CURRENT THERAPEUTIC RESEARCH

VOLUME 66, NUMBER 5, SEPTEMBER/OCTOBER 2005

Therapy for Treatment-Refractory Chronic Hepatitis C Virus Genotype 1b Infection: A Retrospective Analysis

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ABSTRACT

Background: The most effective current therapy for hepatitis C virus (HCV) infection is the combination of pegylated interferon (peg-IFN) plus ribavirin (RBV).

Objective: The aim of this retrospective analysis was to determine the rate of response to this therapy, and the factors affecting outcome, in patients with treatment-refractory chronic HCV genotype 1b.

Methods: The records of patients with chronic HCV infection and HCV genotype 1b who failed (nonresponse or relapse) previous treatment with standard interferon (IFN) + RBV were retrospectively analyzed for demographic data, virologic load, liver histology, biochemistry, treatment-related adverse effects (AEs), and the effects of dose reduction during treatment with peg-IFN + RBV for 48 weeks. *Early virologic response* (EVR) was defined as ≥2-log (copies/mL) decrease from baseline in serum HCV RNA concentration or the absence of detectable serum HCV RNA at treatment week 12. *End-of-treatment response* (ETR) was defined as the absence of detectable serum HCV RNA at treatment week 48. *Sustained virologic response* (SVR) was defined as the absence of detectable serum HCV RNA 24 weeks after treatment was discontinued. Factors affecting treatment outcome were determined using correlation analyses.

Results: Data from the files of 17 patients (12 men, 5 women; mean [SD] age, 48 [2] years) were analyzed. EVR was achieved in 7 patients; however, viral breakthrough occurred in 2 of these patients during the treatment period, and 5 of these patients discontinued treatment because of severe treatment-related AEs (depression [1 patient] and neutropenia [4]). Seven patients achieved ETR, but HCV infection relapsed during the follow-up period. Three (18%) patients achieved SVR. Data concerning previous patterns of response to IFN + RBV therapy were available in 10 patients. Of these, 3 of 6 patients who had experienced relapse with the previous treatment achieved SVR with peg-IFN + RBV; neither of the 2 patients with nonresponse to the previous treatment achieved SVR. Major determinants of failure to reach SVR in these patients included previous

Accepted for publication July 13, 2005.
doi:10.1016/j.curtheres.2005.10.002
0011-393X/05/$19.00
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nonresponder pattern, noncompliance with the therapy, and advanced-stage liver fibrosis. Tolerability was similar to that with the previous treatment.

Conclusions: In this study in patients with chronic HCV genotype 1b infection and a history of relapse or nonresponse to standard IFN + RBV treatment, treatment with peg-IFN + RBV achieved an SVR rate of 18%. Further research is needed to determine the role of peg-IFN + RBV in the re-treatment of HCV infection. (*Curr Ther Res Clin Exp.* 2005;66:451–462) Copyright © 2005 Excerpta Medica, Inc.

Key words: hepatitis C, treatment, nonresponders, ribavirin combination, pegylated interferon, treatment failure, retrospective.

INTRODUCTION

The current optimal therapy for patients with chronic hepatitis C virus (HCV) infection is the combination of pegylated interferon (peg-IFN) plus ribavirin (RBV). Two large, randomized, controlled trials have shown that sustained virologic response (SVR) rates achieved with this treatment were significantly higher compared with those achieved with standard interferon (IFN) + RBV.[1,2] These improved response rates with peg-IFN led to the question of whether patients with nonresponse to standard IFN + RBV should be treated with the newer combination.

Based on a literature search using MEDLINE (key terms: *hepatitis C, retreatment,* and *pegylated interferon*; years: 2000–2005), few published studies assessing the role of peg-IFN + RBV are available. However, it is generally anticipated that this regimen will be shown to be more efficacious compared with other existing IFN-based regimens because peg-IFN–based therapies are associated with higher SVR rates compared with standard IFN–based therapies in treatment-naive patients. Preliminary data[3] available from an ongoing study of 212 nonresponders to IFN monotherapy or combination IFN + RBV who were retreated with peg-IFN alfa-2a 180 μg/wk plus RBV 1000 to 1200 mg/d showed that although 55% of patients experienced end-of-treatment response (ETR), only 20% achieved SVR.

