

Update on the Use of Consensus Interferon in Difficult-to-Treat Hepatitis C Patients

A Review of Selected Posters
From Digestive Disease Week
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Hepatitis C Epidemiology and Treatment Issues

Approximately 20,000 new infections with hepatitis C virus (HCV) occur annually in the United States. A minority of HCV cases are diagnosed in the acute stage. Anywhere from 55% to 85% of patients develop chronic infection,¹ and a recent estimate suggests that about 3.2 million people in the United States have chronic HCV infection.² The primary mode of transmission in adults is through sharing of needles in injection drug use, whereas other modes of transmission, including transfusion, are now extremely rare.³

Over the past decade, success rates with antiviral therapy have improved significantly. Pegylation (ie, attachment of an inert polyethylene glycol molecule) of standard interferon alfa reduces drug clearance rates. This has allowed for the implementation of once-weekly dosing regimens instead of the earlier required dosing of three times per week for standard interferon. Peginterferon (PEG IFN) alfa in combination with daily oral ribavirin therapy has been found to be more effective than PEG IFN monotherapy or standard interferon/ribavirin⁴⁻⁷ and is now a standard of care for patients with new and chronic HCV infection.⁸

Despite the recent advances in treatment, however, about 40–50% of patients with chronic HCV initially treated with PEG IFN/ribavirin fail to achieve a sustained virologic response (SVR) and require re-treatment.⁹ Up to 50% of patients who have relapsed on interferon/ribavirin achieve SVR after re-treatment with PEG IFN plus ribavirin, whereas the SVR in patients who failed PEG IFN/ribavirin is less well established.⁹ Strategies under investigation among PEG IFN/ribavirin nonresponders or relapsers include the use of more intensive PEG IFN/ribavirin therapy (ie, longer treatment or higher doses) as well as the use of consensus interferon (CIFN; interferon alfacon-1, [Infergen, Valeant]) plus ribavirin.⁹

CIFN is a synthetic recombinant type-I interferon that was approved by the US Food and Drug Administration in 1997 for the treatment of adults with chronic HCV infection, compensated liver disease, and anti-HCV serum antibodies and/or detectable HCV RNA.¹⁰ CIFN was developed using a method that assigned the most frequent amino acid sequences found at specific positions

in several natural interferon-alfa subtypes to generate a consensus molecule.¹¹

CIFN has demonstrated a 5- to 10-fold stronger immunologic effect than other interferons *in vitro*,¹² and in a large, randomized phase III trial, it demonstrated stronger inhibition of HCV replication compared with naturally occurring alpha-interferon, especially in HCV genotype 1-infected patients.¹³ In addition, a phase III study of 337 patients with chronic HCV who had not responded to or had relapsed after discontinuing monotherapy with either CIFN 9 µg or interferon alfa-2b 3 MU three times weekly for 24 weeks, found that retreatment with a higher dose of CIFN (15 mg tiw) led to normalized serum alanine aminotransferase (ALT) levels, reduction of serum HCV RNA concentrations to undetectable amounts (<100 copies/mL), and improved liver histology, especially among relapsed patients.¹⁴ The trial also found that among monotherapy nonresponders to interferon alfa-2b, 13% were able to achieve an SVR with CIFN 15 µg.

Several studies are underway to further explore ways in which CIFN might benefit patients with HCV who did not respond to or who have relapsed on standard treatment. For example, a recently published study by Cornberg and colleagues¹⁵ investigated two dosing strategies for CIFN given daily in combination with 1,000/1,200 mg ribavirin. A total of 77 patients, 90% with genotype-1 HCV infection, received either an 8-week induction-dosing regimen of 18 µg/day CIFN followed by 9 µg/day for 40 weeks or treatment with 9 µg/day CIFN for 48 weeks.

