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Lamivudine as first- and second-line treatment of hepatitis B infection after liver transplantation

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Abstract Lamivudine and famciclovir have expanded therapeutical options for HBV infection after liver transplantation. First studies confirm good antiviral effects of both, but at present the major problem seems to be a rapid resistance formation in immunosuppressed patients. Thirty-four adult patients with HBV recurrence despite passive immunoprophylaxis and seven with de novo infection after orthotopic liver transplantation (OLT) were treated with 100–150 mg lamivudine daily. Patients were either treated directly after infection ($n = 14$) or after breakthrough of viral replication during an initial famciclovir therapy ($n = 27$). All patients except two responded to treatment with a reduction of serum HBV-DNA of over 50%. Thirty-one patients (76%) turned HBV-DNA-negative during lamivudine therapy. Viral breakthrough was observed in 14 of these patients after 4–13 months of treatment. A total of17 patients (40%) remained HBV-DNA-negative for more than 12 months. Only nine patients eliminated HBsAg, of which four had and an HDV coinfection. None of the HBeAg-positive patients converted to anti-HBe. Most patients showed a prompt and significant reduction of aspartate aminotransferase (ALAT) levels. No severe complications occurred. Therefore, a safe and effective therapy of HBV infection after transplantation is possible with lamivudine. Viral replication is suppressed even in patients who revealed breakthrough during famciclovir therapy. Resistance formation as a major drawback occurred in one third of the patients within the first year of treatment.

Key words Liver transplantation · Hepatitis B · Reinfection · Lamivudine · Famciclovir breakthrough

Abbreviations *ALAT* Aspartate aminotransferase · *HBIg* Anti-hepatitis B-surface immoglobulin · *OLT* Orthotopic liver transplantation

Introduction

Hepatitis B infection either as reinfection or de novo infection of the graft is a serious complication after orthotopic liver transplantation (OLT). As a consequence, progressive liver disease and graft failure evolves among a certain percentage of recipients [7]. Until the introduction of passive immunoprophylaxis, HBV recurrence was the most common cause of death in patients who had undergone transplantation for chronic hepatitis B [27]. Long-term passive immunoprophylaxis with anti-hepatitis B-surface immunoglobulin (HBIg) has now commonly been accepted as effective means to prevent reinfection of the graft [19]. But despite HBIg prophylaxis, about 35% of the patients develop recurrent HBV infection within 3 years after OLT [24]. In these

Table 1 Number of patients in the two study groups and number of coinfected patients in the different groups

Group	Lamivudine	Total (*n*)	HBV (*n*)	HBV + HDV (*n*)	HBV + HCV (*n*)
1 (Reinfection)	first-line	12	6	6	0
	second-line	22	18	1	3
2 (De novo)	first-line	2	2	–	–
	second-line	5	5	–	–

patients, HBV recurrence is supposed to be partially due to the formation of virus mutants with an altered HBsAg structure [10].

Apart from passive immunoprophylaxis, options for the treatment of hepatitis B after transplantation have been limited since interferon-α monotherapy failed to show efficacy in the treatment of transplant patients [21, 23]. Within the last years, however, new nucleoside analogues have expanded therapy and prophylaxis of hepatitis B infection after OLT. Famciclovir and lamivudine, two oral nucleosid analogues, have also been used successfully for the treatment of HBV infection among patients without transplants [8, 16]. The purine analogue famciclovir is activated by viral enzymes and leads to chain termination of DNA. Antiviral effects have been found against herpes viruses and the hepatitis B virus [3]. Lamivudine is a potent inhibitor of reverse transcriptase [17], which was originally developed for the treatment of HIV infection. However, an effect against HBV was subsequently recognized patients coinfected with HBV and HIV [26]. Preliminary data after OLT showed a good suppression of HBV replication by both famciclovir [20] and lamivudine [5, 14] in most patients. The major problem concerning the application of these agents in imunosuppressed patients seems to be the formation of resistant virus strains in a high percentage of patients after several months of therapy [20]. The following study analyzes the efficacy of lamivudine either as first-line therapy after HBV infection or as second-line therapy after breakthrough during initial famciclovir therapy in liver transplant patients.

