

# Review of consensus interferon in the treatment of chronic hepatitis C

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**Abstract:** Consensus interferon (CIFN) is an artificially engineered interferon that reflects most of the human genotype 1 interferons and shows a higher biological and antiviral capacity in vitro. It has been used internationally to treat patients with chronic hepatitis C (HCV) infection before pegylated IFN became available. To mimic the half-life of PEG-IFN it has to be administered on a daily basis. The gold standard in the treatment of hepatitis C is well established and recommended. Today patients are being treated with a combination therapy of pegylated IFN and ribavirin. Length and dosage of therapy depends on the genotype of the virus. Patients with genotype 1 and 4 and high viral load should be treated for 48 weeks; for patients with these genotypes along with either low viral load or early virological response, therapy for 24 weeks is sufficient. Patients with genotype 2 and 3 should be treated for up to 24 weeks. However, daily dosing of IFN- $\alpha$ , eg, CIFN, resulting in a higher cumulative dosage, might be beneficial and more efficacious in some chronic HCV-infected patients. Patients with genotype 1, having initially high viral load (>800,000 IU/mL) and showing advanced liver disease with progressive fibrosis or even cirrhosis comprise the difficult-to-treat in order to overcome the infection. This review summarizes and critically discusses the published data on the treatment of HCV with CIFN.

**Keywords:** CIFN, interferon-alfacon-1, early virological response, sustained virological response, PCR, pegylated IFN- $\alpha$ -2a/b

## Background

Under physiological conditions, interferon- $\alpha$  (IFN- $\alpha$ ) is a key cytokine produced by virtually all cells in the mammalian organism in response to a variety of bacterial and viral stimuli. In response to viral infection, IFN- $\alpha$  produced by the infected target cells induces a number of cellular genes involved in inhibition of viral replication. In addition, IFN- $\alpha$  is secreted by stimulated NK-cells and T-cells, and exerts a multitude of immune stimulatory effects of innate and adaptive immunity (Pestka 1997). Examples of IFN-stimulated gene products include 2'5'oligoadenylate synthetase (2'5'OAS) and  $\beta$ 2-microglobulin.

The current standard to treat patients with chronic hepatitis C (HCV) infection is IFN- $\alpha$  with or without ribavirin, and great advances have been achieved (Cornberg et al 2002). So far 2 allelic  $\alpha$ -2 species, IFN- $\alpha$ -2a and IFN- $\alpha$ -2b, have been used. Introduction of pegylated IFN in 2001 showed a slight increase in the overall sustained virological response rates (approximately 55%) compared with conventional IFN- $\alpha$  (36%) (Manns et al 2001; Fried et al 2002). However, recent studies showed that these response rates depend on several factors, including HCV genotype, baseline viral load, ethnicity, body weight and presence of advanced liver disease (Manns et al 2001). More than 75% of patients in western Europe are infected with genotype 1 showing a high viral load and these patients are so called "difficult to treat" and therefore remain at

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risk not to respond to standard HCV treatment (Di Bisceglie and Hoofnagle 2002). There is still a need for improved therapies, especially for difficult to treat patients such as HCV-genotype 1 infected individuals, patients with liver cirrhosis, or patients of any genotype who did not respond to a previous IFN- $\alpha$ -based therapy (Shiffman 2004). Even the new standard therapy of pegylated IFN- $\alpha$  (PEG-IFN- $\alpha$ ) in combination with ribavirin is not very effective for the so called non-responder patients. Relapsed patients may benefit from retreatment but patients with HCV-genotype 1 who were true non-responders to IFN and ribavirin demonstrated only 12% sustained virological response (SVR) with PEG-IFN and ribavirin as second-line therapy (Shiffman 2004; Poynard et al 2005). However, viral eradication should be still the first achievable goal whenever possible.

## IFN-alfacon-1

IFN-alfacon-1, a non-natural recombinant interferon, is a second-generation cytokine that was engineered to contain the most frequently occurring amino acids among the non-allelic IFN- $\alpha$  subtypes in humans (Blatt et al 1996) to form a consensus molecule. In rhesus monkey LLC cell line and golden Syrian hamster BHK cell line *in vitro* studies have shown that IFN-alfacon-1 causes a more dramatic decrease of HCV-RNA compared with IFN- $\alpha$ -2b (Sjogren et al 2007) and showed a 10-fold higher antiviral efficacy (Blatt et al 1996). These studies have been confirmed in further *in vivo* studies.

