Pegylated Interferon Alpha-2b Plus Ribavirin for Naive Patients With HCV-related Cirrhosis

Annarosa Floreani, MD, Vincenzo Baldo, MD,† Erik Rosa Rizzotto, MD,* Isabella Carderi, MD,* Tatjana Baldovin, PhD,† and Eliseo Minola, MD‡*

Background: Data on the efficacy of antiviral therapy in patients with HCV-related compensated cirrhosis are generally drawn from analyzing subgroups in larger trials.

Aims: (1) To analyze the safety and efficacy of combination therapy in naive patients with HCV-related cirrhosis; (2) to evaluate the factors influencing the sustained virologic response (SVR) in cirrhotic patients by comparison with a group of noncirrhotic patients; (3) to analyze the outcome of cirrhotic patients either acquiring SVR and nonresponders to the antiviral therapy during the posttreatment follow-up.

Methods: We consecutively enrolled 365 patients with biopsy-proven HCV-related chronic hepatitis meeting the inclusion criteria for pegylated interferon a-2b plus Ribavirin: 87 patients had compensated liver cirrhosis and 278 had histologic stages between 1 and 4 according to Ishak's classification.

Results: The 2 groups were comparable for genotype, viral load, and alanine transferase at presentation. Cirrhotic patients were significantly older and had significantly higher body mass index, serum ferritin, and gamma-glutamyl transpeptidase. The rate of side effects was similar in the 2 groups, whereas the rate of SVR was significantly lower in cirrhotic (45.9%) than in noncirrhotic patients (65.8%). Logistic regression analysis showed that genotype 1 to 4 and high viral load were independent variables correlating with nonresponse in the sample as a whole. During follow-up, hepatocellular carcinoma developed in 5/38 (13.2%) cirrhotic patients not responding or relapsing after treatment. No cases of hepatocellular carcinoma were seen among cirrhotic or noncirrhotic patients with a SVR.

Conclusions: Cirrhotic patients with compensated disease have a reasonably good chance of virologic response and should be offered treatment, carefully monitoring any side-effects.

Key Words: HCV, treatment, cirrhosis

(*J Clin Gastroenterol* 2008;42:734–737)

Received for publication October 26, 2006; accepted February 7, 2007.

From the Departments of *Surgical and Gastroenterological Sciences; †Hygiene and Public Health, University of Padova; and ‡Department of Infectious Disease, Ospedali Riuniti, Bergamo, Italy.

The authors declare no conflict of interest.

The study was partially supported by a Ministerial grant.

Reprints: Annarosa Floreani, MD, Department of Surgical and Gastroenterological Sciences, Via Giustiniani, 2, 35128 Padova, Italy (e-mail: annarosa.floreani@unipd.it).

The introduction of combined therapy with pegylated interferon (PEG-IFN) and Ribavirin has dramatically improved the sustained virologic response (SVR) in patients with chronic hepatitis C. According to current management guidelines, the SVR in HCV infection is negatively associated to several variables, including advanced histologic fibrosis, genotype 1, old age, and high viral load.[1] Patients with cirrhosis are generally considered difficult to treat because they are less likely to respond and pose problems related to side-effects. On the other hand, cirrhosis is a precancerous condition carrying a high risk of hepatocellular carcinoma (HCC), estimated to be as high as 3.5% a year in HCV-related cirrhosis.[2] Several retrospective and prospective studies have been conducted to assess the protective role of IFN against the development of HCC,[3–8] generally showing that IFN may have a preventive role, especially in patients with a SVR. Results are contrasting in some cases, however, mainly due to patient selection bias, because the untreated group contains the majority of patients with advanced disease are with contraindications to the treatment. A recent multicenter study on 1214 Child A cirrhotics with HCV infection treated with IFN monotherapy reported a SVR in 16.4% of cases.[9] In the long term, the SVR was independently associated with a lower risk of developing HCC and a significant increase in life expectancy.[9] A recent pilot study on patients with HCV-related compensated cirrhosis taking PEG-IFN plus Ribavirin suggests that achieving a SVR may reduce the incidence of HCC in Taiwan.[10]

The aims of our study were, therefore, (1) to analyze the safety and efficacy of combination therapy in naive patients with HCV-related cirrhosis; (2) to evaluate the factors influencing SVR in cirrhotic patients by comparison with a group of noncirrhotic patients; (3) to analyze the outcome of cirrhotic patients either acquiring SVR and nonresponders to the antiviral therapy during the posttreatment follow-up.

