• *VIRAL HEPATITIS* •

# Interferon β-1a alone or in combination with ribavirin: A randomized trial to compare efficacy and safety in chronic hepatitis C

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## Abstract

**AIM:** To compare the efficacy and safety of recombinant human IFN β-1a alone or in combination with ribavirin in treatment-naïve subjects with chronic hepatitis C.

**METHODS:** Open, randomized trial was performed in 6 Italian tertiary centers: 102 of the 108 patients screened were randomized to receive 6 MIU of recombinant human IFN β-1a subcutaneously daily for 24 wk, alone (Group 1, *n* = 51) or in combination with ribavirin 1 000 to 1 200 mg/d (Group 2, *n* = 51).

**RESULTS:** The end-of-treatment virologic response rate was 29.4% in Group 1 and 41.2% in Group 2 (non-significant). Twenty-four weeks after stopping therapy, sustained virologic response rate was 21.6% in Group 1 and 27.4% in Group 2 (non-significant). All subjects in Group 1 completed treatment, while two subjects in Group 2 stopped therapy due to treatment-related adverse events.

**CONCLUSION:** Recombinant human IFN β-1a, alone or in combination with ribavirin, has an excellent safety profile and, may represent an alternative for chronic hepatitis C patients who are unable to tolerate pegylated α-interferon.

## INTRODUCTION

The safety of current treatments for chronic hepatitis C is still under debate. Studies published to date demonstrate that pegylated interferons (both alpha [α]-2a and α-2b) in combination with ribavirin could eradicate the hepatitis C virus (HCV) in 47-56% of infected subjects[1,2]. However, a consistent number of patients experience significant adverse events, such as severe gastrointestinal symptoms, psychiatric disorders, dermatological symptoms, autoimmune disorders and significant laboratory abnormalities (neutropenia, anemia, thrombocytopenia)[3]. The severity of these adverse events has led to treatment discontinuation in both controlled trials and in clinical practice. In the first clinical trial[1] of pegylated interferon (PEG-IFN) α-2b with ribavirin, side effects prompted withdrawal of therapy in 13-14% of patients. In the first clinical trial of PEG-IFNα-2a with ribavirin[2], 22% of patients treated with the combination and 32% treated with PEG-IFNα-2a alone, discontinued therapy. The discontinuation rates reported with standard formulations of IFN-α were high. The pivotal IFN-α-2b and ribavirin trial performed by McHutchinson *et al*[4], demonstrated a discontinuation rate of 21% in patients treated for 48 wk.

Not surprisingly, the side effects may have pronounced negative impact in the general population than in clinical trial subjects; Gaeta and colleagues found that 24.5% of patients treated with IFN-α plus ribavirin in the regular clinical-practice setting failed to complete treatment due to adverse events[5]. Therefore, safe and effective alternatives to IFN-α could be of value to patients who cannot tolerate PEG-IFN.

Previous pilot studies have shown that IFNβ-1a is effective in HCV eradication[6] and its use is safe and well tolerated[7,8]. A trial was performed in patients resistant to a previous treatment with IFN-α treated with recombinant human interferon (IFN) β-1a at different schedules

(up to 24 MIU every d for 48 wk) but it failed to induce a significant response rate. A post hoc analysis was performed to stratify the patients according to the race and it showed a sustained virological responses of 21.7% in the Chinese subjects enrolled in the trial[9].

In this open clinical trial, we investigated the safety and efficacy of subcutaneous r-hIFNβ-1a alone or in combination with ribavirin in the treatment of chronic hepatitis C patients naïve to therapy.

## MATERIALS AND METHODS

### Study design

Using a 4-block, centralized randomization list, patients were randomly assigned to receive r-hIFNβ-1a 6 MIU/d (22 μg/d) subcutaneously for 24 wk, either alone (Group 1, $n = 51$) or in combination with ribavirin (Group 2, $n = 51$).

