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Antiviral therapy and fibrosis progression in patients with mild–moderate hepatitis C recurrence after liver transplantation. A randomized controlled study

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ABSTRACT

Backgrounds/aims: We evaluated the effect of antiviral therapy on fibrosis progression in patients with histological features of mild/moderate HCV disease recurrence defined by a Grading score ≥ 4 and Staging score up to 3 (Ishak) at 1 year after liver transplantation.
Methods: Seventy-three consecutive patients with mild/moderate recurrence were randomized either to no treatment or to receive Pegilated-Interferon-alfa-2b and ribavirin for 52 weeks. Liver biopsies obtained at baseline (1 year after transplantation) and 2 years afterwards were evaluated for assessment of disease progression, defined as worsening of at least 2 staging points or progression to stage 4 or higher.
Results: As for these two major histological end points there were no statistically significant differences between the 2 groups (36.1% vs. 50%, $p = 0.34$ and 36.1% vs. 38.9%, $p = 1$). Fifteen treated patients (41%) achieved a sustained virological response which was associated with a reduced risk of fibrosis worsening for both endpoints when compared to viremic patients ($p = 0.04$).
Conclusions: Although antiviral-therapy was beneficial in preventing fibrosis progression in patients achieving a sustained virological response, the majority of the overall population of our patients with mild–moderate disease recurrence could not benefit from antiviral therapy either because they either could not be treated or did not respond to treatment (EudraCT number: 2005-005760).

1. Introduction

The management of recurrent hepatitis C represents one of the most challenging topics in the field of LT [1–3] the most common approach being combined antiviral therapy with standard or pegylated interferon (INF) and ribavirin started at the time of significant histological disease [4–9]. In this respect, it is widely accepted that antiviral therapy is offered to patients with severe recurrence, such as fibrosing cholestatic hepatitis or progressive fibrosis, and not to patients with only minimal histological disease [4,6,10]. Unexpectedly, the issue of whether this therapeutic approach is beneficial for patients in between these two extremes has never been specifically addressed. This is why we designed this prospective, controlled, multicenter, randomized study which included only patients with histological mild–moderate liver HCV recurrence, as assessed at the time of the liver biopsy performed 1 year after transplantation. These patients were randomized either to receive combined antiviral therapy or to be followed up as controls. The primary aim of the current study was to evaluate the impact of antiviral therapy on the natural course of mild–moderate histological recurrent HCV disease.

2. Methods

2.1. Patients

Adult first liver transplant patients were eligible in this trial if they were older than 18 years of age and had mild–moderate

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histological recurrent hepatitis C. The diagnosis of HCV hepatitis was established by the presence of HCV-RNA in the serum and a liver biopsy supporting the diagnosis at any time during the first year of follow-up (acute/lobular hepatitis or chronic hepatitis irrespective of the serum levels of liver enzymes). Confirmation of histological recurrence at the time of the first year protocol liver biopsy was required in all cases. The minimal histological criterion to confirm disease recurrence was an Ishak grading score higher than 3.

Patients were not randomized if either they presented signs of cholestatic hepatitis (defined by a total bilirubin > than 3 mg/dL) at any time before randomization, or had an Ishak staging score higher than 3, at the time of the 1 year protocol liver biopsy: all these patients were offered antiviral therapy. Other exclusion criteria were previous organ transplantation, co-infection with hepatitis B or with the human immunodeficiency virus, ongoing biliary tract disease at the time of randomization, major vascular problems (portal vein or hepatic artery thrombosis), renal failure defined by a serum creatinine higher than 2 mg/dL and contraindications to interferon and ribavirin therapy.

