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Antiviral combination therapy for lamivudine-resistant hepatitis B reinfection after liver transplantation

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Abstract Development of resistance is a major issue in antiviral treatment of hepatitis B reinfection after liver transplantation. Antiviral combination therapy is discussed for therapy or prevention of this breakthrough of viral replication. Eight patients were enrolled into this retrospective analysis after liver transplantation for chronic hepatitis B infection. All had reinfection of the graft and breakthrough of HBV during consecutive famciclovir and lamivudine monotherapy. Subsequently a combination therapy with lamivudine and interferon-α 2a (group I, $n = 4$) or lamivudine and famciclovir (group II, $n = 4$) was initiated. Combination therapy was started 61 months (group I) and 25 months (group II) after liver transplantation. It markedly reduced the viral replication rate in all patients despite lamivudine resistance. In group I three of four patients and in group II two of four patients became HBV-DNA negative. Two long-term responders were observed in group I, and none in group II. No patient became HBsAg negative or lost HbeAg. Pretreatment elevated ALT and AST levels were significantly reduced. No severe complications, and especially no rejection episodes, occurred. Lamivudine in combination with other antiviral agents, especially interferon-α, might be a therapeutic option for hepatitis B reinfection after liver transplantation. Suppression of virus replication to the point of undetectable values is possible even in patients with lamivudine-resistant virus mutations.

Key words Hepatitis B · Liver transplantation · Lamivudine · Interferon · Resistance · Combination therapy

Introduction

HBV infection or reinfection after liver transplantation is mostly more severe and more rapidly progressive than in patients without immunosuppression [1]. It occurs despite passive immunoprophylaxis in 30–40% of patients [2]. After HBV recurrence, resistance formation is a major issue in antiviral treatment [3]. Resistance is based chiefly on a single amino acid substitution of the hepatitis B reverse transcriptase. One approach to prevention or treatment of virus resistance is to combine different antiviral agents [4] in parallel with HIV infection, where combination therapy is a standard clinical protocol and reveals better outcome and delayed development of resistance [5]. Because drugs with anti-hepatitis B activity are limited, at the moment either a combination of different nucleosoide analogues like lamivudine and famciclovir [6] or a combimation of interferon plus nucleoside analogue [7] is possible. Whether these combinations have synergistic effects remains to be analysed. The following preliminary report describes the experience of antiviral combination therapy in eight patients with lamivudine resistance after liver transplantation.

Patients and methods

From September 1988 to December 1998 178 patients with HBV infection underwent liver transplantation at our centre. Eight of these patients who underwent combination therapy for lamivudine-resistant hepatitis B recurrence were then retrospectively analysed. All eight patients were transplanted for chronic HBV infection and were HBsAg positive before the transplant. Five of the patients had a positive HBeAg at the time of transplantation, and five were positive for HBV DNA. Two patients were also positive for anti-HCV antibodies. All patients developed reinfection despite long-term passive immunoprophylaxis with a target titre of over 100 U. For all patients initial antiviral therapy after reinfection consisted of famciclovir in a renal clearance adapted dosage (500–1500 mg daily). Therapy was switched to lamivudine (150 mg daily) if HBV-DNA increased again with laboratory signs of hepatitis.

After a second breakthrough with elevated liver enzymes a combination therapy of lamivudine and interferon-α2a (group I, $n = 4$) or lamivudine and famciclovir (group II, $n = 4$) was initiated. Lamivudine dosage was 150 mg p.o. daily, famciclovir dosage 500–1500 mg p.o. per day. Interferon-α (Roferon A, Hoffmann La Roche, Germany) was administered s.c. in a dose of 3 million units three times weekly. Doses were decreased if significant side effects occurred, especially if leukopenia or thrombopenia appeared despite stimulation with filgrastim (Neupogen, Amgen-Roche, Munich, Germany).

All patients were monitored at least monthly with biochemical (AST, ALT, bilirubin, PT) and haematological (white blood cells, platelets, haemoglobin) blood tests using standard clinical methods. Serological markers of HBV and levels of HBV-DNA were also determined on a regular basis. Levels of HBV DNA were measured by a radiological molecular hybridization assay (Abbott Laboratories, Wiesbaden, Germany).

