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PEGYLATED INTERFERON AND RIBAVIRIN FOR TREATMENT OF RECURRENT HEPATITIS C AFTER LIVER TRANSPLANTATION: a single-liver transplant center experience in Brazil

José Huygens Parente **GARCIA**[1], Antônio Haroldo de **ARAÚJO FILHO**[2], Lucia Libanez Bessa Campelo **BRAGA**[3], Cyntia Ferreira Gomes **VIANA**[2], Tarciso Daniel Santos **ROCHA**[2] and Karla Brandão **PEREIRA**[2]

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ABSTRACT - ***Background*** - Treatment of hepatitis C virus infection in post-transplantation patients is a challenge due to poor tolerance and low success rates. ***Objective*** - To determine the response rate to pegylated interferon and ribavirin in post-liver transplant patients with hepatitis C recurrence. ***Methods*** - Between 18 May 2002 and 18 December 2011, 601 patients underwent liver transplantation at our service (Hospital Universitário Walter Cantídio, University of Ceará), 176 (29.2%) of whom were hepatitis C virus positive. Forty received antiviral therapy and were included in this cohort study. Twenty-eight (70%) completed the treatment protocol, which consisted of pegylated interferon and ribavirin for 48 weeks. ***Results*** - The sustained virological response rate was 55% according to intention-to-treat analysis. Recipient age and exposure to antiviral drugs prior to liver transplantation were associated with sustained virological response in the multivariate analysis. Patients were followed for 57 months on the average. Survival at 1 and 5 years was 100% in responders, versus 100% and 78%, respectively, in non-responders. ***Conclusion*** - Sustained virological response rates were satisfactory in our series of liver transplantation patients, and decreased with increasing recipient age. Non-exposure to antiviral drugs prior to liver transplantation was positively associated with sustained virological response. The overall survival of responders and non-responders was similar.

HEADINGS - Chronic hepatitis C. Antiviral agents. Liver transplantation. Sustained virological response.

INTRODUCTION

It is estimated that approximately 2.35% of the world population is chronically infected with hepatitis C virus (HCV)[14]. HCV infection is one of the main causes of end-stage liver disease. In Europe and in the United States, HCV-related cirrhosis is currently the leading indication for liver transplantation[16, 22].

As a consequence of the recurrence of hepatitis C infection, survival is shorter in HCV-infected grafts and patients than in non-HCV-infected patients[9, 17], and retransplantation may be the only option in severe cases[6]. Preventive strategies include post- liver transplantation (LT) eradication of HVC[5]. Viral clearance is associated with better long-term outcomes, particularly in patients who achieve sustained virological response[18].

The most widely used regimen is the association of pegylated interferon (PEG-INF) and ribavirin (RBV) for 48 weeks[4, 11]. However, treating this patient population is no easy task: sustained virological response (SVR) rates are far from desirable, side effects are numerous, and the incidence of antiviral drug discontinuation is considerable[4, 8]. The addition of protease inhibitors may improve success rates. Telaprevir and boceprevir, the two first protease inhibitors approved by the food and drug administration (FDA), are indicated for genotype 1 infection, but

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[1]Departamento de Cirurgia de Fortaleza, Universidade Federal do Ceará, Fortaleza, CE; [2]Hospital Universitário Walter Cantídio, Fortaleza, CE; [3]Departamento de Medicina Interna, Universidade Federal do Ceará, Fortaleza, CE. Brasil.
Correspondence: Antônio Haroldo de Araújo Filho. Rua Capitão Francisco Pedro, 1290. Rodolfo Teófilo - CEP: 60430-370 - Fortaleza, CE, Brasil. E-mail: haroldoaf@hotmail.com

their use in LT patients is limited by potential interactions with calcineurina inhibitors[13]. More recently, news drugs have been approved for the treatment of hepatitis C, as sofosbuvir, a potent inhibitor of HCV NS5B polymerase[15]. Thus, large well-designed prospective studies are required to develop safer and more efficacious drugs and improve the management of LT patients with recurrent hepatitis C infection. This study shows the experience in the treatment of recurrent hepatitis C in a national referral center for liver transplantation.

