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Famciclovir therapy for recurrent hepatitis B virus infection after liver transplantation

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Abstract Between November 1993 and June 1995 18 patients received oral famciclovir (3 × 500 mg) for treatment of hepatitis B virus (HBV) reinfection after liver transplantation. Reinfection was defined as the reoccurrence of HBsAg in the serum. In the first 15 patients, famciclovir therapy was initiated after clinical signs of graft hepatitis, whereas the last 3 patients received treatment immediately after HBV-DNA was detected. Famciclovir was well-tolerated in all patients. HBV-DNA values were decreased to undetectable levels in 8 out of 18 patients. Clinical status improved in 7 patients, whereas 5 patients remained unchanged and 6 patients progressed to deteriorating graft function and death. When famciclovir was initiated early after reinfection, a response rate of approximately 66 % was observed. Late onset of therapy in patients with fulminant hepatitis generally failed to provide any clinical benefit.

Key words Liver transplantation · Hepatitis B · Famciclovir

Introduction

Hepatitis B virus (HBV) reinfection is the major cause of fatal outcome after liver transplantation in HBsAg-positive patients. Two-year survival rates are currently estimated at between 50 and 70 % [1–4]. In the case of severe recurrent graft hepatitis, retransplantation is the only treatment option, although associated with disappointing results. Neither short-term immunoprophylaxis, nor interferon treatment have been shown to have a major impact on graft and patient survival. Long-term immunization with anti-HBs hyperimmunoglobulin appears most effective [1–5].

Famciclovir, the oral form of penciclovir, is a novel nucleoside analog with known antiviral effects against herpes simplex and herpes zoster infections. Famciclovir suppresses HBV replication as has been shown in Pekin ducks and humans [6–9]. The results of a phase II trial in patients with chronic hepatitis B seemed promising and may allow expectations for prevention and treatment of HBV recurrence in HBsAg-positive liver transplant patients in the future.

Patients and methods

Patients transplanted because of hepatitis B cirrhosis and acute liver failure due to fulminant hepatitis B, received anti-HBs hyperimmunoglobulin (Hepatect, Biotest Dreieich, Germany) during and after transplantation, commencing on a daily basis and subsequently according to anti-HBs titer [5]. Reinfection was defined by the occurrence of HBsAg after liver transplantation. Between November 1993 and June 1995, 18 patients received famciclovir therapy after reinfection, when HBV-DNA was proven. In the first group of patients ($n = 15$), famciclovir therapy (3 × 500 mg/day) was initiated after clinical signs of recurrent graft hepatitis. The later group of patients ($n = 3$) received famciclovir treatment immediately after diagnosis of reinfection (HBV-DNA- and HBsAg-positive status). Hyperimmunoglobulin therapy was terminated at the onset of reinfection. HBV-DNA was measured by hybridization assay (Abbott, Wiesbaden, Germany).

Results

Famciclovir therapy was well-tolerated in all patients. HBV-DNA levels were decreased below the detection limit in 8 of 18 patients. In 7 of these patients, clinical

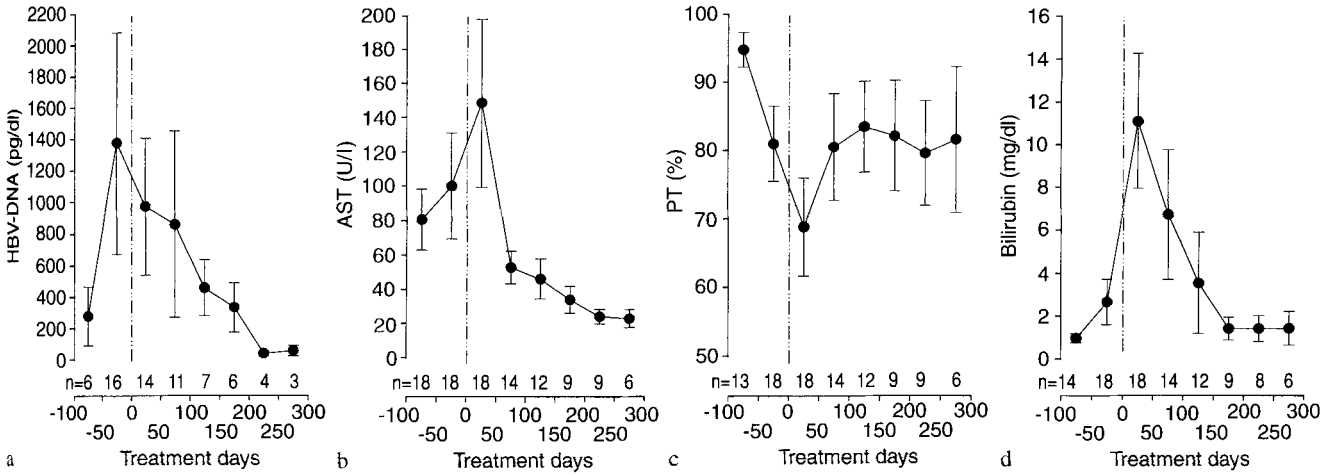

Fig. 1 **a** Serum hepatitis B virus DNA *(HBV-DNA)*, **b** asparagine transaminase *(AST)*, **c** prothrombin time *(PT)* and, **d** bilirubin during famciclovir treatment. All values are expressed as mean ± SEM

improvement of recurrent graft hepatitis was observed, as reflected by normalization of asparagine transaminase, alanine transaminase, and bilirubin levels, and prothrombin time (Fig. 1). Five patients remained unchanged in clinical status, while in 6 patients a progressive hepatitis with deteriorating graft function occurred. Four of the 6 patients who died had only famciclovir therapy for 8–28 days and were assessed too late for this therapy.

Discussion

When famciclovir first became available, treatment was initiated during the course of recurrent graft hepatitis, irrespective of the time of conversion to HBV-DNA-positive status. Subsequently, treatment was immediately started in all patients proven to be HBV-DNA positive. These differences in therapeutic approach may be responsible for differences in outcome under treatment.

Early treatment of recurrent hepatitis B with famciclovir reduced HBV-DNA levels to virtually zero in 44 % of patients. These patients seemed to profit from famciclovir therapy. However, some patients remained relatively unchanged in clinical status, despite a reduction in HBV-DNA levels.

Success with famciclovir was observed in patients who either developed mild recurrent hepatitis late after reinfection, or in patients treated immediately after they were assessed HBV-DNA-positive, leading to a response rate of approximately 66 %. Furthermore, late onset of famciclovir therapy in patients with fulminant graft hepatitis generally failed to provide any clinical benefit. Therefore, the optimal indication and time point for famciclovir treatment seems to be prophylactic therapy immediately after transplantation. For this purpose, a clinical multicenter study is currently underway.

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