Different doses of consensus interferon plus ribavirin in patients with hepatitis C virus genotype 1 relapsed after interferon monotherapy: A randomized controlled trial

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Abstract

AIM: To assess the efficacy of different schedules of consensus interferon (CIFN) plus ribavirin in retreating chronic hepatitis C patients who relapsed after recombinant interferon (rIFN) monotherapy.

METHODS: Forty-five patients (34 males and 11 females) with chronic hepatitis due to hepatitis C virus (HCV) genotype 1 who relapsed after a previous course of rIFN monotherapy were randomized to receive 9 μg CIFN three times per week for 52 wk (group A, *n* = 22) or 18 μg CIFN three times per week for 52 wk (group B, *n* = 23) in combination with ribavirin 800 to 1200 mg daily for 52 wk (according to body weight). Virological response was evaluated at week 24 (EVR), at the end of treatment (ETR) and at 76 wk (SVR).

RESULTS: By intention-to-treat analysis, subjects in group A had an EVR in 35% of cases, an ETR in 35% and a SVR in 27.3% of cases. Subjects in group B had an EVR in 32% of cases, an ETR in 35% and a SVR in 26.1% of cases. Treatment was stopped because of adverse effects (mostly intolerance) in 15 patients (6 in group A and 9 in group B). IFN dose reduction was needed in 2 patients (1 in group A and 1 in group B). Ribavirin dose was reduced in 2 patients in group A and 1 in group B respectively. Among the 15 subjects who received at least 80% of the intended schedule, the rate of SVR was 80% (6 in group A and 6 in group B).

CONCLUSION: CIFN in combination with ribavirin when given to HCV genotype 1 relapsers after rIFN monotherapy obtains an unsatisfactory rate of sustained viral clearance independently of dosage of the drug. This may be due to its scarce tolerability.

INTRODUCTION

Retreatment of hepatitis C patients who relapsed after recombinant interferon (rIFN) monotherapy has a fair rate of success when ribavirin is added to the original protocol. About 30% of patients infected with hepatitis C virus (HCV) genotype 1 can clear their viral infection when retreated with rIFN plus ribavirin[1]. The efficacy of pegylated IFN (PEG-IFN) in this context has not been explored in large phase Ⅲ registration trials, but an increased effectiveness has been shown in investigator-driven smaller trials. Lawitz *et al*[2] have recently obtained a sustained viral response of 38% in HCV genotype 1 relapsers (24 out of 63 patients) upon retreatment with PEG-IFN plus ribavirin.

Consensus interferon (CIFN) is an engineered IFN α molecule containing the most frequently occurring amino acids among the non-allelic IFN α subtypes[3]. It was reported that CIFN can significantly decrease HCV-RNA in naïve patients with chronic hepatitis C as compared with IFN α -2b[4]. It is thus conceivable that this increased antiviral effect can lead to a better rate of HCV clearance in subjects with a former incomplete response to other types of IFN. Heathcote *et al*[5] found that CIFN monotherapy at a dose of 9 mg three times per week, can obtain a SVR in 39% (24 wk) and 52% (48 wk) of relapsers as compared to rIFN that can obtain a SVR in 12% (24 wk) and 17% (48 wk) of relapsers.

In order to further clarify the role of CIFN in retreatment, we explored its efficacy at different doses in combination with ribavirin in subjects with chronic hepatitis infected with HCV genotype 1 who relapsed after a course of rIFN monotherapy.

MATERIALS AND METHODS

Patients

Subjects enrolled between January and December 2001, were eligible if they had the following criteria: age 18-65 years, abnormal alanine aminotransferases (ALT), HCV-RNA positive by PCR (Amplicor® HCV, Roche Diagnostic Systems, Basel, Switzerland), genotype 1. All patients received monotherapy with rIFN (alfa-2a or alfa-2b) with an end-of-treatment virological response (HCV-RNA negative by PCR) and subsequent virological and biochemical relapse prior to this study.

Exclusion criteria were: decompensated cirrhosis, hepatocellular carcinoma, autoimmune hepatitis and other autoimmune diseases, metabolic liver diseases (Wilson's disease, haemochromatosis, α-1-antitripsin deficiency), active drug addiction or alcohol abuse, HBV and/or HIV infection, decompensated diabetes mellitus, haemoglobin concentration at baseline less than 120 g/L in women and 130 g/L in men, platelets below $100000/mm^3$ and white blood cells (WBC) below $3000/mm^3$.

