Nephrol Dial Transplant (2007) 0: 1–5
doi: 10.1093/ndt/gfm678
Advance Access publication xx xx xxxx

Original Article

NDT
Nephrology Dialysis Transplantation

Alpha-interferon therapy for chronic hepatitis C may induce acute allograft rejection in kidney transplant patients with failed allografts

Hugo Wéclawiack[1], Nassim Kamar[1], Marion Mehrenberger[1], Céline Guilbeau-Frugier[2], Anne Modesto[2], Jacques Izopet[3], David Ribes[1], Federico Sallusto[4] and Lionel Rostaing[1]

[1]Department of Nephrology, Dialysis and Multiorgan Transplantation, [2]Department of Histopathology, CHU Rangueil, 1 av. Jean Poulhès, TSA 50032, 31059, Toulouse Cédex 9, France, [3]Laboratory of Virology, CHU Purpan, Place Dr Baylac, TSA 40031, 31059 Toulouse Cédex 9, France and [4]Department of Urology and Renal transplantation, CHU Rangueil, 1 av. Jean Poulhès, TSA 50032, 31059, Toulouse Cédex 9, France

Abstract

Background. In hepatitis C virus (HCV) positive kidney transplant (KT) patients, the use of alpha-interferon (αIFN) is contraindicated due to the risk of acute rejection (AR). Conversely, if these HCV(+) KT patients lose their allograft, re-transplantation might be contemplated provided αIFN therapy has been attempted.

Methods. Between 01/01/1989 and 31/12/1994, 261 kidney transplantations were performed; of these 174 were HCV(-) (group I) and 87 were HCV(+) (group II).

Results. At last follow-up (2006), in group I, the number of patients with a functioning graft, the number of patients who died with a functioning graft, and the number of patients who lost their graft before or after month (M) 12 were 92 (52.8%), 14 (8%), 20 (11.5%) and 48 (27.7%), respectively. In group II, the corresponding figures were 22 (25.3%; $P < 0.0001$), 8 (9.1%; ns), 9 (10.3%; ns) and 48 (55.3%; $P < 0.0001$). In group I, 19 of 48 (39.5%) patients with failed allografts after M12 underwent transplantectomy (TX) compared to 14 of 48 (29%; ns) in group II. In group II, 11 of 48 (23%) patients were offered αIFN therapy after their allograft failed: of these, four (36.3%) developed AR during αIFN therapy leading to TX. Histology, in addition to chronic allograft lesions, showed acute cellular and vascular lesions. In patients who were not offered αIFN therapy, TX was performed less frequently, i.e. in only six cases (16.2%).

Conclusions. We conclude that even αIFN-treated KT patients with a failed allograft can experience acute allograft rejection that requires transplantectomy during therapy.

Keywords: acute allograft rejection; αIFN therapy; chronic hepatitis C; failed allograft; kidney transplant patient

Introduction

Several cross-sectional studies have indicated that ∼25% of HCV-infected patients who are evaluated for kidney transplantation have significant liver fibrosis (bridging fibrosis or cirrhosis) [1–3]. Compared to those remaining on dialysis, kidney transplantation confers a survival advantage to hepatitis C virus (HCV)-infected patients; therefore, kidney transplantation should be considered as the treatment of choice for end-stage renal disease (ESRD) [4,5]. However, although HCV-infected patients fare better with a kidney transplant than those on maintenance dialysis, there is good evidence that HCV-infected kidney recipients have worse patient and allograft survival after transplantation when compared to uninfected kidney transplant recipients [6–8]. The increased mortality after kidney transplantation in this population has, in part, been attributed to progressive liver disease after transplantation [6].

