

# Retreatment with pegylated interferon alpha-2a and ribavirin in patients with chronic hepatitis C who have relapsed or not responded to a first course of pegylated interferon-based therapy

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EM Yoshida, M Sherman, VG Bain et al; on behalf of the Canadian Pegasys Study Group. Retreatment with pegylated interferon alpha-2a and ribavirin in patients with chronic hepatitis C who have relapsed or not responded to a first course of pegylated interferon-based therapy. *Can J Gastroenterol* 2009;23(3):180-184.

**BACKGROUND:** Pegylated interferon (pegIFN) and ribavirin combination therapy remains the first-line treatment for chronic hepatitis C virus (HCV) infection. In contrast to the wealth of studies in treatment-naïve patients, the effectiveness of retreatment in patients who have previously failed pegIFN-based therapy is largely unreported.

**AIM:** To assess the effectiveness of the retreatment of patients who have previously failed an initial course of pegIFN-based therapy with pegIFN $\alpha$ -2a and ribavirin.

**METHODS:** A post-hoc analysis of a multicentre open-label study was performed. Patients received pegIFN $\alpha$ -2a and ribavirin at a dose of 800 mg/day and later 1000 mg/day to 1200 mg/day for 24 to 48 weeks at the discretion of the investigator. Outcomes at week 12 (early virological response [EVR]) and week 24 (sustained virological response [SVR]) were analyzed.

**RESULTS:** Eighty-seven patients who had relapsed after previous pegIFN-based therapy (n=28; 78% genotype 1) or were nonresponders (n=59; 71% genotype 1) were analyzed. Of the relapsers, 86% achieved an EVR and 68% achieved an SVR. In relapsers to pegIFN monotherapy (n=15) or pegIFN plus ribavirin (n=13), 60% and 77% achieved an SVR, respectively. Fibrosis and genotype did not affect the likelihood of SVR in relapsers although this may be the result of the relatively small number of patients. In previous nonresponders, an EVR was achieved in 53% but an SVR occurred in only 17%. In nonresponders to pegIFN monotherapy (n=9) and pegIFN plus ribavirin (n=50), 33% and 14% achieved an SVR, respectively. Genotype did not affect SVR in nonresponders. Only 10% with a METAVIR score of F3 or F4 on liver biopsy achieved an SVR.

**CONCLUSIONS:** Relapse after previous pegIFN-based therapy is associated with a strong probability of treatment success whereas retreatment of those with previous nonresponse does not.

**Key Words:** Failure; Hepatitis C; Nonresponse; Peginterferon; Relapse; Ribavirin; Treatment

**La reprise du traitement à l'interféron pégylé alpha-2a et à la ribavirine chez des patients atteints d'hépatite C chronique qui font une rechute ou n'avaient pas réagi à une première thérapie à base d'interféron pégylé**

**HISTORIQUE :** La bithérapie à l'interféron pégylé (IFNpeg) et à la ribavirine demeure le traitement de première ligne de l'infection par le virus de l'hépatite C chronique (VHC). Contrairement à la multitude d'études chez des patients n'ayant jamais été exposés au traitement, l'efficacité de la reprise du traitement chez les patients qui n'avaient pas réagi auparavant à la thérapie à base d'IFNpeg est très peu étudiée.

**OBJECTIF :** Évaluer l'efficacité de la reprise du traitement auprès de patients qui n'avaient pas réagi auparavant à une première thérapie à base d'IFNpeg au moyen d'IFNpeg $\alpha$ 2a et de ribavirine.

**MÉTHODOLOGIE :** Les auteurs ont procédé à une analyse *a posteriori* d'une étude multicentre ouverte. Les patients ont d'abord reçu une dose de 800 mg/jour d'IFNpeg $\alpha$ 2a et de ribavirine, puis une dose de 1 000 mg/jour à 1 200 mg/jour pendant 24 à 48 semaines, à la discrétion du chercheur. Les résultats ont été analysés lors de la semaine 12 (réponse virologique précoce [RVP]) et de la semaine 24 (réponse virologique soutenue [RVS]).