Krawitt et al[4] evaluated 604 patients (73% male; mean age, 49.9 years; 77% white) with HCV, of whom 64% had previously been treated with IFN + RBV. The mean estimated duration of HCV infection was 26.5 years, 89% had HCV genotype 1, 75% had serum HCV RNA concentrations >1.5 million IU/mL, and 39% had cirrhosis. After treatment with peg-IFN + RBV, HCV RNA was undetectable in 35% of patients, and 18% achieved SVR. Factors associated with the greatest likelihood of SVR included previous treatment with IFN monotherapy, HCV genotype 2 or 3, serum HCV RNA concentration $<1.5 \times 10^6$ IU/mL, and the absence of cirrhosis. Black patients responded poorly to treatment; SVR was observed in only 6% of these patients. Similarly, white patients with multiple poor prognostic factors, including prior treatment failure with IFN + RBV, HCV genotype 1, serum HCV RNA concentration $>1.5 \times 10^6$ IU/mL, and cirrhosis, also had an SVR rate of only 6%.

The objectives of the present retrospective study were to determine the rate of response to peg-IFN + RBV, and the factors affecting treatment outcome, in patients with chronic HCV genotype 1b infection and nonresponse or relapse with previous standard IFN + RBV treatment.

MATERIALS AND METHODS

Data Collection

From January 2002 to October 2004, 62 white patients with chronic HCV infection were seen in the hepatology outpatient clinic at the Department of Gastroenterology, Gazi University, Ankara, Turkey. Of these, data from patients aged ≥18 years with chronic HCV genotype 1b infection who had not achieved SVR with previous IFN + RBV therapy, and who were then given peg-IFN alfa-2a 180 μg/wk combined with RBV 1000 mg/d (body weight, <75 kg) or 1200 mg/d (body weight, ≥75 kg), depending on body weight, for 48 weeks were included in this retrospective analysis. Histories were taken from the patients, available family members (especially regarding alcohol use), and the medical archives of our department. Data from patients who tested positive for serum HIV antibody or had other types of liver disease (eg, metabolic, vascular, toxic, viral coinfection) were excluded. Data from patients who consumed >30 g of alcohol per day were also excluded. Local ethics committee approval was not required because the research was done using the previously recorded data. The patients provided written informed consent prior to participation in the treatment protocol.

Assessment of Treatment Response

Using patient records obtained from the clinic's electronic database, which included regular follow-up data measured at 12, 24, 36, and 48 weeks of treatment for our research purposes, we analyzed the demographic characteristics, virologic load (serum HCV RNA concentration), liver histology, biochemistry, treatment-related adverse effects (AEs), thyroid function, and the effects of dose reduction. Patients were classified based on their response to previous treatment with standard IFN + RBV, as follows: nonresponders, relapsers, or treatment failures (discontinuation due to AEs). HCV RNA levels were assessed throughout the peg-IFN + RBV treatment period using a real-time qualitative polymerase chain reaction (PCR) assay (Cobas Amplicor HCV test version 2.0, Roche Diagnostics, Inc., Somerville, New Jersey) (detection limit, <50 IU/mL [100 copies/mL]) and quantified by the Cobas Amplicor HCV Monitor test version 2.0 (Roche Diagnostics, Inc.) (detection limit, <600 IU/mL).[5–8] As recommended in the National Institutes of Health Consensus Development Conference Statement on the management of hepatitis C published in 2002,[8] combination therapy was to be discontinued if the HCV RNA level failed to decrease >2 logs (copies/mL) or remained within detectable limits by quantitative PCR assay at week 12. An experienced pathologist blinded to treatment assignment performed the histopathologic evaluation using liver biopsy data

from the previous treatment period. All biopsy specimens were assigned a Histologic Activity Index[9] (HAI) inflammatory score (scale: 0 = no periportal bridging or necrosis and portal inflammation to 18 = multilobular necrosis, marked [involvement of >2/3 lobules or nodules] intralobular degeneration, and focal necrosis) and a fibrosis score (scale: 0 = none to 4 = cirrhosis) based on criteria from Ishak et al.[10] The dose was to be reduced if the patient had an absolute neutrophil count $<1 \times 10^3$ cells/mL, platelet count $<50 \times 10^3$ cells/mL, or a hemoglobin concentration <10 g/dL. If the laboratory AEs persisted after dose reduction, treatment was to be discontinued. Furthermore, treatment was to be discontinued if the patient developed severe depression (major depressive episode based on criteria defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[11]) despite antidepressant medication during the treatment period. Treatment compliance was assessed using counts of empty pill boxes and syringes at each study visit.

