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ORIGINAL PAPER

Consensus Interferon and Ribavirin in Patients with Chronic Hepatitis C Who Were Nonresponders to Pegylated Interferon alfa-2b and Ribavirin

Carroll B. Leevy

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Abstract Recent studies suggest that consensus interferon and ribavirin is effective in retreating patients with chronic hepatitis C who failed therapy with interferon alfa and ribavirin. The objective of the present study was to assess the efficacy, safety, and tolerability of consensus interferon and ribavirin in patients who did not respond to pegylated interferon alfa-2b and ribavirin. We retrospectively identified 137 consecutive nonresponders to pegylated interferon alfa-2b and ribavirin and initiated patients on daily treatment with consensus interferon 15 μg subcutaneously and weight-based ribavirin for 48 weeks. If patients were HCV RNA negative at 12 weeks, the dose was reduced to 15 μg three times weekly for the remaining 36 weeks. The sustained virologic response rate was 37%. Daily consensus interferon therapy was safe and well tolerated in all patients. No dose reductions were required, and no patient discontinued therapy. Further studies of consensus interferon and ribavirin in nonresponders are warranted.

Keywords Chronic hepatitis C · Nonresponders · Consensus interferon · Pegylated interferon · Treatment failure · African-American · Clinical trial

Introduction

The majority of treatment-naïve patients with hepatitis C virus (HCV) infection are treated with pegylated interferon alfa (peg-IFN) in combination with ribavirin [1]. However, a significant proportion of patients will fail on this therapy or be unable to tolerate it, and about half will not achieve a sustained virologic response (SVR) [2, 3]. SVR rates are even lower in "difficult-to-treat" patients, such as those with genotype 1 HCV infection [2, 3], high baseline viral load [4], or HIV coinfection [5–7]. African-American ancestry is also an important cause of IFN treatment failure [8–10]. A study in 196 African-American and 205 Caucasian patients infected with HCV genotype 1 showed that initial therapy with peg-IFN alfa-2a (180 mcg/wk) and ribavirin for 48 weeks produced a significantly lower SVR rate among the African-American patients (28% vs 52%; $P < 0.0001$) [10].

Patients who fail to respond to therapy are a growing public health concern. Nonresponders have a significantly higher incidence of cirrhosis and hepatocellular carcinoma [11, 12], and hepatitis C-related liver disease is associated with a substantial health and economic burden [1, 13]. An estimated 166,000 deaths will occur from HCV-related chronic liver disease and 27,000 deaths from hepatocellular carcinoma from the year 2010 through 2019, costing more than US$10 billion in direct medical expenses [14].

Nonresponse to therapy is often predictable early in the course of therapy. In a pivotal study by Fried et al. [2], patients with a less than 2 $\log_{10}$ drop in HCV RNA at treatment week 12 had only a 3% SVR rate, while those with a greater than 2 $\log_{10}$ drop had a 65% SVR rate. Prompt detection of viral response at week 12 is therefore essential to allow an expedient switch to an alternative therapy when appropriate.

Consensus interferon (CIFN) is a genetically engineered molecule developed by assigning the most commonly observed amino acids of natural IFN alfa subtypes to develop a novel "consensus" IFN [15]. CIFN has shown

C. B. Leevy (✉)
Department of Medicine, Division of Gastroenterology/Hepatology, University of Medicine & Dentistry of New Jersey, New Jersey Medical School Liver Center, 185 South Orange Ave, Newark, NJ 07103, USA
e-mail: leevycb@umdnj.edu

higher biologic activity than naturally occurring type 1 IFNs [15]. Compared with IFN alfa-2a and alfa-2b on a mass basis, CIFN exhibits higher antiviral, antiproliferative, and natural killer cell activation activity [15]. CIFN was reported to produce up to 3 $\log_{10}$ greater activity than the peg-IFNs [15–17]. Retreatment with peg-IFN and ribavirin in nonresponders to IFN or peg-IFN and ribavirin is effective in only 3–12% of patients [18–24]. In contrast, therapy with CIFN has been effective in 23–30% of the IFN and ribavirin nonresponders [25–28]. Data are now pending from a large phase 3 registration trial [DIRECT trial (Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy trial)] of the safety and efficacy of daily CIFN in combination with ribavirin in retreating peg-IFN and ribavirin nonresponders.