Patient disposition is shown in Fig. 1. Three hundred and seven consecutive first transplants patients were screened, 257 survived at least 1 year after transplant (84%) and therefore were eligible for the liver biopsy set 1 year after grafting. Seventy-three out of 257 patients (28%) underwent randomization: 36 were treated and 36 were followed up as controls; the last patient withdrew the informed consent before starting therapy. One-hundred-eighty four patients (72%) were not eligible for randomization due to various reasons: 36 (20%) for severe recurrent disease, 23 (12.5%) because they had no or only minimal recurrent disease defined as a grading score less than 4 and no fibrosis, 27 (15%) for unresolved biliary complications, 23 (12.5%) for refusal to participate and 37 (20%) for various other reasons such as HCV-RNA negativity (10 patients), lost to follow-up (6 patients), early PTLD (4 patients), early HCC recurrence (6 patients), vascular problems (3 patients), symptomatic cryoglobulinemia (2 patients), poor adherence to study protocol procedures (3 patients), "de novo" HBV infection (2 patients), severe relapse of ethanol consumption (1 patient) and 38 (21%) due to contraindications to antiviral therapy (anaemia in 2 pts with thalassemia trait, epilepsy in 3 pts, ischaemic heart disease in 3pts, "suspected" concurrent autoimmune hepatitis in 9 pts, major psychiatric disorders in 5 pts, non-compliance in 4 pts, severe thrombocytopenia in 3 pts, chronic rejection in 4 pts, chronic renal failure in 3 pts, recurrent drug addiction in 1 pt, combined psychiatric and cardiologic problems in 1 pt).

Baseline demographic and clinical characteristics of the patients were well balanced between the two study groups (Table 1).

2.2. Study design and randomization

The design of this multicentre, randomized, controlled, open-label study was developed by the physicians at the coordinating centre, and involved 6 sites from 3 European countries: two sites (Milan and Palermo) were involved throughout the entire period of randomization which lasted 5 years whilst the remaining 4 sites (Brussels, Innsbruck, Padua and Bergamo) joined the study for a shorter time period of at least 12 months. Adult patients with first liver transplants with mild–moderate recurrent hepatitis at 1 year from transplantation, consecutively recruited between January 2002 and March 2007 were evaluable. Last visit of last patient was performed on 15 May 2010.

Patients were randomly assigned in a 1:1 ratio either to no therapy (control group) or to antiviral treatment (treated group) (Fig. 1). Randomization was centralized and performed by an independent unit according to a randomization list prepared by a biostatistician. The control group did not receive placebo as weekly subcutaneous injection of placebo was considered unethical.

Treated patients had to receive peginterferon alfa-2b plus ribavirin for 52 weeks (this duration was the standard of care at the time of the design of the study) followed by another 52 weeks of follow-up period without antiviral therapy. Patients in the control group did not receive an anti-viral treatment and were followed for a period of 104 weeks.

The study was approved by each site local Ethical Committee. All patients gave their written consent before entering the study. The study was conducted according to the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. A full trial protocol copy may be provided on demand.

2.3. Treatment regimen and dose modification

Treated patients received escalating doses of peginterferon alfa-2b (Pegintron®, Schering-Plough) starting from 0.5 to 1 μg/kg once weekly, up to 1.5 μg/kg within 2–4 weeks if tolerated together with escalating doses of ribavirin (Rebetol®, Schering-Plough) starting from 400 to 600 mg once daily, up to a maximal tolerated dose of 14 mg/kg/day for 52 weeks. Treatment with growth factors for red cell lines (erythropoietin) and white cell lines (granulocyte stimulating factors) was allowed after 2004, to support the red and white cells counts (i.e. EPO when haemoglobin level dropped below 10 g/dL and G-CSF when neutrophils dropped below 750/mm^3).

2.4. Liver biopsies

All patients underwent protocol liver biopsies at randomization (12 months after transplantation), and at 24 and 36 months after transplantation. The median number of complete portal spaces was 14 (range 8–38). Biopsies with less than 8 complete portal tracts were considered inadequate. Biopsy samples were reviewed and scored by an independent histopathologist who was unaware of the timing of the biopsy or the patient's treatment assignment. Ranked assessment of necroinflammatory activity and fibrosis was performed according to Ishak's classification [11].