METHODS

This was a descriptive and analytical observational cohort study. Between18 May 2002 and 18 December 2011, 601 patients underwent orthotopic liver transplantation for end-stage liver disease at our service, 176 of whom had HCV-related disease as indication for LT.

At our institution, HCV RNA-positive post-LT patients are submitted to protocol liver biopsies once a year or when clinically indicated. HCV recurrence is diagnosed histologically, with activity and fibrosis stage scored according to METAVIR.

In this study, patients were eligible for treatment if positive for serum HCV RNA and if recurrence (fibrosis stage ≥1 or activity grade ≥2) was detected on histology. Patients with the following findings were excluded: baseline platelet count <30.000 cells/mm^3, baseline neutrophil count <1000 cells/mm^3, decompensated liver disease, evidence of acute cellular rejection within 3 months of starting therapy, and history of or ongoing severe psychiatric disorders.

The antiviral treatment regimen consisted of 180 mcg PEG-INF (Pegasys, Roche, Basel, Switzerland) once a week plus 1000 mg RBV (Rebetol, Schering-Plough, Brazil) a day for 48 weeks, regardless of genotype and whenever possible. Adjustments of the initial doses were permitted according to clinical status.

After starting treatment, patients were followed weekly during the first month to evaluate side effects and make dosage adjustments, then at intervals ranging from one to four weeks.

Following standard criteria, the doses of PEG-INF and RBV were adjusted during therapy in case of significant cytopenia. Patients were started on erythropoetin (40.000 UI/week) when hemoglobin levels reached ≤ 10g/dL. Red blood cell transfusion was indicated when hemoglobin levels were <6g/dL or whenever considered appropriate by the hepatologist in charge. Granulocyte colony-stimulating factor (GCSF) was administered when the neutrophil count was below 750/mm^3.

HCV-RNA was measured before initiating therapy and at weeks 12, 48 and 72. The primary endpoint was sustained virological response defined as undetectable HCV-RNA in the serum at week 72. On-treatment response was early virological response (EVR) defined as undetectable HCV-RNA or a >2log10 decrease of the viral load in serum at week 12, and end-of-treatment response (EOTR) defined as undetectable HCV-RNA in serum at the end of the treatment. Biochemical response was defined as the normalization of serum alanine aminotransferase (ALT) levels.

At our service, standard immunosuppression is induced with tacrolimus plus corticosteroids, with the addition of mycophenolate mofetil in case of renal impairment (serum creatinine level >1.5mg/dL). Corticosteroid therapy was discontinued within4 months after surgery. During antiviral treatment all patients were kept on their usual maintenance immunosuppression regimen. In patients with biopsy-proven acute cellular rejection, antiviral treatment was stopped and immunosuppression therapy administered according to institutional protocol.

Survival was defined as the time between study entry (start of antiviral treatment) and the endpoint (death) or end of the observation period (September 2013).

The results were expressed as mean or median values. Differences between variables were analyzed with Fisher's test, Student's *t* test, the Mann-Whitney test or Pearson's Chi-Square test, as appropriate. Factors potentially associated with SVR were submitted to univariate analysis followed by multivariate logistic regression using a forward procedure. The level of statistical significance was set at 5% (P<0.05). Patient survival was calculated with the Kaplan-Meier method and analyzed with the log-rank test. All statistical analyses were performed with the software SPSS, version 17.0.

RESULTS

Baseline patient data

Forty patients were included in the study and started on antiviral treatment for recurrent HCV infection. At the time of transplantation, the mean age was 53.33 years (range 42-68), most patients (n=32) were male, and the mean time elapsed between LT and onset of antiviral therapy was 22.58 months (range 4-43). Eight (20%) patients had been treated with PEG-INF and RBV prior to transplantation.

