Retreating Chronic Hepatitis C with Daily Interferon Alfacon-1/Ribavirin After Nonresponse to Pegylated Interferon/Ribavirin: DIRECT Results

Bruce R. Bacon,[1] Mitchell L. Shiffman,[2] Flavia Mendes,[3] Reem Ghalib,[4] Tarek Hassanein,[5] Giuseppe Morelli,[6] Shobha Joshi,[7] Kenneth Rothstein,[8] Paul Kwo,[9] and Norman Gitlin[10]

Up to 50% of patients with chronic hepatitis C fail to respond to initial therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV). With unsuccessful viral eradication, these patients remain at risk for developing progression of their liver disease. Retreatment with PEG-IFN/RBV yields sustained virologic response (SVR) rates that are under 10%. A wholly synthetic interferon, interferon alfacon-1 or consensus interferon (CIFN) given with RBV, was evaluated in patients who failed initial PEG-IFN/RBV therapy. The intent-to-treat analysis included 487 patients; 245 received CIFN 9 μg/day and RBV, and 242 received CIFN 15 μg/day and RBV. Within this group of patients, 59.3% had documented advanced fibrosis at baseline liver biopsy (stage F3 or F4). SVR rates were 6.9% (17/245 patients) in the 9 μg group and 10.7% (26/242) in the 15 μg group. In the intent-to-treat analysis, SVR rates were higher among patients with a >2-$\log_{10}$ decrease in hepatitis C virus RNA during prior PEG-IFN/RBV therapy: 11% (4/38) in the 9 μg group and 23% (7/31) in the 15 μg group. Among patients with lower baseline fibrosis scores (F0-F3), SVR rates were 7.8% (15/192) in the 9 μg group and 13.1% (23/175) in the 15 μg group. In this same group of patients (F0-F3), if a >2-$\log_{10}$ decrease in hepatitis C virus RNA with previous PEG-IFN/RBV treatment was achieved, SVR rates improved to 10.7% and 31.6% in the 9 μg and 15 μg groups, respectively. CIFN/RBV combination retreatment was safe and well tolerated. *Conclusion:* Retreatment of PEG-IFN and RBV nonresponders with CIFN and RBV is safe and efficacious and can be considered a retreatment strategy for patients failing previous therapy with PEG-IFN/RBV, especially in interferon-sensitive patients with lower baseline fibrosis scores. (HEPATOLOGY 2009;49:1838-1846.)

Since 2001, the standard of care for patients with chronic hepatitis C has been the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV).[1,2] This combination has produced sustained virologic response (SVR) rates of 50%-60% in patients infected with hepatitis C virus (HCV) genotype 1 who adhere to their therapeutic regimens and 40% in intention-to-treat populations.[1,2] However, because only about 65% of patients become HCV RNA–undetectable when treated with this regimen, more than one-third of all patients are classified as nonresponders. Some of these patients have relatively mild liver disease but may have symptoms of HCV viremia, while other patients have advanced fibrosis and are at risk for developing complica-

Abbreviations: AE, adverse event; bDNA, branched DNA; CIFN, consensus interferon; DIRECT, Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy; Hb, hemoglobin; HCV, hepatitis C virus; ITT, intention to treat; PEG-IFN, pegylated interferon; RBV, ribavirin; REPEAT, REtreatment with PEgasys in PATients Not Responding to Peg-Intron Therapy; SVR, sustained virologic response; TMA, transcription-mediated amplification.

From the [1]Saint Louis University Liver Center, Saint Louis University School of Medicine, St. Louis, MO; the [2]Hepatology Section, Virginia Commonwealth University Medical Center, Richmond, VA; the [3]Division of Hepatology, University of Miami Miller School of Medicine, Miami, FL; the [4]Liver Institute at Methodist Hospital, Dallas, TX; the [5]Division of Gastroenterology and Hepatology, University of California San Diego, San Diego, CA; the [6]Division of Gastroenterology and Hepatology, University of Florida, Gainesville, FL; the [7]Division of Gastroenterology and Hepatology, Tulane University Hospital and Clinic, New Orleans, LA; the [8]Albert Einstein Center for Liver Disease, Philadelphia, PA; the [9]Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN; and the [10]Division of Gastroenterology and Hepatology, Emory Crawford Long Hospital, Atlanta, GA.

Received August 21, 2008; accepted January 24, 2009.

Sponsored by InterMune, Inc., and Valeant Pharmaceuticals International. Support for the study publication was provided by Three Rivers Pharmaceuticals.

Address reprint requests to: Bruce R. Bacon, M.D., Division of Gastroenterology and Hepatology, Saint Louis University School of Medicine, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110-0250. E-mail: baconbr@slu.edu; fax: 314-577-8125.

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.22871

Potential conflict of interest: See Disclosures section at end of article.

tions of chronic liver disease, including decompensated cirrhosis and hepatocellular carcinoma, and may require liver transplantation.[3-5]

The optimal approach to PEG-IFN/RBV nonresponders has not been well defined. Some clinicians have used the "watchful waiting" approach[6] and are anticipating new antiviral therapies with either protease inhibitors or polymerase inhibitors. However, it remains to be determined just how effective these new agents will be when combined with PEG-IFN and RBV in the retreatment of PEG-IFN/RBV nonresponders.[7]

Alternative therapies have included retreatment with the alternative brand of PEG-IFN not used in the initial therapy, although most results with this approach have been disappointing. Other approaches have included prolonged treatment with PEG-IFN, maintenance therapy, or the use of higher dosages of either PEG-IFN and/or RBV.[8-12] The strategy studied in the current investigation included high doses of daily consensus interferon (CIFN) (Infergen; interferon alfacon-1) 9 or 15 μg/day given with RBV.

