Incidence and Severity of Acute Allograft Rejection in Liver Transplant Recipients Treated With Alfa Interferon

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Interferon alfa-2b (IFN-α) therapy has been shown to be effective in the treatment of viral hepatitis B (HBV) or viral hepatitis C (HCV) in patients who did not undergo transplantation. However, in allograft recipients, treatment with IFN-α often leads to allograft rejection. The aim of the present study was to determine if IFN-α therapy increases the incidence or severity of acute rejection in human liver allograft recipients. One hundred five orthotopic liver transplant (OLT) recipients with HBV (n = 32), HCV (n = 58), or Non A Non B Non C (n = 15) viral infections were treated with a 6-month course of IFN-α, 5 million U subcutaneously three times a week, which began 2 to 97 months after transplantation. The mean hepatitis activity index (HAI) at the beginning of the therapy was 10.1 ± 3.0. The baseline immunosuppression was achieved by tacrolimus in 77 patients and by cyclosporine A (CyA) in 28 patients. Contemporaneous controls consisted of 132 OLT patients (100 who received tacrolimus and 32 who received CyA) who did not receive IFN-α. A retrospective analysis was performed on this group of patients. The incidence of rejection and the baseline immunosuppression were compared. All biopsies were reviewed without knowledge of clinical data and scored for HAI and for rejection activity index (RAI). The biochemical response to IFN-α was also examined. The mean baseline maintenance dose of prednisone was greater by 2 mg daily in patients who received IFN-α with tacrolimus compared with control patients who did not receive IFN-α with tacrolimus (IFN-α 5.3 ± 5.2 mg daily v controls 3.3 ± 4.9 mg daily; P ≤ .05). Similarly, the mean maintenance dose of prednisone was greater by 2.5 mg daily in patients who received IFN-α compared with controls who received CyA-based immunosuppression (IFN-α 9.8 ± 3.1 mg daily v controls 7.3 ± 3.3 mg daily; P = .01). Acute rejection episodes were detected in 10.5% (n = 11) of IFN-α–treated patients compared with 8.8% of controls for the similar time period from OLT and period of exposure to risk of rejection. Mean RAI was 2.0 ± 2.4 for the IFN-α–treated group and 2.1 ± 1.7 for controls. Rejection episodes with IFN-α treatment were mild and responded to steroid therapy. In OLT recipients, the risk of acute rejection was not increased by the introduction of IFN-α. However, in this study, patients were exposed to greater levels of immunosuppression. *Copyright © 1998 by the American Association for the Study of Liver Diseases*

R ecurrent infection with either hepatitis B virus (HBV)[1-4] or hepatitis C virus (HCV)[5-7] is an important cause of allograft dysfunction after orthotopic liver transplantation (OLT). As first reported by Corman et al[1] and confirmed many times since, these hepatitides can progress to end-stage liver disease and allograft failure. The accelerated progression of recurrence with second transplants[3,4] has called into question the probity of retransplantation as an option in such cases.

Interferon alfa-2b (IFN-α) therapy has been shown to be effective for viral hepatitis caused by HBV[8] or HCV[9-13] in nonimmunosuppressed patients. This treatment has been less effective in virally infected liver allograft recipients.[14-18] Furthermore, IFN-α is known to increase the expression of human lymphocyte antigen class I[19,20] and may lead to allograft rejection.[16] This concern has been

reinforced by the induction of rejection with IFN-α in experimental animals,[21] and by reports of irreversible episodes of acute renal allograft rejection in up to 29% of humans treated prophylactically with a

course of this cytokine for cytomegalovirus,[22,23] and even more frequently when kidney transplant recipients were treated for hepatitis.[24]

The aim of the present study was to determine whether, and to what extent, IFN-α treatment increased the incidence and severity of acute rejection episodes in human liver allograft recipients. Because it is well known that the incidence of both acute allograft rejection and viral replication are influenced by the level of immunosuppression, the doses and blood plasma levels of the immunosuppressive drugs before and during IFN-α treatment were compared with those in control OLT recipients who did not have hepatitis and did not receive IFN-α.

Patients and Methods

Between March 1990 and June 1992, 105 OLT recipients were treated with IFN-α for HBV (n = 32; 30.5%), HCV (n = 58; 55.2%), or hepatitis Non A Non B Non C (n = 15; 14.3%). Fifty-seven patients (56.2%) underwent transplantation in the 1980s, and HCV serology was not available. However, 20 of 32 patients (62.5%) from the HBV group, 33 of 58 patients (56.9%) from the HCV group, and 6 of 15 patients (40%) from the Non A Non B Non C group had documented diagnoses of HBV, HCV, and Non A Non B hepatitis before OLT, respectively. They were considered to be recurrences of the original disease, whereas the remaining 46 patients could have had either recurrent or de novo hepatitis. A retrospective study was performed on these 105 patients for the incidence and severity of acute rejection and baseline immunosuppression. The results were compared with a contemporaneous control group of 132 OLT recipients who did not receive IFN-α.

