Pegylated Interferon α-2a and Ribavirin Combination Therapy in HCV Liver Transplant Recipients. Experience of 7 Cases

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Abstract

Background: Hepatitis C virus (HCV) related cirrhosis represents the leading indication for liver transplantation (LT) worldwide and HCV reinfection is the rule among transplant recipients. Combination therapy with interferon and ribavirin is the treatment of choice for established recurrent hepatitis C. **Aim:** To evaluate the efficacy and safety of the combination of pegylated interferon α-2a and ribavirin in LT recipients with histological recurrence of hepatitis C. **Methods**: Seven LT recipients with chronic hepatitis C recurrence were treated with peginterferon α-2a with an initial intended dose of 180 μg/week and an intended dose of ribavirin 800-1000 mg/day for at least 12 months and followed-up for at least 24 weeks. **Results:** Early virological response rate was 57.1%. Three patients (42.8%) had end of treatment virological response and all had also sustained viral response (SVR). Five patients had end of treatment biological response, out of which 4 had also sustained biochemical response. Three patients had both SVR and sustained biochemical response. Four patients had end of treatment histological response, out of which 3 patients had also SVR. Cytopenia was the most common adverse event: anemia (57.1%), leucopenia/neutropenia (71.4%), thrombocytopenia (42.8%). **Conclusion:** Combination of pegylated interferon and ribavirin can be safely and successfully used in liver transplant recipients.

Key words

Liver transplantation - recurrent hepatitis C - antiviral therapy

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Abbreviations

HCV: hepatitis C virus, LT: liver transplantation, SVR: sustained virological response, PEG-IFN: pegylated interferon, PCR: polymerase chain reaction, HBV: hepatitis B virus, RBV: ribavirin, G-CSF: granulocyte-colony stimulating factor, EVR: early virological response, EOTR: end of treatment virological response, ALT: alanin aminotransferase, AST: aspartat aminotransferase, GGT: gammaglutamyl transpeptidase , ALP: alkaline phosphatase, HCC: hepatocellular carcinoma, MELD: Model for end stage liver disease.

Introduction

Hepatitis C virus (HCV) related cirrhosis represents the most common indication for liver transplantation (LT) worldwide. Unfortunately, HCV infection invariably recurs after LT [1]. At least 50% of recipients develop histological evidence of recurrent disease within 1 year posttransplant [2] and the progression of fibrosis occurs at a 1.4 times accelerated rate compared to the nontransplant HCV infected population [3]. The estimated allograft cirrhosis reaches 10-30% at 5 years of follow-up [4], leading to increasing retransplantation in HCV recipients [5], with significantly poorer outcomes compared to retransplanted patients without HCV infection [6].

Currently available antiviral regimens have established indications and are highly effective in immunocompetent HCV patients with sustained virological response (SVR) rates of over 50% in most series [7-9], which seems to be long-lasting and associated with long-term benefits [10, 11]. In the transplant setting, antiviral therapy has become also the mainstay of managing recurrent HCV disease. However, there is no consensus on optimal timing for initiation of antiviral therapy, duration of treatment or dose regimen for patients with recurrent hepatitis C. Most studies have focused on treating liver transplant recipients with evidence of histological disease. The sustained virological response (SVR) rates are much lower even when the gold standard of antiviral therapy is used. In an intention to treat analysis [12], the reported median end of treatment virological response (EOTR) was 29.5% (0-75%) and the median SVR was

20.5% (0-43%). Overall, treatment is poorly tolerated with a requirement of dose reductions and drug discontinuations in up to 50% of patients [13]. Cytopenias are the most frequent limiting factor in achieving the full dose of interferon or ribavirin (RBV) and the use of growth factors is not an established approach in all centers.

The aim of this study was to evaluate the efficacy and safety of the combination of pegylated interferon (PEG-IFN) α-2a and RBV in liver transplant recipients with a histological recurrence of hepatitis C.