Patients and methods

Patients

Between April 1996 and April 1998, 41 adult patients with hepatitis B infection after OLT were enrolled into this open prospective trial on a compassionate-use basis. The trial was approved by the local ethics comittee. Thirty-four patients underwent liver transplantation for HBV infection (group 1) and were HBsAg-positive before OLT. At least 18 of these patients showed viral replication at the time of transplantation, indicated by positive HBeAg ($n = 4$), a positive HBV-DNA ($n = 8$), or both markers ($n = 6$). In two patients neither HBV-DNA nor HBeAg was determined prior to OLT, in four patients no preoperative HBV-DNA was available. A coinfection with either HDV or HCV was present in ten patients (Table 1). Seven of the 41 patients underwent transplantation for liver disease unrelated to HBV (primary biliary cirrhosis, carcinoid metastases, acute liver failure of unknown etiology, and four patients for alcoholic cirrhosis) and were HBsAg-negative at the time of transplantation. These patients developed de novo hepatitis B infection after OLT (group 2). A hepatocellular carcinoma was found in the explanted liver in three patients.

Postoperative management

Fifteen patients (37%) received a cyclosporine-based, 26 (63%) a tacrolimus-based immunosuppression. During lamivudine treatment, six patients (15%) were still treated with steroids, the other 35 (85%) were steroid-free. In all patients from group 1, an intravenous passive immunoprophylaxis with anti-hepatitis B-surface hyperimmunoglobulin was performed after OLT following a standard scheme: 10, 000 U of hepatitis B immunoglobulin (Hepatect; Biotest, Dreieich, Germany) was applied during the anhepatic phase and further 10, 000 U an subsequent days until HBsAg became negative. After that, repeated doses of 1000–2000 U were given intravenously to maintain anti-HBs levels higher than 100 IU/l. HBIg was discontinued after diagnosis of reinfection by a positive HBsAg (Sorin; Biomedica, Germany) and a quantitative HBV-DNA level of more than 10 pg/ml in the hybridization assay (Abbott, Germany). De novo infection was diagnosed correspondingly. An antiviral therapy in group 1 was started after HBV recurrence. It consisted of famciclovir (Famvir; SmithKline Beechham) between November 1993 and April 1996. In the case of viral breakthrough during famciclovir administration after April 1996, therapy was switched to lamivudine ($n = 22$). For antiviral therapy started after April 1996, lamivudine (Epivir, Glaxo Wellcome) was used as first-line therapy ($n = 12$). Patients from group 2 (de novo infection) did not receive HBIg and were either treated with lamivudine primarily (infection after April 1996) or after famciclovir breakthrough (before April 1996, for numbers see Table 1). The patients received an oral dose of 100 mg lamivudine daily as study medication. When lamivudine became available commercially, the dosage was changed to 150 mg daily. Lamivudine was continued until the level of HBV-DNA markedly increased with laboratory or histological evidence of severe viral hepatitis. Lamivudine was not discontinued when HBV-DNA increased with modest laboratory signs of hepatitis.

Postoperative monitoring

Aspartate aminotransferase (ALAT) and serological markers of HBV as well as levels of HBV-DNA were determined at least on a monthly basis. Levels of HBV-DNA were measured by a radiological molecular hybridization assay (Abbott Laboratories, Wiesbaden, Germany). The efficacy of treatment was monitored mainly by quantitative determination of HBV-DNA. The treatment response at different time points was classified as: total response (HBV-DNA-negative), partial response (HBV-DNA decrease of

more than 50% compared to pretreatment values), and no response (HBV-DNA decrease of 50% or less). In 12 randomly selected patients with HBV-DNA breakthrough after total or partial response, resistance to lamivudine was tested using standard methods of genotypic analysis of blood samples as described in detail elsewhere [1]. All sequencing reactions were performed at the Glaxo Wellcome Sequencing Facility using an ABI DNA sequencer. For monitoring of possible side effects, routine laboratory parameters including blood counts, creatinine, and coagulation times were determined at least once every month. The patients were seen at the outpatient department regularly every 6 months or at shorter intervals and were questioned for potential side effects.

Statistical analysis

Values are depicted as mean and standard error of mean (SEM). Differences were compared using the Wilcoxon test for matched pairs. The percentage of HBV-DNA-negative patients during therapy was calculated using the Kaplan-Meier estimation, and statistical analysis was performed using the log rank test. Differences were considered significant at P values of was less than 0.05 and highly significant at P values of was less than 0.01.