Patients and Methods

This study, referred to as the DIRECT (Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy) trial, was designed by the sponsor and by several of the academic investigators. The data were managed by the sponsor and the academic investigators. The sponsor performed the statistical analysis. The academic investigators were responsible for the development of the final manuscript and had unrestricted access to the data. An author involved with the design or execution of this study either wrote or edited every section of the manuscript. Both an academic author (B. R. B.) and an industry representative (Michael Beckloff, Three Rivers Pharmaceuticals, Cranberry Township, PA) attest to the completeness and accuracy of the data.

Study Design. This was a phase 3, randomized, open-label, multicenter, U.S.-based registration trial conducted to investigate the efficacy, tolerability, and safety of daily CIFN at dosages of 9 and 15 μg/day (interferon alfacon-1, Infergen; Three Rivers Pharmaceuticals, LLC, Cranberry Township, PA) administered with daily RBV (Ribasphere, Three Rivers Pharmaceuticals, LLC) compared with no treatment in patients who did not respond to prior therapy with either PEG-IFN alfa-2a or alfa-2b and RBV. The trial was divided into 2 sections: DIRECT-001 and DIRECT-002 (Fig. 1).

Patients were randomized at a 1:1:1 ratio into three study groups: CIFN 9 μg/day (group 1), 15 μg/day (group 2) plus oral RBV 1,000-1,200 mg/day (based on body weight), or a control, no-treatment group (group 3).

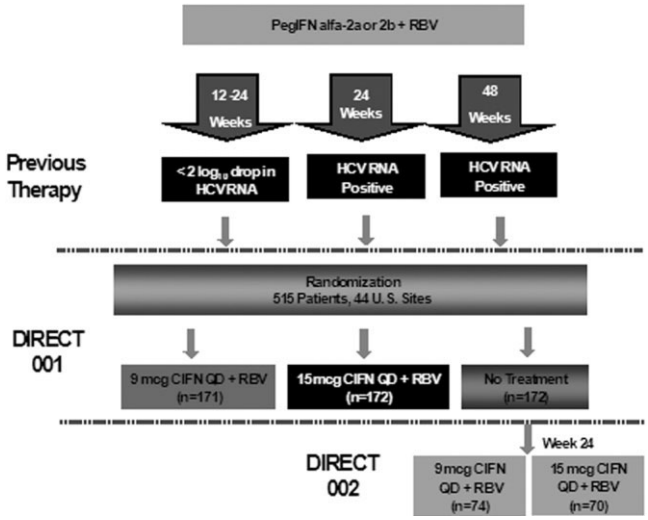

Fig. 1. DIRECT study design: a randomized, open-label study of CIFN and RBV in patients who did not respond to previous combination therapy with PEG-IFN and ribavirin.

The no-treatment group was mandated by the U.S. Food and Drug Administration in order to provide a comparison of safety for the two treatment groups. It was not anticipated that any of the patients randomized to the control group would have a spontaneous response. After 24 weeks of observation, all patients in the control group of DIRECT-001 were offered randomization into DIRECT-002 to receive CIFN 9 or 15 μg/day plus RBV.

At week 24, patients who had undetectable plasma HCV RNA by branched DNA (bDNA) assay, confirmed by transcription-mediated amplification (TMA) assay, or who had a $\geq$2-log$_{10}$ decrease from baseline in HCV RNA were assigned to continue therapy to week 48. Patients with a $<$2-log$_{10}$ decrease from baseline in plasma HCV RNA (bDNA assay) were considered nonresponders and were withdrawn from treatment. At week 48, patients with undetectable plasma HCV RNA (by bDNA and TMA assays) were assigned to return for regular visits in the follow-up period (weeks 52, 60, 68, and 72) until 24 weeks after their last dose of study drug (week 72). Patients with detectable plasma HCV RNA (bDNA or TMA assay) at any time between weeks 48 and 72 were classified as relapsers.

All patients who discontinued therapy early at any time were instructed to return for a single follow-up visit 30 days after their last dose of study drug to complete early termination/discontinuation assessments. Patients who had undetectable plasma HCV RNA by bDNA and TMA assays at the time of stopping therapy or at the early termination/discontinuation visit were to return for follow-up plasma HCV RNA assessments through week 72, as long as their plasma HCV RNA levels remained unde-

tectable by both bDNA and TMA assays. Patients who discontinued for nonresponse at weeks 12 or 24 did not undergo a follow-up HCV RNA measurement.

Patients in the no-treatment group in DIRECT-001 were given the option to enroll in DIRECT-002 under the following conditions: if they achieved a $<2\text{-log}_{10}$ decrease in plasma HCV RNA at week 24 compared with baseline or if they had detectable plasma HCV RNA by bDNA or by TMA at week 48. These patients were then treated according to the same protocol followed in DIRECT-001. The results of DIRECT-001 and DIRECT-002 were pooled for the purpose of this analysis.

Patients. Men and women were eligible for enrollment if they were chronically infected with HCV of any genotype. Chronic infection was identified based on a history of being positive for serum anti-HCV and/or HCV RNA. A liver biopsy performed within 3 years of screening must have demonstrated evidence of chronic HCV infection. Hepatic fibrosis was interpreted by local pathologists based upon the Metavir scoring system. Patients with advanced liver disease, including bridging fibrosis (F3) and cirrhosis (F4), were eligible for the study as long as they had normal liver function as evidenced by serum albumin >3.5 mg/dL, platelet count $>75{,}000/\text{mm}^3$, and no prior episode of hepatic decompensation (variceal hemorrhage, hepatic encephalopathy, ascites, or hepatocellular carcinoma).