Ribavirin was given at a dose of 1 000 mg/d (five capsules) to patients weighing less than 70 kg and 1 200 mg/d (six capsules) to those weighing 70 kg or over.

Randomized patients who withdrew from the study without taking the first treatment dose were substituted. Patients who withdrew from the study after receiving the first treatment dose were not substituted and were considered as dropouts.

### Patient selection

Patients from six tertiary centers in Italy were recruited. Subjects were eligible for inclusion in the trial if they met the following criteria: age between 18 and 70 years; positive serum anti-HCV and HCV-RNA tests; no previous therapy with IFN; alanine-aminotransferase (ALT) level more than 1.5 times the upper normal limit, on two different assessments in the past 12 mo and at the screening visit; and a liver biopsy performed within 36 mo prior to enrollment consistent with a diagnosis of chronic hepatitis C without cirrhosis.

Patients were excluded if they had leukopenia (less than $3.0 \times 10^9$/L), neutropenia (less than $1.5 \times 10^9$/L), anemia (hemoglobin less than 12 g/dL in women and 13 g/dL in men), thrombocytopenia (less than $100 \times 10^9$/L), serum albumin less than 30 g/L, total bilirubin more than three times the upper normal limit, other significant hepatic diseases (including HBV infection), psychiatric disorders requiring treatment, or serious chronic diseases (including tumors and HIV infection). Patients were also excluded if they had received antiviral or immunosuppressive drugs during 6 mo preceding inclusion in the study. Females were included if they were pregnant or breast-feeding, and were not considering childbearing for the entire treatment period.

The therapeutic protocol was approved by the local ethical committee and the study was carried out according to the 1975 Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before treatment was initiated.

### Assessment of efficacy

Quantitative viremia was assessed at baseline to allow patient classification on the basis of viral load. A cut-off limit of 800 000 IU/mL (corresponding to 2 million copies/mL) was used to classify patients as having either low or high viral counts. From the fourth week of treatment to the end of follow-up, the virologic assessment was performed using qualitative viremia. Evaluations were performed using a polymerase chain reaction (PCR) assay (Cobas Amplicor HCV test, version 2.0; Roche Diagnostics, Basel, Switzerland; lower limit of detection 100 copies, corresponding to 40 IU/mL).

The trial endpoints were: (1) the rate of sustained virological responses (SVR); (2) the percentage of patients with normal aminotransferase levels at 24 wk of treatment (wk 24) and 24 wk post-treatment (wk 48); and (3) the safety and tolerability of r-hIFN β-1a alone or in combination with ribavirin.

Data were evaluated using an intention-to-treat analysis and included all subjects who received at least one treatment dose. Patients were considered as sustained virologic responders, if the qualitative serum HCV-RNA test performed 24 wk post-treatment (wk 48) was negative. Patients treated with r-hIFNβ-1a alone were withdrawn from the trial if HCV viremia persisted after 12 and 18 wk of treatment.

### Safety assessment

Patients were examined at baseline, after 4, 8, 12, 18, and 24 wk of treatment and at wk 12 and 24 post treatment. Routine laboratory tests, and autoantibody and IFN-β binding antibody (BAB) assessments were performed at each visit.

The following autoantibody evaluations were conducted at the coordinating center: ANA (anti-nuclear), AMA (anti-mitochondrial), ASMA (anti-smooth muscle), LKM (anti-liver/kidney microsome type 1), APC (anti-parietal cells), ABBA (anti-brush border), MT (anti-thyroid microsomal), TGA (anti-thyroglobulin), MB (anti-basement membrane of tubule/glomerular), R1 (anti-R1 type reticulin) and R2 (anti-R2 type reticulin). Autoantibodies were tested by indirect immunofluorescence on murine liver, kidney and stomach and human thyroid. IgA, IgG, and IgM were detected with fluorescein isothiocyanate[10]. BABs were determined using a radioimmunobinding assay (RIBA)[11].