Genotype 1 was detected in 26 (65%) patients, and the median serum HCV-RNA level was 2,299,587 UI/mL.

Baseline immunosuppression consisted of tacrolimus monotherapy (n=30), tacrolimus plus mycophenolate mofetil (n=9) or cyclosporine plus mycophenolate mofetil (n=1). All patients received deceased donor liver allografts aged 42.88 years (range: 21-72) on the average. Two patients received both liver and kidney grafts. (Table 1).

Virological response

Patients were evaluated for EVR, EOTR and SVR according to the intention-to-treat principle. At week 12, 38 patients were tested: HCV-RNA serum levels were undetectable or had decreased >2log in 30 patients, accounting for an EVR rate of 75%. At the end of treatment, 33 patients were tested: HCV-RNA serum levels were undetectable in 23, corresponding to an EOTR rate of 57%. Six months after treatment, 32 patients were tested: HCV-RNA levels remained undetectable in 22 patients, reflecting a SVR rate of 55%.

TABLE 1. Characteristics of 40 treated patients at baseline

Gender	
Male (%)	32 (80%)
Female (%)	8 (20%)
Mean recipient age (years)	53.33 (42-68)
Mean donor age (years)	42.88 (21-72)
Prior INF/RBV use (%)	8 (20%)
HCV-RNA load	2.3 X 10^6
Mean time from LT to AT (months)	22.58 (4-43)
HCV genotype	
1(%)	26 (65%)
3 (%)	14 (35%)
METAVIR	
A1	7 (17.5%)
A2	18 (45%)
A3	15 (37.5%)
F0	12 (30%)
F1	17 (42.5%)
F2	7 (17.5%)
F3	3 (7.5%)
F4	1 (2.5%)
Immunosuppression	
Tacrolimus	30 (75%)
Tacrolimus + mycophenolate	9 (22.5%)
Cyclosporine + mycophenolate	1 (2.5%)

INF: interferon; RBV: Ribavirin; HCV: hepatitis C virus; LT: liver transplantation; AT: antiviral therapy.

Tolerability

28 (70%) patients completed treatment. The remaining 12 (30%) patients discontinued treatment for a number of reasons: clinical decompensation due to disease progression (n=2), severe asthenia (n=1), depression (n=1), chronic cellular rejection (n=1), generalized rash (n=1), cholestasis (n=1), retinal changes (n=1), rising aminotransferase levels (n=1),severe infection (visceral leishmaniasis) (n=1), withdrawal from treatment (n=1) and death of undetermined cause (n=1).

Chronic cellular rejection was observed during antiviral therapy in one (2.5%) patient who had discontinued immunosuppression therapy without consulting his physician. Antiviral treatment was stopped and the patient eventually progressed to infection and death, probably precipitated by the resumption of immunosuppression therapy in an attempt to save the graft.

As expected, all patients experienced adverse events typical of the combined use of PEG-INF and RBV, such as appetite loss, weight loss, malaise and fever. Although these events had an impact on the patient's quality of life during treatment, they were generally mild and did not compromise patient compliance.

The dose of RBV was reduced in 27 (67%) patients, erythropoetin was administered to 26 (65%) patients, and 12 (30%) patients received red blood cell transfusion. GCSF was required in 19 (47.5%) patients. In 9 (22.5%) patients the PEG-INF dose was reduced.

Biochemical response was evaluated in 32 patients, 25 (78.12%) of whom completed therapy with normal ALT levels.

Factors associated with SVR

In the univariate analysis the factors analyzed were gender, donor and recipient age, genotype, baseline HCV RNA load, baseline histology (METAVIR), exposure to antiviral drugs prior to LT, time from LT to start of antiviral therapy, use of erythropoietin, use of GCSF and red blood cell transfusion. Only exposure to antiviral drugs prior to LT was significantly associated with SVR (P=0.0019). (Table 2).