Because the serum levels of consensus IFN (CIFN) given 3 times a week drops almost below the detection limit by the next dose, daily dosing of CIFN has been used in some studies (Kaiser et al 2005). In some studies, a high initial dosing has been used as induction therapy to reduce viral load and obtain an early virological response (EVR), reasoning that this would lead to a higher SVR (Lam et al 1997). CIFN is approved for use in the US at the dose of 15  $\mu$ g and in Europe at the dose of 9  $\mu$ g sc in therapy-naïve HCV infected patients 3 times a week (tiw) for up to 6 months.

To date, several controlled but small studies have been published investigating the role, safety and efficacy of IFN-alfacon-1 in patients with chronic HCV who were either naïve to antiviral therapy or did not respond to antiviral combination therapy with IFN- $\alpha$  or PEG-IFN- $\alpha$  in combination with ribavirin.

However, due to economic reasons and after a merger of the former company distributing CIFN the drug has been taken off the market by the manufacturer, at least in Germany, in 2006.

## Methods

This article reviews the results of recent published and preliminary studies involving IFN-alfacon-1 and ribavirin in the treatment of chronic HCV. The published literature was identified using a MEDLINE/PubMed search with secondary review of cited publications. All articles have been carefully read and are critically discussed.

## Results

In an early multicenter, randomized, controlled, double-blind, phase III study with 704 patients with chronic HCV infection, Tong et al (1997) compared CIFN at doses of 3  $\mu$ g and 9  $\mu$ g to a standard regimen of recombinant IFN- $\alpha$ -2b at 15  $\mu$ g 3 times weekly for 24 weeks with a 24 week follow-up period in a therapy-naïve cohort. The beneficial effect was greater with the 9  $\mu$ g dose than the 3  $\mu$ g dose. The sustained alanine aminotransferase (ALT) and HCV RNA response rates were 20.3% and 12.1%, respectively, in the 9  $\mu$ g CIFN cohort and 19.6% and 11.3%, respectively, in the 15  $\mu$ g IFN- $\alpha$ -2b cohorts (Tahara et al 2007). Patients with HCV genotype-1 did respond better in the high dose CIFN cohort (24% vs 15%). Improvements in liver histology were noted in all 3 treatment groups. The adverse-event profiles were similar in all cohorts.

In a subsequent multicenter trial, a higher dose of CIFN (15  $\mu$ g) was reinstated in patients who either had relapsed or were non-responders to prior CIFN or IFN- $\alpha$ -2b therapy. Patients were randomized to receive 24 or 48 weeks of retreatment followed by 24 weeks of observation. The SVR were 28% in relapsers and 5% in non-responders, respectively, in the 24-week retreatment cohort and 58% and 13%, respectively, in the 48-week retreatment cohort, indicating that longer treatment in relapsers and non-responders results in a better overall response rate. The administration of 9  $\mu$ g or 15  $\mu$ g CIFN was well tolerated and adverse effects were similar to those of IFN- $\alpha$ -2b. 15  $\mu$ g of CIFN provided meaningful response in both relapsers and non-responders (Keeffe and Hollinger 1997).

In a randomized study of Pockros et al (1998), 704 patients have been treated with CIFN. Two-hundred and thirty-two patients received 3  $\mu$ g CIFN tiw, 232 patients received 9  $\mu$ g CIFN tiw, and 240 patients were treated with IFN- $\alpha$ -2b at 3 MU tiw. Fifty-three percent of patients (120/225) who had normal ALT concentrations showed undetectable HCV RNA at the end of treatment. At the end of follow up, 47% presented a sustained virological response. In contrast, of the patients with undetectable HCV RNA, 75% (120/161) and 84% (51/61) had normal serum ALT activities

**Table 1** Studies investigating the role of IFN-alfacon-1 and ribavirin in the treatment of therapy-naïve patients with chronic hepatitis C