Prior nonresponse and adherence after initial therapy with PEG-IFN alfa-2a (180 μg/week) or PEG-IFN alfa-2b (1.5 μg/kg/week) plus RBV was determined via careful chart review completed by the study site principal investigator and confirmed by an external study monitor. Nonresponders had to have had a $<2\text{-log}_{10}$ decrease in HCV RNA between weeks 12 and 24 or detectable HCV RNA at weeks 24 or 48. Patients were required to have had completed a minimum of 90 days between discontinuation of their prior regimen and the start of the current study medication. All patients had to have received at least 80% of the cumulative standard dosages of PEG-IFN and RBV for at least 38 weeks (80% of the planned treatment duration). Patients were excluded if this previous treatment was prematurely discontinued, dosing was interrupted, or if the dose of PEG-IFN was reduced because of noncompliance, safety, or tolerability issues (including hematologic or psychiatric side effects).

Patients were also excluded if they were pregnant or lactating women or male partners of pregnant women, or if they were not suitable candidates for enrollment or unlikely to comply with the requirements of the study in the opinion of the investigator or sponsor.

Treatment and Assessments. Screening took place between 8 weeks and 1 day before the first day of treatment. After providing informed consent, patients were screened for inclusion criteria, underwent a physical examination, provided a baseline medical history, and had blood drawn for laboratory testing. After screening, eligible patients were randomized in a 1:1:1 ratio to receive CIFN 9 or 15 μg/day plus RBV 1,000 mg/day (body weight <75 kg) or 1,200 mg/day (body weight >75 kg) or no treatment (Fig. 1). RBV was provided as capsules containing 200 mg of active drug. An independent data monitoring committee conducted regular interim safety assessments throughout the study.

Plasma HCV RNA levels were determined first using the bDNA quantitative assay, which has a sensitivity of detection of 615 IU/mL and a reportable range of 615 to 6,920,000 IU/mL. The Bayer TMA assay, with a sensitivity of detection of 5 IU/mL, was used whenever HCV RNA levels were undetectable via bDNA assay.

Patients developing anemia, defined as hemoglobin (Hb) <10 g/dL, were managed by reducing the dose of RBV to 600 mg/day. The use of growth factors was not permitted. If the Hb increased to >10 g/dL, the RBV dose could be increased in 200-mg/day increments as tolerated according to the discretion of the site principal investigator. RBV dose was not increased after being reduced to 600 mg/day for patients with a history of cardiovascular disease whose Hb decreased by 2 g/dL or more during any 4-week period. RBV was permanently discontinued in patients whose Hb dropped below 8.5 g/dL. In those patients with a history of cardiac or cerebrovascular disease, Hb remaining below 12 g/dL after 4 weeks on a reduced dose required permanent discontinuation of RBV. Neutropenia was managed by CIFN dose reduction; in patients whose absolute neutrophil count fell to $<0.75 \times 10^9$/L, starting doses of 15 μg were lowered to 9 μg and then to 6 μg, and starting doses of 9 μg were lowered to 6 μg.

Efficacy Variables. The primary efficacy variable was the proportion of patients with SVR, defined as undetectable plasma HCV RNA by both bDNA and TMA assays at 24 weeks after the last dose of study drug. In addition, SVR was further explored for the effect of race, genotype, sex, age, baseline HCV RNA, presence/absence of cirrhosis, body weight, and previous response to PEG-IFN/RBV.

Safety and Tolerability. All adverse events (AEs) and serious AEs were recorded for patients who received at least 1 dose of study medication (active-treatment groups) or who completed baseline assessments (no-treatment group). AEs were recorded until either 30 days after the last dose of study medication (active-treatment groups) or until the last study visit (no-treatment group). AEs were graded from 1 to 5 (1, mild; 2, moderate; 3, severe; 4,

life-threatening or disabling; 5, death) based on the Common Toxicity Criteria for Adverse Events v3.0. An AE was considered a serious AE if it resulted in death, was life-threatening, required inpatient hospitalization, or resulted in persistent or significant disability or incapacity.

Statistical Methods. At least 170 patients were needed in each of the three study groups (for a total of 510 patients) to provide an approximately 91% power to detect a difference in SVR between each of the active treatment groups and the no-treatment group. This analysis was performed using a two-sided Fisher's exact test at $\alpha = 0.05$ significance level, with adjustment for multiple comparisons, and assumed an SVR rate of 10% for either of the active treatment groups and 1.2% for the no-treatment group. The study was not powered to detect differences between the 9 μg and the 15 μg arms.

Data were summarized and analyzed for two patient populations: the intention-to-treat (ITT) population and patients who did not receive any dose modifications. The ITT group consisted of all patients who were randomized to receive CIFN in DIRECT-001, as well as all patients from the no-treatment group in DIRECT-001 who went on to receive at least 1 dose of CIFN in DIRECT-002. Data from the ITT population were used in all efficacy and safety analyses.

Descriptive statistics were determined for continuous variables (patient counts, mean, standard deviation, median, minimum, and maximum) and categorical variables (number and percentage of patients for each category). Percentages were calculated using the number of patients without missing data as the denominator unless otherwise indicated. Calculations of virologic response (both sustained and at specific visits) used the number of ITT patients as the denominator. All statistical testing was conducted at the 0.05 level of significance using SAS software, version 8.2.

Results

Patients and Disposition. Five hundred fifteen patients were randomized at 44 sites in the United States and Puerto Rico to receive CIFN 9 μg/day plus RBV 1,000 or 1,200 mg/day (n = 171), CIFN 15 μg/day plus RBV (n = 172), or no treatment (n = 172). Of the 172 patients in the no-treatment group in DIRECT-001, 144 continued on to DIRECT-002. Of these, 74 received CIFN 9 μg/day plus RBV 1,000 or 1,200 mg/day, and 70 received CIFN 15 μg/day plus RBV 1,000 or 1,200 mg/day. The final ITT population included 487 patients (245 who received CIFN 9 μg/day and 242 who received CIFN 15 μg/day).