Material and methods

Study population

The study population comprised 7 liver transplant recipients with chronic hepatitis C recurrence. The antiviral therapy was initiated between January 2003 – November 2006. Patients were eligible for antiviral therapy if they fulfilled the following inclusion criteria: (1) positive HCV RNA (quantitative HCV RNA: Abbott Real TimeTM HCV RNA assay, Abbott Diagnostics, lower detection limit 50 IU/mL); (2) histological evidence of recurrent HCV infection (Knodell histological activity index). Patients were excluded for any of the following reasons: white blood count < 3,000/mm3; neutrophils < 1,500/mm3; platelet count < 80,000/mm3; decompensated liver cirrhosis; hepatitis B virus or HIV coinfection; other concurrent causes of liver disease; alcohol abuse or drug dependence within the previous 6 months, as well as for all other exclusion criteria from antiviral therapy. All patients were treated with PEG-IFN α-2a (Pegasys®, Hoffmann-La Roche) with an initial intended dose of 180 μg/week and an intended dose of RBV (Copegus®, Hoffmann-La Roche) of 800-1000 mg/day for at least 12 months. All patients started therapy after the first 6 months post LT and were followed for at least 24 weeks post-treatment.

The patients had on-treatment complete blood count and liver function tests assessed weekly in the first 4 weeks, then every 2 or 4 weeks or whenever required.

RBV dose was reduced if hemoglobin levels decreased below 10 g/dL and discontinued if hemoglobin levels were <8.5 g/dL despite erythropoietin therapy. Erythropoietin was started in patients with hemoglobin levels below 9.5 g/dL. PEG-IFN dose was reduced to 135 μg/week for platelet counts between 50,000 – 65,000/mm3 and for leucocyte counts between 1,700 – 2,000/mm3 and 90 μg/week for platelet counts less than 50,000/mm3 and for leukocyte counts less than 1,700/mm3, when G-CSF was concomitantly administered (300μg/week). PEG-IFN was discontinued in cases of platelet counts <25,000/mm3 or white blood cell counts <1,000/mm3.

Thyroid-stimulating hormone and thyroxin levels were monitored every 12 weeks during treatment.

Quantitative HCV RNA was tested before therapy, at week 12, 24, at the end of therapy and at follow-up week 24. HCV RNA was measured also whenever clinically indicated (persistent elevated or increases of ALT during therapy).

Protocol biopsies were recommended at least every 1 to 2 years after LT. All patients underwent liver biopsies 1 to 3 months before starting therapy and at 6 months after the end of therapy when assessing SVR. The patients repeated a liver biopsy during antiviral therapy if they had worsening of liver biochemistries in order to exclude rejection or other etiologies.

Response assessment and treatment endpoints

Early virological response (EVR) was defined as at least $2\log_{10}$ drop or undetectable HCV RNA at week 12, after the start of therapy. EOTR was defined as undetectable viral load at the end of antiviral therapy. SVR was defined as undetectable serum HCV RNA 24 weeks after cessation of therapy. End of treatment biochemical response was defined as normalization of serum ALT activity at week 48 and sustained biochemical response as presence of normal ALT 24 weeks after end of therapy. End of treatment histological response was considered when a decrease of 2 or more points in the grading score in association with unchanged or improved fibrosis score was observed.

The following parameters were collected and analyzed:

- related to the recipient: age at LT, gender, presence of diabetes mellitus type 2, presence of posttransplant early biliary complications, administration of bolus corticosteroids for acute rejection episodes, type of immunosuppression, time to histologic diagnosis of recurrent hepatitis, stage of fibrosis, presence of steatosis, ALT, AST, GGT, ALP and bilirubin level before starting therapy;
- related to the virus: level of viremia before onset of therapy and during therapy;
- related to the donor: living or cadaveric donor, age and gender;
- related to the antiviral therapy: administration of pretransplant antiviral therapy, the need to decrease the doses, complete therapy regimen, adherence to the therapy.

Adherence to therapy was defined as the ability to achieve more than 80% of the recommended dose of either drug and more than 80% of the intended duration of therapy (80/80/80 rule) [14].

Safety and tolerability were assessed through monitoring of adverse events and laboratory abnormalities. Adverse events were graded as mild, moderate or severe when requiring stopping of therapy.

Results

Baseline features

Pre and peritransplant, as well as pre and posttreatment patient characteristics are shown in Tables I and II.

