Famciclovir Treatment of Hepatitis B Virus Recurrence After Liver Transplantation: A Pilot Study

Martin Krüger, Hans Ludger Tillmann,* Christian Trautwein,* Ulrike Bode,† Karl Oldhafer,† Hansjörg Maschek,‡ Klaus H. W. Böker,* Christoph E. Broelsch,‖ Rudolf Pichlmayr,† and Michael P. Manns**

Despite hepatitis B immunoprophylaxis hepatitis B virus (HBV) recurrence is a frequent and often fatal complication after orthotopic liver transplantation (OLT). The purine nucleoside analogues *penciclovir* and its oral form *famciclovir* (FCV) proved to be well tolerated and effective against herpes simplex and zoster virus infections. In addition, an effective reduction of duck and human HBV replication was observed. Therefore, we conducted an uncontrolled pilot study of famciclovir in patients with HBV recurrence after OLT. Twelve patients have received famciclovir for at least 3 months in an open compassionate-use protocol. FCV was administered orally 500 mg three times a day for all patients (except one patient who was started on 750 mg three times a day for the first 2 weeks). Immediately after starting famciclovir, serum HBV DNA levels declined in 9 of 12 patients (75%) with a mean reduction from baseline levels of 80% after 3 months, 90% after 6 months, and >95% after 12 months of treatment. With continued treatment, 5 of these 9 patients became negative by conventional hybridization assay, and in one of these HBV DNA became undetectable by polymerase chain reaction (PCR) 28 weeks after the start of treatment. Three patients showed no (sustained) reduction in HBV DNA after at least 3 months of treatment; therefore, FCV was stopped. Latest serum alanine aminotransferase (ALT) levels decreased in 6 of 12 patients (50%) with a median decrease of 80% (range, 40%-95%) in comparison to pretreatment ALT values. ALT levels normalized in 4 patients (33%). One patient died due to sepsis and peritonitis in week 13 of treatment. This event was not related to FCV. No clinically significant side effects were noticed in any patient. The oral nucleoside analog famciclovir reduces HBV replication and transaminase levels in patients with HBV recurrence after liver transplantation. Because long-term FCV treatment is well tolerated, famciclovir appears to be a promising antiviral strategy in the treatment of HBV in immunocompromised patients.

Chronic hepatitis B infection is a major cause of chronic liver disease often leading to liver cirrhosis and organ failure with the need for organ replacement.[1] Patients with active HBV replication prior to orthotopic liver transplantation (OLT) usually develop HBV recurrence and subsequent hepatitis leading to graft failure or death.[2-4] Immunosuppressive therapy after OLT stimulates HBV replication and promotes reinfection of the grafted liver either by circulating viral particles or by mature virions released from extrahepatic sites.[5,6] An effective treatment of HBV reinfection after OLT is not available.[2,7] However, the rate of HBV recurrence can be decreased by long-term hepatitis B imunoglobulin.[4,8,9] The use of interferon alfa (IFN-α) before OLT leads to inhibition of replication in patients with chronic HBV infection[10] but administration after transplantation remains controversial.[11] Nucleoside analogues are of particular interest in HBV infection. However, the use of former antiviral substances was often limited by high toxicity. Recently, less toxic nucleoside analogs became available.

Penciclovir and its oral form famciclovir (FCV)[12] are purine nucleoside analogues with *in vitro* activity against herpes simplex and varicella zoster virus. In addition, an antiviral effect against various DNA

*From the *Department of Gastroenterology and Hepatology, †Department of Abdominal- and Transplant-Surgery, ‡Institute of Pathology, Medizinische Hochschule Hannover, Germany; and ‖Department of Surgery, Universitätsklinik Eppendorf, Hamburg, Germany.*

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Address reprint requests to Michael P. Manns, MD, Professor of Medicine and Chairman, Department of Gastroenterology and Hepatology, Medizinische Hochschule Hannover, D-30623 Hannover, Germany.

