Retreatment of patients with chronic hepatitis C relapsers to a previous antiviral treatment

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Background **The efficacy of retreatment with pegylated interferon (PEG-IFN) plus ribavirin for patients relapsing after a previous treatment remains to be fully elucidated, although extended treatment seems to be the best option in such cases.**

Aim **To evaluate the efficacy of two extended protocols in patients with genotypes 1 or 4, or those with genotypes 2 or 3.**

Methods **A total of 181 patients who had relapsed after a previous antiviral treatment with PEG-IFNα2a plus weight-based ribavirin were offered retreatment with the same dose of both PEG-IFN plus ribavirin, to be continued for 48 weeks in those with genotypes 2 or 3 (group 1), and for 72 weeks in those with genotypes 1 or 4 (group 2).**

Results **A total of 59 patients (32.5%) refused the retreatment, while 122 (78 men, 44 women) patients were enrolled in the study: 41 were allocated in group 1 and 81 in group 2. Cirrhosis at baseline (staging 5/6 according to Ishak's score was recorded in 11 patients, six in group 1 and five in group 2). Nine patients (7.3%) in group 2 discontinued the treatment (due to lack of response). The remaining patients completed the treatment and were followed-up for at least 12 months after the treatment. Sustained virological response (SVR) rate was 82.9% in group 1 and 50.6% in group 2.**

Conclusion **Patients with chronic hepatitis C with 'easy genotypes' relapsers to a previous antiviral treatment have more than 80% probability of achieving a SVR with a 48-week retreatment. Patients with 'difficult genotypes' have more than 50% chance of a SVR after a 72-week extended treatment.** ***Eur J Gastroenterol Hepatol*** **23:711–715 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: antiviral therapy, genotypes, hepatitis C virus, relapsers, retreatment

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Introduction

Combination therapy with pegylated interferon (PEG-IFN) and ribavirin is the current strategy for treating hepatitis C [1]. New data have emerged on the effectiveness of this therapeutic strategy in recent years, including predictors of response (particularly regarding the early decline in viral load and the 'easy genotypes' 2 and 3 compared with the genotype 1). Individualized treatment seems to be the best strategy for a rational use of resources [2]. However, the optimal approach to patients failing to respond to this treatment has yet to be established. Among the nonresponders, relapsers are those who maintain viral clearance while on treatment, but hepatitis C virus (HCV)-RNA becomes detectable once again when therapy is stopped [3].

A panel of experts convened by the US Food and Drug Administration recently issued a position statement containing the recommendation that relapser patients should be studied separately [4]. Retreatment of relapsers still remains a nonclarified argument. Relapsers have been included in several published studies, generally representing a small size group included in multicenter trials (Table 1, [5–11]), only three of which were randomized [5,8,9], and the first-line treatment offered was a combination of PEG-IFN plus ribavirin for 48 weeks. This regimen proved effective in 27–53% of cases with genotype 1 and in 59–70% of those with non-genotype 1 (Table 1).

An extended treatment for relapsers has been proposed by German authors to reinforce the sustained virological response (SVR) in 107 patients, predominantly with genotype 1 [12]. A 72-week retreatment with PEG-IFNα2a plus ribavirin achieved a 51% SVR, whereas the SVR rate was as high as 97% in patients who had HCV-RNA undetectable at 4 weeks [12]. Based on these data, it may be appropriate to consider extending the duration of retreatment in relapsers.

The aim of this study was to assess the efficacy of two extended protocols for relapsing patients divided by their genotype (1 or 4, vs. non-genotype 1).

