A randomized, open-label, multicenter study evaluating the efficacy of peginterferon alfa-2a versus interferon alfa-2a, in combination with ribavirin, in naïve and relapsed chronic hepatitis C patients

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Abstract

***Background/Aims* : A large multicenter trial to compare the efficacy of peginterferon alfa-2a with interferon alfa-2a, in combination with ribavirin, in chronic hepatitis C patients. Efficacy data for prior relapsers are reported because treatment recommendations for this patient population are not well defined.**

***Patients and methods :* This study was a multicenter, prospective, randomized clinical trial. The primary efficacy endpoint was sustained virologic response in naïve patients (n = 348) and relapsers (n = 95).**

***Results :* Sustained virologic response rates were similar in naïve patients and relapsers, both for non-pegylated and pegylated interferon (respectively 27 and 26% and 54 and 43%). Pegylated interferon given for 48 weeks did not improved the relapse rate : 15.9 and 27.3% for non-pegylated and 16.7 and 30.4% for pegylated interferon, naïve vs relapsers respectively. Stepwise logistic regression analysis revealed a significant association between slow response (detectable HCV RNA at week 12 and undetectable at week 24) and relapse in patients with an end-of-treatment response (55% versus 13% respectively ; p = 0.02 ; odds ratio = 6.07).**

***Conclusions :* This trial confirms the value of using peginterferon alfa-2a in both naïve and relapsed patients and provides support for a more tailored approach to treatment for relapsers and particulary for patients with a slow viral response.** (Acta gastroenterol. belg., **2010**, 73, **223-228**).

Key words : Chronic Hepatitis C, Pegylated interferon, Relapse treatment, Slow viral response.

Introduction

The combination of pegylated interferon-alfa plus ribavirin has become the standard therapy for naïve patients with chronic hepatitis C (CHC) (1). However, the best way of treating patients who relapse after a previous treatment with non-pegylated interferon has not been well established. In the majority of the reported studies, patients with a prior relapse were pooled with the non-responders and/or were retreated in the absence of a control arm (2-5). Furthermore, there are no uniform recommendations for the optimum dosage and treatment duration (48 or 72 weeks) for this difficult to treat patient population. We previously demonstrated that an extended treatment duration might reduce the relapse rate in naïve patients treated with non-pegylated interferon plus ribavirin (6).

This paper reports the results of the Belgian Randomized trial in Naïve and Relapsers 1 (BeRNaR 1). This large, multicenter study was initiated to compare the efficacy and safety of peginterferon alfa-2a with conventional interferon, in combination with ribavirin, in both naïve and relapsed patients with CHC. Subgroup analyses, according to protocol, were planned to assess the efficacy of peginterferon alfa-2a in relapsers versus naïve patients.

Patients and methods

Study design and patients

This phase III, multicenter, prospective, randomized, open-label clinical trial was conducted in Belgium to evaluate the efficacy and safety of peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin in patients with CHC. The study was designed to comply with the standards of Good Clinical Practice (International Conference on Harmonization guidelines) and was in accordance with the Declaration of Helsinki and with Belgian laws. Written, informed consent was obtained from all individuals who participated in the study.

Patients were screened for inclusion and exclusion criteria (Table 1) at week 1 of the study. Four-hundred and forty-three patients were randomly assigned to one of two treatment groups at week 2. Group A (n = 230) received subcutaneous injections of peginterferon alfa-2a (40KD) (PEGASYS®, Roche, Basel, Switzerland) 180 µg/week plus ribavirin (COPEGUS®, Roche, Basel, Switzerland). Group B (n = 213) received subcutaneous injections of interferon alfa-2a (Roferon®-A, Roche, Basel, Switzerland) 6 MIU three times a week for the

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Table 1. — **Main inclusion and exclusion criteria for the this study**