Overall, 82% of patients achieved an early virologic response, 65% achieved an end-of-treatment response, and 30% achieved an SVR. In HCV genotype 1 patients only, the SVR rate was 22%. In addition, the induction dosing strategy was found to cause a greater first-phase HCV-RNA decay, although this effect did not correlate with an improved SVR rate, potentially because of an increase in dose modifications in the induction arm.¹⁵ This finding is similar to those of other trials that have evaluated the use of an induction phase with interferon alfa.¹⁶ In most cases, rates of end-of-treatment and on-treatment responses have improved, but SVR rates have not, poten-

tially because of the high relapse rates after treatment discontinuation. Thus, the results from the Cornberg study support the use of CIFN 9 µg/day in combination with ribavirin for patients who have not responded to either standard interferon or interferon/ribavirin.

Moskovitz and colleagues¹⁷ have also evaluated the efficacy of treatment with high-dose CIFN (15 µg/day) in nonresponders. Patients (n=24) with undetectable HCV RNA at 12 weeks continued therapy with CIFN 15 µg three times per week for an additional 36 weeks. Again, approximately 25% of the patients withdrew before 12 weeks because of side effects. Among those who completed therapy, 9 (38%) had undetectable levels of HCV RNA. HCV RNA remained undetectable in 3 of 7 patients who continued therapy for 48 weeks. Thus, these early studies indicate that high-dose therapy with CIFN has robust efficacy in pretreated patients.

The following is a review of selected studies investigating CIFN in difficult-to-treat patients with chronic HCV. The studies were presented at Digestive Disease Week, held May 20–25, 2006, in Los Angeles, and evaluate some of the current approaches for using CIFN in this setting. Investigational approaches include the use of a longer 72-week course of CIFN; the use of CIFN in patients who have failed PEG IFN/ribavirin; and high-dose CIFN induction therapy. Differences that may exist among patients previously treated with PEG IFN alfa-2a versus PEG IFN alfa-2b are also explored.

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S1060 Comparison of Daily Consensus Interferon versus Peginterferon alfa 2a Extended Therapy of 72 Weeks for Peginterferon / Ribavirin Relapse Patients with Chronic Hepatitis C¹

S Kaiser, H Hass, B Lutze, L Bissinger, and M Gregor

In patients with previously untreated chronic HCV infection, the combination of PEG IFN and ribavirin has been found to result in relapse rates of about 20–30% after 48 weeks of treatment.² More recently, response rates with PEG IFN have been improved further with an extension of treatment duration to 72 weeks.³ Studies indicate that high-dose CIFN in combination with ribavirin for 48 weeks can result in an SVR of about 30%.⁴ Thus, Kaiser and colleagues¹ sought to compare 72-week treatment with ribavirin plus either daily CIFN or weekly PEG IFN alfa-2a in patients with HCV who had previously relapsed.

CIFN was administered at a dose of 9 µg once daily; PEG IFN alfa-2a was administered at 180 µg once weekly. Weight-based dosing was used for ribavirin. A total of 81 patients were included in the analysis; of those, 83% had HCV genotype 1. All patients had histologically confirmed chronic HCV infection and had previously relapsed on treatment with 48 weeks of PEG IFN alfa-2a or -2b in combination with ribavirin.

Patient characteristics were well balanced between groups and were distributed as follows: cirrhosis, 21% in the CIFN group versus 17% in the PEG IFN group; male, 69% versus 77%; average age, 53.2 years versus 49.7 years; genotype 1 and 4, 80% versus 74%; and HCV RNA greater than 850 kIU/mL, 56% versus 67%.

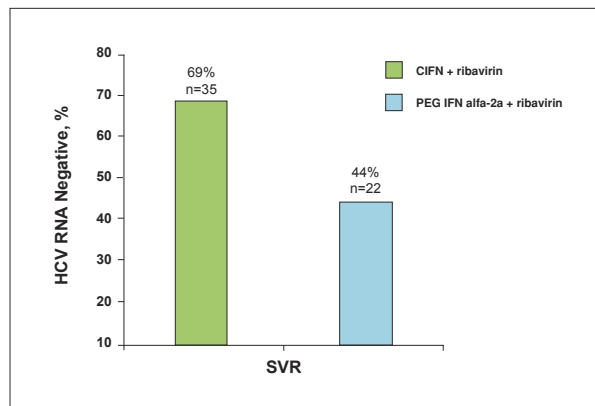


Figure 1. Daily consensus interferon (CIFN) vs peginterferon (PEG IFN) alfa-2a extended therapy for chronic hepatitis C: sustained virologic response (SVR) rates at 72 weeks.