Table 2 Demographic data, time of reinfection, and therapy start

	Group 1 (n = 34)	Group 2 (n = 7)
Age (in years)	48 ± 2	46 ± 3
Male / Female	31 / 3	3 / 4
Time of HBV infection (after OLT)	11.6 ± 3.1 months	7.1 ± 1.3 months
range	0–96 months	3–13 months
Therapy start (after HBV infection)	20.9 ± 4.6 months	18.7 ± 7.9 months
Range	0.3–87 months	1–52 months

Table 3 Best obtained response during lamivudine therapy in groups 1 and 2

	Group 1 (n = 34)	Group 2 (n = 7)
HBV-DNA-negative	26 (76%)	5 (71%)
– more than 12 months	15 (44%)	2 (28%)
– HBsAg-negative	9 (26%)	–
HBV-DNA reduction > 50%	6 (18%)	2 (28%)
No response	2 (6%)	–

Results

The follow-up period for the enrolled patients ranged from 12 to 36 months after the start of lamivudine treatment. Demographic data are shown in Table 2. All patients except two showed a total or partial response to lamivudine treatment. Thirty-one patients (76%) became HBV-DNA-negative during lamivudine therapy. Viral replication in these patients disappeared at an average of 35 days after initiation of lamivudine therapy (range 4–113 days). Seventeen patients remained HBV-DNA-negative for more than 12 months, the other 14 remained HBV-DNA-negative for less than 12 months. The mean duration of HBV-DNA negativity was 15 months (range 4–33 months). A partial response with a decrease in HBV-DNA of more than 50% of the pretreatment value during the course of therapy was observed in eight patients. Only two out of 41 patients (5%) did not respond to lamivudine treatment. Both had previously received a course of famciclovir treatment and were HBeAg-positive before transplantation. One of them had an HCV coinfection before transplantation. A total of nine patients eliminated HBsAg: four out of the seven patients with HDV coinfection eliminated HBsAg, whereas only five of the 31 patients with HBV monoinfection did so. The best obtained treatment responses are shown in Table 3. Coinfection with HDV was accompanied by a significantly improved response rate: all seven patients became HBV-DNA negative and are still negative at present (Fig. 1). Patients with de novo infection after liver transplantation (group 2) showed a slightly but not significantly worse therapy response. Only five of these seven patients (71%) became HBV-DNA-negative, and none remained negative for more than 14 months.

The quantitative HBV-DNA declined rapidly and the mean HBV-DNA was significantly lowered 1 month after the onset of lamivudine. After 12 months, the mean HBV-DNA reached pretreatment values again (Fig. 2). The mean ALAT level after 1 month of therapy was also significantly lower than before. Despite high HBV-DNA at 12 and 18 months of follow-up, the mean ALAT value remained low (Fig. 2). The therapy response of group 1 as percentage of HBV-DNA-negative patients during the course of lamivudine therapy is indicated in Fig. 3. In this group, patients that were HBeA-negative before transplantation revealed a significantly better response to lamivudine than HBeAg-positive patients (Fig. 3).

Despite a comparable rate of initially HBV-negative patients, a faster resistance formation was observed in a high percentage of patients in the second-line group (Fig. 4). The response of the first line-group was also superior when only HBV-monoinfected patients with preoperative negative HBeAg were compared ($P < 0.05$, grey lines in Fig. 4). Immunosupression, preoperative HBV-DNA, pretreatment HBV-DNA levels, and pretreatment ALAT levels had no significant influence on the obtained treatment response, measured by negative HBV-DNA.

