Evidence that Clearance of Hepatitis C Virus RNA after α-Interferon Therapy in Dialysis Patients Is Sustained after Renal Transplantation

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Abstract. To date, there is no available treatment of hepatitis C virus (HCV) infection after renal transplantation (RT). Among 55 anti-HCV–positive/HCV RNA–positive hemodialysis patients who were treated with IFN-α (9 MU/wk during 6 or 12 mo), 21 of them (38%) had a sustained virologic response. Of these, 16 (76%) underwent RT 38 mo (range, 2 to 57 mo) after α-IFN therapy. There were 13 men and 3 women aged 46 yr (range, 27 to 68 yr). At RT, HCV serology was still positive in 15 patients, and HCV viremia was negative in all patients. Immunosuppression relied on anticalcineurin agents with or without steroids and/or antimetabolites; in addition, 12 of them received induction therapy with antithymocyte globulins. At the last follow-up after RT, at 22.5 mo (range, 2 to 88 mo), HCV viremia remained negative in all patients. Moreover, HCV RNA was not present in peripheral blood mononuclear cells when assessed in eight patients. HCV serology was found to be still positive in 13 patients. Three patients presented with acute rejection, one presented with a suppurative lymphocele, one died from a sepsis, and four presented with a cytomegalovirus infection. None of them developed posttransplant diabetes mellitus. In conclusion, hemodialysis patients waiting for a RT need to be treated with α-IFN because when HCV RNA clearance occurred, they experienced no relapse after transplantation despite chronic immunosuppressive treatment.

Despite the screening of blood donors for hepatitis C virus (HCV) and the use of recombinant erythropoietin for the treatment of anemia in end-stage renal failure, *de novo* cases of HCV infection still occur that result from nosocomial transmission. Hence, the prevalence of HCV infection in hemodialysis patients and renal transplant recipients remains high. HCV-positive renal transplant recipients' survival is higher than that of HCV-positive hemodialysis patients. Nevertheless, patient and graft survivals are lower in HCV-positive renal transplant patients compared with HCV-negative renal transplant recipients (1). After RT, immunosuppression results in a significant increase in HCV viremia (2). Moreover, there is no efficient and safe treatment of HCV infection in renal transplant recipients. The treatment of HCV-positive renal transplant recipients with IFN-α is associated with a low rate of HCV RNA clearance and a high rate of acute rejection (3). Ribavirin monotherapy in renal transplant recipients is associated with an improvement in liver enzymes; however, HCV viremia did not change significantly. In contrast, liver fibrosis progressed significantly after 1 yr of ribavirin monotherapy (4). The treatment of HCV-positive hemodialysis patients with IFN-α is associated with a sustained virologic response ranging from 20% to 92% of the cases (5,6). We report on 16 cases of HCV-positive patients who cleared HCV viremia while they were treated with IFN-α during hemodialysis, and who did not relapse after renal transplantation (RT).

Between 1993 and 1998, 55 anti-HCV–positive/HCV RNA–positive hemodialysis patients were treated with IFN-α. A virologic sustained response (*i.e.*, 6 mo after the end of IFN-α therapy) was observed in 21 patients (38%); 16 of these (76%) underwent RT. The five other patients are still on the waiting list and remain HCV RNA negative.

In the 16 patients who underwent RT (13 men and 3 women), ranging in age from 27 to 68 yr (median, 46 yr), the median time on dialysis and the median duration of HCV infection determined by using frozen sera at −20°C at the beginning of the treatment were, respectively, 83 mo (range, 36 to 188 mo) and 36 mo (range, 1 to 264 mo). IFN-α was provided at a dose of 3 MU three times per week after each hemodialysis session for a period of 6 mo (3 patients) or 12 mo (13 patients). Before 1994, the duration of IFN-α therapy was 6 mo. Thereafter, all patients were treated for 12 mo. Liver biopsies were performed before IFN-α therapy in 11 of the 16 patients and were graded according to the Knodell (7) and