Table 1. DIRECT-001 and DIRECT-002: Baseline Characteristics

	CIFN 9 μg/day + RBV (n = 245)	CIFN 15 μg/day + RBV (n = 242)
Mean age ± SD, years	51 ± 6.65	50 ± 6.59
Male	68%	72%
HCV genotype 1	95%	96%
High viral load ≥850,000 IU/mL	68%	68%
Mean weight ± SD, kg	89.1 ± 18.64	89.4 ± 17.59
Mean body mass index ± SD, kg/m^2	29.3 ± 5.20	29.6 ± 5.02
Race		
Caucasian	64%	65%
African American	21%	17%
Liver biopsy results		
Cirrhosis (F4)	22%	28%
Bridging fibrosis (F3)	36%	34%
(F0-F2)	42%	38%
Steatosis*	52%	51%
Response to prior therapy		
<2-log$_{10}$ drop	78%	80%
>2-log$_{10}$ drop	15%	12%
Unknown	7%	8%
Washout interval, days		
Mean ± SD	453 ± 345	594 ± 372
Median	448	506

Abbreviation: SD, standard deviation.
*Steatosis defined as present or absent.

Baseline demographic and clinical characteristics of the two CIFN treatment groups are presented in Table 1. The majority of patients were male (70%) and Caucasian (64%). Of the enrolled patients, 59.3% had advanced liver disease on biopsy, including bridging fibrosis (F3; 35%) or cirrhosis (F4; 25%). In addition, 52% of patients had hepatic steatosis. The average time between biopsy sampling and study day 1 was 1.6 years. Patients included in the DIRECT trial were required to be off PEG-IFN/RBV therapy for at least 3 months prior to starting CIFN therapy. The median washout period between previous treatment and day 1 of CIFN therapy was 448 days (15 months) and 506 days (16.8 months) for the 9 μg and 15 μg groups, respectively. Sixty-eight percent of the patients had high baseline HCV RNA levels of >850,000 IU/mL. The majority of patients (79%) failed to achieve an early virologic response (at least a 2-log$_{10}$ drop in HCV RNA from the pretreatment baseline) to previous PEG-IFN therapy.

Antiviral Efficacy. By ITT analysis, pooled end-of-treatment response via TMA assay in the pooled 9 μg arm was 14.7% (36/245), with a subsequent SVR of 6.9% (17/245). In the 15 μg arm, pooled end-of-treatment response via TMA assay was 18.5% (45/242), with an SVR rate of 10.7% (26/242). Relapse rates pooled for both arms were 52% (19/36) and 42% (19/45) for the 9 μg and 15 μg groups, respectively. Post hoc analysis re-

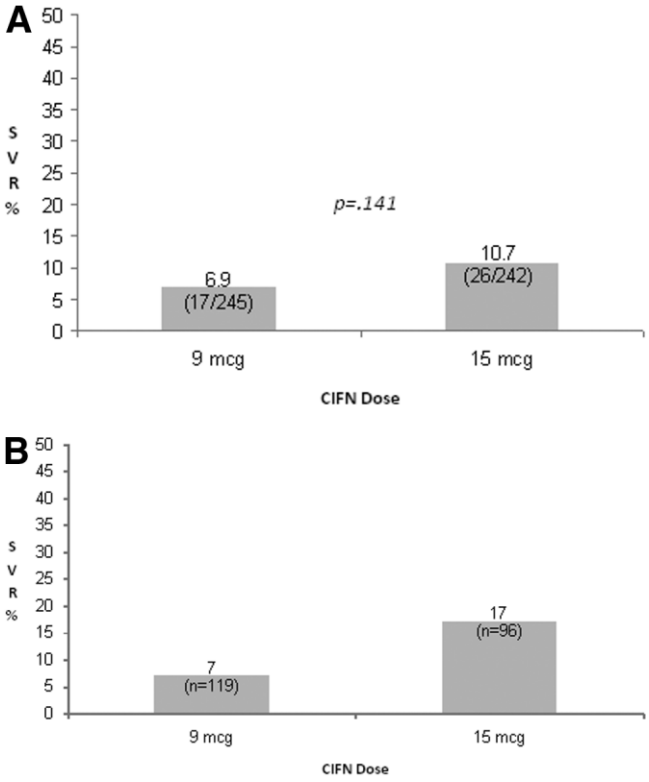

Fig. 2. Rates of SVR, defined as undetectable viral levels at least 24 weeks after the end of treatment with CIFN and RBV, in (A) the ITT population (n = 487) and (B) patients who did not receive dose modifications (n = 281). Active versus no treatment (n = 172).

vealed steatosis and time to viral negativity had the most impact on relapse rates.[13] As expected, in DIRECT 001, patients in the no-treatment arm achieved a 0% SVR. In patients who did not have dose modifications, overall SVR rates were 7% in the CIFN 9 μg group and 17% in the 15 μg group (Fig. 2A,B). The SVR rates were not significantly different between the 001 and 002 arms (P = 0.818). Although the study was not powered to detect differences between the 9 μg and 15 μg groups, a post hoc analysis revealed no difference in SVR rates between the two (P = 0.141, 95% CI −8.8%-1.2%).