Diagnosis of Virus Infection

The pretransplantation diagnosis of HBV infection was made by the detection of hepatitis B surface antigen (HbsAg) in the serum. Before accepting the diagnosis of recurrent (or de novo) posttransplantation viral hepatitis in the allograft, all increases in liver enzyme levels, with or without an increase in the serum bilirubin level, were investigated with a liver biopsy and a Doppler ultrasound examination of the liver to determine the patency of hepatic vessels and the configuration of the biliary tract. A cholangiogram was performed whenever clinically indicated.

Recurrent HBV was diagnosed by the presence of HbsAg in the serum and expression of HbsAg and hepatitis B core antigen (HbcAg) by liver cells by means of immunoperoxidase techniques on biopsy specimens.

A diagnosis of HCV infection was made by detection of anti-HCV antibodies by either a first-generation enzyme-linked assay (Ortho Diagnostic, Raritan, NJ) or second-generation enzyme-linked assay (Abbott 100, Abbott Park Road, IL) and confirmed by reverse-transcriptase polymerase chain reaction in a minority of liver biopsies. The diagnosis of Non A Non B Non C hepatitis was made when serum aminotransferase levels were elevated and there was histologic evidence of hepatitis. The histopathologic criteria included a portal and parenchymal mononuclear cell infiltrate and diffuse spotty hepatocyte necrosis without significant bile duct damage and the absence of any serologic evidence of hepatitis A, B, C, or D, cytomegalovirus, Epstein-Barr virus, or herpes simplex virus infection. All biopsies in the treatment and control groups were reviewed by pathologists who had no knowledge of treatment regimen or clinical course. These were scored for hepatitis activity index (HAI) by using Knodell's system[25] and rejection activity index (RAI) by international consensus document.[26] All patients who received additional bolus doses of steroids and showed biochemical improvement in liver function were considered as rejection in both groups. The biopsies were also scored for RAI in both groups for comparison.

Immunosuppression

Two different postoperative regimens were used. One (n = 52) was based on tacrolimus (FK506) and low-dose prednisone.[27] The second (n = 53) was based on cyclosporine-A (CyA) and generally higher doses of prednisone, to which azathioprine was frequently added.[27] Twenty-five of 53 patients started on CyA therapy were subsequently converted to tacrolimus therapy 12 ± 7 months before IFN-α therapy was initiated. Thus, there were 77 patients who received tacrolimus and 28 who received CyA at the time IFN-α treatment was started. The results of IFN-α treatment were stratified in these two cohorts. Rejection episodes occurring with either regimen were treated with a 1-g methylprednisolone bolus or with 1 g of hydrocortisone alone, with or without a tapered burst of methylprednisolone (total, 600 mg over 5 days); steroid-resistant rejection was treated with 5 to 10 mL per day of OKT3 (Ortho Biotech, Raritan, NJ) for 5 to 14 days.[28]

Interferon Therapy

Patients were taught to give their own subcutaneous injections of 5 million U of IFN-α three times per week. The IFN-α course began 2 to 97 months posttransplantation. In 27 of 105 patients (25.7%), the dose of IFN-α was reduced because of leukopenia (n = 10) and various combinations of thrombocytopenia, anorexia, fatigue, weight loss, weakness, or malaise.

Table 1. Liver Function Before and After IFN-α Therapy

	Total Bilirubin (mg/dL)		AST (U/L)		ALT (U/L)		GGT (U/L)		AP (U/L)	
	Before	After	Before	After	Before	After	Before	After	Before	After
Nonresponder (n = 70)	1.2 ± 1.1	1.6 ± 3.6	163 ± 163	138 ± 93	177 ± 159	139 ± 90	359 ± 811	400 ± 591	210 ± 211	182 ± 171
Complete responder (n = 35)	1.0 ± 0.6	0.8 ± 0.7	139 ± 99	42 ± 26	139 ± 167	33 ± 10	351 ± 376	184 ± 233	192 ± 121	116 ± 67

NOTE. All values expressed as mean ± standard deviation.
Abbreviations: AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; GGT, Gamma-glutamyltransferase; AP, Alkaline phosphatase.

