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ORIGINAL ARTICLE

Antiviral Response of HCV Genotype 1 to Consensus Interferon and Ribavirin Versus Pegylated Interferon and Ribavirin

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Abstract Achieving an antiviral response at a reasonable cost is a challenge in the treatment of patients with chronic hepatitis C. A previous study indicated that consensus interferon with ribavirin had promising activity against hepatitis C virus (HCV) genotype 1. The objective of this study was to determine the virologic response with consensus interferon or pegylated interferon α-2b plus weight-ribavirin in patients chronically infected with HCV genotype 1. Intention-to-treat analysis showed response in 37% and 41% of subjects treated with consensus interferon/ribavirin or pegylated interferon/ribavirin, respectively, with response rates of 42% and 44% observed in analysis of the per-protocol population, not a significant difference. Tolerability of the two treatment regimens was similar. In conclusion, both treatment regimens were safe and gave a similar antiviral response. It is possible that if consensus interferon is administered daily rather than three times weekly, eradication of HCV could be achieved in a larger proportion of patients infected with HCV genotype 1.

Keywords Viral hepatitis · Viral load · Depression · Quality of life · African-American · Interferon alfacon-1

Introduction

Chronic infection with hepatitis C virus (HCV) is a significant health issue in the United States: the third National Health and Nutrition Examination Survey reported in 1999 that approximately 3 million people were chronically infected with HCV [1]. The true prevalence is likely to be higher if groups who were not included in this survey, such as the prison population, are considered. For example, epidemiological data estimate that in the United States, 15% of prison inmates, 22% of homeless people, 6.6% of veterans, and up to 90% of illicit injecting drug users are infected with HCV [2]. Untreated chronic HCV infection is associated with chronic liver disease, which progresses to cirrhosis

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and/or hepatocellular carcinoma in up to 20%–30% of patients [3].

The current standard therapy for chronic HCV infection is pegylated interferon α in combination with the nucleoside analogue ribavirin [4]; however, approximately half of all patients do not respond to this therapy [5, 6]. In addition, response rates are influenced by several factors, such as HCV genotype, baseline viral load, ethnicity, gender, body weight, and advanced liver disease [5–8]. Response rates are significantly lower in patients infected with HCV genotype 1, those with a high viral load at baseline, and African-Americans [5–8]. In two large randomized multinational trials, only 30%–31% of American subjects who were infected with HCV genotype 1 and had a high baseline viral load achieved successful hepatitis C eradication with pegylated interferon α in combination with ribavirin [9]. Another multicenter trial reported that only 26% of African-Americans chronically infected with HCV genotype 1 achieved undetectable HCV RNA after therapy with pegylated interferon α and ribavirin [7]. Given that more than 70% of patients in the United States are infected with HCV genotype 1, and more than 50% have a high viral load [1, 10, 11], it is clear that there is a need to identify new or improved therapeutic options for this large subpopulation.

Three α interferons, in pegylated and/or nonpegylated form, are licensed in the United States for the treatment of chronic hepatitis C. Interferon α-2b and interferon α-2a are recombinant human interferons, whereas consensus interferon (also known as interferon alfacon-1) is a non-naturally occurring recombinant interferon, derived by scanning the sequences of several natural interferon α subtypes and assigning the most frequently observed amino acid in each corresponding position. Consensus interferon has been shown to exhibit 10- to 100-fold higher specific antiviral, antiproliferative, natural killer cell induction, and gene induction activities than the naturally occurring interferons in vitro [12, 13]. In an early phase III trial in 704 patients with chronic HCV infection, consensus interferon monotherapy was shown to produce a significantly greater decrease in HCV RNA than treatment with interferon α-2b [14]. A recent study in treatment-naïve HCV-infected patients demonstrated that consensus interferon in combination with ribavirin gave a significantly better response than that observed with interferon α-2b and ribavirin and similar to that reported for pegylated interferon and ribavirin [9]. Furthermore, this study indicated that consensus interferon with ribavirin had promising activity against HCV genotype 1, particularly when the viral load was high [9]. The aim of this study was to assess the safety and antiviral response of consensus interferon and ribavirin versus pegylated interferon α-2b and ribavirin in previously untreated patients chronically infected with HCV genotype 1. Because depression and fatigue are frequently reported side effects of interferon treatment, a secondary objective was to measure depression, fatigue, and quality of life in HCV-infected patients treated with these medications.

