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Interferon Therapy of Hepatitis Following Liver Transplantation Under FK 506 or Cyclosporine

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VIRAL hepatitis is a major disease indication for liver transplantation. Both fulminant hepatic failure due to any of a number of hepatotrophic viruses such as hepatitis A, B, C, B+D, -E, cytomegalovirus (CMV), Epstein-Barr (EBV), herpes, or NANBNC and chronic hepatitis associated with cirrhosis and liver failure due to hepatitis B, C, B+D, or NANBNC are among the four or five more frequent specific indications for liver transplantation at most transplant centers. For this later group of patients, in particular, with chronic viral liver disease, disease recurrence is an important clinical problem following successful transplantation.[1-3]

Two issues of particular concern relative to viral hepatitis following liver transplantation are the effects of the required immunosuppressive agent upon viral replication and the role, if any, of interferon therapy upon either rejection induction or persistence. Because of the size of the transplant program at the University of Pittsburgh and the availability of both cyclosporine (CyA) and FK 506 as immunosuppressive agents at this institution, experience with both agents has been obtained in liver allograft recipients with either recurrent or de novo viral hepatitis who have been treated with α-interferon.

MATERIALS AND METHODS

Subjects

A total of 84 liver allograft recipients with viral hepatitis have been treated with α-interferon. Twenty-two of these individuals were receiving CyA, and 62 were receiving FK 506 as their major immunosuppressive agent. Twenty-eight of these hepatic allograft recipients had hepatitis-B, 37 had hepatitis-C, and 19 had hepatitis-NANBNC as the cause of their hepatitis.

Disease Detection

Abnormal liver injury tests, particularly abnormalities of the aminotransferase levels that were resistant to minor changes in the immunosuppressive regimen, or that were not attributable to a recognized drug toxicity, identified an allograft recipient as requiring a liver biopsy. Immediately prior to each liver biopsy, a complete panel of viral serologic studies, including assays for HAV, HBV, HCV, HDV, EBV, and CMV was obtained. A percutaneous liver biopsy was obtained from each with a Tru-cut needle and was processed by the Clinical Pathology Department.

Therapy and Disease Monitoring

Individuals identified as described above, who were found to have a liver biopsy consistent with viral hepatitis consisting of a pattern of lobular inflammation and patchy hepatocellular necrosis, as well as a mononuclear cell infiltrate in the portal areas, but without evidence of acute cellular rejection (vasculitis or bile duct injury), were treated with α-interferon (Schering) at a dose of 5 million U, 3 times a week, for 6 months. During the course of interferon therapy, the liver injury parameters (ALT, AST, bilirubin, and alkaline phosphatase), as well as hematologic parameters (WBC and platelet counts), were monitored weekly for the first month, then twice monthly for a second month, and then monthly until the termination of a 6-month course of therapy. After 6 months, a second liver biopsy was obtained and the interferon therapy was discontinued. Six weeks later, a third liver biopsy was obtained and the liver injury parameters were assessed monthly thereafter, for an additional 6 months.

Response Definitions

A full response was defined as a complete normalization of the assessed liver injury parameters (ALT and AST levels) and in the case of HBV disease, a seroconversion from HBeAg-positive to HBeAb-positive.

A partial response was defined as a greater than 50% reduction in the baseline liver injury parameters, but not a complete normalization of these parameters of liver injury.

RESULTS

The time from date of transplantation to the time at which the viral hepatitis in liver allograft recipients was documented histologically is shown in Table 1. Hepatitis due to the HBV tended to occur earlier than did hepatitis C or NANBNC hepatitis in these allograft recipients. More importantly, those receiving FK 506 developed their hepatitis earlier than did those who were receiving CyA, regardless of the type of hepatitis.

Overall, 10% of the patients treated experienced a complete remission; 50% experienced a partial remission, while 40% failed to respond to a 6-month course of α-interferon therapy at the dose utilized. The response rates for those individuals receiving FK 506 as their primary immunosuppressive agent were less than those receiving CyA, and consisted of fewer individuals experiencing a partial remission and a slightly greater number of

Table 1. Time to Hepatitis Following Transplantation

Virus	FK 506	CyA	P Value
HBV	381 ± 53	991 ± 210	<.001
HCV	564 ± 88	1346 ± 313	<.002
NANBNC	599 ± 162	910 ± 235	NS
All	516 ± 102	1082 ± 235	<.0001

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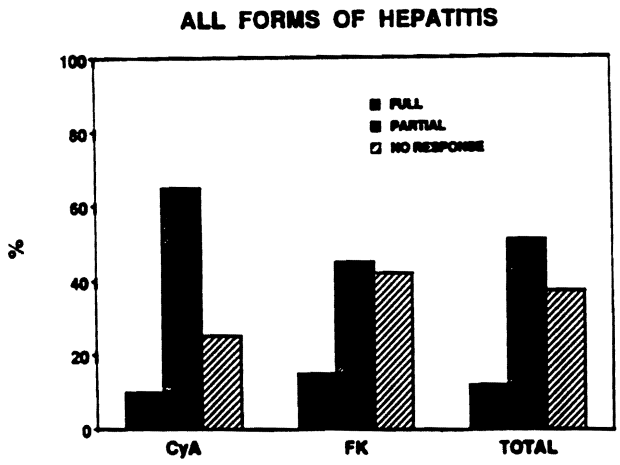

Fig 1. The bars show the percentage of patients in each group treated with either FK 506 or CyA experiencing a full, partial, or no response to 6 months of interferon therapy.

nonresponders (Fig 1). Despite the normalization (full response) or greater than 50% reduction in the levels of the assessed measures of liver injury (partial response), the liver histology failed to improve in most subjects. Worse yet, as assessed by the Knodell criteria for disease activity,[5] the histologic disease either remained stable in a third of the subjects studied or worsened slightly in the remaining two thirds.

DISCUSSION

This is the first report of the use of α-interferon in a large group of liver allograft recipients treated for viral hepatitis occurring after successful transplantation. Several observations can be made as a result of this unique experience. First, immunosuppression with FK 506, as compared to CyA, is associated with a statistically earlier onset of posttransplant hepatitis, regardless of the specific type of hepatitis being considered. More importantly, FK 506, as compared to CyA, is associated with a reduced number of clinical responses to α-interferon therapy. Third, despite a good clinical response as assessed by liver injury parameters, the histologic evidence for viral hepatitis in liver allograft recipients either remain unchanged or actually worsens as a result or during the period of interferon therapy. Fourth, and importantly, no episodes of acute cellular rejection or cases of chronic rejection were ascribable to the use of α-interferon in these allograft recipients. These data suggest that the enhanced immunosuppression associated with FK 506 as opposed to CyA results in an enhanced rate of viral replication and, as a result, a reduction in the number of responses to α-interferon therapy experienced. Moreover, these data suggest that the use of newer and more powerful immunosuppressive agents such as FK 506 mandate the identification and use of more specific antiviral agents if viral hepatitis is to be successfully treated in liver allograft recipients.

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