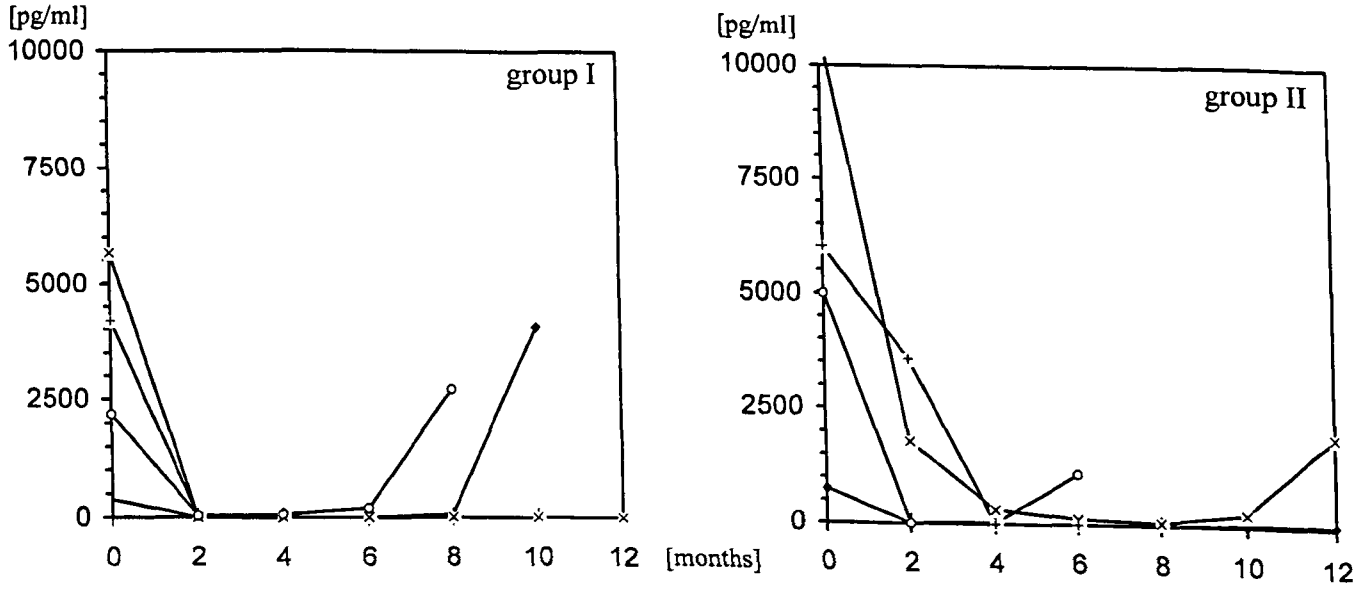
Results

Mean age was 49 ± 3 and 47 ± 4 years in groups I and II, respectively. All patients were male. Immunosuppression was ciclosporin in three patients and tacrolimus in one patient of each group. Time of reinfection was 6 ± 3 months (group I) and 9 ± 4 months (group II) after liver transplantation. Combination therapy was started 52 ± 8 months after reinfection in group I and 16 ± 4 months in group II. Both combination therapies markedly reduced viral replication rate and levels of liver enzymes in all patients despite lamivudine resistance. In group I three of four patients became HBV-DNA negative, while in the fourth the level declined to minimal viral replication. Two patients revealed viral breakthrough after initial response after 6 and 8 months of therapy. At the last clinical visit the other two patients were still HBV-DNA negative 14 and 16 months after the onset of combination therapy. No patient became HBsAg negative or seroconverted to aHBe. In group II two of four patients became HBV-DNA negative. One of these patients had viral breakthrough after 6 months, and the other had to be reconverted to monotherapy owing to leukopenia. Courses of quantitative HBV-DNA and GPT-activity within the 1st year of combination therapy are shown in Figs. 1 and 2. No severe complications, and especially no rejection episodes, occurred in group I. In one patient the interferon dosage had to be reduced owing to leukopenia despite filgrastim.