2.5. Virological assessment

HCV genotype and viral load were determined locally depending on available kits which changed overtime (sensitivity between 12 and 600 IU/mL). In treated patients viral load was obtained at 0, 3, 12, 18 and 24 months after randomization. EVR was defined as a complete response at 3 months.

2.6. Efficacy measures

Efficacy analyses included all randomized patients and, for the treated group only, those who received at least one dose of study medication (intent-to-treat population).

The study had two predetermined primary measures of efficacy: the histological worsening in fibrosis staging according to Ishak at 24 months of follow-up, and sustained virological response (SVR) at 6 months after the end of antiviral therapy. For the assessment of histological worsening, we evaluated the change in the fibrosis staging between the paired liver biopsies performed at baseline (12 months after LT), and at the end of follow-up period (36 months after LT). In this respect we considered the following three endpoints: (a) worsening of at least 1 point of fibrosis (b) worsening of at least 2 points of fibrosis (c) progression to fibrosis stage 4 or higher.

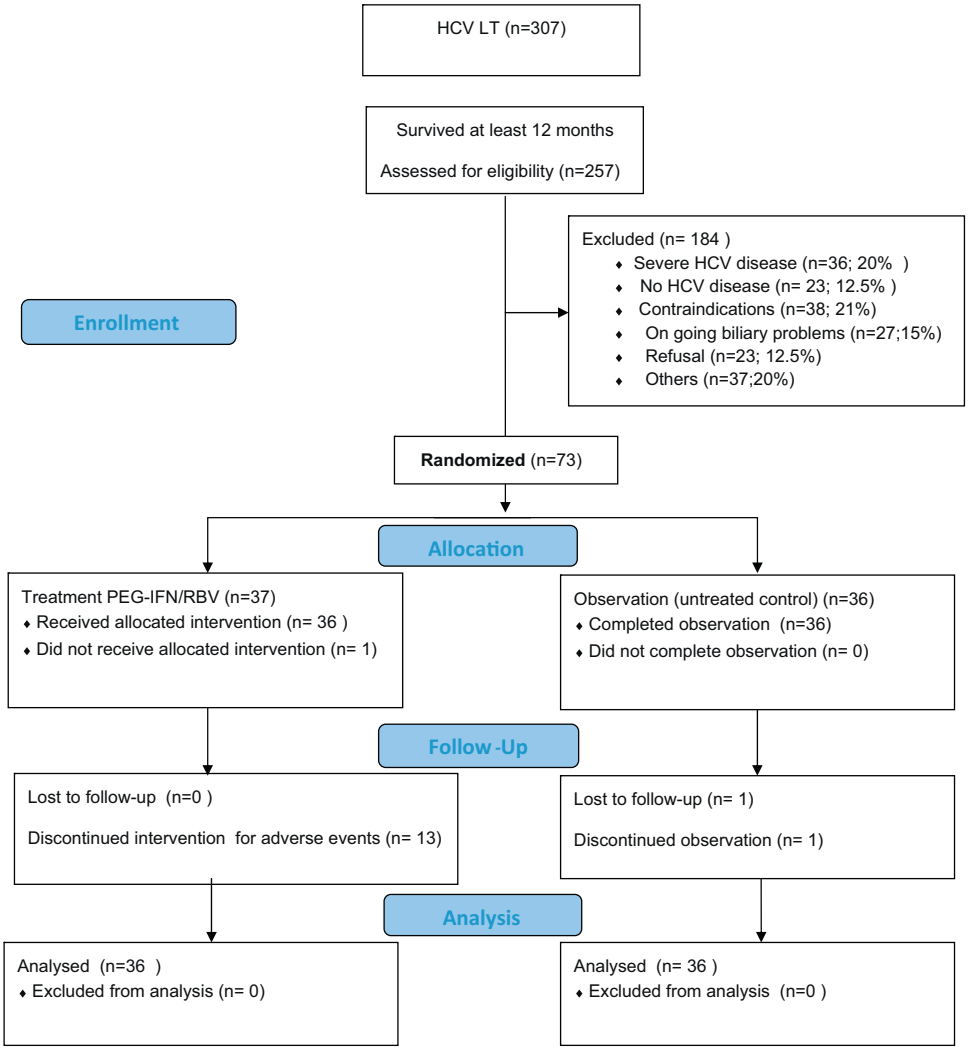

Fig. 1. CONSORT study flow-chart. HCV, Hepatitis C virus; LTX, liver transplantation; PEG:IFN/RBV, PEG-Interferon and ribavirin.

