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Original Article

Efficacy and tolerance of interferon-α_{2b} in the treatment of chronic hepatitis C virus infection in haemodialysis patients. Pre- and post-renal transplantation assessment

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Abstract

Background. Hepatitis C virus (HCV) infection represents an important problem for the dialysis population due to its high prevalence and the long-term development of chronic liver disease, particularly following renal transplantation.

Methods. In order to assess the efficacy and tolerance of interferon (IFN) in the treatment of chronic hepatitis C in haemodialysis (HD) patients and their clinical course following renal transplantation, a multicentre, randomized, open-label study was conducted to compare IFN therapy *vs* a control group.

Results. Nineteen HCV RNA-positive patients received 3×10^6 U of IFN s.c., three times a week (post-HD), and 17 HCV RNA-positive patients were assigned to the control group. Tolerance to IFN therapy was good in nine patients, while treatment was discontinued in the other 10 due to the occurrence of side effects. HCV RNA was negative at the end of treatment in 14 out of 19 patients (74%) receiving IFN and in one patient (5%) in the control group. Six out of the 14 patients who initially responded to IFN therapy had a virological relapse (43%). Eight patients (42%) remained HCV RNA-negative, three of them until the day that renal transplantation (RT) was performed (7, 12 and 27 months, respectively), as did five patients on HD during the follow-up (27 ± 5 months). Eight out of the nine patients (89%) who completed therapy were HCV RNA-negative at the end of treatment, and seven of them (78%) remained HCV RNA-negative during the follow-up on dialysis (21 ± 8 months). Mean transaminase (ALT) values were significantly decreased following IFN therapy, while no changes were observed during the follow-up period in the control group. Fifteen patients (10 in the treatment group and five in the control group) underwent RT. Three patients in the treatment group were HCV RNA-negative at RT, and one of them had a virological relapse 20 months after RT, while the other two remained HCV RNA-negative at 3 months and 24 months after RT, respectively. In contrast to the control group, transaminase (ALT) remained within normal limits in all patients in the treatment group. Finally, during the post-RT follow-up, the transaminase mean values were significantly lower in treated patients *vs* patients in the control group ($P < 0.05$).

Conclusions. It is concluded that the biochemical and virological response to IFN therapy is good in HD patients. In addition, IFN therapy appears to exert a beneficial effect on the course of liver disease following RT, regardless of the virological response. Despite the fact that IFN therapy was discontinued in 10 out of the 19 patients due to the occurrence of side effects, these disappeared following discontinuation of therapy. Therefore, IFN therapy is advisable for HCV-infected dialysis patients who are candidates for RT.

Key words: hepatitis C virus; interferon; haemodialysis; renal transplantation

Introduction

The prevalence of hepatitis C virus (HCV) infection among haemodialysis (HD) patients ranges between 10 and 68% [1–3]. HCV infection is the main cause of chronic liver disease among renal transplantation (RT) recipients [4–6], this being the fourth most prevalent cause of mortality in the renal-transplanted population.

Interferon (IFN) has proven effective for the treatment of HCV-induced chronic hepatitis in immuno-

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competent subjects [7,8], with variable response rates (25–60%) depending on the status of the patients. Efficacy and tolerance studies for IFN therapy showing relatively high response rates in the HD population are still limited [9–14]. The limited response to IFN therapy [15] together with the high risk of acute graft rejection and/or renal graft dysfunction during IFN therapy [15–17] make it inadvisable for renal transplant recipients. For this reason, it is essential to administer IFN therapy during the dialysis period and prior to inclusion on the waiting list for RT.

The objective of the present study was to assess the efficacy and tolerance of IFN-α_{2b} in the treatment of HCV-induced chronic hepatitis in HD patients and their evolution following RT. A multicentre, randomized and open-label study comparing IFN therapy *vs* an observational control group was conducted.