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viruses (EBV, CMV) was observed *in vitro*.[13] Clinical trials have shown famciclovir to be well tolerated and effective against herpes simplex and zoster virus infections in the treatment of more than 3,000 patients.[13,14] Oral famciclovir is easily absorbed and efficiently converted in the upper intestinal mucosa and liver to penciclovir.[12] The bioavailability of penciclovir, from famciclovir, is high (> 77%),[15] and the pharmacokinetic parameters for penciclovir are linear over the clinical doses of FCV (125-750 mg).[15] In herpes virus–infected cells, penciclovir is phosphorylated, initially by the viral thymidine kinase, to form penciclovir triphosphate[13,16] which inhibits the viral DNA polymerase. In contrast, HBV does not code for an enzyme that would phosphorylate penciclovir. However, an antiviral activity against HBV was shown in hepatoma cell lines and the Pekin duck.[17,18] In vitro studies indicate that the intracellular phosphorylation of penciclovir to penciclovir triphosphate is strongly inhibitory to the polymerases of both duck and human HBV.[19] Penciclovir triphosphate inhibits the synthesis of the short viral DNA primer by a chirally dependent mechanism, thereby suppressing hepadnavirus reverse transcription. The very low concentration of penciclovir triphosphate formed in uninfected cells (about 0.04 μmol/L) is comparable to that in HBV infected cells, and this may be sufficient to inhibit HBV replication.[15]

After *in vitro* studies suggested an activity against human hepatitis B virus,[18] a phase II study in immunocompetent patients with chronic hepatitis B infection indicated that FCV is effective in the treatment of chronic HBV by decreasing HBV DNA replication.[20] A 10-day course of FCV induced a greater than 90% decrease in HBV DNA levels in 6 of 11 patients treated, whereas none of the patients receiving placebo showed such a decrease in HBV replication. In addition, our group reported an effective suppression of HBV replication in a liver transplant patient with recurrent HBV infection.[21]

Here we report the results of a pilot study with famciclovir in 12 liver transplant recipients with HBV reinfection.

Patients and Methods

In an open compassionate use protocol, 12 adult patients with hepatitis B recurrence after orthotopic liver transplantation (OLT) received treatment with famciclovir for at least 3 months. HBV recurrence was diagnosed by elevated serum aminotransferase levels and return of hepatitis B surface antigen (HBsAg) and HBV DNA in serum. Patients were included if they had persistently elevated serum aminotransferase activities before therapy. After evaluation and percutaneous liver biopsy, patients were administered famciclovir orally (generously provided by SmithKline Beecham, London, UK) at a dosage of 500 mg three times a day. One patient received 750 mg three times a day for the first two weeks, then continued at a dose of 500 mg three times a day. FCV was administered for at least 3 months at a constant dose adjusted to renal function as follows: creatinine clearance > 60 mL/min, 3 × 500 mg (standard dose); creatinine clearance 30-60 mL/min, 2 × 500 mg; creatinine clearance < 30 mL/min, 1 × 500 mg. Patients were examined and blood samples were obtained for complete blood counts and routine serum biochemical parameters before treatment, weekly for the first month and then monthly while receiving FCV. Serum enzymes (including aminotransferases) and hepatitis B markers in serum were determined by standard methods. HBV DNA was measured using polymerase chain reaction (PCR) as described earlier.[22] Quantification of serum HBV DNA was performed by hepatitis B viral DNA hybridization assay (Abbott®, Wiesbaden, Germany) with a detection limit of 1 pg/mL HBV DNA in serum. The normal range of alanine aminotransferase (ALT) is < 22 IU/L.

The effects of FCV on hepatitis B virus infection in liver transplant recipients were assessed from changes in HBV replication (as indicated by serum HBV DNA levels) and ALT serum activities. Patients were classified as *responders* (sustained reduction in HBV DNA levels) or *nonresponders*, based on the changes in serum levels of HBV DNA and ALT activities under therapy in comparison with individual pretreatment baseline values.

Liver biopsy specimens were obtained before the start of treatment. Additional biopsies were not performed routinely under FCV therapy; therefore, histological results and immunohistochemical detection of hepatitis B markers in liver tissue are not shown. The details of the treatment protocol with FCV were approved by the local ethics committee of the Medizinische Hochschule Hannover. All patients gave written informed consent when included in the study.

