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Long-term results of famciclovir for recurrent or *de novo* hepatitis B virus infection after liver transplantation

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Abstract: Since the introduction of famciclovir in the treatment of hepatitis B virus (HBV) infection after liver transplantation, promising results have been published. In this study, the long-term efficacy and safety of famciclovir were assessed. Twenty-four patients with recurrent hepatitis B and 6 patients with *de novo* infection after liver transplantation were enrolled in an open prospective trial. Patients received oral famciclovir, 500 mg three times daily. Serum HBV-DNA, viral serology, and liver enzymes were measured sequentially; liver histology was taken before and during treatment in 12 patients. In the reinfected patients, 17 patients initially responded well to treatment, with a mean decrease of HBV-DNA of 82%, 5 patients became HBV-DNA negative. The drug was effective for 1–51 months (mean 16 months), then viral replication increased again in 13 out of 17 patients. One patient did not respond to treatment. Six out of 24 patients already had severe cirrhosis at the time of enrolment and died shortly afterwards, due to the HBV infection. The 6 patients with *de novo* infection all had a decline of HBV-DNA for 2–42 months (mean 14 months); 1 patient converted to HBV-DNA negative. Five out of 6 patients experienced a viral breakthrough later on. No severe side-effects were observed. Therefore, famciclovir is effective in certain HBV-infected patients after orthotopic liver transplantation (OLT), but in the long term, most of the patients relapse.

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Liver transplant recipients with recurrent hepatitis B virus (HBV) infection or *de novo* infection after orthotopic liver transplantation (OLT) have a decreased patient and organ survival (1, 2) and only few therapeutic options. The reinfection or *de novo* infection leads to cirrhosis much faster (1–2 yr) than in immunocompetent patients (3), possibly because of a glucocorticoid responsive enhancer region in the HBV-DNA genome and impaired T-cell response caused by cyclosporin A or tacrolimus and other factors attributable to immunosuppression. Histological changes in reinfected livers showed chronic active hepatitis in 47%, chronic persistent hepatitis in 14%, and submassive necrosis in 7% of cases after at least 18 months of follow-up. Only 9% had a chronic carrier status (4). The results of retransplantation are disappointing: Crippin et al. (5) found that out of 20 patients, 55% died within 60 d. The long-term survival was only 5% in their series, as compared to 24% in other European studies (6). Recurrent disease could be detected after only 2.8 months versus 6 months in the first transplant.

Ganciclovir and acyclovir have not proven to be effective enough for treatment of HBV reinfection (7). One group has tried to continue the prophylaxis with hepatitis B hyperimmunoglobulin (HBIg), despite conversion of negative hepatitis B surface antigen (HBs-Ag) to positive HBs-Ag and HBV-DNA and presumed resistance to HBIg and could achieve HBV-DNA negativity again (8, 9). Interferon alpha has shown some beneficial effect, but much less than in immunocompetent patients, and carries the risk of inducing rejection (10).

With the introduction of lamivudine and famciclovir, more potent anti-viral drugs were available. Promising results have been published for both drugs, but for famciclovir, only in very small patient groups and with a short follow-up (11–14). In an open prospective trial, we assessed the long-term efficacy and safety of famciclovir in patients with HBV reinfection or *de novo* infection after OLT.

Patients and methods

Between October 1988 and October 1997, 174 liver transplantations were performed for HBV-related cirrhosis or acute liver failure at our center. Of these patients, 34% developed reinfection, despite prophylaxis with HBIg (Hepatect®, Biotest, Dreieich, Germany). During the anhepatic phase, 10000 units of HBIg were given, then 2000 units/d for 1 wk. Titers of anti-HBs antibody were held above 100 units/L until reinfection. In 6 patients transplanted for various indications, *de novo* HBV infection was diagnosed. HBV infection was confirmed by HBs-Ag positivity (Sorin, Biomedica, Düsseldorf, Germany) and the detection of more than 10 pg/nL HBV-DNA in the serum (Hybridization assay, Abbott, Germany).

Immunosuppression consisted of either tacrolimus (n = 15), 11 together with low-dose (5 mg) prednisolone, or cyclosporin A (n = 15), in 10 patients as dualtherapy with low-dose prednisolone. Tacrolimus serum trough levels were held at 5 ng/mL (IMX assay), cyclosporin A levels at 200–300 ng/mL (polyclonal TDX assay).