Table 1
Demographic and baseline characteristics of the patients.

Characteristic	Treated group ($n=36$)	Control group ($n=36$)	p-Value
Male gender – n (%)	32 (89)	30 (83)	0.73
Age at liver transplantation – yrs Mean ± SD	55 ± 6.6	53 ± 9.0	0.67
Donor male gender – n (%)	21 (58)	20 (56)	0.77
Donor age – yrs Mean ± SD	51 ± 17.3	45 ± 19.2	0.20
HCV genotype – n (%)			0.77
1,4	28 (78)	30 (83)	
2,3	8 (22)	6 (17)	
History of pre LT anti-viral therapy – n (%)	11 (31)	10 (28)	0.58
HCV-RNA viral load – $\log_{10}$ IU/mL Mean ± SD	5.98 ± 0.7	5.93 ± 0.8	0.94
ALT above upper limit of the normal range – n (%)	30 (83)	32 (89)	0.74
CyA/FK	19/17	15/21	0.34
Previous acute rejection episodes – n (%)	2 (6)	4 (11)	0.67
Ishak's fibrosis score – n (%)			0.90
S0	1 (3)	1 (3)	
S1	11 (31)	8 (22)	
S2	13 (36)	17 (47)	
S3	8 (22)	7 (20)	
S4[a]	3 (8)	3 (8)	
S0–S1	12 (34)	9 (25)	0.60
S2–S4[a]	24 (66)	27 (75)	

Abbreviations: HCV, Hepatitis C virus; LT, liver transplantation; CyA, cyclosporin; FK, tacrolimus.

[a] 3 patients in each group were assessed locally as having an Ishak stage 3 but after central revision they were re-classified as stage 4.

2.7. Safety analysis

Measures of safety included clinical adverse events, haematologic measurements, clinical chemistry measurements, and vital signs.

2.8. Statistical analysis

The trial was originally designed as a superiority study to detect clinically meaningful differences in the rates of histological worsening (1 Ishak point increase after 2 years from randomization). A total of 44 patients per group had to be included in the study considering a statistical power of 80% to detect a significant absolute difference in rates of histological worsening of 30 percentage points (from 50% to 20%).

Patients with missing or inadequate biopsy specimens obtained at 24 months of follow-up were considered to have had a histological worsening. Similarly, patients experiencing chronic rejection during the 24 months of follow-up were considered to have had a histological worsening.

Differences in baseline characteristics between the two groups were assessed with the use of the Chi-square test or Fisher's exact test for discrete variables, and the two-sided *t*-test for continuous variables. The Fisher's exact test was also used to compare differences in response between the treatment groups.

Logistic regression analysis involving the effect of recipient gender, recipient age at LT, donor age, primary immunosuppressant (cyclosporin or tacrolimus), HCV genotype, history of previous therapy for HCV, baseline body-mass index, staging of liver fibrosis, alanine-aminotransferase level, cumulative dose of PEG-IFN and ribavirin (> or <50% of the theoretical dose) and HCV-RNA viral load, were undertaken to determine if any of these factors were predictive of SVR and of histological worsening. All reported *p*-values are two-sided and the level of significance was set at 0.05. No adjustment for multiple testing was adopted. Statistical analysis was carried-out using the SAS System version 9.2.

