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ORIGINAL ARTICLE

Pegylated interferon-α-based treatment for chronic hepatitis C in renal transplant recipients: an open pilot study

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Summary

Treatment of hepatitis C in renal transplant recipients remains a controversial issue, as interferon therapy has been associated with a high risk of rejection and poor efficacy. We report here the use of pegylated interferon-α, alone or in combination with ribavirin, in renal transplant recipients with chronic hepatitis C. Eight renal transplant recipients with chronic hepatitis C were recruited. The mean delay between renal transplantation and antiviral therapy was 198.8 months. Sustained virological response was observed in four of out eight patients. Three patients with sustained virological response were genotype 2, one was genotype 1; fibrosis stages were F1 for one patient, F2 for 2, F3 for one. At baseline, renal dysfunction was moderate in seven patients and severe in one patient. No patient experienced rejection episodes during or after pegylated interferon-α therapy. One patient developed haemolytic uraemic syndrome, which eventually resulted in graft loss and return to dialysis. In conclusion, for renal transplant recipients treated with pegylated interferon-α-based therapy, we observed a low risk of renal dysfunction, acceptable tolerance and significant virological efficacy. This is therefore the first study to suggest that pegylated interferon-α could be proposed late after transplantation to renal transplant recipients.

Introduction

Renal transplantation is associated with a more severe evolution of chronic hepatitis C when compared with an hepatitis C virus (HCV)-infected immunocompetent population [1]. Moreover, it has been demonstrated that renal transplant recipients with anti-HCV antibodies have an increased risk of mortality and graft failure compared to anti-HCV negative recipients [2]. Treatment of hepatitis C in renal transplant recipients remains a controversial issue, as interferon therapy has been associated with a high risk of rejection and poor efficacy. In various studies in renal transplant recipients, interferon treatment was associated with a rejection risk of up to 60%, a 20% graft loss rate and an increase in viral load after discontinuation of therapy [3]. Thus, interferon is considered contraindicated in these patients, except in those who develop cholestatic fibrosing hepatitis [4]. Attempts to treat these patients with other antiviral drugs were disappointing. Ribavirin monotherapy and amantadine monotherapy were associated with no change in HCV viral load and an absence of improvement in liver fibrosis [5–7]. We report here for the first time the use of pegylated interferon-α, alone or in combination with ribavirin, in renal transplant recipients with chronic hepatitis C, analysing efficacy, tolerance and safety of this antiviral therapy.

Patients and methods

Renal transplant recipients with chronic hepatitis C were recruited regardless of renal graft function, with the following inclusion criteria: renal transplantation at least 1 year previously, absence of rejection episodes over the past 12 months, liver biopsy-proven chronic hepatitis. Renal graft dysfunction was defined as follows: absent for creatinine clearance >60 ml/min, moderate for creatinine clearance between 30 and 60 ml/min and severe for creatinine clearance <30 ml/min. Creatinine clearance was estimated with the Cockroft–Gault formula.

Chronic hepatitis C was defined as follows: presence of HCV antibodies and HCV RNA associated with histological lesions. HCV antibodies were assessed by third generation Elisa tests. The HCV genotype was determined by the Inno-LiPA method (Bayer Diagnostics, Tarrytown, NY, USA) or by the TRUGENE HCV 5′NC genotyping kit (Bayer Diagnostics). HCV RNA was quantified using bDNA VERSANT HCV RNA 3.0 method (Bayer Diagnostics), or real time PCR Cobas Taqman (Roche Molecular Systems, Branchburg, NJ, USA). Each patient had a liver biopsy before starting antiviral therapy. The grade of inflammatory lesions and the stage of fibrosis were assessed by the Metavir score.

Pegylated interferon-α-2a, 180 μg/week or α-2b, 1.5 μg/kg/week, was given to all patients. In five patients, low doses of ribavirin (400 mg/day) were added to pegylated interferon for the following reasons: nongenotype 1 infection with severe Metavir score (F3/F4) or genotype 1 hepatitis C infection. The period of treatment was 24–48 weeks in patients with genotype 2 hepatitis and 48 weeks in all other patients.

The following study end-points were assessed at the beginning of treatment, at the end of treatment and 6 months after treatment discontinuation: alanine aminotransferase, HCV viral load, serum creatinine and creatinine clearance. Response to treatment was defined by the absence of detection of HCV RNA and classified as follows: end-of-treatment response and sustained virological response (6 months after the end of treatment).

