN	RBV dose	Growth factor use allowed?	Randomization	Overall SVR		SVR patients without RVR and with EVR		SVR patients without EVR	
			Lower limit of HCV PCR		48 wks	72 wks	48 wks	72 wks	48 wks	72 wks
Berg <i>et al.</i> ³² (n=455)	Alfa-2a 180 µg/week	800 mg/d	No 50 IU/mL	Patients randomized at start of antiviral treatment	53%	54%	Any HCV – RNA + wk 12 = 17%* RVR + cEVR = 80% [†]	Any HCV – RNA + wk 12 = 29%* (p=.04) RVR + cEVR = 76% [†]	4%	11%
Sanchez-Tapias <i>et al.</i> ⁵⁰ (n=326)	Alfa-2a 1.5 µg/kg/wk	800-1200 mg/d	No 50 IU/mL	Patients randomized at week 4 if detectable viremia	28% (gen.1)	44% (gen.1) (p=.003)	pEVR + cEVR = 43%	pEVR + cEVR = 56% [†]	8%	15%
Pearlman <i>et al.</i> ³³ (n=101)	Alfa-2b 1.5 µg/kg/wk	800-1400 mg/d	No 10 IU/mL	Slow responders (pEVR) randomized to 48 vs. 72 weeks [‡]	NA	NA	18%	38% (p=.03)	NA	NA
Mangia <i>et al.</i> ¹⁹ (n=696)	Alfa-2a/ Alfa-2b 180 µg/wk	1000-1200 mg/d	Yes 50 IU/mL	Patients randomized to 48 weeks vs. variable treatment for 24, 48, or 72 wks if PCR negative at wks 4, 8, or 12, respectively	45.1%	48.8% [§]	cEVR = 38.1% [¶] pEVR = 0%	cEVR = 63.5% [¶] pEVR = 7.5%	NA	NA
Ferenci <i>et al.</i> ³⁴ (n=551)	Alfa-2a 180 µg/wk	1000-1200 mg/d	Yes 50 IU/mL	Patients without RVR randomized at week 12 if pEVR or cEVR	51.1% (relapse 33.6%)	58.6% (relapse 18.5%, p<0.025)	pEVR 30.6% [¶] cEVR 71.8%	pEVR 37% [¶] cEVR 82.9%	NA	NA

*SVR rate for patients that were HCV RNA positive (>50 IU/ml) at week 12 (includes nonresponder (<2log₁₀ drop in viremia from baseline) and pEVR patients but does not include cEVR patients). Patients who were HCV RNA negative at weeks 4 (RVR) and/or 12 (cEVR) had SVR rates of 80% in the 48 week and 76% in the 72 week treatment groups. Patients who were HCV RNA positive at week 24 were discontinued from the study.

[†]Patients with EVR are considered patients without an RVR at week 4 but with at least a ≥2log drop at week 12 (did not distinguish pEVR and cEVR). These results include all genotypes. Patients with pEVR and cEVR were grouped together and had 43% and 56% SVR rates in the 48 and 72 week arms, respectively.

[‡]Slow responders include patients with a ≥2 log₁₀ decrease in HCV RNA but still HCV RNA detectable (>10 IU/mL) by week 12 (pEVR) and undetectable HCV RNA by week 24.

[§]Variable Treatment Group: Patients HCV negative at week 4 were treated for 24 weeks; patients HCV negative at week 8 were treated for 48 weeks, and patients who became HCV negative at week 12 were treated for 72 weeks. Patients who had a ≥2 log₁₀ drop in HCV-RNA at week 12 (pEVR) were treated for 72 weeks if they were HCV RNA negative at week 24.

^{||}Not applicable due to the fact that patients with <2log decline at week 12 had to stop treatment per protocol and were considered nonresponders.

[¶]Note these results do not include any patients with RVR.

PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response; RVR, rapid viral response; EVR, early virologic response; NA, not applicable.

sers. SVR with re-treatment occurred in 4-6% of patients with genotype 1 infection compared to 36% with genotype 2 or 3 infection.⁴⁶

In another study involving prior PEG-IFN and RBV failures, retreatment with PEG-IFN and RBV for 72 weeks compared to 48 weeks appeared beneficial (SVR 16% and

8%, respectively; $p=0.0006$).⁴⁷ There was no statistical difference in SVR with PEG-IFN alfa-2a 360 $\mu\text{g}/\text{week}$ induction versus 180 $\mu\text{g}/\text{week}$ in combination with RBV (SVR 13% and 10%, respectively; $p=0.92$). Achieving EVR was a positive predictor of response; in patients with undetectable HCV RNA (<50 IU/mL) by week 12