Extrahepatic post-transplant complications of HCV infection, such as new onset diabetes [9], post-transplant glomerulonephritis [10] and sepsis [11], are additional complications that contribute to the inferior outcomes observed in these patients. Because of the above considerations, it is important to treat HCV infection while the patient is on dialysis, before kidney transplantation, in order to eradicate HCV [12]. A particular setting is represented by those dialysis patients with a previous failed kidney allograft who are to be treated with alpha-interferon (αIFN). Alpha IFN in combination with ribavirin is a well-established therapy for HCV(+)/RNA(+) immunocompetent patients with normal renal function. In the setting of ESRD, ribavirin therapy is contraindicated. Therefore, anti-HCV therapy in dialysis patients relies on αIFN alone [13]. However, αIFN has immuno-stimulating properties that might promote allograft rejection. This has been well-documented in kidney transplant patients [14,–16], whereas it is less frequent in liver-transplant patients [17]. Recently, Carbognin *et al.* reported on a case of a repeat-allograft recipient who presented with neutropenic fever after 5 months of pegylated

Correspondence and offprint requests to: Prof. Lionel Rostaing, Nephrology, Dialysis, and Multiorgan Transplant Unit, CHU Rangueil, 1 av. Jean Poulhès, 31059, Toulouse Cédex 9, France. Tel: +33-5-61-32-25-84; Fax: +33-5-61-32-28-64; Email: rostaing.l@chu-toulouse.fr

Table 1. Patient and allograft long-term outcomes in a cohort of consecutive KT patients who received grafts between 01/01/1989 and 31/12/1994

	Patients with failed allografts before M12	Patients with failed allografts after M12	Patients with a functioning allograft	Patients who died with functioning allograft	Transplantectomy	HCV treatment after return to dialysis
Group I [HCV (−) patients] (n 174)	20 (11.5%)	48 (27.7%)	92 (52.8%)	14 (8%)	19 (39.5%)	NA
Group II [HCV (+) patients] ($n = 87$)	9 (10.3%)	48 (55.3%)	22 (25.3%)	8 (9.1%)	14 (29.3%)	11 (23%)
P-value	ns	0.0001	0.0001	ns	ns	NA

Abbreviations: M, month; HCV, hepatitis C virus; KT, kidney transplant; NA, not applicable.

αIFN therapy, which was initiated 6 months following the functional loss of his third graft and the re-initiation of haemodialysis (HD) [18]. This led to allograft nephrectomy; the pathologic findings supported a diagnosis of acute-on-chronic rejection. Herein, we report on four cases of acute-on-chronic rejection, which occurred in dialysis patients with failed kidney allografts while receiving αIFN for chronic HCV infection. This represents the largest series of cases reported so far.

Patients and methods

Between 01/01/1989 and 31/12/1994, 261 cadaveric adult kidney transplantations have been performed in our institution. Based on the study of frozen serum samples from the day of transplantation (D0) we have been able to separate the patients on the basis of HCV status at D0. The D0 serum was first assessed for the presence of HCV antibodies. If they were found to be negative, no further test was performed. Conversely, if they were HCV seropositive, we assessed HCV RNA. Thus, 174 patients were HCV seronegative, whereas 87 patients were HCV/RNA positive. Based on the findings of D0 HCV status, 174 patients were HCV seronegative (group I), whereas 87 were HCV RNA positive (group II). These patients were followed-up prospectively until 2006, i.e. a follow-up of 11–17 years. Group II patients were not offered αIFN therapy because it was shown that αIFN induced transplant acute rejection (AR) [14–16]. At last follow-up in group I, the number of patients with a functioning graft, the number of patients who died with a functioning graft, the number of patients who lost their graft before or after month (M) 12 were 92 (52.8%), 14 (8%), 20 (11.5%) and 48 (27.7%), respectively. In group II, the corresponding figures are 22 (25.3%; $P < 0.0001$), 8 (9.1%; ns), 9 (10.3%; ns) and 48 (55.3%; $P < 0.0001$) (see Table 1). For those patients who lost their allograft function, when they went back to chronic dialysis therapy, immunosuppressive drugs were abruptly stopped overnight except for low-dose prednisolone. The latter was maintained at a dose ranging from 5 mg on alternate days to 5 mg/day; it was eventually stopped 6 months after dialysis therapy was resumed, provided there was no evidence of adrenal insufficiency. When the patients with failed allografts resumed dialysis, αIFN therapy was offered to those for whom a subsequent kidney transplant was contemplated. Of those kidney transplant patients with failed allografts, when signs of allograft intolerance/rejection were present, i.e. allograft tenderness, allograft pain with fever, gross haematuria, uncontrolled inflammatory syndrome, or resistance to recombinant erythropoietin in the absence of iron deficiency, an allograft transplantectomy (TX) was undertaken. Hence, in group I, 19 of 48 (39.5%) patients with failed allografts after M12 underwent TX compared to 14 of 48 (29%; ns) patients in group II. In group II, 11 of 48 (23%) patients were offered αIFN therapy after their allograft failed: in four cases (36.3%) TX was performed before implementation of αIFN therapy, in four cases (36.3%) TX had to be performed during αIFN therapy for allograft rejection and in three cases (27.4%) TX was never performed. Conversely, in group II, in those patients who were not offered αIFN therapy, TX was performed much less frequently, i.e. in only six cases (16.2%), although this difference was not statistically significant.