The determination of genotypic resistance to lamivudine in 12 randomly selected patients after lamivudine breakthrough with screening for amino acids at loci 528 and 552 revealed wildtype virus only in two patients

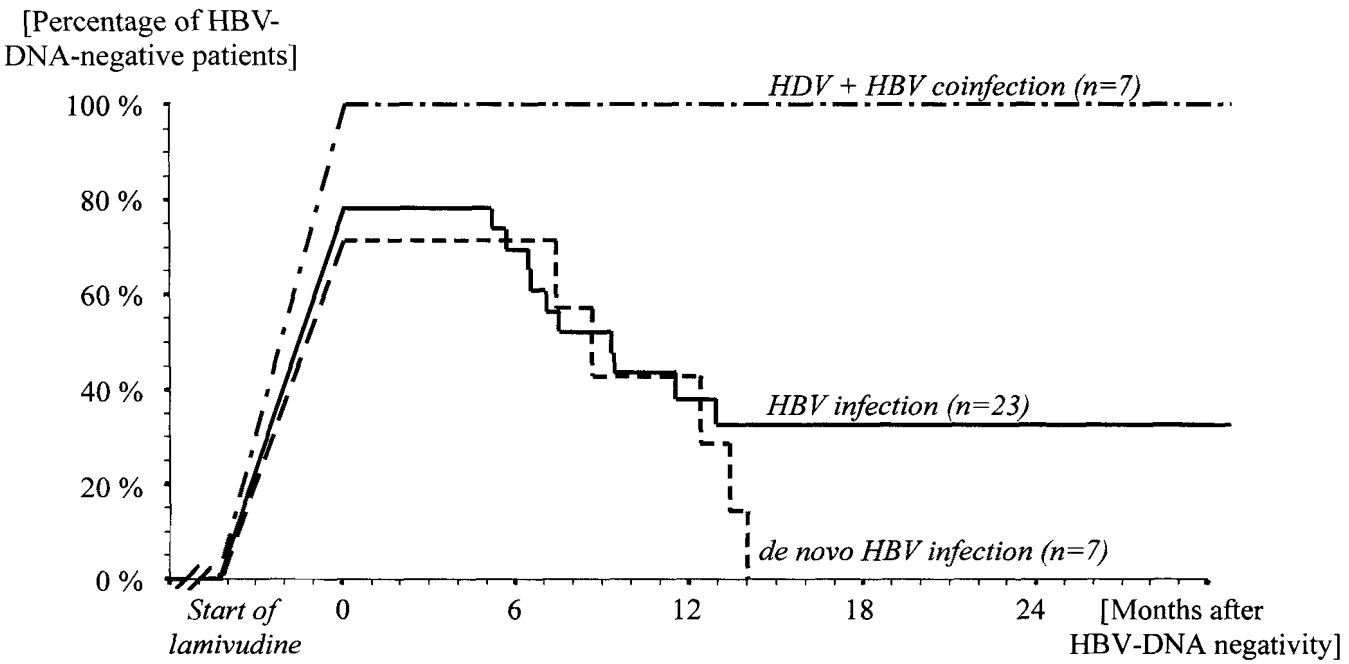

Fig. 1 Therapy response to lamivudine as percentage of HBV-DNA-negative patients for different indications of lamivudine treatment after orthotopic liver transplantation. Kaplan-Meier estimation reveals a significantly better response in HDV-coinfected patients than in HBV monoinfection ($P = 0.01$), but no significant difference between HBV and de novo infection ($P = 0.36$ by log rank test)

and mutations in the other ten: one patient had the M552 V mutant, one the M552I mutant, and eight a M552 V and L528 M double mutation.

Three patients died during lamivudine therapy. One died seven months after reinfection and six months after the start of lamivudine treatment due to HBV- and HCV-reinfection in combination with mesenteric vein thrombosis. He did not become HBV-DNA-negative during antiviral therapy. One patient died due to the recurrence of a hepatocellular carcinoma (HBV-DNA was negative at the time) and one due to trauma. One patient underwent retransplantation due to chronic rejection, which was already present before the start of antiviral treatment, and one due to HBV-induced cirrhosis of the graft.

Lamivudine was well tolerated by all patients. No severe complications occurred during the application, and no patient had to be removed from the study due to adverse events.

Discussion

The present study confirms a fast and effective suppression of hepatitis B virus replication by oral lamivudine in liver transplant recipients. This study is to our knowledge the largest published single-center experience with lamivudine for the treatment of hepatitis B infection after OLT so far. Of the treated patients, 94% showed a marked response with respect to their HBV-DNA levels and 77% became HBV-DNA-negative. These good results under immunosuppression indicate antiviral mechanisms that are not dependent on an intact immune system. In contrast, interferon-α, which is the standard treatment for nontransplant hepatitis B infection [28], has failed to show efficacy in the treatment of hepatitis B after transplantation [19, 21, 29]. Despite good suppression of viral replication, lamivudine could not completely eliminate HBV, indicated by the persistence of HBsAg in all but nine patients. This fact is also emphasized by the recurrence of HBV after a certain period of HBV-DNA negativity in a high percentage of patients. The consequence is a need for continuous antiviral therapy; otherwise, a fast rebound might occur as suspected in other reports [12].

