Pegylated-Interferon and Ribavirin for Chronic Hepatitis C Virus Infection in Decompensated Cirrhotics Awaiting Liver Transplantation

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Abstract: Sustained virologic response (SVR) to the antiviral therapy for chronic hepatitis C virus infection before liver transplantation (LT) can prevent graft infection. Pegylated (PEG)- interferon (IFN) may ameliorate the SVR, improving the risk-to-benefit ratio of antiviral therapy in cirrhotics awaiting LT. From January 2001 to March 2009, 21 HCV-infected cirrhotics eligible for LT were treated with PEG-IFN alpha-2b (1.5 μg/kg weight/week) and ribavirin (800-1200 mg/day). Mean age was 53.7±7.9 years. There were 11 men. Eleven had genotype 1b. Child-Pugh score was 9.5±1.2, Model for End-Stage Liver Disease score 16.6±1.8. Besides virologic failure, full dosage and planned length of therapy were tolerated in 5 patients (23.8%). Adverse events occurred in all patients, life-threatening in 9 (42.9%). No patient died during treatment. Adverse events caused treatment withdrawal in 11 patients (52.4%), ribavirin and/or PEG-IFN reduction in 7 (33.3%). On an intention-to-treat basis, SVR was obtained in 4 patients (19.0%). None of the genotype 1 or 3 patients obtained SVR; 50.0% of genotype 2 patients obtained SVR. All patients with SVR experienced rapid virological response (RVR). Six patients (three nonresponders, two relapsers, one sustained responder) were transplanted; six died; four are awaiting LT; two are under evaluation for listening; three refused LT. The risk-to-benefit ratio is against treatment with PEG-IFN and ribavirin of severely decompensated genotype 1 cirrhotics. In contrast, antiviral therapy is probably beneficial in genotype 2 subjects, due to an expected SVR rate of 50%. However, one must carefully consider the high risk for severe adverse events.

Keywords: Antiviral therapy, hepatitis C virus infection, liver cirrhosis, decompensated cirrhosis, liver transplantation.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection represents the most common indication for liver transplantation (LT) in the Western world [1]. After LT, HCV reinfection occurs in all patients with pretransplant viremia. Although recurrent HCV infection has a variable course, it leads to cirrhosis in 10 to 25% of transplant recipients within 5 to 10 years, substantially reducing the benefits of LT [2].

Sustained serum HCV clearance by antiviral therapy, either before or after LT, can prevent graft infection or avoid the establishment of a chronic infection.

Current therapy for chronic HCV infection with pegylated (PEG)-interferon (IFN) and ribavirin (RBV) allows persistent eradication of HCV from the serum in more than half of the treated patients [3, 4]. Although this therapy is widely accepted for patients with advanced fibrosis or early-compensated cirrhosis, its feasibility in decompensated cirrhotics is still debated [5]. In studies on therapy with IFN and RBV in patients with decompensated liver disease, a reduced rate of serum HCV-RNA clearance is associated with an increased risk of severe, life-threatening adverse events [6-12]. However, the use of PEG-IFN instead of IFN may ameliorate the virologic response, improving the risk-to-benefit ratio of antiviral therapy in cirrhotic patients awaiting LT.

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In our study, we evaluated the efficacy and safety of current standard antiviral therapy for chronic HCV infection in cirrhotic patients listed for LT at our Institution.

MATERIALS AND METHODOLOGY

From January 2001 to March 2009, all consecutive cirrhotic patients with chronic HCV infection eligible for LT at our Institution were evaluated for antiviral therapy. Inclusion criteria were: total bilirubin <5.0 mg/dL, albumin >2.0 g/dL, international normalized ratio <1.7, platelet (PLT) count >40,000/μL, absolute neutrophil (NEU) count >1,000/μL, hemoglobin (Hb) >10.0 g/dL, creatinine <1.5 mg/dL, esophageal varices not at risk of bleeding, Child-Turcotte-Pugh (CTP) score <12, Model for End-Stage Liver Disease (MELD) score <20. Immunological, cardiac, pulmonary, metabolic, and psychiatric contraindications to IFN e RBV, viral co-infections, hepatocellular carcinoma (HCC), recurrent bacterial infections, previous/present hepatic encephalopathy (HE), refractory ascites were considered as exclusion criteria.