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Metavir scores (8) (Table 1). The five other patients declined to undergo a liver biopsy. During IFN-α therapy, flu-like syndrome, gastrointestinal disorders, weight loss, and depressive syndrome were observed, respectively, in 10 (62.5%), 7 (44%), 7 (44%), and 7 (44%) patients. All patients presented with anemia, leucopenia, and thrombopenia during anti-HCV therapy. These patients underwent a cadaveric RT at 38 mo (range, 2 to 57 mo) after the end of the anti-HCV therapy. Anti-HCV antibodies and HCV RNA were negative in all cadaveric donors. Four patients were highly sensitized at transplantation. Consequently, they received an induction therapy based on antilymphocyte or antithymocyte globulins followed by anti-calcineurin-based immunosuppression. The other patients received an immunosuppressive treatment according to the immunosuppressive protocols used in the transplantation center at that time. Twelve patients received induction therapy that was based on antilymphocyte (Lymphoglobulines; Pasteur Mérieux, Lyon, France) or antithymocyte globulins (Thymoglobulines; Pasteur Mérieux). Antithymocyte and antilymphocyte globulins were administrated at a daily dose of 1 mg/kg for 3 d and, thereafter, the dose was adapted according to CD2 lymphocyte counts (target: CD2 $<50/mm^3$) until the serum creatinine level was under 22 mg/L; then calcineurin inhibitors were introduced. Two other patients received, as induction therapy, anti–IL-2 receptor antibodies (Basiliximab, Simulect) given at a dose of 20 mg on days 0 and 4 after transplantation. The last two patients did not have any induction therapy. Baseline immunosuppression relied on the association of a calcineurin inhibitor and steroids with either azathioprine (three patients) or mycophenolate mofetil (13 patients) (Table1). The targets of cyclosporin and tacrolimus levels were, respectively, 150 to 200 and 10 to 15 ng/ml during the first year and 100 to 150 and 5 to 10 ng/ml, respectively, thereafter. In two patients (patients 5 and 11), azathioprine was replaced with mycophenolate mofetil at 18 and 28 mo after transplantation. Two other patients (patients 7 and 10) were switched from cyclosporin A to sirolimus at 7 and 8 mo after transplantation because of a biopsy-proven anticalcineurin nephrotoxicity. The target of sirolimus through level was fixed between 5 and 10 ng/ml.

Materials and Methods

HCV Serology

The anti-HCV status of the patients was assessed with a 3-D–generation ELISA (ELISA III; Ortho Diagnostics Systems, Roissy, France). The duration of HCV infection was assessed retrospectively on stored sera.

HCV Genotyping

The HCV genotype was determined by the Inno-LiPA II HCV method (Innogenetics, Ghent, Belgium). The products of standardized quantitative reverse-transcription PCR (RT-PCR) amplification were hybridized to immobilized probes specific for the different genotypes and subtypes.

Serum HCV Concentration

The HCV RNA concentration was measured by a standardized quantitative RT-PCR assay (Roche COBAS, Amplicor HCV Quantitative Monitor Assay, Branchburg, NJ) according to the manufacturer's instructions.

Assessment of HCV in Peripheral Blood Mononuclear Cells

A modified HCV Amplicor assay was used to detect HCV RNA in PBMC (9). Briefly, the internal control was added to a 2×10^6–cell pellet before RNA extraction. Cells were lysed by thermal shock (three rounds of 15 s in liquid nitrogen and 30 s at 60°C) and incubation for 1 h at 60°C. Proteinase K was inactivated by incubation at 95°C for 10 min, and RNA was extracted with phenol and precipitated with ethanol. An aliquot of 50 μl of extracted RNA and internal quality standard were amplified, and RT-PCR products were detected by a COBAS Amplicor HCV system. The assay detection limit in PBMC was 100 copies/10^6 cells.

Statistical Analyses

Quantitative variables were compared by the Wilcoxon test. A P value below 0.05 was considered statistically significant.

Results

The posttransplantation follow-up was 22.5 mo (range, 2 to 88 mo). At that time, the median through level of cyclosporin was 102 ng/ml (range, 90 to 142 ng/ml). In the two patients receiving tacrolimus, levels were, respectively, 8.4 and 9.8 ng/ml. The median maintenance dose of mycophenolate mofetil was 2 g/d (range, 1 to 2 g/d).

