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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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-naive 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 pegIFNα-2a and ribavirin.

METHODS: A post-hoc analysis of a multicentre open-label study was performed. Patients received pegIFNα-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 relapers, 86% achieved an EVR and 68% achieved an SVR. In nonresponders 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 relapers 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 META VIR score of F3 or F4 on liver biopsy achieved an SVR.

CONCLUSIONS: Retreatment 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
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 pegIFNα-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 pegIFNα-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 quantification 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 90×10^9/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 pegIFNα-2a 180 µg/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-log10 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 pegIFNα-2a.

**Statistical analysis**

The present study was a retrospective descriptive analysis.

**RESULTS**

A total of 87 patients were enrolled and retreated with pegIFNα-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 pegIFNα-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.

**Patients with previous nonresponse to pegIFN-based therapy:**

Of 59 patients who had not achieved an SVR, 34 (57.6%) patients achieved an SVR. The majority of the patients who had not achieved an SVR were infected with HCV genotype 1 virus (n=38 [64.4%]). Sixty-four per cent achieved an SVR. The remaining 25 patients were infected with genotypes 2 or 3. Five patients (20%) achieved an SVR.
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 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

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**Table 1**

**Baseline characteristics of patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Previous relapse (n=28)</th>
<th>Previous nonresponse (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>48 (23–61)</td>
<td>49 (37–63)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>17 (61)</td>
<td>44 (75)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>27 (96)</td>
<td>50 (85)</td>
</tr>
<tr>
<td>Median body mass index, kg/m² (range)</td>
<td>27 (20–40)</td>
<td>27 (19–37)</td>
</tr>
<tr>
<td>Liver biopsy performed, n (%)</td>
<td>27 (96)</td>
<td>52 (88)</td>
</tr>
</tbody>
</table>

**Table 2**

**Retreatment regimens**

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

*At the treating physician’s discretion*

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**Table 3**

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

<table>
<thead>
<tr>
<th>Previous treatment</th>
<th>SVR according to previous treatment response, n/n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pegIFNα-2a monotherapy (n=7)</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>pegIFNα-2b monotherapy (n=17)</td>
<td>6/10 (60)</td>
</tr>
<tr>
<td>pegIFNα-2a plus ribavirin (n=13)</td>
<td>8/9 (89)</td>
</tr>
<tr>
<td>pegIFNα-2b plus ribavirin (n=50)</td>
<td>2/4 (50)</td>
</tr>
</tbody>
</table>

*pegIFN Pegylated interferon*
 Pegylated interferon and ribavirin therapy

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pegIFN and ribavirin nonresponder patients had been treated with pegIFNα-2b and ribavirin (Pegtron, Schering-Plough, Canada) (n=46). Within this subgroup, 33 patients were assigned to 48 weeks of retreatment with pegIFNα-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 pegIFNα-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 pegIFNα-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 pegIFNα-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 relapers 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, Rebetron, 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 relapers 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 pegIFNα-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
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 pegIFNα-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.

**REFERENCES**

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