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REVIEW

Extended-therapy duration for chronic hepatitis C, genotype 1: The long and the short of it

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Abstract

With pegylated interferon and ribavirin, more than half of all chronically-infected hepatitis C patients can achieve a sustained virologic response; however, patients with genotype 1 infections and those with other poor prognostic factors have relatively inferior treatment response rates. Since new therapies are still years away from approval, it is incumbent upon providers to maximize the therapeutic efficacy of today's treatment. The later the virus is undetectable in serum during treatment, the less likely it will be eradicated. Patients with a delayed or slow virologic response to therapy (at least a 2-$\log_{10}$ decrease in baseline hepatitis C RNA yet detectable viremia at 12 wk of therapy and undetectable virus 12 wk subsequently) may, therefore, benefit from an extended therapy course beyond one of standard duration. Although higher rates of treatment discontinuation may plague this approach, 72 wk of treatment for genotype 1-infected slow-responders may improve response rates and diminish relapse rates relative to those of 48 wk. Based on data from both viral kinetic and clinical studies, therapy prolongation in slow responders may be a reasonable strategy to improve response rates in these treatment-refractory patients.

Key words: Hepatitis C virus genotype; Peginterferon alpha; Ribavirin; Slow-responder; Extension

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INTRODUCTION

One hundred and seventy million persons worldwide are infected with the hepatitis C virus (HCV)[1], and liver-related deaths from the virus are expected to nearly triple by the year 2020[2]. Three years prior to the virus' identification in 1986, interferon alpha-2b was first utilized for the treatment of non-A, non-B hepatitis[3]. Although sustained virologic response (SVR) rates to interferon monotherapy for 6 mo were only about 8%, treatment extension to 12 mo nearly doubled response rates[4]. With the advent of the nucleoside analog ribavirin, used in combination with interferon, rates of SVR more than doubled again[5,6]. Whereas 48 wk of standard interferon with ribavirin achieved sustained response rates as high as 43%[6], 48 wk of the newer pegylated interferons plus ribavirin improved rates of SVR to 54%-56% as shown in two multinational, randomized controlled trials[7,8].

Nevertheless, SVR rates are inferior for patients with genotype 1 infection[7-9] despite a 48 wk recommended treatment course of peginterferon with weight-based ribavirin[10,11]. Although preliminary evidence indicates that small molecule inhibitors in combination with peginterferon and ribavirin may improve response rates even further for genotype 1-infected patients with merely 24 wk of therapy[12,13], the combination of peginterferon and ribavirin alone is likely to remain the recommended treatment regimen for chronic HCV for the next 3-5 years[14]. Thus, it is incumbent upon clinicians to maximize their patients' chance of treatment success with existing therapy.

Methods utilized to improve the treatment response in genotype 1-infected patients include the bolstering of patient adherence through aggressive side effect management and increasing the dose of therapy through induction dosing of interferon or through higher doses

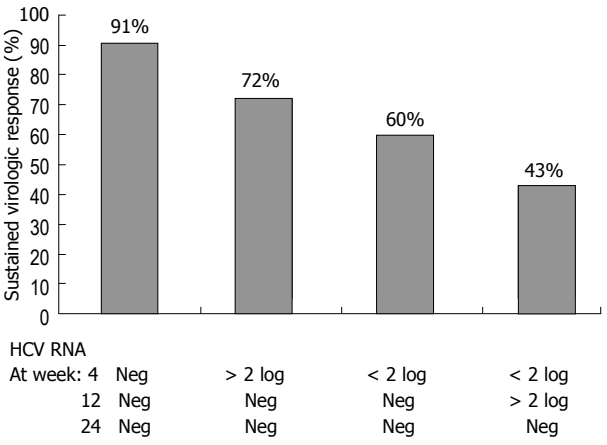

Figure 1 Relationship between hepatitis C viremia and sustained virologic response with pegylated interferon alpha-2a and ribavirin therapy[19]. The later the virus becomes undetectable on therapy, the less likely it will be ultimately cleared. Data are from retrospective analysis[19] of a registration trial for peginterferon alpha-2a plus ribavirin involving over 1000 chronic, treatment-naive hepatitis C-infected patients[8]. Neg: Undetectable RNA; > 2 log: At least a 2 log_{10} decrease in viral RNA compared to pre-treatment value; < 2 log: Less than a 2 log_{10} decrease in viral RNA compared to pre-treatment value.