Methods

Patient population

Individuals aged 18 years or older presenting with the diagnosis of chronic HCV genotype 1 were eligible for this study. An institutional review board approved the study, and the study protocol conformed to the guidelines of the Declaration of Helsinki. Written, informed consent was obtained from each patient prior to study entry. Inclusion criteria required that patients had detectable serum HCV RNA and a liver biopsy compatible with a diagnosis of chronic HCV infection. Patients with cirrhosis were eligible for inclusion. Exclusion criteria included decompensated liver disease, hemoglobin <13 g/dl for men and <12 g/dl for women, white blood cell count of $<3000/\text{mm}^3$, neutrophil count of $<1500/\text{mm}^3$, platelet count of $<75{,}000/\text{mm}^3$, and prothrombin time >2 sec above the upper limit of normal. Patients were also excluded if they demonstrated any cause for liver disease other than chronic hepatitis C or had a history of major depression or other severe psychiatric conditions.

Study design

This was a proof-of-concept, open-label, multicenter, randomized, controlled, prospective clinical trial with enrollment of treatment-naïve patients chronically infected with HCV genotype 1. Patients were randomized to one of two study groups using a computerized system. One group received consensus interferon (Infergen; InterMune, Inc., Brisbane, CA), 15 μg subcutaneously three times weekly, plus oral generic weight-based ribavirin (Ribasphere; Three Rivers Pharmaceuticals, Cranberry Township, PA) daily (1000 mg/day if $\leq$75 kg, 1200 mg/day if $>$75 kg), while the other group received pegylated interferon α-2b (PEG-INTRON; Schering-Plough, Kenilworth, NJ), 1.5 μg/kg subcutaneously once weekly, plus oral weight-based ribavirin (Rebetol; Schering-Plough) daily (1000 mg/day if $\leq$75 kg, 1200 mg/day if $>$75 kg). If HCV RNA was detectable in serum at week 24, the treatment was considered a failure and stopped; if HCV RNA levels were undetectable after 24 weeks, treatment was continued as per the original randomization for a total of 48 weeks. Patients were monitored for an additional 24 weeks after completion of treatment.

Serological and virological assays

HCV RNA and HCV genotype were tested at a central laboratory (National Genetics Institute, Los Angeles, CA). HCV

RNA was measured at baseline and at weeks 12, 24, 48, and 72 utilizing the Superquant quantitative reverse-transcription polymerase chain reaction (National Genetics Institute) test (limit of detection 100 copies/ml).

Assessment of efficacy

The primary endpoint of the study was assessment of sustained virologic response (SVR), defined as undetectable HCV RNA at 24 weeks posttreatment (week 72).

Assessment of safety

Safety assessments were performed at weeks 1 and 4, then every 4 weeks through week 48, and at 12 and 24 weeks posttreatment. All adverse events, serious adverse events, laboratory test results, discontinuations, and dose reductions were recorded and evaluated.

Depression and quality of life assessments

The Beck Depression Inventory-II (BDI-II) [15], the Center for Epidemiological Studies Depression Scale (CES-D) [16], the Fatigue Severity Scale (FSS) [17], and the Hepatitis Quality of Life Questionnaire (HQLQ) [18] were completed by patients at baseline, at weeks 4, 12, 24, 36, and 48, and at 24 weeks posttreatment. Factor analysis and correlation analysis were used to identify factors related to depression and to make comparisons between the questionnaires.

Statistical analysis

Analyses were performed on both the intention-to-treat (ITT) and the per-protocol (PP) populations. The SVR rates in the two treatment groups were compared using the Mantel–Haenszel chi-square test. The Mann–Whitney *U* test was used to compare the change in depression scores, fatigue levels, quality of life scores, and week 72 serum alanine aminotransferase (ALT) levels between the two treatment groups. In addition, a repeated-measures analysis of variance (ANOVA) was done to compare quality of life scores during the study period. In addition, a repeated-measures ANOVA was done to compare quality of life scores over the time of the study.

Results

Patient population

A total of 59 patients were enrolled in the study. The baseline characteristics of the study groups are shown in Table 1. There were no significant differences among the groups in terms of baseline demographics and clinical variables.