Materials and methods

Study design

This study was designed as prospective open-label, uncontrolled trial enrolling patients with chronic hepatitis C

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Table 1 Studies including retreatment in relapsers

Author and references	Type of study	Previous treatment	*N*	Percentage of genotype 1 (%)	Overall SVR rate (%)	Type of retreatment
Berg *et al.* [5]	Multicenter randomized	PEG-IFNα2a + ribavirin	67	70	5	48 weeks of PEG-IFNα2a + ribavirin ($\geq$ 800 mg/day or $\geq$ 1000 mg/day)
Parise *et al.* [6]	Multicenter open label nonrandomized	Conventional IFN + ribavirin	37	73	44 in genotype 1 70 in nongenotype non 1	48 weeks of PEG-IFNα2a + ribavirin (800 mg/day)
Krawitt *et al.* [7]	Multicenter open label nonrandomized	Conventional IFN (N.15), combination (N.51)	66	74	53 in genotype 1 59 in nongenotype 1	48 weeks of PEG-IFNα2b + ribavirin
Jacobson *et al.* [8]	Multicenter randomized open label	IFN + ribavirin	55	–	42	48 weeks of PEG-IFNα2b + ribavirin (800 mg/day) vs. PEG-IFNα2b + ribavirin (1000–1200 mg/day)
Herrine *et al.* [9]	Multicenter randomized open label	Conventional IFNa2β + ribavirin	106	78–84	38–45 in groups including ribavirin	48 weeks of: PEG-IFNα2a + ribavirin PEG-IFNα2a + MMF PEG-IFNα2a + amantadine PEG-IFNα2a + amantadine + ribavirin
Poynard *et al.* [10]	Multicenter open label	PEG-IFN + ribavirin	647	–	27 in genotype 1 61 in nongenotype 1	48 weeks of PEG-IFNα2b + ribavirin
Sherman *et al.* [11]	Multicenter open label	Conventional IFN or PEG-IFN + ribavirin	100	69	41	PEG-IFNα2a + ribavirin for 24 or 48 weeks

MMF, mycophenolate mofetil; PEG-IFN, pegylated interferon; SVR, sustained virological response.

who had relapsed to a previous treatment with PEG-IFNα2a plus weight-based ribavirin.

All patients included had been previously treated with PEG-IFNα2a (180 μg/week) plus weight-based ribavirin (800 mg/day for body weight < 60 kg; 1000 mg/day for 60–75 kg; 1200 mg/day for body weight > 75 kg). The duration of treatment was 24 weeks according to genotypes 2 or 3, and 48 weeks according to genotypes 1 or 4. The study was approved by the local ethics committee, and all patients gave their written informed consent.

Inclusion criteria were:

(1) HCV-RNA levels higher than 1000 IU/ml by quantitative reverse-transcription polymerase chain reaction (Amplicor Monitor HCV v 2.0; Roche Molecular Systems, Mannheim, Germany; lower limit of detection 600 IU/ml);
(2) Alanine aminotransferase at least twice the upper normal value;
(3) Neutrophil and platelet counts of at least 2000 and 90 000/ml, respectively;
(4) Compensated chronic liver disease;
(5) Hemoglobin values of at least 12 g/dl for women and 13 g/dl for men; and
(6) Creatitinine levels below 1.5 mg/dl.

Exclusion criteria were:

(1) Decompensated liver disease;
(2) Other causes of liver disease (autoimmunity, infection with hepatitis B, and/or immunodeficiency virus) and alcohol intake of more than 20 g per ethanol per day;
(3) Clinically significant cardiac or cardiovascular abnormalities;
(4) Organ grafts;
(5) Systemic infections;
(6) Evidence of malignant neoplastic disease; and
(7) Concomitant immunosuppressive medication.

Further exclusion criteria were: pregnancy, lactation, and male partners of pregnant women.

Each patient underwent liver biopsy before the previous treatment in which they relapsed; the liver specimens were all read blindly by the same pathologist and classified according to Ishak's numerical scoring system.

Treatment

Eligible patients were offered a different treatment regimen according to HCV genotype:

(1) PEG-IFNα2a (40 kDa; Pegasys; Roche, Basel, Switzerland) at a dose of 180 μg (0.5 ml of prefilled syringe) subcutaneously once a week plus weight-based oral ribavirin (Copegus, Roche) for 48 weeks in those with genotypes 2 or 3;
(2) PEG-IFNα2a (40 kDa) at a dose of 180 μg (0.5 ml of prefilled syringe) subcutaneously once a week plus weight-based oral ribavirin for 72 weeks in those with genotypes 1 or 4.

