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The safety and tolerability of daily infergen plus ribavirin in the treatment of naïve chronic hepatitis C patients

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SUMMARY. The treatment of chronic hepatitis C patients was enhanced when the combination of interferon alfa-2b and ribavirin was shown to be safe and more effective than interferon monotherapy. To date, no published reports have addressed the use of consensus interferon (CIFN) when combined with ribavirin. We conducted a pilot study to compare the safety and tolerability of daily CIFN plus ribavirin to CIFN monotherapy for the initial treatment of chronic hepatitis C patients. Forty subjects were randomized to two treatment groups: CIFN 9 μg daily, or CIFN 9 μg daily plus ribavirin 1000 or 1200 mg daily. All subjects received 48 weeks of therapy except for nongenotype 1 subjects in the combination treatment group who received only 24 weeks of therapy. The results show that at baseline, age, gender, risk factors, race, RNA titres, and liver histology were not different between the two groups. The proportion of subjects with genotype 1 infection was 50% (10/20) and 55% (11/20) for the monotherapy and combination therapy groups, respectively. Fifty (10/20) and sixty-five (13/20) per cent of subjects in the monotherapy and combination therapy groups exhibited a 2-log or greater decrease in viral titre at week 12 (P = NS). Using intent-to-treat analysis, 20% and 40% of enrolled subjects exhibited a sustained viral response in the monotherapy and combination therapy groups, respectively (P = NS). The proportion of subjects requiring dose reduction was 55% (11/20) and 65% (13/20), respectively. Study discontinuations for any reason were 25% (5/20) and 35% (7/20) for the monotherapy and combination groups, respectively. Discontinuations due to adverse events related to study drug were 20% (4/20) and 25% (5/20), respectively. A total of four serious adverse events occurred, two in each treatment group, only one of which was determined to be study-drug related. It is concluded that the safety and tolerability profiles of the two treatments were similar suggesting that daily dosing of CIFN may be difficult to tolerate resulting in discontinuation of therapy in a significant proportion of patients. The combination regimen resulted in a trend towards a higher viral response rate than monotherapy treatment. These data suggest that CIFN may be safely combined with ribavirin and may enhance the sustained response rate but is not well tolerated in US patients when given in a daily dosing regimen.

Keywords: daily, HCV, interferon, ribavirin, safety, tolerability.

INTRODUCTION

Hepatitis C (HCV) is the most common chronic, blood-born infection in the US, with greater than 4 million people believed to be infected [1,2]. As the disease can progress over time from chronic hepatitis (CHC) to cirrhosis, hepatocellular carcinoma (HCC) and ultimately death, HCV infection is now a major public health issue [1,3–6]. By 2008, rates of cirrhosis and HCC may increase by 65%, liver decompensation threefold, the need for liver transplantation fivefold and liver-related deaths caused by CHC twofold [7].

Current available treatments for patients with CHC include interferon alone (standard interferon), interferon plus ribavirin, pegylated interferon alone and pegylated interferon plus ribavirin. Treatment with pegylated interferon or interferon plus ribavirin significantly increases the virological response and decreases the risk of relapse and is, therefore, considered to be the current standard of care for patients with CHC [5,8–11]. A body of evidence now

Abbreviations: ALT, alanine aminotransferases; ANC, absolute neutrophil count; CIFN, consensus interferon; CHC, chronic hepatitis C; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PCR, polymerase chain reaction; RT-PCR, reverse-transcription-polymerase chain reaction; TSH, thyroid stimulating hormone; WNL, within normal limits.

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exists, demonstrating that pegylated interferons are more effective in achieving sustained virological response than natural or recombinant standard interferons [12–15]. Recent, randomized clinical trials of pegylated interferons plus ribavirin have shown enhanced sustained virological responses compared with interferon plus ribavirin [16,17].