The study design was approved by the University's Ethical Committee. Patients provided their written informed consent before entering the study. All subjects after starting treatment were monitored as outpatients. All had a liver biopsy within 12 mo before starting treatment.

Treatment schedule

All patients were randomized into two groups: group A (n = 22) received 9 μg CIFN plus ribavirin while group B (n = 23) received 18 μg CIFN plus ribavirin three times per week for 52 wk. Dose of ribavirin ranged according to body weight (800 mg < 65 kg, 1000 between 65 and 75 kg, 1200 > 75 kg). Treatment was stopped if HCV-RNA was still positive at 26 wk.

Patients were seen monthly up to the end of 24 wk post-treatment follow-up. At each visit symptoms and adverse event were recorded, physical examination, and biochemical tests were performed, and a serum sample was collected and stored at -80℃ for virology.

All blood tests were performed at our hospital laboratory. HCV-RNA was determined by qualitative and/or quantitative assays (Amplicor® HCV and Monitor® HCV, ver. 2.0, Roche Diagnostic Systems, Basel, Switzerland) with a detection limit of 100 (Amplicor®) and 1000 (Monitor®) genomes/mL.

The effects of treatment were evaluated in patients who obtained an ETR: early virological response (EVR): HCV-RNA negative after 24 wk of treatment; end-of-treatment response (ETR): HCV-RNA negative at the end of 52 wk of treatment; sustained virological response (SR): HCV-RNA negative 24 wk after stopping therapy.

Statistical analysis

Statistical analysis was performed by using SPSS software version 11.0.1 for Windows. Means and standard deviation were calculated for continuous variables. The differences in mean values for each group were assessed by using the parametric Student's t test for unpaired data. The statistical significance of differences between subgroups of patients was analyzed using the chi square test for categorical data. Statistical significance was set at $P < 0.05$. Positive predictive value (PPV) was defined as the percent of patients who were observed to have SVR out of the patients predicted to have SVR by a certain criterion (HCV-RNA suppression at the end of therapy).

RESULTS

Features of patients

Forty-five subjects were enrolled between January and December 2001. All patients were infected with HCV genotype 1, and had relapse after an EVR to rIFN monotherapy given 3 to 9 years before. Four subjects had blood transfusions and 4 had a history of i.v. drug abuse, but 37 subjects did not have major risk factors. Twenty-two patients were randomized into group A and twenty-three into group B. The mean age of patients was 41.9 ± 10.9 years. Liver biopsy showed that 3 patients had severe fibrosis (F3 by METAVIR) and 2 had cirrhosis (F4).

Efficacy of treatment

At 24 wk 9 patients (4 in group A and 5 in group B) discontinued their therapy because they were still HCV-RNA positive. An ETR was observed at 52 wk in 15/45 patients (33.3%) and evolved into a SVR at 76 wk in 12/45 patients (26.6%). At all time points the highest dose of CIFN was not better in obtaining suppression of HCV-RNA replication (ETR: 31.8% in group A vs 34.8% in group B, P = NS) and had ultimately a sustained viral clearance (SVR: 27.3% in group A vs 26.1% in group B, P = NS, Table 1). The overall PPV value for SVR of negative HCV-RNA in patients with ETR was 80%.

ALT values (Table 2) were comparable between the two groups at different time points. ALT levels became normal under treatment in a number of patients who were still HCV-RNA positive. However, the concordance between ALT and HCV-RNA at 76 wk was 100% in both groups.

Tolerability and safety

Treatment was stopped in 15 patients (6 in group A and 9 in group B). Five subjects in group A and 7 in group B stopped therapy between wk 1 and 12 (early withdrawal,

Table 1 HCV-RNA clearance at different time points in 2 groups after treatment n (%)

	Group A (n = 22)	Group B (n = 23)	P
At 26 wk (EVR)	7 (31.8)	8 (34.8)	NS
At 52 wk (ETR)	7 (31.8)	8 (34.8)	NS
At 76 wk (SVR)	6 (27.3)	6 (26.1)	NS

EVR: Early virological response; ETR: End-of-treatment response; SVR: Sustained virological response; NS: Not significant.

Table 2 ALT normalization at different time points in 2 groups after treatment *n* (%)

	Group A (*n* = 22)	Group B (*n* = 23)	*P*
At 4 wk	12 (54.5)	10 (43.5)	NS
At 12 wk	13 (59.1)	13 (56.5)	NS
At 26 wk (EVR)	13 (59.1)	13 (56.5)	NS
At 52 wk (ETR)	12 (54.5)	10 (43.5)	NS
At 76 wk (SVR)	6 (27.3)	6 (26.2)	NS

EVR: Early virological response; ETR: End-of-treatment response; SVR: Sustained virological response; NS: Not significant.