HCV = hepatitis C virus.

After 12 weeks of treatment, 83% of patients in the CIFN group achieved undetectable serum HCV RNA levels compared with 78% in the PEG IFN alfa-2a group. After 72 weeks of treatment, 89% of the CIFN group achieved a negative polymerase chain reaction (PCR), compared with 76% of the PEG IFN group, which was not significantly different.

However, SVR rates were significantly different between groups: 69% of patients achieved an SVR in the CIFN group compared with 44% of patients receiving PEG IFN alfa-2a ($P < .05$), suggesting that relapse rates were significantly higher with PEG IFN alfa-2a than with CIFN (Figure 1).

The tolerability of CIFN was similar to that of PEG IFN alfa-2a. None of the patients received growth factor support. Overall, no patients experienced grade 4 neutropenia or thrombocytopenia, but 3 patients had grade 3 thrombocytopenia. Grade 3 hematologic changes were more common in the PEG IFN alfa-2a group than in the CIFN group. More injection site reactions were

Table 1. CIFN/RBV vs PEG IFN/RBV: Dose Reductions and Safety Results

	CIFN + RBV, %	PEG IFN + RBV, %
IFN dose reductions	15	31
RBV dose reductions	11	17
Therapy discontinuations	8	6
Serious adverse events	0	1
White blood cell count <1,500/ μ L	3.2	4.7
Platelet count <35,000/ μ L	3.4	7.6

CIFN = consensus interferon; PEG IFN = pegylated interferon; RBV = ribavirin.

observed in the CIFN group and slightly more patients receiving CIFN withdrew from the study (8% vs 6% for the CIFN vs PEG IFN alfa-2a groups, respectively). More dose reductions due to interferon side effects were observed in the PEG IFN compared with the CIFN treatment groups (31% vs 15%, respectively; Table 1).

The authors concluded that 72-week dosing with CIFN resulted in promising response rates compared with a treatment of similar duration with PEG IFN alfa-2a when used in combination with ribavirin. Given that most of the patients were genotype 1 relapsers, long-term (72-week) treatment with CIFN in combination with ribavirin appears to be an appropriate treatment modality for this difficult-to-treat patient group.

S1926 Successful Treatment With High Dose Consensus Interferon and Ribavirin of Patients With Chronic Hepatitis C Who Are Resistant to Peg-Interferon and Ribavirin Therapy⁵

KD Rothstein, R Koka, A Fernandez, H Hargrove, S Singh, V Araya, and SJ Munoz

Most patients with HCV who relapse or do not respond to initial therapy are unable to maintain an SVR from treatment with PEG IFN/ribavirin. This is especially true for patients with genotype 1 and/or advanced HCV infection. CIFN has demonstrated greater antiviral activity in vitro compared with interferon alfa-2a and -2b.⁶ In addition, patients who have failed to respond to treatment with PEG IFN/ribavirin have demonstrated higher response rates with high-dose CIFN/ribavirin.⁷

Rothstein and colleagues⁵ sought to evaluate the efficacy and tolerability of high-dose daily CIFN/ribavirin in 50 patients who had failed previous therapy with PEG IFN/ribavirin (97% genotype 1). Patients were eligible for the current study if they had advanced liver disease and had tolerated treatment with PEG IFN/ribavirin. Of the patients, 79% had stage 3 or higher fibrosis, just over half of the patients had cirrhosis, and 82% were nonresponders.

For the first 4 weeks, patients received CIFN 27 μ g/day and ribavirin 400 mg twice daily. This was followed by 8 weeks of treatment with CIFN 18 μ g/day and ribavirin 400 mg twice daily. After 12 weeks of treatment, patients received 15 μ g/day of CIFN and the dose of ribavirin was increased to 1,000–1,200 mg/day for 36 weeks.

At weeks 24 and 48, 59% of 41 patients and 52% of 39 patients, respectively, had undetectable levels of HCV RNA. A total of 33 patients completed 72 weeks of treatment, and of those, 21% achieved an SVR (Figure 2).