In both groups, ribavirin was administered orally in two daily doses for a total of 800 mg per day for patients weighing up to 70 kg, or 1000 mg/d for patients weighing 71–80 kg, or 1200 mg per day for those weighing more than 80 kg.

The treatment was withdrawn if patient failed to achieve a virological response (VR), defined as a serum HCV-RNA

decrease of at least two logarithmic steps after 24 weeks of treatment compared with baseline levels; these patients were considered as nonresponders, based on the guidelines of the European Association for the Study of Liver Disease [13]. We also considered rapid VR defined as serum HCV-RNA undetectable after 4 weeks of treatment and the complete early VR defined as serum HCV-RNA undetectable after 12 weeks of treatment.

End-of-treatment response was defined as a normalization of alanine transferase and HCV-RNA negativity at the end of the treatment. The treatment lasted 72 weeks for patients with genotypes 1 or 4 and 48 weeks for those with genotypes 2 or 3.

SVR was defined as the absence of serum HCV-RNA and normal alanine transferase 24 weeks after completing the treatment.

Follow-up

Once a month, each patient had a physical examination and biochemical tests, which included: hemoglobin, white blood cell count, platelet count, transaminases, and γ-glutamyl-transpeptidase. Polymerase chain reaction for HCV was assessed at weeks 0, 4, 12, 24, 48, 72, and 24 and 48 weeks after the end of treatment. Nonorgan-specific autoantibodies (antinuclear, anti-smooth muscle, antimitochondrial, antiliver, and kidney microsomes), and antithyroid antibodies were assessed before starting treatment, and at weeks 12 and 24 during treatment.

Statistical analysis

Data were analyzed using the χ^2 test (the Mantel–Haenszel and Fisher's exact test). A P value of 0.05 or less was considered significant, and the odds ratio with a 95% confidence interval was calculated for each parameter. Multivariate logistic regression analysis was performed to evaluate independent predictors of a SVR. Analyses were performed with the Statistical Package for the Social Sciences (SPSS rel. 11.5, Chicago, Illinois, USA).

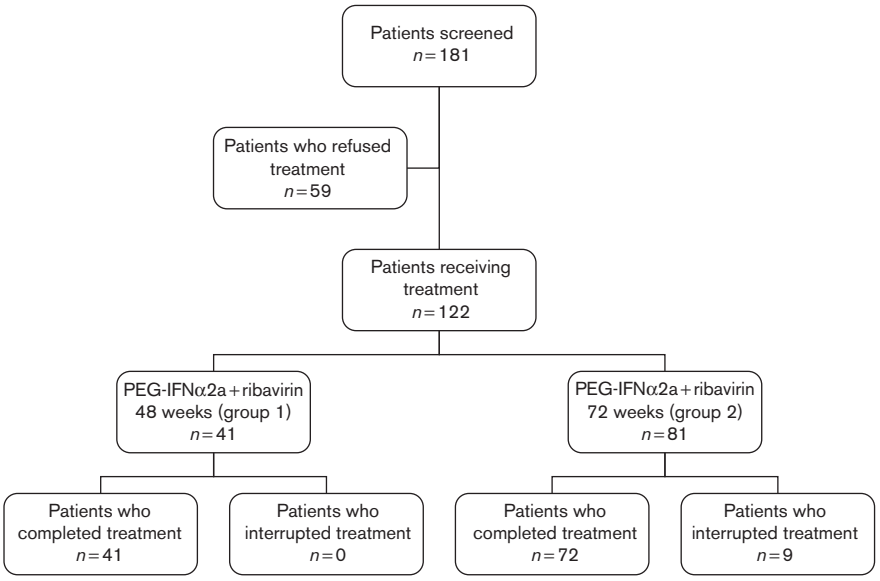
Results

A total of 181 patients fulfilled the criteria of inclusion in the study and were offered retreatment according to the previously described protocol. Fifty-nine of them (32.5%) refused, whereas 122 (80 men, 42 women) were enrolled in the study: 41 with genotypes 2 or 3 received extended retreatment for 48 weeks, and 72 with genotype 1 received extended retreatment for 72 weeks (Fig. 1). The patients' demographic, biochemical, and virological characteristics are listed in Table 2. Eleven patients had cirrhosis (six in group 1 and five in group 2).