In the multivariate analysis, the analyzed factors included exposure to antiviral drugs prior to LT, recipient age and use of GCSF. The first two were significantly associated with SVR, showing a lower chance of SVR those patients with older age and who were exposed, before the transplant, to antiviral treatment for hepatitis C. (Table 3).

TABLE 2. Univariate analysis of parameters associated with sustained virological response

Factors evaluated	SVR	non-SVR	*P*
Gender (Male/Female)	19/3	8/2	0.637
Recipient age (years)	51.36	56.20	0.183
Donor age (years)	39.86	39.30	0.928
Pior INF/RBV use (Y/N)	2/20	5/5	0.0019
HCV RNA load (post-LT)	15.22	11.56	0.515
Time from LT to AT (months)	22.95	20.00	0.469
Genotype (1/3)	12/10	8/2	0.248
Erythropoetin use (Y/N)	15/7	8/2	0.681
GCSF use (Y/N)	9/13	7/3	0.127
Red blood cell transfusion (Y/N)	5/17	4/6	0.407
Baseline histology (activity)			0.688
A1	5	1	
A2	7	5	
A3	10	4	
Baseline histology (fibrosis)			0.627
F0-1	18	8	
F2-4	4	2	

SVR: sustained virological response; INF: interferon; RBV: Ribavirin; HCV: hepatitis C virus; LT: liver transplantation; AT: antiviral therapy; GCSF: granulocyte colony-stimulating factor; GCSF: Granulocyte colony-stimulating factor.

TABLE 3. Multivariate analysis of parameters associated with sustained virological response

Factors evaluated	SE	Wald	*P*	OR	95%CI
GCSF use	1.284	0.363	0.547	2.16	0.17-26.85
Recipient age	0.125	4.147	0.042	1.29	1.01-1.64
Prior PEGINF/ RBV use	1.695	5.249	0.022	48.52	1.75-1343.94

PEGINF: pegylated-interferon, RBV: Ribavirin; OR: odds ratio; CI: confidence interval; Wald: wald test; SE: standard error; GCSF: granulocyte colony-stimulating factor

Patient survival

The median duration of follow-up was 57 months (range: 18-110). Eleven patients died during follow-up (8 during treatment; 3 after treatment). Only two of these died due to HCV disease progression while receiving treatment. The other six died of recurrence of hepatocellular carcinoma, sepsis, portal vein thrombosis/hepatic insufficiency, Budd Chiari syndrome, visceral leishmaniasis and undetermined causes. Only one of the three patients who died after the treatment period achieved SVR, and died after 5 years of follow-up. The causes of death were recurrence of hepatocellular carcinoma (n=1) and lymphoproliferative disease (n=2).

The average 1- and 5-year survival calculated with the Kaplan-Meier method was 100% in responders, and 100% and 78% in non-responders (log-rank test, P=0.308), showing improved survival in responders, but not statistically significant (Figure 1).

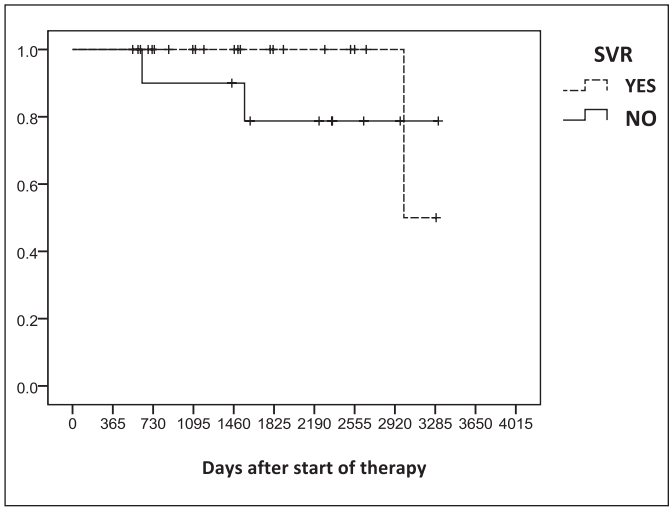

FIGURE 1. Kaplan-Meier analysis showing survival in patients with and without sustained virological response (SVR) (n=32) after start of antiviral therapy. 1-, 3- and 5-year patient survival was 100% in patients achieving SVR, versus 100%, 90% and 78%, respectively, in non-responders.

