

The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients

Kronik hepatit C hastalarında pegile interferon alfa 2a ya da 2b artı ribavirinin etkinliği

Necati YENİCE, Özgür MEHTAP, Mübeccel GÜMRAH, Nurten ARICAN

Department of Internal Medicine 3rd Section, Okmeydanı Training Hospital, Istanbul, Turkey

Background/aims: We aimed to compare viral responses to pegylated interferon 2a plus ribavirin with pegylated interferon alpha 2b plus ribavirin. **Methods:** Patients with the following characteristics were included: anti HCV(+); normal and/or elevated serum transaminase levels; positive HCV RNA by quantitative PCR; and at least stage 1 fibrosis according to Knodell Scoring System on liver biopsy. Patients were assigned into two groups. Group 1 consisted of 37 patients (24 female, 13 male) who received pegylated interferon alpha 2a 180µg s.c. weekly plus ribavirin adjusted for patient's weight. All patients were genotype 1. Group 2 consisted of 37 patients (27 female, 10 male) who received pegylated interferon alpha 2b 1.5µg/kg s.c. weekly plus ribavirin adjusted for patient's weight. At week 24, the treatment was discontinued in patients positive for HCV RNA by PCR, while patients negative for HCV RNA continued treatment up to 48 weeks. The end of treatment and sustained virologic responses of the patients were ascertained by assessing HCV RNA levels at the end of the treatment and after 24 weeks follow-up after the cessation of treatment. **Results:** At week 48, the proportion of patients with negative HCV RNA (end of treatment viral response) was 28/37 (75.7%) in Group 1 and 27/37 (73%) in Group 2. The group sustained virologic response rates were 48.6% and 35.1% for Group 1 and Group 2, respectively. No significant differences were noted between the two groups. **Conclusion:** The two pegylated interferon molecules were similar in terms of sustained virologic response rate.

Key words: Pegylated interferon alpha 2a, pegylated interferon alpha 2b, ribavirin, chronic hepatitis C

INTRODUCTION

Hepatitis due to hepatitis C virus (HCV) is an important public health problem worldwide (1). HCV causes hepatitis, cirrhosis and hepatocellular carcinoma (HCC), and globally reported anti HCV prevalence ranges between 1% and 3% (2). It has been previously reported as 1.3% for Turkey (3). In chronic HCV infection, a sustained response to

Amaç: Bu çalışmada pegile interferon alfa 2a artı ribavirine ve pegile interferon alfa 2b artı ribavirine verilen viral yanıtlar karşılaştırılmıştır. **Yöntem:** Aşağıdaki özelliklere sahip hastalar çalışmaya alınmıştır: anti HCV(+); normal ve/veya yükselmiş serum transaminaz düzeyleri; kantitatif PCR ile pozitif HCV RNA; karaciğer biyopsisinde Knodell skorlama sistemine göre en az evre 1 fibrozis. Hastalar iki ayrı gruba ayrılmışlardır. Grup 1'deki 37 hasta (24 kadın, 13 erkek) haftada bir 180µg subkutan pegile interferon alfa 2a ile birlikte dozu hastanın kilosuna göre ayarlanmış ribavirin almışlardır. Hastaların tümü genotip 1'dir. Grup 2'deki 37 hasta (27 kadın, 10 erkek) haftada bir 1.5µg/kg subkutan pegile interferon alfa 2b ile birlikte gene dozu hastanın kilosuna göre ayarlanmış ribavirin almışlardır. Yirmi dördüncü haftada, PCR ile HCV RNA'sı pozitif olan hastalarda tedavi kesilmiş, negatif olan hastalarda ise 48. haftaya kadar tedaviye devam edilmiştir. Hastaların tedavi sonu ve tedavi kesildikten sonraki yirmi dört haftalık izlem sonu HCV RNA düzeyleri ölçülerek tedavi sonu ve kalıcı viral yanıtları tespit edilmiştir. **Bulgular:** Kırk sekizinci haftada HCV RNA'sı negatif olan hastaların oranı (tedavi sonu viral yanıt) Grup 1 ve Grup 2'deki hastalar için sırasıyla %75.7 (28/37) ve %73.0 (27/37) olarak bulunmuştur, grupların kalıcı viral yanıt oranları sırasıyla 1. grup için %48.6 (18/37); 2. grup için %35.1 (13/37) tespit edilmiştir. İki grup arasında anlamlı bir farklılık saptanmamıştır. **Sonuç:** İki pegile interferon molekülü kalıcı viral yanıtları açısından benzerdir.