A complete biochemical response to IFN-α was defined as a normalization of the serum alanine aminotransferase level at the end of 6 months of IFN-α therapy. All others were considered nonresponders.

The control patients also were stratified according to immunosuppression. There were 100 consecutive contemporary tacrolimus-treated primary liver transplant recipients who survived at least 3 postoperative months, and 32 similar recipients who received CyA-based immunosuppression.

Because the incidence of acute allograft rejection varied with the postoperative time,[27,28] the treatment group who received tacrolimus and their companion controls were divided into three subgroups, defined by the interval between OLT and the initiation of IFN-α.

Patients treated with IFN-α while on CyA were 11 to 97 months posttransplantation (mean, 42 months). These patients and their 32 non–hepatitis-infected controls had a similar range of follow-up.

Analytic Methods and Statistics

The tacrolimus dose and plasma trough level and the prednisone dose were recorded before, at the 3-month midpoint, and at the end of IFN-α treatment. For each time point, the values for the IFN-α–treatment subgroups were compared with the controls by using the nonparametric Mann-Whitney U test. All results were expressed as mean ± standard deviation. P less than .05 was considered significant.

Results

Response Rate of Hepatitis

Thirty-five of the 105 patients (33%) with hepatitis had a complete biochemical response to the 6-month IFN-α course. Table 1 lists the liver function tests and clinical response classifications before and after the 6-month IFN-α therapy. The rate of complete biochemical response was 40% with Non A Non B Non C hepatitis, 38% with HCV, and 22% with HBV.

These treatment benefits were not evident in the HAI scores by means of the Knodell's system.[25] In 47 patients who had serial biopsies, the mean IFN-α HAI score was 10.1 ± 3.0 before and 10.9 ± 4.1 after the IFN-α treatment.

Nine of the 35 patients (25.7%) who showed a complete biochemical response relapsed within 6 months of stopping treatment. Biochemical relapse rates for the Non A Non B Non C, HCV, and HBV groups were 16.6%, 27%, and 28.5%, respectively. These were treated with further courses of IFN-α.

Incidence and Severity of Allograft Rejection

There were 11 episodes (10.5%) of acute allograft rejection in the IFN-α group during the 6 months

Table 2. Changes in Liver Function With Acute Rejection

Rejection	Total Bilirubin (mg/dL)	ALT (U/L)	AST (U/L)	GGT (U/L)	AP (U/L)
Before	0.8 ± 0.7	302 ± 148	170 ± 171	194 ± 158	70 ± 127
During	1.4 ± 1.0	406 ± 251	306 ± 191	513 ± 322	196 ± 85
After antirejection therapy	0.8 ± 0.5	116 ± 107	93 ± 61	246 ± 84	144 ± 70

NOTE. Values are expressed as mean ± standard deviation.

that required additional antirejection medication and showed an improvement in biochemical parameter of liver injury (Table 2). These episodes were controlled with 1 g of methylprednisone (nine occasions) or 1 g of hydrocortisone (two occasions). No OKT3 treatment was required and no graft was lost from acute rejection.
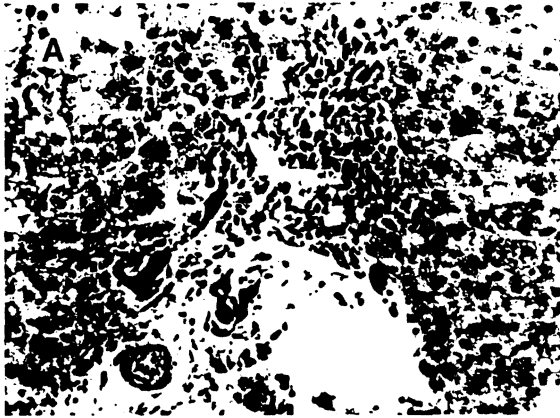

Table 3. Incidence of Liver Allograft Rejection in IFN-α and Control Patients

Time After Transplantation (months)	IFN-α Patients Rejection/ Patients Exposed to Risk (%)	Control Patients Rejection/ Patients Exposed to Risk (%)
Tacrolimus		
2-12	6/43 (14%)	15/100 (15%)
12-24	3/22 (14%)	9/95* (9%)
24-36	0/12 (0%)	2/93* (2%)
Cyclosporine		
42-48	2/28 (7%)	2/32 (6%)
Total	11/105 (10.5%)	28/320† (8.8%)
Rejection Activity Index	2.0 ± 2.4	2.1 ± 1.7

*The decrease in the number of control patients is because of the deaths that occurred during that period of time.
†Total number of exposures over the interval.