Results

Patients

Eight renal transplant recipients with chronic hepatitis C, transplanted between 1978 and 2003, were recruited (Table 1). The eight patients were male and all were recipients of a cadaveric kidney transplant. The mean age at renal transplantation was 35.8 years (range 22–63).The mean age at the time of diagnosis of hepatitis C infection was 40.1 years (range 29–57). The mean age at the beginning of antiviral therapy was 52.2 years (range 37–65). The mean delay between renal transplantation and antiviral therapy was 198.8 months (range 20–336). Immunosuppression was based on cyclosporin A in four patients, in addition to corticosteroids (CS) and azathioprine (AZA), in three and two patients respectively. Two patients were on tacrolimus, in addition to CS and mycophenolate mofetil (MMF) in two and one patients respectively. Finally, one patient was on CS and AZA and one patient was on CS and MMF.

HCV infection

The baseline characteristics of HCV infection in the eight patients are presented in Table 2. Four patients were infected with genotype 2, two patients were infected with genotype 1 and two patients were infected with genotype 5. The mean HCV viral load was 1 554 250 IU/ml (range from 14 000 to 3 850 000). The fibrosis stage was F1 in one patient, F2 in two patients, F3 in three patients, F4 in one patient. The protocol and the results of antiviral treatment are presented in Table 3. Four patients received pegylated interferon-α alone and four patients received pegylated interferon-α in association with a reduced dose of ribavirin, empirically adapted to creatinine clearance. The scheduled duration of treatment was 48 weeks for

Table 1. Demographic and kidney transplantation characteristics of patients.

Patients	Gender	Age at Tx	Indication for Tx	IS regimen	Graft dysfunction	Age HCV diagnosis
1	M	22	Undetermined nephropathy	Tac/Ste	Moderate	37
2	M	63	Diabetes mellitus	Tac/MMF/Ste	Moderate	57
3	M	40	Alport syndrome	CsA/Ste	Moderate	40
4	M	56	Chronic glomerulonephritis	CsA/Aza/Ste	Moderate	51
5	M	21	Nephroblastoma	CsA/Aza/Ste	Moderate	31
6	M	32	IgA nephropathy	Aza/Ste	Severe	36
7	M	24	IgA nephropathy	MMF/Ste	Moderate	ND
8	M	29	Undetermined nephropathy	CsA/Ste	Moderate	29

M, male; Tx, transplantation; IS, immunosuppressive; Tac, tacrolimus; Ste, steroids; MMF, mycophenolate mofetil; Aza, azathioprin; CsA, cyclosporin; HCV, hepatitis C virus.

Table 2. Baseline characteristics of HCV infection.

Patients	Time Tx/treatment (months)	Age at treatment	Genotype	Viral load (UI/ml) before treatment	Metavir score	ALT (normal value) before treatment
1	312	46	2b	2.200.000	A1F3	26 (37)
2	23	65	2c	1.300.000	A2F1	80 (43)
3	156	53	2	14.000	A1F2	24 (37)
4	20	58	1b	2.500.000	A2F4	163 (37)
5	192	37	5a	540.000	A2F3	117 (37)
6	228	51	5a	730.000	A3F3	40 (37)
7	336	52	2	3.850.000	A2F2	16 (33)
8	324	56	1b	1.300.000	A1F2	143 (37)

Tx, transplantation; ALT, alanine aminotransferase.

Table 3. Type and results of antiviral treatment.

Patients	Treatment	Scheduled duration (weeks)	Completed duration (weeks)	ALT ETR (normal value UI/l)	ALT SVR (normal value UI/l)	RNA ETR (normal value UI/l)	RNA SVR (normal value UI/l)
1	Peg-∝-2b 1.5 μg/kg/week Riba 400 mg/day	48	48 Peg-∝-2a 12 Riba	10 (<43)	15 (<43)	<50	<50 SVR
2	Peg-∝-2a 180 μg/week	24	24	12 (<43)	15 (<43)	<50	<50 SVR
3	Peg-∝-2a 180 μg/week	24	24	21 (<37)	20 (<37)	<15	<15 SVR
4	Peg-∝-2b 1.5 μg/kg/week Riba 400 mg/day	48	35 (Depression)	25 (<41)	ND	117.490 NR	ND
5	Peg-∝-2b 1.5 μg/kg/week Riba 400 mg/day	48	12 (Anaemia)	46 (<60)	ND	1.056.003 NR	ND
6	Peg-∝-2a 180 μg/week	48	16 (Anaemia, HUS)	25 (<40)	ND	<43	26.705 R
7	Peg-∝-2a 180 μg/week	48	16 (Anaemia)	24 (<33)	ND	<50	4.012.369 R
8	Peg-∝-2a 180 μg/week Riba 400 mg/day	48	24 (Papillary oedema)	25 (<37)	22 (<37)	<15	<15 SVR