Six patients—four in the consensus interferon/ribavirin group and two in the pegylated interferon/ribavirin group—withdrew from the study during the first weeks of therapy. Twenty-six (87%) of the 30 patients in the consensus interferon/ribavirin group and 27 (93%) of the 29 patients in the pegylated interferon/ribavirin group completed at least 24 weeks of therapy (Fig. 1). Reasons for early withdrawal

Table 1 Patients' baseline characteristics

	Consensus interferon/ribavirin ($n = 30$)	Pegylated interferon/ribavirin ($n = 29$)
Median age (range)	45 (19–68)	46 (23–55)
Gender, %		
Male	70	65.5
Race, %		
Caucasian	60	59
African-American	30	31
Asian	7	7
Hispanic	3	3
Median weight, kg (range)	91 (56–122)	82 (45–118)
Median BMI (range)	29 (21–39)	27 (20–37)
Median baseline ALT, U/L (range)	69 (27–223)	65 (18–267)
Median baseline HCV RNA, IU/L	2,887,333	2,797,379
High viral load (≥850,000 IU/L)		
n (%)	22 (73)	22 (76)
Median IU/L	3,783,636	3,609,091
Low viral load (<850,000 IU/L)		
n (%)	8 (27)	7 (24)
Median IU/L	422,500	246,285

Note. ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus.

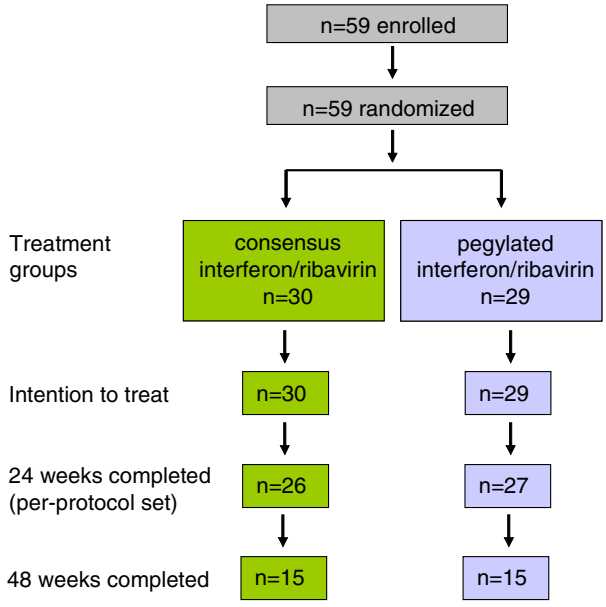

Fig. 1 Flow diagram of subject progress

included alcohol recidivism, elective surgery, pyelonephritis, and psychosis.

Virologic response

Table 2 shows the virologic response for the ITT population at weeks 12, 24, 48, and 72, both for the overall population and stratified by baseline viral load. Table 3 shows the virologic response as assessed by PP analysis. Virologic response rates in both groups peaked at week 24. There was no statistically significant difference in virologic response between the two treatment groups at any time point in either analysis.

Table 4 shows a subgroup analysis of the ITT population SVR rates by gender, ethnicity, and baseline weight. Overall, female patients had a higher SVR rate than male patients, and non-African-Americans had a higher SVR rate compared with African-Americans. Patients <75 kg who were treated with consensus interferon/ribavirin had a higher SVR rate than patients ≥ 75 kg; a smaller benefit was observed for patients <75 kg who were treated with pegylated interferon/ribavirin. There were no statistically significant differences in SVR rates between the two treatment groups as stratified by gender, ethnicity, or baseline weight.

Safety

The adverse events occurring during therapy are shown in Table 5. The rates of adverse events were similar for the two treatment groups.

Dose modifications, which ranged from reducing the dose of medication(s) to briefly halting the drug (<2 weeks) until the adverse event was resolved, were required in 11 of 30 (37%) of the patients in the consensus interferon/ribavirin group and 17 of 29 (59%) of the patients in the pegylated interferon/ribavirin group ($P = 0.12$). In approximately 40% of the cases, dose modification required reduction of both interferon and ribavirin.

Table 2 Virologic response rates of the intention-to-treat population: *n* (%)

	Consensus interferon/ribavirin	Pegylated interferon/ribavirin	*P* value[a]
Week 12			
Overall	12/30 (40)	14/29 (48)	0.604
HVL	7/22 (32)	10/22 (45)	0.537
LVL	5/8 (62)	4/7 (57)	1.000
Week 24			
Overall	15/30 (50)	15/29 (52)	1.000
HVL	10/22 (45)	10/22 (45)	1.000
LVL	5/8 (62)	5/7 (71)	1.000
Week 48			
Overall	11/30 (37)	15/29 (59)	0.299
HVL	6/22 (27)	10/22 (45)	0.347
LVL	5/8 (62)	5/7 (71)	1.000
Week 72			
Overall	11/30 (37)	12/29 (41)	0.792
HVL	6/22 (27)	8/22 (36)	0.747
LVL	5/8 (62)	4/7 (57)	1.000

Note. HVL, high viral load at baseline ($\geq$ 850,000 IU/L); LVL, low viral load at baseline ($<$ 850,000 IU/L).