DISCUSSION

Antiviral therapy can reduce the impact of recurrence HCV infection on the graft and on patient survival[19]. The present study describes antiviral treatment of recurrent HCV infection in 40 liver transplantation patients at a Brazilian service, 22 of whom achieved sustained virological response, representing a treatment success rate of 55%.

In our knowledge, this is the largest series of patients treated for hepatitis C recurrence post-liver transplant published in Brazil.

In Brazil, Balbi et al.[2] studied 25 patients who underwent antiviral therapy for recurrent hepatitis C found an SVR rate of 28%, using various therapeutic regimens. In this series, some patients used schemes with monotherapy, which classically decreased the chances of SVR.

In two large systematic reviews[4, 11], the average SVR rate was below 32%. In one of them, Berenguer[4], covering 19 studies with over 600 patients, the average SVR rate was 30.2% (range: 8%-50%). Unlike our study, in which only patients with histologically confirmed recurrent HCV infection were included, the two reviews included studies with patients receiving preemptive treatment, which classically yields lower SVR rates.

In another review from 2012, Akamatsu and Sugawara[1] included only studies with patients receiving antiviral treatment for recurrent HCV infection after liver transplantation (as in the present study) and found an average SVR rate of 33%.

Few previous studies, such as Schimidt et al.[20], have found recipient age to significantly impact SVR rates. In our study, responders were younger on the average (51.36 years) than non-responders (56.20 years). The difference was not significant in the univariate analysis, but in the multivariate analysis recipient age was negatively and significantly associated with SVR. Among several other factors, this finding may influence the decision of whether to submit LT patients to antiviral therapy.

Exposure to antiviral drugs prior to LT is by some considered predictive of SVR[3, 8, 23].According to Wang et al.[23], the absence of antiviral therapy prior to transplantation was the only factor significantly associated with SVR in both the univariate and multivariate analysis. In the present study, 80% of the patients not exposed to antiviral drugs prior to LT achieved SVR. The corresponding figure for previously exposed patients was 28%. In other words, non-exposure to previous antiviral therapy was positively associated with the achievement of SVR. The difference was significant in both the univariate and multivariate analysis. If previous exposure to IFN and RBV in fact reduces chances of achieving SVR in post-LT patients, perhaps the indication of antiviral therapy (with itswell-known side effects and low response rates) to severe patients awaiting transplantation should be reconsidered. Importantly, the fact that non-responders exposed to antiviral drugs prior to LT may be resistant to INF and RBV and therefore achieve low SVR rates potentially introduces a bias into the evaluation.

The drugs currently available to treat recurrent HCV infection often induce cytopenia, making it necessary to reduce the dosage and, consequently, making it more difficult to achieve SVR. On the other, growth factors may be administered in this patient population to make antiviral therapy more effective[10]. In a study by Jain et al.[12] involving 60 post-LT patients, 50% received GCSF while 43.3% received erythropoietin. In our series, GCSF and erythropoetin were used in 47.5% and 65%, respectively, while 30% received blood transfusion. Although our analysis of the factors associated with SVR failed to detect significant differences between the use and non-use of GCSF and blood transfusion, we believe these strategies contributed to maintaining effective doses longer and, consequently, achieving higher SVR rates. The study was limited by our failure to calculate the total dose of RBV administered, but

the high incidence of erythropoetin use and blood transfusion during treatment reflect our efforts to maintain RBV doses as close to optimal as possible.