Growth factor support was required in 42% of the patients; 28% required epoetin alfa, 20% required filgrastim, and 8% required both.

The most common side effects were fatigue, headache, irritability, weight loss, bone pain, and depression. Less common side effects were alopecia and tinnitus. Discontinuations and dose reductions at week 48 were reported in 18% and 34% of 39 patients, respectively (Table 2).

The researchers concluded that the tolerability of high-dose CIFN/ribavirin was acceptable and that discontinuation and dose reduction rates were comparable to other trials of nonresponders to PEG IFN/ribavirin. Thus, high-dose CIFN/ribavirin appears to be an effective treatment option for HCV patients with advanced liver fibrosis who have failed previous therapy with PEG IFN/ribavirin.

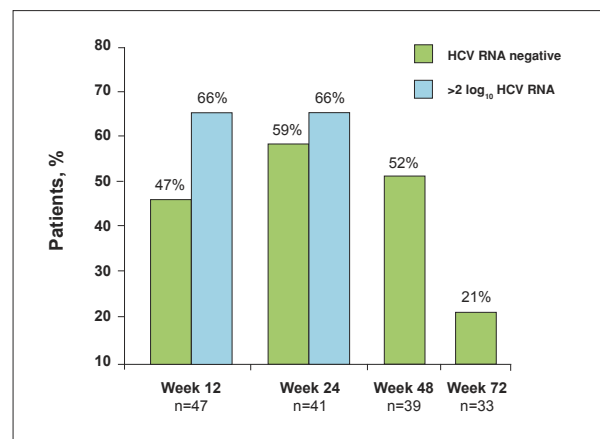


Figure 2. High-dose consensus interferon + ribavirin for hepatitis C resistant to peginterferon and ribavirin: overall response to therapy.

It should also be noted that the initial ribavirin dose of 800 mg daily is lower than weight-based doses generally in use and may account for any increased rate of relapse in the study.

Table 2. High-Dose Consensus Interferon + Ribavirin for Hepatitis C Resistant to Peginterferon and Ribavirin: Discontinuations Due to Adverse Effects

	(N=39)
Discontinuations	18%
Dose reductions	34%
Reason for Discontinuation	(n)
Adverse effects	2
Symptomatic gallstones	2
Retinopathy	1
Bacteremia	1
Exacerbation of psoriasis	1

T1839 Consensus Interferon Plus Ribavirin Therapy: End of Treatment Viral Response in Patients Who Were Nonresponders or Relapsers to Prior PEG IFN Plus Ribavirin Therapy⁸

R Ghalib, C Levine, M Mouti, J Weinstein, A Schwartz, A Mejia, and S Cheng

Another study evaluated the viral response to CIFN/ribavirin in patients who had failed to respond to or relapsed after treatment with PEG IFN/ribavirin. Ghalib and colleagues⁸ presented findings from a retrospective cohort analysis of outcomes in 49 patients treated with CIFN/ribavirin. Participants received CIFN, 15 µg/day, plus weight-based ribavirin therapy (11 mg/kg/per day). Levels of HCV RNA were tested after 4 weeks and every 3 months thereafter.

Overall, 82% of the participants (90% of the nonresponders and 68% of the relapsers) had HCV genotype 1. All had compensated liver disease; 65% were male; and 69% were biopsy stage 3–4. HCV load was greater than 200,000 IU/mL in 43% of the patients. Of the patients, 30 (61%) had been nonresponders and 19 (39%) had relapsed after at least 12 weeks of adequate dosing with PEG IFN/ribavirin therapy.

At week 12, 23% of prior nonresponders versus 63% of prior relapsers were HCV RNA negative (<5 IU/mL;

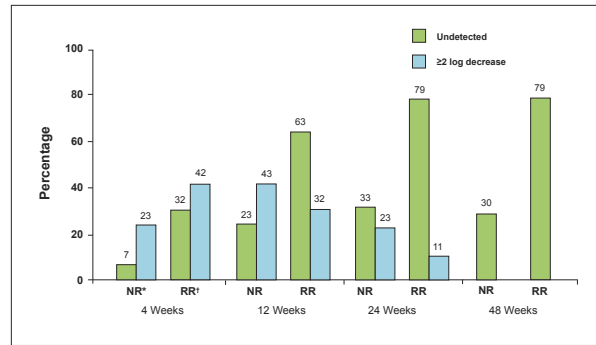


Figure 3. Consensus interferon + ribavirin following prior peginterferon + ribavirin: response to treatment (intent-to-treat analysis).

