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Long-term results of treatment of chronic hepatitis B, C and D with interferon-α in renal allograft recipients

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Abstract The aim of this study was to evaluate the efficacy and safety of interferon-α (IFN-α) therapy of chronic hepatitis B, C and D (HBV, HCV and HDV, respectively) in renal transplant recipients. A group of 42 patients (30 males, 12 females, mean age 38 years) with documented viraemia and chronic active hepatitis (CAH) were studied, of whom 1 had HBV infection alone, 11 had HCV infection alone, 3 had HBV and HDV infection concomitantly, 12 had HBV and HCV infection concomitantly, and 2 had HBV, HCV and HDV infection concomitantly. Patients received 3 MU IFN-α three times weekly for 6 months. After IFN-α therapy, 18 patients (43%) achieved normal alanine aminotransferase (ALT) activity and a partial response was observed in 12 (29%) patients. Two patients relapsed (one with HCV and one with HBV + HCV infection) immediately after the cessation of IFN-α therapy. Repeated liver biopsy was performed in 16 patients after 6–24 months of therapy and revealed progression to cirrhosis in five patients, remission in two and stable disease in nine. None of the patients cleared HCV RNA, four patients cleared HBeAg (two also HDV), and one both HBV and HCV. Five patients died during IFN-α therapy (one as a consequence of liver failure), and four died during the 6 months after therapy (two as a consequence of liver failure). During IFN-α therapy renal allograft function remained stable in 31 patients and acute rejection episodes occurred in 7, of whom 5 lost their graft and all had experienced rejection episodes before. In 16 patients normalization of ALT continued during long-term follow-up (median 22 months, range 0–84 months). IFN-α seemed to be moderately effective in the treatment of chronic HBV or HCV infections, but cannot be recommended for recipients infected with both HBV and HCV.

Key words Chronic hepatitis B · Chronic hepatitis C · Renal transplantation · Interferon-α

Introduction

Interferon-α (IFN-α) has been shown to be a most promising antiviral agent in the treatment of chronic hepatitis B virus (HBV) or C virus (HCV) infection. However, it is not recommended for the recipients of transplanted organs because of its immunomodulating effects and the risk of activation of rejection [6, 7]. In our institute the prevalence of HBV infection is 20% and HCV infection 50%, while 9% of renal transplant recipients are infected with both HBV and HCV. Among seropositive patients, 20% develop chronic liver disease (CLD) after transplantation and liver failure is a common cause of late death in these patients. Since

Table 1 Liver function and viral serology at the end of IFN-α therapy

Number of patients	HBV 17 (3 with HDV)	HCV 11	HBV + HCV 14 (2 with HDV)	Total 42
ALT activity:				
Normalization	8 (47%)	3 (27%) (relapse 1)	7 (50%) (relapse 1)	18 (43%)
50% reduction	5	4	3	12 (29%)
HBeAg → anti-HBe	3 (18%)		2 (14%)	5
HDV → negative	1		1	2
HCV RNA → negative	–	0	1	1
Liver biopsy 6–24 months after IFN-α	6 Stable 6 Responders 2 Partial responders 2 Nonresponders 2	6 Stable 2 Partial responders 2 CH 2 Nonresponders 2 Regression 2 Responders 2	4 Stable 1 Responder 1 CH 3 Nonresponders 2 Responder 1	16 Stable 9 CH 5 Regression 2

1989 we have treated patients with chronic viral hepatitides with IFN-α. In this study we evaluated the efficacy and safety of IFN-α treatment of chronic hepatitis B, C and D in renal transplant recipients.

Patients and methods

A group of 42 recipients of cadaveric kidneys (30 males and 12 females) with a mean age of 38 years (range 20 to 63 years) with CLD, defined as an increase in ALT activity of twice the upper normal limit for at least 6 months, were included in the study. The mean interval between renal transplantation and IFN-α therapy was 60 months (range 6 to 180 months). Patients were treated with prednisone and cyclosporine ($n = 34$) or prednisone and azathioprine ($n = 8$). Hepatitis B surface antigens and hepatitis B e antigens (in three patients with concomitant HDV infection) were found in 17 patients, antibodies against HCV were found in 11 patients who were also HCV RNA-seropositive, and 14 patients had concomitant infection with HBV and HCV (HBsAg, HBeAg-seropositive and anti-HCV, HCV RNA-seropositive) two of whom were also HDV-seropositive. Mean posttransplant time of elevated ALT before IFN-α therapy was 40 months (range 6 to 168 months). Of the 42 patients, 40 had biopsy-proven chronic active hepatitis (CAH).