When famciclovir became available in November 1993, we started treatment with 3×500 mg/d orally on a compassionate use basis in an open prospective trial. Dosage was reduced in case of renal impairment and adjusted to creatinine clearance (30–59 mL/min = 500 mg daily, < 30 mL/min = 250 mg daily). Liver enzymes (ASAT, ALAT, GGT, AP, bilirubine), renal function (urea, creatinine), hematology (white blood cells, hemoglobine, platelets), coagulation tests (PTT, quick), HBV serology (HBs-Ag, anti-HBs, HBc-Ag, anti-HBc, HBe-Ag, anti-HBe), and HBV-DNA were measured weekly in the first month, then every other week in our outpatient clinic. Side-effects were routinely monitored by general practitioners or by our outpatient clinic. Liver biopsies were performed routinely at 1, 3, and 5 yr after OLT or if rejection or reinfection was suspected, in case of increasing liver enzymes. Liver biopsies were stained with hematoxylin and eosin.

Results

Twenty-four patients with HBV reinfection and 6 patients with *de novo* infection were enrolled in the trial from November 1993 to October 1998.

Hepatitis B virus reinfection (n = 24)

The male/female ratio was 21/3 and the mean age was 46 yr (34–63 yr). Twelve patients were HBV-DNA negative prior to OLT, 7 patients were positive (8–176 pg/nL), and in 5 patients, HBV-DNA was not available. Twelve patients had positive HBe-Ag before OLT; the other 12 were HBe-Ag negative.

Five patients were coinfected with HDV, and 2 patients were coinfected with HCV.

Twenty-one patients received passive immunoprophylaxis with hyperimmunoglobulin until reinfection, as described above; 3 patients had been transplanted before the prophylaxis was introduced at our center.

HBV reinfection occurred 1–15 months (mean 6 months) after transplantation. Famciclovir was initiated 1 wk to 78 months after reinfection (mean 13 months) as soon as the drug was available.

Responders (n = 17) (Table 1). Seventeen out of 24 patients (71%) responded to treatment, with a decrease of HBV-DNA from 14 to 100% (mean 82%) 1 wk to 9 months (mean 3 months) after famciclovir was started. Five out of these 17 patients were HBV-DNA positive prior to OLT, 7 of these patients were negative. Liver enzymes decreased between 22 and 99% (mean 57%). Five out of 17 patients became HBV-DNA negative 1–5 months (mean 2 months) after treatment was started. One of these patients also eliminated HBe-Ag after 3 months of famciclovir. Two of these patients had a positive HBV-DNA before OLT; in the other 3 patients, HBV-DNA had not been measured before OLT.

Histology was available in 12 out of the 17 responders. In 5 patients, the grade of hepatitis and fibrosis expressed in the Knodell score improved during treatment; in 2 patients, the index did not alter during treatment; and in 5 patients, the hepatitis activity index (HAI) increased (Table 3).

The positive effect of famciclovir was maintained for 1–51 months (mean 16 months) during treatment. Afterwards, HBV-DNA and liver enzymes increased again in 13 out of 17 patients (80%). These 13 patients were then switched to lamivudine 5–40 months (mean 22 months) after initiation of famciclovir therapy. Four patients

Table 1. Data of reinfected patients with response to famciclovir

Patient	Pre-operative HBV-DNA (pg/nL)	Pre-operative HBe-Ag	Time from reinfection to therapy (months)	HBV-DNA before therapy	Lowest HBV-DNA	Coinfection	Response period (months)
1	–	+	4	20	0	HDV	12
2	–	+	7	10	6	HDV	51
3	?	–	72	7837	0		36
4	–	–	0.5	2221	420		12
5	20	–	14	1121	0		14
6	?	+	42	292	0		12
7	?	+	54	145	67		21
8	90	+	12	3158	0	HCV	24
9	176	+	0.5	560	44	HCV	31
10	–	+	1	1225	46		3
11	11	+	0.5	22	8		8
12	–	–	12	1682	467		1
13	–	–	18	2882	9		18
14	92	–	1.5	145	67		16
15	?	–	42	1456	88		5
16	–	–	2	141	17		8.5
17	?	–	78	4040	484	HDV	1

–, negative; +, positive.

stayed on famciclovir with good results. Three of them died, due to *de novo* neoplasia (n = 2) and pulmonary embolism (n = 1) 10, 21, and 51 months after the start of famciclovir. One patient continues to receive famciclovir 4 yr later.

There was no correlation between type of immunosuppression, HBV-DNA or HBe-Ag prior to OLT, HDV or HCV coinfection, or amount of HBV-DNA before treatment and effect of famciclovir. Patients in whom famciclovir was initiated late after reinfection, but before development of cirrhosis, tended to respond better and longer to therapy than patients who received famciclovir shortly after reinfection. This fact is probably due to biological selection because these patients had a milder form of reinfection that had not caused cirrhosis so far.

Non-responders (n = 7). In 6 patients (2 HBV-DNA positive, 4 HBV-DNA negative prior to OLT), famciclovir was started when they already had severe cirrhosis proven by biopsy and liver function was severely impaired. All of them died between 10 d and 2 yr after initiation of therapy (mean 160 d), due to complications of HBV cirrhosis.