3. Results

3.1. Efficacy of antiviral treatment

3.1.1. Histological response

Paired liver biopsies at baseline and at the end of follow-up were available in 69 out of the 72 patients analysed. The 3 patients with inadequate/missing biopsies were considered as having had histological worsening. Results of the individual histological parameter are shown in Fig. 2. The rate of a worsening of at least one point of fibrosis was 61% in both groups, whereas the rate of worsening of at least two points of fibrosis was 36.1% in the treated group and 50% in the control group ($p = 0.34$). Finally, there were no significant differences between treated and control group in the proportion of patients with a fibrosis staging ≥ 4 at the end of follow-up: 36% and 39% ($p = 1.0$), respectively. These results were confirmed after excluding the 3 patients without biopsy at end of follow-up and the 6 patients who were already S4 at randomization.

Logistic regression analyses to examine the influence of potentially important prognostic factors on worsening in the fibrosis staging indicated that donor age (older) was associated with worsening in the fibrosis staging for all the histologic parameters considered: worsening of at least 1 point ($p = 0.002$), worsening of at least two points ($p = 0.002$) and also for the progression of fibrosis to stage ≥ 4 ($p = 0.003$) (Table 2).

When considering treated patients only, there was a trend ($p = 0.08$) for an association between histological worsening and virological non response at 6 months after the end of antiviral therapy (Table 3). More in detail, 3 of 15 patients (20%) with SVR had a histological worsening according to the 2 predefined endpoints, as compared to 10 of 21 patients (47.6%) without SVR. Notably, none of the 3 events in the group of patients with SVR were due to disease progression, as we observed 2 cases of chronic rejection and unfortunately 1 case of missing biopsy. Conversely, in the control group a histological fibrosis worsening of at least 2 points or beyond stage 3 was observed respectively in 50% and 38.9% of the patients.

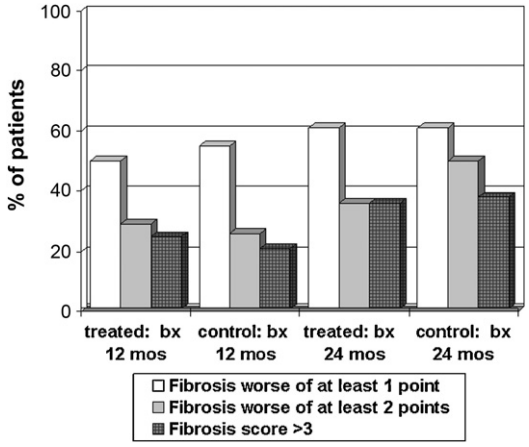

Fig. 2. Histological response. Bx 12 mos: fibrosis score comparison between intermediate liver biopsy set 12 months after randomization and randomization liver biopsy in treated and control patients. Bx 24 mos: Fibrosis score comparison between end of follow-up liver biopsy set 24 months after randomization and randomization liver biopsy in treated and control patients.

3.1.2. Virological response

At the 6-month follow-up assessment of treated patients, the proportion of HCV-RNA negative patients (SVR) was 42% (15/36). Surprisingly, a delayed virological relapse after extended follow-up was observed in a single patient for whom a new infection cannot be excluded. Logistic regression analysis did not show independent pre-therapy predictors significantly associated with SVR.

Differently, virological clearance after 3 months of treatment (Early Virological Response, EVR) was confirmed as a strong positive and negative predictor of SVR: 14 out of 16 patients (87.5%) with a EVR became sustained responders whereas 19 out of 20 patients (95%) without a EVR remained non responders. In the control group no spontaneous viral eradication occurred.

3.1.3. Treatment compliance and safety

The cumulative median dose of peginterferon alfa-2b and of ribavirin was 2960 μg (interquartile range 1845–4160 μg) and 197 g (interquartile range 68–291 g) respectively. The median of the cumulative doses of peginterferon alfa-2b and ribavirin was higher of about 30% in patients that achieved an SVR with respect to those who did not, but the differences were not statistically significant.