Historically, interferon therapy for 6 months duration has been associated with sustained virological response rates of 10–12%. It appears that currently available type 1 interferons have equal efficacy in this clinical situation. However, one study has suggested a benefit of consensus interferon (CIFN) over interferon alfa-2b (Intron-A) in patients with HCV genotype 1 infections with HCV RNA polymerase chain reaction (PCR) titres greater than 2 million copies per millilitre [18]. These differences have become less relevant to clinical practice since the introduction of combination therapy.

Although it is clear that ribavirin monotherapy is ineffective [19], the benefit of adding ribavirin to interferon therapy is substantiated. The aim of this pilot study was to evaluate the safety and efficacy of combination therapy with CIFN and ribavirin.

MATERIALS AND METHODS

The patient population eligible for participation in this study included chronic hepatitis C patients that were naïve to prior interferon treatment and who had compensated liver disease. This study was conducted at four centres within the US and received Investigation Review Board (IRB) review and approval from the appropriate committees at each institution. All patients provided written informed consent to participate in the study. Potential subjects had stable haematological parameters with haemoglobin (Hgb) values of 12 g/dL (females), 13 g/dL (males), WBC > 3000/mm^3, neutrophil count > 1500/mm^3, and platelet count > 75 000/mm^3. A minimum of two alanine aminotransferase (ALT) determinations within 6 months of enrollment was required and both results had to be above the upper limit of the normal reference range (6–43 U/L). A liver biopsy consistent with chronic hepatitis C was required within 12 months of enrollment. Patients were also required to have compensated thyroid function. Subjects who were pregnant or breastfeeding, those with co-infection (HIV or HBV), a history of conditions that predisposed to seizure, significant cardiovascular or renal dysfunction, autoimmune disease, history of solid organ transplantation, drug or alcohol abuse within the 6 months preceding enrollment, uncontrolled diabetes, or current, significant psychiatric disease were excluded from the trial. All patients provided informed consent prior to participation.

Enrolled subjects were sequentially assigned to one of two treatment arms via a centralized randomization process. The two treatment regimens to which subjects were randomized were CIFN 9 μg daily (group 1) (Infergen®, Thousand Oaks, CA, USA) or CIFN 9 μg daily plus ribavirin 1000–1200 mg daily on a weight adjusted basis (group 2). Patients who weighed < 75 kg received 1000 mg of Ribavirin and patients who weighed > 25 kg received 1200 mg of Ribavirin. A ribavirin placebo was not utilized to blind subjects and investigators to treatment allocation. The treatment period was 48 weeks for both groups with one exception; nongenotype 1 subjects assigned to group 2 received 24 weeks of treatment. This aspect of the study design was based on previously published data indicating no additional benefit of 48 weeks of treatment over 24 weeks for this subgroup of patients [9]. Subjects were not withdrawn from the study prior to completing the treatment course based on serum HCV RNA measurements. All patients were followed for 24 weeks after completing the treatment period to determine a sustained viral response.

The primary objective of the study was to compare the 12-week safety and tolerability profiles of CIFN administered with and without ribavirin in naïve, chronic hepatitis C patients. The secondary objectives were to assess the 48-week safety and tolerability profiles of CIFN administered with ribavirin, and to evaluate the sustained response rate of CIFN plus ribavirin and CIFN alone.

Viral load concentrations by reverse-transcription-polymerase chain reaction (RT-PCR) was measured at screening, baseline, weeks 24, 48 and 72. (The non-genotype 1 patients did not have a week 72 visit). The RT-PCR is a quantitative assay with a lower limit of detection of 100 copies/mL (National Genetics Institute, Los Angeles, CA, USA).

Owing to the exploratory nature of this pilot study, the size of the study population was not based on methods intended to produce generally accepted levels of statistical power. All comparisons between groups were performed using non-parametric statistical methods.

RESULTS

Forty subjects were enrolled in 1999 with 20 each randomized to group 1 and group 2. Baseline demographics were similar between the groups (Table 1). Of note, genotype 1 infected subjects comprised a relatively low (50% and 55%) proportion of both groups.