In cases of grade III adverse events (according to the WHO classification), the dose of r-hIFNβ-1a was reduced to 3 MIU/d. If anemia occurred, the dose of ribavirin was reduced according to the investigator's judgment.

### Statistical analysis

Statistical analyses and data processing were performed using SAS software (version 8 for Windows). Both descriptive analyses and inferential tests were used to analyze the data. The significance level of all tests was set at 5%. The baseline characteristics of the two groups were compared using *t*-test and $\chi^2$ test. $\chi^2$ test was used to evaluate the significant difference between two treatment groups for end-of-treatment response rate (ETR), SVR rate, and ALT/AST normalization. Logistic regression model was used to evaluate the SVR rate adjusting the ORs for factors predictive of treatment response, like viral levels, genotype, class of age, etc.

The proportion of patients in each treatment group experiencing at least one adverse event that was likely related

to the study drug(s) was compared using the $\chi^2$ test.

## RESULTS

### Patient characteristics

One-hundred-and-eight patients were enrolled from May 29, 2000 to June 1, 2001. One-hundred-and-two met the inclusion criteria and were randomized to one of the two study groups: 51 patients received r-hIFNβ-1a alone and 51 received r-hIFNβ-1a in combination with ribavirin. Of the six subjects not admitted into the trial (i.e., not included in the intention-to-treat analysis), two did not meet the inclusion criteria and four refused to sign the informed consent form.

The baseline characteristics were similar in the two groups (Table 1). Twenty-one patients (41.1%) in Group 1 and 24 (47%) in Group 2 had high viral levels. Thirty-one patients (60.8%) treated with r-hIFNβ-1a alone and 33 (64.7%) treated with combination therapy were infected with HCV genotype 1.

**Table 1** Summary of demographic and clinical characteristics at baseline

|  | Group 1 | Group 2 |
|---|---|---|
| Patients (n) | 51 | 51 |
| Sex (M/F) | 29/22 | 36/17 |
| Mean age (yr) ± SD | 45±11.7 | 43.9±9.0 |
| Hemoglobin (g/dL) | 14.8±1.3 | 15±1.3 |
| Platelets (×10⁹/L) | 195.9±45 | 203.9±54 |
| Leukocytes (×10⁹/L) | 6.7±1.4 | 6.8±1.9 |
| ALT (mean±SD) | 142.7±86.2 | 123.2±78.7 |
| HCV-RNA quantitation (Meq/mL) |  |  |
|    Low viremia | 27 | 23 |
|    High viremia | 21 | 24 |
|    Undetermined | 3 | 4 |
| Genotype |  |  |
|    1 | 31 | 33 |
|    2 | 6 | 8 |
|    3 | 12 | 8 |
|    4 | 2 | 1 |
|    Undetermined | 0 | 1 |

### Virologic response

After 12 wk of treatment, 41.2% (21/51) of patients in Group 1 and 47.1% (24/51) in Group 2 showed clearance of serum HCV-RNA (Table 2). By the end of the treatment period (wk 24), the response rate had diminished to 29.4% (15/51) and 41.2% (21/51) in Groups 1 and 2, respectively. After the 24-wk post-therapy follow-up (wk 48), 11 patients (21.6%) in Group 1 and 14 (27.4%) in Group 2 maintained a SVR . There was no statistically significant difference between the two groups in the percentage of patients negative for viremia at the end of the treatment period ($P = 0.2138$) or at the completion of follow-up (wk 48) ($P = 0.4898$).

Multivariate analysis showed that genotype (OR = 0.39; 95%CI, 0.21-0.72; $P = 0.0025$) and baseline viremia level (OR = 2.1; 95%CI, 1.17-3.96; $P = 0.0141$) were factors predictive of response. Among patients with genotype 1, the rate of response was 12.9% (4/31) in Group 1 and 12.1% (4/33) in Group 2, respectively vs 35% (7/20) in Group 1 and 52.9% (9/17) in Group 2 patients with genotype non-1 (NS, Table 3). The genotype was not determined in one patient in Group 2 who responded to therapy.

