Comparative Study Concerning the Efficacy of Peg-IFN alpha-2a versus Peg-IFN alpha-2b on the Early Virological Response (EVR) in Patients with Chronic Viral C Hepatitis

Ioan Sporea¹, Mirela Danilâi¹, Roxana Șirli¹, Alina Pupescu¹, Ariana Laza¹, Luminița Bădițoiu¹

1) Department of Gastroenterology. 2) Department of Epidemiology, University of Medicine and Pharmacy Timișoara

Abstract

Background. Pegylated interferons (Peg-IFNs) represent, in association with Ribavirin, the first line of treatment in chronic C viral hepatitis. The aim of our paper was to compare the efficacy of Peg-IFN alpha 2a (Pegasys) and Peg-IFN alpha 2b (PegIntron) in a group of patients from the Department of Gastroenterology in Timișoara. Material and method. 116 patients with chronic C viral hepatitis were treated. The patients were randomized in chronological order (1:1), so that 58 patients were treated with Peg-IFN alpha 2a 180 μg/kg/week + Ribavirin (group 1) and 58 were treated with Peg-IFN alpha 2b 1.5 μg/kg/week + Ribavirin (group 2). Ribavirin was administered in the recommended doses, according to weight. The mean age was: group 1 – 49.3 years, group 2 – 50.9 years (p=0.37). Group 1 consisted of 37 women and 21 men and group 2 of 44 women 14 men (p=0.22). In group 1, 48 patients were naïve (N1), 7 were relapers after previous treatment (RL1) and 3 non-responders to previous treatment (NR1). In group 2, 33 patients were naïve (N2), 18 relapers (RL2) and 7 non-responders (NR2). After 12 weeks of treatment we evaluated the early virological response (EVR), defined as a drop in the viral load with 2 logs compared to the baseline viremia. Results. The following EVR rates were found: in group 1 – 82.2% (48/58); in group 2 – 67.2% (39/58) (p=0.08). There were also no significant statistical differences between the response rates in the subgroups: naïve patients [89.6% vs. 75.2%, p = 0.61], relapers [57.1% vs. 66.6%, p = 0.67] and non responders [33.3% vs. 28.6%, p = 1]. Conclusion. Our head to head comparative study showed that there are no statistically significant differences in the EVR between the patients treated with Peg-IFN alpha 2a and Peg-IFN alpha 2b.

Key words

Peg-IFN alpha 2a - Peg-IFN alpha 2b - early viral response - chronic viral C hepatitis - therapy

Rezumat

Premize. Prima linie în tratamentul hepatitei cronice HCV o constituie asocierea unui Interferon pegylat (Pegasys, sau PegInterferon alfa 2b  -PegIntron) cu Ribavirina. Se consideră cã ambele produse au eficienþã similarã. Scopul studiului nostru a fost compararea eficacitãþii celor douã produse administrate unui grup de pacienþi aflaþi în evidenþa Clinicii de Gastroenterologie din Timiºoara. Material și metodã. Au fost inclusi în studiu 116 pacienþi cu hepatitã cronicã HCV. Pacienþii fost randomizaþi 1:1, astfel încât 58 de pacienþi au fost trataþi cu Peginterferon alfa 2a 180 μg/kg/sãpt + Ribavirina (grupul 1) ºi 58 cu Peginterferon alfa 2b 1,5 μg/kg/sãpt. + Ribavirina (grupul 2). Ribavirina a fost administratã în dozele recomandate în funcþie de greutate. Vârsta medie a fost 49,3 ani în subgrupul 1ºi 50,9 ani în subgrupul 2 (p=0,37 NS). Grupul 1 a fost constituit din 37 femei ºi 21 de bãrbaþi, iar grupul 2 din 44 femei ºi 14 bãrbaþi (p=0,22 NS). In grupul 1, 48 de pacienþi erau naivi (subgrup N1), 7 erau relapseri la terapie anterioarã (subgrup RL1) ºi 3 erau non-responderi la terapie anterioarã (subgroup NR1). In grupul 2, 33 de pacienþi erau naivi (subgrup N2), 18 erau relapseri (subgrup RL2) ºi 7 erau non-responderi (subgrup NR2). Dupã 12 săptãmâni de tratament am evaluat la toþi pacienþii rãspunsul virusologic precoce (EVR), definit ca o scãdere a viremiei cu 2 logi (de cel puþin 100 de ori) faþã de viremia iniþialã. Rezultate. Ratele EVR au fost: în grupul 1 82,2% (48/58); în grupul 2 67,2% (39/58). Nu am gãsit diferenþe semnificative statistice între cele douã grupuri în ceea ce priveºte EVR (p=0,08 NS). Diferenþele dintre cele douã produse rãmân nemesnificative din punct de vedere statistic ºi în ceea ce priveºte subgrupurile de pacienþi naivi [89,6% vs. 75,2%, p = 0,61], relapseri [57,1% vs. 66,6%, p = 0,67] ºi non-responderi [33,3% vs. 28,6%, p = 1]. Concluzie. Studiul nostru comparativ cap-la-cap a
demonstrated that no existing significant statistic in cee ce privește răspunsul virusologic precoce la pacienții tratați cu Peginterferon alfa 2a compared with those treated with Peginterferon alfa 2b.