In the current study, we investigate the efficacy and safety of CIFN for the retreatment of patients who failed to respond to therapy with peg-IFN alfa-2b and ribavirin, and specifically whether SVR rates might be increased by switching patients being treated with peg-IFN alfa-2b and ribavirin who failed to achieve at least 2 $\log_{10}$ reductions at week 12 to CIFN. We also examined whether several baseline characteristics—sex, age, body weight, race, HCV genotype, viral load, and liver histology—were significantly associated with SVR.

Methods

Patient selection

Adult patients who had previously received peg-IFN alfa-2b 1.5 μg/kg subcutaneously once weekly and weight-based oral ribavirin daily, and did not have a decline in HCV RNA concentrations of at least 2 $\log_{10}$ after 12 weeks of therapy, were eligible for this study. Since this study was retrospective, patients did not need to provide written consent.

Study design

This investigation was an open-label, retrospective study (Fig. 1). With no washout period, patients started treatment with subcutaneous CIFN 15 μg daily and oral daily ribavirin (1,000 mg for patients weighing <75 kg, and 1,200 mg for patients weighing >75 kg). HCV RNA levels were assessed at weeks 12, 24, 48, and 72. Serum HCV levels were measured at Quest Diagnostics Incorporated, Laboratory Corporation of America, and the New Jersey Medical School University laboratory; the sensitivity of the quantitative polymerase chain reaction assay used was 99%. HCV viral load levels were measured using Roche Monitor Assay Version 2.0.

If patients were HCV RNA negative at 12 weeks, the dose of CIFN was reduced to 15 μg three times weekly for a further 36 weeks. Patients with a greater than 2 $\log_{10}$ decrease in HCV RNA were continued on daily CIFN/ribavirin for 36 weeks; treatment was discontinued in patients with a less than 2 $\log_{10}$ decrease in HCV RNA. All patients were followed for 24 weeks after completion of treatment. Patients were provided with the appropriate medication instructions and obtained the study drugs through private pharmacies or other independent providers as dictated by their individual insurance companies.

Assessment of efficacy

The primary measure of efficacy was the rate of SVR, defined as undetectable HCV RNA in serum at the end of the 24-week follow-up period.

Assessment of safety

Safety was assessed by laboratory test results and by evaluation of adverse events, which was done once a

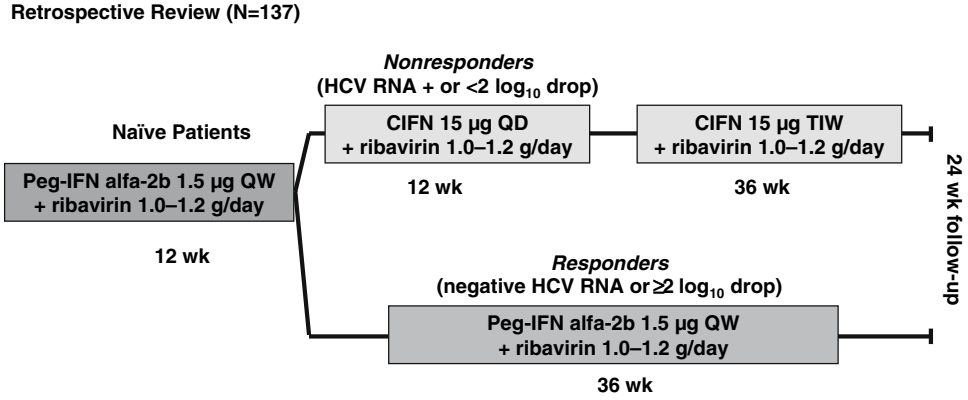

Fig. 1 Study design

month. Biochemical and hematologic testing was performed by Quest Diagnostics Incorporated, Laboratory Corporation of America, and New Jersey Medical School laboratory.