All patients in group 1 completed the treatment, whereas nine in group 2 did not (eight due to lack of response for poor compliance and one failed to turn up for treatment).

A rapid virological response was reached in 21 patients (51.2%) in group 1 and in 12 (14.8%) in group 2 ($P < 0.001$). The early virological response (EVR) was reached in 39 (95.1%) in group 1 and in 43 (53.1%) in group 2 ($P < 0.001$). A VR after 24 weeks of treatment was reached in 41 cases (100%) in group 1 and 72 (88.9%) in group 2 ($P = 0.55$). An end-of-treatment response was reached in 41 (100%) and 64 (79%) cases, respectively ($P = 0.001$), and a SVR in 82.9 and 50.6%, respectively

Fig. 1



Design of the study. PEG-IFN, pegylated interferon.

($P < 0.001$; Table 3). Among the 11 patients with cirrhosis only four reached a SVR (two patients in group 1 and two in group 2).

Logistic regression analysis only identified 'easy genotypes' as significant predictors of the SVR rate (adjusted odds ratio: 8.528; 95% confidence interval: 2.829–25.703; $P < 0.001$).

Discussion

Our findings indicate that patients with chronic hepatitis C with 'easy genotypes' who relapse to a previous antiviral treatment have approximately 88% probability to obtain a SVR with a 48-week treatment, whereas patients with genotype 1 have more than 50% chance of achieving a SVR with a 72-week extended treatment. These results warrant further comment.

First of all, there is still a shortage of studies on retreatment for relapsers. All published studies are multicenter (Table 1), and the retreatment considered lasted for 48 weeks. In the studies that considered the SVR rate by genotype, the overall SVR rate was 59–70% in genotypes 2 and 3, and 27–44% in genotype 1 [6,7,10]. The only study proposing an extended treatment for relapsers with genotype 1 was published in an abstract form [12]. In contrast, the duration of extended treatments was evaluated in naïve patients with HCV type 1 infection in a multicenter trial involving 18 centers in Germany [14]; the researchers concluded that extended treatment was not to be recommended for HCV type 1 infection and should be reserved only for patients with a slow VR (defined as HCV-RNA positive at week 12 but negative at week 24).

Relapsers are assumed to be slow responders and it is on this hypothesis that an extended treatment was given to patients with genotype 1 in a German multicenter study [12], and preliminary data indicated that a 72-week extended treatment gave to genotype 1 relapsers patients a 51% chance of a SVR [12]. Our single-center study divided relapsers into two groups, one with the 'easy' genotypes 2 and 3 and the other one with type 1, which should be regarded from a different point of view. In fact, the SVR in the group with type 1 genotype is lower than in the German study [12]. Unfortunately, the baseline viral load was not reported in the preliminary results from the German study, although the VR recorded at week 4 indicated 27% HCV-RNA positivity, which is similar to our findings. In contrast, our SVR rate of 41% in genotype 1 patients is similar to the rates reported in studies on relapsers using PEG-IFN plus ribavirin for 48 weeks [6,7]. The lowest SVR rate in type 1 genotype (27%) was reported by Poynard *et al.* [10] using PEG-IFNα2b plus ribavirin. This result raises the question of whether PEG-IFN (40 kDa) could be more beneficial than PEG-IFNα2b, also in light of recently published trials [15,16]. Although PEG-IFN (40 kDa) has been shown to have a more favorable effect than PEG-IFNα2b in naïve patients with genotype 1, this result cannot be transferred to the case of retreatment for relapsers with genotype 1. There are also no convincing data available as yet to support recommending extended retreatment for 72 weeks for genotype 1 patients.