Introduction

For more than 10 years, interferon (IFN) has been the standard treatment for chronic C viral hepatitis. Subsequent changes of therapy aimed to increase the response rate. Both the association of Ribavirin to treatment with standard IFN, as well as pegylation of IFN increased the response rate with 10-20%.

Two pegylated IFNs are currently in use: Peg-IFN alpha 2a (40KD) and Peg-IFN alpha 2b (12KD) (1). Peg-IFN alpha 2a (40KD) is a covalent conjugate of recombinant alpha 2a interferon with a single branched molecule of polyethylene glycol (PEG). After s.c. injection the absorption is prolonged, so that the maximum serum concentration occurs 72-96 hours post-dose (2). Because of the size of the PEG molecule, the distribution volume available for this type of Peg-IFN is limited, so that the dose of Peg-IFN alpha-2a (Pegasys) is the same, no matter the weight of the patient (180 μg /week).

Peg-IFN alpha-2b (12KD) has a distribution volume four times larger than Peg-IFN alpha–2a (40 l vs. 10 l), a mean half-life two times shorter (40 vs. 80 hours) and a maximum serum concentration at 15-44 hours (3). Therefore, Peg-IFN alpha-2b (Pegintron) is administered according to the weight of the patient. The recommended dose is 1.5 μg/kg/week (4-6).

For both types of Peg-IFN the standard therapy regimen includes Ribavirin. The recommended dose of Ribavirin is 800-1200 mg/day (according to the patient’s weight). The reduction of Ribavirin dose, especially in the first 12-24 weeks of treatment, diminishes the rate of sustained virological response (SVR) (5, 7, 8). The predictors of the viral response are: genotype 2 and 3, absence of advanced fibrosis, low viral load, female gender, lower weight (old predictors of response), lack of steatosis, compliance, early response, Ribavirin dose, ethnicity (9).

Because there are two types of Peg-IFN on the market, it was considered important to perform comparative studies on their efficacy in association with Ribavirin. The study IDEAL (Individualized Dosing Efficacy vs. flat dosing to Assess optimal pegylated interferon therapy) performed in the United States (accepted by the FDA) is a head-to-head comparative trial with three arms, comparing the efficacy of two dosages of Peg-IFN alpha-2b plus Ribavirin and Peg-IFN alpha-2a plus Ribavirin (3). The first end-point of this study is to compare the efficacy of Peg-IFN alpha-2b 1 μg/kg/week plus Ribavirin to that of Peg-IFN alpha-2a 1.5 μg/kg/week plus Ribavirin. The second end-point is to compare the efficacy of Peg-IFN alpha-2b 1.5 μg/kg/week plus Ribavirin to that of Peg-IFN alpha-2a 180 μg/week plus Ribavirin. The investigators are going to enroll in this multicentric American study 2,880 naïve patients with genotype 1 chronic viral C hepatitis.