**RÉSULTATS :** Les auteurs ont analysé 87 patients qui avaient fait une rechute après une thérapie antérieure à base d'IFNpeg (n=28; 78 % de génotype 1) ou qui n'y avaient pas réagi (n=59; 71 % de génotype 1). Parmi ceux qui avaient fait une rechute, 86 % avaient obtenu une RVP et 68 %, une RVS. Chez ces patients après une monothérapie à l'IFNpeg (n=15) ou à l'IFNpeg associé à la ribavirine (n=13), 60 % et 77 % avaient obtenu une RVS, respectivement. La fibrose et le génotype n'avaient pas d'incidence sur la probabilité de RVS chez ceux qui avaient fait une rechute, même si ce résultat peut découler du nombre relativement faible de patients. Chez les patients qui n'avaient pas réagi au traitement auparavant, 53 % avaient obtenu une RVP, mais seulement 17 %, une RVS. Chez ceux qui n'avaient pas réagi à la monothérapie à l'IFNpeg (n=9) ou à l'IFNpeg associé à la ribavirine (n=50), 33 % et 14 % avaient obtenu une RVS, respectivement. La fibrose et le génotype n'avaient pas d'incidence sur la probabilité de RVS chez ces patients. Seulement 10 % des patients ayant obtenu un indice METAVIR de F3 ou F4 à la biopsie hépatique ont obtenu une RVS.

**CONCLUSIONS :** Les rechutes après une thérapie à base d'IFNpeg s'associent à une forte probabilité de réussite du traitement, mais pas chez les patients qui n'avaient pas réagi à ce traitement auparavant.

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Received for publication July 13, 2008. Accepted November 25, 2008

The current recommended treatment for chronic hepatitis C infection is combination therapy with pegylated interferon (pegIFN) and ribavirin (1-3). This recommendation generally applies to patients who have not previously received pegIFN-based therapy for chronic hepatitis C, in whom the overall probability of achieving a sustained virological response (SVR) exceeds 50% (depending on hepatitis C virus [HCV] genotype) (4-6), as well as several other reported prognostic factors that may affect treatment success. Effective therapy, however, is still needed for patients who have not achieved an SVR after a first course of interferon-based therapy – especially those who have failed a course of therapy with pegIFN and ribavirin (2). Recent treatment guidelines have avoided recommending the retreatment of these latter individuals (1,3), largely because of a lack of peer-reviewed published data on which to base a recommendation.

The Canadian Pegasys expanded access program (EAP), an open-label national program that provided pegIFN $\alpha$ -2a (Pegasys, Hoffmann-La Roche, Canada) and ribavirin (Copegus, Roche, Canada) with registration in a database and data collection, enrolled more than 2500 patients with chronic hepatitis C including many who had not achieved an SVR after treatment with previous interferon-based therapy. The outcomes in patients who had failed to respond to a course of conventional non-pegIFN-based therapy have previously been reported elsewhere (7). In the present post hoc analysis, we report the efficacy of retreatment with pegIFN $\alpha$ -2a plus ribavirin in patients who had failed to respond to a first course of pegIFN-based therapy.

## METHODS

### Patients

Patients eligible for the Canadian Pegasys EAP were adults 18 years of age and older, whose chronic HCV infection was confirmed by a commercial quantitative polymerase chain reaction (PCR) HCV RNA assay (Cobas Amplicor HCV Monitor Test v2.0, limit of quantitation 600 IU/mL [Roche Diagnostics, Canada]). Patients with cirrhosis were eligible provided they had compensated liver disease (Child-Pugh class A). Interferon-naïve and previously treated patients were eligible for enrollment. For patients who had received previous treatment, investigators were required to record the type and duration of previous treatment, and the nature of the response (relapse or nonresponse) to previous treatment on the case report form. Investigators were not required to record the dosages of medications administered or the magnitude of the response (ie, results of HCV RNA tests) during previous treatment.

In the first phase of the EAP, all patients were required to undergo a liver biopsy. This procedure was optional in later phases of the program. All biopsies were interpreted by the local hospital pathologist. In addition to whatever histological scoring system was used at the local institutions, all liver biopsies were graded by the METAVIR system (8) for fibrosis.

