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## INTERFERON- $\alpha$ -INDUCED ACUTE RENAL ALLOGRAFT REJECTION

MARIO MAGNONE,<sup>1</sup> JEAN L. HOLLEY,<sup>1</sup> RON SHAPIRO,<sup>2</sup> VELMA SCANTLEBURY,<sup>2</sup> JERRY MCCAULEY,<sup>1</sup>  
MARK JORDAN,<sup>2</sup> CARLOS VIVAS,<sup>2</sup> THOMAS STARZL,<sup>2</sup> AND JOHN P. JOHNSON<sup>1,3</sup>

*Renal-Electrolyte Division and the Division of Transplant Surgery, University of Pittsburgh Medical Center,  
Pittsburgh, Pennsylvania 15213*

The immunomodulating effects of interferons have led to their use in the treatment of a variety of illnesses, including cancer (1), and virally mediated infections, such as hepatitis (2). In addition, IFN has been given to immunosuppressed patients in an attempt to reconstitute the immune response to prevent viral infections such as CMV and herpes simplex (3). Since CMV and viral hepatitis are potentially serious complications of renal transplantation (3, 4), the use of IFN for prophylaxis or treatment has been advocated in this setting. However, the potential effects of giving an immunomodulator such as IFN to immunosuppressed transplant patients raises theoretical concerns about activation of immune responses and an increased risk of allograft rejection.

Current immunosuppressive regimes for renal transplantation include CsA or FK506 in combination with steroids and sometimes AZA. While the mechanisms of action of CsA and FK506 are not completely understood, these agents appear to inhibit T cell activation through binding to specific binding cellular proteins (immunophilins), thereby altering intracellular signaling pathways and ultimately inhibiting expression of IL-2 and other cytokines (5). Both CsA (6) and FK506 (7) may inhibit IFN production, and low levels of circulating IFN- $\alpha$  have been described in renal transplant recipients (8). Although IFN modulate the immune response both at the level of T cell activation (9) and antigen expression (10), the exact roles of these compounds in the immunosuppressive action of CsA and FK506 are not known.

A number of studies have claimed efficacy of IFN- $\alpha$  preparations in the treatment of chronic persistent hepatitis (2) and trials of IFN preparations for viral prophylaxis in renal transplant recipients have been reported (3, 11, 12). The results of such trials suggested a benefit of prophylaxis for viral infections (3, 11), but, at times, at the expense of increased rejection (12). The complex issues involved in using IFN to treat hepatitis in a transplanted, immunosuppressed population prompted us to review our experience with IFN- $\alpha$  treatment in renal transplant patients.

### CASE STUDIES

Between June 1990 and April 1994, 11 renal transplant patients were treated with recombinant IFN- $\alpha$  at our center. Seven patients had undergone renal transplantation alone (group 1) and 4 patients had received renal transplants following orthotopic liver transplantation (group 2). The mean age of all patients was  $38 \pm 3.8$  years; there were 6 men and 5 women. Renal transplantation had been performed  $25 \pm 6$  months previously (range, 4–67 months). Seven patients had experienced early rejection during the first month after transplantation, but no patient had experienced more than one episode of rejection. The mean rejection-free interval before starting interferon was  $28.4 \pm 5.7$  months, and the baseline serum creatinine was  $1.8 \pm 0.2$  (range, 1.0–3.8) mg/100 ml. Patients received immunosuppression with either FK506 (6 patients) or CsA (4 patients) and prednisone. Five patients (1, 2, 4, 5, and 8) were also receiving AZA. One patient was on FK506 alone (patient 6). No patient had immunosuppression reduced at the initiation of IFN therapy. The indications for IFN therapy were persistently elevated liver function tests with seropositivity for hepatitis C in 10 patients and surface antigenemia for hepatitis B in 1 patient (patient 2), with liver biopsy evidence of chronic hepatic inflammation.