Results

We have detailed the data of four patients with failed allografts who developed acute kidney allograft rejection following αIFN therapy for chronic hepatitis C infection (see Table 2). With respect to histological findings, in addition to chronic allograft lesions, two patients presented with acute interstitial inflammation; interstitial oedema was diffuse in two cases; there were microthrombi within the arteries of two cases, and interstitial haemorrhages in two cases. C4d staining was not performed because no frozen material was available. Donor-specific anti-HLA alloantibodies were positive before αIFN therapy in two patients, became positive during αIFN therapy in one patient, and remained negative in the latter.

Case 1: A 32-year-old (HCV(+)/RNA(+) kidney recipient underwent a second allograft in 1989. Despite immunosuppression, which included ciclosporine A (–CsA–Neoral®), azathioprine (AZA), and low steroid doses, he developed chronic allograft nephropathy, which lead to end-stage renal failure (ESRF) in October 2003. Immunosuppression was then withdrawn except for a low dose of prednisone (5 mg/day). A liver biopsy was performed, which showed a Metavir score of A1F2. In September 2005, we started pegylated αIFN therapy (Pegasys® 135 μg s.c./week), scheduled for 1 year, before contemplating a third kidney transplant. Two months after starting αIFN therapy, while his HCV RNA had become negative, the patient developed gross haematuria, a painful transplant, and had a mild inflammatory syndrome. We decided to

Table 2. Characteristics of four patients with failed allografts who presented with allograft AR while on αIFN therapy

	Time since allograft loss (months)	Residual immunosuppression	Type of αIFN	Time on αIFN (months)	Symptoms of AR	Treatment of AR	Kidney weight (g)
Patient 1	23	Pred, 5 mg/day	Pegasys, 135 μg/week	2	Gross haematuria, painful KT, inflammatory Sd	Tx	778
Patient 2	4	Pred, 5 mg/day	αIFN 3 M × 3/ week	2.5	Fever, haematuria, painful KT	Tx	200
Patient 3	14	0	αIFN 3 M × 3/week	12	Gross haematuria, painful KT	Tx	120
Patient 4	9	Pred, 5 mg/day	αIFN 3 M × 3/week	0.75	Fever, painful KT, inflammatory Sd	Tx	90

Abbreviations: KT, Kidney transplant; αIFN, alpha interferon; AR, acute rejection; Pred, prednisone; Tx, transplantectomy; Sd, syndrome; Pegasys, Peginterferon alfa-2a.

perform a transplantectomy. The histology, in addition to chronic allograft lesions, showed diffuse interstitial haemorrhage, diffuse interstitial infiltration by lymphocytes and plasmocytes and arterial thrombi.

Case 2: A 28-year-old HCV(+)/RNA(+) patient received his first kidney allograft in 1992: he progressively developed chronic allograft dysfunction, which lead to ESRF in March 1999. At this point, CsA and AZA were withdrawn, and prednisone was continued at 5 mg/day. At 2 months later, because he presented with a persisting increase in alanine aminotransferase (ALT) levels, we decided to start αIFN therapy at 3×10^6 units three times a week. By 75 days later, he had developed high grade fever (40°C), haematuria, and pain within his allograft. Biological tests showed C-reactive protein of 328 mg/l and new onset anaemia (haemoglobin at 9.7 g/dl). At this point he underwent transplantectomy. We found interstitial haemorrhage, peritubular capillaritis, and venous thrombi, supporting acute humoral rejection on chronic rejection.