MATERIALS AND METHODS

Patients

Between January 2000 and December 2004, all consecutive patients meeting the inclusion criteria were treated with PEG-IFN plus Ribavirin. The inclusion criteria were (1) naive HCV-RNA–positive patients aged between 18 and 70 years with alanine transferase (ALT)

values above 1.5 (the upper normal value); (2) liver biopsy performed in the last 12 months before enrolment compatible with chronic hepatitis; (3) hemoglobin > 12 g/dL, white blood cell count > 3000/mm^3, platelets > 75,000/mm^3, bilirubin, albumin, and serum creatinine levels within normal limits. Exclusion criteria were (1) coinfection with HBV and/or HIV; (2) alcohol abuse (> 20 g/d for women, 40 g/d for men); (3) a history of parenteral drug addiction unless they had abstained for at least 2 years; (4) complications of portal hypertension [large esophageal varices (F2 or more)], a history of gastrointestinal bleeding, ascites, encephalopathy; (5) concomitant liver disease of other etiology (autoimmune hepatitis, cholestatic liver disease, nonalcoholic fatty liver disease).

Each patient underwent liver biopsy before treatment and the liver specimens were all read blindly by the same pathologist and classified according to Ishak's numerical scoring system.[11]

Patients with a fibrosis score of 5 or 6 were allocated to the group with cirrhosis (study group); those scoring between 0 and 4 served as controls and constituted the noncirrhotic group.

Treatment

After obtaining their written consent to participate in the study, patients were given PEG-IFN alpha-2b (PEG-Intron, Schering Corp, Kenilworth, NJ) subcutaneously at a dose of 100 μg a week for those weighing 65 kg or more, or 80 μg for those under 65 kg plus Ribavirin (Rebetol, Schering Corp) in 2 daily doses for a total dose of 1000 mg/d for patients weighing up to 75 kg, or 1200 mg/d for those weighing more than 75 kg.

The treatment was withdrawn if patients failed to achieve a virologic response, defined as serum HCV-RNA undetectable by polymerase chain reaction 24 weeks after starting the treatment; these patients were considered as nonresponders. This end point was based on the guidelines of the European Association for the Study of Liver Disease (EASL).[12] End-of-treatment virologic response was defined as a normalization of ALT and HCV-RNA negativity at the end of the treatment. Treatment duration was 48 weeks for patients with genotypes 1 to 4 and 24 weeks for those with genotypes 2 to 3.

Sustained virologic response (SVR) was defined as the absence of serum HCV-RNA and normal ALT 24 weeks after completing the treatment.

Statistical Analysis

Data analyses were performed using the χ^2 test (Mantel Haenszel and Fisher exact test). A P value of ≤ 0.05 was considered significant, and the odds ratio (OR) with a 95% confidence interval (CI) was calculated for each parameter.

Multivariate logistic regression analysis was performed to evaluate independent predictors of SVR. The multivariate OR for each variable was adjusted for age, sex, body mass index (BMI), ALT, gamma-glutamyl transpeptidase, ferritin, grading, viral load ($< 1.5 \times 10^6$ vs. $\geq 1.5 \times 10^6$), genotype (types 1 to 4 vs. 2 to 3) and cirrhosis. Analyses were performed with the Statistical Package for the Social Sciences (SPSS rel. 11.5, Chicago, IL).

TABLE 1. Baseline Characteristics of Patients

Variable	Cirrhotics (N = 87)	Noncirrhotics (N = 278)	*P*
Age (y)	55.7 ± 9.1	44.5 ± 11.1	< 0.0001
Male sex [n (%)]	49 (56.3%)	185 (66.5%)	n.s.
BMI	25.3 ± 3.1	24.4 ± 3.1	n.s.
ALT	168.2 ± 85.0	156.9 ± 116.2	n.s.
Gamma-glutamyl transpeptidase	105.3 ± 74.4	67.9 ± 66.4	< 0.0001
Ferritin	315.5 ± 286.0	210.5 ± 194	< 0.0001
Grading	7.0 ± 2.1	5.7 ± 1.9	< 0.0001
Viral load			
$< 1.5 \times 10^6$	37 (42.9%)	91 (32.8%)	n.s.
$\geq 1.5 \times 10^6$	50 (57.1%)	187 (67.2%)	n.s.
Genotype			
1	44 (50.6%)	107 (38.5%)	n.s.
2	30 (34.5%)	93 (33.5%)	n.s.
3	13 (14.9%)	70 (25.2%)	n.s.
4	—	8 (2.9%)	n.s.

