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ORIGINAL ARTICLE

Liver–kidney recipients with chronic viral hepatitis C treated with interferon-alpha

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Summary

Antiviral therapy with interferon-alpha (IFN-alpha) and pegylated IFN-alpha (PEG-IFN-alpha) for chronic hepatitis C (HCV)-infected kidney recipients remains controversial. IFN-alpha is not recommended in most cases because it induces severe acute graft rejection. However, IFN-alpha, as PEG-IFN-alpha, is associated with a more pronounced immune response, and is well tolerated in HCV-infected liver recipients without causing graft rejection. In combined liver–kidney transplant (LKT) recipients, IFN-alpha has been occasionally used and appears to be well tolerated. All LKT recipients with a functioning kidney and liver having a HCV replication and who needed IFN-alpha therapy have been included in the study. The occurrence of liver and/or renal acute rejection as well as the HCV replication has been collected. A total of 12 LKT patients treated with PEG-IFN-alpha plus ribavirin have been studied. No acute rejection was observed. Renal function remained stable during and after discontinuing treatment, without any graft dysfunction. Two patients had a partial viral response and four had a sustained viral response. All patients, whatever their viral response, had decreased liver-enzyme levels. Response to PEG-IFN-alpha therapy was correlated with steroid dose and transaminase level when PEG-IFN-alpha was started. These data suggest that the combination therapy of PEG-IFN-alpha plus ribavirin did not have a higher risk of acute kidney-graft rejection after liver–kidney transplantation.

Introduction

Chronic hepatitis C virus (HCV) infection is a potentially serious complication of renal transplantation (KT), which can lead to the development of cirrhosis and/or hepatocarcinoma. Interferon-alpha (IFN-alpha) is an immunomodulator therapy used to treat viral hepatitis. However, the use of this molecule remains controversial in KT recipients. One recent study suggests that IFN-alpha can be used in renal transplant recipients [1], whereas several studies have highlighted an unacceptably high rate of allograft rejection because of the activation of immune responses induced by IFN-alpha, which frequently leads to graft loss and requires chronic dialysis within weeks [2–10].

In contrast, treating HCV reinfection in liver-transplant (LT) patients with IFN-alpha plus ribavirin is not associated with an increased risk of rejection [11–14]. Treatment is frequently well tolerated in terms of rate of rejection and is associated with improved liver-enzyme levels and, in some cases, offers a sustained viral response (SVR) despite maintaining immunosuppressive treatments.

Few data are available on combined liver–kidney transplant (LKT) patients; thus, the incidence of acute or

chronic rejection of the liver and/or kidney needs to be determined. Do both organs respond similarly or do they behave independently during IFN-alpha therapy? We, and others, have shown that LKT is associated with improved graft acceptance [15] compared with KT patients. In contrast, Katznelson *et al.* reported similar rates of acute rejection for LKT and KT patients, suggesting that rejection rates with IFN-alpha therapy would be similar for LKT and KT patients [16]. Magnone *et al.* reported on four patients who received a KT following an orthotopic LT, and seven patients who had undergone a KT alone [6]. Only one of the four LKT recipients experienced acute rejection, whereas six of the seven KT recipients experienced acute rejection following IFN-alpha therapy.

Recently, pegylated-IFN-alpha (PEG-IFN-alpha) has been developed to replace IFN-alpha and, when it is combined with ribavirin, it is more effective in curing HCV [17–21]. Its ability to induce a better response to HCV may be associated with the higher risk of acute rejection in transplant patients. However, in LT recipients, PEG-IFN-alpha plus ribavirin therapy to treat chronic HCV is well tolerated and is not necessarily associated with acute graft rejection [22]. One LKT recipient has already been treated with PEG-IFN-alpha plus ribavirin therapy for HCV-induced cryoglobulinemia, and had no acute graft rejection [23]. Van Wagner *et al.* reported on 10 LKT recipients treated for recurrence of HCV with PEG-IFN-alpha plus ribavirin: no patient had a liver or kidney rejection [24].

In this study, we report on our experiences using PEG-IFN-alpha plus ribavirin to treat HCV in patients who had undergone a combined LKT and who had received minimal immunosuppression.

