

Seventy-Two Weeks of Peginterferon and Ribavirin for Patients with Partial Early Virologic Response?

See Article on Page 1688.

Current American Association for the Study of Liver Diseases and American Gastroenterological Association guidelines recommend 48 weeks of treatment with peginterferon and ribavirin (1000-1200 mg/day) for patients infected with hepatitis C genotype 1.^{1,2} The goal of treatment is a sustained virologic response (SVR) defined as a negative hepatitis C virus (HCV) RNA 6 months after therapy is stopped. In registration trials, approximately 45% of HCV genotype 1-infected subjects achieved an SVR; lower SVR was reported in nonregistration studies.^{3,4} SVR is associated with a greater than 99% chance of being free of HCV infection 5 years later⁵ and, in retrospective studies, a reduced rate of liver disease complications.⁶

Both pretreatment and on-treatment variables predict the likelihood of achieving an SVR. Hepatitis C genotype is the strongest pretreatment variable predicting response, with SVR lowest for genotype 1 followed by genotypes 4, 3, and 2. Other pretreatment variables associated with reduced SVR include higher weight/body mass index, higher viral load, older age, advanced liver fibrosis, and being male.⁷ For unclear reasons, African Americans, in comparison with Caucasians, with genotype 1 HCV infection have a significantly reduced SVR.⁸

Virologic response at treatment week 4 and at treatment week 12 predicts the likelihood of achieving, or not achieving, an SVR. The earlier in treatment HCV RNA becomes undetectable in the blood, the greater the likelihood of achieving SVR is.⁹ Ninety percent of patients with a rapid virologic response (RVR; defined as undetectable HCV in serum at treatment week 4) will have an

SVR, and some patients may require only 24 weeks of treatment.¹⁰ Patients with an early virologic response (EVR; defined as undetectable or greater than 100-fold decline in HCV RNA level at week 12 of treatment) have a 70% probability of achieving an SVR, whereas those without such a response are unlikely to achieve SVR (<3%), and most guidelines recommend discontinuation of treatment. Patients with an EVR consist of two subgroups with differing probabilities of achieving SVR. The majority of subjects with EVR have undetectable HCV RNA.¹¹ Absence of HCV RNA in the serum at treatment week 12 has been termed a complete early virologic response (cEVR). Less commonly, subjects have a 100-fold decline in the HCV RNA level but continue to have detectable HCV RNA. This response has been called a partial early virologic response (pEVR), and such patients are less likely to achieve an SVR than are subjects with cEVR.⁹

The definition of EVR and those of pEVR and cEVR are based largely, but not entirely, on the measurement of HCV RNA by quantitative polymerase chain reaction (PCR) assays with an upper limit of 800,000 IU/mL (in undiluted serum) and a lower limit of detection (LLOD) of 600 IU/mL (that is, Roche Amplicor HCV Monitor) and by qualitative HCV RNA PCR assays with an LLOD of approximately 50-100 IU/mL (that is, Roche Amplicor HCV). TaqMan real-time polymerase chain reaction (RT-PCR) is a PCR-based quantitative HCV assay with an LLOD of 10 IU/mL and a greater dynamic range than prior quantitative PCR assays. Importantly, among subjects with a viral load of more than 1,000,000 IU/mL, the viral load as measured by TaqMan RT-PCR assays is approximately 0.45 log greater than the viral load as measured by the Roche Amplicor HCV Monitor assay.¹² This difference in measurement of the HCV viral load would result in a greater number of subjects with a high viral load achieving an EVR when assessed by TaqMan RT-PCR than when measured by PCR. Also, it might alter the usefulness of EVR (as defined with PCR assays) to predict nonresponse to 48 weeks of combination treatment.

In an effort to improve SVR among patients with genotype 1 hepatitis C, investigators have increased the dose of interferon/ribavirin (for example, induction dosing, daily interferon, and higher doses of ribavirin) and extended treatment from 48 to 72 weeks. Although several clinical trials are in progress, the existing data are not convincing that higher doses of interferon or ribavirin or

Abbreviations: cEVR, complete early virologic response; ETR, end-of-treatment response; EVR, early virologic response; HCV, hepatitis C virus; LLOD, lower limit of detection; PCR, polymerase chain reaction; pEVR, partial early virologic response; RR, relapse rate; RT-PCR, real-time polymerase chain reaction; SVR, sustained virologic response.