RESULTS

Table 1 summarizes the patients' baseline clinical details. Patients with cirrhosis were significantly older (mean age 55.7 ± 9.1 vs. 44.5 ± 11.1 y, $P < 0.0001$) and had significantly higher serum levels of gamma-glutamyl transpeptidase and ferritin ($P < 0.0001$), and significantly higher histologic grading (7.0 ± 2.1 vs. 5.7 ± 1.9, $P < 0.0001$). No significant differences emerged between the groups with and without cirrhosis as concerned the prevalence of male sex, body mass index, serum ALT, viral load, or genotype.

Outcomes

The daily dose of PEG-IFN and Ribavirin, and the time of treatment were comparable in the 2 groups (Table 2). The cirrhotic group had significantly lower end-of-treatment virologic response and SVR rates than noncirrhotic patients (Table 2), and a higher proportion of patients with posttreatment relapse ($P < 0.03$).

Overall, the reason for discontinuing the treatment was nonresponse in 27/87 cirrhotics (31.0%) and 62/278 noncirrhotics (22.3%); the difference was not statistically significant. The percentage of side-effects was similar in the 2 groups (Table 3).

The rate of SVR was higher in patients with low viral load ($< 1.5 \times 10^6$) compared to those with high viral load ($\geq 1.5 \times 10^6$) in either cirrhotic and noncirrhotic group (P = n.s.). Moreover, SVR was significantly higher in those with 1 to 4 genotype compared to those with 2 to 3 genotype ($P < 0.01$) among the same groups of patients. However, cirrhotic and noncirrhotic patients with "easy genotype" (i.d. 2 to 3 genotype) had a similar rate of SVR (Table 4).

TABLE 2. Efficacy of Treatment in Cirrhotic and Noncirrhotic Patients

	Cirrhotics (N = 36)	Noncirrhotics (N = 80)	*P*
Daily dose of PEG-IFN/ patient (μg—mean ± SD)	87.0 ± 15.6	89.0 ± 14.3	0.270
Daily dose of Ribavirin/ patient (mg—mean ± SD)	1000 ± 0	1000 ± 0	0.577
Duration of treatment/ patient (months—mean ± SD)	8.9 ± 3.7	8.9 ± 3.2	0.991
Drop-outs	36 (39.2%)	80 (28.8%)	0.0001
End-of-treatment response	51 (55.4%)	198 (71.2%)	0.03
Relapse	11/51 (21.5%)	15/197 (7.5%)	0.03
Sustained virologic response	40 (45.9%)	183 (65.8%)	0.0001

Multivariate analysis showed that 2 variables correlated significantly with the lack of any SVR, that is, genotypes 1 to 4 (OR 6.798, 95% CI 3.690-12.523) and high viral load ($\geq 1.5 \times 10^6$) (OR 2.241, 95% CI 1.152-4.358).

The mean follow-up after treatment was 23.4 ± 11.1 and 25.2 ± 12.4 months in the cirrhotic and noncirrhotic groups, respectively. During the follow-up, 5/38 (13.2%) cirrhotic nonresponders or relapsers to the antiviral treatment developed HCC, whereas there were no cases of HCC onset among the cirrhotics with SVR or in the noncirrhotic group.

DISCUSSION

The results of our study show that patients with HCV-related cirrhosis have a nearly 46% chance of achieving a SVR with antiviral therapy, albeit with a significantly higher risk of relapse than among noncirrhotic patients with viral hepatitis. After the antiviral treatment, HCC developed in 5/38 (13.2%) cirrhotic nonresponders or relapsers. These results warrant further comment.

