A three-month course of lamivudine therapy in HBeAg-positive hepatitis B patients with normal aminotransferase levels

Normal aminotransferaz düzeylerine sahip HBeAg pozitif hepatit B'li hastalarda 3 aylık lamivudin tedavi sonuçları

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Background/aims: *HBeAg-positive patients with normal ALT levels are unlikely to respond to current therapy. In addition, there is a high risk of hepatocellular carcinoma in HBeAg-positive patients in the natural course of HBV infection. For this purpose, we aimed to investigate the clinical efficacy and safety of a three-month course of lamivudine therapy in HBeAg-positive hepatitis B patients with normal aminotransferase levels for assessing a more practical and economical approach to these patients.* ***Methods:*** *Forty-six patients were prospectively randomized into two groups. Group A consisted of 13 patients treated with lamivudine 100 mg/day, for 12 weeks [7 males, mean age 23.30±5.82 years, median ALT of 27 IU/L (21-40), median HBV DNA of 4116 pg I ml (2885-6628)]. Group B consisted of 33 patients without treatment [18 males, mean age 24.75±6.92 years, median ALT of 30 IU/L (19-39), median HBV DNA of 4094 pg/ml (782-7387)]. Main outcome measure was sustained virologic response, which was defined as loss of HBV DNA in serum with HBeAg seroconversion at least 12 months thereafter. Follow-up lasted 12 months after the first dose.* ***Results:*** *No significant effects were observed in the treated population in the reduction of HBV DNA to undetectable levels, in HBeAg/anti-HBe seroconversion, or in transaminase levels. At the end of follow-up, sustained virologic response was almost similar in the study as well as control group (7.6% vs. 3.0%, p=0.502). None of the 13 patients who received lamivudine therapy had HBeAg seroconversion during the study period. In addition, the suppression of serum HBV DNA was temporary; prolonged suppression could be achieved in only one patient in the follow-up period. The median levels of HBV DNA and ALT values between baseline and month 12 did not differ significantly between groups. All patients remained HBsAg positive and none developed anti-HBs. The therapy was well tolerated and post-therapy flare was not observed in any patient after stopping lamivudine therapy.* ***Conclusions:*** *A short course of lamivudine therapy resulted mostly in only temporarily depressed serum HBV DNA levels without significant change in viral clearance. Whether permanent suppression of HBV DNA can be achieved in this special population of HBsAg carriers by long-term treatment with lamivudine awaits further controlled trials. New and safe modalities of therapy are needed for the satisfactory treatment of these asymptomatic but viremic patients.*

Key words: Hepatitis B virus, HBeAg, lamivudine, treatment, normal ALT levels

Amaç: *ALT düzeyleri normal seyreden HBeAg-pozitif hastalar mevcut tedavilere yanıt vermemektedirler. Bununla birlikte HBV infeksiyonunun doğal seyrinde HBeAg-pozitif hastalarda yüksek bir hepatoselüler karsinoma riski vardır. Bu nedenle, bu çalışmada ALT düzeyleri normal olan HBeAg-pozitif hepatit B'li hastalarda daha ekonomik ve pratik bir tedavi yaklaşımı olan 3 aylık lamivudin tedavisinin klinik etkinliğini ve güvenliğini araştırmayı amaçladık.* ***Yöntem:*** *Çalışmaya alınan 46 hasta prospektif olarak 2 grup halinde randomize edildi. Grup A, 12 hafta boyunca günde 100 mg lamivudin alan 13 hastadan oluşmaktaydı (7 erkek, ortalama yaş 23.30±5.82 yıl, medyan ALT 27 IU/L (21-40), medyan HBV DNA 4116 pg/ml (2885-6628). Grup B, ise herhangi bir tedavi almayan 33 hastadan oluşmaktaydı (18 erkek, ortalama yaş 24.75±6.92 yıl, medyan ALT 30 IU/L (19-39), medyan HBV DNA 4094 pg/ml (782-7387). Tedavi sonunda amaç, en az 12 ay sonra serumda HBV DNA kaybı ile birlikte HBeAg serokonversiyonu içeren kalıcı virolojik yanıt olarak belirlendi. Tedavi sonrası takip ilk dozdan sonra 12 boyunca yapıldı.* ***Bulgular:*** *Çalışma bitiminde, gruplar arasında, serum HBV DNA kaybı, HBeAg/anti-HBe serokonversiyonu ve transaminaz düzeyleri bakımından anlamlı bir fark saptanmadı. Takip süresi sonunda kalıcı virolojik yanıt çalışma ve kontrol grubunda benzer bulundu (%7.6 vs. %3.0, p=0.502). Lamivudin tedavisi alan 13 hastada, tedavi süresi boyunca HBeAg serokonversiyonu gözlenmedi. Tedavi sonrası takiplerde, tedavi alan grupta HBV DNA süpresyonunun geçici özellikte olduğu ve kalıcı süpresyonun sadece bir hastada geliştiği gözlendi. Her iki grupta da, giriş ve 12 . aya ait HBV DNA ve ALT değerleri arasında istatistiki bir fark bulunamadı. Hiçbir hastada HBsAg/anti-HBs serokonversiyonu gelişmedi. Lamivudin tedavi kesildikten sonra yine hiçbir hastada tedavi sonrası alevlenme görülmedi. Sonuçlar: Kısa süreli lamivudin tedavisi viral klirenste anlamlı bir değişikliğe neden olmaksızın sadece geçici bir süre serum HBV DNA düzeyinde süpresyona neden olmaktadır. Bu özel hasta grubunda uzun süreli lamivudin tedavisiyle kalıcı HBV DNA süpresyonunun sağlanıp sağlanamayacağını gösteren ileri kontrollü çalışmalara gereksinim bulunmaktadır. Asemptomatik ancak viremik seyreden bu hastaların tatmin edici tedavileri için yeni ve güvenli tedavi yöntemlerine ihtiyaç bulunmaktadır.*