Patients and methods

Patients

A total of 36 patients with chronic renal failure undergoing HD and with active HCV infection were enrolled. All patients were anti-HCV positive [second generation enzyme-linked immunosorbent assay (ELISA)] and HCV RNA-positive as determined by polymerase chain reaction (PCR using primers of the 5′-untranslated region of the viral genome) [18]. Patients were from seven haemodialysis units in Catalonia and were included on a waiting list for RT. Patients gave written consent to therapy. None of them was positive for hepatitis B virus nor had antibodies for human immunodeficiency virus. The protocol was approved by the Ethics and Research Committee in our centre and by the Ministry of Health and Consumer Affairs.

The 36 patients enrolled were randomized, and 19 were assigned to the IFN group and 17 to the control group. Patients in the IFN group received s.c. IFN-α_{2b} (Intron A, Schering-Plough) at a dose of 3×10^6 U three times a week, following every HD procedure for 6 months. Acetaminophen (600 mg) was administered concomitantly with IFN therapy in order to prevent flu-like syndrome. The control group were merely observed, no therapeutic changes were introduced nor was placebo administered.

The demographic features were similar in both groups, with no significant differences with respect to the period on dialysis and the time of HCV infection (Table 1). Transaminases (AST/ALT) were monitored before, during and after IFN therapy on a monthly basis. HCV was genotyped in 20 patients. HCV genotyping was performed by restriction fragment length polymorphism (RFLP) analysis of the 5′-untranslated region as described by López-Labrador *et al.* [19]. The viral replicative activity (HCV RNA) was determined for both patient groups every month during the treatment period and every 2 during the follow-up period. Haematology tests were also performed every week during the first month of treatment and every month for the remainder of treatment.

A transient response was defined as a negative serum HCV RNA during IFN therapy and subsequent reappearance, and sustained response was defined as a negative HCV RNA at the end of treatment which remained negative throughout follow-up on HD or until the date of RT.

Tolerance to IFN and side effects which developed during treatment were also assessed. Side effects were classified as flu-like syndrome (fever, asthenia, arthralgias, myalgias) associated with the first IFN dose, specific gastrointestinal side effects (nausea, vomiting, diarrhoea), bone marrow depression with leukopenia and thrombocytopenia, and psychic profile of depression. RT was performed regardless of response to IFN therapy.

Results are expressed as mean ± standard deviation. The differences between the means in both groups were compared using analysis of variance. Ratio comparison was performed using a χ^2 test, and the comparison of results pre- and post-IFN-α_{2b} therapy was performed using the Wilcoxon test. A P-value <0.05 was considered significant.

Table 1. Epidemiological and biochemical features of patients in the interferon-α_{2b}-treated and control groups

	Treatment group ($n=19$)	Control group ($n=17$)
Age (years)	42 ± 12	48 ± 10
Gender (M/F)	9/10	10/7
THD (years)	6.4 ± 4	8 ± 4
Previous RT	63% (12)	59% (10)
Pre-treatment AST	31 ± 13 IU/l[a]	39 ± 36 IU/l
Pre-treatment ALT	42 ± 16 IU/l[a]	48 ± 40 IU/l
Post-treatment AST	23 ± 8 IU/l[b]	49 ± 46 IU/l
Post-treatment ALT	27 ± 11 IU/l[b]	45 ± 25 IU/l
Hepatic profile changes (pre-treatment) (*)	10/19 (53%)	10/17 (59%)
Hepatic profile changes (post-treatment) (*)	0/19 (0%)[c]	8/17 (47%)

THD = time on haemodialysis; RT = renal transplantation; AST = aspartate aminotransferase; ALT = alanine aminotransferase; (*) = transient or persistent AST/ALT increase more than twice the normal limit (normal limit of AST and ALT: 10–40 IU/l).
[a]$P<0.05$ *vs* treated group 'post-treatment'; [b]$P<0.05$ *vs* control group 'post-treatment'; [c]$P<0.05$ *vs* control group.
All values are means ± SD.