Author	Method	No patients	Dosing regimen	Results EVR, SVR	Conclusion
Hwang et al 1999	Randomized, double-blind, controlled	75 Chinese	9 or 3 µg of CIFN tiw vs placebo for 24 weeks	EOT response was 56%, 42.3% and 4.2% at week 24; SVR at week 48 40%, 11.5% and 0%	Safe and effective to reduce ALT and HCV RNA concentration
Jensen et al 1999	Multicenter phase 3	472 US	9 µg CIFN vs 3 MU IFN- $\alpha$ -2a tiw for 24 weeks	EOT response was 51% vs 31%	Genotype and baseline viral load are independent factors predicting response
Yao et al 2000	Multicenter, randomized, controlled	187 Chinese	15 or 9 µg CIFN or 3 MU IFN- $\alpha$ -2a tiw for 24 weeks	SVR response was 55.7% vs 49.2% vs 39.3%	CIFN is safe and effective, 15 µg CIFN is more effective than 3MU IFN- $\alpha$ -2a
Kao et al 2000	Multicenter	48 Taiwanese	9 µg vs 3 µg. of CIFN tiw for 24 weeks	EOT 48 vs 44%, SVR 16 vs 12%	9 µg CIFN is safe and effective
Hwang et al 2001	Multicenter, open-label	35 Chinese	15 vs 9 vs 3 µg CIFN vs placebo tiw	SVR 66% vs 20% vs 36% vs 31%	15 µg CIFN is similarly effective as compared with 9 µg CIFN, and there is benefit for pre-treated patients
Layden et al 2002 (31)	Multicenter	173 US	Induction therapy for 4 wks followed by 9 µg CIFN tiw	SVR: 11% in GT-1 and 41 in non-GT-1 patients	Induction dosing of CIFN did not improve SVR rates
Pockros et al 2003 (37)	Randomized pilot study	40 US	9 µg CIFN alone daily vs 9 µg CIFN daily plus RBV for 48 weeks	GT-1 response 50 (10/20) vs 55% (11/20)	Trend towards higher response rate (compared with monotherapy), enhanced SVR by combined therapy; daily dosing seems feasible
Fattovich et al 2003 (15)	Open-label, randomized study	193 Italian	9 or 18 µg CIFN tiw plus RBV daily for 24 or 48 weeks (GT-1)	SVR GT-2/3 is 69 vs 66%, GT-1 40 vs 36%; overall SVR was 67 vs 38% (GT-2/3 vs GT-1)	Higher dosing of CIFN did not increase SVR rate
Saito et al 2006 (40)	Open-label, randomized	28 Japanese	CIFN 9 µg/daily prior induction therapy with/without IFN- $\beta$ ( $2 \times 3$ million IU/daily)	SVR was 81.3% with induction vs 58.3% without induction, SVR with HVL was 70 vs 75%	Induction therapy has no beneficial effect on efficacy, high drop-out rates, lot of adverse events
Witthöft et al 2007	Open-label, pilot-study	58 German	18 µg of CIFN daily for 8 weeks followed by 9 µg CIFN daily plus RBV for 16 or 40 weeks	SVR in 48% of patients with GT-1; 62% of all patients responded at week 24 or 48	Rate of EOT is lower compared with standard therapy; daily CIFN is safe and tolerable

**Abbreviations:** CIFN, consensus interferon; EOT, end of treatment; GT-1, genotype 1; GT-2/3, genotype 2 or 3; HVL, high viral load; IFN, interferon; IU, international units; LVL, low viral load; RBV, ribavirin; SVR, sustained virological response; tiw, 3 times weekly.

at the end of treatment and post-treatment observation period, respectively. Most patients with undetectable HCV RNA had normal ALT values. In contrast, only half of the patients with normal ALT values were negative for HCV. At the end of treatment, HCV RNA response predicted sustained virological response better than did the ALT response (Pockros et al 1998).

In a large multicenter trial, 472 patients have been treated with either CIFN or IFN- $\alpha$ -2b for up to 6 months. The purpose of the analysis was to compare the efficacy parameters (eg, clearance of HCV RNA, normalization of ALT values, and improvement of histology) in non-fibrotics, fibrotics, and cirrhotics. Patients with cirrhosis and chronic HCV infection showed the same benefit from IFN treatment as non-cirrhotic patients when efficacy was assessed by clearance of serum HCV RNA or by histological benefit. Sustained virological responses were similar when measured among non-fibrotic (11%), fibrotic (13%), and cirrhotic (11%) patients. Cirrhotic patients had a lower sustained ALT response rate (12%) than did non-fibrotic patients (23%). Ninety percent of non-fibrotics but only 71% of fibrotics and 67% of cirrhotics who sustained a virological response showed normalized ALT. In conclusion, liver cirrhosis should not be a reason for excluding patients from therapy, because both cirrhotic and fibrotic HCV patients benefited from IFN therapy, not only by clearance of the virus but by improvement in liver histology (Everson et al 1999).