Because of the high costs of combined therapy with Peg-IFNs and Ribavirin, of their frequent side-effects and of the rather unsatisfactory results (SVR for genotype 1 is 42-52%) (10), new early predictors of the response were searched for. Analyses of data from two pivotal trials showed that the early virological response (EVR) at 12 weeks was a strong predictor of a subsequent SVR (0% and 3% negative predictive value) (10-12).

The aim of this study was to compare in a randomized trial the EVR to Peg-IFN alpha-2a plus Ribavirin vs. Peg-IFN alpha-2b plus Ribavirin in patients with chronic C viral hepatitis.

Material and method

We performed a prospective, head-to-head, randomized 1:1 trial, between October 2003 and June 2005. The inclusion criteria were the presence of chronic C viral hepatitis (proven by liver biopsy performed maximum 6 months before the treatment) and the quantification of the viral load (by PCR) before treatment and after 12 weeks of treatment. The patients were randomized in chronological order to be treated with either one of the two products.

The EVR was defined as a drop in the viral load of ≈2 log 10 after 12 weeks of treatment.

According to the Romanian legislation and to the Guidelines of the National Health Insurance Company, only patients with chronic viral C hepatitis having a necroinflammatory score of = 6 may do receive therapy with Peg-IFN, no matter the fibrosis score, or patients with a fibrosis score 3 no matter the necroinflammatory activity.

We compared the two groups of patients (treated with Peg-IFN alpha 2a and Peg-IFN alpha 2b, respectively) regarding age, gender and severity of the morphopathological lesions. These were assessed by means of Knodell score (maximum necroinflammatory score of 18 and fibrosis score ranging from 0 to 4).

In both groups, if EVR was not obtained after 12 weeks, treatment was discontinued. The patients who presented a decrease in the viral load of more than 2 log after 12 weeks of treatment, but were not aviremic, were treated for another 12 weeks. Only the patients aviremic after 24 weeks of treatment (<50 UI/ml or 23 UI/ml) continued the treatment up to 48 weeks.

Since we included in our study both naïve patients and patients who previously received antiviral therapy (non-responders and relapsers), we also compared the EVR in the subgroups of naïve, non-responder and relapser patients treated either with Peg-IFN alpha 2a or with Peg-IFN alpha 2b.

For statistical analysis we used the SPSS (EPI INFO 2002) program. The percentages were compared using the chi² test and the Fisher exact test. The variable distribution was assessed by the Kolmogorov-Smirnov test. To compare the means we used the unpaired t test. In order to compare the fibrosis and Knodell scores we used nonparametric tests
Results

The two groups of patients matched with regard to age, gender, initial viral load and necroinflammatory score (Table I). We found statistically significant differences between the two groups only regarding the fibrosis score.

In the group treated with Peg-IFN alpha 2a, 48 out of 58 patients were naïve (subgroup N1), 7 were relapers (subgroup RL1) and 3 were non-responders (subgroup NR1). In the group treated with Peg-IFN alpha 2b, 33 out of 58 patients were naïve (subgroup N2), 18 were relapers (subgroup RL2) and 7 were non-responders (subgroup NR2).

The subgroups of naïve patients, relapers and non-responders matched with regard to mean age, gender, initial viral load, necroinflammatory score and fibrosis score (Table I).

We did not find significant statistical differences in the EVR between the subgroups of naïve patients treated either with Pegasys or PegIntron, nor in the non-responders patients or relapers (Table II). As expected, the best results were obtained in naïve patients (89.6 vs. 75.2%), followed by relapers (57.1 vs. 66.6%) and the worst results in non-responders (33.3 vs. 28.6%).

In the responders, there were no statistically significant differences between the two groups regarding age, level of aminotransferases, total Knodell score and fibrosis score (Table III). No significant differences between the two groups were found in the non-responders (Table IV).

EVR did not correlate with either age, gender or fibrosis score in the two groups of patients (Table V).

The power calculated for our study was 39.3%, probably due to the small number of patients.