Patients who achieved a complete early virologic response (defined as viral negativity at week 12 via TMA assay) were more likely to demonstrate an SVR than the general study population. In the 9 μg group, 81.3% (13/16) of patients with complete early virologic response achieved SVR, whereas in the 15 μg group, 63.6% (14/22) of patients with complete early virologic response demonstrated SVR. In patients deemed slow responders (>2-log drop at week 12, viral-negative at week 24), SVR rates were 11.7% (2/17) and 35.4% (11/31) in the 9 μg and 15 μg groups, respectively. Two patients in the 9 μg arm and one patient in the 15 μg arm achieved SVR despite being viral-positive at week 24.

Patients achieving the greatest log reduction in terms of viral response to initial PEG-IFN/RBV therapy had the best likelihood of responding to retreatment with CIFN and RBV (Fig. 3A,B). Among F0-F2 patients with >2-$\log_{10}$ decreases in HCV RNA during their prior PEG-IFN/RBV therapy, SVR rates were 13.3% (2/15) and 30.0% (3/10) in the 9 μg and 15 μg groups, respectively. A similar trend was seen in the 15 μg arm in patients with bridging fibrosis (F3). SVR for the F0-F2 group of patients was 8.7% (9/104) in the 9μg group and 14.9% (14/94) in the 15 μg group. With patients displaying bridging fibrosis only on biopsy, overall SVR was 6.8% (6/88) and 11.1% (9/81) in the 9 and 15 μg groups, respectively. Complete SVR for noncirrhotics (F0-F3) was 7.8% (15/192) in the 9 μg group versus 13.1% (23/175) in the 15 μg group, whereas cirrhotics achieved SVR rates of 3.8% (2/53) and 4.5% (3/67) in the 9 μg and 15 μg groups, respectively. In the cirrhotic cohort, patients required at least a 1-log drop on prior therapy to benefit from retreatment with CIFN and RBV. African American patients achieved lower SVR rates than Caucasians (4.2% versus 11%, respectively). In this population, pooled analysis between the two dosage arms revealed that 35.4% of the patients had failed at least two or more prior treatment regimens, with 52.7% having obtained a <1-log

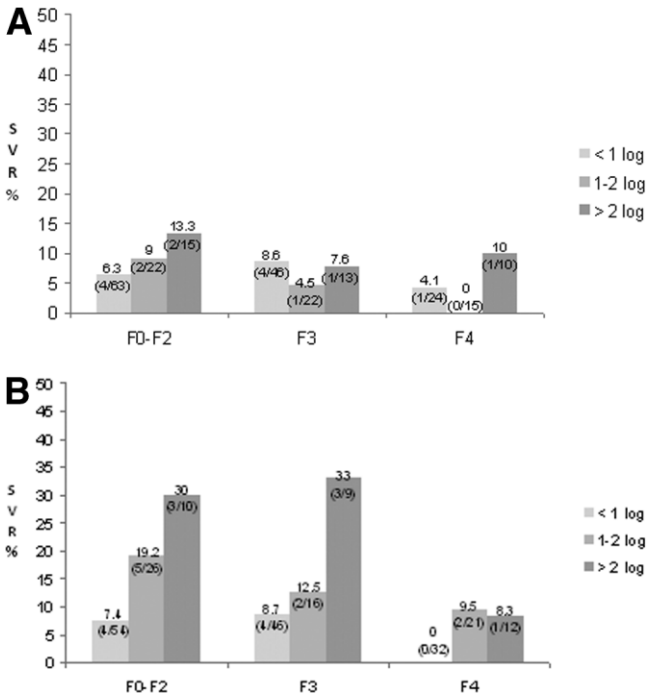

Fig. 3. Rates of SVR, defined as undetectable viral levels at 24 weeks after the end of treatment, in the ITT analysis by known previous response to therapy among patients without F0-F2 fibrosis, F3, and with cirrhosis (F4) in the (A) 9 μg and (B) 15 μg treatment groups. One patient in the 9 μg group and two patients in the 15 μg group achieving SVR had unknown prior response to PEG-IFN/RBV therapy.

Table 2. Univariate Predictors of SVR

	n (% SVR)	*P* Value
Treatment group		
9 μg/day (n = 245)	17 (6.9)	NS
15 μg/day (n = 242)	26 (10.7)	
Sex		
Male (n = 342)	30 (8.8)	NS
Female (n = 145)	13 (9.0)	
Fibrosis scores		
F0-F2 (n = 198)	23 (11.6)	NS
F3-F4 (n = 289)	20 (6.9)	
Genotype		
1 (n = 464)	32 (6.9)	<0.001
Non–genotype 1 (n = 23)	11 (47.8)	
Viral load		
<850,000 IU/mL (n = 155)	25 (16.1)	<0.001
>850,000 IU/mL (n = 331)	18 (5.4)	

Abbreviation: NS, not significant.

drop on prior PEG-IFN/RBV therapy. In addition to this, 60.2% had dose reductions while on CIFN/RBV therapy. Finally, non–genotype 1 patients (genotype 2/3) achieved an overall SVR rate of 23.1% (3/13) and 88.8% (8/9) in the 9 μg and 15 μg groups, respectively. Further univariate predictors of response are discussed in Table 2.

Safety and Tolerability. A total of 83.6% of patients in the 9 μg group and 71.7% of patients in the 15 μg group received at least 80% of their cumulative CIFN dose. The most common reason for early termination was treatment failure. Discontinuation due to not achieving a >2-log drop at week 24 was similar between the pooled dosage arms of 001 and 002 (32.3% versus 28.4%, *P* value not significant). Other reasons for treatment discontinuation are listed in Table 3.