Week 12, 24, 48 and 72 RNA and ALT results are shown in Table 2 using an intent-to-treat analysis. By week 12, normalization of ALT levels occurred more frequently in group 2 than group 1, (10/20 *vs* 4/20, $P < 0.05$, respectively). The proportion of subjects at weeks 24 and 48 who had an ALT level within the normal range was similar between the two treatment groups (Table 4). Fourty per cent of combination patients maintained Sustained Virologic Response (SVR). However, SVR was lost to relapsers in half of the monotherapy patients.

Table 1 Baseline demographics and selected clinical parameters

	Group 1 (Mono) $n = 20$	Group 2 (Combo) $n = 20$
Mean age	48 ± 7.1	47 ± 7.3
Gender (F/M)	7/13	5/15
Race (AA/C/H/As)	3/15/1/1	3/16/1/0
Risk (drugs/tattoo/trans/multiple/UNK)	8/0/3/6/3	13/1/4/2/0
Genotype 1	10	11
Mean viral RNA titre ($\times 10^6$)*	4.0 ± 4.7	3.2 ± 3.1
Viral RNA titre ≥ 2M*	10	11
Mean ALT	135 ± 134.8	111 ± 57.3
Mean haemoglobin	15.0 ± 1.2	15.5 ± 1.3
Cirrhosis/bridging fibrosis	2/20	2/20

Plus/minus values are mean ± SD. All differences between groups were not significant.
*In copies/millilitre (PCR by National Genetics Laboratories, Los Angeles, CA, USA).

Table 2 HCV RNA(PCR) and ALT results for two groups

	WK 12		WK 24		WK 48		WK 72		
	HCV RNA <100 c/mL	ALT WNL	HCV RNA <100 c/mL	ALT WNL	HCVRNA <100 c/mL	ALT WNL	HCV RNA <100 c/mL	SVR by genotype <100 c/mL	
Therapy	(%)	(6–43 U/L)	(%)	(6–43 U/L)	(%)	(6–43U/L)	(%)	Gen1	Non 1
Mono	11/20 (55)	5/19	10/20 (50)	9/18	8/20 (40)	12/15	4/20 (20)	1/10 (10%)	3/10 (30%)
Combo	11/20 (55)	12/18	9/20 (45)	11/14	8/20 (40)	8/15	8/20 (40)	2/11 (18%)	6/9 (67%)
P-values	NS	$P = 0.025$	P = NS	P = NS	P = NS	P = NS	P = NS	P = NS	$P = 0.05$

ALT denotes alanine aminotransferases. HCV RNA denotes serum hepatitis C virus RNA, shown as copies per millilitre × 10^6(c/mL × 10^6).

Table 3 lists the number of subjects experiencing events with at least a 10% incidence occurring through week 72. Myalgia, chills, dizziness, fatigue, headache and depression were more often observed in the monotherapy group than the combination group. Irritability and insomnia were observed more frequently in the combination group. The majority of adverse events occurred within the first 12 weeks of treatment. Only five new events with an incidence of at least 10% presented after that time. These were constipation, decreased libido, hair loss, leg cramps and emotional lability.

Of interest, hypocalcaemia (values less than 8.4 mg/dL), without clinical sequelae, was noted in 11 patients (two in group 1 and nine in group 2). In addition, 9 subjects experienced a decrease in serum total calcium of at least 1 mg/dL. These nadirs were transient and resolved in all but two subjects. All decreases of at least 1 mg/dL occurred very early in treatment with only two of 9 subjects experiencing this decrease after week 8. Hypocalcaemia irrespective of decrease in magnitude, also occurred early in treatment and resolved rapidly in all of subjects.