Statistical analysis

Statistical analyses were performed using the Mantel-Haenszel chi-square test.

Results

Patient characteristics

The study included 137 consecutive patients who were eligible for treatment. In total, 92% of patients were HCV genotype 1, with an average baseline viral load of 3.3 ± 0.4 million copies/ml before peg-IFN therapy and 1.6 ± 0.2 million copies/ml before CIFN therapy. The study population was 57% male and had an average weight of 78 kg. About one-third of patients were of African-American descent. Further baseline characteristics of the patients are described in Table 1.

Prior response to Peg-IFN treatment

In accordance with the protocol, all patients in this study showed a less than 2 $\log_{10}$ reduction of HCV RNA after 12 weeks of treatment with peg-IFN and ribavirin. Several patients showed reductions of 0.5–1.0 $\log_{10}$ in response to the initial therapy. While technically treatment failures, these patients were considered to be sensitive to peg-IFN therapy.

Virologic response

An SVR was observed in 37% of nonresponders to previous therapy with peg-IFN and ribavirin after retreatment with CIFN and ribavirin, with an end-of-treatment (week 48) response observed in 43% of patients (Fig. 2). Notably, the number of patients who became HCV RNA negative over the treatment duration continued to increase from week 12 to 48. The overall relapse rate in this study was 14%.

Table 1 Baseline patient characteristics

Characteristic	Value
Sex	57% male; 43% female
Age	48 years
Weight	78 kg
Race	33% African-American; 67% other
HCV genotype 1	92%
Viral load before peg-IFN therapy	3.3 million copies/ml ± 0.4
Viral load before CIFN therapy	1.6 million copies/ml ± 0.2

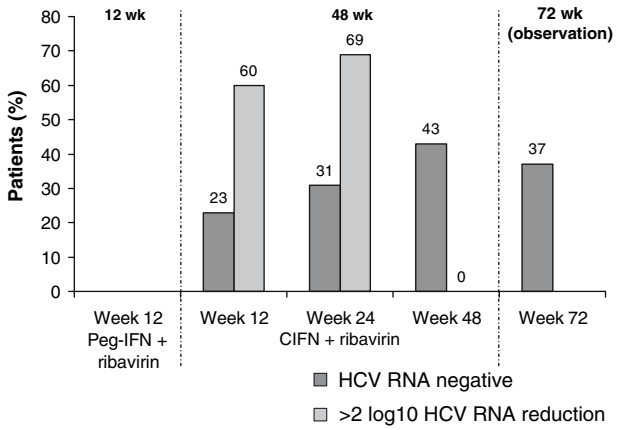

Fig. 2 Log_{10} change in HCV RNA after therapy with peg-IFN alfa-2b and ribavirin (12 weeks) by response to therapy with CIFN and ribavirin ($n = 137$ at all time points)

Effect of prior treatment response on SVR rates

The extent of the prior treatment response had a direct effect on response to subsequent retreatment with CIFN (Fig. 3). Patients who had an SVR to CIFN had shown significantly greater reductions in HCV RNA after the 12 weeks of previous peg-IFN alfa-2b and ribavirin therapy ($P < 0.01$, chi square) compared with patients who did not have an SVR.