of either interferon or ribavirin. Another strategy is to lengthen duration of treatment in those that are slow-responders to standard doses of peginterferon and ribavirin. The purpose of this survey is to review the justification for therapy prolongation in appropriate patients using viral kinetic data and to summarize the clinical trials supporting this approach.

VIRAL KINETICS DURING TREATMENT

An initial decrement in HCV RNA level, referred to as phase 1, occurs hours after the administration of interferon; it represents the blocking of viral replication. A subsequent, slower decrease in viremia (phase 2) represents the clearance of HCV-infected hepatocytes and typically occurs days to months after interferon therapy is initiated. The phase 2 decline in virus is the better predictor of ultimate HCV clearance[15,16]. Phase 2 decline is significantly slower in genotype 1-infected patients than in those infected with genotypes 2 and 3[17,18]. Thus, by measuring virus concentrations of various points along a slope of a phase 2 decline in viremia, treatment outcome may be better predicted, and ultimately modified, based on an individual patient's response to therapy.

HCV-infected patients who achieve undetectable viremia as early as 4 wk into standard therapy have excellent sustained response rates; these rapid virologic responders achieve SVR about 90% of the time[19]. In fact, support exists for truncating therapy duration for genotype 1-infected rapid responders with low baseline HCV viral loads[20]. Conversely, patients who show undetectable virus for the first time 24 wk into therapy have less than one-third chance of ultimately achieving SVR[8]. Therefore, the earlier the HCV is undetectable in serum during treatment, the greater the likelihood of a successful treatment response (Figure 1).

Similarly, longer durations of viral suppression on treatment may improve virologic response rates. Investigators have sought to determine if the standard 48 wk treatment duration of patients with genotype 1 infection is adequate. Using data from the peginterferon alpha-2b and ribavirin phase Ⅲ trial[7], Drusano and Preston developed a prediction model based on the duration of viral suppression on therapy[21]. The model was built on the basis of eleven covariables including demographics and virologic characteristics from 771 HCV-infected patients. Among the variables, the durations of viral clearance had the strongest bearing on the likelihood of a SVR. When the model was applied to a validation group of 229 patients, it predicted SVR with a positive predictive value of 97% and a negative predictive value of 91%. To achieve an 80% chance of SVR in genotype 1-infected patients, an undetectable HCV RNA was required for at least 32 wk on therapy, and to achieve a 90% chance of SVR, RNA undetectability was necessary for 36 wk. Since the average time to clear genotype 1 viremia was 30 wk, the authors concluded that the standard 48 wk treatment course for this genotype is inadequate. Problems with this study are its retrospective analysis and the model's requirement for monthly viral loads which may be cost-prohibitive. Furthermore, the model was based on the use of suboptimal ribavirin dosing (800 mg daily) which limits its applicability in genotype 1 infection. However, the study suggests that patients who don't achieve undetectable virus at certain time points may enjoy improved rates of SVR with treatment extension.

A failure to achieve an early virologic response (EVR), defined by an undetectable HCV RNA level or at least a 2-log_{10} decrement in RNA from baseline at 12 wk of therapy, has excellent negative predictive value for treatment success[22,23]. An analysis of the peginterferon with ribavirin registration trials[7,8] suggests that patients who do not achieve a 12 wk EVR have a 3% or lower chance of ultimately achieving SVR[23]. Nonetheless, there is a large disparity in treatment response between patients who, at 12 wk, have at least a 2-log_{10} decrease in baseline HCV RNA yet still have detectable virus (partial EVR) compared to those who achieve undetectable viremia (complete EVR). In the registration trial for peginterferon alpha-2b with ribavirin, patients in the latter group achieved SVR about four times more frequently than those in the former[23]. These former patients are said to be slow or late responders to therapy. Patients have also been characterized as slow responders to therapy if they have detectable virus at 4 wk; either definition necessitates undetectable virus at 24 wk of treatment, since detectable viremia at this time point virtually guarantees treatment failure.