In Canada, 467 patients chronically infected with HCV were treated with either CIFN at 9  $\mu$ g or 3 MU IFN- $\alpha$ -2b tiw. Eighteen percent of patients showed a breakthrough of HCV-RNA, and 19% showed a breakthrough of ALT. When the patients who were initially non-responders to IFN treatment were re-treated with CIFN (15  $\mu$ g) for 12 months, 27% of those with viral breakthroughs had a sustained viral response compared with 8% in prior non-responders without breakthroughs. Sustained ALT responses were observed in 39% with breakthroughs compared with 10% in those without breakthroughs. Heathcote et al (1999) concluded that prior non-responders with breakthroughs have a greater chance of responding to retreatment than do non-responders without breakthrough (defined as re-occurrence of the virus throughout therapy). However, repeated HCV-RNA testing has to be conducted during therapy.

Genotyping has been shown to predict response to IFN, but it is expensive. HCV serotyping is less expensive and simple, and may be equally useful. In a large multicenter trial, 704 patients with chronic HCV infection treated with CIFN 3  $\mu$ g, 9  $\mu$ g or IFN- $\alpha$ -2b tiw, the end of treatment HCV

RNA rate of response (defined as undetectable serum on two consecutive assessments) was 29% for serotype 1 vs 24% for genotype 1 after CIFN. The corresponding rates with IFN- $\alpha$ -2b were 14% vs 15%, respectively. Independently of treatment, patients infected with serotype or genotype 2 or 3 had a better therapeutic response than those infected with genotype 1 (Keeffe et al 1999a).

Patients with genotype 1 showed lower response rates than those with genotype 2 and 3. In a multicenter trial, 472 patients with chronic HCV treated with either CIFN or IFN- $\alpha$ -2b, neither virological sustained responders nor relapsers differed in the pattern of serum HCV RNA decrease based on genotype. Relapsers had a slower rate of serum HCV RNA decrease than did virological sustained responders. HCV genotype 1 treated with CIFN had a greater decrease in HCV RNA during therapy than did patients treated with IFN- $\alpha$ -2b. However, there was no difference in the magnitude of serum HCV RNA decrease between the two IFN treatments for patients with genotype 2 or 3 (Keeffe et al 1999b). Patients who relapsed after a prior treatment with CIFN at doses of either 3 or 9  $\mu$ g may benefit from a re-treatment with 15  $\mu$ g.

IFN is a potent cytokine with multiple targets. From previous studies it is very well known that patients being treated with IFN- $\alpha$  for chronic HCV infection may develop either hypo- or hyperthyroidism with destructive thyroiditis. In a prospective Italian trial, 51 patients with chronic HCV infection and without pre-existing thyroid disease received antiviral therapy with IFN- $\alpha$ -2b plus ribavirin or CIFN plus ribavirin. Ten out of 36 patients developed thyroid autoimmunity during therapy with IFN- $\alpha$ -2b. Under CIFN treatment, 5 out of 15 patients developed thyroid autoimmunity and stopped antiviral treatment. All patients did recover from thyroidism without specific treatment. However, CIFN may induce thyroid autoimmunity in a larger proportion compared with IFN- $\alpha$ -2b (Mazziotti et al 2002).

In a small study in Brazil, 14 patients were treated with a rather high dose of CIFN of 15  $\mu$ g plus ribavirin (1000 mg) daily for 4 weeks followed by 9–15  $\mu$ g every second day for 44 weeks. In 10 patients there was a marked decrease of viral load at week 2, and 10 patients showed a loss of HCV RNA by the end of treatment. SVR was seen in 4 out of 11 patients (36%) who completed 24 weeks of follow up (Da Silva et al 2002).