Table 4 summarizes the most common AEs experienced by patients in the pooled 001 and 002 arms of the DIRECT trial. Most AEs were grade 2 or 3 and were more commonly related to administration of both CIFN and RBV than either drug alone. Most patients experienced at least one AE in the study. Individual AEs resulting from treatment with CIFN were typical of those reported with IFN-based therapy. All AEs were more common in the CIFN 9 and 15 μg groups than in the no-treatment group. RBV-induced hemolytic anemia occurred in 6.4% of patients. In general, most AEs were either not drug-related based on the opinion of the study site principal investigator or were thought to be related to the combination of study drugs rather than to either CIFN or RBV alone. The most common AEs leading to dose modifications in both CIFN treatment groups included neutropenia, fatigue, leukopenia, depression, nausea, myalgia, lymphopenia, and anemia. Overall, discontinuations for AEs occurred in 14% of the 9 μg group and 21% of the 15 μg group in the pooled ITT analysis.

Discussion

Retreatment of PEG-IFN/RBV nonresponders with daily CIFN/RBV resulted in an SVR rate of 6.9% with 9 μg/day CIFN and 10.7% with 15 μg/day CIFN. Patients whose doses were not reduced achieved SVR rates of 7% in the 9 μg group and 17% in the 15 μg group. These findings are consistent with a previous clinical trial demonstrating encouraging SVR rates with this higher dose of CIFN, 15 μg/day.[14] The best response rate, 31.6%, was observed in noncirrhotic patients (F0-F3) who had a partial virologic response with a >2-$\log_{10}$ decline in HCV RNA during their previous course of PEG-IFN treatment.

These results were achieved even though the patients in the DIRECT trial had numerous poor prognostic factors for a successful response. Approximately 95% had HCV genotype 1, about 20% were African American, 68% had a high baseline HCV RNA level of >850,000 IU/mL, and almost 90% had a baseline HCV RNA level of >400,000 IU/mL. Approximately 80% had a <2-$\log_{10}$ decline in HCV RNA during prior treatment. Sixty percent of patients had advanced liver disease, including cirrhosis (25%) and bridging fibrosis (35%), and 52% had steatosis on biopsy. All of these factors have been shown to significantly reduce rates of SVR.

Table 3. Early Treatment Discontinuation: ITT Population

	Patients, n (%)		
	CIFN 9 μg/day + RBV (n = 245)	CIFN 15 μg/day + RBV (n = 242)	Total (N = 487)
Treatment failure	127 (51.8)	107 (44.2)	234 (48.0)
<2-$\log_{10}$ reduction in HCV RNA at week 24	96 (39.2)	64 (26.4)	160 (32.9)
Detectable HCV RNA at week 48	31 (12.7)	43 (17.8)	74 (15.2)
Adverse events	35 (14.3)	51 (21.1)	86 (17.7)
Withdrawal of consent	20 (8.2)	18 (7.4)	38 (7.8)
Decision by principal investigator or sponsor	3 (1.2)	9 (3.7)	12 (2.5)
Lost to follow-up	9 (3.7)	9 (3.7)	18 (3.7)
Other	15 (6.1)	7 (2.9)	2 (4.5)

Table 4. Adverse Events Reactions Occurring Regardless of Attribution

Body System/Preferred Term (MedDRA)	Retreatment* CIFN 9 μg/day for 48 weeks (n = 244)	Retreatment* CIFN 15 μg/day for 48 weeks (n = 242)
Blood and lymphatic disorders		
Anemia	13	12
Hemolytic anemia	16	19
Leukopenia	24	34
Lymphopenia	7	14
Neutropenia	36	44
Thrombocytopenia	3	5
Eye disorders		
Vision blurred	8	7
Gastrointestinal disorders		
Abdominal pain	7	7
Abdominal pain upper	8	7
Constipation	9	10
Diarrhea	18	19
Dry mouth (saliva decreased)	3	5
Dyspepsia	6	7
Nausea	45	45
Vomiting	12	19
General disorders and administration site conditions (or body as a whole)		
Asthenia	6	9
Fatigue	75	77
Influenza-like illness (or symptoms)	40	42
Injection site erythema	16	16
Injection site pain	3	5
Injection site reaction	15	12
Injection site rash	2	5
Pain (or body pain)	5	6
Pyrexia (or fever)	13	17
Rigors	19	22
Infections		
Sinusitis	7	6
Upper respiratory tract infection	5	6
Investigations		
Blood ALT increased	4	6
Blood AST increased	6	10
Blood phosphorus decreased	7	5
Blood uric acid increased	3	5
Lymphocyte count decreased	3	5
Neutrophil count decreased	5	4
WBC count decreased	6	5
Weight decrease	16	22
Metabolism and nutrition disorders		
Anorexia	15	21
Decreased appetite	17	18
Hyperglycemia	3	7
Hypertriglyceridemia	7	7
Hyperuricemia	8	10
Musculoskeletal and connective tissue disorders		
Arthralgia	31	31
Back pain	12	9
Muscle cramp	5	6
Myalgia	24	34
Nervous system disorders		
Dizziness	14	19
Dysgeusia	6	95
Headache	46	39
Memory impairment	5	6
Syncope	2	5
Psychiatric disorder		
Agitation	6	2
Anxiety	12	11
State of confusion	4	5
Depression	27	25
Insomnia	39	38
Irritability	21	17
Respiratory, thoracic, and mediastinal disorders		
Cough	14	17
Dyspnea	15	20
Dyspnea exertional	10	9
Epistaxis	1	5
Pharyngolaryngeal pain	5	6
Skin and subcutaneous tissue disorders		
Alopecia	10	10
Dry skin	9	8
Hyperhidrosis (or sweating increased)	2	5
Pruritus	15	11
Rash	17	12

Only events that occurred at a frequency of ≥5% in any treatment group of both IRHC-001 and IRHC-002 studies combined are included. Patients can appear more than once in Table 5. All values are percentages.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell.