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Table 1. A Comparison of the End-of-Treatment Virologic Response (ETR), Relapse Rate (RR), and Sustained Virologic Response (SVR) with 48 Weeks Versus 72 Weeks of Peginterferon and Ribavirin Among Subjects Failing to Achieve a Rapid Virologic Response (RVR) or Failing to Achieve a Complete Early Virologic Response (cEVR)

	Definition of Nonresponse	Treatment Duration	Sample Size	Genotype 1	Body Mass Index	Peginterferon	Ribavirin	Discontinue	ETR	RR	SVR	P Value‡
Retrospective subgroup analyses												
Berg et al. (Germany) ¹³	Without RVR (>50 IU/mL at week 4)	48 weeks	179	100%	~25.6	Alfa-2a	800		69%	37%	44%	
		72 weeks	190	100%	~25.3	180 µg			64%	23%	49%	0.26
	Without EVR (>50 IU/mL at week 12)	48 weeks	100	100%		Alfa-2a	800		47%	64%	17%	
72 weeks		106	100%		180 µg			49%	40%	29%	<0.05	
Prospective clinical trials												
Sanchez-Tapias et al. (Spain) ¹⁴	Without RVR (>10 IU/mL at week 4)	48 weeks	165	90%	25	Alfa-2a	800	18%	61%	48%	32%	
		72 weeks	161	88%	24	180 µg	800	36%	61%	26%	45%	<0.05
Pearlman et al. ¹⁶ (United States)	PEVR (>10 IU/mL at week 12)	48 weeks	49	100%	29	Alfa-2b	800-1400*	14%	45%	59%	18%	
		72 weeks	52	100%	29	1.5 µg/kg	800-1400*	15%	48%	20%	38%	<0.05
African American†		48 weeks	23						24%	50%	12%	
		72 weeks	25						26%	19%	21%	<0.05
Caucasian†		48 weeks	26						62%	63%	23%	
		72 weeks	27						67%	19%	56%	

*Weight-based ribavirin: <64 kg, 800 mg; 65-84 kg, 1000 mg; 84-105 kg, 1200 mg; and 105 kg or more, 1400 mg.

†The number of patients, ETR, RR, and/or SVR are estimated on the basis of data presented in the article.

‡The P value compares SVR in subjects receiving treatment for 48 weeks with SVR in subjects receiving treatment for 72 weeks.

a longer treatment duration improves SVR among unselected, treatment-naïve, HCV genotype 1-infected patients.

However, retrospective analyses suggest that selected patients may benefit from 72 weeks of treatment. For example, retrospective analysis of a German study of subjects treated with peginterferon alfa-2a and ribavirin (800 mg/day) for 48 or 72 weeks demonstrated improved SVR with 72 weeks of treatment among subjects with persistent HCV RNA at week 12 of treatment¹³ and especially among subjects with a pEVR. The improved SVR was due to a reduced relapse rate, not to an improvement in end of treatment virologic response. Similarly, retrospective analysis of a different clinical trial also demonstrated improved SVR with 72 weeks of treatment in comparison with 48 weeks of treatment among patients with a pEVR.¹⁴

A recent prospective Spanish study compared treatment with peginterferon alfa-2a and ribavirin (800 mg/day) for 48 weeks with treatment for 72 weeks among subjects with detectable HCV RNA after 4 weeks of treatment (that is, subjects not achieving an RVR).¹⁵ Although end of treatment virologic response was similar in both groups (61%), SVR was significantly higher among subjects receiving 72 weeks of treatment (45% versus 32%, $P < 0.03$) because of a reduced relapse rate with prolonged treatment (Table 1). The frequency and severity of hematologic adverse events were similar among patients

receiving treatment for 48 or 72 weeks. However, subjects randomized to 72 weeks of treatment were more likely to discontinue treatment (36% versus 18%).