We would like to stress the SVR rate of 82.9% obtained in relapsers with 'easy genotypes', which is higher than in other studies [6,7,10] using the same duration of treatment. Our treatment group included 59% of patients with genotype 2, and 41% with genotype 3. Given this small number of patients and the high SVR rate, it was impossible to distinguish the SVR rate by genotype (2 or 3). Moreover, we could not identify other cofactors responsible for relapsing in our patients, in particular the effect of the overweight; however, only three patients in group 1 and four patients in group 2 had a BMI of more than 30 suggesting the presence of a metabolic syndrome.

Table 2 Demographic, biochemical, and virological characteristics at baseline

Characteristics	Group 1 ($n=41$)	Group 2 ($n=81$)
Sex		
Male	29	51
Female	12	30
Age (years)		
Mean ± SD	52.6 ± 10.1	49.1 ± 9.9
Range	30–71	30–67
BMI (kg/m^2)		
Mean ± SD	25.3 ± 3.1	25.1 ± 3.4
Range	20.1–34.2	16.2–34.7
ALT levels (IU/l)		
Mean ± SD	155 ± 126	103 ± 85
Range	27–569	23–617
GGT levels (IU/l)		
Mean ± SD	93 ± 98	79 ± 78
Range	9–568	11–385
HCV genotype		
1		76 (94%)
2	24 (59%)	
3	17 (41%)	
4		5 (6%)
HCV RNA ($\times 10^6$ IU/ml)		
Mean ± SD	6.55 ± 6.9	6.64 ± 6.8
Range	4.1–7.6	3.51–7.48
Cirrhotic stage	6 (14.6%)	5 (6.1%)

ALT, alanine transferase; HCV, hepatitis C virus; SD, standard deviation.

Table 3 Virological responses to the extended treatment

Response	Group 1 [$n=41$ (%)]	Group 2 [$n=81$ (%)]	OR (CI)	P
Rapid virological response	21 (51.2)	12 (14.8)	6.04 (2.34–15.83)	<0.001
Early virological response	39 (95.1)	43 (53.1)	17.23 (3.69–110.6)	<0.001
Virological response	41 (100)	72 (88.9)	–	0.55
End of treatment response	41 (100)	64 (79.0)	–	0.001
Sustained virological response	34 (82.9)	41 (50.6)	4.74 (1.75–13.32)	<0.001

CI, confidence interval; OR, odds ratio.

Our data nonetheless suggest that a 48-week retreatment for relapsers with 'easy genotypes' is an excellent option; none of the patients in this group experienced side-effects severe enough to induce them to abandon the treatment, so they all completed the 48 weeks of treatment and achieved an end-of-treatment response.

Finally, logistic regression analysis showed that only an easy genotype could predict the SVR rate.

In our study, we did not perform the interleukin 28B (IL28B) genotype testing. During the last 2 years, several studies demonstrated that possession of the favorable genotypes (CC at the SNP rs12979860 or TT at the SNP rs8099917) were associated with the highest SVR, mainly in patients with genotype 1 [17,18]. However, the clinical application of this genomic assay in individualizing the antiviral treatment has not been proven to be realistically useful. In fact, ILB28 genotyping is insufficient for deciding whether a patient is likely to respond to PEG-IFN and ribavirin [19]. Moreover, although we await prospective studies and randomized controlled trials stratifying patients in accordance to IL28B type, the cost-effectiveness of the inclusion of IL28B evaluation in a response-guided therapy algorithm remains to be clarified [20]. In conclusion, patients with chronic hepatitis C with 'easy genotypes' relapsers to a previous antiviral treatment have more than 80% probability of achieving a SVR with a 48-week treatment, whereas patients with 'difficult genotypes' have more than 50% likelihood of a SVR with an extended 72-week treatment.

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Conflicts of interest: none declared.

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