There was one non-responder with pre-operative negative HBV-DNA, in whom HBV-DNA and liver enzymes even increased under famciclovir. He was switched to lamivudine after 6 wk of famciclovir, but HBV-DNA remained high.

De novo hepatitis (n = 6)

Six patients developed *de novo* HBV infection 3–36 months (mean 12 months) after OLT (Table 2). The indication for OLT had been primary biliary cirrhosis (PBC) (n = 3) and alcoholic cirrhosis (n = 3). The age varied between 36 and 59 yr (mean 45 yr). Famciclovir was started 5 d to 3 yr after diagnosis of infection. All patients initially responded well to famciclovir, with a decrease of HBV-DNA between 76 and 100% (mean 86%) and a decrease of liver enzymes of 20–66% (mean 23%). One patient became HBV-DNA negative 8 months after the start of therapy. His liver enzymes also normalized. Six months later, he had a viral breakthrough and was switched to lamivudine.

In the remaining 5 patients, the response to famciclovir, measured by HBV-DNA, lasted for 2–42 months (mean 14 months). Famciclovir was given for 8–42 months (mean 17 months); in 1 patient, therapy is still ongoing (Table 2).

Sequential histology was not available in these patients. Immunosuppression, amount of viral replication before therapy, or time between infection and therapy did not influence the effectiveness of famciclovir.

No side-effects and no rejection episodes were noted. The mean HBV-DNA in all 30 patients before and during treatment with famciclovir is shown in Fig. 1; the mean ALAT is shown in Fig. 2. Interestingly, the ALAT remained relatively low, even when the HBV-DNA increased after viral breakthrough.

Discussion

In this series of 30 patients with HBV reinfection or *de novo* infection, famciclovir could achieve an initial response rate of 96% when initiated before

Table 2. Data from patients with *de novo* infection

Patient	Time from infection to therapy (months)	HBV-DNA before therapy (pg/mL)	Lowest HBV-DNA	Response period (months)
1	0.5	2572	609	13
2	0.5	11 580	103	42
3	36	2884	466	12
4	0.5	4558	997	2.5
5	20	2305	0	14
6	5 d	4345	993	2

development of severe cirrhosis. The response could be demonstrated as reduction of HBV-DNA, liver enzymes, and, in some cases, even grade of hepatitis and fibrosis. In 6 patients (20%) a conversion to negative HBV-DNA could be achieved, but only for a short time. HBV-DNA was measured by hybridization assay in this study. Mason et al. (15) could demonstrate that, even in patients with negative results for HBs-Ag and HBV-DNA in the hybridization assay, HBV-DNA could still be detected by polymerase chain reaction (PCR) in the serum (15). Therefore, HBV might still circulate in the blood in small amounts when DNA tests were negative in this study and could be responsible for the hepatitic flare-up in the long-term follow-up. HBe-Ag became negative only in 1 patient, comparable to a HBe-Ag conversion rate of 0–12% under lamivudine (16).

Promising results have been shown by Krüger et al. (11). From 12 liver transplant recipients with recurrent HBV infection treated with famciclovir, 9 had a 95% reduction of HBV-DNA and 6 became HBV-DNA negative after 12 months; 5 patients clinically improved.

In 6 out of 11 patients with chronic HBV infection without immunosupression, HBV-DNA could be decreased for 90% after 2–10 d of famciclovir treatment and only 2 out of 6 patients deteriorated after withdrawal of famciclovir (7).

Singh et al. (17) started famciclovir in 8 patients with positive HBV-DNA before OLT. Two patients became HBV-DNA negative, were transplanted, and were still negative 21 and 22 months after OLT, with a combination of famciclovir and immunoprophylaxis. Two more patients had a sustained and 3 had a transient decline of HBV-DNA. Controlled studies with larger numbers of patients and longer follow-up periods have not been published yet.

Although the results of clinical studies with famciclovir seem to be promising, the most striking problem of the new anti-viral drug is the relapse of hepatitis during long-term treatment. In this study, only 4 out of 17 initial responders with HBV reinfection and 1 out of 6 responders with *de novo* infection had a sustained decline, the longest being treated for 4 yr now. The remaining patients experienced a breakthrough of viral replication after the mean 11 months.

Aye et al. (18) could detect three mutations in the HBV polymerase gene involving the B-domain with a conserved C-domain after 370 d of famciclovir treatment, causing resistance to the drug. Although this assay could not be performed in our patients, the relapse is most likely due to resistance formation.

HBV mutations have also been detected during long-term HBIg prophylaxis (8); a mutation rate of

Table 3. Histological changes in 12 responders under famciclovir (HAI activity index, Knodell score)

No.	HAI score before therapy	HAI score during therapy	Time of biopsy after therapy start (months)
1	8	6	13
2	5	1	33
3	7	5	15
4	8	7	29
5	13	12	24
6	4	4	5
7	8	8	4
8	1	4	15
9	2	4	29
10	2	5	22
11	4	8	23
12	2	8	32

0–33% could be shown in the 'a'-determinant of HBV.