Patients with genotype 2 and 3 may respond better to antiviral therapy compared to genotype 1 patients. Fattovich et al (2003) determined the efficacy and safety of different doses of CIFN plus ribavirin in the initial treatment of chronic

HCV infection. Patients with GT 2/3 received either 9  $\mu$ g (group A) or 18  $\mu$ g (group B) of CIFN tiw plus ribavirin for 24 weeks. Genotype 1 patients were treated with 9  $\mu$ g (group C) or 18  $\mu$ g (Group D) for 48 weeks. In an ITT analysis, the sustained virological response at 24-week follow up was 69% and 66% for groups A and B and 40% and 36% for groups C and D. The overall SVR was 67% and 38% in patients with genotype 2/3 and 1, respectively. Therefore, a higher CIFN dose does not increase SVR.

Despite the genotype, the response to antiviral treatment depends also on a different racial and ethnic background. Three-hundred and thirty patients with chronic HCV infection were treated with CIFN as a daily induction therapy at 15  $\mu$ g daily for 30 days followed by a randomized 1:1 ratio of either 9 or 15  $\mu$ g every other day. Thirty percent of patients were non-white. An overall SVR was achieved in 24% of white, 12% of Hispanic, and 4% of African-American patients. Fifteen percent of white and 13% of Hispanic genotype 1 patients achieved SVR compared with 2% of African-American. Surprisingly, a SVR of 50% and 40% was achieved in African-American and white genotype 2 patients, compared with 10% in Hispanic patients (Gaglio et al 2004).

Combination therapy with PEG-IFN ( $\alpha$ -2a or -2b) and ribavirin is the most effective therapy for patients with HCV infection. However, responses are less than optimal in some subgroups of patients. Viral kinetics might be useful to predict therapeutic outcome. Rapidity of virological response seems to be a better predictor than genotype and initial viral load. Weight-based dosing of ribavirin has emerged as another important consideration. This strategy seems to be the most important for difficult-to-treat patients with genotype 1 or advanced fibrosis, and for African Americans, and is possibly important for patients who have genotype 3 and high viral load. Re-treatment of non-responders with IFN-based therapy has been associated with low rates of sustained virological response. CIFN might offer a new option for patients who did not achieve an early treatment response to standard or PEG-IFN plus ribavirin (Brown 2007).

In an open-label single-center study, 58 patients with chronic HCV were treated with a high-dose induction therapy with CIFN and ribavirin. The rationale for daily dosing in this study was based on the observation that serum levels of IFN- $\alpha$  given 3 times a week were dropping almost below the detection limit every other day and therefore reducing the antiviral capability. High initial dosing reduced the viral load even further and EVR yielded a higher SVR than 9  $\mu$ g daily (Lam et al 1997).

A more recent study compared the virologic response with CIFN or PEG-IFN- $\alpha$ -2b plus weight-based ribavirin in patients chronically infected with HCV genotype 1. The ITT analysis showed a response of 37% vs 41%, respectively, with response rates of 42% vs 44% observed in an analysis of the per-protocol population. Tolerability of the 2 treatment regimens was similar. In conclusion, both treatment regimens were safe and gave a similar antiviral response. If CIFN is administered daily rather than 3 times weekly, eradication of HCV could be achieved in a larger proportion of patients infected with HCV genotype 1 (Sjogren et al 2007).

Even though enormous advances in treating patients with chronic hepatitis C have been achieved over the last decade (Cornberg et al 2007), there is still a need for improved therapies, especially for the difficult-to-treat patients such as HCV genotype 1-infected individuals, patients with liver cirrhosis, or patients who did not respond to a previous IFN- $\alpha$ -based therapy (Shiffman 2004). In an open label pilot study Cornberg et al (2007) investigated the efficacy of CIFN plus ribavirin on viral kinetics, sustained virological response, and histological response in HCV non-responders. Seventy-seven patients were enrolled to receive CIFN given daily in combination with ribavirin 1000/1200 mg. An 8-week induction-dosing regimen of 18  $\mu$ g CIFN, followed by 9  $\mu$ g for 40 weeks was compared with 9  $\mu$ g CIFN for 48 weeks. Ninety percent of patients were infected with HCV genotype 1. Overall, 82% of the patients demonstrated an EVR, 65% had an end of treatment response, and the SVR was 30%. IFN/ribavirin non-responders demonstrated a SVR of 22%. Induction dosing resulted in a greater first-phase HCV RNA decay, which, however, did not translate to a better SVR, presumably due to more dose modifications. High ALT, younger age, and second-phase viral kinetics were associated with SVR. Only sustained responders and relapse patients showed an improved liver histology. In conclusion, daily dosing of CIFN plus ribavirin may be a promising concept for selected non-responders before considering therapies that are anti-viral but not curative. However, motivation and compliance are requisite and a CIFN induction is not required (Cornberg et al 2006).