[a]Determined by Mantel–Haenszel chi-square test.

Table 3 Virologic response rates of the per-protocol patient population: *n* (%)

	Consensus interferon/ribavirin	Pegylated interferon/ribavirin	*P* value[a]
Week 12			
Overall	12/26 (46)	14/27 (52)	0.786
HVL	7/19 (37)	10/21 (48)	0.538
LVL	5/7 (71)	4/6 (67)	1.000
Week 24			
Overall	15/26 (58)	15/27 (56)	1.000
HVL	10/19 (53)	10/21 (48)	1.000
LVL	5/7 (71)	5/6 (83)	1.000
Week 48			
Overall	11/26 (42)	15/27 (56)	0.414
HVL	6/19 (32)	10/21 (48)	0.349
LVL	5/7 (71)	5/6 (83)	1.000
Week 72			
Overall	11/26 (42)	12/27 (44)	1.000
HVL	6/19 (32)	8/21 (38)	0.748
LVL	5/7 (71)	4/6 (67)	1.000

Note. HVL, high viral load at baseline ($\geq$ 850,000 IU/L); LVL, low viral load at baseline ($<$ 850,000 IU/L).

[a]Determined by Mantel–Haenszel chi-square test.

Table 4 Sustained viral response by gender, ethnicity, and body weight: *n* (%)

	Consensus interferon/ribavirin	Pegylated interferon/ribavirin	*P* value[a]
Gender			
Male	6/21 (29)	6/19 (32)	1.000
Female	5/9 (56)	6/10 (60)	1.000
Ethnicity			
Non-African-American	9/21 (43)	11/20 (55)	0.538
African-American	2/9 (22)	1/9 (11)	1.000
Baseline weight			
≥ 75kg	6/22 (27)	8/20 (40)	0.515
< 75kg	5/8 (62)	4/9 (44)	0.637

[a]Determined by Mantel–Haenszel chi-square test.

Quality of life assessments

There was a moderate positive correlation between the two scales used to measure depression: the BDI-II and the CES-D ($P = 0.50$). Patients in the pegylated interferon/ribavirin group had a greater increase in depression during treatment as measured by increase in depression score from baseline on both scales than patients in the consensus interferon/ribavirin group, but the difference did not reach statistical significance (BDI-II, 29.5 and 25.7, respectively [$P = 0.376$]; CES-D, 28.6 and 27.4, respectively [$P = 0.0787$]). Figure 2 shows the average depression scores, measured by both scales, over the entire observation period. The differences between treatment groups were not significantly differently at any time point on either measure. Factor analysis by age, gender, weight, or ethnicity did not show any correlation with mental depression.

The level of fatigue during the study, assessed using the FSS, is illustrated in Fig. 3. There were no statistically significant differences in FSS scores between the two treatment groups at any time point.

The HQLQ was used to assess whether there was an effect on the patient's quality of life while on treatment. It was given to all patients at baseline, weeks 12, 24, and 48, and follow-up week 24. A repeated-measures ANOVA revealed no significant differences between treatment groups during the study period on any of the measured dimensions (physical functioning, $P = 0.250$; role physical, $P = 0.836$; bodily pain, $P = 0.60$; general health, $P = 0.743$; vitality, $P = 0.178$; social functioning, $P = 0.594$; role emotional, $P = 0.345$; mental health, $P = 0.984$). Both groups trended to have decreased scores while on treatment and show increases at baseline and follow-up week 24. The treatment groups did not differ statistically on any of 10 dimensions studied at baseline, week 12, week 48, or follow-up week 24. However, a near-significant difference appeared on the dimension of vitality and a significant difference appeared on the dimension of role emotional at week 24. The patients

Table 5 Frequency (%) of adverse events

	Consensus interferon/ribavirin ($n = 30$)	Pegylated interferon/ribavirin ($n = 29$)	*P* value[a]
Expected adverse events			
Overall	100	97	0.492
Flu-like symptoms	100	93	
Headache	63	38	
Mood changes	67	66	
Serious adverse events	10[b]	7[c]	NA
Neutropenia			
Overall	17	35	0.252
<1000	7	10	
<750	13	24	
<500	0	0	
Anemia			
Hemoglobin <10	27	14	0.333
Hemoglobin <8.5	0	0	
Thrombocytopenia			
<75,000	0	7	0.237
<50,000	3	3	1.000

[a]By chi-square test.
[b]Pyelonephritis, alcohol recidivism, and seizures.
[c]Psychosis and cellulitis.