Recombinant IFN-α was given subcutaneously three times a week at a dose of 3 MU. Patients were treated for a mean period of 6.2 ± 2.2 (3–12) months. The patients were observed for a median of 22 (range 0–84) months after completion of the IFN-α therapy. Clinical status and serum chemistry (ALT/AST activity, creatinine, complete blood count, prothrombin time, bilirubin, total protein and albumin in serum) were monitored weekly for the first month and monthly thereafter. During the follow-up period viral serology was monitored once a year by means of enzyme immunoassays (Hepanostika, Organon Teknika, Boxtel, The Netherlands; UBI HCV EIA, Beijing United Biomedical Co, China) and HCV RNA by polymerase chain reaction (RT PCR, Roche). Repeated liver biopsies were performed in 16 patients 6–24 months after IFN-α therapy. Biochemical response was defined as a normalization of ALT activity at the end of treatment and partial response as a reduction in serum ALT activity by more than 50% at the end of treatment. Clearance of virus denoted disappearance of HCV RNA or HBe antigen (HBV DNA was not estimated) at the end of treatment.

Results

The effects of IFN-α therapy on liver function and viral serology are presented in Table 1. After completion of IFN-α therapy, 18 patients (43%) showed normal ALT activity (8 infected with HBV, 3 HCV, 7 HBV + HCV), while in 12 patients (29%) a partial response was achieved (5 with HBV, 4 HCV and 3 HBV + HCV). There was no improvement of liver function in 12 patients (29%) (4 with HBV, 4 HCV and 4 HBV + HCV). Two patients relapsed immediately after discontinuation of IFN-α treatment. In patients with HBV infection, a biochemical response was observed in eight (47%) and three of these (one with concomitant HDV infection) eliminated HBe antigen from the peripheral blood. Liver biopsy was repeated in six patients (two responders, two partial responders and two nonresponders) after the therapy, and these all showed the same histological lesions without progression of CAH. None of 11 HCV-infected patients eliminated HCV RNA from the plasma, but 3 (27%) of these responded biochemically, and repeated liver biopsy revealed regression of CAH in two of them; the third responder relapsed immediately after cessation of therapy and protocol biopsy was not performed. In nonresponders repeated liver biopsy after IFN-α treatment revealed progression to cirrhosis (CH) in two and stable CAH in two partial responders.

Biochemical response was observed in seven patients (50%) infected with both HBV and HCV with partial

Table 2 Causes of death in patients treated with IFN-α

	HBV	HCV	HBV + HCV	Total
Number of patients	17	11	14	42
Number of deaths	6 (35%)	2 (18%)	6 (43%)	14 (33%) Responders 4 Partial responders 5 Nonresponders 5
With functioning graft	5	2	5	12
During IFN-α therapy (3–6 months after the beginning of IFN-α)	2 Cardiovascular 1 Acute meningitis 1	0	3 Liver failure 1 Sepsis 1 Pancreatitis 1	5 Responder 1 Partial responders 2 Nonresponders 2
Early after IFN-α (6 months)	3 Acute meningitis 1 Liver failure 1 Gastric bleeding 1	0	1 Liver failure 1	4 Partial responders 2 Nonresponders 2
Late death	1 HCC 1	2 Liver failure 1 Cardiovascular 1	2 Stroke 1 Cardiovascular 1	5

Table 3 Renal allograft function in patients treated with IFN-α

	HBV	HCV	HBV + HCV	Total
Number of patients	17	11	14	42
Stable during IFN-α	13	9	9	31 (74%)
Graft loss	5	2	4	11
IFN-α therapy	3	0	2	5
During follow-up	2	2	2	6
Rejection episodes during IFN-α	3	1	3	7

responses in three of them. One patient cleared both HBV and HCV after 12 months of therapy, one cleared HBeAg, and another HDV without HBV. Repeated liver biopsy was performed in four patients and revealed progression to CH in three (one of whom responded biochemically and cleared HBV) and an unchanged lesion in one biochemical responder only. During the follow-up period liver function remained stable in 16 biochemical responders and viral serology did not change.

The rate of death was 33% (14) in the study group (Table 2). Five deaths occurred during IFN-α therapy. One patient died after 3 months of therapy as a result of liver failure, one responder after 5 months from myocardial infarction and two other patients after 3 and 6 months, one because of sepsis and one from acute pancreatitis. During the early period after cessation of IFN-α therapy there were four deaths including two nonresponders who died as a result of liver failure. The highest rate of death was observed in patients coinfected with HBV and HCV (43%). Death occurred in 25% of permanent biochemical responders, in 42% of partial responders and in 36% of nonresponders. One responder died from hepatocellular carcinoma (HCC) after IFN-α treatment with continuously normal liver function tests for 2 years.