Despite advances in the therapy of chronic HCV, a large number of patients do not respond to current therapies. In an open-label, prospective, randomized, controlled study, 128 patients with chronic HCV were treated either with CIFN 15  $\mu$ g tiw, plus ribavirin 1000 mg/day, or 3 MU IFN- $\alpha$ -2b tiw plus ribavirin 1000 mg/day for 48 weeks. The endpoint of the study was a SVR (defined as undetectable HCV RNA at 24 weeks post 48 weeks of treatment).

Overall, 57% of subjects in the CIFN/ribavirin group achieved a sustained viral response, compared with 40% of subjects in the IFN- $\alpha$ -2b/ribavirin group. In the subset of subjects with a high viral load, HCV RNA was successfully eradicated in more individuals who received CIFN/ribavirin than subjects who received IFN- $\alpha$ -2b/ribavirin (57 vs 31%). Among individuals with genotype 1 and high viral load, the sustained antiviral response was significantly higher with CIFN/ribavirin than with IFN- $\alpha$ -2b/ribavirin (46 vs 14%). In conclusion, the study demonstrated that the combination of CIFN and ribavirin provides a significantly better treatment response than the combination of IFN- $\alpha$ -2b and ribavirin in chronic HCV subjects infected with genotype 1 and high viral RNA load (Sjogren et al 2005).

Recently, one study showed that daily dosing of 9  $\mu$ g CIFN significantly increased the SVR compared with a 9  $\mu$ g tiw regimen (Rustgi et al 2005). Preliminary data from a single center study suggested that daily dosing of CIFN in combination with ribavirin can achieve SVRs of 38%–45% in non-responders to standard IFN and ribavirin depending on the CIFN dose (Kaiser et al 2005). High-dose-induction therapy seemed to further improve SVR in this study (Kaiser et al 2005), even though it was not effective in studies with standard IFN- $\alpha$ -2a or -2b (Carithers et al 2000; Fried et al 2000; Hadziyannis et al 2001). In a recent study it has been assessed that the first-phase viral kinetics in 20 previously non-responders after a single dose of 15  $\mu$ g or 30  $\mu$ g CIFN and demonstrated a significantly sharper decline (0.8 vs 1.5) of the HCV-RNA with the higher dose after 24 hours (Cotler et al 2003). Sjogren et al (2005) have shown that combination therapy of CIFN and ribavirin provides a significantly better treatment response compared with the combination of IFN- $\alpha$ -2b and ribavirin in chronic HCV subjects infected with genotype 1 and a high viral load.

Patients who failed prior treatment with IFN- $\alpha$  may benefit from a re-treatment with CIFN and ribavirin. One-hundred and three patients (69 non-responders and 34 relapsers) were randomly assigned to high-dose induction therapy (group A) (CIFN 27  $\mu$ g  $\rightarrow$  9  $\mu$ g daily for 24 weeks, 9  $\mu$ g for 24 weeks) or low-dose-treatment (group B) (CIFN 18  $\mu$ g tiw for 12 weeks, followed by 9  $\mu$ g tiw for 36 weeks); each with ribavirin at 800 mg daily. Non-responders treated with high-dose induction had a higher early virological response rate (63% vs 39%). The initial positive effect was lost during the last 24 weeks. Relapse patients revealed SVR in 70% and 38% in groups A and B. Treatment was well tolerated with side effect-related pre-term discontinuation in 8% and 5%. Viral elimination rates might

be further increased by continuous daily administration of CIFN and weight-based ribavirin (Böcher et al 2006).