Inclusion criteria	**Exclusion criteria**
Male and female patients ≥ 18 years of age	Women with ongoing pregnancy or who are breast feeding
Serologic evidence of chronic hepatitis C infection by an anti-HCV antibody test	Male partners of women who are pregnant
Serum HCV RNA quantifiable at >1000 IU/mL by the Roche Amplicor™ HCV MONITOR Test	Therapy with any systemic antineoplastic or immunomodulatory treatment (including supraphysiologic doses of steroids and radiation) ˝6 months prior to the first dose of study drug
Elevated serum ALT activity (defined as ALT activity higher than the upper limit of normal)	Any investigational drug ˝6 weeks prior to the first dose of study drug
Patients who are *either* naïve to any therapy (i.e. have not been previously treated with an interferon or with interferon plus ribavirin) *or* who have had a relapse during or after a previous treatment Relapsers must have had one of the following during a previous therapy with interferon or interferon plus ribavirin : • Undetectable HCV RNA during therapy and a return to positive HCV RNA during or after therapy • Normal ALT level (below the upper limit of normal) during therapy and a return to abnormal ALT values during or after therapy	History or other evidence of a medical condition associated with chronic liver disease other than HCV (e.g. hemochromatosis, autoimmune hepatitis, metabolic liver disease, alcoholic liver disease, toxin exposures) or history of severe psychiatric disease, especially depression
Chronic liver disease consistent with chronic hepatitis C infection on a biopsy obtained within the past 18 months (for naïve patients) as judged by a local pathologist	Evidence of hepatocellular carcinoma.Serum AFP > 100 ng/mL (patients with a serum AFP > 50 ng/mL had an abdominal ultrasound, CT scan, or MRI scan within 2 months of randomization)
Compensated liver disease (Child-Pugh grade A clinical classification)	Positive test at screening for anti-HAV IgM Ab, HBsAg, anti-HBc IgM Ab, anti-HIV Ab
Negative urine or blood pregnancy test (for women of childbearing potential) documented within the 24-hour period prior to the first dose of study drug	Hemoglobin < 11 g/dL in women or < 12 g/dL in men at screening or any patient with a baseline increased risk for anemia (e.g. thalassemia, spherocytosis, history of gastrointestinal bleeding, etc.)
All fertile males and females receiving ribavirin must be using two forms of effective contraception (including their partner) during treatment and during the 6 months after treatment end	Neutrophil count < 1500 cells/mm^3 or platelet count < 90,000 cells/mm^3 at screening

AFP = alfa-fetoprotein ; ALT = alanine aminotransferase ; HCV = hepatitis C virus.

first 8 weeks and 3 MIU three times a week thereafter plus ribavirin (COPEGUS®, Roche, Basel, Switzerland). Ribavirin was administered orally at doses of 1000 or 1200 mg/day (for patients with body weight < 75 or ≥ 75 kg respectively) in both treatment groups. The treatment duration for all patients was 48 weeks, with the exception of treatment-naïve HCV genotype 2/3 patients who received a treatment of 24 weeks Patients were considered as treatment completers if they met the primary endpoint and had complete follow-up data.

Treatment was interrupted in non-genotype 2 and 3 patients if HCV RNA was detectable after 24 weeks of treatment. These patients were considered as non-responders.

Randomization was stratified by pretreatment status (treatment-naïve, relapsed after interferon monotherapy or relapsed after interferon plus ribavirin combination therapy), cirrhosis state (presence or absence) and study center. Patient randomization numbers were allocated sequentially in the order of patient enrollment and corresponded to numbers on medication labels. A treatment-free follow-up period of 24 weeks completed the study. Patients with incomplete follow-up data were considered as non-responders. The intent-to-treat (ITT) population included all patients randomized to treatment and the safety analysis population included all patients who received at least one dose of either study drug and had at least one post-baseline safety assessment (physical examination, laboratory tests or patient-reported adverse event during study treatment and follow-up).

