Weekly Pegylated Interferon α-2b *vs* daily Interferon a-2b *versus* standard regimen of Interferon a-2b in the treatment of patients with chronic hepatitis C virus infection

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Abstract

Background and study aims : **The combination of Pegylated (PEG)interferon α-2b and ribavirin is considered to be the standard treatment for naïve chronic hepatitis C patients. Study aims are to evaluate the differences between standard interferon and PEG-interferon by conducting a multi-centre, controlled randomized trial comparing 3 groups. Group A : daily interferon alfa-2b at a dose of 4 MIU + ribavirin, Group B : PEG-interferon alfa-2b at a dose of 100 mcg/week + ribavirin ; Group C : interferon alfa-2b at a dose of 3 MIU TIW + ribavirin**

Patients and methods : **Multicentrer, open label study including naïve chronic Hepatitis C Virus patients randomised in three groups with a ratio of 2:2:1. Group A : daily interferon α-2b (4 MIU s.c. for patients > 65 kg or 0.06 MIU/kg < 65 kg) and ribavirin, group B : PEG-interferon α-2b (100 µg s.c. weekly for patients > 65 kg or 1.5 µg/kg weekly for patients < 65 kg) and ribavirin and group C (reference arm) : interferon α-2b (3MIU s.c. TWI) and ribavirin. The duration of the treatment was 48 weeks for all 3 groups, with a 6 month follow-up period. 336 patients were enrolled in the study and included in the intention-to-treat analysis ; 78 never started treatment (35 in group A, 28 in group B and 15 in group C) : 101 in group A, 98 in group B and 59 in group C.**

Results : **Demographic data, PCR results and reasons for early withdrawal have been statistically analysed. At baseline, the 3 groups did not show any statistical difference regarding age, gender, race, genotypes and METAVIR score. At week 24 on treatment, HCV ribonucleic acid RNA was undetectable in 87% in group A, in 79% in group B and in 69% in group C. At the end of treatment, 73% 74% and 58% respectively, had a negative PCR result. At week 24 of follow-up, these results were 71%, 64% and 48%, respectively. When comparing the efficacy of the daily interferon (+ ribavirin) and the PEG-interferon (+ ribavirin) regimen, no statistical difference was found (p = 0.32). In group A, 38% of drop-outs were due to adverse events compared to 37% in group B and 58% in group C. No statistical differences were observed regarding safety.**

Conclusion : **Daily weight based interferon α-2b dosing and PEG interferon α-2b weighed based dosing once weekly both in combination with Ribavirin offer the same efficacy and safety rates.** (Acta gastroenterol. belg., **2008**, 71, **293-297**).

Key words : chronic hepatitis C, interferon, daily administration, pegylated interferon.

Introduction

Hepatitis C virus (HCV) infection can progress to chronic hepatitis, cirrhosis, and occasionally, to hepatocarcinoma (1,2). Treatment of HCV-infected patients with interferon-alfa can achieve viral clearance resulting in improved histology and prognosis (3). In the early studies with standard interferon alfa and ribavirin, the success rate was limited (4). At that time, in most trials the administered dose of standard interferon was 3×10^6 units 3 times a week (TIW) combined with ribavirin. Studies using higher doses or induction doses of standard interferon combined with ribavirin did not demonstrated any superiority compared with standard doses (5).

More recently, standard interferon has been chemically modified by attaching polyethyleneglycol (PEG) moieties in order to optimise the delivery, to maintain constant therapeutic pressure on the virus and to improve antiviral efficacy. Higher sustained virologic response rates in patients with chronic hepatitis C have been reported for the pegylated forms of interferon compared to standard interferon in monotherapy and, as well, with respect to combination therapy with ribavirin (6,-8). Additional prospective trials in patients with genotype 2 or 3 chronic infection showed that the time-scale of treatment can be reduced from 48 to 24 weeks without compromising antiviral efficacy (9).

The PEG-interferon superiority could be the result of different factors : increased absorption half-life, restricted volume of distribution, reduction in renal clearance due to the presence of the PEG moiety, and the capacity to provide higher levels of interferon relative to the conventional form (10,11).

In all the performed to-date, PEG-IFN was compared with standard interferon, administered at a dose of 3×10^6 TIW.