Liver Parameters

At transplantation, median serum aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transferase (γ-GT) levels were, respectively, 13 IU/L (range, 7 to 41 IU/L), 17 IU/L (range, 6 to 77 IU/L), and 18 IU/L (range, 13 to 79 IU/L) (Table 2). At last follow-up, alanine aminotransferase and γ-GT levels were, respectively, 17.5 IU/L (range, 11 to 74 IU/L) and 26 IU/L (range, 11 to 107 IU/L) ($P > 0.05$ as compared with alanine aminotransferase and γ-GT levels at RT). By contrast, serum aspartate aminotransferase level increased significantly from 13 IU/L (range, 7 to 41 IU/L) to 22.5 IU/L (range, 10 to 46 IU/L) ($P = 0.04$).

Virologic Parameters

Before antiviral treatment, HCV serology and viremia were positive in all patients. Median HCV RNA concentration before treatment was 144,770 copies/ml (range, 578 to 3,368,960 copies/ml). Serum HCV RNA cleared at 3 mo (range, 1 to 4 mo) after the initiation of IFN-α therapy. At transplantation, HCV serology was positive in all patients but one, and HCV viremia was negative in all patients. At last follow-up, at 22.5 mo (range, 2 to 88 mo), HCV viremia remained negative in all patients. In addition, HCV RNA, which was determined by PCR in PBMC of 8 patients after transplantation, was found to be negative. HCV serology was still positive in 13 patients.

Graft Function

After transplantation, three patients (19%; patients 3, 5, and 9) presented with an acute rejection episode; all three were successfully treated with steroids boluses. One patient (patient

Table 1. Patient characteristics[a]

Patients	Primary Renal Disease	Duration of α-IFN Therapy (mo)	Liver Biopsy before Treatment (Total Knodell/Metavir Scores)	Time Since End of α-IFN Therapy and RT (mo)	HLA A/B/DR Matching	Induction Therapy	Immunosuppressive Treatment	
							3 mo after RT	Last Follow-up
1	Polycystic renal disease	6	NA	56	1A/1B	ATG	CsA/MMF/C	CsA/MMF/C
2	Henoch-Schölein purpura	6	3/A1F0	31	1B/1DR	ATG	CsA/MMF/C	CsA/MMF/C
3	NA	12	1/A0F1	36	1A/1DR	ATG	CsA/MMF/C	CsA/MMF/C
4	CIN	12	NA	6	1B/1DR	—	FK506/MMF	FK506/MMF
5	CGN	12	5/A1F1	17	1A/1B/1DR	ATG	CsA/AZA/C	CsA/MMF/C
6	Polycystic renal disease	12	NA	57	2A/1B/2DR	ATG	CsA/MMF/C	CsA/MMF/C
7	Malformative uropathy	12	1/A0F0	42	1A/2B/1DR	Anti-IL2R	CsA/MMF/C	SRL/MMF/C
8	IgA nephropathy	12	NA	2	2A/1B	—	FK506/MMF/C	FK506/MMF/C
9	CGN	12	3/A0F1	11	2DR	ATG	CsA/AZA/C	CsA/AZA/C
10	Henoch-Schölein purpura	12	5/A1F0	45	1A/1B/1DR	ATG	FK506/MMF/C	SRL/MMF/C
11	Malformative uropathy	6	4/A1F0	45	1A/1DR	ATG	CsA/AZA/C	CsA/MMF/C
12	Diffuse crescentic glomerulonephritis	12	8/A2F2	40	2DR	Anti-IL2R	CsA/MMF/C	CsA/MMF
13	Malformative uropathy	12	4/A1F1	44	1A/1B/2DR	ATG	CsA/MMF/C	CsA/MMF/C
14	NA	12	4/A1F1	38	2A/2B/2DR	ATG	CsA/MMF/C	CsA/MMF/C
15	Fanconi's syndrome	12	7/A2F2	31.5	2A/2B/1DR	ATG	CsA/MMF/C	CsA/MMF/C
16	MGN	12	NA	5	1B/1DR	ALG	CsA/MMF/C	CsA/MMF

[a] Abbreviations: RT, renal transplantation; NA, not available; CIN, chronic interstitial nephropathy; CGN, chronic glomerulonephritis; MGN, membranous glomerulonephritis; ATG, antithymocyte globulins; ALG, antilymphocyte globulins; CsA, cyclosporin A; MMF, mycophenolate mofetil; AZA, azathioprin; C, corticosteroids; FK506, tacrolimus; SRL, sirolimus.