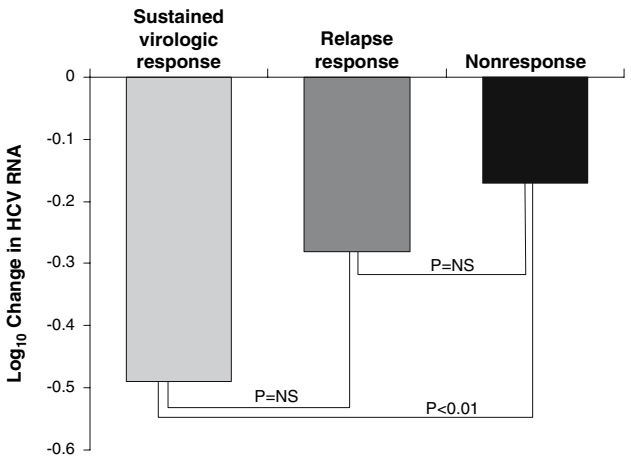

Fig. 3 Change in HCV RNA levels following treatment with peg-IFN alfa-2b and ribavirin stratified by subsequent response to CIFN and ribavirin

There were no significant differences in $\log_{10}$ response to prior peg-IFN-based therapy between patients who showed an SVR to retreatment with CIFN and those who relapsed after retreatment. There were also no significant differences between patients who relapsed and those who did not respond. These effects were independent of ethnic group (Table 2).

Effect of demographic variables

Patients not of African-American ethnicity were significantly more likely to achieve an SVR than African-American patients (41 vs 27%; $P < 0.09$) and were more likely to be HCV RNA negative at all time points investigated (Fig. 4). Increases in duration of treatment were correlated to increases in HCV RNA viral negativity independent of race throughout the treatment interval.

Safety

Although 46.7% of patients reported flulike symptoms, therapy was generally well tolerated in all patients. No patient discontinued therapy. Mean hematocrit values decreased from 42.3 at baseline to 37.8 at week 48 (end of treatment).

The median platelet counts remained close to baseline throughout treatment. The median white blood cell counts decreased from 6.88 $\times$ 10^9/l at baseline to 2.25 $\times$ 10^9/l at week 48. Twenty-two patients (16%) had an absolute neutrophil count drop below 0.75 $\times$ 10^9/l and were treated with granulocyte colony-stimulating factor 300 μg weekly.

Discussion

Peg-IFN in combination with ribavirin is now the standard treatment for HCV infection [1]. However, approximately

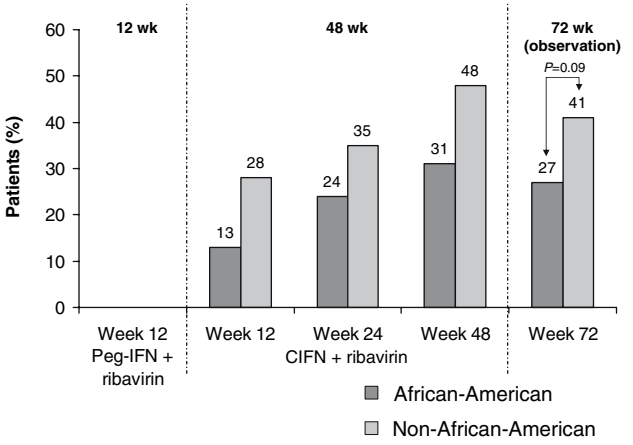

Fig. 4 Percentage of nonresponders to pegylated IFN/ribavirin who were HCV RNA negative following retreatment with CIFN/ribavirin by ethnic group ($n = 137$ at all time points) [30]

half of all HCV-infected patients do not achieve an SVR following this therapy [2, 3]. There are few options currently available for patients with chronic hepatitis C who have failed to respond to therapy with peg-IFN and ribavirin. Clinical development programs researching the protease inhibitor and polymerase inhibitor drug classes as options in the treatment of HCV nonresponder patients remain in the distant future. Furthermore, retreatment with the same regimen would not be expected to provide benefit, as it has been shown that retreatment of nonresponders to IFN and ribavirin with peg-IFN and ribavirin is effective in only 4–12% of patients [18–23]. In a recent study, peg-IFN alfa-2a was shown to produce an SVR rate of only 3% in 34 nonresponders to prior peg-IFN and ribavirin-treated patients [24]. These results are surprising because there is very little difference between the IFN alfa-2a and IFN alfa-2b molecules [15, 31]. However, only a small number of patients were involved and the results await confirmation from larger studies.