As expected, anaemia and decreases of greater than 2 g/dL in Hgb concentration were observed more frequently in group 2. Anaemia was observed in two group 1 subjects and 16 group 2 subjects during treatment. The mean decrease was 3.5 g/dL with a range of −5.2 to −1.2 g/dL. Decreases in Hgb greater than 2 g/dL are presented in Fig. 1. Those patients with a significant fall in Hgb in group 2 were more likely to discontinue drug prior to week 48 of therapy.

Mean Absolute Neutrophil Count (ANC) changes for both groups were similar. Neutrophils were reduced by 50% by week 4 in both groups and the pattern of partial recovery by week 48 were comparable. In contrast, the mean platelet counts for group 2 were consistently and moderately higher than those for group 1. The patterns of mean platelet counts during treatment show a relative recovery to baseline in group 2 that is not present in the group 1 data (Fig. 2).

Table 3 Frequency and severity of adverse events occurring through week 72

Event	Group 1 (Mono)			Group 2 (Combo)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Dyspnoea	1	0	0	3	0	0
Myalgia	6	5	0	2	2	0
Chills	10	2	0	6	0	0
Fever	7	2	0	7	1	0
Dizziness	4	2	0	0	0	1
Fatigue	4	9	2	6	5	0
Nausea	3	2	1	3	3	0
Diarrhoea	2	0	0	0	1	0
Headaches	2	5	1	5	0	1
Injection site reaction	1	0	0	2	0	0
Irritability	1	5	0	5	3	0
Anxiety	0	3	1	0	0	0
Inability to concentrate	2	1	0	1	0	0
Insomnia	0	3	0	5	0	0
Depression	3	3	0	0	1	0
Upper respiratory infection	0	2	0	0	1	0
Constipation	0	3	0	0	0	1
Decreased libido	1	1	0	0	0	0
Hair loss	2	0	0	1	0	0
Leg cramps	0	2	0	0	0	0
Emotional lability	0	0	0	0	2	0

Actual events which occurred in 10% of patients in any group.

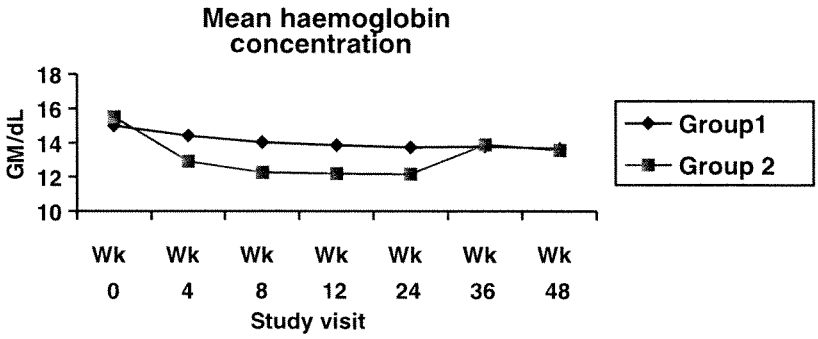

Fig. 1 Changes in mean haemoglobin concentration during treatment in two groups during weeks 0, 4, 8, 12, 24, 36 and 48.

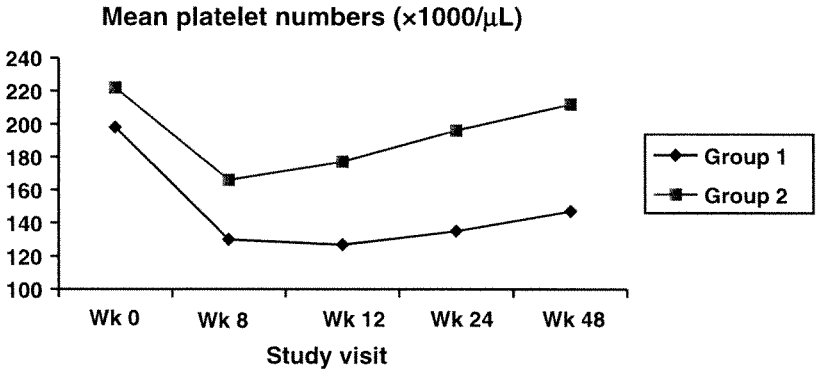

Fig. 2 Changes in platelet count during treatment in two groups during weeks 0, 8, 12, 24 and 48.