All patients had HCV genotype 1 infection and 3 patients had past exposure to HBV (negative HBs antigen, positive HBc antibodies, positive HBs antibodies with protective titres). Patients 4 and 5 were transplanted for hepatocellular carcinoma (HCC) and HCV liver cirrhosis; patient 4 had associated non-malignant portal vein thrombosis; both patients are HCC recurrence free 3 years after LT. All patients

Table I. Pretransplant and early posttransplant characteristics of the study patients

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age at LT (years)	47	38	54	45	51	47	40
Gender	F	M	F	M	M	F	M
Child-Pugh class	C	B	B	B	B	B	B
MELD score	17	20	15	12	15	17	14
Past HBV exposure	yes	no	no	yes	no	yes	no
Pre LT SBP	no	no	no	no	no	yes	no
Pre LT variceal bleeding	no	yes	no	no	no	yes	no
Pre LT HRS	yes	yes	no	no	no	no	no
Pre LT HE	no	no	no	no	yes	no	no
Number of acute rejection episodes	4	4	0	2	2	0	0
Post LT early biliary complication/cholestasis	no	yes	yes	yes	no	no	no

LT, liver transplant; MELD, Model for end stage liver disease; SBP, spontaneous bacterial peritonitis; HRS, hepato-renal syndrome; HE, hepatic encephalopathy

received deceased donor liver allograft and the median donor age was 26.7 (range 12-40 years).

The first 6 patients received initially double or triple immunosuppressive regimen tacrolimus or cyclosporine + prednisone (up to 3-6 months) + mycophenolate mofetil (3 to 12 months), allowing decrease in calcineurin inhibitors while as maintenance immunosuppression patients received tacrolimus or cyclosporine monotherapy. Patient 7 with combined liver–pancreatic islets transplantation had a completely steroid free immunosuppression regimen, receiving induction immunosuppression with tacrolimus, sirolimus and daclizumab, followed by maintenance therapy with tacrolimus and sirolimus. After 12 months, during antiviral therapy, the regimen was changed to tacrolimus and mycophenolate mofetil. Four patients experienced acute cellular rejection episodes. All were treated and responded to metilprednisolone 1000 mg for 3 days. None of the patients had a rejection episode within 3 months before initiation of antiviral therapy.

The patients were followed-up for a mean of 22.6 ± 6.7 months after the end of antiviral treatment.

Presentation of case series

Patient 1 received PEG-IFN α-2a 135μg/week and RBV 1000 mg/day. This patient needed to stop the therapy due to persistent marked neutropenia despite G-CSF use and due to increase of viral load after 12 weeks. There was also an increase of the ALT value concomitant with an increase of the necroinflammatory score to 9 on liver biopsy performed after 13 weeks of therapy. At 7 years after LT she has compensated recurrent HCV cirrhosis.

Patient 2 completed the intended treatment duration, but he had concomitant decrease of PEG-IFN α-2a to 135μg/week after the first 2 doses of 180μg/week and weekly use of G-CSF in the first 12 months. He had platelet counts between 50,000 and 65,000/mm3.

He had a decrease of viral load at 12 weeks but less than $2\log_{10}$ drop and undetectable HCV RNA at week 24, but positive viral load at the end of therapy. He had a very rapid decrease of ALT within the first month after starting the therapy (Fig. 1) and sustained biochemical response, but without SVR. Liver biopsy performed after 1 year of antiviral therapy showed progression of fibrosis score from 3 to 4 and only minimal decrease of necroinflammatory score from 9 to 7. Due to the good tolerance of PEG-IFN, the patient continued for another 24 months the monotherapy with 90μg/week PEG-IFNα-2a in order to prevent cirrhosis decompensation. Between month 12 and 36 he did not need to use G-CSF. During this treatment period he remained HCV RNA positive, but with normal ALT and with good liver function as he stays also now at 5 years after LT. It is to note that this patient had serological reactivation of cytomegalovirus infection during therapy who responded to ganciclovir therapy.

Patient 3 completed the one year intended treatment duration and had even prolonged therapy in order to maintain the good virologic and histologic response. She also managed to receive >80% of intended PEG-IFN and RBV dose, although she had to lower both PEG-IFN and RBV dose. The patient did not require G-CSF because she responded well to decrease of PEG-IFNα-2a to 135μg/week after the first 3 doses of 180μg/week and continued for the whole treatment duration. Anemia (hemoglobin level between 9.5-10 g/dL) was corrected only by decreasing RBV from 800 to 600 mg/day. The patient had sustained biochemical response and end of treatment histological response (with normal liver histology without inflammation or fibrosis).