In genotype 1 infection with the standard therapy duration of 48 wk, slow responders have higher relapse rates compared to those that clear virus earlier in treatment[19]. High rates of relapse in slow responding patients may indicate that therapy was of insufficient duration; therefore, it has been hypothesized that extending therapy in these patients may improve rates of SVR (Figure 2).

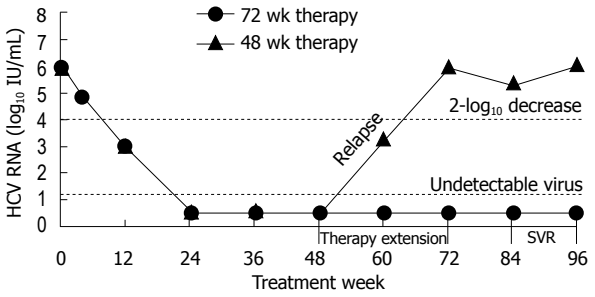

Figure 2 Virologic responses of slow-responders to 48 wk *vs* 72 wk of therapy. Treatment extension may improve chance of SVR by lessening the chance of relapse. Slow-responders to standard duration therapy (48 wk) may see relapse after an end-of-treatment response is achieved; those receiving extended duration therapy (72 wk) are not as apt to relapse after treatment is completed.

EXTENDED DURATION THERAPY WITH STANDARD INTERFERON

Several years before the term slow-responder was popularized, investigators attempted to improve response rates by extending therapy duration utilizing older medications. Using standard interferon monotherapy, authors have demonstrated improved biochemical, histologic and virologic responses with treatment ranging from 60 to 76 wk compared to treatments of shorter durations[24,25]. In one of these studies[24], the investigators noted a reduced tendency for patients to relapse after treatment cessation when therapy was extended to 60 wk relative to previously published studies with shorter durations.

The first randomized, controlled trial to show that prolongation of interferon-based therapy combined with ribavirin for 18 mo reduced rates of relapse was performed in the Netherlands and Belgium[26]. Three hundred treatment-naive chronic HCV patients were randomized to 6 or 18 mo of standard-interferon (3 million units thrice weekly) plus ribavirin (1000-1200 mg daily) or to 18 mo of the same dose of standard interferon monotherapy plus placebo. The majority of patients were genotype 1-infected with high viral loads. Although end-of-treatment responses were similar in the two combination therapy arms (55% and 41% in 6 and 18 mo arms, respectively), relapse rates were significantly lower in the 18 mo combination arm (13%) compared to those in the 6 mo treatment arm (38%, $P = 0.006$). It should be noted that the rate of relapse in the group treated with 18 mo of monotherapy was still high at 38%; these results demonstrate that extending the duration of interferon alone is inadequate to decrease relapse rates and attests to ribavirin's effect on relapse diminution. In an intention-to-treat analysis, SVR rates were 16% for 18 mo monotherapy, 34% for 6 mo combination therapy and 43% for 18 mo of combination therapy ($P < 0.05$). Although 25% of patients withdrew from both 18 mo treatment arms prematurely, this withdrawal rate is similar to those from standard interferon plus ribavirin treatment trials of 48 wk duration (21%-27%)[5,6]. Prolongation of combination therapy had no significant effect on rates of relapse or SVR in genotype 2- or 3- infected patients; nevertheless, extension of treatment from 6 to 18 mo had an independent effect on relapse and SVR rates in patients infected with genotype 1 virus (SVR: OR 4; CI: 2-10, $P = 0.004$). Slow responders, those with detectable viremia at 12 wk, enjoyed a decline in relapse rate from 70% to 30% when treatment was prolonged from 24 to 72 wk. The study's major limitation was the absence of a 12 mo treatment arm.

