Sustained response with negative serum HCV-mRNA and disappearance of antibodies after interferon-α therapy in a kidney transplant recipient with chronic active viral hepatitis C

Giovanna Luciani[1], Maurizio Bossola[1], Maurizio Muscaritoli[3], Nicola Panocchia[1], Angela Ferrante[1], Giuseppe Nanni[1], Emanuele Piccioni[1], Luigi Tazza[1], Rita Luciana Grillo[2], Filippo Rossi Fanelli[3], Marco Castagneto[1]

[1]Institute of Clinical Surgery and [2]Institute of Microbiology, "Cattolica del S. Cuore" University, Rome - Italy
[3]Department of Clinical Medicine, "La Sapienza" University, Rome - Italy

ABSTRACT: *Background:* **The use of interferon-α (IFN-α) to treat viral hepatitis C (HCV) occurring in kidney transplant recipients is controversial. This study reports an HCV patient successfully treated with IFN-α therapy achieving sustained response, negative serum HCV-mRNA and the disappearance of HCV antibodies, without impairment of renal function.**
Method: **A young kidney transplant recipient developed a proven HCV infection 70 months post-transplantation. The patient received IFN-α therapy, and for a 32-month follow-up period was evaluated clinically, serologically and virologically.**
Results: **IFN-α therapy resulted in normal transaminase activities within 2 months. Serum HCV-mRNA was negative after 4 weeks of treatment and is still negative. Ten months after IFN-α therapy withdrawal, the enzyme immunoassay revealed that HCV antibodies (HCVAb) were absent in the serum. IFN-α therapy was safe, well tolerated and renal function was not impaired.**

Key words: *HCV, Hepatitis, Interferon-α, Kidney transplant*

INTRODUCTION

Before the introduction of routine screening for viral hepatitis C antibodies (HCVAb) in blood and organ donors in 1990, HCV infection could be transmitted by hemotransfusions and transplantations (1).
HCV is now considered a major cause of chronic hepatitis in kidney transplant recipients (1). Data reported on the prognosis of HCV in infected kidney transplant recipients are controversial (2-3), although it has been recently described that the adverse effects of HCV on liver function and patients' long-term survival are progressive (1). The real effect of immunosuppression on the natural history of HCV infection is also uncertain (4-5).
Monotherapy for HCV infection with interferon-α (IFN-α) in immunocompetent patients has been associated with initial response rates as high as 40%, but the rates of sustained response are less than half (6). Data on the effects of IFN-α therapy on HCV infection in kidney transplant recipients are scanty and controversial (1, 5, 7-11). IFN-α in kidney transplant recipients can induce a rejection crisis due to its immunomodulating action (1, 5, 7-11).
We report the case of a kidney transplant recipient who developed an HCV infection, and was treated with IFN-α and, 32 months after therapy, still maintains a sustained response with negative serum HCV-mRNA and the disappearance of HCVAb.

CASE REPORT

The patient, affected by end-stage renal failure secondary to left kidney congenital hypoplasia, underwent hemodialysis (HD) since he was 10 years old. At

the age of 11 (June 1987), he received his first kidney transplantation with a very short-term graft failure due to vascular torsion; two units of compatible blood were transfused following the graft's removal. Four years later, at the age of 15 (March 1991), he received another kidney transplantation using standard techniques. Four units of blood were transfused during and after the second transplant. He had immediate graft function and received induction therapy with oral CSA (13 mg/kg/day), azathioprine (25 mg/day and every second day 50 mg/day) and prednisone (500 mg/day for 1st post-operative day; then the dose was progressively tapered until the 6th post-operative day to 6 mg/day). As an outpatient he was routinely followed-up every 4 months. The CSA dose was periodically modified to maintain CSA plasma trough levels between 200-400 ng/mL during the 1st year and 200-250 ng/mL thereafter. In July 1991, the prednisone dose was reduced to 8 mg/day.