* 5 patients not tested.

† 2 patients not tested.

NR = prior nonresponders (n=30); RR = prior relapsers (n=19).

$P=.008$). At week 24, 33% of the nonresponders versus 79% of the relapsers achieved undetectable virus ($P=.001$). Treatment was withdrawn in 13% of nonresponders and 5% of relapsers who had an insufficient decline in viral load (<2 logs) at week 24 of treatment. At week 48, 30% of the nonresponders versus 79% of the relapsers achieved undetectable virus ($P=.001$; Figure 3).

At week 48, significantly fewer African American patients were HCV RNA–negative: 17% (2/12) versus 59% (22/37) of non–African American patients ($P=.01$). Of patients with genotype 1, 38% (15/40) were HCV

Table 3. Consensus Interferon + Ribavirin Following Prior Peginterferon + Ribavirin: Hematologic Adverse Events by Week 24

		Patient Groups		Total
		NR (n=30) pts, (%)	RR (n=19) pts, (%)	
Anemia (hemoglobin level, g/dL)	<10	8 (27)	5 (26)	3 (27)
	<8.5	1 (3)	1 (5)	2 (4)
Neutropenia (white blood cell count, cells/mm ³)	<750	10 (33)	6 (32)	16 (33)
	<500	3 (10)	2 (11)	5 (10)
Thrombocytopenia (platelet count, cells/mL)	<50	7 (23)	2 (11)	9 (18)
	<25	1 (3)	1 (5)	2 (4)

NR = nonresponders to prior therapy; RR = patients relapsing after prior therapy.

RNA-negative at week 48 versus 100% (9/9) of non-genotype 1 patients ($P=.001$). Patients with a weight greater than 85 kg were less likely to achieve undetectable HCV RNA than those with weight 85 kg or less ($P=.03$).

Overall, CIFN/ribavirin appeared to be well tolerated, with 71% of patients continuing treatment beyond week 24 (60% of nonresponders and 89% of relapsers). A total of 25 patients (51%) completed 48 weeks of treatment (33% of nonresponders and 79% of relapsers). Hematologic adverse events are listed in Table 3. Growth factors were used for anemia and neutropenia.

Two variables were related to likelihood of undetectable HCV RNA at week 48: prior response (favoring relapser vs nonresponder) and genotype (favoring non-1 vs 1; $P<.0001$). Overall rate of correct classification was 79.6%.

The authors suggest that factors predictive of SVR in previously nonresponding and relapsing patients require further study so that appropriate decisions can be made about which patients would benefit most from treatment with CIFN/ribavirin.

S1061 Higher Susceptibility of Peginterferon Alfa 2a Versus Peginterferon Alfa 2b Nonresponder Patients With Chronic Hepatitis C to Retreatment With Consensus Interferon Daily Dosing and Ribavirin⁹

S Kaiser, HG Hass, B Lutze, L Bissinger, and M Gregor

More than half of patients treated with PEG IFN and ribavirin infected with genotype 1 HCV relapse or do not respond to treatment, and only 31–47% of patients achieve an SVR. CIFN combined with ribavirin has shown encouraging results in this setting in terms of improved efficacy; however, it is unclear how patients might respond differently to treatment with CIFN with regard to the type of interferon they have previously received (eg, PEG IFN alfa-2a versus -2b).

Kaiser and colleagues⁹ evaluated the efficacy of CIFN, given daily, and induction therapy followed by CIFN/ribavirin in 95 patients who had not responded to prior treatment with PEG IFN/ribavirin. They evaluated response based on the previous form of interferon they had received.

