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Treatment of chronic hepatitis B and C with interferon-alpha in renal allograft recipients: preliminary results

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Abstract We evaluated the effects of treatment with interferon (IFN) on liver disease and renal allograft function in ten immunosuppressed cadaver kidney recipients. Two females and eight males (mean age 39 years) with biopsy-proven chronic active hepatitis ($n = 8$) or persistent hepatitis ($n = 2$) and serum positive for hepatitis B surface antigen (HBsAg) and HBe antigen ($n = 5$) or serum positive for anti-HCV antibodies ($n = 3$) or serum positive for HBsAg, anti-HCV and anti-HDV antibodies ($n = 2$) received 3 million units IFN thrice weekly of 6 months. All patients responded with a reduction in serum aminotransferase activity and in five of them liver function completely normalized. Three patients among five infected with HBV cleared HBeAg. During the follow-up period liver function remained stable in 9 patients after discontinuation of IFN therapy. Three patients lost their grafts due to rejection 1, 2, and 4 months after IFN therapy, respectively. In six patients renal function remained stable during and after IFN therapy. We conclude that in selected groups of renal allograft recipients IFN can be used safely and effectively for the treatment of chronic viral hepatitis.

Key words Hepatitis B and C
Renal allograft · Interferon-alpha

Introduction

Liver disease due to hepatitis B and C virus (HBV, HBC) infection contributes substantially to late morbidity and mortality after successful kidney transplantation [1]. Interferon-alpha (IFN-α) has been shown to be the most promising agent in the treatment of chronic viral hepatitides [2]. However, it is not recommended for kidney allograft recipients due to the high risk of inducing a rejection process [3]. Therefore, there are no available data concerning the influence of IFN-α therapy on liver function in renal transplant patients.

We treated a group of kidney allograft recipients with chronic viral hepatitis with IFN-α and the effect of the treatment on liver and renal allograft function was evaluated.

Patients and methods

Ten recipients of cadaver kidney transplant (2 females, 8 males) with a mean age of 39 years (range: 26–64) were studied. Patients received the following immunosuppressive protocols: prednisone + cyclosporine ($n = 7$), prednisone + azathioprine ($n = 2$) and prednisone + cyclosporine + azathioprine ($n = 1$). During the 6-month period before the start of IFN-α therapy, eight patients had stable graft function and two recipients experienced acute rejection episodes that were treated with methylprednisolone pulses. All patients gave informed consent to participate in the study.

In the post-transplant period, all of the patients had evidence of chronic liver disease, i.e. a two-fold or greater increase in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels for at least 6 months. Serum samples were analysed by means of enzyme immunoassay (Organon Teknika, Borstel, The Netherlands) for the presence of serological markers of hepatitis: hepatitis B surface antigen (HBsAg) antibody against HBsAg (anti-HBs), hepatitis Be antigen, and antibody against hepatitis Be antigen, antibodies against HCV (second generation ELISA), and antibodies against delta antigen. All results positive for anti-HCV antibodies were confirmed by immunoblot assay (LiaTek, UBI). Also, serum samples were tested for the evidence of infection with other hepatotropic viruses: cytomegalovirus (Abbott Laboratories, Chicago, Ill.), Epstein-Barr virus (Biotest, Dreieich, Germany) and herpes simplex virus (Sigma, St. Louis, Mo.). Five patients were poisitive for hepatitis B surface and e antigens, three recipients had anti-HCV antibodies and two patients presented with serological markers of concomitant hepatitis B (HBsAg and HBeAg positive), C (anti-HCV positive) and D (anti-delta positive) viral infection. None of the patients was diagnosed as having an active infection with other hepatotropic viruses.

Percutaneous liver biopsy, performed immediately before the beginning of IFN-α therapy, revealed chronic active hepatitis in eight and chronic persistent hepatitis in two patients. Patients were treated with IFN-α (Roferon, La Roche or Intron, Schering), 3 million units subcutaneously three times weekly for 3 months (3 patients) or 6 months (7 patients). Therapy was initiated after a mean post-transplant period of 19.2 months (range: 6–69 months). Clinical and biochemical criteria were monitored once a week in the first month and once every month thereafter. Biochemical tests included measurements of serum ALT, AST, creatinine, complete blood count, prothrombin time, alkaline phosphatase, bilirubin, total protein, and albumin. Mean follow-up after IFN-α therapy was 12.8 months (range: 1–42 months).

The immunomodulatory effect of IFN-α was estimated by changes in the expression of HLA-DR antigens and interleukin-2 receptor on peripheral blood T lymphocytes by means of indirect immunofluorescence and antibodies against HLA-DR (Behring) and against rIL-2 (Becton Dickinson).