Case 3: In 1989, a 32-year-old HCV(+)/RNA(+) man underwent a second transplant. He progressively developed chronic allograft nephropathy, possibly related to HCV infection, and resumed HD in January 2001. At this point, CsA and AZA were withdrawn and prednisone was maintained at 5 mg/day. In March 2001, he underwent a liver biopsy, which showed a Metavir score of A2F2. Because he wanted a third transplant, we began treating his HCV infection with αIFN at 3×10^6 units, three times a week, from March 2002 for 1 year; it should be noted that prednisone was stopped in December 2001. Twelve months after starting αIFN therapy, while his HCV RNA had become negative, he presented with gross haematuria, pain within the allograft, and mild fever. We performed a transplantectomy, which showed acute rejection upon chronic lessions.

Case 4: In February 1991, a 57-year-old HCV(+)/RNA(+) patient underwent his second kidney transplant. In 1993, because of chronic active hepatitis, he underwent αIFN therapy (3×10^6 units three times a week) while serum creatinine was normal at 120 μmol/l. Despite immunosuppression (CsA, AZA, steroids) he developed acute cellular and vascular rejection, which was treated with methylprednisolone pulses (10 mg/kg/day for three consecutive days). There was a partial response to steroid therapy; however, despite the withdrawal of αIFN, he rapidly experienced ESRF, which lead to chronic HD in September 1994. Because he wanted a third transplant and because his liver biopsy showed chronic active hepatitis, in June 1995, he underwent a second session of αIFN therapy (3×10^6 units three times a week). Immunosuppression was based on prednisone (5 mg/day). Three weeks later, he presented with fever (39°C), high CRP level (173 mg/dl), a decrease in Hb (9.5 g/dl), and a painful graft. He underwent TX, which disclosed interstitial oedema, capillaritis lesions and chronic rejection lesions (see Figure 1).

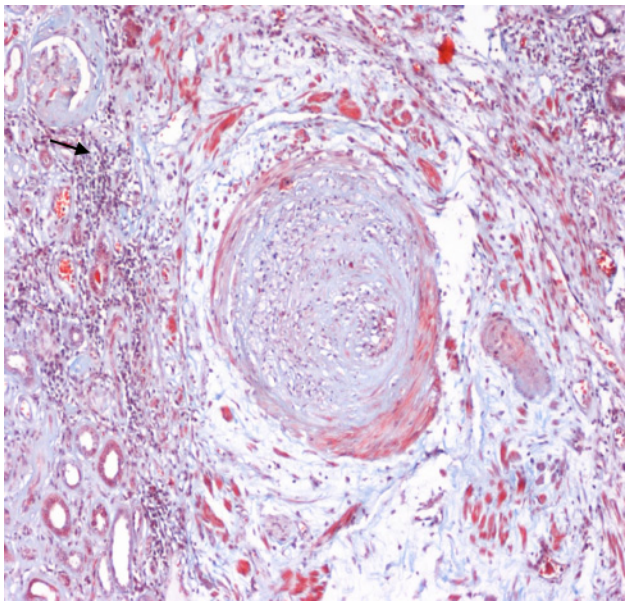

Fig. 1. Case 4: renal histology showing fibroproliferative endarteritis surrounded by oedema, interstitial inflammation and fibrosis. Note peritubular capillaritis (*arrow*). Masson staining, magnification ×200.

Discussion

Alpha IFN is effective for viral eradication in HCV-infected patients, especially when combined with ribavirin. However, administration of interferon after kidney transplantation can be deleterious to the allograft and should generally be avoided in kidney transplant recipients unless there is indication of worsening hepatic injury e.g. fibrosing cholestatic hepatitis [19]. This suggestion is supported

by evidence of kidney graft dysfunction during interferon therapy [14–16]: reported rates of kidney graft dysfunction range from 9 to 100%, with most episodes occurring between 0.3 and 8 months after initiation of therapy. In several cases, graft dysfunction limited the benefit of interferon and was followed by graft loss. Most kidney graft dysfunction was related to increased rates of AR associated with the use of this immunostimulatory agent. It was shown that some patients developed antibody-mediated humoral rejection [16]. In non-transplant patients, αIFN has also been associated with the exacerbation of cryoglobulinemia [20], as well as acute renal failure [21] and glomerulopathy [22].