Anahtar kelimeler: Pegile interferon alfa 2a, pegile interferon alfa 2b, ribavirin, kronik hepatit C

treatment can be achieved with interferon alpha in 10% to 20% of patients, in spite of high relapse rates (4). The addition of ribavirin to this treatment results in a more than two-fold increase in sustained response rates (5-6).

Currently, the aim of treatment in hepatitis C infection is the eradication of HCV, which helps to

delay the progression to terminal liver disease and to prevent the development of HCC (7).

Genotype 2-3, low viral burden, low body weight, female gender, young age, and the absence of bridging fibrosis or cirrhosis in biopsy are associated with a sustained viral response in the treatment of chronic HCV infection (8-9). The covalent binding between polyethylene glycol molecule and interferon alpha represents the most important recent development in the treatment of chronic HCV infection. The activity of pegylated interferon alpha is enhanced, and the terminal half-life is prolonged compared to the original interferon alpha molecule (10). The advantages of the new interferon molecule were also reflected in improved compliance and response rates. Currently, two different types of pegylated interferon are used clinically: pegylated interferon alpha 2a (40 KD) and pegylated interferon alpha 2b (12 KD). The superiority of the combination of the pegylated interferons and ribavirin over standard combinations has been consistently demonstrated in several studies (11-12).

In this study, we evaluated sustained virologic response (SVR) rates with pegylated interferon alpha 2a plus ribavirin versus pegylated interferon alpha 2b plus ribavirin in genotype 1 patients.

MATERIALS AND METHODS

Patient Selection

Patients admitting to the Hepatology Division, 3rd Department of Internal Medicine, Okmeydani Research and Training Hospital (Istanbul, Turkey) who were naive to interferon monotherapy and/or ribavirin combination were included in the study if they met the following criteria: anti HCV (+); normal and/or elevated serum transaminase levels; positive HCV RNA by quantitative polymerase chain reaction (PCR); and at least stage 1 fibrosis according to Knodell Scoring System on liver biopsy. A total of 80 patients were included. Also a criterion for inclusion, patients had to have the following minimal biochemical and hematological values: hemoglobin 12 g/dl for women and 13 g/dl for men; leukocyte $3 \times 10^3/\text{mm}^3$; neutrophils $1.5 \times 10^3/\text{mm}^3$; and platelets $100 \times 10^3/\text{mm}^3$; and bilirubin, albumin, and creatinine levels had to be within normal range. No patient had positive test results for hepatitis B virus (HBV), hepatitis D virus (HDV) or human immunodeficiency virus (HIV) antibodies or antigens. Patients with abdo-

minimal ascites; history of bleeding from esophageal varicosities; HCC or other malignant disorders; use of antidepressants or tranquilizing agents for more than three months; a history of depression, psychosis or suicide attempt; and significant cardiac or pulmonary problems were excluded.

Methods

Consecutive patients who met the selection criteria were randomly assigned into two treatment groups. Treatments were not simultaneously started and data were collected after the last patient's treatment was completed. Two treatment groups of 40 patients each were formed. In Group 1 the mean age was 48.2 years in male and 50.9 years in female patients. Patients received pegylated interferon alpha 2a 180 μg s.c. weekly plus ribavirin adjusted for patient's weight (40-64 kg: 800 mg; 65-85 kg: 1000 mg; > 85 kg: 1200 mg, p.o. in two divided doses). All patients were genotype 1 (1=28, 1a=7, 1c=2). Study protocol was approved by the ethics committee of the institution. All patients gave informed consent prior to study entry.

In Group 2 the mean age was 50.8 years in male and 50.85 years in female patients. Patients received pegylated interferon alpha 2b 1.5 $\mu\text{g}/\text{kg}$ s.c. weekly (40-64 kg: 80 mcg, 65-75 kg: 100 mcg, 76-85 kg: 120 mcg, >85 kg: 150 mcg) plus ribavirin adjusted for patient's weight (40-64 kg: 800 mg, 65-85 kg: 1000 mg, >85 kg: 1200 mg; p.o. in two equally divided doses). The numbers of patients with normal transaminase levels were 11 and 9 in Groups 1 and 2, respectively (Table 1).

In line with the recommendations of the National Institutes of Health (NIH) Report issued in 2002, treatment was discontinued in patients whose HCV RNA was positive by PCR at week 24 (13), while patients with a negative HCV RNA continued the treatment for an additional 24-week period. At the completion of 48 weeks, the virological response at the end of treatment was assessed by HCV RNA and after 24 weeks' follow-up a second HCV RNA level was measured for assessing SVR. Most patients refused a follow-up biopsy at the end of treatment; therefore, histological improvement was not assessed in this study due to the low number of follow-up biopsies.