Results

Patient Baseline Characteristics

Twelve liver transplant recipients were enrolled in the study (Table 1); all patients but 1 were males with a mean age of 50 years (range, 35-68 years). Orthotopic liver transplantation was performed between January 1990 and June 1994, showing advanced cirrhosis of the explanted liver in all patients and additional hepatocellular carcinoma in 4 cases. Before OLT, all 12 patients were seropositive for HBsAg; 10 patients were positive for HBV DNA (Abbott® assay), ie, serum HBV DNA > 1 pg/mL. Nine were positive for HBeAg before transplant, the remaining 3 patients (patients 2, 3, and 11) were negative for HBeAg and positive for anti-HBe antibodies. In these 3 patients, a stop mutation in codon 28 of the precore region was confirmed by sequencing of the hepatitis B genome (data not shown). Hepatitis D

Table 1. Characteristics of 12 Patients Treated With Famciclovir for Recurrent Hepatitis B Virus Infection After Orthotopic Liver Transplantation

Patient	Sex	Age (yr)	Indication for OLT	Immuno-suppression	Prednisolone Dose* (mg)	Time From OLT to HBV Recurrence (mo)	Time From Recurrence to FCV Therapy (mo)	Duration of FCV Therapy† (mo)
1	M	50	HBV-Ci, HCC	CSA, Pred	5	5	3	30
2	M	35	HBV + HDV-Ci	CSA, Pred	5	24	7	17
3	F	57	HBV + HDV-Ci	CSA, Pred	10	6	2	14
4	M	38	HBV-Ci	CSA, Aza, Pred	5	13	28	20
5	M	63	HBV-Ci	FK506, Pred	5	4	40	7
6	M	60	HBV-Ci	CSA, Pred	5	22	24	21
7	M	43	HBV + HDV-Ci‡	FK506, Pred	5	10	19	22
8	M	45	HBV-Ci	FK506	—	17	4	3
9	M	68	HBV-Ci, HCC	CSA, Pred	5	7	6	3
10	M	35	HBV-Ci	FK506	—	5	9	7
11	M	59	HBV-Ci, HCC	CSA, Pred	10	2	3	11
12	M	42	HBV-Ci, HCC	FK506, Pred	5	28	11	9

Abbreviations: Aza, azathioprine; CSA, Cyclosporin A; HBV-Ci, cirrhosis due to hepatitis B virus infection; HBV + HDV-Ci, cirrhosis due to hepatitis B + D virus infection; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; Pred, prednisolone.
*Prednisolone dose at time of reinfection.
†Duration of famciclovir therapy to date (September 1995).
‡Additionally anti-HCV positive, HCV RNA negative.

virus antibodies (anti-HDV) were found in 3 patients (patients 2, 3, and 7) before OLT and while receiving treatment with FCV. HDV RNA was detectable in 2 patients (patients 2 and 7) before and during FCV treatment. HDV RNA was undetectable in one patient (patient 3) in all samples tested. Additionally, antibodies to hepatitis C virus (with negative HCV RNA) were detected in one patient (patient 7).

The liver transplant recipients were treated with different immunosuppressive regimens, consisting of prednisolone with either Cyclosporin A (trough levels continuously kept at 100-120 ng/mL) or FK506; two patients received FK506 without prednisolone. After OLT prednisolone was initially administered at a dosage of 30 mg daily, then rapidly tapered over 6 months to 5 mg/d. Under FCV treatment immunosuppression remained unchanged, and there was no evidence of acute or chronic rejection. Ten of the patients developed HBV reinfection despite continuous hepatitis B imunoglobulin prophylaxis (Hepatect®, Biotest Company, Germany) with levels of anti-HBs constantly kept above 100 IU/L. In 2 patients, HBV-reinfection occurred 24 months after OLT, when passive immunoprophylaxis was routinely discontinued.