Patients were excluded if they had a history of decompensated liver disease, a hemoglobin concentration of less than 100 g/L, a neutrophil count of less than 1500 cells/mL, a platelet count of less than  $90 \times 10^9/L$ , or evidence of infection with hepatitis B virus or HIV. Other exclusion criteria included a history of autoimmune disease, organ transplantation, uncontrolled major psychiatric conditions, active substance abuse or other serious chronic disease. The EAP was approved by the ethics board at each institution and patients provided informed consent before enrolment.

### Study design

The EAP was an open-label multicentre study in which eligible patients were assigned to 24 or 48 weeks of treatment with subcutaneous injections of pegIFN $\alpha$ -2a 180  $\mu$ g/week plus oral ribavirin at the physician's discretion.

In the first phase of the program, all patients received ribavirin 800 mg/day. Physicians were allowed to prescribe ribavirin at a dose of 1000 mg/day for patients with body weight of less than 75 kg or 1200 mg/day for those weighing more than 75 kg, after evidence became available that these doses were optimal in patients with HCV genotype 1 infection.

### Assessments and outcomes

Serum HCV RNA levels were determined at baseline and at week 12 by quantitative PCR assay. Samples from patients with unquantifiable HCV RNA were retested with a more sensitive qualitative PCR assay (Cobas Amplicor HCV Test v2.0, limit of detection 50 IU/mL). All HCV RNA assays were performed at the virology laboratory of the BC Centre for Disease Control, Vancouver, British Columbia. An early virological response (EVR) at week 12 was defined as undetectable HCV RNA by qualitative PCR, or a 2- $\log_{10}$  or greater reduction in HCV RNA relative to the baseline value by quantitative PCR. SVR was defined as undetectable HCV RNA (less than 50 IU/mL) by qualitative PCR 24 weeks after administration of the last dose of pegIFN $\alpha$ -2a.

### Statistical analysis

The present study was a retrospective descriptive analysis.

## RESULTS

A total of 87 patients were enrolled and retreated with pegIFN $\alpha$ -2a and ribavirin. Twenty-eight patients had a history of virological relapse and 59 patients were nonresponders to pegIFN monotherapy or combination pegIFN-ribavirin therapy. The baseline characteristics of these patients are presented in Table 1. The two groups were similar with respect to most baseline demographic characteristics. More patients with a previous nonresponse were infected with HCV genotype 1 (78% versus 71% of previous relapsers). A higher proportion of nonresponders had been previously treated with combination pegIFN and ribavirin therapy (85%) than pegIFN monotherapy (15%) compared with previous relapsers (46% and 56%, respectively).

Most of the patients with a history of previous relapse (26 of 28 [93%]) and nonresponse (50 of 59 [85%]) were assigned to 48 weeks of treatment with pegIFN $\alpha$ -2a plus ribavirin. More than one-half of patients with a history of relapse (15 of 28 [53%]) and a history of nonresponse (40 of 59 [68%]) were assigned to an initial ribavirin dose of 1000 mg/day or 1200 mg/day (Table 2).

### Efficacy

#### Patients with previous relapse to pegIFN-based therapy:

Overall, an EVR was achieved in 24 of 28 patients (86%) and an SVR was achieved in 19 of 28 previous relapse patients (68%). All but one patient with an SVR achieved an EVR. The majority of the patients were infected with the genotype 1 virus (n=20 [71%]). Sixty-five per cent achieved an SVR. The remaining eight patients were infected with genotypes 2 or 3. Five patients (62.5%) achieved an SVR.

Among patients who had previously been treated with pegIFN monotherapy, nine of 15 (60%) achieved an SVR.