Definitions and assessment of endpoints

The primary efficacy endpoint was sustained virologic respons (SVR) rate (percentage of patients with undetectable serum HCV RNA 24 weeks after the end of treatment), as assessed by qualitative PCR (Roche Amplicor™ HCV Test, v2.0 (Roche Diagnostics, Branchburg, NJ) ; limit of detection 50 IU/mL). Secondary efficacy endpoints were sustained biochemical response rate (percentage of patients with normal alanine aminotransferase (ALT) levels 24 weeks after the 48-week treatment period) and the proportion of patients with undetectable HCV RNA at weeks 12, 24 and 48 (as assessed by Roche Amplicor™ HCV Test, v2.0). Safety endpoints constituted assessments of the incidence of adverse events, changes in hemoglobin levels and results of other laboratory tests.

Quantitative HCV RNA measurements were determined during the screening phase using Roche Amplicor™ HCV MONITOR Test, v2.0 (Roche

Diagnostics, Branchburg, NJ ; limit of quantitation 600 IU/mL). Qualitative HCV RNA measurements were determined at weeks 12, 24 and 48 of the treatment period and at week 24 of follow-up (Roche Amplicor™ HCV Test, v2.0, as above). ALT levels were assessed at treatment weeks 2, 4, 8, 12, 24, 36 and 48 and at weeks 4, 12 and 24 of follow-up.

Compliance and dosing of study drugs

Treatment compliance was monitored via patients' and drug-dispensing diaries and the return of used and unused pre-filled syringes and pill vials. Physician-initiated dose reductions of peginterferon and of ribavirin were permitted in order to manage adverse events or laboratory abnormalities. Once dose-reductions had been initiated, physicians were permitted to gradually increase the dose again at their discretion. Physicians discontinued therapy if patients had an absolute neutrophil count of < 500 cells/mm^3, a platelet count < 25,000 cells/mm^3 and progressively increasing ALT after dose reduction or when accompanied by increased bilirubin or hepatic decompensation. Ribavirin was discontinued if hemoglobin levels decreased to < 8.5 g/dL (patients without significant cardiovascular disease) or remained below 12 g/dL despite ribavirin dose reductions (patients with stable cardiovascular disease). In these cases, patients were permitted to remain on peginterferon alfa-2a (40 KD) or interferon monotherapy. Ribavirin monotherapy was not permitted.

Statistical analysis

The objective of the study was to compare the efficacy and safety of the treatments in the two groups. This analysis was performed using two-tailed hypothesis tests : the null hypothesis stated equality of the two treatment groups for the parameter tested, while the alternative hypothesis corresponded to a difference in either direction. In order to detect a 30-40% improvement in SVR rates for the peginterferon alfa-2a plus ribavirin group versus the interferon alfa-2a plus ribavirin group with a power of ≥ 80% and a significance level of 4.8%, a sample size of 178 patients per group was required. To avoid the dilution of treatment effects due to protocol violations and drop-outs (as expected in 20% of patients recruited), a sample size of 224 patients per group was necessary. All primary and secondary efficacy analyses were made using the ITT population. Categorical variables for pairwise treatment comparisons were analyzed using the Cochran-Mantel-Haenszel test stratified by pretreatment status, cirrhosis status, HCV genotype and baseline HCV viral load. Stepwise logistic regression analyses were performed to examine the relationship between predictors of relapse and previous treatment status, HCV RNA status at week 12 and week 24, age, body mass index (BMI), cirrhosis status, baseline viral load and level of ALT. All statistical tests were performed at the 5% level of significance.

Results

This study was carried out from 3 October 2000 to 7 January 2003 and involved 46 Belgian academic and non-academic centers. Data became available in 2007. The ITT population consisted of the 443 patients that were randomized to treatment and received at least one dose of study medication (230 in group A and 213 in group B). The treatment status of patients within this population was naïve (344 patients), relapser (95) or unknown (4). Of the relapsers, 27 (28.4%) had been previously treated with interferon monotherapy and 68 (71.6%) with interferon plus ribavirin combination therapy. The proportions of each type of relapser were similar in the two treatment arms.

Table 2a and Table 2b show that the baseline characteristics of patients were well matched in the two treatment groups and according to prior treatment status. The study population was representative for the Belgian situation. Of patients with abnormal ALT levels at screening, ALT levels had normalized in 9% of these at therapy initiation.