ETR, end of treatment response; SVR, sustained virological response; SBR, sustained biochemical response; NR, nonresponder; R, relapser; ALT, alanine aminotransferase; Riba, ribavirine; HUS, haemolytic uraemic syndrome; ND, not determined.

patients infected with genotype 1 and 5, and 24 weeks for patients infected with genotype 2, except for two patients with severe fibrosis score and/or high viral load.

Virological response

An end-of-treatment virological response was observed in six out of eight patients and a sustained virological response in four out of eight patients. Sustained virological response according to genotype was 75% for genotype 2, 50% for genotype 1, 0% for genotype 5. Three patients with sustained virological response were genotype 2 and one was genotype 1, whereas fibrosis stages were F1 for one patient, F2 for two and F3 for one. These four patients completed their pegylated interferon-α treatment as scheduled, except for one. For one of the patients, ribavirin was discontinued at week 12 because of anaemia. The two patients with HCV relapse were genotype 2, fibrosis stage F2 and genotype 5, fibrosis stage F3 respectively. Pegylated interferon-α was discontinued at week 16 in these two patients because of anaemia. The 2 nonresponder patients were genotype 5, fibrosis stage F3 and genotype 1, fibrosis stage F4. Pegylated interferon-α was discontinued because of anaemia at week 12 in one patient and at week 16 in a second patient, because of depression at week 35 in one patient and because of papillary oedema at week 24 in another patient.

Safety

Renal graft function before treatment and during antiviral therapy is shown in Table 4. At baseline, renal dysfunction was moderate in seven patients and severe in one patient (biopsy-proven chronic rejection). No patient

Table 4. Evolution of renal function during antiviral therapy.

Patients	Creatinine BT μmol/l	Clearance BT ml/mm	Creatine ET μmol/l	Clearance ET ml/mm	Creatine FU μmol/l	Clearance FU ml/mm
1	216	36	190	44.7	214	39
2	130	47.5	106	58.2	122	49.9
3	194	30.7	177	33.7	250	23.9
4	175	40.7	167	42.1	158	44.5
5	163	39	161	37.9	149	42.7
6	207	30.9	268	25.2	Haemodialysis	
7	164	41	159	40.1	ND	ND
8	169	40	125	53	138	48

BT, before treatment; ET, end of treatment; FU, follow-up; ND, not determined.

experienced rejection episodes during or after pegylated interferon-α therapy. One patient, with severe initial graft dysfunction, developed haemolytic uraemic syndrome, which eventually resulted in graft loss and return to dialysis. In this patient, pegylated interferon-α was discontinued at week 16 because of anaemia, and haemolytic uraemic syndrome (HUS) was diagnosed at week 18.

Discussion

Combination antiviral hepatitis C therapy, the standard of care in the nontransplant population, is generally contra-indicated in renal transplant recipients, because of documented renal graft rejection secondary to interferon treatment and poor efficacy [8]. The viral hepatitis guidelines for haemodialysis and transplantation patients published in 2004 concluded that 'the evaluation of efficient therapeutic strategies for these patients requires further clinical studies' [3]. The results of our pilot study suggest for the first time that pegylated interferon-α may be safely and efficiently used in renal transplant recipients with hepatitis C.

From an ethical point of view, the decision to treat renal transplant recipients was justified by the severity of liver injury – three patients were METAVIR F2 and four patients were ≥METAVIR F3 – the long follow-up after transplantation and the favourable genotype 2 in the patient whose liver injury was least severe (METAVIR F1).