We recently compared in a single center study the safety and efficacy of high dose daily CIFN (18  $\mu$ g daily for initially 8 weeks followed by 9  $\mu$ g daily) plus ribavirin and PEG-IFN- $\alpha$ -2b plus ribavirin in therapy-naïve patients with chronic HCV infection (Witthöft et al 2007). Treatment regimen with PEG-IFN- $\alpha$ -2a and ribavirin is superior for SVR and tolerability. In genotype 1 the SVR was 58% vs 48%, and in genotype 2 and 3, 85% vs 73%, respectively. Side effects are more common and more severe in patients taking CIFN daily resulting in a higher drop out rate (15.4% vs 0%) and lower SVR. CIFN in combination with ribavirin might be favorable for difficult-to-treat patients with high viral load or non-response to conventional standard therapy. Patients with genotype 1 and low viral load (<800,000 IU/mL) did respond in both arms significantly better to antiviral treatment compared with those with high viral load.

The side effects of IFN- $\alpha$  are fairly similar: influenza-like symptoms, headache, cough, leucopenia and thrombocytopenia, hyper- or hypothyroidism, multiple effects on the immune system, and development of auto-antibodies. These side effects may sometimes be dose-dependent. Systemic sclerosis is an autoimmune disease that might be triggered by the IFN- $\alpha$  and may cause a stiffness of the skin but can affect the heart and the gastrointestinal tract as well. A few cases have been reported after the treatment of HCV with IFN- $\alpha$ -2a or 2b and also with IFN- $\alpha$ -1 (Tahara et al 2007).

## Discussion

Combination of pegylated IFN- $\alpha$ -2a or 2b plus ribavirin is the gold standard in the therapy of chronic viral HCV infection. Most of the studies that have been reviewed are small in patient numbers and have dealt with IFN- $\alpha$ -1 plus ribavirin alone, some have compared its efficacy with that of IFN- $\alpha$ -2a plus ribavirin, but only a few trials have compared CIFN with the newer standard of care such as PEG-IFN- $\alpha$ -2a or 2b plus ribavirin.

But even with this newer pegylated regimen only 50% (eg, in genotype 1 and 4) or up to 80% (eg, in genotype 2 and 3) of patients will achieve a sustained virological response (Fried et al 2002). However, comparing studies is always a problem. Defining the patient who is really a non-responder to prior therapy or who was just not compliant makes a big difference. Adherence is an important factor for the success of the treatment (Fattovich et al 2003). Therapies that induce severe side effects might in the end be less effective despite higher antiviral efficacy. Head-to-head studies

**Table 2** Studies investigating the role of IFN-alfacon-1 and ribavirin in patients with chronic hepatitis C non-responding to or relapsing after therapy with conventional interferon and ribavirin

Author	Method	No patients	Dosing regimen	Results EVR, SVR	Conclusion
Heathcote et al 1999	Open-label, multicenter	176 Canadian (86 break-through, 90 non-responder) after 9 µg CIFN or 3 MIU IFN-α-2a tiw for months	15 µg CIFN daily for 12 months	SVR in 27 vs 8% (break-through vs non-responder), sustained ALT response in 39 vs 10%	Prior non-responders with breakthrough responded better than non-responders without prior breakthrough
Da Silva et al 2002	Open-label	14 Brazilian non-responder to IFN-α-2a plus RBV	15 µg CIFN plus RBV daily for 4 weeks followed by 9–15 µg CIFN plus RBV daily for 44 weeks	EOT in 71% (10/14), in GT-1 EOT of 67%, SVR in 4 of 11 patients (36%)	Rapid decrease of viral load, high SVR of 36% after 24 weeks of follow up
Moskovitz et al 2003	Open-label	24 Canadian non-responders	15 µg CIFN daily in non-responders for 48 weeks	SVR in 2 patients (8%) after 72 weeks	Loss of RNA at EOT in 50% of patients, SVR only 8%
Cornberg et al 2006	Open-label, pilot study	77 German non-responders	8 week induction with 18 µg CIFN daily plus RBV followed by 9 µg CIFN daily or 9 µg CIFN plus RBV for 48 weeks	Overall EVR of 82%, EOT of 65% and SVR of 30%, induction therapy resulted in better SVR rate	Daily CIFN may be promising in selected non-responders
Böcher et al 2006	Open-label	103 German (69 non-responders, 34 relapsers)	27 µg CIFN daily as induction followed by 9 µg CIFN tiw for 24 weeks or 18 µg CIFN tiw for 12 weeks followed by 9 µg CIFN plus RBV	EVR 63 vs 39%, but SVR 26% in both groups	Induction of considerable SVR rates in non-responders, but weight-based RBV might further increase SVR
Alaimo et al 2006	Open-label, randomized	34 Italian non-responders with GT-1	9 µg CIFN plus RBV tiw vs 18 µg CIFN plus RBV tiw for 52 weeks	EVR 35 vs 32%, EOT 35 vs 35%, SVR 27.3 vs 26.1%	Low SVR rate independent of dosage, scarce tolerability
Aladag et al 2006	Open-label	11 Turkish non-responders and relapsers	Re-treatment with CIFN monotherapy with daily dosing (9 µg) in prior CIFN non-responders or relapsers	EOT in NR 60 %, EOT in relapsers 83%; SVR in NR 40%, SVR in relapsers 66%	CIFN in combination with RBV needs further investigation for difficult-to-treat patients