We sought to evaluate the differences between standard interferon and PEG-interferon by conducting a multi-centre controlled randomized trial comparing 3 groups. Group A : daily interferon alfa-2b at a dose of

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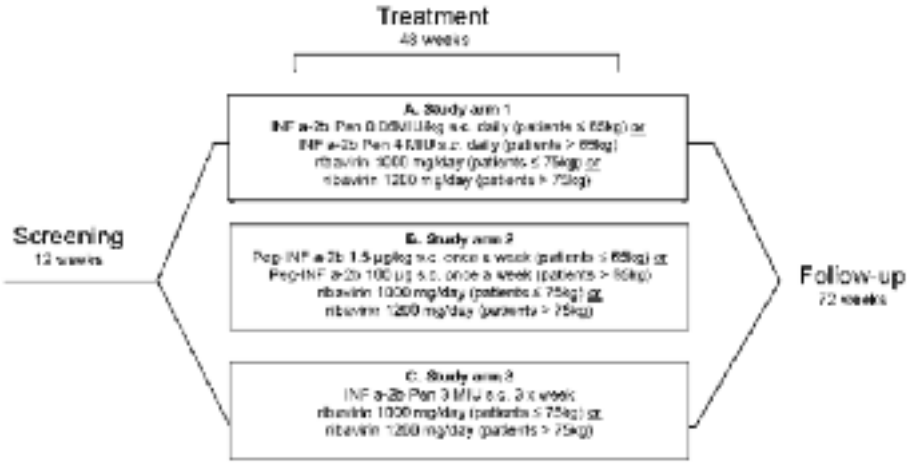

Fig. 1. — Study Design

4 MIU + ribavirin, Group B : PEG-interferon alfa-2b at a dose of 100 mcg/week + ribavirin ; Group C : interferon alfa-2b at a dose of 3 MIU TIW + ribavirin. The main objective of the study was to compare group A and B in terms of SVR at 6 months of follow up.

Materials and methods

Patients

Untreated patients between 18 and 70 years with chronic HCV infection were recruited between October 2000 and March 2002**.** The diagnosis of chronic HCV was made on the basis of elevated alanine aminotransferase (ALT) activity (above the upper limit of normal ; ULN) and the presence of HCV RNA in the serum. Patients with decompensated liver cirrhosis or with other chronic liver diseases (viral hepatitis B, auto-immune hepatitis, haemochromatosis, alpha 1 antitrypsin deficiency, Wilson's disease) or co-infected with human immunodeficiency virus (HIV), were excluded. Active alcohol abuse (> 80 g/day) and intravenous drug abuse were also exclusion criteria. Patients with contraindications to ribavirin (chronic renal failure, anaemia, haemoglobinopathy), leucocyte blood count < 3000/ml and platelet count < 100 000/ml were not eligible.

This trial involved sixty centres in Belgium (all participants are mentioned in the Appendix) and coordinated by the Belgian Association for the Study of the Liver (BASL). The protocol was approved by the Ethical Committee of each participating centre and the study was conducted according to the Declaration of Helsinki.

Patients were randomized into the 3 treatment groups on a 2/2/1 basis. In Group A, the patients received daily interferon alfa-2b s.c. (4 MIU/day for patients > 65 kg and 0.06 MIU/kg/day for patients ≤ 65 kg). In the Group B, the patients received weekly peg-interferon alfa-2b s.c. (100 mcg/week for patients > 65 kg and 1.5 mcg/kg/week for patients ≤ 65 kg). In Group C, the patients received interferon alfa-2b 3 MIU s.c. administered thrice weekly (TIW). All patients received ribavirin *per os* at a daily dose of 1 g (patients weighing < 75 kg) and 1.2 g (patients weighing > 75 kg). All patients were treated for 48 weeks, then followed for an additional 24 weeks (Fig. 1). The patients with disease relapse were randomised in Groups A and B.

Patients were evaluated for safety, tolerance and efficacy on a monthly basis in the outpatient clinics of the participating hospitals.

The drug was provided by Schering-Plough and the final analysis was performed independently by the Center for Statistics of the Hasselt University.

Methods

Qualitative HCV RNA was assessed using a Cobas Amplicor Roche. The lower detection limit (LDL) of this assay is 50 IU/ml.

Quantitative HCV was determined by Bayer B-DNA (HCV-RNA 3) and Amplicor HCV monitor version 2.0. The LDL for the assay is 600 IU/ml.

HCV genotyping was performed by InnoLipa (Innogenetics, Zwijnaarde, Belgium). Serum ALT activity was determined using commercial reagents on an automated analyser.