Results

In the IFN group, the mean follow-up period post-IFN therapy was 21 ± 10 months (range: 3–33 months) while on HD, and 17 ± 9 months (range: 3–31 months) post-RT for the 10 transplant recipients. In the control group, the mean follow-up period was 27 ± 10 months (range: 12–46 months) while on HD, and 20 ± 15 months (range: 3–40 months) post-RT for the five transplant recipients.

Efficacy of IFN

Nine (47%) out of the 19 patients in the treatment group were treated for 6 months as scheduled, and 10 were withdrawn from treatment due to intolerance or side effects. Eight (89%) out of the nine patients who completed treatment were HCV RNA-negative at the end of treatment, and seven (78%) had a sustained response.

Loss of HCV RNA was documented at discontinuation for six (60%) out of the 10 patients who did not complete the 6 months of treatment, and five of them

(83%) had a virological relapse during follow-up. Only one patient who was treated for 1 month had a sustained response. The period on dialysis was similar in both groups, responders and non-responders, without statistical differences.

The sustained response rate for the treated group was 42% overall (eight out of 19 cases). HCV RNA remained negative in three patients until the day on which RT was performed at 7, 12 and 27 months of follow-up, respectively. In five patients, HCV RNA remained negative while on HD (27 ± 5 months) (Table 2). Eighteen patients were genotyped in the drug group: 15 were 1b and only 10 of them responded to treatment, while two patients who were type 1a and one patient who was type 3a responded to IFN therapy.

One patient in the control group became HCV RNA-negative during follow-up. Eight patients were genotyped: 10 patients were 1b and the other was 1a.

There were no significant differences between baseline transaminase (ALT/AST) values in either study group (Table 1). Ten (53%) out of the 19 patients in the treatment group had a history of transient and/or persistent transaminase increase 2-fold greater than normal limits (10–40 IU/l); this ratio was 10/17 patients (59%) in the control group. A significant and sustained decrease of mean transaminase values was observed following completion of IFN-α_{2b} therapy; no significant changes were observed in the control group during the follow-up period (Table 1). Normalization of the hepatic profile was observed during follow-up in all IFN-treated patients ($n = 10$) regardless of the virological response and prior elevations of the transaminase levels. No significant changes in the hepatic profile were observed in the control group during follow-up.

Tolerance and safety of IFN

Treatment was discontinued in 10 out of the 19 patients in the IFN group due to tolerance problems and/or side effects not corrected by IFN dose reduction to 1×10^6 U, while the other nine patients tolerated IFN therapy well for 6 months. The reasons for IFN discontinuation were: persisting leukopenia ($< 2000/mm^3$) in three patients, severe anaemia with haematocrit of 21% (previous haematocrit was 33%) despite an increase of the recombinant human erythropoietin dose in one patient, severe diarrhoea in one patient and occurrence of depressive syndrome in another. IFN therapy was discontinued in four patients subsequently to the occurrence of severe flu-like symptoms with limited response to acetaminophen. Side effects to IFN therapy subsided in all patients following discontinuation of treatment, and no related serious adverse effects or deaths were reported.

Post-renal transplantation course

Ten patients in the IFN group and five in the control group underwent RT from cadaver donors. Fourteen out of the 15 transplant recipients were treated with conventional immunosuppressive therapy with cyclosporin plus prednisone. One patient received induction with ATG. Two patients died during the post-

Table 2. Tolerance and virological features of IFN-α_{2b}-treated patients during the follow-up period while on haemodialysis or until renal transplantation