Three patients (patients 1, 3, and 11) had developed HBV reinfection 2 to 6 months after OLT with an acceleration 1 to 5 months later. Aminotransferases rapidly increased to very high ALT levels (up to 2,500 IU/L in one case) accompanied by biopsy-proven severe liver inflammation, deterioration of liver synthesis, and prothrombin time less than 30% that of controls. Before starting on FCV these 3 patients were treated with intravenous prostaglandin E (Minprog Paed®, Upjohn Co.) with the aim of decreasing inflammation by reducing the macrophage activity until FCV became available. Prostaglandin E was started in a dosage of 15 μg/h, increased to a maximum of 50 μg/h in steps of 5 μg/h every 4 hours clinically adapted to side effects.[21] The duration of prostaglandin E treatment ranged from 7 to 14 days. Before starting FCV therapy, the following changes in HBV DNA and ALT levels were observed: in one patient 1 a drop in HBV DNA (110 pg/mL to 12 pg/mL; reduction 89%) and ALT (330 IU/L to 131 IU/L; reduction 60%) was observed. In patient 3 serum HBV DNA remained unchanged (18 pg/mL to 17 pg/mL), whereas ALT levels decreased rapidly (1,580 IU/L to 98 IU/L; reduction 94%). For patient 11, baseline HBV DNA (day 0 of prostaglandin therapy) was not available, whereas ALT values remained unchanged (363 IU/L to 360 IU/L).

Effects of Famciclovir on HBV DNA Levels

Immediately after starting famciclovir, a decrease in serum HBV DNA levels (expressed as percentage change of the most recent HBV DNA value in comparison to individual pretreatment baseline levels) was observed in 9 of 12 patients (75%). In these 9 patients, the median reduction in serum HBV DNA was 99% (range; 55%-100%; see Table 2).

The changes in serum levels of HBV DNA under FCV treatment are presented in Fig 1. In responders (Fig 1A), HBV DNA decreased immediately after starting FCV. This decrease was maintained thereafter, with a mean reduction in comparison to baseline HBV DNA levels of 80% after 3 months, 90% after 6 months, and more than 95% after 12 months of FCV treatment. With continued therapy 5 of these 9 patients became negative by conventional hybridization assay, and in 1 of these patients HBV DNA became undetectable by PCR in week 28 of treatment.

Three patients (patients 10-12) showed no (sustained) reduction in HBV DNA levels after at least 3 months of FCV therapy and were, therefore, classified as nonresponders (Fig 1B). In 1 of these patients, HBV DNA decreased immediately after starting FCV treatment. However, after 2 months of therapy levels increased again. The latest HBV DNA value in all 3 patients was approximately twofold higher compared with the baseline level. Therefore, FCV treatment has been discontinued.

Effects of Famciclovir on ALT Levels

Serum ALT levels decreased in 6 of 12 patients (50%) while receiving famciclovir (Table 3). In these 6 patients, the median decrease in comparison to pretreatment ALT values under FCV was 80% (range; 40%-95%). ALT levels normalized in 4 patients (33%).

Figure 2A shows the mean changes in serum ALT activity for all 9 patients who are defined as *responders* to FCV therapy (sustained reduction in serum HBV DNA levels). ALT values decreased after 1 week of FCV treatment and continuously decreased with a mean reduction from pretreatment ALT values of 25% after 3 months, 30% after 6 months, and approximately 50% after 12 months of FCV therapy.

Figure 2B shows individual changes in serum ALT for all 3 patients classified as *nonresponders* (based on their increase in HBV DNA). In 1 patient, ALT and HBV DNA levels increased while receiving FCV therapy, which is regarded as a hepatitis flare up despite famciclovir therapy. However, two nonresponders (patients 10 and 11) had an ALT reduction of 74 and 83%.

In the subgroup of patients with ALT levels > 100 IU/L before starting FCV treatment, the decrease was more impressive; 5 of 6 patients (83%) had a reduction in ALT. The median decrease in ALT in these 5 patients was 84% (range, 40-95%). Normalization of ALT was observed in 3 of 6 patients (50%) within this subgroup.

Table 2. Changes in Serum HBV DNA Levels Under Famciclovir Treatment in 12 Liver Transplant Recipients With Recurrent Hepatitis B Virus Infection

	HBV DNA				
Patient	Before FCV (pg/mL)	After 2 months (pg/mL)	Most Recent (pg/mL)	PCR	HBV DNA Reduction (%)
1	12	<1	<1	neg.	>99
2	7	<1	<1	pos.	>99
3	17	<1	<1	pos.	>99
4	104	37	<1	pos.	>99
5	1133	50	<1	pos.	>99
6	470	113	7	pos.	98
7	234	18	28	pos.	88
8	451	171	171	pos.	62
9	576	833	262	pos.	55
10	131	441	277	pos.	no reduction
11	248	7	467	pos.	no reduction
12	474	271	888	pos.	no reduction

Abbreviations: neg., negative; pos., positive.