Patient 4 had both SVR and sustained biochemical response, but he had persistent ALT levels >2 times upper normal value for 6 months after beginning of therapy despite undetectable viral load at week 12, followed by normalization of aminotransferases up to month 8 (Fig. 2). Due to this persistent hepatocytolisis at month 6 of antiviral therapy he underwent a liver biopsy which showed maintenance of fibrosis score (Knodell fibrosis 1), but significant decrease of

Table II. Patients characteristics at baseline and results of antiviral therapy

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Time LT - recurent hepatitis (months)	23.4	25.5	6.1	15.1	18.7	58.4	11.4
Necroinflammatory score (Knodell)	6	9	9	7	7	7	11
Fibrosis score (Knodell)	1	3	0	1	1	0	0
Steatosis grade	2	0	0	1	0	0	1
BMI (kg/m^2)	27.9	27.3	20.2	22.2	23.1	24.4	24.2
Baseline AST (IU/l)	129	214	117	74	108	61	180
Baseline ALT (IU/l)	143	93	323	132	123	82	167
Baseline ALP (IU/l)	127	214	64	75	130	42	89
Baseline GGT (IU/l)	154	88	89	32	100	17	75
Baseline bilirubin (mg/dl)	1	1.3	0.9	1.03	1.2	0.9	0.8
Baseline creatinine (mg/dl)	1	1.1	0.8	1.03	1.1	1.12	0.8
Baseline HCV RNA (IU/ml)	1,050,000	319,000	12,000,000	2,830,000	3,660,000	974,000	36,000,000
EVR	no	no	yes	yes	yes	yes	no
EOTR	no	no	yes	yes	yes	no	no
SVR	no	no	yes	yes	yes	no	no
Calcineurin inhibitor type	CSA	TAC	TAC	TAC	CSA	TAC	TAC
Antiviral therapy duration (months)	3.25	36	19	19	17	3.75	5.75

BMI, body mass index; CSA, cyclosporine; TAC, tacrolimus. Normal range AST = 15-37 IU/L; ALT = 30-65 IU/L; ALP = 50-136 IU/L; GGT = 5-85 IU/L; bilirubin = 0-1 mg/dL; creatinine = 0.6-1.3 mg/dL

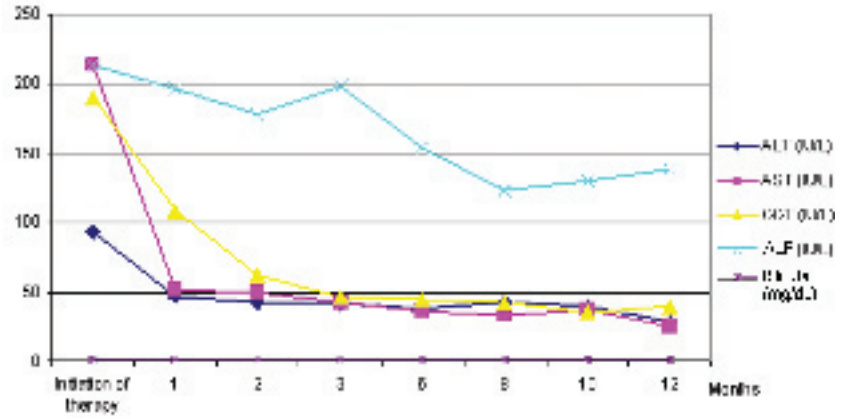

Fig 1. Serial changes in liver chemistries during antiviral therapy in the patient with progressive liver disease and lack of virological response

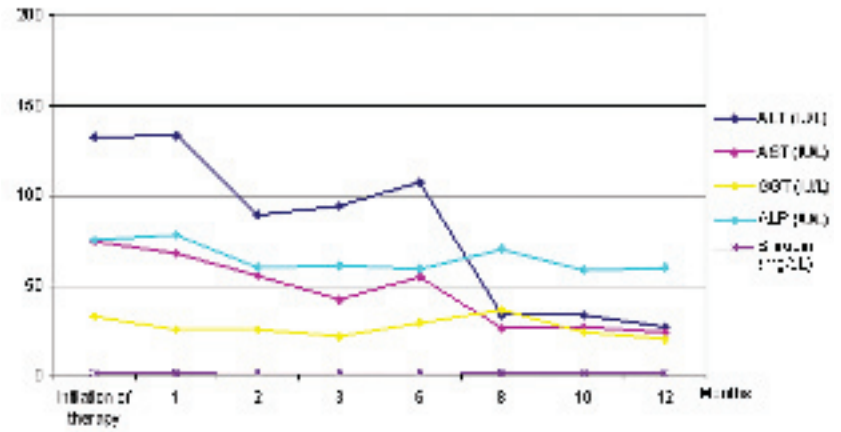

Fig 2. Serial changes in liver chemistries during antiviral therapy in the patient with sustained virological and histological response