Discussion

This study performed in 116 patients aimed to assess if there was a statistically significant difference between the response rate to the treatment with Peg-IFN alpha 2a plus Ribavirin versus Peg-IFN alpha 2b plus Ribavirin in patients with chronic C hepatitis. We tried to compare in a 1:1 randomized, head-to-head study the efficacy of the two drugs, based on the EVR. This is only the first step of the study, which will be extended by comparing the sustained virological response (SVR) The standard combined therapy in chronic viral C hepatitis with Peg-IFN and Ribavirin has been introduced in Romania since October 2003. At least one year is needed in order to have a large enough group of patients who finished the treatment for at least 6 months in order to compare the SVR after combined therapy with...
Table II The EVR in the two groups of patients

| Patients          | No. patients | Responders | Non-responders | P         
|-------------------|--------------|------------|----------------|-----------
| Total             |              |            |                | 0.08 (chi² 2.9) |
| 1- Peg-IFN alpha 2a | 58 (100%)    | 48 (82.75%)| 10 (17.25%)    | OR = 2.33 (0.97<OR<5.60) |
| 2- Peg-IFN alpha 2b | 58 (100%)    | 39 (67.24%)| 19 (32.76%)    | RR = 1.23 (0.99<RR<1.52) |
| Nadve             |              |            |                | 0.61 (0.81<OR<9.33) |
| N1- Peg-IFN alpha 2a | 48 (100%)    | 43 (89.6%) | 5 (10.4%)      | OR = 2.33 (0.97<OR<5.60) |
| N2- Peg-IFN alpha 2b | 33 (100%)    | 25 (75.2%) | 8 (24.8%)      | RR = 1.23 (0.99<RR<1.52) |
| Relapers          |              |            |                | 0.67 |
| RL1- Peg-IFN alpha 2a | 7 (100%)     | 4 (57.14%) | 3 (42.8%)      | OR = 0.66 (0.11<OR<3.99) |
| RL2- Peg-IFN alpha 2b | 18 (100%)    | 12 (66.6%) | 8 (33.3%)      | RR = 0.85 (0.41<RR<1.76) |
| Non-responders    |              |            |                | 1 |
| NR1- Peg-IFN alpha 2a | 3 (100%)     | 1 (33.3%)  | 2 (66.6%)      | OR = 1.25 (0.06<OR<22.89) |
| NR2- Peg-IFN alpha 2b | 7 (100%)     | 2 (28.6%)  | 5 (71.4%)      | RR = 1.16 (0.16<RR<1.25) |

Regarding the pharmacokinetics of IFN, after injecting Peg-IFN alpha 2b, the serum concentration slowly decreases, being almost 0 after 168 hours (7 days). When Peg-IFN alpha 2a is administered, the serum concentration after 168 hours is about 20 mg/ml (13). Peg-IFN alpha 2b has a half-time of about 40 hours (14), and its serum concentration decreases under the detection limit before the end of the period between injections (7 days) (4). Some studies on the viral kinetics showed a closed relation between the plasma level of Peg-IFN and the rebound level of HCV RNA (14, 15). It was even suggested to administer Peg-IFN alpha 2b twice a week in order to improve the viral dynamics (15, 16).

The viral kinetics under therapy is a good therapeutic guide. The 2 log decrease of the viral load after 12 weeks of therapy is already used as a criteria for continuing the therapy in all available guidelines of therapy in chronic C viral hepatitis. Other strategies using the viral dynamics are evaluated. Berg et al proposed that the patients in whom after 12 weeks of combined therapy the viral load decreased by more than 2 log, but are not aviremic, the therapy should be continued up to 72 weeks instead of 48 weeks, thus obtaining a higher rate of SVR (18). Another strategy would be to determine the viral load after 4 weeks of therapy so that the patients who do not have a rapid virological response by week 4 should have a treatment longer than 48 weeks (19).