First of all, there is still a shortage of studies on antiviral therapy in patients with advanced liver disease. The largest cohort of cirrhotic patients treated with IFN monotherapy was enrolled at 23 Italian referral centers[3]: in this multicenter study, 16.4% of subjects achieved a SVR, which was independently associated with a lower risk of developing HCC and a significant increase in life expectancy. The Taiwan study,[10] conducted in a group of cirrhotic patients without a noncirrhotic control group, used a combined therapy with PEG-IFN and Ribavirin and recorded a SVR in 55% of the cirrhotic patients.

TABLE 3. Reasons for Discontinuing Treatment (Drop-Outs)

	Cirrhotics (N = 36)	Noncirrhotics (N = 80)	*P*
No response	27 (75.0%)	62 (77.5%)	n.s.
Side-effects	9 (25.0%)	18 (22.5%)	n.s.
Hematologic	1	2	—
Endocrinologic	3	4	—
Cutaneous rash	5	13	—

TABLE 4. SVR According to Viral Load and Genotype

	Cirrhotics (N = 87)	Noncirrhotics (N = 278)
Viral load		
$< 1.5 \times 10^6$	22/37 (59.5%)	64/91 (70.3%)
$\geq 1.5 \times 10^6$	18/50 (36.0%)	119/187 (63.6%)
Genotype		
1-4	9/44 (20.5%)	50/115 (43.5%)
2-3	31/43 (72.1%)*	133/163 (81.6%)*

*$P < 0.01$ vs. genotypes 1-4.

Our single center study included a control group of consecutive noncirrhotic HCV-positive chronic hepatitis patients for comparison and demonstrates that compensated cirrhotic patients with a platelet count > 75,000 and white blood cell count > 3000 should be considered as candidates for antiviral treatment. In fact, the 45.9% rate of SVR in cases with HCV-related cirrhosis observed in our study should be considered a good result. Surprisingly, the rate of drop-outs for side-effects was much the same among the noncirrhotic and cirrhotic patients—though strict patient monitoring is to be recommended nonetheless.

The problem of whether to offer antiviral treatment to a wider range of patients with HCV-related cirrhosis has arisen over the last 7 to 8 years, after analyses on the related reduction in the risk of HCC. It is generally agreed in the literature that patients responding to IFN therapy carry a lower risk of HCC[3–7] and our data also point in this direction. In cost/benefit terms, therefore, all patients with chronic hepatitis C should be considered as potential candidates for antiviral therapy.

In conclusion, cirrhotic patients with compensated disease have a reasonably good chance of achieving a virologic response and should be offered antiviral treatment, assuring a careful monitoring of side-effects.

REFERENCES

1. Poynard T, Ratziu V, Charlotte F, et al. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *J Hepatol*. 2001;34:730–739.
2. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology*. 1997;112:463–472.
3. Nishiguchi S, Kuroki T, Nakatani S, et al. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet*. 1995;346: 1051–1055.
4. Mazzella G, Accogli E, Sottili S, et al. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. *J Hepatol*. 1996;24:141–147.
5. Benvegnù L, Chemello L, Noventa F, et al. Retrospective analysis of the effect of interferon therapy on the clinical outcome of patients with viral cirrhosis. *Cancer*. 1998;83:901–909.
6. Lau DT, Kleiner DE, Ghany MG, et al. 10-year follow-up after interferon-alpha therapy for chronic hepatitis C. *Hepatology*. 1998; 28:1121–1127.

7. Hino K, Kitase A, Satoh Y, et al. Interferon retreatment reduces or delays the incidence of hepatocellular carcinoma in patients with chronic hepatitis C. *J Viral Hepat*. 2002;9:370–376.
8. Omata M, Yoshida H. Resolution of liver cirrhosis and prevention of hepatocellular carcinoma by interferon therapy against chronic hepatitis C. *Scand J Gastroenterol*. 2003;237(suppl):47–51.
9. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-α is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology*. 2007;45: 579–587.
10. Hung C-H, Lee C-M, Lu S-N, et al. Long-term effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. *J Viral Hepat*. 2006;13:409–414.
11. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol.* 1995;22: 696–699.
12. EASL International Consensus Conference on Hepatitis C Paris. 26-27 February 1999 Consensus Statement. *J Hepatol*. 1999;31: S3–S8.