The mean time from the initiation of IFN-α treatment to onset of acute rejection was 12.4 ± 5.3 weeks (range, 4 to 19 weeks). An example of an acute rejection episode that occurred during IFN-α treatment and response to 1 g of methylprednisone is shown in Figure 1. The mean RAI scores of the biopsies with rejection were 2.0 ± 2.4 (range, 0 to 6). In the control group, 8.8% of the patients experienced episodes of rejection that required additional antirejection treatment. The mean RAI in this group was 2.1 ± 1.7 (range, 0 to 6) (Table 3).

Patterns of Immunosuppression

IFN-α and recurrent hepatitis with tacrolimus therapy. The deviations from control management for the 77 transplant recipients who received IFN-α for recurrent hepatitis are shown in Figure 2. Frequent

Figure 1. (A) An example of a patient with chronic hepatitis, showing portal lymphocytic inflammation with mild interface activity. Note the lack of bile duct damage and endothelitis of portal veins. (B) This patient experienced an episode of acute rejection during IFN-α treatment. Note that the portal mononuclear inflammation is now directed at the bile ducts and portal vein endothelitis has appeared. (C) After 1 g of methylprednisone, the portal infiltrate has lessened and the duct damage and endothelitis have largely disappeared. There is, however, some residual interface activity (hematoxylin-eosin stain x200).
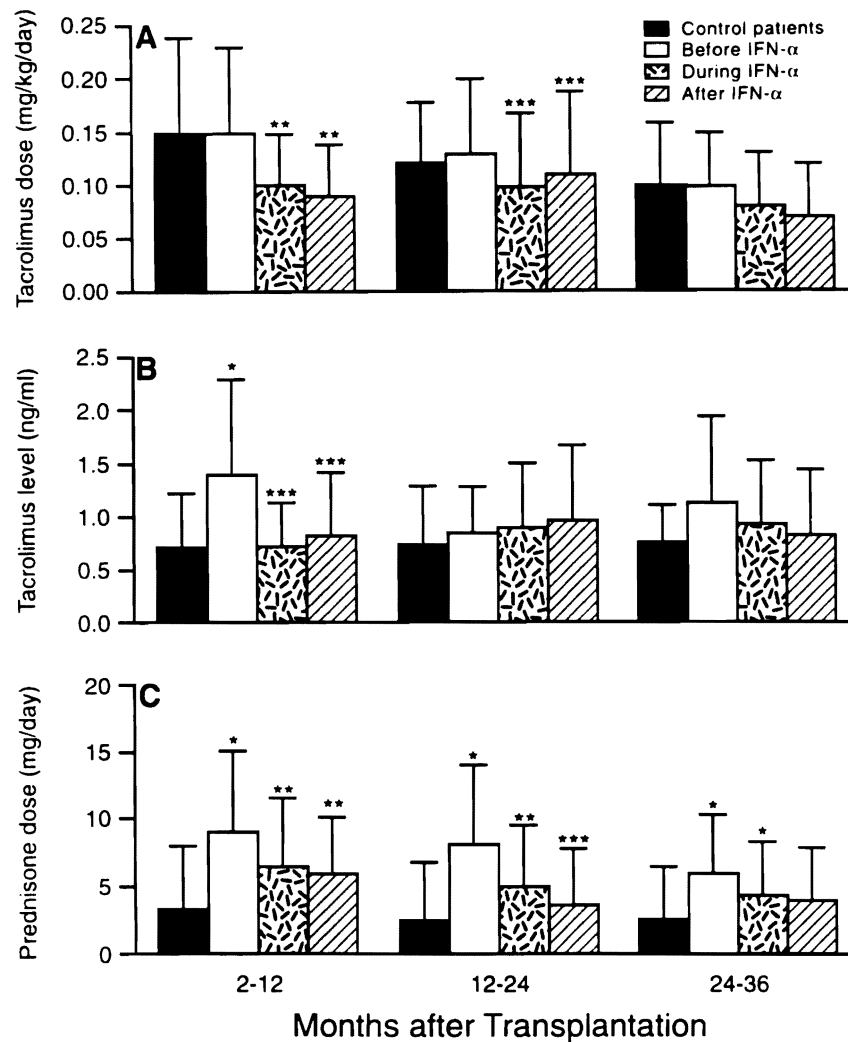
Figure 2. (A) Tacrolimus dose and (B) level and (C) prednisone dose in control patients and in patients who received IFN-α therapy from 2 to 12 months, 12 to 24 months, and 24 to 36 months after liver transplantation. *$P <$ .05 *v* controls; **$P <$ .05 *v* controls and before IFN-α; ***$P <$ .05 *v* before IFN-α.

reductions were made in the tacrolimus dosages (Fig 2A) because of high blood levels of tacrolimus secondary to hepatic dysfunction (Fig 2B). These dose reductions were most dramatic when the recurrent hepatitis developed early posttransplantation. With the dose reductions, the elevated plasma trough concentrations of tacrolimus decreased thereafter into the general range of the non–hepatitis-infected controls (Fig 2B).