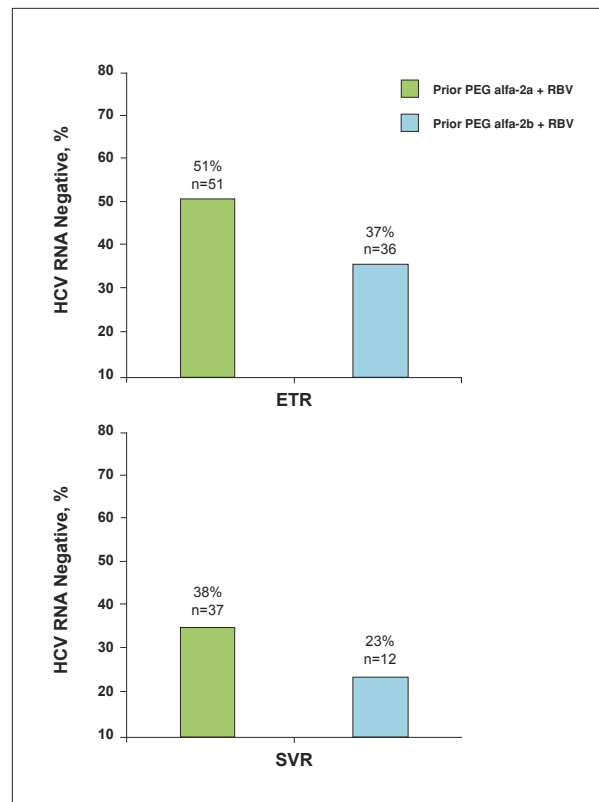


Figure 4. Daily consensus interferon + ribavirin following PEG alfa-2a or -2b + ribavirin: end-of-treatment response (ETR) and sustained virologic response (SVR) rates.

Table 5. Dose Reductions and Side Effects in Prior Nonresponders to PEG IFN alfa-2a and -2b Treated With Daily Consensus Interferon + Ribavirin

Prior Treatment	PEG IFN alfa-2a, %	PEG IFN alfa-2b, %
CIFN dose reductions	15	11
RBV dose reductions	11	17
Therapy discontinuations	8	6
Serious adverse events	0	1
WBC <1,500/ μ L	3.2	4.7
Platelets <3,500/ μ L	1.4	1.6

CIFN = consensus interferon; RBV = ribavirin; WBC = white blood cell.

Approximately 90% of the patients had genotype-1 or -4 HCV infection. Patients received either CIFN 9 µg once daily for 16 weeks or CIFN 27 µg daily for 4 weeks followed by 12 weeks of CIFN 18 µg daily (high-dose). Subsequently CIFN 9 µg daily, plus weight-based ribavirin were administered to all patients for 32–56 weeks, starting in sufficient time for a patient to receive treatment for a total of 48 weeks while having a negative PCR assay.

After the first 12 weeks of monotherapy with CIFN, 35% of nonresponders to PEG IFN alfa-2b demonstrated an undetectable serum HCV RNA level compared with 51% of PEG IFN alfa-2a nonresponders. At the end of treatment, a negative PCR was observed in 37% and 51% of PEG IFN alfa-2b and -2a nonresponders, respectively. Rates of SVR were 38% and 23% for PEG IFN alfa-2a and -2b nonresponders, respectively (Figure 4).

Sustained viral response rate for PEG IFN alfa-2b nonresponders was 18% in patients in the 9 µg CIFN arm compared with 25% in the high-dose CIFN arm. For PEG IFN alfa-2a nonresponders, the SVR rates were 34% and 41% for the two treatment arms, respectively.

The CIFN 9 µg regimen appeared to be comparable in tolerability to standard therapy with PEG IFN and ribavirin. By contrast, the high-dose CIFN regimen was less tolerable during the high-dose induction phase, although the rates of therapy discontinuation were comparable between the two arms. The number of dose reductions and adverse events were similar regardless of whether a patient had previously received PEG IFN alfa-2a or -2b (Table 5).

The researchers concluded that daily dosing of CIFN plus high-dose induction therapy and subsequent ribavirin combination therapy showed an encouraging response

rate in patients who failed to respond to prior PEG IFN combination therapy. In particular, nonresponders to PEG IFN alfa-2a showed more benefit from treatment than nonresponders to PEG IFN alfa-2b.

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Commentary: Does Consensus Interferon Have a Role Yet?