the necroinflammatory score (Knodell histological activity index 2). After 12 months of therapy a new liver biopsy was performed indicating only mild portal inflammation and no fibrosis. Regarding the safety of antiviral therapy, the patient had mild anemia that required only transient decrease of RBV; thrombocytopenia was mild, not requiring any dose adjustment.

Patient 5 had both end of treatment and sustained biochemical response. Liver biopsy performed at the end of antiviral therapy showed mild portal and lobular hepatitis and absence of fibrosis. During antiviral therapy he experienced anemia requiring decrease of RBV and concomitant use of erythropoietin, neutropenia and thrombocytopenia. The use of erythropoietin permitted to increase again the RBV to the initial dosage. Patients 4 and 5 had only transient decrease of PEG-IFN to 135 or 90 μg/week for 2-4 weeks due to neutropenia, being able to return to the initial 180 μg/week after concomitant weekly administration of G-CSF.

Patient 6 received PEG-IFN 180 μg/week for the whole period. The initial dose of RBV was 1000 mg/day, but due to anemia, it required reduction to 800 mg/day and also concomitant use of erythropoietin. The patient wanted to stop the antiviral therapy despite presence of EVR (>2log10 decrease in HCV RNA level after 12 weeks) due to nausea and vomiting and marked fatigue.

Patient 7 associated pretransplant diabetes mellitus and he received concomitant pancreatic islets transplantation. Normalization of blood glucose homeostasis and a significant reduction of exogenous insulin requirements (64 IU/day pretransplant to 14 IU/day one year after transplant) were induced by islets transplantation. He received pretransplant antiviral therapy (low dose PEG-IFN α-2a and RBV) while on the waiting list for 14 months, well tolerated, with biochemical response, but without virological response and HCV RNA level at LT was 1,220,000 IU/mL. The patient had recurrent hepatitis C within less than 1 year after LT. He discontinued therapy after 23 weeks due to worsening of liver biochemistries associated with increase in fibrosis from F0 to F2 and lack of viral response. After initial improvement of transaminases and decrease of viral load from 36,000,000 IU/mL to 1,500,000 IU/mL at week 12, the patient experienced marked increase of ALT (up to 8-9 times normal value), increase in cholestatic enzymes (GGT and ALP) and mild increase of viremia (2,850,000 IU/mL). The liver biopsy performed at this moment showed marked portal, periportal and lobular hepatitis and progression of fibrosis (septal fibrosis), perisinusoidal collagenisation and hepatic steatosis grade 1. After discontinuation of antiviral therapy the patient developed acute hepatic insufficiency and died within 2 months thereafter. The liver histology obtained at necropsy showed lesions due to cholestatic fibrosing hepatitis and veno-occlusive disease (Figs. 3 and 4).

Biochemical, virologic and histological responses

EVR rate was 57.1%. Three patients (42.8%) had EOTR and all of them had also SVR. Five patients had end of treatment biochemical response, out of which 4 had also normal ALT 6 months after finishing the therapy.

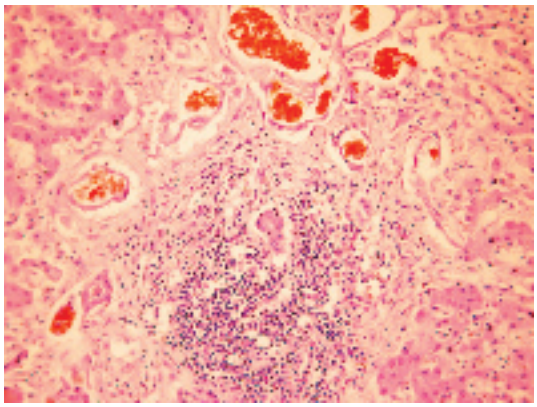

Fig 3. Portal lymphocyte inflammation with lymphoid aggregates, interface hepatitis, and marked cholestasis (biliary plugs) (HE, 400x).