Among subjects with high viral loads, the response rate was 4.8% (1/21) and 16.6% (4/24) in Groups 1 and 2, respectively, compared to 33.3% (9/27) and 34.8% (8/23) in patients with low viremia in Groups 1 and 2, ($P = 0.2972$, Table 4). The viral load was not determined in three patients in Group 1 and four patients in Group 2.

**Table 3** Rate (number responding/total treated) of patients with negative viremia after the 24-wk post-therapy follow-up according to genotype

|  | 1 | Non-1 | Not determined |
|---|---|---|---|
| r-hIFN β-1a | 12.9% (4/31) | 35.0% (7/20) | – |
| r-hIFN β-1a + ribavirin | 12.1% (4/33) | 52.9% (9/17) | (1/1) |

Between group difference not significant.

**Table 4** Rate (number responding/total treated) of patients with negative viremia after the 24-wk post-therapy follow-up according to viral load (cut-off 800 000 IU)

|  | Low | High | Not determined |
|---|---|---|---|
| r-hIFN β-1a | 33.3% (9/27) | 4.8% (1/21) | (1/3) |
| r-hIFN β-1a + ribavirin | 34.8% (8/23) | 16.6% (4/24) | (2/4) |

Between group difference, $P = 0.2972$.

### Biochemical response

At the end of the treatment period, 27.5% of patients (14/51) in Group 1 and 39.2% (20/51) in Group 2 exhibited normal aminotransferases associated with a virologic response. At the end of the follow-up period (wk 48), 21.6% (11/51) and 25.5% (13/51) of patients in Groups 1 and 2, respectively, maintained normal aminotransferase levels; the $\chi^2$ test showed no significant difference between

**Table 2** Rate (number responding/total treated) of patients with negative viremia during the course of the trial

|  | Screening | T4 | T8 | T12 | T18 | T24 | T48 |
|---|---|---|---|---|---|---|---|
| r-hIFN β-1a (n = 51) | 0 (0%) | 18 (35.3%) | 16 (31.4%) | 21 (41.2%) | 16 (31.4%) | 15 (29.4%) | 11 (21.56%) |
| r-hIFN β-1a + ribavirin (n = 51) | 0 (0%) | 13 (25.5%) | 22 (43.1%) | 24 (47.1%) | 21 (41.2%) | 21 (41.2%) | 14 (27.45%) |

treatment groups ($P$ = 0.2076 at wk 24; $P$ = 0.6406 at wk 48). Three patients showed abnormal levels of aminotransferase despite the clearance of HCV-RNA in serum, possibly due to concomitant steatohepatitis.

Among the patients who remained viremic, 22.2% (8/36) of those in monotherapy and 36.6% (11/30) of those in combination treatment exhibited normal aminotransferase levels at the end of therapy ($P$ = 0.1969); Of these patients, 17.5% (7/40) in Group 1 and 37.8% (14/37) in Group 2 maintained normal levels at wk 48 ($P$ = 0.0453).

### Safety evaluation

Ninety-nine of the one hundred and two patients enrolled completed treatment according to protocol. Drug discontinuation due to adverse events occurred in three (all in the combination therapy group) of the 102 patients. One patient stopped treatment due to the incidental discovery of ovarian cancer (not related to the study drugs). In the remaining two cases, treatment was discontinued due to depression and acute psychosis; both events were considered to be related to therapy.

At each time-point of the study, between 86.4% and 100% of patients received the expected doses of IFN-β and ribavirin according to protocol. No patient failed to complete the study due to poor compliance.