In 31 patients (74%) renal allograft function did not deteriorate during IFN therapy (Table 3). In seven patients acute rejection episodes were observed and five of these lost their graft, two after 6 months of therapy and three within 4 months thereafter; all of these patients had experienced unstable graft function before IFN-α therapy. Two of them showed complete and one partial response to IFN-α. Two patients experienced acute rejection episodes during the 5th month of therapy, and their renal function improved after methylprednisolone pulses treatment. For two patients who lost their graft, antirejection therapy was not offered because of severe liver damage, and IFN-α was deliberately continued. Six patients lost their graft during follow-up. Five HCV-infected patients showed proteinuria, and glomerulonephritis was found in three of these (two IgA nephropathy, one membranous glomerulopathy). At the time of writing, 28 patients were still alive, 19 with a functioning graft and 9 on hemodialysis.

Side effects experienced during IFN-α treatment were generally mild and well tolerated, and did not require withdrawal from the study. A 'flu-like syndrome was observed in 12 patients and a slight reduction in white blood cell and platelet counts in 19 patients.

Discussion

CLD has become an important complication in long-term allograft recipients. Administration of immunosuppressive drugs after transplantation facilitates viral replication and is associated with an increased frequen-

cy of CAH, indicating the need for antiviral therapies. IFN-α is the most effective agent in the therapy of HCV- and HBV-related chronic hepatitides. Indications for IFN-α administration in renal allograft recipients are still a matter of controversy, and data on only a limited number of patients have been reported, showing equivocal benefits [1, 12]. Our previous pilot study showed that renal allograft recipients with CLD may benefit from IFN-α therapy [2]. The present study, involving the long-term observation of 42 patients, estimated the efficacy and safety of IFN-α therapy of viral hepatitides in renal allograft recipients. Decreased ALT activity was found in 71% of patients and a sustained biochemical response was observed in 16 (38%).

Roasting et al. found a biochemical response to IFN-α in 77% of 14 HCV-positive patients, but 80% subsequently relapsed [12]. Threvet et al. did not observe any effect of IFN-α in 13 patients infected with HCV or with both HCV and HBV [14]. Biochemical but not virological responses to IFN-α have been found in a small series of HCV-infected renal allograft recipients [4, 5, 9]. Inability to achieve a virological response in renal allograft recipients is probably related to immunosppressive therapy, which facilitates viral replication. However, repeated liver biopsies in our study showed that IFN-α therapy may stop progression of liver disease (nine patients), and even regression of CAH was observed in a few patients.

The rate of death was high in the study group, especially in patients multiple virus infections. An increased risk of bacterial and cardiovascular complications may be related to IFN-α therapy or to the natural course of CLD. Generally, in patients with CLD from infection with multiple hepatitis viruses the prognosis is poor, and frequent progression to CH is observed [10]. Sepsis and cardiovascular complications are reported as a common cause of death in CLD patients with long-functioning grafts [15]. In our study IFN-α therapy did reduce the incidence of liver failure as a cause of death in sustained responders.

Only in 16 patients was liver biopsy performed after IFN-α therapy. Because of the lack of a relationship between ALT activity and histologic diagnosis in immunosuppressed patients liver biopsy seems to be necessary for the definitive evaluation of the efficacy of IFN-α therapy. In our study we observed a patient who responded biochemically to IFN-α, but in whom CAH progressed to CH and HCC. In another sustained responder infected with both viruses, who cleared only HBeAg, biopsy performed 2 years later revealed progression to asymptomatic CH. Surprisingly, two patients who did not clear HCV RNA exhibited regression of CAH. This could have been related to extrahepatic viral persistence. These findings strongly support the view that biochemical evaluation is not sufficient in transplanted-organ recipients [11]. In HCV-infected patients the response was poor, but the rate of death was low. The clinical course of CLD in HCV infection seems to be mild compared to its course in HBV infection or coinfection.

In the majority of our patients renal allograft function remained stable during IFN-α therapy. We have previously reported that in patients with initial stable graft function, IFN-α therapy does not increase the risk of rejection [3]. This finding is opposite to the findings of others who have reported a high rate of irreversible rejection episodes or acute renal failure in recipients treated with IFN-α, even in those with initially stable biopsy-confirmed graft function [8, 13]. These differences may be related to differences between the populations studied, in the length of time posttransplant, in the administered immunossupression and in the dose of IFN-α used.

We conclude that IFN-α seems to be moderately effective in the treatment of chronic hepatitis from HBV or HCV infection. It can effectively control disease activity but not viral replication. Histopathological evaluation is necessary for proper evaluation of IFN-α therapy. In patients with stable initial renal function IFN-α dose not increase the risk of graft rejection. IFN-α therapy cannot be recommended for recipients infected with both HBV and HCV.

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