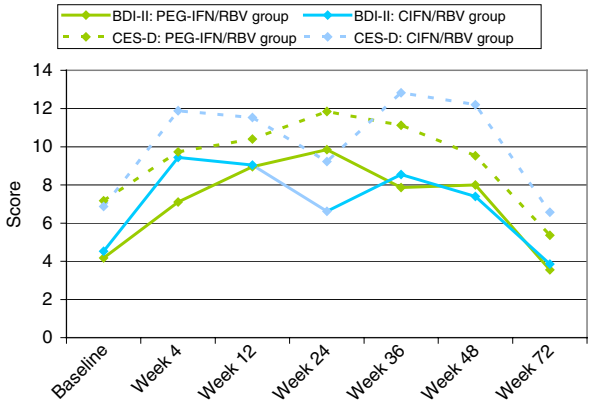

Fig. 2 Mean average depression scores assessed by the Beck Depression Inventory-II (BDI-II) and the Center for Epidemiological Studies Depression Scale (CES-D). CIFN, consensus interferon; PEG-IFN, pegylated interferon; RBV, ribavirin

receiving the consensus interferon/ribavirin showed increased vitality ($P = 0.055$) and fewer work-related problems due to emotional issues ($P = 0.045$) than the patients receiving pegylated interferon/ribavirin.

Discussion

The primary objective of this study was to evaluate the SVR rate and tolerability of consensus interferon and ribavirin compared with pegylated interferon α-2b and ribavirin in patients chronically infected with HCV genotype 1. It has been reported previously that the SVR observed with consensus interferon and ribavirin is similar to those reported in the clinical studies of the pegylated interferons and ribavirin [9]. However, a direct comparison of the two treatment regimens was not performed in those studies. In particular, it is important to compare treatment regimens in similar patient populations. The clinical studies of the pegylated interferons were multinational, and when the United States populations

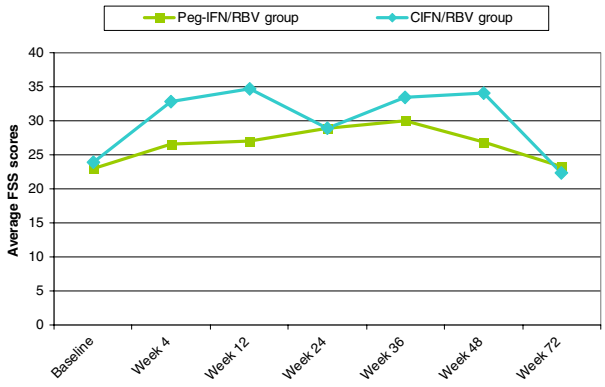

Fig. 3 Mean average visual analogue scores on the fatigue severity scale. CIFN, consensus interferon; PEG-IFN, pegylated interferon; RBV, ribavirin

were analyzed separately, they were shown to have lower overall SVR rates (42%–49%) compared with SVR rates in the total population (54%–56%) [9].

In the present study, ITT analysis showed that 37% of patients in the consensus interferon/ribavirin group achieved an SVR, compared with 41% of patients who received pegylated interferon/ribavirin. Per-protocol analysis showed that 42% of and 44% of patients in the consensus interferon/ribavirin and pegylated interferon/ribavirin groups achieved an SVR, respectively. The difference in SVR rate between the two groups was not statistically significant in either analysis. There was also no significant difference in virologic response between the two treatment groups at any time point. However, a very low relapse rate was observed for patients treated with consensus interferon/ribavirin; the SVR was the same as the end-of-treatment (week 48) virologic response. In contrast, the end-of-treatment virologic response for patients in the pegylated interferon/ribavirin group was not sustained. Low relapse rates for patients treated with consensus interferon/ribavirin have previously been observed both in treatment-naïve patients [9] and in nonresponders to previous therapy with pegylated interferon/ribavirin [19]. The low relapse rates associated with consensus interferon may be related to a particularly effective action during the initial phase of viral decline, since it has been shown that rapid viral elimination is associated with a low incidence of relapse in end-of-treatment virologic responders [20]. The first phase of viral decline is related to interferon α-induced inhibition of HCV replication [21], and preclinical studies have shown that consensus interferon has 10–100 times higher antiviral and antiproliferative activity compared with pegylated and other nonpegylated interferon α molecules [12, 13, 22–24].