Anahtar kelimeler: Hepatit B virüsü, HBeAg, lamivudin, tedavi, normal ALT düzeyi

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INTRODUCTION

Hepatitis B virus (HBV) infection in the early immune-tolerant phase is characterized by minimal liver damage, despite a high level of HBV replication. These patients are asymptomatic, have normal levels of serum alanine aminotransferase (ALT), have minimal changes on liver biopsy and are positive for hepatitis B e antigen (HBeAg) with a high level of hepatitis B DNA in serum (1-3). During this phase, there is a very low rate of spontaneous HBeAg clearance (4, 5). HBeAg is an important marker for the evaluation and treatment of patients with chronic HBV infection. There is a central role of virus replication in the outcome of HBV infection and a need to induce sustained suppression of HBV replication as early in the course of the disease as possible (6). In addition, clearance of HBeAg, whether spontaneous or after antiviral therapy, reduces the risk for hepatic decompensation and improves survival in individuals with chronic HBV infection (3).

Lamivudine is the pyrimidine nucleoside analogue, the negative enantiomer of 2'-deoxy-3'-thiacytidine, that inhibits viral DNA synthesis by terminating the nascent proviral DNA chain (7). Lamivudine has potent direct antiviral effects against HBV both in vitro and in vivo and may also enhance HBV-specific T-cell responses (8,9). Previous studies in patients with chronic hepatitis B have shown that therapy with lamivudine led to a marked decrease in serum HBV DNA levels followed by improvements in aminotransferase levels, and in histological outcome.

Alpha interferon (α-IFN) even with prednisone priming is of less use in placebo controlled studies in HBeAg positive patients with normal ALT levels, possibly due to the lack of an endogenous T-cell response to the HBV, and the patients are immunotolerant to HBV (10, 11).

These data suggest a utility of lamivudine in this special population. Thus, we aimed to investigate the effect of three months of lamivudine therapy on HBV replication and HBeAg seroconversion, as well as to determine whether a short-term antiviral therapy might be followed by restored T-cell reactivity associated with clearance of viral replication and HBeAg seroconversion. This would also be a more practical and economical approach to these patients.

Moreover, patients with HBeAg-positive chronic hepatitis B and normal aminotransferase levels are at risk for developing hepatocellular carcinoma (12). The low rate of response to currently approved treatments is necessitating new clinical trials with treatment that is more potent and/or effective in overcoming the lack of host immune response and should include patients with HBeAg-positive chronic hepatitis B and normal aminotransferase levels.

MATERIALS AND METHODS

Patients

Adult patients who had not previously received any antiviral treatment were eligible for the study if they met the following criteria at screening: (HBsAg) positive for more than six months, positive HBeAg, serum HBV DNA levels of at least 1 pg/ml (Digene Hybride Capture System, Beltsville, MD, USA), persistently normal serum ALT values on at least three occasions in the six months before the study entry, histological evidence of absent or minimal changes in liver biopsy, and negative urine or serum pregnancy test (for women of childbearing potential). Additionally, all fertile men with partners of childbearing age and premenopausal women were required to use reliable contraception during the study and for six months after treatment completion.

Patients were excluded at screening if they had been treated previously with interferon or had received antiviral or immunosuppressive medications; tested positive for antibody to hepatitis D virus (HDV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) and for pregnancy; had decompensated liver disease; had a medical condition associated with chronic liver disease other than viral hepatitis; and alcohol and/or drug abuse within one year of study entry.

Detailed information was given about the treatment protocol and the disease, and all enrolled patients provided written informed consent. The study was carried out in accordance with the Declaration of Helsinki and its amendments and was approved by the local ethics committee.

Study design

This was a randomized study that utilized a prospective controlled design (treated vs. untreated) to look at the effects of a short course of lamivudine on the virologic response at 12 months in patients with HBeAg-positive chronic hepatitis B with normal ALT levels. Due to the risk of lamivudine resistant tyrosine-methionine-aspartate-aspartate

(YMDD) mutants, the duration of therapy was limited to 12 weeks. The primary endpoint was virologic response [defined by the seroconversion of HBeAg to anti-HBe and the disappearance of HBV DNA in serum by polymerase chain reaction (PCR)] at month 12. All patients returned for assessments every four weeks in the first three months after the baseline visit and thereafter every three months with complete biochemical and hematologic blood tests using conventional methods (Aeroset Autoanalyzer, Abbott Diagnostics Division, Abbott Laboratories, Abbott Park, Illinois). Analysis of response was performed after three and 12 months. Flare of hepatitis B was defined as intermittent elevations of aminotransferase activity to more than 10 times the upper limit of normal (ULN for ALT was 35 IU/L). Post-treatment follow-up was for 12 months after the first dose.