Discussion

Whereas passive immunoprophylaxis has lowered the incidence of hepatitis B reinfection, the introduction of new antiviral agents has reduced the mortality of rein-

Fig. 1 Course of HBV-DNA in patients in groups I and II after start of combination therapy



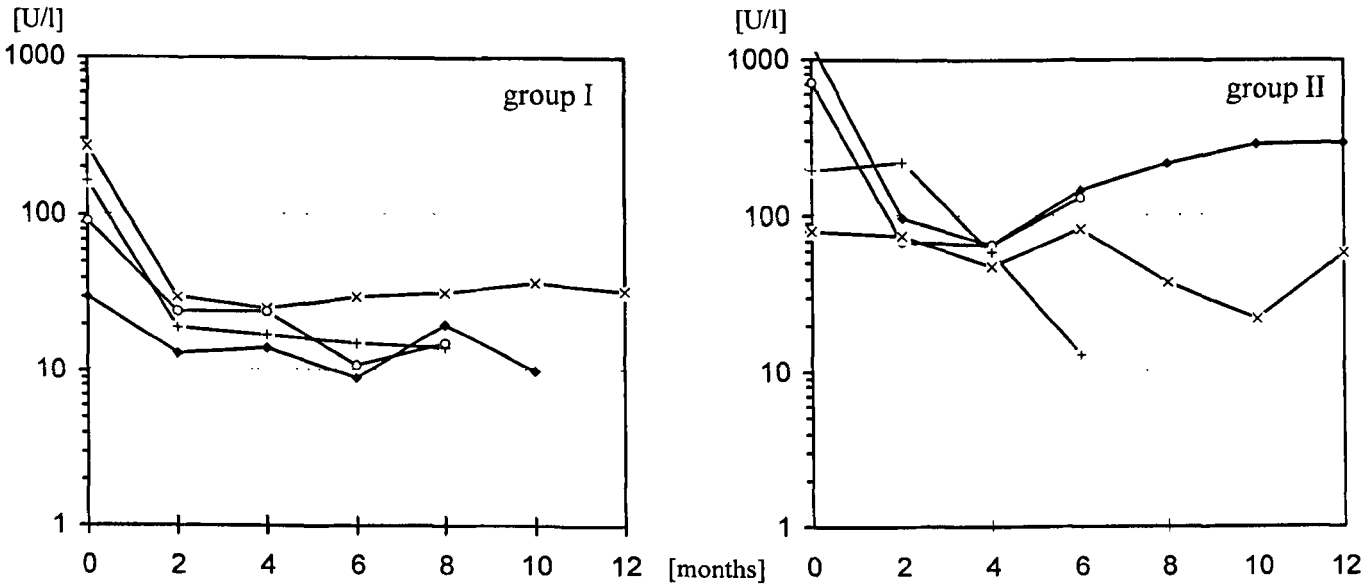


Fig. 2 Course of ALT activity in patients of group I and II after onset of combination therapy

fection. The development of resistance now become one of the major issues of managing post-transplant hepatitis B infection [3, 4]. In parallel with the treatment of HIV [5], combination therapy is also discussed for HBV, either for treatment of resistant strains or for prevention of resistance formation.

In vitro studies suggest a synergistic inhibition of HBV replication by combined lamivudine and famciclovir [6]. With this combination, an inhibition of viral replication was also found in the present study despite lamivudine resistance, although the effect was only temporary. The drawback of this combination is that there is cross-resistance of the two agents in a certain percentage of resistant virus strains [4]. Therefore other drugs, without cross-resistance, are needed. One possibility is interferon-α, which stimulates the immune system and has direct antiviral effects and is the standard treatment of chronic hepatitis B in nontransplanted patients [8]. In contrast, interferon-α monotherapy has no proven beneficial effect after liver transplantation [9–12]. A combination with nucleoside analogues after transplantation has not been evaluated so far. First preliminary results of combined interferon with lamivudine are shown in the present study. Two long-term responders (50%) represent first promising results, which might refer to a synergistic effect of this combination also on lamivudine resistant virus types. Other side effects than known interferon side effects were not observed in the present study; in particular there were no rejection episodes such as have been described in other reports in liver transplant recipients [9, 12].

In conclusion, antiviral combination therapy with lamivudine might extend the therapeutic options for hepatitis B reinfection after liver transplantation. Suppression of virus replication to undetectable values is possible even in patients with lamivudine-resistant virus mutations. The definite therapeutic benefit of this combination therapy as indicated in this preliminary study has to be proven in a longer follow-up with a larger number of patients. Whether a primary combination therapy can delay or prevent virus resistance, as in HIV treatment, remains to be proven in further studies.

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