Patients and methods

We performed a retrospective review of data from 25 patients who had undergone an LKT between 1990 and 2009 for HCV infection. Twelve of them had a recurrence of the viral infection and were treated with PEG-INF-alpha plus ribavirin for recurrence of HCV after transplantation. We have collected the data of these 12 patients.

Collected data included age, gender, post-transplant immunosuppressive regimen, duration of antiviral treatment, side effects from antiviral treatment, serum creatinine, hepatic enzymes, and viral load before, during, and after antiviral treatment.

Hepatic biopsies were systematically performed before introducing PEG-IFN-alpha and in cases where liver-enzyme levels were elevated. A kidney biopsy was suggested when serum creatinine increased by more than 20% compared with the basal value observed when the IFN therapy started. Glomerular filtration rate (GFR) was determined according to the Cockcroft and Gault formula.

HCV load was determined using real-time polymerase chain reaction at day 0, and at 3, 12, and 18 months after the start of treatment. A SVR was defined as a negative viral load at 6 months after stopping antiviral treatment. Antiviral treatment was interrupted for side effects or for a nonviral response after 3 months of treatment.

Statistical analysis was done using the nonparametric Wilcoxon test to compare quantitative values from patients who had, or did not have, a SVR. Results were considered significant if the p-value was <0.05.

Results

Population characteristics

Twelve patients were studied. Their average age at the time of the LKT was 51 years (range: 35–74). Median duration between transplantation and antiviral treatment was 19 months (range: 5–170). Eight patients were genotype 1b for HCV, two patients were genotype 1a, one patient was genotype 4a, and the genotype was unknown for one patient (Table 1). Three patients received antiviral treatment (Peg-IFN + ribavirin) before transplant but were nonresponders.

Immunosuppressive therapies at the time of starting interferon therapy are shown in Table 1. Most patients received a dual therapy of anti-calcineurin inhibitor and

Table 1. Patient characteristics.

No. of patients	12
Male/female	9 (75%)/3 (25%)
Age: median (range) median duration of LKT before PEG-IFN-alpha (range)	59.7 years (35–74.9 years) 19 months (5–170)
Virus genotype HCV	
1b	8
1a	2
4a	1
Unknown	1
Immunosuppressive regimen	
MMF	3 patients (25%)
CSA	6 patients (50%)
FK 506	6 patients (50%)
Cortico-steroid	11 patients (91.6%)
Antiviral treatment	
Pegylated IFN-alpha	12 patients (100%)
Ribavirin	11 patients (91.6%)
Median duration of antiviral treatment (range)	10 (6–17) months

LKT, liver–kidney transplantation; PEG-IFN-alpha, pegylated Interferon alpha; MMF, Mycophenolate Mofetil; CSA, Cyclosporine A; FK506, Tacrolimus.

steroid. Only three patients also received mycophenolate mofetil (2 grs/day; 0.5 grs/day, and 0.25 grs/day). Histological analyses of the liver at the start of treatment are shown in Table 2. The initial activity score was 2.17 ± 0.72 and fibrosis was 2.17 ± 0.83. Only four patients had a liver biopsy at the end of treatment. No graft experienced rejection.

The initial dosage of PEG-INF-alpha was 135 mg/week for eight patients, 80 mg/week for three patients, and 180 mg/week for one patient. Ribavirin was adapted to renal function: three received 800 mg, three received 600 mg, three received 400 mg, and one patient received 1 000 mg/day. One patient did not receive any ribavirin. The duration of antiviral treatment was 10.6 months (range: 6–17).

Table 2. Liver histologic activity and fibrosis.