In the present study, the level of fibrosis was not related to the possibility of SVR. This fact has been shown by other authors, as reported in a systematic review published by Berenguer[4], in which the relationship between SVR and fibrosis was evaluated at 10 studies and only 2 showed the intensity of fibrosis as a predictor of response to antiviral treatment. Nevertheless, wherever possible we try to start the treatment of recurrent hepatitis C earlier, still believing in a better result, which explains the number of patients F0 and F1 in this sample.

Recently, new drugs have been released for treatment of hepatitis C. Sofosbuvir, semiprevir and daclatasvir are among the most described and included in the therapeutic arsenal in the international guidelines. Unfortunatly, published efficacy data are limited in post-liver transplant context yet. Recently, Charlton et al.,reported that the combination of sofosbuvir and RBV yielded an SVR 12 weeks after the end of therapy of 70% in treatment of patients after liver transplant[7].

In our series, survival was slightly but not significantly longer in patients achieving SVR. Selzner et al.[21] followed 172 post-LT patients submitted to treatment for HCV infection and observed an SVR rate of 50% and a 5-year survival rate of 96% among responders compared to 69% in non-responders, a statistically significant difference. The absence of a significant difference in the present study may be explained by the small sample size. Unfortunately, this study also shows a not negligible mortality of patients during treatment, showing how difficult is the management of the treatment of these patients, already immunosuppressed and most often with unsatisfactory clinical condition before starting treatment.

In conclusion, we obtained satisfactory results in this study using standard therapy (PEG-INF +RBV) to treat recurrent HCV infection in post-LT patients. A comparison between the SVR rates obtained with new drugs and standard therapy is necessary.

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Authors' contributions

Garcia JHP and Braga LLBC: designed research; Araújo Filho AH: performed research; Gomes CVF, Rocha TD and Pereira KB: collected data.

Garcia JHP, Araújo Filho AH, Braga LLBC, Viana CFG, Rocha TDS, Pereira KB. Interferon peguilado e ribavirina no tratamento da recorrência da hepatite C após transplante hepático: experiência de um centro de transplante hepático no Brasil. Arq Gastroenterol. 2015,52(3):216-21.

RESUMO - ***Contexto*** - O tratamento da infecção do vírus da hepatite C pós-transplante é um desafio devido à baixa tolerância dos pacientes e às baixas taxas de resposta. ***Objetivo*** - Determinar a taxa de resposta ao interferon peguilado e ribavirina no tratamento da recorrência da hepatite C após transplante de fígado. ***Métodos*** - Entre 18 de maio de 2002 e 18 de dezembro de 2011, 601 pacientes realizaram transplante hepático no Hospital Universitário Walter Cantídio, 176 (29,2%) desses eram infectados pelo vírus da hepatite C. Quarenta pacientes receberam terapia antiviral e foram incluídos nesse estudo. Vinte e sete (70%) completaram o protocolo de tratamento, que consistia de interferon peguilado e ribavirina por 48 semanas. ***Resultados*** - A taxa de resposta virológica sustentada foi de 55% de acordo com a análise por intenção de tratar. A idade dos receptores e a exposição prévia ao transplante de antivirais foram fatores associados com a resposta virológica sustentada na análise multivariada. Pacientes foram acompanhados por 57 meses em média. A sobrevida em 1 e 5 anos foi de 100% em respondedores, enquanto que em não respondedores foi de 100% e 78% respectivamente. ***Conclusão*** - A resposta virológica sustentada foi satisfatória na série de pacientes transplantados e diminuiu com o aumento da idade. A não exposição prévia ao transplante a drogas antivirais teve impacto positivo na chance de resposta virológica sustentada. A sobrevida global foi similar em respondedores e não respondedores.

DESCRITORES - Hepatite C crônica. Antivirais. Transplante de fígado. Resposta virológica sustentada.

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