Response to treatment was classified as follows. *Virologic response* was defined as the absence of detectable serum HCV RNA at 24 weeks after starting treatment. *Early virologic response* (EVR) was defined as ≥2-log (copies/mL) decrease from baseline in serum HCV RNA concentration or the absence of detectable serum HCV RNA at treatment week 12. *Viral breakthrough* was defined as the reappearance of HCV RNA during continuous therapy after previous response. *ETR* was defined as the absence of detectable serum HCV RNA at treatment week 48. *SVR* (primary end point) was defined as the absence of detectable serum HCV RNA 24 weeks after treatment was discontinued.

Statistical Analysis

Correlation analyses to determine factors affecting treatment outcome were performed using the Spearman correlation analysis. Statistical analyses were performed using SPSS version 9.0 (SPSS Inc., Chicago, Illinois). $P < 0.05$ was considered statistically significant.

RESULTS

Study Population

Seventeen patients (12 men, 5 women; mean [SD] age, 48 [2] years) were included in the study (**Table I**). Two patients were nonresponders and 6 patients were relapsers with previous treatment. Two patients were considered treatment failures with standard IFN + RBV due to premature discontinuation as a result of AEs. Data concerning previous patterns of response were lacking in 7 patients. However, based on the fact that these patients were still HCV-RNA–positive after IFN + RBV treatment, they were considered nonresponders or treatment failures (**Table II**). Based on liver biopsy data from the previous treatment period, 14 patients underwent liver biopsy before treatment with peg-IFN + RBV; the remaining 3 did not (1 patient had undergone a liver biopsy within the previous 12 months, and 2 were unwilling to undergo the procedure).

Table I. Baseline demographic and clinical characteristics of the study patients (N = 17).

Characteristic	Value
Age, y	
Mean (SD)	48 (2)
Range	29–60
Race	
White	17
Sex, no.	
Male	12
Female	5
Estimated duration of infection, y	
Mean (SD)	7.8 (5.6)
Range	1–15
Weight, kg	
Mean (SD)	79.6 (16.3)
Range	65–96
Body mass index, kg/m^2	
Mean (SD)	28.1 (6.6)
Range	20–34
Liver enzymes	
ALT, mean (SD), × ULN	
Mean (SD)	2.16 (0.98)
Range	0.52–5.60
AST/ALT ratio	
Mean (SD)	0.87 (0.54)
Range	0.42–2.55
HCV RNA, copies/mL	
Serum concentration	
Mean (SD)	5.5×10^6 (4.3×10^6)
Range	5.0×10^5 to 2.4×10^8
Log_{10} serum concentration	
Mean (SD)	5.4 (2.1)
Range	5.0–8.0
HAI*	
Median (SE)	6 (0.9)
Range	1–14
Fibrosis stage†	
Mean (SD)	2 (0.2)
Range	1–4

(continued)

Table I. (Continued)

Characteristic	Value
Cytology, cells × 10^3/mL	
Leukocytes	
Mean (SD)	5.2 (1.52)
Range	3.8–9.6
Neutrophils	
Mean (SD)	3.2 (1.1)
Range	1.9–4.6
Platelets	
Mean (SD)	175.0 (60.6)
Range	110–545
Hb concentration, g/dL	
Mean (SD)	16.3 (4.4)
Range	10.7–19.5

ALT = alanine aminotransferase; ULN = upper limit of normal; AST = aspartate aminotransferase; HCV = hepatitis C virus; HAI = histologic activity index; Hb = hemoglobin.
*HAI scale: 0 = no periportal bridging or necrosis, portal inflammation to 18 = multilobular necrosis, marked (involvement of >2/3 lobules or nodules) intralobular degeneration and focal necrosis.[9]
†Fibrosis scale: 0 = none to 4 = cirrhosis.

Table II. Previous patterns of response to treatment with standard interferon (IFN) plus ribavirin (RBV) and current patterns of response to treatment with pegylated IFN + RBV in the study group (N = 17).

Previous Pattern of Response	Current Pattern of Response
Relapse (6/17 patients)	SVR (3/6 patients) ETR (3/6 patients)
Nonresponse (2/17 patients)	Viral breakthrough (2/2 patients)
Discontinued due to ≥1 AE (2/17 patients)	Discontinued due to ≥1 AE (2/2 patients)
NA* (7/17 patients)	ETR (4/7 patients) Discontinued due to ≥1 AE (3/7 patients)

SVR = sustained virologic response; ETR = end-of-treatment response; AE = adverse effect.
*Detailed data regarding the pattern of response was not available in these patients.