As stated previously, some patients discontinued the treatment due to adverse events associated with pegylated interferon and/or ribavirin. The assessments were limited to patients who received the full dose of pegylated interferon for 48 weeks.

Table 1. Baseline characteristics of patients

Patient characteristics	Pegylated interferon alpha 2a (n=37)	Pegylated interferon alpha 2b (n=37)
Mean age M/F	48.2/50.9	50.8/50.85
Age (y)		
≤40	7	6
>40	30	31
Gender (n) M/F	13/24	10/27
Normal ALT (n)	11	9
Genotype1(n)		
1a	7	2
1b	28	35
1c	2	-

Follow-up visits were performed biweekly in the first two months and monthly thereafter. In each visit, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin, hematocrit, leukocyte, and neutrophil counts were assessed. Interferon treatment was stopped if the neutrophil count fell below 500/ml. Ribavirin dose was reduced to 600 mg in patients with a hemoglobin level below 10 g/dl who had no cardiac problems. The same dose was maintained until the end of treatment. Ribavirin treatment was discontinued when hemoglobin fell below 8.5 mg/dl.

Statistical Analyses

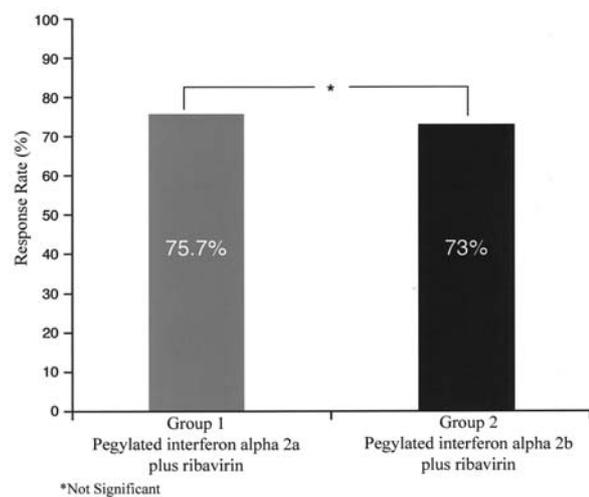
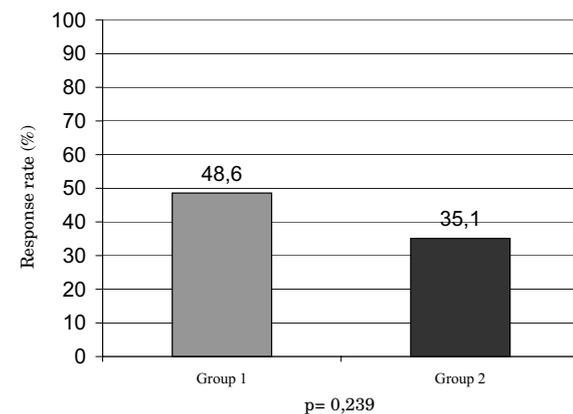
Pearson chi-square method was used for the statistical analyses. A p value below 0.05 was considered significant.

RESULTS

In Group 1, three patients discontinued treatment due to adverse effects (pancytopenia in 2 patients and deep anemia in 1 patient). Therefore, 37 patients (24 female, 13 male) continued the treatment.

In Group 2, three patients discontinued the treatment (1 patient lost to follow-up and pancytopenia in 3 patients). Thus, 37 patients with genotype 1 HCV (1b=35, 1a=2) (27 female, 10 male) continued treatment.

All patients completed 48 weeks of treatment. At the end of week 48, the proportion of patients with negative HCV RNA (end of treatment viral response) was 28/37 (75.7%) in Group 1 and 27/37 (73%) in Group 2. No significant differences were noted between the two groups ($p=0.79$) (Figure 1). None of the patients whose HCV RNA had become negative at week 24 returned to a positive HCV RNA status at week 48. SVR rates were ascertained as 48.6% (n:18) and 35.1% (n:13) in Groups 1 and 2, respectively ($p=0.239$) (Figure 2). In both

**Figure 1.** End of treatment viral responses for two groups at 48 weeks**Figure 2.** Sustained virologic responses

groups, all patients with positive HCV RNA at week 24 were ≥ 40 years of age. There were two patients in each group under age 40, with no SVR. With regard to gender distribution in patients,

there was only one male patient in both groups with no end of treatment response (1 male, 8 female; and 1 male, 9 female; in Groups 1 and 2, respectively). Ribavirin dose was reduced to 600 mg due to anemia in three and two patients in Groups 1 and 2, respectively. Those patients whose ribavirin dose was reduced were non-responders at the end of the treatment.