In patients treated with combination therapy, the mean hemoglobin level dropped from 14.9 to 12.6 g/dL, while in Group 1 from 14.8 to 14.3 g/dL. Treatment interruptions or dose reductions were not required in any subject. In patients treated with monotherapy, there was a mean drop in platelet count from $195.9 \pm 45 \times 10^9$/L to $175.0 \pm 41.5 \times 10^9$/L; in Group 2, there was a mean increase from $204.1 \pm 54.0 \times 10^9$/L to $206.1 \pm 66.4 \times 10^9$/L. The leukocyte count dropped from $6.7 \pm 1.4 \times 10^9$/L to $5.8 \pm 1.3 \times 10^9$/L and from $6.7 \pm 1.9 \times 10^9$/L to $5.2 \pm 1.8 \times 10^9$/L in Groups 1 and 2, respectively.

Thirty-seven percent of subjects (19/51) treated with IFN-β and 49% (25/51) of those in Group 2 reported at least one mild adverse event during the study (Table 5). The difference between the two groups was not significant.

Only mild titer increases of pre-existing autoantibodies were observed. Compared to baseline, ANA increased in two patients and decreased in one; ASMA decreased in two cases and MT as well as MB increased in one patient. None of the patients developed autoimmune disease.

**Table 5** Adverse events possibly or probably related to study treatment, occurring with a frequency higher than 5%

| | r-hIFN β-1a (n = 24, %) | r-hIFN β-1a + ribavirin (n = 35, %) |
| --- | --- | --- |
| Fatigue | 4 (16.7) | 4 (11.4) |
| Pyrexia | 2 (8.3) | 6 (17.1) |
| Anemia | 0 (0.0) | 6 (17.1) |
| Erythema | 4 (16.7) | 2 (5.7) |
| Headache | 4 (16.7) | 0 (0.0) |
| Thrombocytopenia | 3 (12.5) | 0 (0.0) |
| Neutropenia | 0 (0.0) | 2 (5.7) |
| Depression | 2 (8.3) | 0 (0.0) |
| Insomnia | 0 (0.0) | 2 (5.7) |
| Weight loss | 0 (0.0) | 2 (5.7) |

BABs developed in 11 patients (12%) and usually appeared within 8 to 12 wk of treatment; titers ranged between 5.0 and 20 AU in three of these patients and were less than 5.0 AU in eight patients. There was no difference between Group 1 and Group 2 with regards to BAB development and no correlation was found between BABs development and response to treatment.

## DISCUSSION

In contrast to the variety of IFN-α, of which there are 25 subtypes with molecular weights ranging from 17.5 to 23 ku[12], only one type of IFN-β has been identified in human beings. Though its amino-acid sequence differs from IFN-α by as much as 70%, IFN-β shares many antiviral properties of interferon alpha, thereby providing an alternative treatment for chronic hepatitis C.

Three forms of IFN-β are available: (1) the fibroblast-derived natural IFN-β[13]; (2) the r-hIFNβ-1a produced by mammalian cells (identical to the IFN-β naturally occurring in humans); and (3) r-hIFNβ-1b produced by *E. coli*. The r-hIFNβ-1a formulation was chosen for this study as it offers several advantages over the other two: it can be produced in unlimited quantities by bioengineering techniques, its batch-to-batch consistency and purity allows for dosage by mass instead of international units, and it is identical to the IFN-β naturally occurring in human beings but more potent and less immunogenic[14].

Previous experience with IFN-α indicates that the efficacy of these agents is related to the frequency of administration. Therefore, the rationale behind the newest pegylated formulation is that a more steady and sustained release of IFN-α is more effective than the thrice-a-week administration.

The pharmacokinetic data obtained with natural IFN-β have demonstrated the significant bioequivalence of the intramuscular, intravenous, and subcutaneous routes of administration[15]. Therefore, we have chosen to administer the cytokine via the more convenient subcutaneous route. Since the safety of r-hIFNβ-1a in combination with ribavirin has not been previously determined, a 6- rather than 12-mo course of therapy was selected for this initial study.