The observed results confirm first preliminary data of Nery et al. [20] who treated eight patients with HBV recurrence after OLT with lamivudine. They found a similar response rate with seven patients turning HBV-DNA-negative and remaining negative for a median time of 15 months.

Compared to other studies [14] and own data [11] using famciclovir for the treatment of HBV after liver transplantation, lamivudine was more effective in suppressing HBV replication. The relatively small number of patients who became HBsAg-negative in the present study, compared to the data of Andreone et al., who reported an approximately 50%-ratio of HBsAg-negative

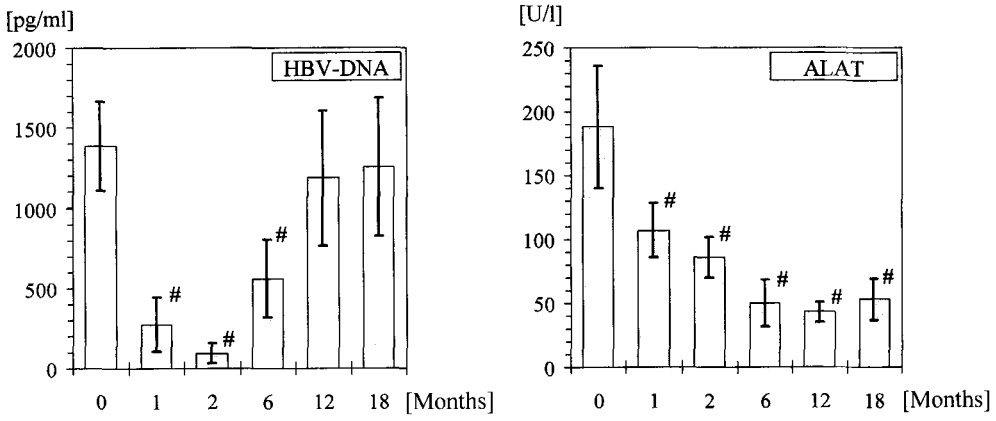

Fig. 2 Mean level of quantitative HBV-DNA (*left*) and aspartate aminotransferase (ALAT) (*right*) at different timepoints after onset of lamivudine therapy (mean ± SEM, #: $P < 0.05$ vs pretreatment value by Wilcoxon test)