**Abbreviations:** CIFN, consensus interferon; EOT, end of treatment; GT-1, genotype 1; GT-2/3, genotype 2 or 3; HVL, high viral load; IFN, interferon; IU, international units; LVL, low viral load; MIU, million international units; NR, non-responder; RBV, ribavirin; SVR, sustained virological response; tiw, 3 times weekly.

comparing PEG-IFN- $\alpha$ -2a or 2b plus ribavirin and CIFN plus ribavirin are completely lacking.

Dosing of CIFN varies from country to country. In the US, CIFN is being used at concentrations of 15  $\mu$ g tiw and in Germany 9  $\mu$ g tiw is approved. However, these doses might be far too low to achieve a higher SVR rate in chronically infected patients. Because of the pharmacology and kinetics of CIFN, its serum levels change daily; high levels after subcutaneous injection are followed by a day of low serum concentrations. Even though CIFN shows a 10-fold stronger antiviral effect in vitro compared with IFN- $\alpha$ -2a (Sjogren et al 2007), these kinetics are the major disadvantage of the 3-times-weekly treatment schedule with CIFN, giving the virus a chance to recover and multiply, and thus may lead to viral breakthrough or viral resistance. High-dose induction protocols with CIFN and ribavirin, using up to 27  $\mu$ g daily, are quite promising but are associated with severe side effects, eg, influenza-like symptoms, myalgia, leucopenia, thrombocytopenia, neutropenia, depression, and weight loss, associated with higher drop-out rates and requiring dose modifications more often (Kaiser et al 2005; Witthöft and Fuchs 2007). Drug companies are aware of this shortcoming and strategies linking CIFN to a larger molecule like polyethylene glycol or albumin are under development. This formula may extend the stay of the molecule in the serum, and therefore enhance its antiviral capability and efficacy. A once-weekly dosing of CIFN may increase compliance in patients, resulting in higher sustained virological response rates.

However, subcutaneous injection every other day followed by IFN-specific side effects such fever and influenza-like symptoms does not make CIFN a favorable drug for patients compared with PEG-IFNs. So far, CIFN given even at high-dose induction therapy in non-responders was well tolerated by treatment-experienced and motivated patients (Cornberg et al 2006).

As expected, patients with advanced fibrosis or even cirrhosis showed low response, and these patients, who would benefit most from curative antiviral treatment, have the worst outcome (Cornberg et al 2006). These patients may benefit from a low-dose IFN maintenance treatment to prevent complications of liver cirrhosis (Curry et al 2005; Erhardt et al 2007).

## Conclusion

PEG-IFNs plus ribavirin are standard of care for the treatment of naïve patients with chronic HCV infection, and long-term maintenance therapy with PEG-IFN might be the therapy of choice for cirrhotic patients (Kaiser et al 2005).

However, selected and highly motivated patients with less fibrotic damage of the liver, and non-responders to previous therapy, may consider alternative therapies such as daily dosing of CIFN plus ribavirin in order to achieve sustained viral treatment, as long as the pegylated formula of CIFN or polymerase or protease inhibitors are not available. CIFN has demonstrated efficacy in the re-treatment of non-responders and relapsers. Although the optimal duration of treatment and the benefits and safety of maintenance therapy have not been determined, an extended duration is likely needed. The antiviral efficacy of CIFN combined with a once-weekly injection of, for example, a PEG-CIFN plus ribavirin might be another therapeutic option in the near future.

## Disclosures

The author has no conflicts of interest to disclose.

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