Liver biopsy specimens were assessed by an experienced pathologist who was 'blinded' with respect to the clinical and biochemical data as well as to treatment regimen and response. Histological results were classified according to internationally standardized criteria (Metavir score).

Complete response at the end of 24-weeks follow-up was defined as an undetectable HCV RNA.

End of treatment viral response (ETR) was defined as an undetectable HCV RNA level at the end of the treatment period.

Statistics

The main objective of this study was to evaluate the sustained, virological response at 6 months follow-up between group 1 (daily Interferon α-2b Pen) and group 2 (weekly PEG-Interferon α-2b).

Table 1. — **Demographics at baseline**

	Group A (n = 117)	Group B (n = 114)	Group C (n = 65)
Gender (male/female)	63/54	62/52	36/28
Age (STD)	45 (13)	46 (14)	45 (13)
Gen 1 / Gen 2&3	64/31	65/35	36/25
Fibrosis (F < 2 / F > 2)	24/62	23/64	12/27

Gen : genotype.

Statistics were performed on an intention-to-treat basis. Parametric and nonparametric tests were used depending on the normality of distribution of the study population. Multivariate analysis was performed using multiple logistic regression. P-values of < 0.05 were considered statistically significant. The study was powered to detect the difference between Groups A and B when a sample size of 388 patients in each group was reached. *A two group c^2 test with a 0.050 two-sided significance level, was foreseen to have 80% power to detect the difference in sustained response between a Group 1 proportion, $\pi 1$, of 0.600 and a Group 2 proportion, $\pi 2$, of 0.500 (odds ratio of 1.500) when the mentioned sample size in each group is reached.*

A drop-out rate of 15% was anticipated, and a total of 894 patients were supposed to be randomized in group 1 or group 2.

Results

The study was expected to enrol the required numbers of patients between 2000 and 2002. However, due to slow recruitment rate the study was stopped prematurely in early 2002.

Prior to study closure, a total of 336 patients had been randomised in this study while 78 had not commenced treatment. Hence, the present analysis includes 258 patients and these were evaluated on an intention-to-treat basis. A total of 101 patients were randomised to Group A (daily IFN), 98 patients to Group B (PEG-IFN) and 59 patients to Group C (TIW IFN).

Patient demographics are summarised in Table 1. The 3 treatment groups were not statistically different with respect to age, gender, genotype 1 or non-1, viral load and degree of fibrosis determined by liver histology.

Viral response

The viral responses at week 24 of treatment, end of treatment, and at the 24 week follow-up are shown in Fig. 2. No statistically differences were observed between daily IFN administration and PEG-IFN administration ; albeit a trend being observed in favour of daily IFN administration. In contrast, a statistically lower number of patients with negative HCV RNA were found in Group C (IFN TIW) compared with Group A and Group B.

Almost the same percentages of patients with negative HCV RNA were found in Groups A and B at the end of treatment whereas a statistically lower number was observed in group C. Similarly, no statistically significant differences were observed between Groups A (71%) and B (64%) at 24 weeks of follow-up (p = 0.31).

With respect to the impact of genotype distribution, the interaction between treatment and genotype was not statistically significant at week 24 of follow-up (p = 0.73) (data not shown), i.e. the effect of treatment did not depend on viral genotype (genotype 1 versus the other genotypes). The probability of negative PCR depends on treatment arm and on genotype ; with the effects being

Negative PCR

	Group A {n(%)}	Group B {n(%)}	Group C {n(%)}	Total {n(%)}	p-value A vs B	p-value A vs C	p-value B vs C
Week 24	86(87)	76(79)	41(69)	203(80)	0.152	0.008	0.174
Week 48	57(73)	63(74)	28(58)	148(70)	0.880	0.086	0.060
Week 24 F-U	50(71)	51(64)	23(48)	124(63)	0.317	0.010	0.079

F-U: follow-up

Fig. 2. — Viral response

additive. The odds-ratio for genotype non-1 versus genotype 1 was 3.16 and no statistically significant difference was found between Groups A and B.

Similar results were obtained at the end of treatment and at 24 weeks of follow-up with odds-ratios of 3.26 and 3.17, respectively.