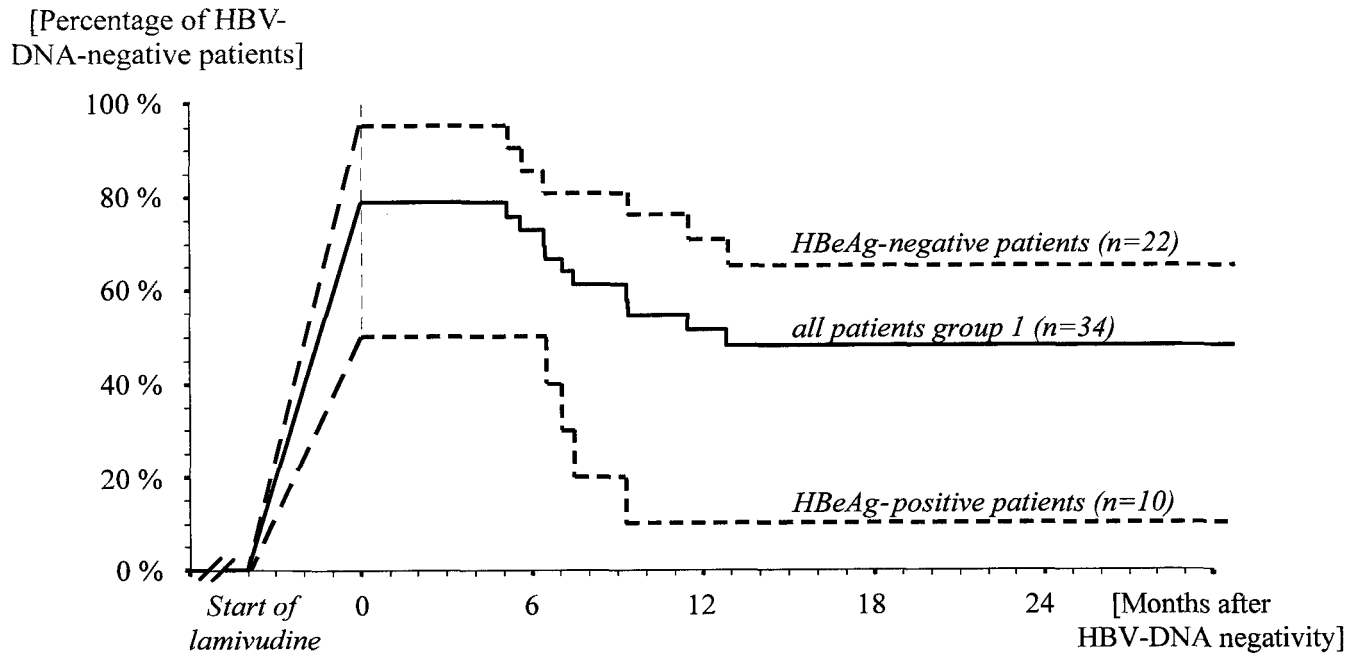

Fig. 3 Kaplan-Meier estimation of HBV-DNA-negative patients during lamivudine therapy in group 1 shows a significantly better response in preoperative HBeAg-negative patients ($P < 0.01$ by log rank test). In two patients no preoperative HBeAg was obtainable

patients [2], might be due to several differences in the study populations. In the present study, patients were partially treated with famciclovir before and the onset of therapy was later after reinfection. In addition, the high percentage of precore mutants in the study of Andreone et al. might also have contributed to the different results. Comparable, although slightly inferior, results to the present study were obtained in a multicenter trial involving 52 patients. In this report by Perillo et al., 60% of the patients became HBV-DNA-negative by hybridization assay, and 6% seroconverted to HBsAg negativity [22].

Parallel to the described lower risk of HBV recurrence after liver transplantation in the presence of HDV coinfection [24], the coinfected patients in the present study revealed a very low risk of HBV breakthrough during lamivudine therapy. This is in accordance with other reports concerning antiviral treatment in HDV coinfection after OLT [13]. A relatively high number regarding spontaneous seroconversion in HDV coinfection is reported by Samuel et. al [25], but was not observed in our patients (data not shown). Likewise, the better response in HBeAg-negative patients has been observed by other authors [19]. De novo hepatitis B infection revealed a slightly worse response to lamivudine, but seems to have a relatively mild course and good outcome even without antiviral treatment [9].