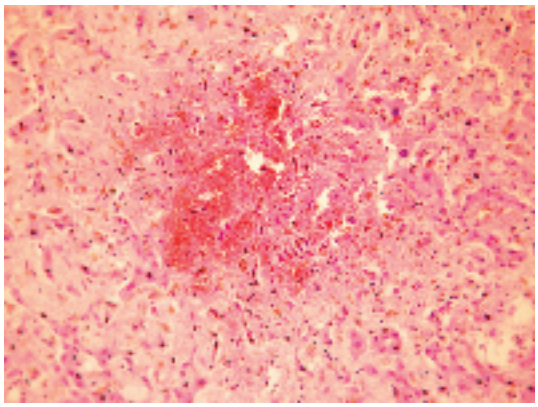

Fig 4. Congestive centrolobular area, centrolobular hemorrhage, necrosis and atrophy of the hepatocytes from centro-and mediolobular areas (HE, 400x).

Three patients had both SVR and sustained biochemical response. Four patients had end of treatment histological response, out of which 3 patients had also SVR. In patients with histological response 3 patients received a liver from a female donor compared to none in patients without histological response. Also the donor mean age was 25.7 ± 9.9 years in patients with histological response compared to 32.3 ± 17.7 years. All patients with histological response were fibrosis stage 0 or 1 at the beginning of therapy.

Safety: side effects, dose reduction and premature withdrawal

Cytopenias were the most common adverse event that necessitated dose adjustments, treatment discontinuation and/or use of growth factors.

Anemia was present in 4 patients (57.1%), all of them with histological response and in all the 3 patients with SVR. Leucopenia and neutropenia were observed in 5 patients (71.4%). Three patients (42.8%) had thrombocytopenia. No patient had platelet counts <50,000/mm3 and none experienced any bleeding.

The most frequent side effect experienced by all the patients was fatigue. Influenza-like symptoms were seen in 4 patients. Nausea and vomiting were experienced by one patient. Mild weight loss (up to 5kg/12 months) was reported in 3 patients. Dermatological side effects did not occurred

in any patient. Four patients developed infections during the course of treatment. Patient 2 had urinary infection managed with antibiotic therapy. Patients 4 and 5 reported acute respiratory tract infections. Patient 7 had maxillary sinusitis with systemic manifestations (high fever, chills, malaise). He had a temporary one month cessation of antiviral therapy. He was not neutropenic during the therapy or at the time of diagnosis of infection. No patient experienced depression requiring antidepressants. Irritability and sleep disturbances were encountered in one patient. Three patients (42.8%) discontinued prematurely the antiviral therapy. No patient developed acute or chronic rejection during interferon therapy.

Discussion

Antiviral therapy for recurrent hepatitis C after LT is increasingly used in order to slow down the increasing rates of cirrhosis and graft loss from recurrent hepatitis C beyond the first 5 years after LT (1, 15, 16). Anyway, there is a diminished efficacy of antiviral regimens after LT and the potential responsible factors are: higher viral loads, non-response to antiviral therapy prior to LT, influence of immunosuppression on drug efficacy and tolerance, predominance of genotype 1 infection, frequent dose reduction due to cytopenia or renal dysfunction and high rates of discontinuation. Also the treatment is not standardized and its best initiating time is not yet established.

A recent review [17] suggests that 24% of HCV transplant recipients treated with standard interferon/RBV and 27% of patients with PEG-IFN/RBV obtain SVR. There are 7 published studies with >20 patients that evaluated the efficacy of PEG-IFN and RBV in the treatment of recurrent HCV after LT and SVR in these studies [18-24] ranged between 31-45%. The SVR obtained in our 7 patients is also within this range – 42.8%. The present paper is the first one reporting SVR in our transplanted patients. The main limitation of this study is the small number of patients and the impossibility to find predictive factors for SVR. Data from previous studies [25, 26] suggest that sustained viral eradication leads in most cases to histologic improvement which is in fact the final target of antiviral therapy. HCV eradication has a positive impact on graft survival. This was also confirmed in our patients. This is the reason why it is important to find factors associated with SVR after combination antiviral therapy in post-LT patients, factors that are not well established yet. In one recent study [27], SVR was higher in patients with mild disease (around 50%), whereas it was significantly lower (15-20%) in patients with severe recurrent hepatitis C. Similar to non-transplant setting, EVR was proved to be predictive of SVR [18, 23, 28]. However, the early stopping rule is not yet applicable for the transplanted patients. In our study, 3 patients with EVR and complete antiviral regimen had also SVR. All patients with SVR from our study had anemia, in concordance to the recent study of Sharma et al [28], who proved that anemia and use of erythropoietin were associated with SVR. It should be pointed out that anemia and use of erythropoietin was related to the higher cumulative dose of RBV. This is in line with the higher cumulative dose of PEG-IFN and RBV that were associated with SVR.