In the setting of a renal patient with a failed allograft requiring chronic dialysis therapy, immunosuppression is usually stopped quite abruptly except for steroids, which are very progressively reduced due to the potential hazard of adrenal insufficiency. In this setting, it may sometimes happen that the failed allograft is rejected requiring a TX. Because chronic HCV infection cannot be safely treated when the patient has a fully functioning allograft, the treatment has to be attempted when the allograft has failed in order to give the patient the opportunity to have sustained clearance of HCV. Hence, in HCV haemodialysis patients treated by αIFN, sustained HCV clearance might be obtained in up to 50% of patients [23–25]. Moreover, these patients are totally cured of HCV infection because, when they subsequently benefit from a kidney transplant, HCV infection does not recur despite immunosuppression, including induction therapy with lymphocyte-depleting agents [12]. In HCV(+)/RNA(+) dialysis patients with a failed allograft, no data are available regarding the efficacy of αIFN. However, most of these patients do not have immunosuppression or at best, are receiving very low steroid doses; therefore, their response to αIFN therapy may not be modified as compared to dialysis patients who have never received a kidney transplant. Also, because αIFN has immunostimulating properties, this might result in acute-on-chronic rejection, even in failed allografts. This was suggested recently in a case report [18]. In our prospective series, TX was no more frequent in HCV(+) than in HCV(-) patients with failed allografts. However, in HCV(+) patients, a TX was required more frequently in those who were given αIFN (36.3%) than in those who did not receive αIFN (16.2%). In those patients who developed acute-on-chronic rejection on their failed allografts, histology studies showed evidence of both cellular and vascular rejection. We looked for the presence of donor-specific alloantibodies: this was found in only one patient after TX. Because we were not able to stain the transplant biopsies for the presence of C4d, we cannot ascertain whether these acute-on-chronic rejections were of the humoral type. Thus, we recommend that dialysis patients with a failed allograft requiring αIFN therapy should be rigorously monitored in order to detect acute allograft rejection. It does not seem reasonable to advocate pre-emptive transplantectomy, nor to increase immunosuppression before αIFN is implemented in these patients.

We conclude that even αIFN-treated kidney transplant patients with a failed allograft can experience acute allograft rejection on chronic rejection that requires transplantectomy during αIFN therapy.

Conflicts of interest statement. The results presented in this paper have not been published previously in whole or part, except in abstract format.