	Activity		Fibrosis	
Hepatic biopsy	Before treatment	After treatment	Before treatment	After treatment
Patient 1	3	2	2	2
Patient 2	3	2	2	2
Patient 3	1	1	1	2
Patient 4	2	nd	3	nd
Patient 5	1	nd	2	nd
Patient 6	2	1	4	4
Patient 7	2	nd	3	nd
Patient 8	2	nd	3	nd
Patient 9	3	nd	2	nd
Patient 10	3	nd	1	nd
Patient 11	2	nd	3	nd
Patient 12	2	nd	1	nd

Evolution of renal and liver parameters

Changes in liver and kidney parameters are shown in Table 3. For all patients, liver-enzyme levels had improved by the end of treatment compared with values at the start of antiviral therapy. The initial median value of alanine-aminotransferase was 95 UI/ml (range 16–370), and this decreased to 52 UI/ml (range 12–138) by the end of treatment (Fig. 1). Ten patients (80%) had improved concentrations of gamma-glutamyl transferase, and two had a slight increase: the initial median value was 122 UI/ml (range 5–1054), and then decreased to 42 UI/ml (range 20–413) by the end of treatment (Fig. 1).

Renal function was very stable during treatment. Median GFR was 54.5 ml/min (range 38–132), at the start of treatment and was 51.6 ml/min (range 35–127) by the end (Fig. 1). No patient had proteinuria before or after interferon therapy.

Viral response

Of the 12 patients, four (25%) had a SVR, two (16.7%) had an initial viral response, but then relapsed under treatment, and six patients (50%) had no viral response. Initial viral load was log 6.45 ± 0.51, and then decreased to 3.75 ± 2.31 by month 6, and to 4.56 ± 2.57 by month 12.

There was no correlation between viral response and age or gender of the patients, the duration of the combined KLT before the PEG-IFN-alpha therapy, viral genotype, initial METAVIR score, viral load before treatment,

Table 3. Evolution of hepatic enzyme and renal function during PEG-IFN-alpha therapy.

	ASAT (UI/L)		ALAT (UI/L)		Gamma GT (UI/L)		Creatinine clearance (ml/min)	
patients	Before T	After T	Before T	After T	Before T	After T	Before T	After T
Patient 1	121	63	370	75	311	78	70	73
Patient 2	180	39	273	68	1054	36	49	51
Patient 3	44	35	51	35	24	29	129	127
Patient 4	28	17	47	12	44	44	34	35
Patient 5	59	47	98	61	329	339	60	51
Patient 6	97	72	246	138	780	89	49	38
Patient 7	44	35	80	63	80	35	45	39
Patient 8	70	30	92	40	63	28	81	71
Patient 9	117	85	194	144	176	225	40	39
Patient 10	130	78	120	68	1003	617	61	70
Patient 11	64	10	62	18	102	98	46	52
Patient 12	17	15	16	17	5	20	61	67
All patients	89	49.8	132	75	333	94	61	61

ASAT, aspartic-amino transferase enzyme; ALAT, alanine-amino transferase enzyme; Gamma GT, gamma-glutamyl transferase; Before (before T) or After (after T) treatment.

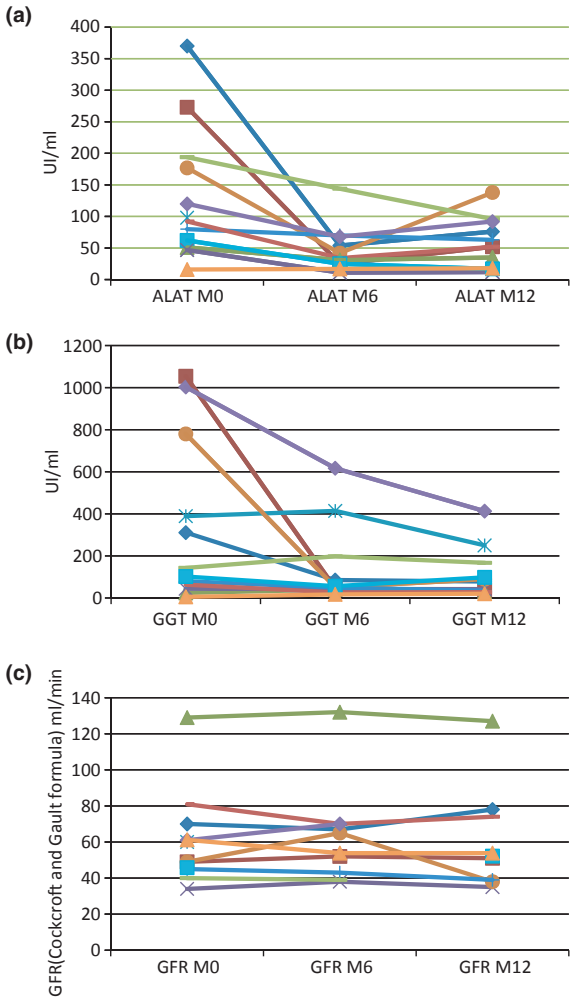

Figure 1 Evolution of alanine-amino transferase (a), gamma-glutamyl transferase (b) and renal function (GFR) (c) during PEG-IFN-alpha.