**TABLE 1**  
**Baseline characteristics of patients**

Characteristic	Previous relapse (n=28)	Previous nonresponse (n=59)
Median age, years (range)	48 (23–61)	49 (37–63)
Men, n (%)	17 (61)	44 (75)
Caucasian, n (%)	27 (96)	50 (85)
Median body mass index, kg/m <sup>2</sup> (range)	27 (20–40)	27 (19–37)
Liver biopsy performed, n (%)	27 (96)	52 (88)
METAVIR fibrosis stage, n (%) <sup>*</sup>		
F1	3 (11)	11 (21)
F2	14 (52)	19 (37)
F3	5 (19)	10 (19)
F4	5 (19)	10 (19)
Other/unknown, n (%)	–	2 (4)
Hepatitis C virus genotype, n (%)		
1	20 (71)	46 (78)
2	2 (7)	4 (7)
3	5 (18)	7 (12)
Other	1 (4)	2 (3)
Median serum hepatitis C virus RNA level, IU/mL x 10 <sup>3</sup> (range)	666 (9.4–19,840)	1280 (5.8–16,000)
Hepatitis C virus RNA ≥400,000 IU/mL, n (%)	22 (79)	39 (66)
Previous treatment, n (%)		
pegIFNα-2a monotherapy	5 (18)	2 (3)
pegIFNα-2b monotherapy	10 (36)	7 (12)
pegIFNα-2a plus ribavirin	9 (32)	4 (7)
pegIFNα-2b plus ribavirin	4 (14)	46 (78)
Median duration of previous treatment, days (range)	330 (120–730)	181 (59–425)

<sup>\*</sup>Only patients who had a liver biopsy were included in the calculation of percentages; pegIFN Pegylated interferon

**TABLE 2**  
**Retreatment regimens**

Retreatment	Previous relapse (n=28)	Previous nonresponse (n=59)
Duration of treatment with pegIFNα-2a plus ribavirin <sup>*</sup>		
24 weeks	2 (7)	9 (15)
48 weeks	26 (93)	50 (85)
Ribavirin dose, mg/day		
600	–	2 (3)
800	13 (46)	17 (29)
1000	4 (14)	13 (22)
1200	11 (39)	27 (46)

<sup>\*</sup>At the treating physician's discretion

Among those who had received previous pegIFN and ribavirin, 10 of 13 individuals (77%) achieved an SVR (Table 3).

When analyzed according to the dose of ribavirin, 13 of 15 patients (87%) assigned to 1000 mg/day or 1200 mg/day, and six of 13 (46%) receiving 800 mg/day achieved an SVR.

Twenty-seven of 28 relapsers underwent a pretreatment liver biopsy (Table 1). An SVR was achieved in 12 of 17 patients (70.6%) with F1 or F2 fibrosis scores, three of five (60%) with F3 fibrosis (ie, transition to cirrhosis) and three of five patients (60%) with cirrhosis (ie, F4).

**Patients with previous nonresponse to pegIFN-based therapy:** Overall, an EVR was achieved in 31 of 59 patients (53%) and an SVR was achieved in 10 of 59 patients (17%) with

**TABLE 3**  
**Sustained virological response (SVR) rates according to previous treatment and genotype**

Previous treatment	SVR according to previous treatment response, n/n (%)	
	Previous relapse (n=28)	Previous nonresponse (n=59)
pegIFNα-2a monotherapy (n=7)	3/5 (60)	1/2 (50)
pegIFNα-2b monotherapy (n=17)	6/10 (60)	2/7 (29)
pegIFNα-2a plus ribavirin (n=13)	8/9 (89)	0/4 (0)
pegIFNα-2b plus ribavirin (n=50)	2/4 (50)	7/46 (15)

pegIFN Pegylated interferon

previous nonresponse. All patients with an SVR achieved an EVR. Of the previous nonresponder patients, 46 (78%) were genotype 1-infected, 11 were genotype 2- or 3-infected (18.6%) and two patients were nongenotype 1, 2 or 3 (genotype not specified). An SVR was achieved in 17% of the genotype 1-infected patients and in 18% of those infected with genotype 2 or 3.

The SVR rate in patients who were previously treated with pegIFN monotherapy was 33% (three of nine). The SVR rate was 14% (seven of 50) in previous recipients of pegIFN and ribavirin (Table 3). The largest subgroup of previous combination

pegIFN and ribavirin nonresponder patients had been treated with pegIFN $\alpha$ -2b and ribavirin (Pegatron, Schering-Plough, Canada) (n=46). Within this subgroup, 33 patients were assigned to 48 weeks of retreatment with pegIFN $\alpha$ -2a plus ribavirin 1000 mg/day or 1200 mg/day, of whom five (15%) achieved an SVR. None of the four patients previously treated with pegIFN $\alpha$ -2a and ribavirin combination therapy achieved an SVR.