The SVR rate for treatment-naïve patients chronically infected with HCV genotype 1 who were treated with consensus interferon/ribavirin in this study is similar to the SVR rate of 44% reported for patients infected with HCV genotype 1 who were treated with consensus interferon/ribavirin in a previous study [9]. The SVR rate for the subgroup of patients with genotype 1 HCV and a high viral load is lower than that reported in the previous study, but this may be because of differences in baseline characteristics between the two study populations. In particular, patients in the present study had a median baseline viral load that was approximately double that in the earlier study.

In addition to high baseline viral load, male gender, African-American ethnicity, and higher baseline body weight were associated with lower SVR rates. This is consistent with other studies of interferon-based therapies in treatment-naïve patients [5–8]. However, subgroup analysis identified no differences in virologic response between the two treatment groups.

Dosing of consensus interferon was three times weekly in this study. Daily dosing is available for more difficult-to-treat

patients, i.e., nonresponders. It has recently been shown that daily administration of consensus interferon is associated with higher SVR rates in treatment-naïve patients than three-times-weekly consensus interferon, which suggests that daily administration of consensus interferon may also be more effective for difficult-to-treat patients, such as those infected with genotype 1 HCV. Further study in this area is warranted.

The two treatment regimens had similar safety profiles, and no significant differences in adverse events were observed between the treatment groups. The most frequently observed adverse events, experienced by the majority of patients in both treatment groups, were flu-like symptoms, headache, and mood changes. Although dose modifications were necessary in a larger proportion of patients in the pegylated interferon/ribavirin group than in the consensus interferon/ribavirin group (59% versus 37%, respectively), this difference did not reach statistical significance.

Depression and fatigue are frequently reported side effects of interferon treatment [25] and can impair quality of life and reduce patient adherence to treatment. A secondary objective of this study was to determine the most appropriate tools to measure depression, fatigue, and quality of life in HCV-infected patients and to assess whether any differences were observed between the two treatment groups. Four scales were used to measure depression, fatigue, and quality of life, including two depression scales with different properties. The BDI-II is regarded as the gold standard and is one of the most widely used depression inventories, whereas the CES-D includes items that can differentiate somatic symptoms of depression from other symptoms of depression. The other two scales employed were the FSS, which was designed to differentiate fatigue from clinical depression, and the HQLQ, which provides a measure of functional disability and quality of life.

An increase in depression during therapy was observed in both groups using the BDI-II and CES-D scales. However, scores decreased after completion of therapy (to below baseline values at week 24 follow-up). Patients treated with pegylated interferon/ribavirin trended to report more depression, measured on both scales, than patients treated with the consensus interferon/ribavirin, but this did not reach statistical significance.

Fatigue is the most common side effect associated with interferon-based therapies [26]. An increase in the level of fatigue was observed in both treatment groups in this study. The mean FSS visual analogue scale score ranged from 23 to 35, which is lower than that reported for chronically ill populations but higher than that for normal healthy adults [27]. However, scores returned to baseline values following completion of therapy. There was no significant difference in fatigue levels between patients receiving consensus interferon/ribavirin and those receiving pegylated interferon/ribavirin.

Interferon-based therapies often cause many adverse side effects which can also contribute to a decrement of quality of life. The scores on the HQLQ were similar for both treatment groups on all dimensions, with higher scores (reflecting improved quality of life) at baseline and follow-up week 24 (after cessation of therapy) and lower scores (indicating poorer quality of life) at weeks 12, 24, and 48. These results are not surprising, as the lower scores are reported while the patients are on therapy. The two differences that were revealed on the dimensions of vitality and role emotional at week 24 allow for speculation. These findings correspond with the results for both the depression and fatigue scales. Subjects receiving consensus interferon reported lesser increases in depression, which is likely to correlate with fewer work-related problems due to emotional issues (role emotional). Similarly, the drop in fatigue at week 24 for those subjects receiving consensus interferon may be linked to the increased vitality at the same time point.

In conclusion, the results of this study show that therapy with three-times-weekly consensus interferon/ribavirin is safe and gives a similar antiviral response to pegylated interferon/ribavirin in patients chronically infected with HCV genotype 1. Furthermore, it is possible that if consensus interferon is administered daily rather than three times weekly, eradication of HCV can be achieved in a larger proportion of patients infected with HCV genotype 1.

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