*Adverse events reported in patients during treatment or posttreatment observation are listed regardless of attribution to treatment.

Overall, the alternative strategies for improving SVR in PEG-IFN/RBV nonresponders have not met with success. Two trials of maintenance IFN therapy were evaluated in PEG-IFN/RBV nonresponders with advanced fibrosis or cirrhosis to determine if this strategy can reduce progression to cirrhosis, complications of cirrhosis, hepatocellular carcinoma, the need for liver transplantation, and death.[8,15] The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis trial demonstrated that maintenance PEG-IFN alfa-2a therapy at a dose of 90 μg/week over 3.5 years provided no overall benefit compared with no treatment.[8] Similar results were observed in the Colchicine versus PEG-Intron Long Term study, which compared PEG-IFN alfa-2b 0.5 μg/kg/week to colchicine over 3.5 years.[15]

In the recently completed REtreatment with PEgasys in PATients Not Responding to Peg-Intron Therapy (REPEAT) trial, nonresponders and relapsers to previous

PEG-IFN alfa-2b and RBV were retreated with either a standard dose of PEG-IFN alfa-2a 180 μg/week or a higher dose of 360 μg/week for 12 weeks, after which the dose was reduced to the standard dose.[16] Patients who became HCV RNA undetectable by week 24 were treated for either 48 or 72 weeks. In a protocol-defined primary analysis, SVR rates after retreatment with PEG-IFN alfa-2a and RBV were only 7% to 9% with 48 weeks of treatment but increased to 14% to 16% in those patients treated for 72 weeks. This increase in SVR resulted from a decline in relapse with the prolonged course of treatment. The use of the higher induction dose of PEG-IFN alfa-2a, 360 μg/week, did not impact SVR rates. The SVR results of this study, using 72 weeks of PEG-IFN alfa-2a are comparable with those achieved with 48 weeks of treatment with CIFN/RBV in the DIRECT trial. Several differences exist between the REPEAT and DIRECT trials that confound direct comparison of the results. It is not known what proportion of patients in the REPEAT trial were treatment-compliant, and the number of relapse patients included in the trial is not clear.[17] Furthermore, the patients enrolled in the DIRECT trial had more advanced liver disease than those in REPEAT (60% versus 27% with stage F3-F4) and contained a higher percentage of African American patients (20% versus 10%).

Recent studies of CIFN and RBV have demonstrated a favorable response in the retreatment of PEG-IFN/RBV nonresponders.[14,18,19] Two open-label trials demonstrated SVR rates ranging from 10% to 37%, with varying CIFN regimens.[17,19] In a third study, 137 consecutive patients who did not become HCV RNA–undetectable during treatment with PEG-IFN alfa-2b with RBV were switched to CIFN 15 μg/day for 12 weeks, followed by CIFN three times weekly for an additional 36 weeks with weight-based doses of RBV.[14] SVR rates were noted in 37% of patients who remained on their full doses of therapy. The SVR rate was 27% in African Americans and 41% in Caucasian patients.

Several other new and promising therapies are under development for the treatment of chronic hepatitis C. These include RBV-like molecules, polymerase and protease inhibitors, and novel IFN formulations.[7,20] Two protease inhibitors, Boceprevir and Telaprevir, are the furthest along in development. Phase III studies are in the midst of enrollment, and these agents may gain U.S. Food and Drug Administration approval in 2 to 3 years. In addition, it has already been demonstrated that both protease and polymerase inhibitors will require the use of both IFN and RBV to achieve an SVR in treatment-naïve or treatment-experienced patients.

In conclusion, the current study shows the benefit CIFN holds for difficult-to-treat patients with chronic hepatitis C who have failed to respond to previous treatment with PEG-IFN and RBV. The present study demonstrated that some patients with chronic hepatitis C who have failed to respond to treatment with PEG-IFN and RBV can be successfully retreated with daily CIFN and RBV. The greatest SVR rate during retreatment in the present study was observed in F0-F3 patients who had a partial virologic response during their prior course of treatment. Therefore, once-daily CIFN in combination with RBV can be considered for select patients with chronic HCV who have failed to respond to prior treatment with PEG-IFN and RBV.

Acknowledgment: The authors would like to thank the DIRECT-001 and DIRECT-002 study investigators (Bashar Aqel, Sanjeev Arora, Carl Berg, David Bernstein, Edmund Bini, Scott Cotler, Michael Fallon, Kenneth Flora, Steven-Huy Bui Han, Joanne Imperial, Mark Jonas, Gerond Lake-Bakaar, Anne Larson, Eric Lawitz, Edward Lebovics, Michael Lyons, Gary Matusow, Douglas Meyer, Abdul Nadir, Robert Reindollar, Adrian Reuben, Maribel Rodriguez-Torres, Vinod Rustgi, Michael Ryan, John Santoro, Muhammad Sheikh, Robert Sjogren, Mark Swaim, Helen Te, Tram Tran, Andrzej Triebling, Harlan Wright, and Nizar Zein) for their participation in the studies. Dr. John Kincaid is also acknowledged for his assistance in the preparation of the first draft of the manuscript. All subsequent revisions of this manuscript were made by Bruce R. Bacon and Mitchell L. Shiffman with some input from the authors on the masthead.

Disclosures: Dr. Bacon received grants from Roche and Bristol-Myers Squibb. He received grants from and is on the speakers' bureau of Roche and Three Rivers. He is a consultant for, received grants from, and is on the speakers' bureau of Schering-Plough. He also received grants from and is a consultant for Coley Pharmaceuticals, ISIS, and Valeant. He received grants and advises GlaxoSmithKline.