In our study, all the three patients with SVR had longer treatment periods (>48 weeks), because the optimal duration of therapy is still unclear. It was proved that in the presence of immunosuppression longer treatment periods may reduce the risk of relapse in those achieving EOTR. In concordance with the study [29] by Yedibela et al (33% of patients free from HCV after a mean follow-up of nearly 3 years), we report long-term results (42.8% after a mean follow-up of nearly 2 years).

Besides the evaluation of virological response, liver histology has been extensively used as a surrogate endpoint of treatment efficacy in immunocompetent patients with chronic hepatitis C. Data evaluating changes in liver histology following treatment in HCV-infected transplant recipients are limited to small patient series and in which there is a lack of serial liver biopsies [30]. In our study, histological response was associated with younger female donor and with mild recurrent hepatitis C. To date, there are only 5 studies with PEG-IFN and RBV which report histological evaluation and 4 of them show benefit [18, 31, 32, 33], while one none [34]. More randomized studies with prolonged histological follow-up using protocol biopsies are still needed in order to evaluate whether fibrosis progression is stopped following posttransplant treatment of recurrent HCV and if maintenance therapy with low dose interferon has any beneficial effect.

The reported rates of early treatment discontinuation and dose reduction of PEG-IFN and RBV varied from 11-37% to 30-60%, respectively. In one recent study [28], 43% patients discontinued antiviral treatment early as a result of adverse events similar to our group (42.8%). Fifty seven percent of the patients were able to complete at least 80% of the intended duration of therapy; however only 26% of patients were able to tolerate at least 80% of the intended dose of PEG-IFN and RBV [28]. In our series, the patients that completed the one year therapy achieved at least 80% of both intended duration and dosage of both drugs. This may be due to the adequate management of cytopenia by administration of erythropoietin and/or G-CSF. Treatment with growth factors increases the costs and complexicity of therapy but seems to be inevitable in the liver transplant setting in order to improve treatment adherence rates, and thus increase of antiviral therapeutic efficacy as recently demonstrated [33]. Concerns have been raised about a possible increase of the risk of allograft rejection caused by interferon based antiviral therapy, but none of our patients experienced acute or chronic rejection during antiviral therapy. This may be due to PEG-IFN combination therapy because in a recent prospective controlled trial [35], patients treated with PEG-IFN did not show a higher incidence of rejection. The patient with cholestatic fibrosing hepatitis had associated hepatic veno-occlusive disease (sinusoidal obstructive syndrome). HCV proved to be a risk factor for

development of severe veno-occlusive disease and sinusoidal obstructive syndrome commonly coexists with cholestatic liver diseases [36].

The optimal time point of starting the antiviral therapy after LT is still a matter of debate. A recently published study found a negative correlation between the length of time between LT and the sustained response to interferon therapy [33]. All the three patients with SVR had histological recurrence and initiation of therapy between 6 to 12 months after LT. Anyway a liver biopsy performed at 1 year post-LT, in the absence of ealier clinical indicated biopsy, can help identify those patients more likely to develop progressive disease and may allow better targeting of antiviral therapy [37].

In **conclusion**, our results showed that combination antiviral therapy can be safely and successfully used in transplant recipients. The small number of patients is a major drawback of our study impeding the generalization of this finding. Anyway, overall SVR rates remain suboptimal. In order to achieve higher response rates, hepatitis C recipients should undergo protocol liver biopsies for detecting progression of fibrosis that should be managed with the best available antiviral therapy, aimed to minimize side effects, optimize dosing, and enhance compliance and thus adherence to treatment. Further research to develop new antiviral drugs may be done in order to enhance both SVR and histological response and to better define predictive factors for long-lasting response in transplanted patients.

Conflicts of interest

There are no conflicts of interest regarding this study.

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