Treatment Response

Rates of virologic response to treatment with peg-IFN alfa-2a + RBV are summarized in **Table II**. Two patients achieved EVR but experienced viral breakthrough during the treatment period. Seven patients achieved ETR; however, their HCV infection relapsed during the follow-up period. Five additional patients achieved EVR, and 3 achieved SVR.

Detailed analysis revealed that the 2 patients who had viral breakthrough were both nonresponders to previous therapy. We were able to obtain the details of previous treatment data in 3 of 7 patients who achieved ETR. These patients all had the same pattern of response to standard IFN + RBV therapy: they responded to the treatment but relapsed at some point after 12 weeks.

The 5 patients who achieved EVR (measured at week 12) discontinued treatment due to severe drug-related AEs. One of these patients developed depression during the first 24 weeks of treatment. In this patient, antidepressant therapy with a selective serotonin reuptake inhibitor was started, and the dose of peg-IFN was reduced to 135 μg/wk and then to 90 μg/wk in a stepwise manner. Although this patient's serum HCV RNA was undetectable, symptoms of depression worsened, and treatment with peg-IFN + RBV was discontinued. Hematologic AEs, mainly neutropenia (neutrophil count, <1000 cells/mL), developed in the other 4 patients, and mild thrombocytopenia developed in 2 patients. Although the peg-IFN dosage was decreased to 90 μg/wk in these 4 patients, neutropenia persisted, and treatment was discontinued in the first 24 weeks. In 2 of these 4 patients, liver histology revealed stage 4 fibrosis. These 2 patients had severe neutropenia in their previous treatment with IFN + RBV, and that treatment was discontinued prematurely.

All 3 of the patients who achieved SVR were previous relapsers. These patients experienced mild treatment-related AEs (flulike symptoms, arthralgia). All of them had EVR in week 12.

Factors Affecting Treatment Outcome

The factors affecting the outcome of peg-IFN + RBV therapy are shown in **Table III**. The main factors in the failure to achieve SVR were advanced-stage liver fibrosis, nonresponse to prior therapy, and noncompliance with therapy (all, $P < 0.01$); prior relapse was also a factor in failure to achieve SVR ($P < 0.05$).

No significant correlation was found between age, sex, viral load, or degree of liver inflammation and current response pattern. However, prior relapse was significantly correlated with achieving SVR ($P < 0.05$; $r = 0.950$). Severe AEs leading to discontinuation of therapy were correlated with stage 4 fibrosis ($P < 0.01$; $r = 0.513$). There was a positive correlation between the HAI score and the log value of the viral load ($P < 0.01$; $r = 0.573$).

DISCUSSION

The currently accepted primary end point of HCV therapy is SVR. With the combination of peg-IFN + RBV, an SVR rate of 40% to 45% can be achieved in patients

Table III. Comparison of demographic, histologic, virologic, and therapy-related features of patients with or without sustained virologic response (SVR) to pegylated interferon plus ribavirin.

Factors Influencing Treatment Success	SVR (n = 3)	Non-SVR (n = 14)
Age, mean (SD), y	45 (4)	47 (2)
Weight, mean (SD), kg	81.4 (12.5)	77.3 (11.4)
BMI, mean (SD), kg/m^2	27.6 (4.5)	29.1 (5.2)
ALT, mean (SD), × ULN	2.15 (1.10)	2.19 (0.96)
HCV RNA		
Serum concentration, mean, copies/mL	7.9 × 10^6	5.1 × 10^6
Log_{10} serum HCV RNA concentration, mean (SD)	5.1 (2.5)	5.4 (1.5)
HAI, median (SE)*	5 (1.6)	6 (0.5)
Fibrosis stage, median (SE)†	1 (0.5)	3 (1.5)‡
Previous pattern of response to therapy, no.§	3	7
Relapse	3	3‖
Nonresponse	0	2‡
Noncompliance	0	2‡

BMI = body mass index; ALT = alanine aminotransferase; ULN = upper limit of normal; HCV = hepatitis C virus; HAI = histologic activity index.
*HAI scale: 0 = no periportal bridging or necrosis and portal inflammation to 18 = multilobular necrosis, marked (involvement of >2/3 lobules or nodules) intralobular degeneration, and focal necrosis.[9]
†Fibrosis scale: 0 = none to 4 = cirrhosis.
‡$P < 0.01$ versus SVR.
§Patients in whom previous response patterns were available.
‖$P < 0.05$ versus SVR.