After obtaining informed consent, all eligible patients underwent to antiviral therapy with subcutaneous PEG-IFN alpha-2b (PEG-Intron, Schering–Plough, Brussels, Belgium; 1.5 μg/kg body weight/week) and oral RBV (Rebetol, Schering–Plough, Brussels, Belgium; 800 mg/day for HCV genotype 2 or 3 and 1000 or 1200 mg based on body weight < or ≥75 kg for HCV genotype 1 or 4). The length of antiviral therapy was 24 weeks for HCV genotype 2 or 3 and 48 weeks for HCV genotype 1 or 4 (5). Erythropoietin (Eprex,

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Janssen-Cilag SpA, Milan, Italy) and granulocyte colony-stimulating factor (Myelostim 34, Italfarmaco SpA, Milan, Italy) were employed respectively in presence of Hb <10.0 g/dL or absolute NEU count <750/μL.

Quantitative HCV-RNA test (Cobas Amplicor HCV Monitor v2.0, Roche Diagnostic; limit of sensitivity 600 IU/mL) and HCV genotyping (Innolipa HCV, Innogenetics) were performed in all patients before the antiviral therapy. Response to treatment was evaluated by a quantitative HCV-RNA test. A qualitative HCV-RNA test (Cobas Amplicor HCV v2.0, Roche Diagnostic; limit of sensitivity 50 IU/mL) was performed when serum virus was undetectable by the quantitative test.

Rapid virologic response (RVR) was defined as undetectable HCV-RNA at week 4 of therapy; early virologic response (EVR) as a ≥2 log drop or loss of HCV-RNA at week 12 of therapy. Patients who did not experience EVR were considered as non-responder (NR) and discontinued therapy. End-of-treatment response (ETR) was defined as undetectable HCV-RNA at the end of therapy; sustained virologic response (SVR) as undetectable HCV-RNA 24 weeks after the end of therapy. Patients were considered to have a virologic relapse (REL) when HCV-RNA reappeared while still on therapy or after the end of therapy (5). Virologic tests were performed at week 4 and at week 12 of therapy in all patients. Thereafter, HCV-RNA test was performed every 12 weeks until the end of therapy in all patients with EVR and 24 weeks after the end of therapy in those with ETR.

All patients had weekly clinical and laboratory controls. Clinical side effects or abnormalities in liver function tests brought to reduction or withdrawal of therapy according to the judgement of the attending physician. A fall of the absolute NEU count <750/μL or of the PLT count <30,000/μL brought to reduction of PEG-IFN. A fall of Hb <10.0 g/dL brought to reduction of RBV. A fall of the absolute NEU count <500/μL or of the PLT count <20,000/μL brought to treatment withdrawal. A fall of Hb <8.0 g/dL brought to RBV withdrawal. For mild infections dose modification was not considered; for moderate or major infections the drug dose was respectively reduced or discontinued.

RESULTS

Twenty-one HCV-infected cirrhotic patients eligible for LT consented to antiviral treatment. Baseline characteristics of these patients are shown in Table **1**.

Treatment for HCC was performed with radiofrequency ablation or transarterial chemioembolization in three patients during 12 months prior to the antiviral therapy. Computed tomography performed immediately before the beginning of the antiviral therapy did not show HCC recurrence.

Besides virologic failure, full dosage and planned length of therapy were tolerated in 5 (23.8%) patients. The mean duration of therapy in genotype 1 and in genotype 2-3 patients was respectively: 9.7±3.9 and 15.7±9.7 weeks. No patient sustained a course of therapy longer than 24 weeks.

Adverse events occurred in all patients. Type and number of significant adverse events registered during therapy are shown in Table **2**.