Serum samples were tested for HCVAb by a second-generation enzyme immunoassay. The patient was HCVAb negative pre-transplant and for 3 years afterwards. Antibody seroconversion occurred in March 1994 and HCV was confirmed by reverse transcription reaction and polymerase chain reaction (PCR). The HCV-mRNA was classified as type 1b. Probably, the HCV infection was secondary to multiple blood transfusions. The patient was well until December 1996, when he then presented with kidney and liver malfunction: serum creatinine levels and blood urea nitrogen were respectively 7.2 mg/dL and 178 mg/dL, and aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gammaglutamyl-transpeptidase (γGTP) raised to respectively 238 UI/L, 602 UI/L and 3540 UI/L. Renal malfunction was considered an expression of cyclosporine toxicity. Azathioprine treatment was immediately withdrawn; cyclosporine was reduced from 200 to 50 mg/day and the prednisone dose adjusted to 6 mg/day. A single HD treatment was performed because of persistent impaired renal funcion and weight gain. At the end of January 1997, renal function was quite normal (serum creatinine: 1.8 mg/dL), while liver function appeared to be still abnormal (serum bilirubin 4.4 mg/dL, ALT 381 UI/L, AST 183 UI/L, alkaline phosphatase 598 UI/L and γGT 2301 UI/L). A liver biopsy was performed. It revealed subcapsular peliotic change with dilated sinusoid filled with erythrocytes; a lymphocyte cluster-like lymphoid follicle was found in the lobular and portal area associated with necrosis. A diagnosis was made of peliotic hepatitis induced by immunosuppressants associated with chronic active hepatitis. Cyclopsorine treatment was halted in February 1997. In March 1997, IFN-α therapy (Wellferon, Wellcome) was started. The patient received a daily 6 million unit (MU) dose of IFN-α for 18 days and then a 6 MU dose of IFN-α three times a week until the end of August 1997. After 10 weeks of IFN-α therapy, cyclosporine was resumed (the starting dose of 0.5 mg/kg/day was progressively increased to 2.5 mg/kg/day). Aminotransferase, γGT and alkaline phosphatase returned to normal values 2 months after the beginning of IFN-α. Serum creatinine levels did not rise above 2.2 mg/dL. Lymphocytes levels monitoring showed that the CD4/CD8 ratio increased from 0.2 (December 1996) to 1.2 (January 2000) without signs and symptoms of kidney rejection. Undetectable serum HCV-mRNA by qualitative RT-PCR (sensitivity of 500-1000 copies/mL) was observed after 4 weeks of treatment (Tab. I). In August 1997, 5 months after the beginning of IFN-α treatment, the immunoblot for c33 was negative. In July and September 1998, c100 and c22 immunoblot results were also negative as was the ELISA test for HCVAb. So far (at December 2002), aminotransferase activites remain at normal levels, the graft function is stable with a serum creatinine of 2.1 mg/dL. Qualitative RT-PCR for serum HCV-mRNA and HCVAb assay is still negative.

Discussion

IFN-α therapy for HCV infection in kidney transplant recipients has been adopted with controversial results (1, 10-16). In 1993, Chan et al (16) described a case of successful IFN-α treatment for chronic hepatitis 9 months after renal transplantation. Thervet et al (13) found normalized liver function tests in only 7.7% of patients during treatment, without long-term effects. In addition, treatment had to be withdrawn before the usual 6-month course in 54% of patients because of poor clinical and laboratory tolerance. Ozgur et al (15) reported their experience relative to the use of IFN-α in five renal allograft recipients with chronic hepatitis C, given a dose of 4.5 MU three times per week for 6 months. IFN-α was effective in two of the five patients, but unfortunately in two patients, renal allograft rejection was observed and in one patient it was irreversible. Magnone et al (12) reported acute deterioration of allograft function in six out of seven kidney transplant recipients treated with IFN-α therapy.

Rostaing et al (11) in a group of renal-graft recipients with chronic hepatitis C selected those patients with stable graft function of at least 1 year and randomly treated them with IFN-α. IFN-α was not very well tolerated, it induced biochemical improvements in 77% of patients, but HCV-mRNA clearance, observed in only 28.6% of patients, was not sustained since HCV-mRNA was detected in all patients 1 month after IFN-α therapy withdrawal. In addition, renal function impairment was observed in 37.5% of patients, a rate considered unacceptable.

TABLE I - RESULTS OF MEASUREMENT OF SERUM ANTIBODIES AGAINST HCV, HCV-MRNA QUALITATIVE DOSAGE, HCV-MRNA GENOTYPE EVALUATION, AND SERUM LEVELS OF AMINOTRANSFERASE FROM THE TIME OF SEROCONVERSION UNTIL THE LAST FOLLOW-UP

Date	Serum Ab* against HCV (ELISA)	HCV-mRNA Qualitative	ALT/AST (UI/L)
3/94	+	+	24/28
10/96	+	+	602/238
12/96	+	+	580/337
1/97	+	+	381/183
2/97	+	+	305/199
3/97	+	-	462/315
3/4/97	+	-	271/248
22/4/97	+	-	46/32
5/97	+	-	28/25
6/97	+	-	22/19
8/97	+	-	22/20
9/97	+	-	13/11
12/97	+	-	16/14
2/98	+	-	12/11
3/98	+/-	-	15/14
6/98	-	-	16/14
9/98	-	-	15/14
10/98	-	-	14/15
5/99	-	-	12/12
5/00	-	-	13/10
5/01	-	-	12/10
5/02	-	-	12/12

** Ab= antibodies.*

In their study of 10 kidney transplant recipients who received IFN-α for HCV infection, Hanafusa et al (1) concluded that IFN-α had insufficient efficacy on the HCV viremia as revealed in 80% of cases; in addition, an increased risk of acute rejection was observed (40% of cases).