Adverse events

The proportion of the patient drop-outs in Group C compared to the other groups : 60% (Group C) versus 46% (Group A) and 45% (Group B) ; the difference being not statistically significant (p = 0.1140). Of note was that the proportion of patients withdrawing from treatment because of adverse events was highest in Group A (17%) compared to 14% in Group B and lowest in Group C (3%) (Group A versus Group B, p = 0.52 NS ; Group A versus Group C, p = 0.005 and Group B versus Group C, p = 0.019).

A total of 55 serious adverse events were observed : 63% of these were considered likely to have been related to the study medication. Less adverse events were observed in Group C, but no statistically significant differences between groups were found.

With regard to haematological side effects, a considerably greater drop in haemoglobin, red blood cells, white blood cells and platelets were observed in Groups A and B compared to Group C. A similar number of patients required dose reduction or treatment discontinuation in Groups A and B (Table 2).

Discussion

The intent-to-treat analysis included 258 patients enrolled prior to study being terminated prematurely. The results showed that a daily dose of 4 MIU IFN (+ ribavirin) was equivalent to a weekly dose of 100 mcg PEG-IFN (+ ribavirin) and was superior to the old standard treatment consisting of 3 MIU TIW IFN (+ ribavirin). There were no significant differences between these two regimens (i.e. daily IFN or PEG-IFN) in terms of adverse events, drug dosage modification requirements or treatment discontinuation.

Since there were no differences between daily IFN and PEG administration, the use of PEG would be favoured because of its convenient weekly administration. This would tend to encourage patient compliance, an important factor in determining optimal clinical outcome.

There are several limitations in our study due, perhaps, to the timing of the trial :

1. PEG intron dosage was similar for all patients except those with a body weight lower than 65 kg. The choice of therapy was based on the limited data available at the time of trial design and on the ease of administering a similar dose in all patients. We need to highlight that this choice of a fixed dose of PEG was the only option that enabled a direct comparison to be made with a fixed dose of standard interferon.
2. A relatively high number of patients elected to stop the standard dose treatment regimen, i.e. 3×10^6 units TIW (Group C). This is not surprising since at that time of the trial most patients were aware of the "new" treatment availability and were disappointed not to receive PEG-IFN. As such, when serious adverse effects occurred with the standard treatment schedule, several patients chose to remove themselves from the trial.
3. All patients were treated for 48 weeks, including those patients infected with genotypes 2 and 3. We did not observe any differences in outcomes as a function of the genotypes.
4. The observed equivalence between a daily dose of 4 MUI IFN and a weekly dose of 100 mcg PEG-IFN is based exclusively on our observations of equivalent clinical outcomes. No pharmacokinetic studies were performed demonstrating an equivalence in serum IFN concentrations. However, our results tend to suggest that the superiority of PEG over that of standard

Table 2. — **Distribution of drop-outs between groups A, B and C**

	Group A {n (%)}	Group B {n (%)}	Group C {n (%)}	Total {n (%)}	p-value		
					A vs B	A vs C	B vs C
Discontinued because of advere event	20 (17)	16 (14)	2 (3)	38 (13)	0,522	0,005	0,019
Treatment failure (detectable PCR at week 24)	10 (9)	15 (13)	16 (25)	41 (14)	0,259	0,003	0,051
Lost to follow-up	7 (6)	3 (3)	4 (6)	14 (5)	0,211	0,963	0,242
Patient did not want to continue	4 (3)	9 (8)	7 (11)	20 (7)	0,140	0,046	0,517
Investigator decision to stop	2 (2)	1 (1)	4 (6)	7 (2)	0,577	0,108	0,039
Non compliance	1 (1)	–	1 (2)	2 (1)	0,323	0,672	0,184
Death	–	–	–	–			
Unknown	10 (9)	7 (6)	5 (8)	22 (7)	0,484	0,841	0,690
Total	117 (100)	114 (100)	65 (100)	296 (100)			

Patients who never started with the treatment were excluded from the statistical analysis (group A, N = 19 ; group B, N = 12 ; group C, N = 9).

interferon that has been observed in pivotal trials is due, mainly, to the better pharmacokinetics of PEG compared to the standard dose regimen of 3×10^6 units TIW

In conclusion, in terms of clinical outcomes, a daily dose of 4 MUI IFN (+ ribavirin) is equivalent to a weekly dose of 100 mcg PEG-IFN (+ ribavirin) and superior to the old standard treatment consisting of 3 MUI TIW IFN (+ ribavirin) in the treatment of chronic hepatitis C virus infection.

Appendix

The following investigators contributed equally to this project :

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