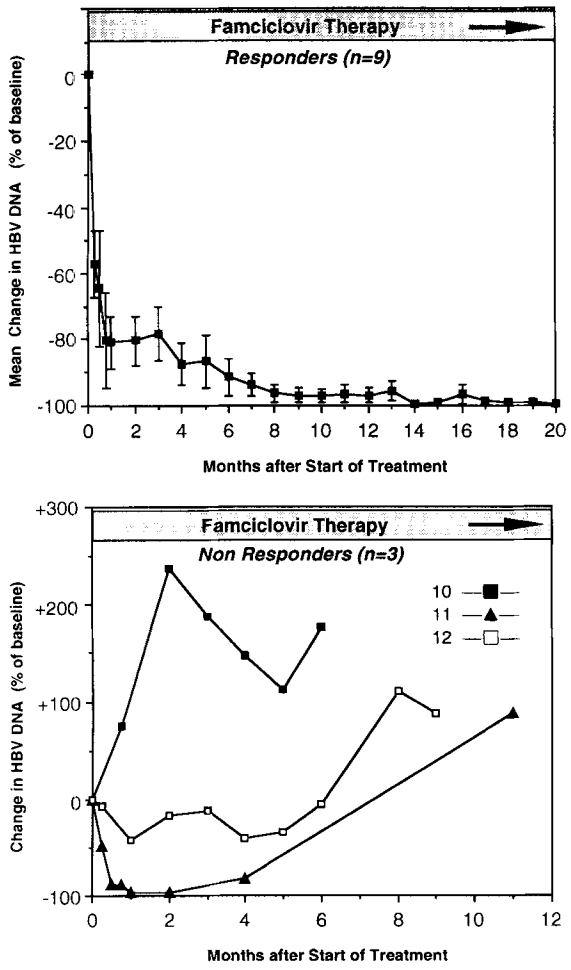

Figure 1. Mean changes (±SEM) in serum HBV DNA values in responders (A) during 20 months after start of famciclovir treatment (expressed as percentage change in comparison with pretreatment baseline HBV DNA values). For nonresponders (B), individual changes are shown as percentage of baseline values for patients 10, 11, and 12. HBV DNA was measured by hepatitis B viral DNA hybridization assay (Abbott®, Wiesbaden, Germany); negative refers to less than 1 pg/mL HBV DNA in serum.

In those patients without significant changes in ALT activity, the levels of ALT fluctuated around baseline levels, varying from 38 to 130 IU/L.

HBeAg/Anti-HBe Seroconversion

Nine patients were seropositive for HBeAg and negative for anti-HBe antibodies at the start of FCV treatment. Two of these 9 patients (22%) underwent HBeAg-anti HBe seroconversion.

Patient 1 became negative for serum HBV DNA by hybridization assay in week 3. After 8 weeks, he became negative for HBeAg and developed anti-HBe antibodies. HBV DNA was undetectable by PCR after 28 weeks of treatment. ALT levels decreased steadily while receiving FCV treatment and normalized by week 16, accompanied by normalization of inflammatory activity (as indicated by liver biopsy). FCV dosage was tapered to 250 mg three times a day after 20 weeks and to 125 three times a day after 6 months of FCV treatment. The patient has now received FCV therapy for 30 months, remained HBsAg positive and returned to work and regular daily life.

Patient 4 underwent seroconversion to anti HBe antibodies after 22 weeks of treatment and became negative for HBV DNA by hybridization assay in week 44. Transaminases normalized after 28 weeks of FCV treatment. This patient has now received 20 months of FCV therapy and remained PCR positive for HBV DNA and HBsAg.