Table 2. Virological and biochemical parameters before and after renal transplantation[a]

Patients	Duration of HCV Infection (mo)	HCV Genotype	Quantitative PCR before Treatment (copies/ml)	Follow-up (mo)	HCV Serology/Viremia			HCV in Mononuclear Cells at Last Follow-up	AST (IU/L)[b]		ALT (IU/L)[c]		γ-GT (IU/L)[c]	
					Before RT	At Transplantation	Last Follow-up		At RT	Last Follow-up	At RT	Last Follow-up	At RT	Last Follow-up
1	1.5	1b	1,200,000	15	+/+	−/−	−/−	—	22	20	77	16	51	28
2	19	1b	433,628	48	+/+	+/−	+/−	NA	26	22	17	17	16	22
3	1	2	240,000	12	+/+	+/−	−/−	—	17	23	12	33	16	22
4	1	1b	600	26	+/+	+/−	−/−	—	9	22	14	27	17	30
5	36	2a	578	88	+/+	+/−	+/−	—	11	16	42	18	52	20
6	264	NA	1,277,500	5	+/+	+/−	+/−	NA	12	21	13	30	27	24
7	5	1b	290,000	12	+/+	+/−	+/−	—	12	25	8	32	16	17
8	168	2	600	22	+/+	+/−	+/−	—	10	36	19	74	28	90
9	NA	1b	115,880	2	+/+	+/−	+/−	NA	14	11	17	17	16	31
10	92	1a	130,000	11	+/+	+/−	+/−	—	21	46	20	17	16	19
11	66	5a	1,009	58	+/+	+/−	+/−	—	24	27	23	28	20	48
12	96	2a/2c	159,541	38	+/+	+/−	+/−	NA	41	40	18	19	79	31
13	106	1a/1b	53,739	31	+/+	+/−	+/−	NA	18	23	12	15	13	11
14	NA	1a	3,368,960	23	+/+	+/−	+/−	NA	11	25	7	16	45	107
15	NA	NA	NA	5	+/+	+/−	+/−	NA	11	17	17	13	19	17
16	7	NA	NA	64	+/+	+/−	+/−	NA	7	10	6	11	15	50

[a] Abbreviations: NA, not available; RT, renal transplantation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, gamma glutamyl transpeptidase.
[b] $P = 0.04$.
[c] $P > 0.05$.

9) presented with severe sepsis a few days after the administration of the antirejection therapy and finally underwent an allograft nephrectomy at 1 mo after transplantation to treat intractable rejection. At last follow-up, the serum creatinine level was 117 μmol/L (range, 91 to 237 μmol/L). Proteinuria and microscopic hematuria were absent in all patients but two. These two patients (patients 7 and 10) had biopsy-proven chronic allograft dysfunction at last follow-up and were therefore switched from calcineurin inhibitors to sirolimus. Finally, none of the patients had a *de novo* glomerulonephritis.

Posttransplantation Complications

Infections. One patient (patient 9) presented with severe sepsis a few days after the administration of the antirejection therapy. Another patient (patient 7) presented with a suppurative lymphocele, which was successfully treated. Four (25%) of the 16 patients (patients 1, 2, 11, and 14) presented with a cytomegalovirus infection.

Diabetes. None of the patients presented with posttransplantation diabetes mellitus.

Discussion

In HCV-positive hemodialysis patients, sustained virologic response is observed in 20% to 92% of cases after IFN-α therapy. The good response to IFN-α observed in this population is possibly related to alteration of the pharmacokinetics. Rostaing *et al.* (10) reported that the area under the curve of IFN-α is twice as high in hemodialysis patients compared with patients with normal renal function. This might explain why, according to previous reports (5,11–14), our patients had a mild tolerance of IFN-α compared with nonhemodialysis HCV-positive patients.

Few cases of clearance of HCV viremia during hemodialysis and sustained virologic response after RT have been previously reported (respectively, 2, 2, and 2 cases (5,11,12)). In the study presented here, 16 (29%) of 55 hemodialysis patients who were treated by IFN-α therapy had a sustained virologic response during the hemodialysis period and did not relapse after RT, whatever the genotype was. In addition, for the first time, when assessed, HCV was found to be absent in mononuclear cells of these patients.