Significantly greater ($p < 0.001$) SVR rates were observed in group A (52% ; 95% confidence interval (CI) : 0.45-0.58) than in group B (27% ; 95% CI : 0.21-0.33) (Fig. 1). There was no significant difference in SVR rates in naïve patients and relapsers in group A (54.5% and 42.9% for naïve patients and relapsers respectively). For those patients who had relapsed, SVR rates were 42.9% and 26.9% in group A versus group B respectively (odds ratio (OR) : 2.13 ; 95% CI : 0.89-5.06 ; $p = 0.131$) (Fig. 1). However, this study was not sufficiently powered to determine the significance at this level of subgroup analysis.

In naïve patients with genotype 1, SVR rates for patients treated with peginterferon alfa-2a plus ribavirin and those treated with interferon alfa-2a plus ribavirin were 47% and 17% respectively (OR : 4.4 ; 95% CI : 2.26-7.94 ; $p < 0.001$). In naïve patients with genotype 2/3, SVR rates for patients treated with peginterferon alfa-2a plus ribavirin and those treated with interferon alfa-2a plus ribavirin were 73% and 45% respectively (OR : 3.3 ; 95% CI : 1.37-7.94 ; $p = 0.010$).

Analysis of SVR according to treatment status showed a significant association between SVR and the following patient baseline characteristics : cirrhosis status ($p = 0.012$), genotype ($p < 0.001$), baseline viral load ($p = 0.025$), age ($p = 0.003$) and weight ($p = 0.013$). The effect of genotype on SVR was significant for both naïve patients ($p < 0.001$) and for relapsers ($p = 0.039$).

Rates of sustained biochemical response in the ITT population were determined for the two treatment groups. Rates for patients treated with peginterferon alfa-2a plus ribavirin compared with those in the interferon alfa-2a treatment groups were 53% (95% CI : 0.47-0.60) and 34% (95% CI : 0.27-0.41) respectively ($p < 0.001$).

The proportion of patients in the ITT population with undetectable (< 50 IU/mL) HCV RNA at treatment

Table 2a. — **Baseline demographic and clinical characteristics of patients in the two treatment groups**

	Group A (peginterferon alfa-2a) (n = 230)	Group B (interferon alfa-2a) (n = 213)
Male (%)	51	58
Caucasian (%)	92	91
Mean age (years)	47	48
Mean BMI (kg/m²)	25.6	25.5
Cirrhosis (%)	16	15
High viral load* (%)	33	34
HCV genotype (%) :		
1	66	60
2/3	23	26
4/5/6	11	14
ALT (%) :		
Normal	8	10
> ULN to ≤ 3 ULN	68	61
> 3 ULN	24	28

* ≥ 800,000 IU/mL.
ALT = alanine aminotransferase ; ULN = upper limit of normal.

Table 2b. — **Baseline demographic and clinical characteristics of the study population by treatment status**

	Naïve patients (n = 344)	Relapsers (n = 95)
Male (%)	52	62
Caucasian (%)	90	94
Mean age (years)	47	50
Mean BMI (kg/m²)	25.3	26.3
Cirrhosis (%)	15	19
High viral load* (%)	33	37
HCV genotype (%) :		
1	60	74
2/3	27	16
4/5/6	13	10
ALT (%) :		
Normal	10	8
> ULN to ≤ 3 ULN	64	67
> 3 ULN	26	26

* ≥ 800,000 IU/mL.
ALT = alanine aminotransferase ; ULN = upper limit of normal.

weeks 12, 24 and 48 was determined. In the peginterferon alfa-2a plus ribavirin group, 70%, 84% and 87% of patients had undetectable HCV RNA at weeks 12, 24 and 48 respectively. In the interferon alfa-2a plus ribavirin group, 42%, 52%, and 73% of patients had undetectable HCV RNA at these respective intervals.