Clinical Improvement

The clinical condition of patients was monitored by questioning and physical examination. A clinical improvement was observed in 5 patients (patients 1, 3, 6, 7, and 11); 2 of these who were unable to work because of illness returned to work while receiving FCV therapy. The clinical condition of 6 patients

Table 3. Changes in Serum ALT Values Under Famciclovir Treatment in 12 Liver Transplant Recipients With Recurrent Hepatitis B Virus Infection

	ALT			
Patient	Before FCV (IU/L)	After 2 Months (IU/L)	Most Recent (IU/L)	ALT Reduction (%)
1	131	61	12	91
2	42	38	40	no reduction
3	98	80	88	no reduction
4	321	52	15	95
5	63	50	21	66
6	48	49	52	no reduction
7	100	106	98	no reduction
8	104	130	95	no reduction
9	128	75	77	40
10	127	57	22	83
11	360	68	94	74
12	38	40	299	no reduction

Abbreviation: ALT, alanine aminotransferase (upper limit of normal, 22 IU/L).

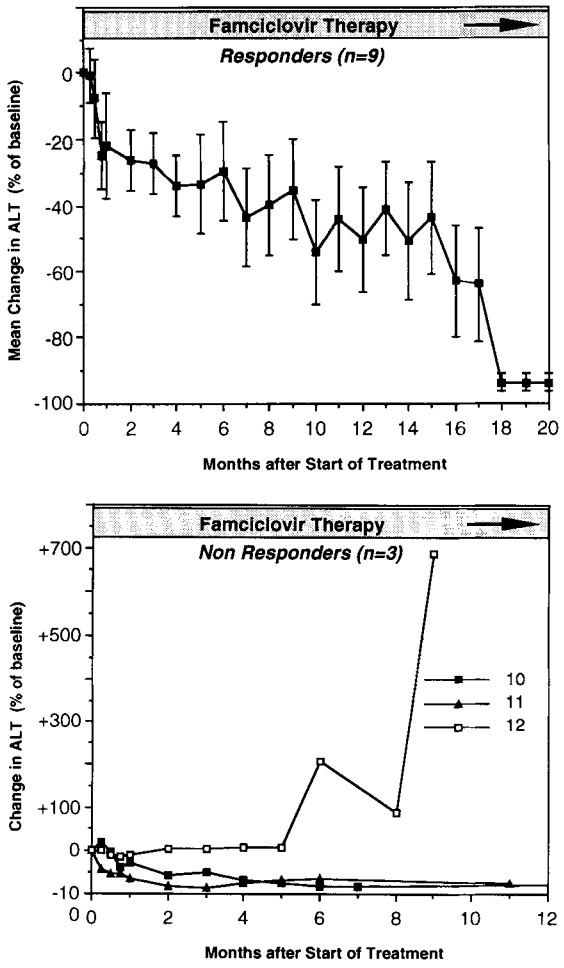

Figure 2. Mean changes (±SEM) in ALT serum activities in responders (A) and (B) individual changes in nonresponders (patients 10, 11, and 12) under famciclovir therapy (expressed as percentage change from pretreatment baseline ALT values).

(patients 2, 4, 5, 8, 10, and 12) remained stable, whereas 1 patient (9) continued to deteriorate under FCV treatment.

Effects on Liver Histology

Liver biopsy specimens obtained before treatment indicated active hepatitis in all patients. Additional liver biopsies to assess histological changes under FCV therapy were not performed routinely, except in two cases (patients 1 and 9). Patient 1 underwent a biopsy before treatment showing severe hepatitis; the liver specimen obtained in week 4 showed marked improvement of cellular infiltration, almost complete normalization of histological changes, and only residual scars were visible. A liver biopsy obtained after 24 months of FCV treatment showed complete normalization of histological changes.

Further biopsies and immunohistochemical detection of hepatitis B markers in liver tissue are planned to investigate histological changes under FCV therapy.

Safety

Famciclovir therapy was generally well tolerated with a low incidence of adverse effects. No patient had clinically significant side effects.