Table 3. Shorter Duration Treatment for Genotypes 2, 3

Reference	PEG-IFN dose	RBV dose	4-wks RVR (%)	Overall 12-16 wks SVR (%)	Overall 24 wks SVR (%)	RVR 12-16 wks SVR (%)	RVR24 wks SVR (%)	No RVR 12-16 wks SVR (%)	No RVR 24 wks SVR (%)	Relapse
Dalgard <i>et al.</i> , 2004 (n=122) ⁵¹ 14 vs. 24 wks	Alfa-2b 1.5 $\mu\text{g}/\text{kg}$	800- 1400 mg/day	78	NA*	56	90 (G2=91) (G3=89)	NA*	NA*	56 (G2=50) (G3=56)	10% (14-wk) 26% (24-wk)
Mangia <i>et al.</i> , 2005 (n=283) ⁵² 12 vs. 24 wks	Alfa-2b 1.0 $\mu\text{g}/\text{kg}$	1000 or 1200 mg/day	63	NA [†]	69	85	91	NA [†]	60 [†]	10% (12-wk) 3.6-6% (24-wk)
Von Wagner <i>et al.</i> , 2005 (n=153) ^{§53} 16 vs. 24 wks	Alfa-2a 180 $\mu\text{g}/\text{wk}$	800- 1200 mg/day	93	NA	74	82	80	NA	36	NR
Shiffman <i>et al.</i> , 2007 (n=1469) ²⁶ 16 vs. 24 wks	Alfa-2a 180 $\mu\text{g}/\text{wk}$	800 mg/day	65	62	70	79	85	NR	NR	31% (16-wk) 18% (24-wk)
Dalgard <i>et al.</i> , 2008, North-C (n=428) ⁵⁴ 14 vs. 24 wks	Alfa-2b 1.5 $\mu\text{g}/\text{kg}$	800- 1400 mg/day	70.6	NA [¶]	74	81.1	90.7	NA [¶]	54.8	10.8% (16 wk) 5.3% (24 wk, with RVR only [#])
Lagging <i>et al.</i> , 2008 (n=382) ⁵⁵ 12 vs. 24 wks	Alfa-2a 180 $\mu\text{g}/\text{wk}$	800 mg/day	60	59 (G2=56) (G3=58)	78 ($p<.001$) (G2=82) (G3=78)	71	91 ($p=0.0001$)	41 ($p=.014$)	62	RVR (26% 12 wks; 4% 24 wks) nonRVR (46% 12 wks; 25% 24 wks)

*This percentage is a combined percentage of all patients treated for 24 weeks, regardless of which treatment group they were assigned to. The paper further distinguishes the SVR rate of the two groups. Of the standard duration group (patients receiving 24 weeks of therapy regardless of their virologic response), the SVR rate of patients that did not have RVR was 48%. Of the variable duration group (patients who did not have RVR were treated for 24 weeks instead of 12 weeks if they had RVR), the SVR rate was 64%.

[†] Only patients who did not have EVR (in the paper, this is defined as undetectable HCV RNA at week 4-RVR-and week 8) were treated for 24 weeks.

[¶] All patients treated for shorter duration of 12 weeks had RVR.

[§] RVR in von Wagner paper is defined as HCV RNA below 600 IU/mL at week 4 of therapy.

^{||} Only patients who had RVR were treated for the shorter duration of 16 weeks.

[¶] Only patients with RVR were treated for shorter duration of 14 weeks.

[#] Study did not report the relapse rate of patients without RVR who were treated for 24 weeks.

SVR, sustained virologic response; RVR, rapid viral response; NA, not applicable; NR, not reported.

Table 4. Comparing 24 vs. 48 Weeks of Therapy for Genotype 2,3: SVR and Relapse Rates in Patients with HCV Genotype 2,3 Not Achieving RVR⁵⁶

ITT analysis	24-wks PEG-IFN α -2a+ RBV 800 mg/d	24-wks PEG-IFN α -2a+ RBV 1,000/1,200 mg/d	48-wks PEG-IFN α -2a+ RBV 800 mg/d	48-wks PEG-IFN α -2a+ RBV 1,000/1,200 mg/d
SVR (%)	14/21 (67)	22/34 (65)	20/30 (67)	28/37 (76)
Relapse rates (%)	5/19 (26)	7/29 (24)	3/23 (13)	1/27 (4)

Patients without follow-up data were considered not to have achieved an SVR.