No.	T	Reason for IFN discontinuation	HCV RNA baseline (genotype)	HCV RNA end IFN	HCV RNA after <6 months	HCV RNA after 6–12 months	HCV RNA after 12–24 months	HCV RNA after >24 months
1	6	No	+ (1b)	+	+	+	+	+(27 months) HD
2	6	No	+ (1b)	−	−	−	−	−(26 months) HD
3	6	No	+ (1b)	−	−	+	+	+(27 months) RT
4	6	No	+ (1b)	−	−	−	−	−(27 months) RT
5	6	No	+ (1b)	−	−	−	−	−(27 months) HD
6	6	No	+ (1a)	−	−	−(7 months) RT		
7	6	No	+ (1a)	−	−	−	−(12 months) RT	
8	6	No	+ (1b)	−	−	−	−(19 months) HD	
9	6	No	+ (1b)	−	−	−	−	−(29 months) HD
10	2.5	FLS	+(1b)	+	+(3 months) RT			
11	1.5	D	+(1b)	+	+	+	+	+(32 months) HD
12	3.5	LP	+(1b)	+	+(5 months) RT			
13	2.5	FLS	+(1b)	+	−(1 month) +(4 months)		+(16 months) RT	
14	3.5	AN	+(1b)	+	−(3 months) +(4 months) RT			
15	1.5	FLS	+(1b)	+	+	+	+	+(32 months) RT
16	1.5	DP	+(1b)	−	−	−	+(17 months) +(22 months) RT	
17	3	LP	+(3a)	−	−	−	+(20 months) HD	
18	1	LP	+(1b)	+	−	−	−	−(33 months) HD
19	1	FLS	+(ND)	−	−	−	−	+(27 months) HD

T = duration of IFN therapy (months); FLS = severe flu-like syndrome; D = diarrhoea; AN = anaemia; LP = leukopenia; DP = depression; RT = peri-renal transplantation lab; HD = last lab on haemodialysis.

Table 3. Virological and hepatic profile evolution prior to and following IFN-α_{2b} therapy whileon haemodialysis, and following renal transplantation (10 patients in the treatment group and five in the control group)

No.	T/C	Hepatic profile pre-IFN	HCV genotype	Resp IFN (time)	Hepatic profile post-IFN	HCV RNA peri-RT	Hepatic profile post-RT	HCV RNA evolution and RT FU
1	T	Normal	1b	No	Normal	Pos	Normal	Exitus RT/18 months*
2	T	>2N	1b	No	Normal	Pos	Normal	Pos RT/18 months*
3	T	Normal	1b	Yes (4 months)	Normal	Pos	Normal	Pos RT/20 months
4	T	Normal	1b	Yes (6 months)	Normal	Pos	Normal	Pos RT/5 months
5	T	>2N	1b	Yes (4 months)	Normal	Pos	Normal	Pos RT/31 months
6	T	Normal	1b	No	Normal	Pos	–	Pos RT/0 months*
7	T	>2N	1b	Yes (27 months)	Normal	Neg	Normal	Neg RT/3 months
8	T	Normal	1a	Yes (7 months)	Normal	Neg	Normal	Neg RT/24 months
9	T	Normal	1a	Yes (12 months)	Normal	Neg	>2N	Pos RT/20 months
10	T	Normal	1b	No	Normal	Pos	Normal	Pos RT/15 months
11	C	>2N	1b	–	–	Pos	>2N	Pos RT/8 months
12	C	Normal	(ND)	–	–	Pos	Normal	Pos RT/32 months
13	C	Normal	1b	–	–	Neg	Normal	Exitus RT/3 months
14	C	>2N	1a	–	–	Pos	>2N	Pos RT/40 months
15	C	Normal	(ND)	–	–	Pos	>2N	Pos RT/18 months

T = treated patient; C = control patient; IFN = IFN-α_{2b}; >2N = transient or sustained transaminases elevation greater than twice normal; Resp IFN = post-IFN loss of HCV RNA; time = duration of loss of HCV RNA; HD = haemodialysis; RT = renal transplantation; RT FU = follow-up of the renal graft; Pos = HCV-RNA-positive. Neg = HCV RNA-negative; *Evolution to HD.

transplant course (one in the IFN group and one in the control group), two patients developed chronic rejection and HD was resumed. Renal graft function was normal in 11 patients (seven in the IFN group and four in the control group). Three patients (3/10) were HCV RNA-negative at transplantation, and all of them had a normal renal function during follow-up.