Thirteen patients (36%) in the treatment arm interrupted treatment for various reasons as reported in Table 4. Dose of study medication was reduced in another 6 patients (16.7%) to manage clinical complications. Growth factors for red and white cells were utilized respectively in 36% and 25% of the treated cases. Chronic rejection was observed in 3 "treated" patients and 2 had major consequences: 1 patient had a stormy clinical course and eventually died of sepsis on a background of chronic rejection and HCV recurrence, 1 patient was successfully retransplanted and the third patient is alive and well, long after transplant (almost 6 years) with very slowly declining levels of GGT and alkaline phosphatase and no HCV virus. The single patient with chronic rejection in the "untreated group" had to be re-transplanted.

Table 2
Predictors of histological worsening at 2 years after randomization (logistic regression analysis).

Predictor[b]	≥1 Ishak fibrosis point worsening		≥2 Ishak fibrosis points worsening		Ishak fibrosis stage ≥4	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Treatment arm (control vs. treated)	1.56 (0.45–5.37)	0.48	2.43 (0.74–7.98)	0.15	1.11 (0.32–3.85)	0.87
Recipient gender (male vs. female)	0.97 (0.18–5.32)	0.98	2.13 (0.32–14.4)	0.44	4.21 (0.42–42.3)	0.22
Recipient age at LT (≤55 vs. >55 yrs)	0.85 (0.22–3.30)	0.81	1.36 (0.39–4.79)	0.63	1.23 (0.34–4.47)	0.75
Donor age (≥50 vs. <50 yrs)	9.23 (2.21–38.5)	0.002	7.11 (2.0–25.2)	0.002	7.86 (2.01–30.8)	0.003
Primary immuno-suppressant (CyA vs. TAC)	3.47 (0.84–14.3)	0.09	0.84 (0.24–2.94)	0.78	0.77 (0.21–2.78)	0.69
HCV genotype (1,4 vs. 2,3)	6.43 (1.18–35.0)	0.03	1.78 (0.34–9.3)	0.49	1.99 (0.36–11.1)	0.43
History of pre LT antiviral therapy (yes vs. no)	1.06 (0.25–4.45)	0.94	1.73 (0.47–6.35)	0.41	1.09 (0.28–4.29)	0.91
Stage at randomization (S0–S1 vs. S2–S3)[a]	7.03 (1.45–34.0)	0.02	1.11 (0.31–3.89)	0.88	0.36 (0.09–1.45)	0.15
BMI at randomization (<25 kg/m^2 vs. ≥25 kg/m^2)	1.31 (0.37–4.61)	0.67	1.77 (0.51–6.24)	0.18	1.74 (0.46–6.57)	0.41
ALT level at randomization (> 3×ULN vs. ≤3×ULN)	2.62 (0.70–9.71)	0.15	1.08 (0.30–3.83)	0.90	1.67 (0.45–6.25)	0.45
HCV-RNA at randomization (<500,000 vs. ≥500,000 IU/mL)	11.8 (1.41–98.0)	0.03	2.0 (0.31–13.0)	0.47	3.50 (0.45–27.4)	0.23

Abbreviations: LT, liver transplantation; CyA, cyclosporin; FK, tacrolimus; HCV, Hepatitis C virus; BMI, body mass index.
[a] 6 patients were assessed locally as having an Ishak stage 3 but after central revision they were re-classified as stage 4.
[b] The second category for each predictor is considered to have risk 1.

Table 3
Histological worsening according to the virological response.

Characteristic	Control	Treated		
	Group (*n* = 36)	SVR (*n* = 15)	Non SVR (*n* = 21)	
Histological Worsening ≥2 points – *n* (%)	18 (50.0)[a]	3(20)[b]	10(47.6)[b]	*p* = 0.08[c] *p* = 0.04[d]
Histological fibrosis score ≥4 at end of f. up – *n* (%)	14 (38.9)[a]	3(20)[b]	10(47.6)[b]	*p* = 0.08[c] *p* = 0.04[d]

Abbreviations: SVR, sustained virological response.
[a] 1 case of chronic rejection and 2 cases of missing biopsies were considered as event.
[b] 3 cases of chronic rejection in treated patients (2 SVR and 1 non-SVR) and 1 case of missing biopsy (1 SVR) were considered as event.
[c] Comparison between SVR and non-SVR in treated group.
[d] Comparison between SVR and non SVR in treated group excluding the single SVR patient with a missing biopsy.