PEG-IFN with ribavirin is currently the gold standard for the treatment of chronic hepatitis C. Though less efficacious than PEG-IFN, that consents to achieve 47-56% of SVR[1,2], our findings suggest that r-hIFNβ-1a alone or in combination with ribavirin, is as effective as conventional non-PEG-IFNα. The overall 21.6% and 27.5% SVR rates achieved in our patients treated with r-hIFNβ-1a alone or in combination with ribavirin, respectively, are comparable to the 6-13% and 31-38% response rates reported with the use of IFNα-2b alone or in combination with ribavirin, respectively, for 24-48 wk[4].

In both treatment groups, viral response rates were higher at 12 wk of therapy than at the end of the treatment period (wk 24). A possible reason for this decrease, which was more pronounced in Group 1, could be the low dosage of IFN-β used in this trial. Analogous to the results of previous IFN-α studies that assessed the efficacy of IFN monotherapy *vs* the association of the same IFN with ribavirin, combination therapy in this trial yielded better

results for both virologic and biochemical endpoints compared to IFN-β monotherapy.

The major factors influencing the response rate in clinical trials of IFN-α were the genotype of the infecting HCV and the level of baseline viremia: genotype 1 and high viremia were associated with a reduced response, while genotypes 2 or 3 and low viremia had a higher response. This was also the case with r-hIFNβ-1a; the end-of-treatment virologic and biochemical response rates were significantly higher in our patients of genotype 2-3 and low viremia, compared to those with genotype 1 and high viremia.

The use of ribavirin, as well as prolongation of IFN treatment up to 48 wk (instead of 24 wk), not only enhances the therapeutic response, but also decreases the relapse rate after the end of treatment. This effect is negligible in patients with easy-to-treat HCV genotype 2 or 3, for whom 24 wk of IFN is sufficient to achieve a maximal SVR. On the other hand, subjects infected with HCV genotype 1 achieve a higher SVR rate after 48 wk of therapy when compared to 24 wk (despite similar end-of-treatment virological response rates after 24 and 48 wk of treatment). Unfortunately, this effect could not be evaluated in the present study, which was designed to provide a 24 wk course of treatment. In fact, several post-therapy relapses occurred in HCV-genotype 1 patients treated with combination therapy for 6 mo, resulting in an off-therapy response rate distinctly lower than that achieved upon completion of treatment.

The overall safety profile of r-hIFNβ-1a, both alone and in combination with ribavirin, was remarkably favorable. Compared to previous IFN-α data, the drop-out rate in our study was low (0/51 [0%] in Group 1 and 3/51 [5.9%] in Group 2) and was due primarily to two patients who withdrew from the study as a result of treatment-related psychiatric problems.

In contrast to the 2% of patients treated with IFN-α who had developed autoimmune disorders[16], none of our patients treated with r-hIFNβ-1a developed clinical features of autoimmune diseases. Furthermore, systematic autoantibody monitoring failed to demonstrate the emergence of autoimmune reactivities during therapy or significant titer increases of pre-existing autoantibodies. Likewise, IFN-β BAB titers rose in only 12% of our patients; these increases were in the low titer ranges and were not clinically significant.

Decreases in WBC and platelet counts observed in the present study (two patients on combination therapy and three subjects on IFN monotherapy respectively) were not clinically relevant to induce discontinuation of therapy. On the contrary, IFN-α led to higher reductions in WBC and platelet counts that are often responsible for premature termination of therapy. The fall in hemoglobin level noted in our patients treated with combination therapy was expected as it is a well-recognized, side-effect of ribavirin[17].

In conclusion, the satisfactory therapeutic effects and excellent tolerability profile of r-hIFNβ-1a could represent a treatment option for patients with chronic hepatitis C who cannot tolerate PEG-IFNs. IFNβ-1a may also be used as initial therapy in subjects at high risk of significant side effects with IFN-α treatment. Future studies should evaluate the efficacy and safety of r-hIFNβ-1a in subpopulations of patients with chronic hepatitis C and cirrhosis or cryoglobulinemia.

## ACKNOWLEDGMENTS

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