EXTENDED DURATION THERAPY WITH PEGYLATED INTERFERON

Investigators from Spain and Israel were the first to report successful treatment extension to 72 wk for slow responders to peginterferon and ribavirin[27]. Slow responders were defined as those patients with at least a 2 $\log_{10}$ decline in HCV RNA from baseline, yet detectable viremia at 12 wk after receipt of 1.0 mcg of peginterferon alpha-2b weekly and 800 mg ribavirin daily. Although only 8 patients were treated in this fashion, 7 of the 8 (88%) achieved an SVR, which is a profound improvement relative to a SVR of 21% in slow responders treated for 48 wk in the phase Ⅲ trial of peginterferon alpha-2b and ribavirin[23]. The suboptimal dosing of ribavirin and the paucity of patients studied are the limitations of this analysis.

Furthermore, results from a large, prospective, multicenter trial from Germany support the extension of therapy duration in slow responders to peginterferon and ribavirin[28]. 459 treatment-naïve genotype 1-infected patients were randomized to 48 wk *vs* 72 wk of peginterferon alpha-2a, 180 mcg weekly and ribavirin, 800 mg daily. 22% of patients were slow virologic responders to therapy, defined by virus detectability at 12 wk of treatment, but with viral undetectability at 24 wk. Slow responders in the 72 wk group had lower relapse rates than did slow responders treated for 48 wk (40% *vs* 64%, respectively; $P = 0.021$) and had similar end-of-treatment responses; thus, rates of SVR for this subgroup of patients were significantly higher when treated for 72 wk compared those treated for 48 wk (29% *vs* 17%, respectively; $P = 0.04$). Patients with low levels of viremia (less than 6000 IU/mL) at 12 wk of treatment derived the greatest benefit from extended duration therapy. Thus, the investigators concluded that in slow virologic responders to treatment, relapse rates could be reduced and rates of SVR could be augmented by extending therapy to 72 wk. Nonetheless, the slow responders represented only a subgroup of those randomized, and the conclusions were garnered retrospectively. Moreover, the 800 mg ribavirin used in the trial is an inadequate dose for most genotype 1-infected patients[9]. It should also be emphasized that, for the majority of patients randomized to 72 wk of therapy, there was no statistical benefit relative to 48 wk of treatment. Overall, SVR rates were 54% and 53%, respectively ($P = 0.8$), and relapse rates were likewise statistically similar. Thus, extended duration

therapy is generally not recommended for all treatment-naïve patients with genotype 1 infection and should be considered only for those with the slow responding phenotype. Finally, although patients in both the standard and extended duration treatment arms had similar rates of medication dose reduction and adverse events, the rate of premature therapy discontinuation was higher in the extended treatment arm compared to that in the standard treatment arm (41% and 24%, respectively).

Another randomized, multicenter clinical trial from Spain, the TeraViC-4 study, prospectively evaluated the effects of extended therapy duration with peginterferon alpha-2a (180 mcg weekly) and ribavirin (800 mg daily)[29]. Treatment-naïve patients with detectable HCV RNA levels at week 4 (n = 326) were randomized to a therapy duration of 48 wk (n = 165, 149 of whom were genotype 1-infected) or to 72 wk (n = 161, 142 of whom were genotype 1-infected). Thus, in this case, a slow responder was defined by absence of a rapid virologic response, and only slow responders were randomized to extended therapy. In TeraViC-4, the 12 wk virologic responses were not reported. Although end-of-treatment responses for patients with genotype 1 infections were statistically similar in both extended and standard treatment arms (62% *vs* 58%, respectively; P = 0.53), SVR rates were superior in the extended treatment arm (44% *vs* 28%, respectively; P = 0.003), by virtue of a diminution of relapse rate (17% *vs* 53%, respectively; P = 0.002). The incidence of adverse events and dose reductions were similar in both groups; yet, treatment discontinuation was more frequent in the extended therapy arm compared to the standard duration arm (36% *vs* 18%, respectively; P = 0.0004). In fact, one of the study's limitations was this inordinate number of premature terminations in those randomized to prolonged therapy, largely because of patient preference. Other limitations were the lack of central testing for viral load measurements and the inclusion of patients with other genotypes besides one. Like that of the German study, the primary weakness of this trial may have been the suboptimal dose of ribavirin utilized (800 mg for genotype 1 virus).