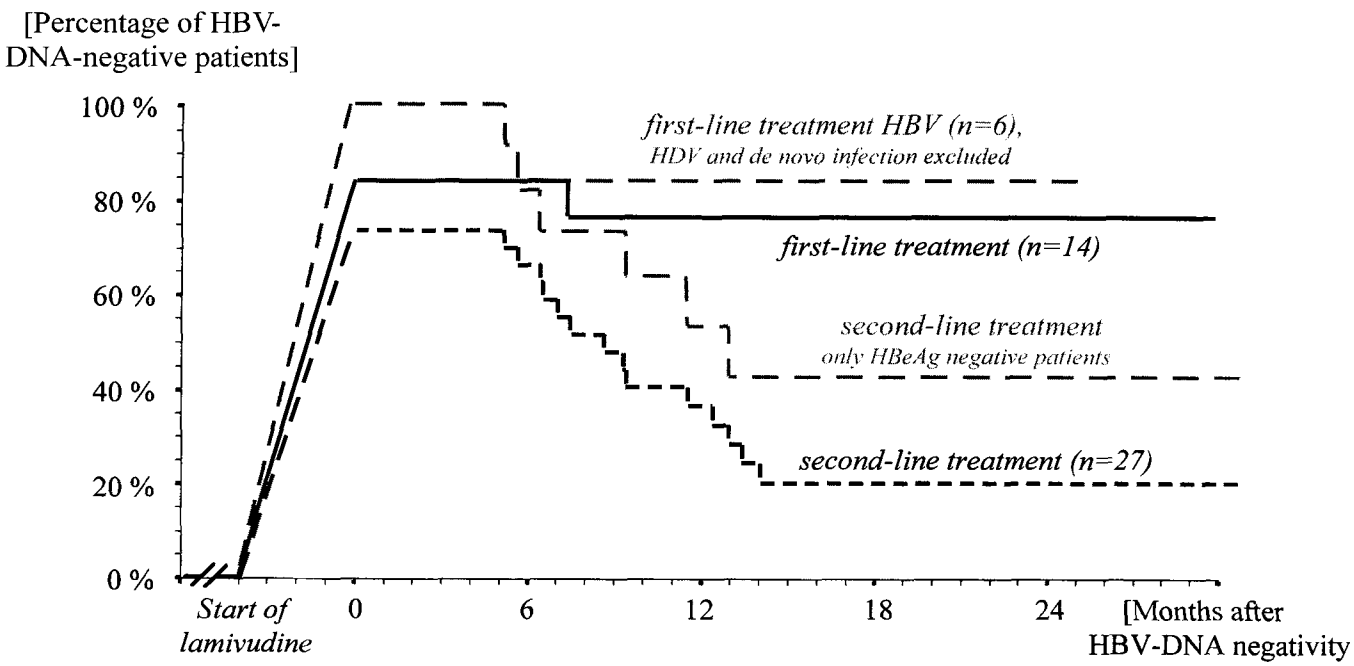

Fig. 4 Percentage of HBV-DNA-negative patients under lamivudine first-line treatment in relation to second-line treatment after famciclovir breakthrough as Kaplan-Meier estimation ($P < 0.01$ by log rank test). Because of a high percentage of HDV coinfection in the first-line group, the Kaplan-Meier estimation was also calculated for HBV monoinfection (*grey line*: $P < 0.05$ vs second-line group by log rank test)

All patients who received lamivudine as first-line therapy showed a response to treatment, referring to a low natural incidence of resistant virus types [8]. The relatively fast resistance formation during lamivudine therapy was the major problem observed in the present study. Although confirmed by DNA analysis only in ten out of 12 tested patients, resistant virus types were assumed in most patients who had an increase of viral replication after initial therapy response. The most common virus mutation has been identified as a single amino acid exchange (mainly methionin to valin) at the YMDD motif of the reverse transcriptase [1, 4]. It bears similar single amino acid exchanges in the reverse transcriptase gene as found in lamivudine-resistant HIV types [4]. There are other, less common mutations of the reverse transcriptase gene resulting in lamivudine resistance [1]. Most of the virus mutants have been found to have a reduced replication rate in vitro [18].

Famciclovir resistance formation is to some extent located at a different locus of the reverse transcriptase [30]. No general parallel resistance has been reported. This is underlined by the study group consisting of patients with previous famciclovir treatment. Only two patients in this group did not respond to lamivudine, although the incidence of early viral breakthrough was significantly higher in patients with a former course of famciclovir. Famciclovir-resistant virus types are rarely lamivudine-resistant, but occasionally lamivudine resistance formation seems to evolve during famciclovir therapy, as observed in two patients. Accordingly, double resistance against lamivudine and famciclovir exists, which has also been confirmed by in vitro studies [18]. Nevertheless, the different sites of mutations might justify an initial antiviral combination therapy with different antiviral agents, as already successfully applied in the therapy of HIV [15]. Whether combination therapy can delay resistance formation significantly in comparison to sequential therapy with famciclovir and lamivudine has yet to be proven in further studies.

In conclusion, lamivudine is an excellent therapeutical option for the treatment of HBV recurrence, even after resistance formation against famciclovir. In the case of lamivudine resistance, treatment might be continued since most viral breakthroughs only result in mild forms of hepatitis. This was also observed in the present study, where liver enzymes remained nearly within normal limits despite an increase of HBV-DNA after breakthrough. A re-emergence of wild type virus due to the discontinuation of therapy has been reported [6]. Further studies should clarify new antivirals like adefovir or the combination of different antiviral agents can yield benefit in the case of severe hepatitis after lamivudine breakthrough.

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