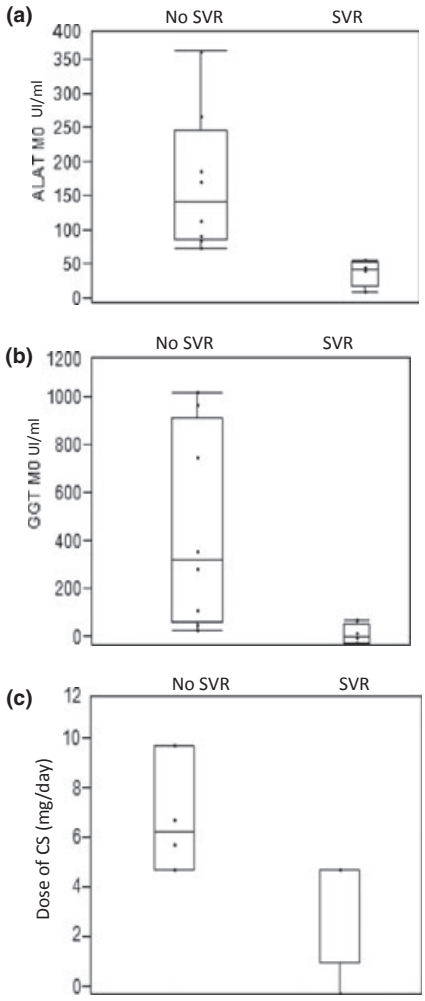

Figure 2 Factors associated with an SVR in LKT patients. (a) alanine-amino transferase, (b) gamma-glutamyl transferase, (c) dose of steroids taken/day.

and initial trough levels of cyclosporine A (105 ± 65 ng/ml) or tacrolimus (6.2 ± 1.9 ng/ml). Serum creatinine tended to be lower in patients with an SVR (92.7 ± 20.6 μmol/l) versus those without an SVR (135.4 ± 28.7 μmol/l, $P = 0.061$), although eGFR (67.5 ± 42.5 and 56.9 ± 13.8 ml/min, respectively) did not significantly differ between the two groups of patients. SVR was correlated with liver-enzyme levels and steroid dosage given at the start of interferon therapy (Fig. 2). Mean concentration of alanine-aminotransferase was 44 ± 19.7 UI/ml for responders versus 175.5 ± 102 UI/ml for nonresponders ($P = 0.007$), and was 43.7 ± 41.9 UI/ml vs. 477.9 ± 408 UI/ml for gamma-glutamyl transferase levels, respectively ($P = 0.017$). Because most patients received steroids, we analyzed differences between patients' daily dosage. Steroid dose was lower for patients with an SVR (3.75 ± 1.2 mg/day) versus those without (7.25 ± 0.85 mg/day) ($P = 0.04$).

Side effects

Treatment of two patients was interrupted because of side effects, and one of these patients died 3 months after antiviral treatment was discontinued. Most patients had side effects (91.6%). The most common were leucopenia (75%), asthenia (25%), and anemia (30%). None of the patients had a significant thrombopenia (below 100 000 platelets/ml) before the treatment. Only one patient had a thrompopenia (82 000/ml) without any symptoms. It was well tolerated and not associated with any complication. No adaptation of the therapy was done. Most patients (10 of 12) received erythropoietin therapy while receiving ribavirin (Fig. 3). The initial dose of erythropoietin was 20 000 Units of beta erythropoietin every week. Mean hemoglobin level before, at month 3, and at the end of therapy was 13.05 ± 1.8 g/dl,