In another prospective study from the United States, we randomized genotype 1-infected slow-responders to 48 or 72 wk of peginterferon alpha-2b (1.5 mcg/kg weekly) and weight-based ribavirin (800 to 1400 mg daily)[30]. In our trial, slow response was defined by achieving at least a 2 $\log_{10}$ decrement in HCV RNA from baseline, yet having detectable viremia at 12 wk but undetectable virus at 24 wk (PCR, lower limit of detection 10 IU/mL). One hundred twelve of our treatment-naïve patients were deemed slow-responders who represented about 30% of our patients. This percentage was felt to be high secondary to difficult-to-treat baseline characteristics: 26% had bridging fibrosis or cirrhosis on pre-treatment liver biopsy; 48% were African American; 34% were obese defined by greater than or equal to 30 kg/m^2; 78% had high baseline viral load (more than 800 000 IU/mL) and 18% had impaired fasting glucose, pre-treatment. Similar to the aforementioned European trials, we did not observe a higher number of adverse events or therapy reductions in the extended treatment arm relative to the control arm. However, unlike in the other studies, we did not see a greater treatment cessation rate in the prolonged therapy arm; in fact, none of the therapy terminations occurred between weeks 48 and 72. Growth factors were prohibited, yet peginterferon dose reductions for neutropenia were made only if counts were less than 500/mm^3. Similar to those of the slow-responders in Spain, our randomized patients saw equivalent end-of-treatment response rates in the 72 wk arm *vs* the 48 wk arm (48% *vs* 45%, respectively; P = 0.75), yet enjoyed improved relapse rates with therapy prolongation (20% *vs* 59%, respectively; P = 0.004). Overall, rates of SVR in slow-responders were superior with treatment extension (38%) compared to those of standard duration therapy (18%, P = 0.03). The primary limitation of our analysis is it was conducted in a single medical center.

African Americans, a group with inferior responses to interferon-based therapy[31-33], may likewise benefit from a treatment extension strategy if slowly responsive to treatment. When compared to non-Hispanic whites receiving combination therapy, African Americans showed smaller phase 1 and phase 2 declines in viral load[34]; thus, it was unclear if African Americans' viral kinetics on therapy would be analogous to those of white "late" responders. Nearly half of our slow responders were self-identified as African American (n = 48) and were randomized to 48 and 72 wk treatment arms in our Atlanta study described above[30]. Although overall, African American slow responders had expected inferior SVR rates to those of whites (17% and 39%, respectively), the former group still benefited from treatment extension because of reduced relapse rates. End-of-treatment response rates were 24% *vs* 26% for 48 and 72 wk of treatment, respectively (P > 0.05), and SVR rates were 12% *vs* 21%, respectively (P = 0.02). Results should be interpreted with caution, however, because this ethnic group's response rates were derived from subgroup analysis.