Following RT, transaminase levels remained within normal limits in all patients of the IFN group, except for a transient increase in one patient who had a relapse of HCV infection. Mean ALT values were significantly lower in patients with a sustained response than in those with relapse of HCV infection (20 ± 7 UI/l *vs* 31 ± 4 UI/l, respectively, $P < 0.05$). Three out of the five renal recipients in the control group had persistent transaminase changes. The mean transaminase values were significantly lower in the IFN group than in the control group (AST 22 ± 6 IU/l *vs* 46 ± 30 IU/l; ALT 28 ± 8 IU/l *vs* 61 ± 23 IU/l; $P < 0.05$).

One out of the three patients who were HCV RNA-negative at RT had a relapse of the infection at 20 months of post-transplantation follow-up, while the other two remained HCV RNA-negative at 3 and 24 months post-RT, respectively. Patients who were HCV RNA-positive at transplantation remained HCV RNA-positive throughout follow-up.

Discussion

Despite the fact that HCV infection in HD patients is usually subclinical, a substantial proportion of patients have histological chronic hepatitis and/or cirrhosis lesions [20–22]. In addition, HCV infection is the main cause of chronic liver disease among renal transplant recipients. Most of the reported series document a prevalence of histologically confirmed active chronic hepatitis ranging between 42 and 59% of the anti-HCV positive patients [4–6]. The immunosuppressive therapy administered following RT accelerates the progression to hepatopathy [5,23–25]. This is probably related to the activation of viral replication, since a significant increase of post-RT HCV RNA levels has been demonstrated [26]. Levels have also been shown to increase during steroid therapy in non-uraemic subjects with chronic HCV hepatitis [27]. Consequently, the inclusion of HCV-positive patients with evidence of chronic liver disease on a waiting list for RT has often been questioned, although a recent study suggests that survival of HCV-positive patients is higher following RT than on dialysis [28]. Discrepancies exist regarding the relevance of HCV liver disease in transplant recipients. Although it has been reported that there are no differences in renal graft survival and patient survival between HCV-infected and non-infected patients during a 10-year follow-up [4,25,29,30], some other studies suggest the opposite [31,32]. Differences in immunosuppressive regimens, pre-transplant liver lesions and follow-up periods would account for these discrepancies. On the other hand, a higher cyclosporin-induced hepatotoxicity in HCV-positive transplantation recipients has been suggested [33].

IFN-α has proven effective for the treatment of HCV infection in immunocompetent subjects [7,8], with a response rate of $\sim 50\%$. However, remission is sustained in only 20–25% of the treated patients [34]. There are a few studies on dialysis populations in the literature, and discrepancies exist on the efficacy and safety of IFN in this population. IFN therapy is not administered universally to the uraemic dialysis population.

In our series, 74% of the patients responded to IFN therapy with loss of HCV RNA. This is a higher rate

than that reported in other HD patient series where response was ~50% [9–12] (Table 4). In our study, 57% of the responder patients (eight out of 14 patients) remained free from active infection throughout the follow-up period (7–33 months) and six patients (43%) relapsed. Eight out of the nine patients who completed the 6 months of treatment (89%) responded to therapy, and seven of them remained free from active infection throughout the entire study period (78%). A significant decrease of ALT values was observed in the IFN group with significant differences compared with the control group. These differences were observed in all IFN-treated patients and were maintained following RT.