DISCUSSION

In patients with chronic hepatitis C, pegylated alpha interferon treatment alone for 48 weeks results in a more than two-fold increase in the SVR rates compared to standard interferon. However, there is a high recurrence rate after the discontinuation of monotherapy (14-15).

The response rate for HCV genotype 1 is lower compared to genotypes 2 and 3 (16). Several studies have shown that improved compliance to treatment results in increased sustained response rates in patients with chronic hepatitis C. This is particularly relevant to patients with HCV genotype 1 infection (17). In the present study, all patients were carriers of HCV genotype 1. Therefore, patients were informed about the importance of compliance, and complete attendance at all visits was provided. As mentioned before, ribavirin dose was reduced in five patients without a change in the pegylated interferon dose. Of the patients with chronic HCV infection, 30% had normal aminotransferase levels persistently (18). Some of these patients had mild to severe histological changes in liver biopsy (19-20). According to recommendations issued by the NIH Consensus Panel in 2002, treatment may be administered for such patients (21). Patients with at least stage 1 fibrosis in biopsy but normal aminotransferase levels were also included in this study. In line with the NIH 2002 report, the treatment was discontinued in patients with a positive HCV RNA at week 24, while 48 weeks of treatment was completed in patients with a negative HCV RNA at week 24. In the latter group, none had returned to positive HCV RNA status at week 48.

In a previous and well-known study, patients were assigned into two dose groups for pegylated interferon alpha 2b (lower and higher dose groups). Optimum ribavirin dose (800 mg) was given to patients in the higher dose group, while patients in the lower dose group received 1000-1200 mg of ribavirin. In that study, viral response rates at the end of treatment were 65% and 56%, respectively

(11). However, in our study, a higher response rate (73%) in patients treated with pegylated interferon alpha 2b was observed compared to Manns' study (11). A possible explanation for the higher end of treatment response rate in the present study is the use of high-dose pegylated interferon alpha 2b in association with ribavirin dose adjusted for body weight. On the other hand, the SVR is different in our study when compared to Manns' study (35% vs 42%). In one of the studies evaluating the combination of pegylated interferon alpha 2a plus ribavirin (1000-1200 mg), the response rate reported at the end of treatment was 69% (22), compared to 75.7% in our study. In the second study, where genotype 1 patients were divided into lower and higher baseline viral burden subgroups, high-dose ribavirin in combination with 180µg of pegylated interferon alpha 2a was administered for 48 weeks (12). At the end of treatment, viral response rates in the overall population and in the low and high burden subgroups were 69%, 78%, and 65%, respectively, and these figures are quite similar to our observed response rate of 75.7%. In the same study, the SVR rates were assessed as 52%, while we determined 48.6% in our study (12).

Age has a negative predictive value for the SVR to treatment in patients with chronic hepatitis C (23-25), and in line with previous findings, patients with no response in our study at week 48 were over 40 years of age; at the end of follow-up, four patients whose HCV RNA was positive were aged under 40. Gender is also associated with the treatment response, but interestingly, in our study female patients were less likely to respond at the end of the treatment, as reflected by the proportion of patients with no response: 33.3% (8/24) of female patients and 7.69% (1/13) of male patients in Group 1; and 33.3% (9/27) of female patients and 10% (1/10) of male patients in Group 2. When we evaluated the non-responses according to gender after follow-up, we observed HCV RNA positivity in five male and 14 female patients in Group 1, and in six male and 18 female patients in Group 2. These results might have been influenced by baseline viral burden, liver histology and individual immune responses (levels of HCV core IgA and IgM; hepatic expression of HLA-A, B and C; CD8+ response; IL-2 receptor levels; Thy-1 cytokine response; expression of TNF alpha; IL-6 levels, etc.). Although ALT concentration is not considered to have predictive value, all except two patients (1 in

each group) had ALT levels above the upper limit of normal range.

To date, no head-to-head comparisons between the two pegylated interferon molecules have been made. In their statistical analysis, Rosenberg *et al.* attempted to evaluate the difference in efficacy between the two pegylated interferons and found no difference (26). In this study, ribavirin doses

were adjusted for body weight and pegylated interferon alpha 2a and pegylated interferon alpha 2b treatments were compared with respect to sustained virologic response. Despite no statistically significant differences being found between the two molecules, we observed 48.6% SVR for peginterferon alpha 2a plus ribavirin, and 35.1% SVR for peginterferon alpha 2b plus ribavirin.

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