A countervailing adjustment that preceded the beginning of IFN-α therapy was an increase in the daily prednisone doses, presumably to cover the possibility that rejection (rather than hepatitis) was responsible for the hepatic dysfunction (Fig 2C). The average steroid doses remained significantly greater throughout the 6 months of IFN-α treatment (Fig 2C). Overall, tacrolimus-treated patients received 2 mg more steroids daily during the IFN-α

treatment than the non–IFN-α controls (mean, 5.3 ± 5.2 mg v 3.3 ± 4.9 mg; $P =$ .05).

IFN-α and recurrent hepatitis with CyA therapy. The same patterns with either prompt or delayed reductions of CyA and azathioprine doses and increases in prednisone dosage were evident compared with the non–hepatitis-infected control groups (Table 4). The dose of prednisone in the IFN-α–treated group who received CyA was 2.5 mg greater daily ($P =$ .01) than the dose used in the group who did not receive IFN-α (Table 4).

Discussion

Whether IFN-α increases the risk of hepatic allograft rejection has been an unresolved controversy. Feray et al[16] noted a high rate of chronic rejection in IFN-α–treated patients with HCV. Dousset et al[14]

Immunosuppression	Control (n = 32)	IFN-α Treatment (n + 28)		
		Before	During	After
CyA dose (mg/kg/d)	4.6 ± 2.5	4.9 ± 5.0	3.4 ± 1.9*	3.3 ± 2*
CyA level (ng/mL)†	342 ± 254	475 ± 314	411 ± 245	474 ± 352
Prednisone (mg/mL)†	7.3 ± 3.8	9.8 ± 4.0*	9.8 ± 3.1*	9.6 ± 3.4*
Azathioprine (mg/d)	28.1 ± 35.2	22.6 ± 33.7	8.7 ± 22.5	7.7 ± 18.4*

Table 4. Immunosuppression of CyA-Treated Patients

*P < .05 = compared to control.
†Fluoroscein polarization immunoassay.

reported that 2 liver transplant recipients lost their grafts to acute chronic rejection that appeared to be associated temporally with IFN-α treatment. However, both of these patients were maintained on lower-than-usual doses and blood levels of CyA. We have observed the same chain of events in individual cases, but in our cumulative experience reported here, blood levels of tacrolimus and CyA remained greater than in the control patients, even though the doses of these immunosuppressants were frequently reduced after IFN-α therapy began (Fig 2 and Table 4).

All clinical and pathological rejections were counted in each group; however, the increase in frequency of acute hepatic rejections was not observed in the IFN-α group compared with the control group, confirming previous claims by Hopf et al[18] and Wright et al.[15,17] Also, RAI scores were comparable for the IFN-α–treatment and control groups. There is no reason, however, to deny the inherent ability of IFN-α to tip the scales toward rejection. This has been well documented in experimental models[21] and by reports of the devastating complications of IFN-α therapy in human kidney transplant recipients,[22,23] including some of our own patients.[24]

The most obvious explanation for the disparity in outcome with liver and kidney transplantation derives from the retarded metabolism of tacrolimus[29,30] and, to a lesser degree, CyA, that occurs with the hepatic dysfunction that is a frequent finding in the post-OLT population, especially so with the supervention of hepatitis. The near doubling of plasma (or blood) levels of the antirejection drugs in the IFN-α–treated group as well as the tendency to increase prednisone doses (Fig 2C) in response to hepatic dysfunction presumably interdict an undesirable IFN-α effect on rejection. The greater resistance of the liver to rejection

compared with other organs[31] or an inherent immune depression caused by the hepatitis virus[32-34] are less likely contributory factors.

The difficulties of balancing immunostimulant (IFN-α) with immunosuppressive therapy are too self-evident to belabor, except to note that the information available in our study precluded their precise quantitation of these two factors. In addition, the diagnosis of HCV infection was made serologically throughout, but reverse-transcriptase polymerase chain reaction was not available for all patients. Consequently, information on serum HCV RNA levels was not available in enough cases to warrant conclusions. However, these shortcomings did not undermine our observation that IFN-α treatment could be administered to liver allograft recipients without an unacceptable increase in acute rejection.

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