No patient experienced acute rejection episodes during and after antiviral treatment and renal function did not deteriorate except in one patient. In this regard, it must be emphasized that the mean delay between transplantation and pegylated interferon-α administration was about 16 years, suggesting that the graft was well-tolerated. This probably reduced the risk of rejection related to pegylated interferon-α use and could explain the stability of renal function during treatment. In the previous studies, the post-transplant delay was shorter. Thus, in five studies demonstrating that graft dysfunction was irreversible and steroid-resistant, the mean interval after transplantation was between 2 and 7 years [9–13]. Another point concerns the time lapse between initiation of therapy and rejection. In previous studies, it varied from a few days to more than 6 months, but the average time to rejection was 3–6 months, irrespective of the duration of stable renal function [8]. In our study, excluding the patient who returned to dialysis after HUS, the remaining seven patients were monitored for 6 months after the end of therapy, resulting in a mean follow-up of 36 months (18–54) and no rejection episode was observed.

Haemolytic uraemic syndrome, characterized by microangiopathic haemolysis, thrombocytopenia and renal dysfunction, was described in one patient, 16 weeks after initiation of pegylated interferon-α. Although treatment was withdrawn, renal dysfunction progressed, resulting in graft loss and dialysis-dependent renal failure. HUS is a well-recognized complication of interferon therapy. Many reports have documented the development of HUS in patients who have undergone treatment with interferon-α for chronic myeloid leukaemia [14–16] or Kaposi's sarcoma [17]. It has also been described in the setting of solid-organ transplantation, where HUS is attributed to calcineurin inhibitor toxicity [18]. In the latter situation, prognosis is poor with up to 50% graft loss in renal transplant recipients and dialysis requirement in nonrenal transplant recipients [18]. In our patient, pegylated interferon-α monotherapy was started 19 years after transplantation, under an azathioprin and steroids immunosuppressive regimen. Thus, HUS is likely to be attributed to pegylated interferon-α. One issue is to differentiate HUS from the side effects of pegylated interferon-α (i.e. thrombocytopenia) and ribavirin (i.e. haemolysis). Our patient did not receive ribavirin because of poor renal function related to chronic rejection.

In a meta-analysis of 12 clinical trials (102 patients), Fabrizi *et al.* [8] showed that the efficacy of interferon-α-based therapy for hepatitis C after renal transplantation was poor: the mean overall estimate for sustained virological response was 12%. This is not so different from the

results of interferon-α monotherapy in nontransplant naive patients with chronic hepatitis C infection [19]. In our study, using pegylated interferon-α in all eight cases combined with low doses of ribavirin in four patients, the end-of-treatment virological response was 75% and the sustained virological response was 50%. These surprising results raise several comments.

First, genotype 1, the most common and the most difficult to treat of all genotypes, was under-represented in our patient population. Secondly, all previous studies in the setting of renal trasplantation used interferon-α alone, 3 million units × 3/week. Pegylated interferon-α monotherapy is more efficient than interferon-α monotherapy, with a two-fold increase in sustained virological response [20,21]. Moreover, pegylation of interferon-α has made it less susceptible to renal clearance than nonpegylated interferon-α [22]. As a result, pegylated interferon-α may be easier to use in patients with renal dysfunction compared with nonpegylated interferon-α. In our population, seven out of eight patients had at least moderate renal dysfunction, assessed by a creatinine clearance <60 ml/min. Our findings are consistent with the results of pegylated interferon-α-based therapy in the nontransplant population: discordance between biochemical and virological response, higher sustained virological response in genotype two patients, poor results if the scheduled duration of treatment is not completed. On the other hand, the benefit of using low doses of ribavirin is not clear. The clinical tolerance of pegylated interferon-α was relatively poor, as five of eight patients dropped out of treatment because of anaemia, depression and papillary oedema. Among them, only one had a sustained virological response. This poor tolerance was partly explained by the use of normal pegylated interferon doses, although it has been proposed to use reduced doses of pegylated interferon in patients with moderate-to-advanced renal failure [23].The three patients who completed the treatment had sustained virological response.

In conclusion, in renal transplant recipients treated with pegylated interferon-α-based therapy, we observed a low risk of renal dysfunction, poor tolerance and significant virological efficacy. Thus, this study suggests for the first time that pegylated interferon-α could be proposed late after transplantation to renal transplant recipients with significant lesions related to chronic hepatitis C and/or favourable genotype.

Authorship

GP: designed study, collected and analysed data, wrote the paper. MN: performed study and collected data. V: performed study and analysed data. M and H: performed study. JP: analysed data. G: designed study, performed study and analysed data.

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