Resistance has been analyzed most exactly for lamivudine. Many authors describe an amino acid substitution in the YMDD motif of the viral DNA polymerase (19–22).

Patients with recurrent HBV or *de novo* infection did not differ in their response to famciclovir in our patient population. There are no comparative studies published, but two authors reported a better spontaneous outcome of *de novo* infections compared to recurrence of HBV (23, 24). The 2 patients with positive HBV-DNA after *de novo* infection became HBV-DNA negative under lamivudine in a study by Nery et al. (20). The numbers of patients in the existing trials are too small to draw any conclusions about the difference between recurrent and *de novo* infection.

There are few alternative therapeutic options for HBV infection after OLT. Reports about the efficacy of interferon alpha are controversial; some authors could not find any beneficial effect (25, 26), other publications find a response rate of up to 29% (28). The immunmodulator thymosin alpha 1 could achieve HBV-DNA negativity in 41% of 98 patients with chronic HBV infection after 26 wk of therapy, but has not been tested in immunocompromised patients (29). Ganciclovir was given to 9 patients with recurrent or *de novo* infection and achieved a decrease of HBV-DNA of more than 85%, but this drug needs intravenous administration (23). Fialuridine cleared HBV-DNA in 25% of patients, but caused severe side-effects, like pancreatitis and acidosis (14).

Gish et al. (30) simply reduced immunosuppression in 13 reinfected patients and had a patient survival of 82%, but reinfection remained.

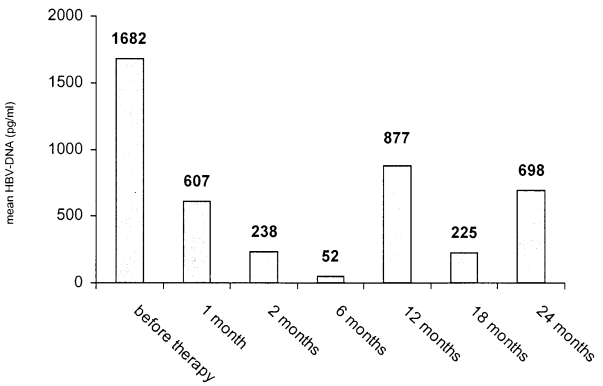

Fig. 1. Mean HBV-DNA of all patients before and during famciclovir therapy.

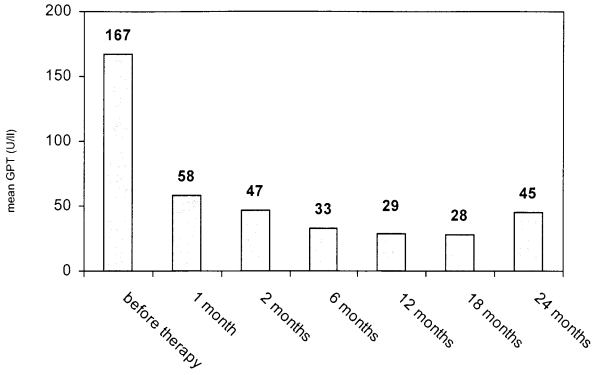

Fig. 2. Mean ALAT of all patients before and during famciclovir therapy.

In a recent study (9), HBIg was continued, despite reinfection under passive immunoprophylaxis. All 5 patients became HBV-DNA negative, but these results have to be confirmed in further investigations.

Thus, with the limited means to treat HBV infection after OLT, there are two main problems to solve: risk factors for reinfection, such as positive HBV-DNA and HBe-Ag prior to OLT (6, 27), which lead to a reinfection rate of 83% in case of positivity versus 58% in case of negativity should be minimized. Pre-operative treatment with lamivudine, famciclovir, or interferon alpha in HBV-DNA-positive patients is a promising possibility (4, 31). On the other hand, there is a need for approaches to avoid resistance formation to anti-viral prophylaxis or treatment. To reach this purpose, combination therapy of agents with a different mechanism of action could be tested in prospective studies (32). Famciclovir terminates the viral DNA elongation, whereas lamivudine irreversibly blocks the reverse transcriptase step. They have no synergistic toxicity, but cross-resistance occurs, especially when famciclovir is used after long-term lamivudine therapy (32). Interferon alpha helps the immune system to eliminate the virus.

In summary, famciclovir monotherapy in patients with HBV reinfection or *de novo* hepatitis B after OLT is a therapeutical option, especially in patients with a mild long-lasting reinfection, but there is a breakthrough of viral replication in nearly all of the responders after prolonged treatment.

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