with HCV genotype 1 and ~80% of patients with genotype 2 or 3 infection.[1,2] Especially for patients with genotype 1 infection, these results are significantly improved compared with those of treatment with standard IFN + RBV.[12] As a result, the patients who were nonresponders to the previous therapies are now considered candidates for treatment with peg-IFN + RBV.[12]

Considerable data are available regarding treatment of HCV infection in nonresponders to previous standard IFN therapies.[13–17] In these trials, the addition of amantadine or thymosin α_1 slightly increased the SVR rate; however, controversies exist.[13–17] These studies were mainly performed in nonresponders. A pilot study revealed an increased benefit with prolonged IFN treatment.[18,19] Trials of intensive or induction therapies with daily or higher doses had conflicting results.[20,21] Experimental therapies, including interleukin (IL)-12 and IL-2, failed to achieve sufficient therapeutic success.[22,23] Consensus IFN (ie, IFN alfacon-1, a recombinant, synthetic type 1 IFN) has been reported to be a suc-

cessful therapy for standard IFN failures; however, this drug is not available in many countries.[24–27]

Although few published trials evaluating the role of peg-IFN + RBV in IFN nonresponders or relapsers are available, it is thought that SVR rates might be improved with this treatment. Preliminary data from the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial[3] were published in 2002. In that study, 212 nonresponders to prior IFN monotherapy or combination therapy were treated with peg-IFN alfa-2a 180 μg/wk plus RBV 1000 to 1200 mg/d. Although 55% of patients achieved ETR, only 20% achieved SVR. Factors positively correlated with achieving SVR were previous relapse, non-1b genotype, and IFN monotherapy nonresponse.

The pattern of response to prior therapy seems to have a strong influence on the rates of response to subsequent treatment, as shown in a report of the HALT-C trial[12] published in 2004, in which only nonresponders were enrolled. The SVR rate was 18% at 48 weeks. In a separate study, the SVR rate in relapsers was 32% to 50%.[28] In another study, the ETR rates at 24 weeks were 71% to 76% in prior relapsers and 26% to 52% in prior nonresponders.[29] These data suggest a better outcome in prior relapsers compared with prior nonresponders when HCV infection was treated with peg-IFN + RBV.

In the present study, all of the patients who achieved an SVR were prior relapsers. Prior nonresponders and patients with premature treatment discontinuation due to AEs failed to achieve SVR. Based on previous work,[2,30] patients who achieved EVR, defined as ≥2 log (100-fold) decline in the serum level of HCV RNA or no detectable HCV RNA within the first 12 weeks of treatment, had a higher rate of SVR. IFN susceptibility of HCV was found to be a major factor in treatment outcome. EVR is the most valuable prognostic factor in HCV treatment. For this reason, nonresponders who failed to achieve EVR with standard IFN + RBV probably will not respond to the newer peg-IFN + RBV combination.

Adherence to therapy has been identified as an important determinant of SVR.[31] *Noncompliance* is sometimes defined as a dose reduction to >80% of the original dose, or treatment discontinuation before 80% of the planned duration of therapy has been completed.[2,32–34] In the patients in the present study, AE-related noncompliance occurred in 5 patients (depression [1 patient], neutropenia [4]). Two of these patients had the same AEs with the previous treatment. None of the patients required a reduction in RBV dose. The main toxicity was neutropenia, which is a common AE of IFN treatment. However, these findings are contrary to the findings reported by Davis et al.[30] In that study, reducing the RBV dose but not the peg-IFN dose in the first 12 weeks was associated with a significant decrease in the virologic response rate. Moreover, reducing the dose of peg-IFN alfa-2a within the first 20 weeks of treatment did not appear to affect the virologic response at week 20 or the SVR rate. After 20 weeks, neither IFN nor RBV dose reduction affected virologic response. For this reason, the potential role of adjuvant hematologic growth factors is being studied.[33]

There were limitations of the present study, including its small sample size, retrospective design, and lack of data concerning previous pattern of response in 7 patients.

CONCLUSIONS

In this study in patients with chronic HCV genotype 1b infection and a history of relapse or nonresponse to standard IFN + RBV treatment, treatment with peg-IFN + RBV achieved an SVR rate of 18%. Major determinants of failure to reach SVR in these patients included advanced-stage liver fibrosis, previous nonresponse pattern, and noncompliance with the therapy. Further research is needed to determine the role of peg-IFN + RBV in the re-treatment of HCV infection.

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