Tolerance to IFN was worse than that reported for the non-uraemic population, and IFN therapy was discontinued in 53% of the patients enrolled. These data are in agreement with the series reported in the literature for dialysis patients [9–12]. However, IFN discontinuation was due to flu-like syndrome in half of the cases and it fully resolved following discontinuation of IFN therapy. Haematological disturbances were the most important adverse effect and included severe leukopenia and/or anaemia resistant to recombinant human erythropoietin therapy. The occurrence of a depressive syndrome in one patient and severe diarrhoea in another were also causes for discontinuation of treatment. However, withdrawal led in all cases to the disappearance of the side effects, and no serious adverse effects were observed.

IFN therapy in HCV-infected renal transplant recipients, despite the achievement of a good biochemical response, does not result in the loss of HCV RNA at standard doses. The potential of IFN to induce acute rejection and/or renal graft dysfunction has been well described in the literature [15–17]. Thus, the limited response and the association of serious side effects contraindicate IFN for HCV-infected renal transplant recipients. However, due to the risk for post-RT progression of liver disease, IFN therapy should be mandatory for HCV-infected patients on dialysis who are candidates for RT, prior to their inclusion on a waiting list. With the exception of one patient, transaminases of the IFN-treated patients remained within normal limits following RT, even without achieving a negative HCV RNA, except for a transient increase in one patient; while three out of the five transplant recipients in the control group had persistent changes of the hepatic profile.

In summary, HD patients who succeed in completing 6 months of therapy with IFN-α_{2b} attain a good response with sustained loss of HCV RNA in 78% of the patients at 2 years following completion of treatment. In addition, IFN-α_{2b} therapy for HCV-positive HD patients waiting for RT appears to exert a beneficial effect on the course of the HCV-induced chronic liver disease following transplantation regardless of the virological response. However, additional studies are needed in order to establish the virological and liver disease evolution following RT in patients treated while on dialysis. In addition, the loss of HCV in HD patients will decrease the risk for nosocomial transmission within HD units. We conclude that IFN therapy is beneficial and, therefore, advisable for HCV-infected dialysis patients prior to RT.

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Table 4. Interferon treatment of chronic hepatitis C infection in dialysis patients

References	No.	IFN (months)	Time (months)	Biological response (ALT)	Post-IFN virological response	Relapse HCV RNA	Sustained virological response
Koenig *et al.* [9]	23	IFN-Ga (4 months)	5	7/14 (50%)	15/23 (65%)	5/15 (33%)	10/23 (43%)
	14*	IFN-α (<3 months)			3/14 (21%)	1/3 (33%)	2/14 (14%)
Pol *et al.* [12]	15	IFN-α_{2b} (6 months)	19	11/13 (85%)	8/15 (53%)	5/8 (62%)	3/15 (20%)
Raptopoulou-Gigi *et al.* [10]	13	IFN-α_{2b} (12 months)	14	13/13 (100%)	10/13 (77%)	0/10 (0%)	12/13 (92%)
	6*	IFN-Ga_{2b} (<2 months)		0/6 (0%)	0/6 (0%)	0/0 (0%)	0/6 (0%)
Casanovas *et al.* [35]	2	IFN-α_{2b} (12 months)					
	8	Lymph-IFN (12 months)	9	9/10 (90%)	1/10 (10%)	0/1 (0%)	2/10 (20%)
Izopet *et al.* [11]	12	IFN-α_{2b} (6 months)	19	11/13 (85%)	11/12 (92%)	6/11 (54%)	5/12 (42%)
	8	IFN-α_{2b} (12 months)			7/8 (90%)	0/7 (0%)	7/8 (90%)
	3*	IFN-α_{2b} (<5 months)			3/3 (100%)	3/3 (100%)	0/3 (0%)
This study	9	IFN-α_{2b} (6 months)	21	5/5(100%)	8/9 (89%)	1/8 (12%)	7/9 (78%)
	10*	IFN-α_{2b} (6 months)		5/5(100%)	6/10 (60%)	5/6 (83%)	1/10 (10%)
	17	Control	27	2/10 (20%)	–	–	–

Time = follow-up (months); (*) discontinued treatment.

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