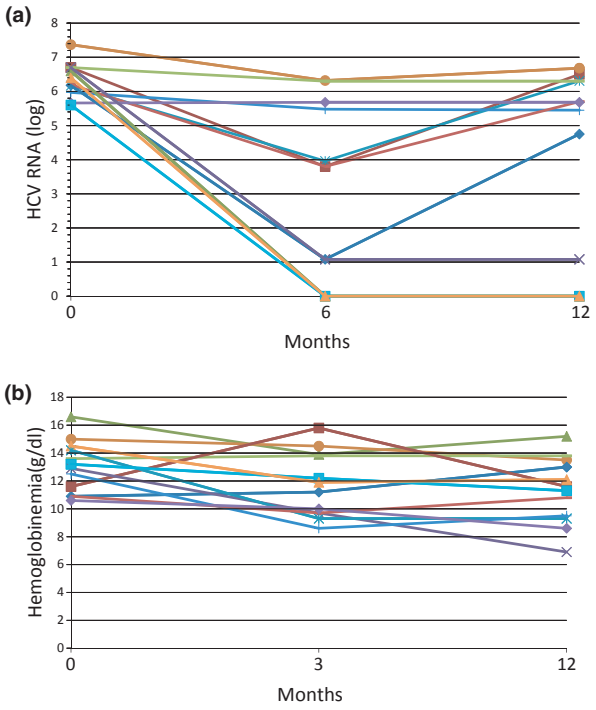

Figure 3 Evolution of HCV viral load (a) and hemoglobin (b) during the course of the treatment.

11.5 ± 2.3 g/dl, and 11.45 ± 2.4 g/dl, respectively. Only four patients had a hemoglobin below 10 g/dl and only one had a value below 9 g/dl. Depression (16%), or hypothyroidism, and/or arthralgia (16%) occurred less frequently.

These results indicate that PEG-IFN-alpha with Ribavirin is not associated with a high risk of acute rejection in LKT patients and can be used to control HCV replication.

Discussion

Antiviral therapy with IFN-alpha to treat chronic HCV-infected KT recipients remains controversial, as it is associated with severe acute allograft rejection. Rejection rates in these patients range between 15% and 86% after starting antiviral therapy [1–9]. Recently, Caeiro *et al.* reported three renal transplant recipients treated with Peg-IFN-alpha in which two of them had a stable renal function at 1 year [25]. On the contrary, Aljumah *et al.* reported a favorable outcome for most of the renal transplant patients treated with Peg-IFN [1]. Nevertheless, the different results have resulted in the classical recommendation that KT patients should not be given IFN-alpha, with the exception of patients with severe HCV cholestatic fibrosing hepatitis [26]. The exact mechanism of how acute rejection is triggered by IFN-alpha is not completely understood. However, IFN-alpha is associated with an increase in cell-surface expression of human leukocyte alloantigens (HLA), induction of the TH1 immune response, direct stimulation of CD8 cytotoxic T cells, and enhancement of antibody production by B cells, which are possible steps that lead to the increased allogenic response [5,27].

Ribavirin as a monotherapy has been proposed and tested in HCV-positive patients after KT. It improves serum aminotransferase levels and proteinuria [28], but has no effect on HCV-RNA viral load, and its effect on liver histology remains limited [28–30]. In contrast, several reports suggest that IFN-alpha-based therapy can be used in LT patients, including the most widely used and effective combination of PEG-IFN-alpha plus ribavirin [17,18]. As well as its greater efficacy, compared to IFN-alpha, PEG-IFN-alpha is not associated with increased risk of graft rejection in LT patients. The combined therapy of PEG-IFN-alpha plus ribavirin appears to be well tolerated regarding acute-rejection risk and is beneficial in treating chronic HCV [22]. In addition, when acute-rejection episodes occur, they can be treated by simply increasing the immunosuppressive regimen.