Results

After the completion of IFN-α therapy all patients responded with a reduction in serum aminotransferase activity. In five patients a complete normalization of liver function was achieved (Fig. 1). Three of five patients with HBV infection cleared HBe antigen from peripheral blood. Repeat liver biopsy was performed 6 months (42 months in one case) after therapy in three of the HBV-infected patients and improvement in hepatic histology was found. Serum aminotransferase activities decreased in each of the three recipients chronically infected with HCV and returned to normal in one of them. In this patient, a second liver biopsy performed 6 months after IFN-α therapy revealed a complete disappearance of piecemeal necrosis. In two patients with severe liver damage and serological evidence of infection with HBV, HCV and HDV, liver function tests were normalized in

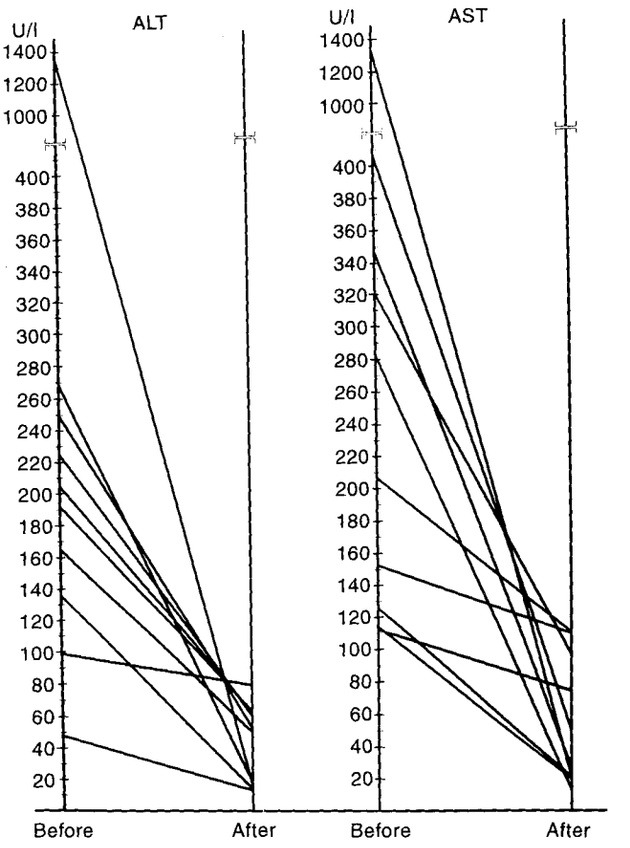

Fig. 1 Serum alanine aminotransferase (*ALT*) and aspartate aminotransferase (*AST*)

one and in the other one a more than 50% decrease of aminotransferase activities was observed. Their viral serology remained unchanged.

During the follow-up period liver function remained stable in nine patients. One patient died due to gastrointestinal bleeding 3 months after therapy.

In six patients kidney function remained stable throughout the entire study period. In this group serum creatinine levels did not change significantly during IFN-α therapy (1.3 ± 0.3 mg/dl and 1.5 ± 0.3 mg/dl) and the follow-up period.

In four patients, IFN-α treatement was associated with a deterioration of kidney function. All of them presented with mild kidney insufficiency before therapy (mean serum creatinine: 2.1 ± 0.5 mg/dl), and two of them were treated for acute rejection 6 months before the study. IFN-α administration was deliberately continued despite an increase in the serum creatinine level because of the marked improvement of liver function. Three patients lost their grafts due to rejection 1, 2 and 4 months after IFN-α therapy and returned to chronic haemodialysis.

Among them were two patients with severe liver disease who were infected with HBV, HCV and HDV.

One patient with a deterioration of kidney function during IFN-α therapy died from gastrointestinal haemorrhage after 3 months of follow-up.

The expression of HLA-DR and IL-2 receptor on T lymphocytes of the recipients did not change during IFN-α therapy.

The side effects experienced during IFN-α treatment were generally mild and tolerable. In none of the patients was it necessary to withdraw IFN-α therapy. "Flu-like" syndrome was observed in two recipients, and in one headache. An almost universal slight reduction in white blood cells and platelet counts was noted but did not necessitate dosage reduction.

Discussion

Chronic viral hepatitis remains one of the major problems in long-term renal allograft recipients, especially in Poland where the prevalence of HCV and HBV infection among dialysis patients is extremely high (60% and 30%, respectively). Immunosuppression therapy used after transplantation directly stimulates viral replication, leading to progressive liver disease [4]. IFN-α is the only therapeutic agent that has consistently been shown to have beneficial effects in all forms of chronic viral hepatitis [5]. Because of the great impact of liver disease on survival in renal transplant patients we decided to undertake this non-controlled trial of the efficacy and safety of IFN-α in this group.

All patients treated with IFN-α experienced decreased aminotransferase levels (by at least 50% of initial values) with complete normalization of liver function in half of them. Therefore our data suggest that IFN-α can be effective in allograft recipients receiving immunosuppression treatment. This is in accord with the results of Wright et al. [6], who showed that viral hepatitis recurring in liver allografts may be controlled by IFN-α. After termination of IFN-α therapy we did not observe a deterioration of liver function. Surprisingly, IFN-α therapy was well tolerated and it seems that certain unwanted side effects (e.g. "flu-like syndrome") may be alleviated by concomitant immunosuppression. Our study did not address the issue as to whether the response rate would be better if higher doses of IFN-α or longer treatment periods were used.

Interferons exhibit immunostimulatory properties and may induce acute rejection of allografts [7]. Four out of ten patients studied lost their grafts due to rejection. All of them had poor kidney function before the initiation of IFN-α therapy and underwent episodes of acute rejection during the early post-transplant period. In contrast, patients with good initial graft function did not experience an increase in creatinine serum levels. The response rate, determined as a normalization of liver function, was similar in both groups.

Our data suggest that in a selected group of renal allograft recipients IFN-α can be used safely and effectively for the treatment of chronic viral hepatitis. Further trials are needed to establish the long-term results of IFN-α treatment.

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