Kidney allograft function following induction of IFN- $\alpha$  therapy is shown in Table 1. The IFN dosage varied from 1.5 to  $5 \times 10^6$  U of rIFN- $\alpha$  given subcutaneously 3 times weekly and was planned as a 6-month course. Only 4 patients completed the entire course of therapy (mean treatment time,  $4.1 \pm 1.1$  months). Six of 7 patients in group 1 and 1 of 4 patients in group 2 experienced acute rejection at periods varying from 11 days to 8 months after initiation of IFN therapy (mean  $2.9 \pm 0.8$  months). Patient 2, who had persistent hepatitis B, received 6 months of  $5 \times 10^6$  U 3 times weekly and experienced rejection 6 weeks after completing the course of IFN- $\alpha$ . Renal function stabilized after a course of intravenous methylprednisone. Two months later he was retreated with IFN at  $10 \times 10^6$  U 3 times weekly because of continuing deterioration of liver function. Within 2 weeks of restarting IFN therapy, the serum creatinine doubled (2.5 mg/100 ml to 5 mg/100 ml) and did not fall despite discontinuation of IFN and a steroid recycle. Two weeks later, dialysis was started and IFN therapy was reinstated. The

<sup>1</sup> Renal-Electrolyte Division.

<sup>2</sup> Division of Transplant Surgery.

<sup>3</sup> Address correspondence to: John P. Johnson, MD, Renal-Electrolyte Division, F1159 Presbyterian University Hospital, University of Pittsburgh Medical Center, 200 Lothrop Street, Pittsburgh, PA 15213.

TABLE 1. Patients, interferon treatment, and outcome

Patient	Age	Baseline Cr (mg/100 ml)	Rejection-free interval (mo)	INF dose (3×weekly)	Mos Rx	Interval to rejection (mo)	Cr at rejection (mg/100 ml)	Therapy and outcome
Group 1								
1	51	1.8	19	2×10 <sup>6</sup>	1.5	1.5	5.8	Steroid recycle, <sup>a</sup> hemodialysis
2	39	1.3	9	(a) 5×10 <sup>6</sup>	6	8	5.1	Steroid recycle, Cr stabilized
				(b) 10×10 <sup>6</sup>	0.5	0.5	7.5	Steroid recycle, hemodialysis
3	33	3.8	56	3×10 <sup>6</sup>	3	3	8.0	Steroid recycle, hemodialysis
4	25	1.7	14	5×10 <sup>6</sup>	6	5	2.3	Steroid recycle, ↓ INF to 3×10 <sup>6</sup> Cr stabilized × 1 mo, then hemodialysis
5	38	1.0	66	3×10 <sup>6</sup>	2.5	2	3.0	Steroid recycle, ↑ CsA, hemodialysis
6	34	1.2	21	5×10 <sup>6</sup>	0.3	0.3	3.7	Steroid recycle, IV FK, Cr required intermittent hemodialysis, stabilized at Cr 2.5
7	25	2.4	36	(a) 5×10 <sup>6</sup>	5	—	—	Stable renal function (Cr 2.0) at 36-mo follow-up
				(b) 3×10 <sup>6</sup>	5	—	—	
				(c) 5×10 <sup>6</sup>	3	—	—	
Group 2								
8	37	1.8	9	3×10 <sup>6</sup>	2.5	2.5	6.1	Steroid recycle, IV FK, hemodialysis
9	24	1.7	25	1.5×10 <sup>6</sup>	1.5	—	—	Discontinued for systemic side effects, renal function stable
10	67	1.6	18	3×10 <sup>6</sup>	2.5	—	—	Still on Rx
11	46	1.8	40	5×10 <sup>6</sup>	6	—	—	Stable renal function 2-yr follow-up

<sup>a</sup> An 8-day tapering course of prednisone was started at 200 mg daily.

patient remained dialysis dependent until his death 6 months later.

Patient 4 was diagnosed with acute allograft rejection by renal biopsy following an increase in serum creatinine 5 months into a course of 5×10<sup>6</sup> U 3 times per week. He was treated with a steroid recycle and lowering of the IFN dosage to 3×10<sup>6</sup> U 3 times per week for the final month of his course. The serum creatinine level initially stabilized but subsequently rose, and dialysis was required 1 month after completing the course of IFN- $\alpha$  therapy. Patients 1, 3, 5, 6, and 8 had IFN discontinued at the time of allograft rejection; all but patient 5 returned to dialysis within 1 month of the rejection episode. Patient 7 received 3 different courses of rIFN over a course of 24 months for persistent hepatitis C-related liver function abnormalities without ever experiencing rejection. This patient has stable allograft function 36 months after treatment.