SVR, sustained virologic response; RVR, rapid viral response; PEG-IFN, pegylated interferon; RBV, ribavirin.

of retreatment, SVR was achieved in 35-57% compared to SVR in 4% of patients in the absence of EVR.⁴⁷

Alternatively, immediately switching to a different type of interferon such as C1FN in combination with RBV has been explored in PEG-IFN/RBV nonresponders (defined as $<2 \log_{10}$ decline in HCV RNA by week 12 of PEG-IFN/RBV treatment).²² Single center, observational studies with C1FN induction ranging from 15-27 mcg daily followed by 9 mcg daily to 15 mcg thrice weekly in combination with RBV for 48-72 weeks achieved an SVR between 23-37%.^{22,48} Preliminary results from a large prospective, randomized, open-label trial (DIRECT, Daily-Dose Consensus Interferon and RBV: Efficacy of Combined Therapy) involving C1FN at 9 or 15 mcg daily plus RBV 1,000-1,200 mg daily for 48 weeks in prior PEG-IFN/RBV nonresponders achieved SVR12 (undetectable HCV RNA levels at 12 weeks post-treatment) in 5-10% of patients. Noncirrhotic patients who had $>2 \log_{10}$ reduction in baseline HCV RNA with prior PEG-IFN/RBV treatment had the highest response rate, with 29% achieving SVR at week 12.⁴⁹

In patients undergoing re-treatment who demonstrate viral response, the duration of therapy should be at least 48 weeks regardless of genotype; in genotype 1-infected patients, extending the treatment duration to 72 weeks may be beneficial.⁴⁷ Achieving EVR was a positive predictor of response, and SVR was achieved in 35-57% with continued treatment. However, the absence of EVR was a predictor of non-response in patients re-treated with either PEG-IFN α -2a or α -2b or C1FN and RBV, and early treatment discontinuation should be considered since the likelihood of achieving SVR is 0-4% with continued treatment.^{46,47,49}

CONCLUSIONS AND RECOMMENDATIONS FOR OPTIMIZING TREATMENT OUTCOMES

Recent data suggest that early response indicators may be strong predictors of SVR and that therapies can be successfully tailored to individuals based on these treatment response indicators and baseline patient and viro-

logic variables. The viral response to therapy should be checked monthly during the initial 6 months of therapy. A RVR at week 4 may allow for a shorter duration of therapy in about 10% to 20% of genotype 1 patients. However, it is still unclear whether RVR portends a similarly high chance of SVR in patients with low viral loads who are typically difficult to treat, such as African Americans, those with fibrosis, hepatic steatosis, insulin resistance, alcohol abuse.⁴ Only 30-35% of genotype 1 patients who ultimately achieve SVR will be HCV RNA negative by the 4th week of treatment. Thus, failure to achieve RVR does not imply that the patient is a non-responder and certainly does not justify discontinuation of therapy.⁴ Conversely, patients with delayed virologic response will require a longer duration of therapy - up to 72 weeks for patients with genotype 1 - in order to optimize chances of a SVR. Patients who fail initial antiviral treatment may be considered for re-treatment. In general, re-treatment outcomes are better in prior relapsers compared to nonresponders, genotype non-1 patients, and noncirrhotics.² PEG-IFN and RBV nonresponders rarely benefit from re-treatment with the same regimen unless treatment doses or adherence can be improved. Overall re-treatment outcomes of prior PEG-IFN and RBV nonresponders are low, with SVR occurring in 6-18%. However, preliminary data indicate that subgroups of patients with low viral load, absence of severe fibrosis and cirrhosis, and an initial virologic response to treatment are much more likely to respond. If re-treatment is undertaken, weekly PEG-IFN or daily C1FN can be combined with RBV up to 1,400 mg/day for genotype 1 infection and RBV 1,000-1,200 mg/day for genotype 2 or 3 infections. There does not appear to be an advantage in using higher doses of PEG-IFN in this setting. If EVR is achieved, treatment may be extended to 72 weeks for genotype 1 infection and 48 weeks for genotype 2 or 3 infection. If EVR is not achieved, the chance for SVR is low and treatment discontinuation should be considered. In conclusion, until newer therapies are improved, use of current PEG-IFN and RBV therapies with a strategy to individualized treatment based on viral genotype, viral load,