4. Discussion

Very few prospective randomized studies [12–15] have explored the role of antiviral therapy in patients with established HCV disease recurrence after liver transplantation and quite surprisingly none of them have specifically addressed the issue of how effective antiviral therapy might be in the most frequent clinical situation of a patient with a mild–moderate recurrence. This is why we designed this multicentre, controlled, randomized trial with the primary aim to investigate the possible histological benefit of antiviral therapy in patients with mild–moderate HCV recurrence as assessed at the time of liver biopsy performed 1 year after grafting. The histological limits of mild–moderate recurrence were arbitrarily defined as a minimal Ishak grading score of 4, and a maximal Ishak staging score of 3. Given the lack of evidence that antiviral therapy is of any benefit in these patients, we felt that a control arm without therapy was justified. In keeping with the design of this study a very recent systematic Cochrane review [16] still confirms the need of such clinical trials, recommending the inclusion of an untreated control group.

The strengths of the present study can be summarized as follows: it considers a large cohort of consecutive HCV liver transplant recipients (more than 300 patients) that were consecutively evaluated and followed up; it separates patients with different degrees of disease severity and randomizes only those with mild–moderate recurrence; it fixes the timing for starting antiviral therapy at 1 year after grafting – this approach is different from that adopted in all previous controlled studies where patients were treated at different time intervals after transplant; it evaluates fibrosis progression, utilizing adequate liver biopsies (at least 8 complete portal spaces) that were analysed centrally by an independent pathologist unaware of the timing of the biopsy or the patient's treatment assignment.

We also acknowledge that the study is limited by the following factors: the randomization phase, lasting 5 years, turned out to be slower than expected mainly due to the low rate of patients meeting the inclusion criteria (about 25% of the total number of HCV recipients); the target enrolment was not met – as a matter of facts the results observed after the first 73 patients indicated that more than 300 cases would be needed to demonstrate a difference of 2 points of fibrosis worsening between the two groups.

Antiviral therapy with PEG-IFN and ribavirin started 1 year after transplantation did not significantly reduce fibrosis progression in comparison with the control group. This finding implies that antiviral therapy in our hands was not as effective as it was reported in a previous similar prospective trial from Carrion et al. in a smaller population of patients (54 vs. 72). Carrion et al. [13] considered 54 patients with mild–moderate recurrence identified by a Fibrosis score 0–2 (Scheuer score which is based on 4 levels

Table 4
Adverse events leading to treatment withdrawal in the treated arm.

	Therapy withdrawal (*n*) (weeks of therapy)
Infection[a]	1 (29)
Rejection[b]	3 (13, 17, 30)
Major depression	3 (22, 26, 26)
De novo tumour[c]	1 (30)
Severe fatigue	3 (13, 22, 27)
Rapidly progressive disease[d]	1 (4)
Clinical decompensation[e]	1 (27)

[a] This patient developed bilateral pneumonitis and died from end stage liver disease 35 months after withdrawal of antiviral therapy.
[b] One patient died of end stage liver disease (chronic rejection and recurrent hepatitis) 54 months after withdrawal of antiviral therapy; 1 patient is alive with increased cholestasis; 1 patient is alive after successful re-transplantation.
[c] Tumour of the larynx, alive.
[d] Retransplant for fibrosing cholestatic hepatitis, alive.
[e] Ascites, alive.