References

1. Glicklich D, Thung SN, Kapoian T *et al*. Comparison of clinical features and liver histology in hepatitis C-positive dialysis patients and renal transplant recipients. *Am J Gastroenterol* 1999; 94: 159–163
2. Sterling RK, Sanyal AJ, Luketic VA *et al*. Chronic hepatitis C infection in patients with end stage renal disease: characterization of liver histology and viral load in patients awaiting renal transplantation. *Am J Gastroenterol* 1999; 94: 3576–3578
3. Martin P, Carter D, Fabrizi F *et al*. Histopathological features of hepatitis C in renal transplant candidates. *Transplantation* 2000; 69: 1479–1484
4. Knoll GA, Tankersley MR, Lee JY *et al*. The impact of renal transplantation on survival in hepatitis C-positive end-stage renal disease patients. *Am J Kidney Dis* 1997; 29: 608–614
5. Pereira BJ, Natov SN, Bouthot BA *et al*. Effects of hepatitis C infection and renal transplantation on survival in end-stage renal disease. The New England Organ Bank Hepatitis C Study Group. *Kidney Int* 1998; 53: 1374–1378
6. Mathurin P, Mouquet C, Poynard T *et al*. Impact of hepatitis B and C virus on kidney transplantation outcome. *Hepatology* 1999; 29: 257–263
7. Batty DS, Jr, Swanson SJ, Kirk AD *et al*. Hepatitis C virus seropositivity at the time of renal transplantation in the United States: associated factors and patient survival. *Am J Transplant* 2001; 1: 179–184
8. Bruchfeld A, Wilczek H, Elinder CG. Hepatitis C infection, time in renal-replacement therapy, and outcome after kidney transplantation. *Transplantation* 2004; 78: 745–750
9. Bloom RD, Lake JR. Emerging issues in hepatitis C virus-positive liver and kidney transplant recipients. *Am J transplant* 2006; 6: 2232–2237
10. Cruzado JM, Carrera M, Torras J, Grinyo J. Hepatitis C virus infection and de novo glomerular lesions in renal allografts. *Am J Transplant* 2001; 1: 171–178
11. Bouthot BA, Murthy BV, Schmid CH, *et al*. Long-term follow-up of hepatitis C virus infection among organ transplant recipients: implications for policies on organ procurement. *Transplantation* 1997; 63: 849–853
12. Kamar N, Toupance O, Buchler M *et al*. Evidence that clearance of hepatitis C virus RNA after alpha-interferon therapy in dialysis patients is sustained after renal transplantation. *J Am Soc Nephrol* 2003; 14: 2092–2098
13. Kamar N, Ribes D, Izopet J, Rostaing L. Treatment of hepatitis C virus infection (HCV) after renal transplantation: implications for HCV-positive dialysis patients awaiting a kidney transplant. *Transplantation* 2006; 82: 853–856
14. Magnone M, Holley JL, Shapiro R *et al*. Interferon-alpha-induced acute renal allograft rejection. *Transplantation* 1995; 59: 1068–1070
15. Rostaing L, Modesto A, Baron E *et al*. Acute renal failure in kidney transplant patients treated with interferon alpha 2b for chronic hepatitis C. *Nephron* 1996; 74: 512–516
16. Baid S, Tolkoff-Rubin N, Saidman S *et al*. Acute humoral rejection in hepatitis C-infected renal transplant recipients receiving antiviral therapy. *Am J Transplant* 2003; 3: 74–78
17. Walter T, Dumortier J, Guillaud O *et al*. Rejection under alpha interferon therapy in liver transplant recipients. *Am J Transplant* 2007; 7: 177–184
18. Carbognin SJ, Solomon NM, Yeo FE *et al*. Acute renal allograft rejection following pegylated IFN-alpha treatment for chronic HCV in a repeat allograft recipient on hemodialysis: a case report. *Am J Transplant* 2006; 6: 1746–1751
19. Toth CM, Pascual M, Chung RT *et al*. Hepatitis C virus-associated fibrosing cholestatic hepatitis after renal transplantation: response to interferon-alpha therapy. *Transplantation* 1998; 66: 1254–1258

20. Gordon AC, Edgar JD, Finch RG. Acute exacerbation of vasculitis during interferon-alpha therapy for hepatitis C-associated cryoglobulinaemia. *J Infect* 1998; 36: 229–230
21. Horowitz R, Glicklich D, Sablay LB *et al*. Interferon-induced acute renal failure: a case report and literature review. *Med Oncol* 1995; 12: 55–57
22. Ohta S, Yokoyama H, Wada T *et al*. Exacerbation of glomerulonephritis in subjects with chronic hepatitis C virus infection after interferon therapy. *Am J Kidney Dis* 1999; 33: 1040–1048
23. Izopet J, Rostaing L, Moussion F *et al*. High rate of hepatitis C virus clearance in hemodialysis patients after interferon-alpha therapy. *J Infect Dis* 1997; 176: 1614–1617
24. Kokoglu OF, Ucmak H, Hosoglu S *et al*. Efficacy and tolerability of pegylated-interferon alpha-2a in hemodialysis patients with chronic hepatitis C. *J Gastroenterol Hepatol* 2006; 21: 575–580
25. Rocha CM, Perez RM, Ferreira AP *et al*. Efficacy and tolerance of interferon-alpha in the treatment of chronic hepatitis C in end-stage renal disease patients on hemodialysis. *Liver Int* 2006; 26: 305–310

Received for publication: 9.7.07
Accepted in revised form: 4.9.07