Table 5. Retreatment Outcomes in Prior IFN+RBV or PEG-IFN+RBV Nonresponders

Reference	Patients	Previous treatment	Study drug/Dose	SVR (%)
Teuber G <i>et al.</i> DDW. 2003 ⁴⁰	240	IFN+RBV	PEG-IFN alfa-2b 100 μ g/wk+RBV 800 mg/d $\times$ 8 wk, PEG-IFN alfa-2b 50 μ g/wk+RBV 800 mg/d $\times$ 40 wk	6.3
Jacobson IM <i>et al.</i> 2005 ⁴³	219	IFN+RBV	PEG-IFN alfa-2b 1.0 μ g/kg/wk+RBV 1-1.2 g/d $\times$ 48 wk PEG-IFN alfa-2b 1.5 μ g/kg/wk+RBV 800 mg/d $\times$ 48 wk	6 10
Sulkowski M <i>et al.</i> DDW. 2003 ⁴¹	517	IFN+RBV	PEG-IFN alfa-2b 1.5 μ g/kg/wk+RBV 800 mg/d $\times$ 48 wk PEG-IFN alfa-2b 100/150 μ g/wk+RBV 800 mg/d $\times$ 48 wk	12
Lawitz E <i>et al.</i> DDW. 2003 ⁴²	486	IFN+RBV	PEG-IFN alfa-2b 1.5 μ g/kg/wk+RBV 1-1.2 gm/d $\times$ 12 wk, PEG-IFN alfa-2b 1.0 μ g/kg/wk+RBV 800 mg/d $\times$ 36/48 wk	5-10
Gross JB <i>et al.</i> (RENEW trial) ⁴⁴	704	IFN+RBV	PEG-IFN alfa-2b 1.5 μ g/kg/wk+RBV 12-15 mg/kg/d $\times$ 48 wk PEG-IFN alfa-2b 3.0 μ g/kg/wk+RBV 12-15 mg/kg/d $\times$ 48 wk	12 17
Shiffman ML <i>et al.</i> (HALT-C trial) ⁵⁷	210	IFN+RBV	PEG-IFN alfa-2a 180 μ g/wk+RBV 1-1.2 g/d $\times$ 48 wk	12
Poynard T <i>et al.</i> EASL 2005, 2008 (EPIC3 trial) ⁴⁶	2,293	IFN+RBV PEG-IFN+RBV	PEG-IFN alfa-2b 1.5 μ g/kg/wk+RBV 0.8-1.4 g/d $\times$ 48 wk PEG-IFN alfa-2b 1.5 μ g/kg/wk+RBV 0.8-1.4 g/d $\times$ 48 wk	18 6-7
Leevy CB <i>et al.</i> ²²	137	PEG-IFN+RBV	CIFN 15 μ g/d+RBV 1-1.2 g/d $\times$ 12 wks then CIFN 15 μ g TIW+RBV 1-1.2 g/d $\times$ 36 wks	37
Kaiser S <i>et al.</i> EASL. 2005 ⁴⁸	60	PEG-IFN+RBV	CIFN 27 μ g/d $\times$ 4 wks then 18 μ g/d $\times$ 12 wks then 9 μ g/d+ wt. based RBV 11 mg/kg/d (32-72 wks) CIFN 9 μ g/d $\times$ 16 wks then combined with wt. based RBV 11 mg/kg/d (48-72 wks)	27 23
Bacon BR <i>et al.</i> AASLD. 2007 (DIRECT trial) ⁴⁹	343	PEG-IFN+RBV	CIFN 9 μ g/d+RBV 1-1.2 g/d $\times$ 48 wks CIFN 15 μ g/d+RBV 1-1.2 g/d $\times$ 48 wks	5 10
Jensen DM <i>et al.</i> 2007 (REPEAT trial) ⁴⁷	942	PEG-IFN+RBV	PEG-IFN alfa-2a 360 μ g/wk $\times$ 12 wk then 180 μ g/wk+ RBV 1-1.2 g/d $\times$ 72 wk PEG-IFN alfa-2a 360 μ g/wk $\times$ 12 wk then 180 μ g/wk+ RBV 1-1.2 g/d $\times$ 36 wk PEG-IFN alfa-2a 180 μ g/wk+RBV 1-1.2 g/d $\times$ 72 wk PEG-IFN alfa-2a 180 μ g/wk+RBV 1-1.2 g/d $\times$ 48 wk	16 7 14 9

SVR, sustained virologic response; IFN, interferon; PEG-IFN, pegylated interferon; RBV, ribavirin.

the presence of advanced fibrosis, and initial virologic response will optimize treatment success for some patients and save resources in others.

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