Patient 9 showed progressive biopsy-proven cholestasis with some features of fibrosing cholestatic hepatitis present before FCV treatment. In this case, HBV DNA levels increased in the first 8 weeks of FCV treatment, followed by a decrease in weeks 9 to 13. In week 13 a progress in cholestasis was observed. Cholangitis occurred associated with rapidly progressive graft dysfunction, sepsis with *Klebsiella pneumonia* and peritonitis. In the liver biopsy specimen, high cytoplasmic expression of viral antigens, prominent cholestasis, perisinusoidal ductular proliferation, and ballooning of hepatocytes with mild inflammation were found. Liver function tests showed markedly abnormal serum bilirubin and prothrombin times but only modest increases in serum transaminase levels. Because HBV was suspected to be the cause of deterioration and there were no established therapeutic alternatives, FCV treatment was continued. This patient died at the end of week 13 of sepsis and cardiac decompensation. The events leading to death are believed to be related to the underlying HBV recurrence and not related to FCV treatment.

One further patient (6) reported transient diarrhea with mild abdominal pain during week 16 of FCV therapy. Treatment was interrupted for 5 days (and in addition for 2 days because of resupply problems). Diarrhea and abdominal pain resolved and did not recur despite restarting FCV. This patient's clinical condition markedly improved after FCV treatment was continued.

Anemia as a possible side effect of most nucleoside analogues was not observed. Hemoglobin levels, red blood cell count, and white blood cell count remained unchanged throughout therapy. Total bilirubin and coagulation parameters (eg, prothrombin time) have slightly improved in most patients (data not shown).

Discussion

Despite hepatitis B immunoprophylaxis, HBV recurrence is a frequent and often fatal complication after

OLT.[9] The level of pretransplant HBV DNA replication is regarded as a reliable predictor of posttransplantation outcome in HBV patients.[23] Immunosuppression after OLT enhances viral replication and thus increases the risk of graft infection.[24] In a substantial number of cases, hepatitis B recurrence takes an accelerated course, leading to progressive hepatitis of the grafted liver and rapid development of cirrhosis.[25]

Efforts to prevent and treat HBV recurrence after OLT have been disappointing. Long-term administration of high-dose hepatitis B imunoglobulins (HBIG) reduces the risk of allograft infection, delays reappearance of the virus, and ameliorates the severity of recurrent hepatitis B, presumably by neutralizing circulating HBV particles.[26] In addition, HBIG improves survival in this group of patients.[4,27,28] However, considerable cost may limit the application of HBIG, and in the majority of cases despite HBIG immunization HBV recurrence cannot be prevented in the long term.[4,29] Once HBV reinfection appears, treatment is difficult because of lack of effective antiviral therapy. Interferon alfa is rarely administered after OLT,[4] because it enhances HLA expression on hepatocytes and may thus precipitate allograft rejection.[30]

Nucleoside analogues are of particular interest for the treatment of HBV in immunocompromised patients, because they act despite an impaired immune system. Nucleoside analogues investigated include *adenine arabinoside (ARA-A)*, *acyclovir, ganciclovir, famciclovir* (the oral form of *penciclovir*), ribavirin, fialuridine (*FIAU*), and *lamivudine.*

Adenine arabinoside (ARA-A)—a synthetic purine nucleoside— and its 5′-monophosphate derivative (ARA-AMP) are effective inhibitors of HBV replication, but their use is limited by the remarkable neurotoxicity.[31,32] *Acyclovir* has inhibitory effects on HBV in duck models, but unfortunately no effect on human HBV replication.[33] Pilot studies with *ribavirin* as an orally administered guanosine nucleoside analog have shown inhibition of HBV replication in patients with chronic HBV. However, the antiviral effect was less compared with Interferon-beta.[34] *Fialuridine (FIAU)* is an orally administered pyrimidine analog that is phosphorylated by viral and cellular enzymes to triphosphate and inhibits viral DNA polymerases.[35] Preliminary trials revealed effective inhibition of HBV DNA replication. However, long-term trials were terminated because of high mortality due to liver failure associated with lactic acidosis and pancreatitis.[36,37] Degeneration of intramitochondrial DNA and mitochondrial dysfunction is believed to be the cause of these severe FIAU side effects.[38] *Lamivudine* (an oral analog of 2-deoxy-3-thiacytidine) has a potent inhibitory effect on human and duck HBV replication *in vitro.* Orally administered in patients it was well tolerated and effective in inhibiting HBV replication.[39,40] Unfortunately, there was a rebound when the drug was stopped. *Lamivudine* is undergoing further investigation in chronic HBV infection and in patients with HBV infection before and after OLT. In contrast to FCV, lamivudine has no antiherpes effect, although its antiviral activity may be higher. *Ganciclovir* is effective in life-threatening cytomegalovirus infection. Although results in a small group of transplant recipients were promising,[41,42] ganciclovir failed to prevent graft reinfection after orthotopic liver transplantation for chronic hepatitis B.[43] In addition, the use of ganciclovir in patients under immunosuppression is limited by its bone marrow suppressing effect.