The effects of LKTs on the immune response are controversial. It is not certain whether the two transplanted organs have their own evolutions and mechanisms of acceptance/rejection, or whether the immune response of the LT is adopted by the second organ, leading to better graft tolerance of the kidney. In LKT patients, independently of the presence of HCV infection, Opelz *et al.* [31] reported that the risk of acute rejection was similar to that observed in KT patients, suggesting that IFN-alpha-based therapy should not be used. However, several other studies, including our case-control study, suggest that LKTs are associated with improved graft acceptance and lower rates of acute graft rejection, despite reduced doses of immunosuppressive drugs [15,32].

Several mechanisms have been proposed to explain the better tolerance observed in LKT patients, such as (i) the production of soluble HLA class I antigens by the liver allograft, which may neutralize both pre-existing alloantibodies and cytotoxic T lymphocytes [33], (ii) the secretion of various immunomodulatory factors or cytokines by the liver, which favor a Th2 immune response [34], (iii) the emergence of regulatory CD4+ CD25+ T cells [35], and/or (iv) the production of soluble HLA-G, which correlates with the absence of acute rejection in LKT patients [36,37]. In addition, HCV-infected transplant patients have greater expression of the TH2 cytokine profile, which would reenforce the tolerogenic profile of LKT patients [38,39]. Interestingly, both IL10 and IFN-alpha induce HLA-G and, therefore, may maintain the tolerogenic profile of LKT patients [40–42].

Magnone *et al.* reported that LKT patients treated with IFN-alpha had a better outcome than KT recipients [6]. They showed that only one of four LKT recipients treated with IFN-alpha experienced a refractory acute kidney rejection within 2 months. In comparison, six of seven KT recipients, who were treated with IFN-alpha had an acute graft rejection. Two cases of LKT treated with Peg-INF-alpha with a good outcome have been reported recently [43]. Van Wagner *et al.* and our results showed that PEG-IFN-alpha, despite having a higher risk of causing acute rejection, was not associated with an increase in acute renal- or liver-graft failures following treatment with PEG-IFN-alpha, despite the low level of immunosuppression [24]. Overall hepatic parameters improved whereas renal function remained stable, indicating that PEG-IFN-alpha can be safely used to treat LKT patients.

As reported for LT patients, SVR was observed in a proportion of patients. A total of 4of our 12 cases (30%) had an SVR. However, most patients had a type-1 genotype, which is associated with a worse response. In addition, all patients had been previously treated with interferon before transplantation without any efficacy, which may explain the low response to PEG-IFN-alpha plus ribavirin. However, this indicates that even in absence of a previous response to interferon-alpha therapy, some patients can be secondary responders to a new course of treatment.

Three factors were associated with SVRs. The first two correspond to the low levels of alanine transaminase and gamma-glutamyl transferase, which suggests that treatment should be initiated before the development of potentially serious liver modifications. Despite the relatively low SVRs among our 12 patients, most of them had significantly improved liver parameters, suggesting that IFN-alpha independent of the effects of viral replication is beneficial for the liver. Therefore, despite the absence of a response in some patients, treatment of patients with severe cholestasis has been continued.

The third parameter, associated with SVRs, was the dosage of steroids given per day: SVRs were correlated with a lower dosage. Thus, a very low dose of steroids or their absence may improve antiviral response. This is in contrast to the commonly held view that a low dosage of steroids is associated with a better outcome for LT patients with HCV reinfection.

In this LKT population, treatment with PEG-IFN-alpha was associated with a high rate of side effects. Most patients developed neutropenia, but this was well tolerated and did not lead to serious infections. However, neutropenia did lead to decreased dosage of PEG-IFN-alpha when it was $<2500/mm^3$, and resulted in complete interruption of the drug in one patient. Serious anemia was rarely observed, as erythropoietin therapy was systematically initiated when PEG-IFN-alpha was started. Transitional asthenia was frequently reported, and impaired the quality-of-life of 23% of patients. In half of these cases, it was associated with depression, which required medical support.

Overall, these results confirm that PEG-IFN-alpha plus ribavirin can be used in selected KLT recipients without causing chronic renal dysfunction or increasing the risk of acute rejection, and that it is efficacious at controlling virus replication and decreasing liver-enzyme levels.

Authorship

QH and CB: collected data for the study. BR: followed patients treated with IFN-alpha. DS: responsible of the liver transplant department. BC: responsible of the renal transplant department. AD: designed the study.

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