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Consensus interferon (CIFN) was initially evaluated as monotherapy for the re-treatment of interferon alfa (IFN)-failed hepatitis C patients in the mid 1990s. There was no clear role for the compound once ribavirin (RBV) and, subsequently, pegylated (PEG) IFNs were introduced. However, treatment failures with the current standard of care and the rapidly growing pool of nonresponders and relapsers have led to a renewed interest in this unique interferon. A multicenter registration study, the DIRECT (Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy) Trial, was initiated to treat nonresponders and relapsers to PEG IFN and RBV combinations with CIFN. The DIRECT Trial has completed enrollment but results are not yet available.

Consensus interferon is a novel, synthetic type-I interferon with 166 amino acids and a molecular weight of 19,500 daltons. It was developed by scanning IFN-alfa subtypes and selecting the most frequently observed amino acids at each position to form a "consensus" IFN molecule. A synthesized DNA coding sequence was then cloned into an *Escherichia coli* expression system, allowing production of this novel compound. In various in vitro cell lines, the measured antiviral activity of consensus interferon is 10- to 100-fold greater than IFN alfa.¹

Data comparing CIFN and RBV to IFN alfa and RBV in treatment-naïve patients are sparse. To date, only abstract data is available. Sjogren and colleagues² presented data in 128 patients using CIFN 15 µg thrice weekly with RBV 1 g daily versus IFN alfa-2b, 3 million IU thrice weekly with RBV 1 g daily for 48 weeks. They reported sustained virologic response (SVR) rates of 57% and 40%, respectively (44% vs 27% in genotype 1, respectively). A smaller study of 59 patients treated with the same regimen of CIFN and RBV versus PEG IFN alfa-2b and 1–1.2 g RBV was presented at the 2004 meeting of the American Association for the Study of Liver Diseases and showed comparable 24-week viral negativity in 52% of genotype 1 patients.³

Treatment of previous nonresponders to non-PEG IFN and RBV with CIFN and RBV is better studied. In a study using two arms of high-dose induction with 18 µg or 27 µg CIFN daily for 4 weeks, followed by 9 µg and

18 µg, respectively, for 8 weeks, then 36 weeks of 9 µg daily with 1–1.2 g RBV daily, SVR rates were 42% and 37%, respectively.⁴ In a recently published study of 77 patients treated with 9 µg CIFN and 1–1.2 g RBV daily, previous nonresponders to IFN alfa and RBV achieved 22% SVR.⁵

Treatment of 60 PEG IFN and RBV nonresponders using CIFN 9 µg daily with RBV 11 mg/kg daily yielded response rates of 23%.⁶ This was lower than the 37% SVR obtained in a 15 µg CIFN with RBV re-treatment regimen of 137 PEG IFN/RBV nonresponders.⁷

At the 2006 Digestive Disease Week meeting, several studies using CIFN were presented and summarized.

Rothstein and colleagues, in a study of 50 patients who had not responded to PEG IFN and RBV (81% nonresponders), used a complex regimen of induction dosing with 27 µg and then 18 µg CIFN daily, with a dose-escalating regimen of RBV of 800 mg for the first 12 weeks, then 1–1.2 g daily for the remaining 36 weeks. Half of the patients were cirrhotic and another quarter had bridging fibrosis, and 96% were genotype 1. The SVR was 21% in this cohort, and although discontinuation occurred in only 18% of patients, dose reductions were needed in one third, and growth factors were used in over 40% of patients. The SVR in the true nonresponder cohort was not reported, but it is likely lower than the overall SVR of relapsers. It is not clear if such a complex dose escalating regimen of RBV with high induction dosing of CIFN is necessary because there was no other arm in this study. Regimens using induction dosing have not achieved higher response rates in PEG IFN nonresponders than that reported with 9 µg daily with RBV.