Previous studies have demonstrated that the combination of CIFN and ribavirin is effective in retreating patients with chronic hepatitis C who failed to respond to IFN and

Table 2 Comparison of baseline characteristics by ethnic group ($n = 137$) [29]

	African-American ($n = 45$)	Non-African American ($n = 92$)	P-value
HCV genotype 1 (n (%))	42 (93)	84 (91)	NS[a]
$\log_{10}$ baseline viral load (copies/ml ± SD)	6.2 ± 0.5	6.2 ± 0.47	NS[b]
$\log_{10}$ viral load before CIFN (copies/ml ± SD)	5.9 ± 0.4	5.9 ± 0.7	NS[b]
Age (year ± SD)	47 ± 8	47 ± 10	NS[b]
Sex	27 males; 18 females	49 males; 41 females	NS[a]

NS, not significant; SD, standard deviation

[a] Chi-squared test

[b] Student t-test

ribavirin, with SVR rates of 23–30% being reported [25–28]. The results of this study demonstrate that the combination of CIFN and ribavirin is also effective for the retreatment of patients who failed to respond to therapy with peg-IFN. An SVR was observed in 37% of nonresponders to previous therapy with peg-IFN and ribavirin after retreatment with CIFN and ribavirin, with an end-of-treatment response observed in 42% of patients. In this study, the impact of treatment duration with CIFN and ribavirin and viral negativity was positively correlated to week 48, suggesting that the 12-week stopping rule may not apply in the treatment of nonresponder patients with CIFN.

Patients who had an SVR after retreatment with CIFN had significantly greater reductions in HCV RNA after therapy with peg-IFN and ribavirin compared with patients who did not achieve an SVR with CIFN. This is consistent with studies showing that high viral load at baseline is considered a negative prognostic factor [4], and suggests that a more potent treatment regimen may be required to achieve an SVR.

Consistent with previous studies [8], patients not of African-American descent were significantly more likely to achieve an SVR compared with African-Americans and were more likely to be HCV RNA negative at all time points investigated. SVR rates in nonresponding African-American patients retreated with peg-IFN have not been reported. However, SVR rates of 19–26% were observed in treatment-naïve African-American patients after therapy with peg-IFN and ribavirin compared with 39–52% for non-African Americans [8, 9]. The SVR rate of 27% observed for nonresponding African-American patients retreated with CIFN in the present study is likely to be lower than that which would be seen in treatment-naïve patients, and the use of CIFN therapy in treatment-naïve African-American patients warrants further investigation.

A unique feature of CIFN is that, unlike the peg-IFNs, it requires daily dosing. This potential inconvenience must be weighed against the benefit of the significantly higher SVR rates observed in nonresponders in both the present study and in others [25–27, 32]. As in another recent study of CIFN using daily dosing, the current trial showed that a daily regimen of CIFN was safe and well tolerated in all patients. A possible explanation for this finding was that patients were switched quickly from once-daily to three-times-weekly dosing upon entering this study. No dose reductions were required, and no patient discontinued therapy. In contrast, in clinical trials of peg-IFN, adverse events prompted dose reduction in 32–42% and therapy discontinuation in 10–14% of patients [2, 3]. The improved tolerance to CIFN may be partly due to patients in the present study being better able to tolerate IFN-related side effects, having experienced these during their previous therapy. However, the majority of patients reported that they preferred daily-dose CIFN over their previous therapy of peg-IFN.

In conclusion, the findings of this study suggest that the combination of CIFN and ribavirin is an effective, safe, and well-tolerated therapy for patients who do not respond to treatment with peg-IFN and ribavirin. Further studies on the use of CIFN to treat nonresponders are warranted.

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