Table 4 Study discontinuations

	Week (no.)	Related to Drug? (Y/N)	Comments	AE or SAE
Group 1 $n = 5/20$ (25%)	2	N	Flu-like symptoms	AE
	20	Y	Depression, fatigue	AE
	36	Y	Abdominal cellulitis	SAE (hospitalized)
	36	Y	Leg numbness	AE
	40	Y	Elevated TSH	AE
Group 2 $n = 7/20$ (35%)	1	Y	Flu-like symptoms	AE
	8	Y	Dizzy spells	AE
	12	N	Grand mal seizure	SAE (hospitalized)
	16	Y	Nausea Neutropenia†	AE
	16	N	Haemorrhoidectomy	SAE (hospitalized)
	20	Y	Increase in pre-existing scabies	AE
	32	Y	Flu-like symptoms, irritability	AE

†Neutropenia noted on lab review, independent of site.
Adverse Event (AE): Severe Adverse Event (SAE).

Neutropenia dose reductions were rare. Three subjects (one mono, two combo) experienced grade 3 neutropenia (< 75 mm^3). Only one monotherapy subject had a dose reduction as a result of neutropenia and was able to complete treatment. One combination therapy subject withdrew because of adverse events at week 16 and the other had neutropenia at week 48, that is, at the end of treatment.

Study discontinuations were similar in the two groups (Table 4). Five monotherapy subjects and seven combination therapy subjects did not complete the study. Adverse events related to study drug were four and five in the monotherapy and combination therapy groups, respectively. There were no common events that lead to the withdrawals among these nine subjects. Discontinuations as a result of severe events numbered two in each group.

DISCUSSION

Two separate studies found that a 48-week regimen of interferon alfa-2b plus ribavirin was associated with a sustained virological response in more patients (38% and 43%, respectively) than was interferon alfa-2b alone (13% and 19%, respectively) [8,9]. Sustained virological responses produced by Interferon alfa-2b plus ribavirin are accompanied by a concomitant increase in histological improvement [20]. The mechanism of the beneficial effect of adding ribavirin to interferon therapy is unknown but may derive from its ability to prevent disease relapse via a beneficial immunological effect that may include a number of mechanisms [21].

The results of the current study suggests the combination of CIFN and ribavirin may improve sustained virological response over CIFN monotherapy. The 40% sustained virological response rate for the combination group is similar to that observed for interferon alfa-2b plus ribavirin in other studies. The end of treatment virological response in the combination group was also 40% indicating that no subject relapsed after completing treatment. This was likely a result of small sample size in this pilot trial.

Similar to observations by others, dose reductions as a result of anaemia were rare and occurred in only two combination treatment subjects. Overall however, dose reductions and interruptions were very common and were required in half of the subjects. This rate is twice that reported elsewhere and most likely because of the intensity of a daily interferon regimen [9,16]. Despite this dosing intensity, study discontinuations as a result of severe events were low and similar to other studies. The time course of platelet changes during treatment was interesting in that the mean counts for the combination group recovered to baseline and those for the monotherapy group did not. This may be because of stimulation of the common myelo-erythroid haematopoietic pathway by the anaemia caused by ribavirin. To date we are unaware of another report of this phenomenon.

This study also suggests that the use of daily CIFN is difficult for patients to tolerate, at least at these four US centres, whether used in combination or as monotherapy. If a combination regimen is to be useful, an alternative dosing schedule of CIFN will need to be evaluated other than daily dosing. Such a trial using CIFN 15 μg three times a week plus ribavirin is currently underway [22].

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