In a retrospective analysis of 49 patients who were either nonresponders to PEG IFN/RBV (n=30) or relapsers (n=19), treatment for 48 weeks with CIFN 15 µg daily and RBV 11 mg/kg daily yielded end-of-treatment response rates of 30% and 79%, respectively. Although 90% of the nonresponder group was genotype 1, only 68% of the relapsers were genotype 1. The 24-week responses were identical to end of treatment, suggesting that there is no further accrual of responders beyond 24 weeks, which is consistent with patterns seen with PEG IFN, but contrary to a report by Leevy in 2004 suggesting that there

was an increasing number of individuals with undetectable virus between 24 and 48 weeks.⁷

Two studies presented by Kaiser and associates focused on extending therapy in relapsers and assessed differences between retreatment with PEG IFN alfa-2a and -2b nonresponders. Both of these are intriguing concepts. The first study was a 72-week treatment study of 81 PEG IFN alfa-2a and -2b relapsers who were retreated with either CIFN 9 µg daily with RBV 1–1.2 g/day or PEG IFN alfa-2a 180 µg weekly with RBV 1–1.2 g/day. The majority of patients were genotype 1 or genotype 4 in both arms (80% and 74%, respectively) and had high viral load. Roughly 20% were cirrhotic. The end-of-treatment response rates in the CIFN and PEG IFN arms were 89% and 76% with SVR in 69% and 44% ($P < .05$) of patients, respectively. This study highlights a clear superiority of CIFN over PEG IFN alfa-2a in the re-treatment of relapsers. The reported relapse rate in the PEG IFN alfa-2a arm was higher than in the CIFN arm, though not all patients have completed therapy yet and the numbers may change. This study also illustrates the fact that relapsers respond very well even to 9 µg daily of CIFN with only 15% requiring dose reductions and fewer cases of cytopenia than seen with PEG IFN alfa-2a.

The head-to-head IDEAL (Individual Dosing Efficacy vs Flat Dosing to Assess Optimal Pegylated Interferon Therapy) trial to determine superiority of PEG IFN alfa-2a versus -2b is underway, but it does appear that the relapse rates seen with PEG IFN alfa-2a are greater by as much as 15% when compared to PEG IFN alfa-2b.⁸⁻¹² Re-treatment of PEG IFN nonresponders with a different PEG IFN has not to date shown benefit. Kaiser and associates assessed re-treatment of both PEG IFN alfa-2a and -2b nonresponders with two doses of CIFN (9 µg daily or 27/18/9 µg induction) with RBV 1–1.2 g/day for 48 weeks in 195 patients, over 90% of whom were genotype 1. Pooled data from both treatment arms showed that SVR rates for the patients that have completed therapy to date are greater in PEG IFN alfa-2a nonresponders versus -2b (38% vs 23%). If this trend remains in results from the entire study cohort, it will suggest an underlying difference that may exist between the two pegylated products. However, a complete data set will be needed, as well as a breakdown of the two arms and how patients were distributed between them before any conclusive remarks can be made.

The increasing number of CIFN studies in the PEG nonresponder population speaks to the need for treatment options in this difficult-to-treat group, who are often genotype 1, have high viral load, and are overweight. In particular, African Americans have a very low response rate to PEG IFN therapy. The various studies using CIFN, however, use different and sometimes unusual dosing regimens of both CIFN and RBV, making it difficult to compare them. To further confuse matters,

nonresponders and relapsers are often pooled together, as are various genotypes. This reduces the ability to analyze data sets and come to meaningful conclusions. The definition of nonresponse varies from study to study, and this also requires a standardized definition for future trials.

These studies of CIFN have all been consistent in showing efficacy in nonresponder and relapse populations. However, a key question remains: does CIFN offer a treatment option for the PEG IFN nonresponder? It appears there is a role for CIFN in this population. There is enough data suggesting CIFN efficacy in the 20–30% range for nonresponders to PEG IFN, but this may represent the ideal scenario. Cirrhotic patients, HIV coinfecting patients, and African Americans may still face very low response rates, regardless of the IFN used. It is hoped that the DIRECT trial will provide some clue as to response rates and overall utility of CIFN in these populations. Data will need to be analyzed with regard to the various negative predictive factors stated above to determine the drug's optimal use and where re-treatment with any IFN and RBV combination is futile. Because it is not a foregone conclusion that small molecule adjuncts such as polymerase and protease inhibitors will add anything to the treatment arena, it is worth assessing CIFN rigorously to determine if it does indeed have a role in nonresponders and relapsing populations.

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