IFN-α therapy was completely successful in the patient in our study as demonstrated by the normalization of clinical and laboratory data and by the sustained absence of the HCV viremia 32 months after IFN-α withdrawal. The side-effects of IFN-α therapy, i.e. fever, chills, myalgias, headache, persistent fatigue, anorexia and sleep disturbances were not observed in our patient. In addition, renal function was not impaired. In this regard, it must be emphasized that IFN-α therapy was given 6 years post-transplantation, when the immunosuppressive therapy was low. This probably reduced the risk of rejections related to IFN-α use and could explain the stability of renal function during IFN-α therapy.

Interestingly, the HCVAb disappeared. As shown in Table I, in June 1998 (10 months after IFN-α therapy withdrawal) the enzyme immunoassay revealed that serum HCVAb were absent ; in addition, 3 months later, c22, c100 and c33 results were also negative

Although it has recently been suggested that IFN-α therapy in unselected kidney transplant recipients with chronic hepatitis B or C should remain restricted to those patients with imminent liver failure (17), the case reported here suggests that, at least in renal allograft recipients with stabilized renal function, IFN-α therapy can prove safe and effective in the eradication of HCV infection.

Address for correspondence:
Maurizio Bossola, M.D.
Istituto di Clinica Chirurgica
Università Cattolica del S.Cuore Roma
L.go A. Gemelli, 8
00168 Roma, Italy
maubosso@tin.it

REFERENCES

1. Hanafusa T, Ichikawa Y, Kishikawa H. Retrospective study on the impact of hepatitis C virus infection on kidney transplant patients over 20 years. Transplantation 1998; 66: 471-6.
2. Preiksaitis JK, Cockfield SM, Fenton JM, Burton NI, Chui LW. Serologic responses to hepatitis C virus in solid organ transplant recipients. Transplantation 1997; 64: 1775-80.
3. Pol S, Cavalcanti R, Carnot F. Azathioprine hepatitis in kidney transplant recipients. Transplantation 1996; 61: 1774-6.
4. Pereira BJ, Natov SN, Bouthot BA, Murthy BV, Ruthazer R, Schmid CH, Levey A, and the New England Organ Bank Hepatitis C Study Group. Effects of hepatitis C infection and renal transplantation on survival in end-stage renal disease. Kidney Int 1998; 53: 1374-81.
5. Stempel CA, Lake J, Kuo G, Vincenti F. Hepatitis C - Its prevalence in end-stage renal failure patients and clinical course after kidney transplantation. Transplantation 1993; 55: 273-6.
6. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001; 345: 41-52.
7. Zein NN, McGreger CG, Wendt NK. Prevalence and outcome of hepatitis C infection among heart transplant recipients. J Heart Lung Transplant 1995; 14: 865-9.
8. Fishman JA, Rubin RH, Koziel MJ, Pereira BJ. Hepatitis C virus and organ transplantation. Transplantation 1996; 62: 147-54.
9. Bouthot BA, Murthy BV, Schmid CH, Levey AS, Pereira BJ. Long-term follow-up of hepatitis C virus infection among renal transplant recipients. Transplantation 1997; 63: 849-53.
10. Ichikawa Y, Masahiro K, Hanafusa T, Hohro T, Kishikawa H, Fukunishi T, Nagano S, Shinji Y. A 20-year case study of a kidney transplant recipient with chronic active hepatitis C. Transplantation 1998; 65: 134-8.
11. Rostaing L, Izopet J, Baron E. Treatment of chronic hepatitis C with recombinant interferon alpha in kidney transplant recipients. Transplantation 1995; 59: 1426-31.
12. Magnone M, Holley JL, Shapiro R. Interferon-α-induced acute renal allograft rejection. Transplantation 1995; 59: 1068-70.
13. Thervet E, Pol S, Legendre CH, Gagnadoux M-F, Cavalcanti R, Kreis H. Low-dose recombinant interferon-α treatment of hepatitis C viral infection in renal transplant recipients: a pilot study. Transplantation 1994; 58: 625-7.
14. Tokumoto T, Tanabe K, Ishikawa N, Simizu T, Oshima T, Noguchi S, Gouya N, Nakazawa H, Hashimoto E, Fuchinoue S, Hayashi N, Toma H. Effect of interferon-alfa treatment in renal transplant recipients with chronic hepatitis C. Transplant Proc 1998; 30: 3270-2.
15. Ozgur O, Boyacioglu S, Telatar H, Haberal M. Recombinant alpha-interferon in renal allografts recipients with chronic hepatitis C. Nephrol Dial Transplant 1995; 10: 2104-6.
16. Chan TM, Lok AS, Cheng LK, Ng IO. Chronic hepatitis C after renal transplantation. Treatment with alpha-interferon. Transplantation 1993; 56: 1095-8.
17. Pohanka E, Kovarik J. Is treatment with interferon-α in renal transplant recipients still justified? Nephrol Dial Transplant 1996; 11: 1191-2.

Received: December 14, 2002
Revised: March 07, 2003
Accepted: April 03, 2003