Dr. Ghalib is on the speakers' bureau of and received grants from Schering-Plough and Roche. He is also on the speakers' bureau of Three Rivers and received grants from Idenix.

Dr. Joshi received grants from Three Rivers, Roche, and Schering-Plough.

Dr. Hassanien is on the speakers' bureau of Three Rivers.

Dr. Kwo is a consultant for, is on the speakers' bureau of, and received grants from Schering-Plough. He is also on the speakers' bureau of and received grants from Valeant and Roche.

Dr. Morelli is on the speakers' bureau of Gilead Sciences.

Dr. Rothstein is on the speakers' bureau of Roche. He is also on the speakers' bureau of and received grants from Valeant.

Dr. Shiffman is a consultant for, and received grants from Valeant, Biotex, and Vertex. He is on the speakers' bureau of and received grants from Schering-Plough. He is a consul-

tant for, is on the speakers' bureau of, and received grants from Roche.

References

1. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975-982.
2. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958-965.
3. Fartoux L, Degos F, Trepo C, Goria O, Cales P, Tran A, et al. Effect of prolonged interferon therapy on the outcome of hepatitis C virus-related cirrhosis: a randomized trial. Clin Gastroenterol Hepatol 2007;5:502-507.
4. Helbling B, Jochum W, Stamenic I, Knopfli M, Cerny A, Borovicka J, et al. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. J Viral Hepat 2006;13:762-769.
5. Kobayashi S, Takeda T, Enomoto M, Tamori A, Kawada N, Habu D, et al. Development of hepatocellular carcinoma in patients with chronic hepatitis C who had a sustained virological response to interferon therapy: a multicenter, retrospective cohort study of 1124 patients. Liver Int 2007; 27:186-191.
6. Shiffman ML. Chronic hepatitis C: treatment of pegylated interferon/ribavirin nonresponders. Curr Gastroenterol Rep 2006;8:46-52.
7. Keeffe EB. Future treatment of chronic hepatitis C. Antivir Ther 2007;12: 1015-1025.
8. DiBisceglie A., Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med 2008;359:2429-2441.
9. Jensen DB, Freilich B, Andreone P, DiBisceglie A, Brandão-Mello CE, Reddy KR, et al. Pegylated interferon alfa-2a (40kD) plus ribavirin (RBV) in prior non-responders to pegylated interferon alfa-2b (12kD)/RBV: final efficacy and safety outcomes of the REPEAT study [abstract LB4]. HEPATOLOGY 2007;46(Suppl):291A–292A.
10. Kaiser S, Hass H, Gregor M. Successful retreatment of peginterferon nonresponder patients with chronic hepatitis C with high dose consensus interferon induction therapy [Abstract 125]. Gastroenterology 2004; 126(Suppl 2):A-668.
11. Kaiser S, Hass HG, Bissinger L, Gregor M. Comparison of daily consensus interferon versus peginterferon alfa 2a extended therapy of 72 weeks for peginterferon/ribavirin relapse patients with chronic hepatitis C [Abstract S1060]. Gastroenterology 2006;130(Suppl 2):A-784.
12. Rustgi VK, Esposito S, Hamzeh FM, Shiffman ML. Peginterferon alfa-2a/ribavirin in hepatitis C virus patients nontolerant or nonresponsive to peginterferon alfa-2b/ribavirin. Aliment Pharmacol Ther 2008;27:433-440.
13. Hassanein T, Ghalib R, Zein N, Rothstein KD, Joshi SN, Kwo PY, et al. Analysis of relapse rates in pegylated interferon and ribavirin non-responders treated with daily consensus interferon and ribavirin [Abstract 1319]. HEPATOLOGY 2007;46:A1319.
14. Leevy CB. Consensus interferon and ribavirin in patients with chronic hepatitis C who were nonresponders to pegylated interferon alfa-2b and ribavirin. Dig Dis Sci 2008;53:1961-1966.
15. Afdhal NH, Levine R, Brown RJ, Freilich B, O'Brien M, Brass C. Colchicine versus peg-interferon alfa 2b long term therapy: results of the 4 year COPILOT trial [Abstract 3]. J Hepatol 2008;48(Suppl):S4.
16. Jensen D, Di Bisceglie A, Gitlin N, Freilich B, Reddy K, Feinman V, et al. Peginterferon alfa-2a (40KD) plus ribavirin (RBV) in pegylated interferon alfa-2b (12KD)/ribavirin non-responders: week 12 efficacy and safety outcomes of the REPEAT study. Gastroenterology 2006;130;T1800.
17. Jensen D, Di Bisceglie A, Gitlin N, Freilich B, Reddy K, Feinman V, et al. Type of response to prior pegylated interferon alfa-2b (12kd)/rbv predicts subsequent response to retreatment with peginterferon alfa-2a (40KD)/RBV. Gastroenterology 2008;134:S1937.
18. Kaiser S, Boecher W, Lutze B, Sauter B, Bissinger L, Werner C, et al. Treatment of peginterferon/ribavirin nonresponders with daily dosing of consensus interferon and ribavirin: preliminary results of the German Consensus Interferon Multicenter Study [Abstract 1306]. HEPATOLOGY 2007;46(Suppl):817A.
19. Ghalib RH, Levine CD, Friedman DA, Rashdan S, Schwartz AG, Weinstein J. Consensus interferon plus ribavirin therapy in patients who are nonresponders or relapsers to prior PEG IFN plus ribavirin. Gastroenterology 2007;46:M1874.
20. Harrison SA. Small molecules and novel treatment for chronic hepatitis C virus infection. Am J Gastroenterol 2007;102:2332-2338.