Table 1. Baseline Characteristics of the Patients Submitted to Antiviral Therapy

Variables	(N= 21)
Male Sex	11 (52.4)
Age, y	53.7±7.9; 37-63
Naïve	10 (47.6)
HCV Genotype	
1	11 (52.4)
2	8 (38.1)
3	2 (9.5)
HCV-RNA, $\log_{10}$IU/mL	5.72±5.66; 4.67-6.28
CTP Score	9.5±1.2; 8-12
MELD Score	16.6±1.8; 14-20
Hemoglobin, g/dL	12.0±0.9; 10.0-13.0
Plateletsx10^3/μL	70±14; 46-95
Neutrophils x10^3/μL	1.8±0.4; 1.2-2.8
Varices	14 (66.7)

Qualitative variables are presented as *n* (%) and quantitative variables as mean ± SD (range).

Table 2. Adverse Events during Antiviral Therapy

Adverse Events	
Intolerance (Severe Fatigue, Prolonged Flu-like Symptoms, Depression)	3
Hb <8.5 g/dL	3
PLT count <35,000/μL	9
NEU count <650/μL	8
Moderate Infection	2 (one hemorrhagic cystitis; one acute bronchitis)
Major Infection	4 (two pneumonia; one pelvic infection; one spontaneous bacterial peritonitis)
Refractory Ascites	1
Hepatic Encephalopathy grade III	3
Variceal Bleeding	2
Hepatocellular Carcinoma	1

Minimal-to-moderate adverse events such as mild fatigue, insomnia, transient flu-like symptoms, hypothyroidism, minimal ascites, mild infections, mild anemia, neutropenia, and thrombocytopenia were considered unsignificant and are not reported. Severe life-threatening adverse events were registered in 9 patients (42.9%). No patient died during antiviral treatment.

Adverse events caused treatment withdrawal in 11 patients (52.4%) between 2nd to 16th week of therapy and RBV and/or PEG-IFN dose reduction in 7 patients (33.3%) between the 1st and 24th week of therapy.

On an intention-to-treat basis, SVR was obtained in 4 patients (19.0%). RVR was obtained in 5 patients (23.8%), EVR in 8 patients (38.1%). Only four patients, all infected by genotype 2, completed the planned course of antiviral therapy and had ETR (19.0%). None of the genotype 1 or 3 patients obtained SVR. Among the HCV genotype 2 subjects, 4 patients (50.0%) obtained SVR. All patients who obtained SVR experienced RVR. Only one patient (HCV genotype 3) with RVR relapsed after the interruption of antiviral therapy at the 16th week due to variceal bleeding.

Six patients (three nonresponders, two relapsers, and one sustained responder) were transplanted between 7th and 40th month after the end of antiviral therapy. Six patients died between 3rd and 37th month after the end of antiviral therapy. Four patients are awaiting LT. Two patients are under evaluation for listening. Three patients refused LT.

DISCUSSION

Available data about IFN and RBV treatment of HCV infection in severely decompensated liver cirrhosis show a low rate of virologic response in front of many life-threatening drug-induced adverse events [6-12]. However, HCV clearance in decompensated cirrhotics may halt disease progression, delaying or avoiding the need for LT, and may reduce or eliminate the risk of recurrent HCV infection in the transplanted liver, improving graft and patient survival [2].

The use of PEG-IFN may ameliorate virologic response, improving the risk-to-benefit ratio of antiviral therapy. In our study, standard PEG-IFN and RBV combination therapy in HCV-infected liver cirrhotics awaiting LT produced significant side effects in all patients and severe life-threatening adverse events in about 40.0% of them. The rate of SVR was very low (19.0%). RVR and HCV genotype 2 were the most strong predictors of SVR. None of subjects infected by HCV genotype 1 obtained SVR. Such a dismal result may be ascribed to the large proportion of patients forced to have prolonged dose reduction or treatment withdrawal by adverse events. The better result obtained in patients infected by HCV genotype 2 was probably due to the fact that even a suboptimal treatment can eradicate this genotype from the serum.

CONCLUSION

The risk-to-benefit ratio is strongly against treatment with PEG-IFN and RBV of severely decompensated cirrhotics infected by HCV genotype 1. In contrast, antiviral therapy is probably beneficial in HCV genotype 2-infected subjects, due to an expected SVR rate of about 50%. However, one must carefully consider the high risk for severe adverse events.

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