EW), 1 in group A and 2 in group B between wk 13 and 52 (late withdrawal LW). Reasons for EW and LW were severe flu-like symptoms and depression.

Reduction of the CIFN dose was needed in two subjects (1 in group A and 1 in group B). Reduction of the ribavirin dose was needed in 2 subjects of group A and 1 subject of group B. Overall, 7 subjects in group A and 8 in group B received at least 80% of the intended cIFN dose and at least 80% of the intended RBV dose. Among these ideally treated patients, the overall rate of SVR was 80% (6 in group A and 6 in group B).

DISCUSSION

Our results do not support a major usefulness of cIFN in retreatment of patients who had a relapse after IFN monotherapy. ITT analysis was able to obtain a SVR only in 26.7% of all patients, without any clear dose. effect in favor of higher doses. Treatment was not particularly well tolerated, since one third of the patients discontinued their regimen, mostly in its early phase due to adverse reactions. When a reasonable compliance to the intended treatment schedule was obtained, the success rate was markedly higher. The main problem in our study was thus the scarce tolerability of combination therapy even at low CIFN doses.

CIFN was assessed in the patients who did not respond to previous courses of IFN. Lindsay[5], who reviewed the comparative virological efficacy of different interferons, stated that in patients who respond to an initial course of alpha interferon and then have a relapse, retreatment with cIFN for 48 wk obtains a high sustained virological response rate, which is similar to that with interferon alpha-2b combined with ribavirin for 24 wk[6]. An Italian group[7] later reported that cIFN given at a dose of 9 g, 5 times per week for 36 wk could obtain a sustained response in 5 out of 12 subjects (42%) who relapsed after combination therapy with interferon alpha-2b and ribavirin. Recently Moskovitz *et al*[8] found that high dose induction therapy with 15 g cIFN/day in prior non-responders to IFN -2b and ribavirin could lead to loss of detectable HCV-RNA in 50% of patients, but this response is only sustained in 8% of patients (2 out of 24) at the end of therapy. Successful retreatment of IFN/RBV non-responders has been reported by Kaiser *et al*[9], who assessed the efficacy of cIFN daily dosing and induction

therapy followed by ribavirin combination treatment in 182 (92% genotype 1) non-responders to former combination therapies. cIFN was given at the dose s of 27, 18 or 9 μg for 4 wk, followed by a reduction to 9 μg for 8 wk in the two higher dosed arms. The sustained SVR was 38%-45% in standard interferon/ribavirin non-responders and 27%-31% in PEG-IFN/ribavirin non-responders. The cIFN dose was reduced in 16%-21% of patients and discontinued in 7%-9% of patients. A randomized controlled trial comparing cIFN plus RBV to standard alfa IFN plus RBV in naïf patients[10] has found a lower rate of treatment withdrawal (less than 10% withdrawals, and treatment within an 80/80/80 schedule achieved in ¾ of all patients). This study also showed that the efficacy of cIFN was higher than that of standard IFN-2b in combination therapy of naïf patients (SVR: 57% *vs* 40%).

The reason for the high rate of treatment interruption in our population is not clear. It was reported that when a formal comparison with IFN-2b was performed in the context or in relapsers after IFN monotherapy[11], the rate of SVR is 58% *vs* 29% in favor of cIFN. However, the overall treatment period was shorter (6 mo for both treatment arms) and 5% of the patients were treated with cIFN and 18% of those on IFN-2b were not infected with HCV genotype 1. Our study could not evaluate whether the low adherence is intrinsic to the drug regimens or attributable to patient-related factors. Since most withdrawals were decided early during therapy at a time when both the patient and the physician were not aware of any virological outcome, and some of these patients had normal or reduced ALT, it is unlikely that any perceived ineffectiveness of therapy may have influenced this choice. An issue that may potentially interfere with the treatment effectiveness is the concurrent diffusion of PEG-IFN based regimens, which are perceived as more tolerable and effective during the period of study. This fact might have oriented the decision of some patients or caregivers to stop therapy in order to receive the newest drug. Since the ultimate results with cIFN are not superior to those with PEG-IFN in the setting of combination therapy, we see no reason to further consider this drug in retreatment of HCV relapsers.

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