The allograft histopathology of all 7 patients who experienced graft dysfunction showed evidence of acute cellular rejection with interstitial cell infiltrates, hemorrhage, and tubulitis. Three patients (3, 4, and 8) had evidence of increased endothelial reactivity and 2 others (patients 1 and 6) had focal necrosis of glomeruli, features that suggests vascular rejection. Of interest, 4 patients had new-onset proteinuria varying from 1 to 5 g/day with minimal glomerular changes by light microscopy.

#### DISCUSSION

Six of 7 renal transplant recipients and 1 of 4 recipients of combined liver-renal transplants experienced acute deterioration of allograft function associated with rIFN- $\alpha$  therapy. Although nephrotoxicity has been reported with IFN therapy (13), it is rare. Biopsy of our patients demonstrated cellular rejection, with some components of vascular rejection that occurred after long periods of graft stability. Rejection was

not reversed by standard therapy and 6 of the 7 patients have returned to dialysis.

Early reports of the use of IFN- $\alpha$  for immunoprophylaxis of CMV infection used dosages similar to those used in our patients and were given over 3 months early after transplantation. There was no associated increased graft loss or rejection episodes (3). These studies were carried out before routine use of CsA or FK506, but this experience has been essentially duplicated (11) in patients immunosuppressed with CsA. In contrast to these reports, high dose IFN therapy (36×10<sup>6</sup> U 3 times weekly) given to CsA-treated renal transplant patients caused a marked increase in the occurrence of steroid-resistant acute rejections with vascular components (12). Although this experience suggested that the toxicity of IFN might be dose related, a recent placebo-controlled trial of IFN prophylaxis using doses similar to those used in our patients also demonstrated a significant increase in irreversible rejection in the IFN-treated patients (14). Thus, the relationship between IFN- $\alpha$  and allograft rejection can be seen irrespective of the dosage.

Differences exist between the studies reviewed above and our experience. In all previous reports, IFN was given prophylactically early after transplantation to patients with normal liver function. In our patients, a significant period of stable allograft function was followed by IFN- $\alpha$  therapy. However, recent experience shows that IFN- $\alpha$  may be quite safe when given to liver transplant recipients with active hepatocellular disease (15). Moreover, our own experience suggests that renal transplant patients with prior liver allografts (patients 8, 9, and 10) may be more tolerant of IFN- $\alpha$  treatment. More experience with IFN- $\alpha$  therapy in patients with different organ transplants is needed to determine whether this speculation is correct.

Another possible factor involved in the precipitation of acute allograft rejection after IFN administration may be the

preparation of IFN used. All reports of renal transplant dysfunction associated with IFN therapy involved the use of rIFN- $\alpha$  (12, 14). Conversely, all reports of successful therapy with IFN have used preparations derived from leukocyte- or lymphocyte-stimulated cultures (3, 11). This raises the possibility that the purified recombinant preparation may actually have greater toxicity for allografts than preparations derived from stimulated cells. Alternatively, the latter preparations may contain some protective factors.

The mechanism of IFN-induced rejection in renal transplants is not known, but the observed clinical cases suggest that suppression of IFN production may be a factor in avoiding rejection in renal transplants. IFN- $\alpha/\beta$  has been shown to accelerate rejection in a model of heart transplantation (16), and it was suggested that this may be due to enhanced expression of class I antigens. IFN have been noted to enhance the expression of both class I and class II antigens (3). Our patients who experienced rejection had a mean  $2.4 \pm 0.49$  class I mismatches (range 0–4) and  $1.1 \pm 0.24$  class II mismatches (range 0–2). Whatever the mechanism, our experience, and that of others, suggests that rIFN- $\alpha$  is associated with the development of resistant rejection in renal transplant patients.

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