Preliminary results are available from a multicenter trial in Europe that also utilized extended therapy for slow-responders to peginterferon alpha-2a (180 mcg weekly) with weight-based ribavirin (1000-1200 mg daily)[35,36]. Of the 373 patients treated, 11% were slow-responders to therapy, defined by having detectable virus at 12 wk (> 50 IU/mL), yet still at least 2 $\log_{10}$ below baseline, and thus randomized to complete standard duration therapy of 48 wk or extended treatment to 72 wk. None of these slow-responders had achieved undetectable virus at 4 wk. Over 90% of patients had genotype 1 infections, and the remainder was infected with genotype 4 virus. As in the previously described studies, extended therapy compared to that of standard duration improved SVR rates in slow-responders (69% *vs* 52%, respectively; P value not available) by virtue of a decrease in relapse rates (18% *vs* 32%, respectively; P value not available). Although treatment discontinuation data are not available for slow-responders specifically,

Table 1 Studies of extended therapy for treatment-naive, genotype 1-infected slow responders to pegylated interferon with ribavirin

Country(ies) in which studies performed	Number of subjects studied	Treatment duration (wk)	Definition of slow response (assay sensitivity)	Pegylated interferon type and weekly dose	Ribavirin daily dose (mg)	End-of-treatment responses	Relapse rates	Sustained virologic response rates	*P* value (sustained response)	Major study limitation (s)
Spain, Israel[27]	8	72	⩾ 2-$\log_{10}$ 12 wk decrease[1] (100 IU/mL)	Alpha -2b 1.0 mcg/kg	800	100%	13%	88%	Not applicable	Few subjects suboptimal ribavirin dose
Germany[28]	100	48	> 50 IU/mL at wk 12 (50 IU/mL)	Alpha 2-a 180 mcg	800	47%	64%	17%	0.04	Retrospective subgroup analysis suboptimal ribavirin dose
	106	72				49%	40%	29%		
Spain[29]	149	48	> 50 IU/mL at wk 4 (50 IU/mL)	Alpha 2-a 180 mcg	800	58%	53%	28%	0.003	Suboptimal ribavirin dose
	142	72				62%	17%	44%		
United States[30]	49	48	⩾ 2-$\log_{10}$ 12 wk decrease[1] (10 IU/mL)	Alpha 2-b 1.5 mcg/kg	800-1400	45%	59%	18%	0.03	Single center
	52	72				48%	20%	38%		
Europe[35,36]	25[2]	48	⩾ 2-$\log_{10}$ 12 wk decrease[1] (50 IU/mL)	Alpha 2-a 180 mcg	1000–1200	Not available	32%	52%	Not available	Few subjects some genotype four infections
	16[2]	72					18%	69%		
Italy[37]	21	48	⩾ 2-$\log_{10}$ 12 wk decrease[1] (50 IU/mL)	Alpha -2b 1.5 mcg/kg or Alpha -2a 180 mcg	1000-1200	5%[3]	100%[3]	0%[3]	0.3[4]	Subgroup analysis
	52	72				19%	60%	8%		
Europe, Canada, Israel[38]	63	48	⩾ 2-$\log_{10}$ 12 wk decrease[1] (30 IU/mL)	Alpha -2b 1.5 mcg/kg	800-1400	Pending	Pending	Pending	Pending	Pending
	63	72								

[1]Detectable viremia at 12 wk and undetectable viremia at 24 wk required; [2]Less than 10% genotype 4 infections; [3]One of twenty patients had an end-of-treatment response, but relapsed; [4]Not statistically significant.

patients who received extended duration therapy had a greater number of treatment discontinuations (17%) compared to those on standard duration therapy (4%). Limitations of this study are the small numbers of slow-responders analyzed (41 patients) and the mixture of genotype 1- and 4- infected patients.

Finally, a recently published, randomized, multicenter study from Italy assessed the utility of variable therapy duration, including a treatment extension strategy, based on the time to a patient's first undetectable HCV RNA[37]. 696 genotype 1-infected treatment-naive patients were randomized to a standard duration or a variable duration therapy arm in a 2:1 ratio. Patients were treated with either peginterferon alpha-2a (180 mcg weekly) or peginterferon alpha-2b (1.5 mcg/kg weekly), both with weight-based ribavirin (1000-1200 mg daily). Irrespective of first time to viral undetectability in serum (< 50 IU/mL), 237 patients in the standard therapy arm received treatment for 48 wk, unless patients did not achieve EVR at week 12 or had detectable virus at week 24, at which time therapy was discontinued. However, in the variable duration arm, patients were treated for 24, 48 or 72 wk if serum HCV RNA were negative at 4, 8, or 12 wk, respectively. Patients were likewise treated for 72 wk in the variable duration arm if they had at least a 2 $\log_{10}$ decline in serum RNA from baseline yet detectable viremia at 12 wk of therapy (slow-responders).