In HCV RNA–positive patients, both after renal and liver transplantation, there was a significant increase in HCV viremia due to the loss of the immune control on HCV under immunosuppressive treatment (15). In liver HCV-positive liver transplant recipients, the use of polyclonal antibodies and corticosteroids has been associated with a more rapid progression to cirrhosis (16). The effect of anti–IL-2 receptor antibodies on HCV remains unknown. In HCV-positive renal transplant recipients, Rostaing *et al.* (17) did not find that, in patients who received antilymphocyte or antithymocyte globulins, this was associated with a worsening of liver function tests, liver histology, or HCV viremia. In contrast, there was a significant increase in HCV viremia after a switch from azathioprine to mycophenolate mofetil in renal transplant recipients (18).

In our report, despite the use of antilymphocyte or antithymocyte globulins in 12 (75%) of 16 patients and the use of mycophenolate mofetil in 13 (81%) of 16 patients, none experienced a relapse of HCV infection. HCV viremia, which was negative at RT, remained negative after 22.5 mo (range, 2 to 88 mo) of follow-up. Only one patient (patient 9) had a short follow-up because he underwent an allograft nephrectomy after an acute rejection treated by corticosteroids pulses, which was complicated by a sepsis.

Does serum HCV RNA reflect intrahepatic HCV RNA? This remains controversial. Barrett *et al.* (19) reported that HCV RNA was not detectable in serum HCV-positive/RNA-negative liver biopsy specimens but was detectable in all serum HCV-positive/RNA-positive control biopsy specimens. They concluded that negative serum PCR status reflects cleared past exposure in the liver (20). More recently, McHutchison *et al.* (21) detected intrahepatic HCV RNA in 7 (2%) of 400 immunocompetent HCV-positive/RNA-negative patients at 24 wk after therapy. Two of them relapsed at 6 mo after the end of treatment. The five others had not relapsed at, respectively, 6, 6, 12, 42, and 42 mo after the end of the treatment. Intrahepatic HCV RNA was not assessed in our study because its persistence at 61.5 mo (range, 13 to 105 mo) after the end of IFN-α therapy was unlikely in view of the absence of HCV RNA in the serum. In addition, in contrast to previous studies, our report concerns renal transplant recipients receiving subsequent immunosuppressive treatment that is usually responsible for a boost in HCV replication, which is then detected in the serum and/or in PBMC. Finally, HCV RNA was not present in mononuclear cells when assessed in eight patients.

In one patient (patient 1), anti-HCV antibodies disappeared after IFN-α therapy during the hemodialysis period. The mechanism is unknown. In two other patients (patients 3 and 4), anti-HCV antibodies disappeared after RT. Both of them received mycophenolate mofetil therapy. This might be the result of a decrease in the synthesis of anti-HCV antibodies because it has been shown that mycophenolate mofetil induces a decrease in the synthesis of antibodies (22).

Legendre *et al.* (23) reported that increased mortality in HCV-positive renal transplant recipients is related to liver disease and sepsis. Huraib *et al.* (24) showed that the treatment of HCV-positive hemodialysis patients with IFN-α is associated with a lesser progression of chronic liver disease after RT compared with nontreated patients, even in the absence of HCV clearance. None of our patients developed liver disease, and only one patient (patient 9) presented with sepsis after receiving antirejection therapy.

Increased graft loss seems to be related to the occurrence of *de novo* glomerulopathy, which is related to HCV (1). None of our patients presented with a *de novo* glomerulopathy. Recently, Cruzado *et al.* (25) suggested that pretransplantation IFN-α therapy prevents HCV-associated glomerulonephritis in renal allografts by HCV clearance. Finally, Cosio *et al.* (26) reported a high rate of acute vascular rejection during the first 6 mo after RT in HCV-positive patients. In this report, only three patients presented with acute rejection, which was treated successfully with corticosteroid pulses.

Several authors have reported the presence of an association

between HCV infection and the development of posttransplantation diabetes mellitus, both after liver transplantation (27) and RT (28,29). None of our patients presented with posttransplantation diabetes mellitus.

In conclusion, the treatment of HCV-positive hemodialysis patients with IFN-α can induce complete and sustained clearance in almost 29% of them, without any relapse after RT despite subsequent immunosuppressive treatment. Therefore, we recommend treating HCV RNA–positive hemodialysis patients who are waiting for RT with IFN-α whenever possible.

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