of fibrosis). This population compares well with our 72 patients with mild–moderate recurrence defined by a Staging score 0–3 according to the Ishak score which is based on 6 categories of stage. In the Carrion study liver fibrosis progressed of at least 1 point in 74% of untreated patients compared to only 26% of treated ones. These extremely favourable results are in contrast with the much less favourable findings of our study. At least two major factors can explain these differences: firstly, the design of the study from Carrion et al. was such that the 54 consecutive patients with mild–moderate recurrence were randomized almost contemporaneously, but at different time intervals from transplantation (between 9 and 40 months after grafting). It is possible that treating the same mild–moderate recurrence observed at 3 years rather than at 1 year from transplantation is associated with different outcomes. This differs from our study in which all patients were randomized 1 year after transplantation. Secondly, patients with no or minimal disease recurrence were not excluded in the Spanish cohort, despite the general acceptance of no need for treatment because of a mostly benign clinical course.

Although our study could not demonstrate a significant difference in terms of fibrosis progression between patients that were treated and those who were not treated, the results derived from the sub-analysis of our treated patients confirmed that antiviral therapy is beneficial in preventing histological progression in sustained virological responders as already reported by many other groups [14,15].

Untreated patients with mild–moderate HCV recurrence showed a significant fibrosis progression, defined by an Ishak staging score of 4 or higher, in almost one third of the cases at 3 years from transplantation thus confirming the severe natural course of the disease also in the specific subset of patients with mild–moderate recurrence. This is, to our knowledge, the first time that such an impressive figure of severe fibrosis progression emerges from a selected group of patients with mild–moderate recurrence.

We finally confirm what already reported by Heydtmann et al. [17] in a small cohort of uncontrolled patients: in our prospective series the number of patients potentially eligible for antiviral treatment was much smaller than expected, as at least one third of them had to be excluded either because there were contraindications or the patients refused antiviral therapy. This information is important as the results of antiviral therapy should be evaluated with respect to the whole population of patients potentially eligible to antiviral therapy and not only with those that could in fact be treated.

Our study confirms and reinforces the "difficult-to-treat" nature of liver transplant patients. Not only many liver transplant patients are ineligible for anti-viral therapy due to comorbid conditions which preclude successful treatment but also the sustained virological response is at least 25% less than that observed amongst non-transplant patients [18]. Therefore the clinical impact of antiviral therapy on the natural course of recurrent disease is much weaker than one might expect. Trying to have a pragmatic approach, we calculated that 8 patients with mild–moderate recurrence need to be treated to avoid the increase of at least 2 Ishak fibrosis score in a single patient. On the same line, 37 patients need to be treated to avoid 1 case of progression to stage 4 or higher. The cost effectiveness of this approach remains to be determined. Finally immunologic complications related to the use PEG-IFN are to be highly feared in this context as we observed 4 cases of chronic rejection (3 in the treated group and one in the control group) which lead to retransplantation in 2 cases and to patient death in 1 case. Despite all its limits, antiviral therapy with PEG-IFN and ribavirin remains at the present time the only therapeutic option to favourably change the natural history of patients with mild–moderate HCV recurrence and therefore it should be always considered. New antivirals will be available in the near future and will be added to the standard combination of PEG-IFN and ribavirin, but it is unlikely that they will substantially change the outcomes of our HCV recipients as tolerability to treatment will remain a major concern. Hopefully, the recent discovery that IL28-B polymorphism [19] significantly affects the response to antiviral therapy will possibly allow a better selection of the candidates for antiviral therapy.

After all this, should patients with mild–moderate recurrence systematically be considered for treatment? The answer is still yes for 2 reasons: (1) if untreated, the disease progresses beyond stage 4 in one third of the cases in the space of 2 years (2) non-viremic patients have a better histologic outcome than viremic ones. We think that the present trial helps to look at antiviral therapy in the correct light and should possibly reduce the initial enthusiasm derived by previous studies. Our main message is that antiviral therapy with PEG-Interferon alfa-2b plus ribavirin is effective but not to the extent that the majority of the patients benefit, as many cannot be treated or do not respond to treatment.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.dld.2012.01.017.

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