Overall, based on the rates of SVR, the standard and variable duration treatment arms were statistically equivalent. Nonetheless, the study proved prospectively that the longer the virus is undetectable on therapy, the better the chance of achieving a SVR, regardless if a patient had received treatment of a standard or variable duration. In the standard duration arm, 87%, 70% and 38% of patients first attaining undetectable viremia at 4, 8 or 12 wk, respectively, achieved SVR; in the variable duration group, corresponding SVR rates were 77%, 72% and 64%.

More pertinent to this discussion is the fact that the study's slow-responders in the standard treatment duration arm (n = 21) did not achieve SVR in a single case (0%), and those slow-responders treated for 72 wk (n = 53) saw an SVR of only 7.5%; nonetheless, the results were not statistically significant (P = 0.3). Moreover, 10 of the slow-responders treated for 72 wk voluntarily withdrew from the study compared to only 3 patients treated for 48 wk, suggesting that prolonged therapy was not well-tolerated. Most intriguing, patients who achieved undetectable virus for the first time at 12 wk of therapy (having detectable viremia at week 8), enjoyed improved SVR rates when treated for 72 wk compared to 48 wk in 64% and 38% of cases, respectively (difference -25.4, CI: 22.3-28.4). Extended therapy, even in these "complete" early virologic responders, seemed to have improved SVR rates because of a decline in relapse (43% in standard group, and 15% in variable group). The authors deemed this difference "…substantial, (and) may warrant a prospective trial."

The most important limitations of this last study are the large number of patients in the variable treatment duration arm who discontinued therapy because of poor

compliance (49% of all treatment discontinuations), and the relative paucity of patients on which subgroup analysis was performed. For example, only 21 slow-responders were treated for 48 wk.

The Study to Assess Treatment with Pegylated Interferon Alpha-2b and Ribavirin in Treatment-Naive Patients with Chronic hepatitis C and slow virologic response (SUCCESS) is a multinational study in 133 centers across Europe, Canada and Israel designed to compare response rates of slow-responders to either 48 or 72 wk of therapy[38]. Slow-response is again defined by patients with genotype 1 infection who had at least a 2 $\log_{10}$ reduction, albeit detectable, HCV RNA levels at 12 wk compared to baseline and undetectable virus at week 24. As of late 2006, 126 patients were deemed slow-responders and were randomized into standard and extended therapy duration arms (Table 1). Final results should be available sometime later in 2008 or in early 2009.

CONCLUSION

Treatment extension has been attempted with varying degrees of success using alternative interferons[39,40], in those with relapse[40] or non-response to peginterferon-based therapies[41] and in those who are HCV-HIV coinfected[42,43]. Details of these analyses are beyond the scope of this review.

Certainly, not every treatment-naive patient with genotype-1 infection benefits from therapy prolongation. However, a subgroup with a delayed or slow response to therapy (approximately 15% of patients) may enjoy improved rates of SVR with treatment extension to 72 wk, largely because of a relapse diminution. Data on therapy prolongation in slow-responders are summarized in Table 1. Compared to patients receiving therapy of standard duration, those in extended treatment groups have experienced higher discontinuation rates in most, but not all, studies to date; however, the numbers of adverse events and dose reductions appear to be equivalent. Clearly, if treatment prolongation is utilized, adherence to therapy is paramount. Finally, the use of 72 wk for slow virologic responders to peginterferon and ribavirin may be cost-effective compared to 48 wk, or standard duration therapy[44]. Thus, therapy extension in slow-responders seems to be a reasonable strategy to ameliorate response rates in a group with notoriously poor treatment results.

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