Apart from the Peg-IFN molecule size and pharmacokinetcs, an important factor that influences the response

Table III Variables analyzed in responders from both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup 1 Peg-IFN alpha 2a</th>
<th>Subgroup 2 Peg-IFN alpha 2b</th>
<th>p</th>
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<tbody>
<tr>
<td>Age</td>
<td>Mean 48.9</td>
<td>Mean 51.4</td>
<td>0.52</td>
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<tr>
<td>Initial GOT</td>
<td>SD 10.2</td>
<td>SD 15.1</td>
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<tr>
<td>GOT after 12 weeks</td>
<td>Mean 32.4</td>
<td>Mean 33.4</td>
<td>0.18</td>
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<tr>
<td>Total Knodell score</td>
<td>Mean 10.0</td>
<td>Mean 12.0</td>
<td>0.65</td>
</tr>
<tr>
<td>Fibrosis score</td>
<td>Mean 1.1</td>
<td>Mean 1.5</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Table IV Variables analyzed in non-responders from both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup 1 Peg-IFN alpha 2a</th>
<th>Subgroup 2 Peg-IFN alpha 2b</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean 51.4</td>
<td>Mean 45.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Initial GOT</td>
<td>SD 10.3</td>
<td>SD 8.0</td>
<td></td>
</tr>
<tr>
<td>GOT after 12 weeks</td>
<td>Mean 61.6</td>
<td>Mean 45.5</td>
<td>0.56</td>
</tr>
<tr>
<td>Total Knodell score</td>
<td>Mean 10.0</td>
<td>Mean 11.5</td>
<td>0.10</td>
</tr>
<tr>
<td>Fibrosis score</td>
<td>Mean 1.2</td>
<td>Mean 1.8</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Table V Correlations between the response rate and various variables in the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFN alpha 2a</td>
<td>Age</td>
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</tr>
<tr>
<td></td>
<td>Gender</td>
<td>0.60</td>
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<tr>
<td></td>
<td>Fibrosis score</td>
<td>0.38</td>
</tr>
<tr>
<td>Peg-IFN alpha 2b</td>
<td>Age</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>Fibrosis score</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Ribavirin and one of the two types of Peg-IFN. Until the results of such a study will be available, these preliminary results may be important.
Early virological response after Peg-IFN in chronic viral C hepatitis

rate is maintaining a minimum dose of Ribavirin of more than 10.8 mg/kg/day, especially in the first three months of therapy (20).

Data from recent multicentric randomized controlled trials (RCTs) on Peg-IFN alpha 2a and Peg-IFN alpha 2b have unequivocally demonstrated that, when administered in combination with Ribavirin, these agents achieved SVR rates significantly higher than those previously obtained by treatment with standard interferon alpha 2a or alpha 2b with or without Ribavirin (5,21,22). Also, a RCT of Peg-IFN alpha 2b plus Ribavirin in patients with chronic hepatitis C previously treated demonstrated that a SVR was only obtained in those who were partial responders to previous IFN monotherapy or combination therapy (23). In contrast, a RCT of Peg-IFN alpha 2a and Ribavirin in chronic hepatitis C patients showed that a SVR can be achieved in those who failed prior antiviral therapy (24).

In our study, we evaluated EVR in both naïve patients and patients that already received antiviral therapy (standard interferon alone or standard interferon plus Ribavirin) and patients that already received antiviral therapy (standard interferon alpha 2a or alpha 2b with or without Ribavirin (5,21,22)). Also, a RCT of Peg-IFN alpha 2b plus Ribavirin in patients with chronic hepatitis C previously treated demonstrated that a SVR was only obtained in those who were partial responders to previous IFN monotherapy or combination therapy (23). In contrast, a RCT of Peg-IFN alpha 2a and Ribavirin in chronic hepatitis C patients showed that a SVR can be achieved in those who failed prior antiviral therapy (24).

In our study, we evaluated EVR in both naïve patients and patients that already received antiviral therapy (standard interferon alone or standard interferon plus Ribavirin) and had been non-responders or relapers. A limit of our study could be the relatively small number of patients included.

Conclusion

Our head-to-head randomized study showed that there were no statistically significant differences in the EVR between patients with chronic hepatitis C treated with Peg-IFN alpha 2a or Peg-IFN alpha 2b plus Ribavirin. The differences remained statistically non-significant in the subgroups of naïve patients, in relapers and in non responders.

Conflicts of Interest

This study was not financed by any of the pharmaceutical companies producing the Peg-IFNs.

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