When analyzed according to the dose of ribavirin, six of 40 patients (15%) assigned to a ribavirin dose of 1000 mg/day or 1200 mg/day and four of 19 (21%) of those assigned to 800 mg/day achieved an SVR.

Of the previous nonresponder group, 52 patients underwent liver biopsy of which 50 yielded interpretable biopsy results. Eight of these individuals (15%) achieved an SVR. Six of 30 patients (20%) with F1 or F2 fibrosis achieved an SVR. Two of the 10 patients with cirrhosis (ie, F4), and none of the 10 patients with F3 fibrosis achieved an SVR. In other words, 10% of all patients with advanced fibrosis achieved an SVR.

## DISCUSSION

Although retrospective in nature, the results of our analysis suggest that retreatment of patients with chronic HCV infection with pegIFN $\alpha$ -2a plus ribavirin may be of value in a very select group of patients who have failed previous pegIFN-based therapy. The results of our analysis clearly demonstrate that the nature of the previous response to pegIFN-based therapy is very important in predicting the outcome of retreatment. The results also identify groups in which retreatment with pegIFN and ribavirin therapy may be worthwhile and those in which it is clearly not worthwhile.

We determined that approximately 70% of patients with a previous relapse achieved an SVR on retreatment with pegIFN $\alpha$ -2a and ribavirin therapy. The proportion experiencing an SVR was highest (77%) in those who previously relapsed with combination therapy. The reason for this paradoxical finding is likely due to the small number of patients. The success of retreatment in this group appears to be independent of whether the previous treatment was pegIFN monotherapy or combination therapy with ribavirin. Moreover, the success of retreatment also appears to be largely unaffected by the fibrosis stage on liver biopsy, although, once again, the number of patients in this group was small. The finding that previous relapsers have a reasonable likelihood of treatment success with a second course of therapy is not surprising. We note that during the 1990s, in the era of non-pegIFN, patients who initially responded to treatment with standard IFN monotherapy, but subsequently relapsed after therapy, had a 5% SVR rate when retreated with a second course of standard IFN monotherapy but a 49% SVR rate when retreated with standard IFN and ribavirin combination therapy (ie, Rebetrone, Schering Canada) (9). Similarly, patients who relapsed after standard IFN and ribavirin combination therapy had a reasonable chance of achieving an SVR with pegIFN and ribavirin combination therapy (7,10). With regard to the retreatment of pegIFN relapsers with pegIFN and ribavirin combination therapy, there are few other comparable studies that match our experience. In one study (11), 64 patients who experienced a virological relapse after 24 weeks of treatment with pegIFN $\alpha$ -2a plus ribavirin were retreated with the same combination for 48 weeks. The SVR rate in that study was 55% (51% for genotype 1 patients and 63% for nongenotype 1 patients). In the

Evaluation of PegIntron in Control of Hepatitis C Cirrhosis (EPIC 3) study (12), which used pegIFN $\alpha$ -2b and ribavirin (Pegatron, Schering-Plough, USA), retreatment of previous pegIFN $\alpha$  relapsers produced SVR rates of 32% for previous pegIFN $\alpha$ -2b relapsers and 34% for previous pegIFN $\alpha$ -2a relapsers. Collectively, these studies suggest that patients who experience relapse shortly after completing treatment with pegIFN plus ribavirin have a reasonable chance of achieving an SVR when retreated with pegIFN $\alpha$  and ribavirin. Thus, physicians should consider retreatment in motivated patients who have previously relapsed, and these patients should not be denied reimbursement by third-party payers.

Unlike pegIFN relapsers, we found SVR rates in previous pegIFN nonresponders to be much less promising. Only 17% of these patients achieved an SVR with retreatment (15% with previous nonresponse to pegIFN and ribavirin). We caution that this result may be somewhat optimistic because the study relied on the veracity of the participating physician's report that the patient was a nonresponder. Given that some of these patients may not have been completely adherent to the previous course of therapy or may have had significant dose reductions by community physicians concerned about adverse events, the true outcome in 100% compliant patients with minimal dose reductions is likely to be worse. The outcome was particularly poor in those with advanced fibrosis (SVR rate of 10%).