Famciclovir is a new nucleoside analog. Tsiquaye et al found that FCV effectively reduces duck HBV replication.[13] First studies in chronic HBV patients indicated that the drug effectively suppresses replication of human HBV.[20,21] Therefore, we conducted an uncontrolled pilot study to evaluate the effect of famciclovir on viral replication and inflammatory activity in liver transplant recipients to stop progression of recurrent hepatitis B infection.

In this pilot study, famciclovir therapy was associated with a significant reduction in HBV DNA. HBV DNA levels decreased in 9 of the 12 patients treated (75%), with a mean change from baseline levels of 80% after 3 months, 90% after 6 months, and more than 95% after 12 months of treatment. One patient became PCR negative. The reduction in viral loads was generally accompanied by a decrease in serum aminotransferase levels; serum ALT levels continuously decreased in 50% of all patients, with a median reduction from pretreatment ALT values of 80%. In the 6 patients with ALT levels greater than 100 IU/L at the start of treatment, a reduction in ALT was observed in 5 of these patients (83%). The median reduction in these 5 patients was 84%. Although levels of HBV replication generally fluctuate in HBV-infected patients, such reductions of virus load and transaminases coincident with the start of famciclovir treatment are usually not observed in liver transplant recipients with recurrent hepatitis B. The antiviral efficacy of FCV against HBV was supported by the clinical changes. A clinical improvement was observed in 5 patients whose baseline conditions were already giving cause for concern. The clinical condition of 6 other patients remained stable while

receiving FCV treatment. For only 1 patient, FCV was unable to stop or reverse the clinical deterioration.

The poor prognosis of OLT recipients with recurrent hepatitis B infection, reduced long-term survival and disappointing results of retransplantation for HBV-infected patients have raised difficult ethical issues because of the limited number of donor organs and the costs of transplantation.[44] Although HBIG improves survival, the use of new antiviral agents such as FCV, together with a better understanding of the effects of immunosuppressive agents on HBV replication, might add substantial benefit to the long-term survival of these patients. The relatively slow decrease in ALT levels found in our study emphasizes the need for longer treatment periods to achieve sustained improvement of the underlying liver disease. Because long-term FCV treatment is well tolerated, we feel encouraged to continue evaluating the antiviral effect of FCV in the treatment of HBV recurrence after liver transplantation. Further studies including larger numbers of patients will allow definition of predictors of response and to develop strategies for long-term management.

In patients requiring a liver transplant because of end-stage liver disease, a large multicenter trial has been initiated to assess the efficacy of oral famciclovir (and intravenous penciclovir perioperatively) in decreasing active HBV replication before transplantation. In this randomized, partly double blind, partly placebo-controlled study famciclovir is also evaluated for the prevention of subsequent hepatitis B reinfection after OLT. In liver transplant recipients, famciclovir treatment might be particularly useful for the prevention and control of recurrent HBV and will simultaneously provide additional cover for the prevention of herpes simplex and varicella zoster infections.

In chronic HBV patients, a multicenter study comparing FCV with placebo is ongoing and will soon definitively determine the inhibitory effect of FCV on HBV in immunocompetent patients. A combination with interferon for interferon nonresponders, a combination with prostaglandin E,[45] or other antiviral agents may offer additional therapeutic options for patients with chronic hepatitis B infection. Additionally, rare HBV-induced diseases (eg, HBV-associated panarteriitis nodosa), in which the viral load is critical for disease progression, might gain benefit from this new therapeutic option (Krüger et al, manuscript in preparation). Nucleoside analogues like famciclovir appear as a promising antiviral strategy in the treatment of HBV infection in immunocompromised patients in general, a population in which interferon is not effective.

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