Relapse rate

We next analyzed relapse rates (RR) in subpopulations of patients who received 48 weeks of therapy. Non-responders (HCV RNA detectable at week 24) and patients with genotype 2 and 3 who were treated with

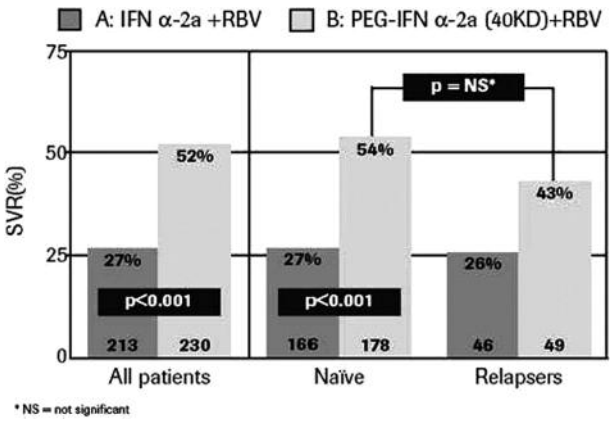

Fig. 1. — Overview of efficacy results (intention to treat population).

peginterferon alfa-2a plus ribavirin for 24 weeks were excluded from this analysis. In keeping with current treatment guidelines, this analysis only included those patients who complied with the protocol-defined 80/80/80 rule (patients that received ≥ 80% target peginterferon alfa-2a or interferon alfa-2a exposure plus ≥ 80% target ribavirin exposure for ≥ 80% of the planned treatment duration). Of the 222 patients who fulfilled these criteria (129 in the peginterferon alfa-2a plus ribavirin group, 93 in the interferon alfa-2a plus ribavirin group), 151 had an assessment of HCV RNA at week 48 and at the end of the 24-week follow-up period, allowing assessment of their RR. RR (%) was defined as ([end-of-treatment response (EOTR) rate - SVR rate)/EOTR rate) × 100.

The overall RR in this study was 19.9% (30/151), with 20.8% occurring in the peginterferon alfa-2a plus ribavirin group and 18.1% in the interferon alfa-2a plus ribavirin group (p = 0.694). RR was further analyzed by treatment status (Table 3a). For treatment-naïve patients, the RR was similar in the two treatment groups (17% versus 16% in the peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin groups respectively). For patients who had relapsed previously, the RR after the current treatment regimen was also similar : 30% and 27% for these respective treatment groups. Overall, the RR was higher in patients who previously relapsed.

Stepwise logistic regression analysis was performed to determine whether any baseline or on-treatment factors were predictive of relapse (Table 3a). HCV RNA status at week 12 and patient age were found to be independent predictors of relapse by stepwise logistic regression analysis. The RR for patients with detectable HCV RNA at week 12 but undetectable HCV RNA at week 48

Table 3a. — **Relapse rate in the different treatment arms by treatment status**

	EOTR	SVR	RR	
Peginterferon alfa-2a				
Naïve	n = 72	n = 60	12/72 (16.7%)	p = 0.151
Relapsers	n = 23	n = 16	7/23 (30.4%)	
Interferon alfa-2a				
Naïve	n = 44	n = 37	7/44 (15.9%)	p = 0.382
Relapsers	n = 11	n = 8	3/11 (27.3%)	

EOTR = end-of-treatment response ; SVR = sustained virologic response ; RR = relapse rate.

Table 3b. — **Predictors of relapse**

Intention to treat population – compliant patients with negative PCR results at week 48 and results after 24 weeks Multivariate stepwise logistic regression model for relapse (n = 126)			
Stepwise logistic regression Variable entered in model*	p-value	Odds ratio	95% CI on odds ratio (1.92-19.12)
Hepatitis C status at week 12 (positive vs. negative)	0.002	6.07	(1.02-14.27)
Age category (≥ 40 years vs. < 40 years)	0.047	3.81	

* The following factors did not meet the 0.05 level of significance for entry into the model : treatment, global treatment status (naïve vs. relapse), body mass index, cirrhosis, HCV viral load at baseline and alanine aminotransferase level.