In relapsers and nonresponders, genotype did not appear to influence the likelihood of an SVR. Although it may be argued that our findings are merely a reflection of small patient numbers, we believe that another possibility should be considered. It may be that after being exposed to the selection pressure of pegIFN-based therapy, this group responds more similarly than a diverse collection of treatment-naive patients with a similar genotype composition. This may be especially true of previous nonresponders. For example, a genotype 2 or 3 nonresponder may be similar to a genotype 1 nonresponder (ie, difficult to treat). If this hypothesis is correct, it suggests that genotype should not greatly influence the decision to retreat a nonresponder to previous pegIFN therapy.

There are only a few studies that have studied the efficacy of retreatment of patients who have not responded to a previous course of pegIFN-based therapy, and as of this writing, have only been presented in abstract form at conferences and have not yet appeared in the peer-reviewed literature. The results of the REtreatment with PEGasys in pATients not responding to prior peginterferon alfa-2b/ribavirin combination therapy (REPEAT) study, a large randomized multicentre study in nonresponders to pegIFN $\alpha$ -2b plus ribavirin, demonstrate that extending the duration of retreatment from 48 weeks to 72 weeks may be the most effective strategy to treat these patients. The SVR rate was higher in patients randomly assigned to an extended 72-week treatment regimen of pegIFN $\alpha$ -2a plus ribavirin than the standard 48-week regimen (16% versus 8%;  $P=0.0006$ ) (10). In our study, we observed an SVR rate of 15% after 48 weeks of retreatment in a similar subset of patients. The response rate in those with advanced fibrosis was poor (SVR rate of 10%). As previously alluded to, the primary differences between our study and the REPEAT study include the fact that our evaluation consisted of a database review of 'real world' patients and was not a prospective, randomized controlled trial (ie, there were fewer dose reductions and treatment withdrawals based on a study protocol and a less rigorous definition of previous nonresponse). The differing study outcomes

may also simply reflect the distribution effect seen with outcomes of similar studies around the 'true' outcome (ie, the normal distribution of outcomes around a true mean value). The previously mentioned EPIC 3 study reported an SVR rate of 7% after 48 weeks of retreatment with pegIFN $\alpha$ -2b plus ribavirin in nonresponders to a previous course of pegIFN plus ribavirin (13), which is more consistent with the 48-week outcome of the REPEAT study. Thus, SVR rates are considerably lower in previous nonresponders than in patients who have relapsed after treatment with pegIFN-based therapy. Interestingly, the REPEAT study revealed an SVR rate of 49% in those with HCV RNA negativity (less than 50 IU/mL) at week 12 of retreatment. These data suggest that it is possible to identify patients more likely to achieve an SVR early during the course of treatment (14). Regardless, the collective experience suggests that the likelihood of success with conventional 48-week duration pegIFN and ribavirin retreatment of previous pegIFN nonresponders is highly unlikely to be successful. New antiviral agents may possess greater promise for these patients.

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## CONCLUSION

The results of the present analysis demonstrate that patients experiencing virological relapse during a first course of treatment with pegIFN alone or in combination with ribavirin have a high probability of achieving an SVR when retreated with pegIFN $\alpha$ -2a plus ribavirin. SVR rates are disappointing in patients retreated after not responding to an initial course of pegIFN-based treatment. However, it may be possible to identify those with the best chance of an SVR after 12 weeks of retreatment. Physicians should consider retreatment for relapse patients who failed to achieve an SVR after a first course of antiviral treatment.

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**ACKNOWLEDGEMENTS:** Nadia Lesnikova, Jennifer Lee and Rob Balshaw of Syreon Corporation, Vancouver, British Columbia, assisted with the statistical analysis. Blair Jarvis provided editorial assistance. None of these individuals are employees of Hoffmann-La Roche. This research was funded by Hoffmann-La Roche Canada, Mississauga, Ontario.

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