In this issue of HEPATOLOGY, Pearlman and colleagues¹⁶ from Atlanta report the results of a prospective, randomized trial of 48 versus 72 weeks of peginterferon alfa-2b and weight-based ribavirin (800-1400 mg/day) among subjects with a pEVR and undetectable HCV RNA at week 24. Although end of treatment virologic response was similar in both groups, the SVR was significantly higher among patients treated for 72 weeks (38% versus 18%) because of a reduced relapse rate with 72 weeks' treatment. Side effects were similar in both groups, and in distinction to the Spanish study, discontinuation rates were relatively low and similar in both groups (approximately 15%).

Several aspects of Pearlman et al.'s study¹⁶ deserve comment. A large number of African Americans participated in the trial, increasing the amount of information available in this difficult-to-cure population. Although SVR was higher among Caucasians than among African Americans, both African Americans and Caucasians with pEVR benefited from 72 weeks of treatment. The dose of peginterferon was reduced when the neutrophil count was less than 500/mm³, with discontinuation when the neutrophil count was less than 250/mm³. Only one patient required a reduction in peginterferon during the first 12 weeks of treatment. The investigators are to be congratu-

lated for maintaining a high dose of peginterferon, given the exclusion of the use of growth factors.

Two aspects of the virologic response among Pearlman et al.'s¹⁶ patients are surprising. First, 31% of subjects who started treatment with peginterferon and ribavirin achieved a pEVR, a high proportion in comparison with prior studies.¹¹ Pearlman and colleagues attribute this to the large number of patients with poor prognostic signs (for example, high body mass index, high viral load, and cirrhosis). Another contributor may be use of the TaqMan RT-PCR assay. Second, although all patients were HCV RNA–negative at treatment week 24, only 45% and 48% remained HCV RNA–negative at the end of treatment, and this indicated a high rate of breakthrough (loss of antiviral effect during treatment). Virologic breakthrough does not appear to be due to discontinuation of treatment (only 15% in each treatment arm) or to reductions in peginterferon or ribavirin. At this time, the reason for the high proportion of subjects with breakthrough is unclear. It would be interesting to know the virologic breakthrough rate among Pearlman et al.'s subjects who achieved a cEVR and received combination treatment for 48 weeks.

Should 72 weeks of peginterferon and ribavirin be recommended for patients who are slow to clear HCV RNA? Pearlman et al.'s study¹⁶ suggests this, but there are several important considerations. First, patients should receive 1000/1200 mg (not 800 mg) of ribavirin daily, should be tolerating treatment well, and should have undetectable HCV RNA after week 24 of treatment. Second, it remains unclear which definition of nonresponse should be used to select patients for 72 weeks of treatment. The data for using failure to achieve undetectable HCV RNA at week 4 (that is, non-RVR) are conflicting, with one retrospective study suggesting no benefit with 72 weeks of treatment and one prospective study suggesting improved benefit.^{13,15} We believe that RVR is better suited to predict success with a shorter duration of treatment and that virologic testing at week 12 is the preferred time point to select patients for prolonged treatment. Retrospective analyses of two clinical trials^{13,14} and the current prospective study¹⁶ suggest that genotype 1 patients who fail to achieve cEVR benefit from 72 weeks of treatment. Furthermore, HCV viral load testing at week 12 identifies patients requiring 48 weeks of treatment (that is, cEVR) and patients in whom treatment should be discontinued (that is, subjects failing to achieve a 100-fold decline in HCV viral load).

Finally, it is important to remember that large, well-conducted, multicenter clinical trials sometimes contradict the findings of small, single-site studies, as was demonstrated recently in clinical trials of shorter duration

treatment for patients infected with genotype 2 or 3 hepatitis C.¹⁷⁻¹⁹ Thus, consideration of prolonged treatment for patients infected with genotype 1 HCV who achieve a pEVR should be re-evaluated following the results of large, prospective trials of 72 weeks of treatment versus 48 weeks of treatment in this group. We await the results of such trials.²⁰

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