(n = 22) was 54.6%, compared with 13.0% for those patients (n = 123) with undetectable HCV RNA at week 12 (p = 0.002 ; OR = 6.07). Patients > 40 years old had an RR of 26.0% versus 9.1% for those < 40 years old.

Safety

A total of 190 patients discontinued therapy prematurely due to lack of efficacy (HCV RNA still positive at week 24 for non-genotype 2 and 3 patients), adverse events, personal reasons, lack of follow-up data or other reasons. The discontinuation rate in the peginterferon alfa-2a plus ribavirin group was 30.9% compared with 55.9% in the interferon alfa-2a plus ribavirin group. There was no difference in the reported frequency and intensity of treatment-emergent adverse events between the two treatment groups. Adverse events related to blood and lymphatic system disorders were frequently reported (52.8% in the peginterferon alfa-2a plus ribavirin group versus 27.8% in the interferon alfa-2a plus ribavirin group). A higher incidence of anemia (29.7% versus 19.8%), thrombocytopenia (23.1% versus < 10%), leukopenia (21.8% versus 10.4%) and neutropenia (18.3% versus < 10%) was reported in the peginterferon alfa-2a plus ribavirin group than the interferon alfa-2a plus ribavirin group.

Discussion

This study, conducted in a large multicenter setting, confirms previously published data demonstrating the superiority of peginterferon alfa-2a over conventional interferon, in combination with ribavirin for the treatment of CHC. This study also establishes the value of peginterferon alfa-2a over interferon alfa-2a in combination therapy for treatment-naïve HCV genotype 2/3 patients (respective SVR rates were 73% versus 45%, OR = 3.30 ; 95% CI : 1.37-7.94 ; p = 0.010) more clearly than a previous trial for peginterferon alfa-2b versus peginterferon alfa-2b (8).

Randomized studies directly comparing the efficacy of peginterferon alfa-2a with conventional interferon in patients with a prior relapse have not been published . In this study, SVR rates for treatment-naïve patients and prior relapsers treated with non-pegylated interferon were not different, supporting the use of peginterferon alfa-2a in both patient populations. Relapse rates after retreatment with peginterferon alfa-2a for 48 weeks remained high for patients who relapsed after previous interferon therapy (~17% versus ~30% for naïve patients and relapsers respectively).

It is generally accepted that a significant reduction in viral load at week 12 is predictive of successful treatment outcomes (9). In our study, patients with undetectable HCV RNA at the end of treatment but who had still detectable HCV RNA at week 12, had relapse rates of ≥ 50%. Also an age > 40 years was found to be predictive of relapse. This might be explained by the fact that older patients had a longer duration of disease, more extensive fibrosis and need greater reductions in study drug exposure due to reduced tolerance.

We previously demonstrated that treatment of naïve patients with conventional interferon for the extended duration of 72 weeks leads to a reduction in relapse rates (6), a finding that has been confirmed by others (10-12). The data presented here suggest that a longer retreatment duration with peginterferon alfa-2a plus ribavirin should be considered for prior relapsers, particularly those with a slow viral response (detectable HCV RNA at week 12 and undetectable at week 24). Thus a more optimized treatment regimen based on

patients' on-treatment responses might improve SVR rates for this difficult to treat population.

Overall, the discontinuation rate was higher in the convential interferon group than in the peginterferon alfa-2a group whilst the overall incidence of adverse events was similar in both treatment groups. Specifically, a higher incidence of hematological adverse events was reported in the peginterferon alfa-2a group than in the conventional interferon arm. However, this is offset by the higher treatment adherence of patients in the peginterferon alfa-2a group, and their correspondingly higher SVR rates. The results of the safety analyses in this study are in line with the established safety profiles for each of the study drugs.

In conclusion, this large, multicenter study representative of the chronic hepatitis C patient population and of physicians' practices in Belgium, confirms superiority of peginterferon alfa-2a over conventional interferon in combination therapy in both naïve and relapsed patients. In addition, the data support the application of response-guided therapy in relapsers and / or patients with slow response to treatment.

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