Additionally, family members of patients, particularly the parents, were tested for serologic parameters of HBV in order to determine possible vertical or horizontal transmission.

Histologic analysis

All patients were requested to have had a liver biopsy within six months of the study baseline. Liver biopsy was performed in all patients and specimens were sent for histological assessment to a single independent histopathologist who was blinded with respect to patient identity, treatment assignment, laboratory data, and date of biopsy specimen. The biopsy specimens were scored according to the original criteria of Knodell histological activity index (HAI) (13).

Serologic studies and assays

Serologic markers were assessed by Macro Enzyme Immune Assay (Roche Diagnostics Corporation, Indianapolis, USA). HBV DNA levels were measured using a liquid hybridization method with the lower limit of detection of ~2.8 x 10^5 copies (1 pg/ml) of serum HBV DNA. All samples that were negative on hybridization assay were analyzed using polymerase chain reaction (PCR) (Techne Cambridge, Duxford, UK) due to the relatively low detection level of liquid hybridization. The PCR assay has a lower limit of detection of-103-104 copies of viral DNA per milliliter of serum.

Statistical analysis

Statistical analyses were done by Mann-Whitney-U test for the comparison of median values of two independent groups, Wilcoxon-matched paired tests as a non-parametric test, and Fisher's exact chi-square test and Student's t test where appropriate. The evaluation was performed using SPSS (Statistical Package for Social Sciences), for Windows, release 11.00., standard version, copyright SPSS Inc., 2001.

RESULTS

Study population

A total of 53 adult patients were screened between 1998-2001 in our center, and 46 of them met the entry criteria and were prospectively randomized in a 1:3 ratio to receive either lamivudine 100 mg daily for 12 weeks (Group A, n=13) or as control group (Group B, n=33). Three patients who did not have sustained positivity for HBV DNA and/or HBeAg and four others with intermittent elevations of ALT were excluded from the study. All treated patients were HBeAg and HBV DNA positive chronic HBsAg carriers with persistently normal ALT levels and without inflammation at liver biopsy. Thirty-three patients with a similar virological status served as controls.

The clinical characteristics of the subject groups and the results of this study are summarized in (Tables 1 and 2). Treatment groups were comparable with respect to baseline demographics and disease characteristics (Table 1). Overall, 54% of patients were male and the mean age was 24.34 (range 14-44) years. All patients in Group A completed the 12 weeks of therapy and all of the patients in the study, except one, completed the one year of follow-up. Intrafamilial mode of transmission, especially through mothers, was a dominant risk factor in both groups.

Virologic results

All patients who received lamivudine therapy had prompt reduction in serum HBV DNA levels within one week of therapy. HBV DNA levels were undetectable at the end of the first month of therapy in all 13 treated patients by liquid hybridization (Table 2). After cessation of therapy HBV DNA became again detectable within 1-2 weeks in all patients except one.

In the treated group, one patient had persistently elevated levels of ALT beginning from the first

Table 1. Baseline demographic and clinical data of 46 patients

Characteristics	Treated group (Group A, n=13)	Control group (Group B, n=33)	p
Age			
Mean (SD)	23.30±5.82	24.75±6.92	NS
Median (range)	23 (14-31)	24 (14-44)	
Sex (Male/female)	7/6	18/15	NS
ALT (IU/L) Median (range)			
Baseline	27 (21-40)	30 (19-39)	NS
Post follow-up	34 (17-271)	28 (15-94)	NS
HBV DNA (pg/ml) Median (range)			
Baseline	4116 (2885-6628)	4094 (782-7387)	NS
Post follow-up	3735 (0-5603)	4080 (0-7067)	NS
Positive for HBeAg (No, %)	13 (100)	33 (100)	
Inflammation score			
Median (range)	1.00 (1-3)	2.00 (0-3)	NS
Fibrosis score			
Median (range)	0 (0-0)	0 (0-0)	
Maternal HBsAg positivity (No, %)	12/13 (92%)	27/33 (82%)	NS
Familial HBsAg positivity[1] (No, %)	12/13 (92%)	31/33 (94%)	NS

NS: Non-significant

Table 2. Loss of HBeAg, serum HBV DNA and ALT elevations during follow-up

Results	Group A (n=13)	Group B (n=33)	p
Seroconversion of HBeAg	1/13	1/33	NS
Loss of HBV DNA			
Transient	13/13	0/33	<0.001
Persistent	1/13	1/33	NS
Loss of HBsAg	0/13	0/33	
Increase in ALT levels (>2X ULN)			
Number of subjects	3/13	3/33	NS
Associated seroconversion of HBeAg	1/13	1/33	NS

ULN: Upper limit of normal (35 IU/L) NS: Non significant

month of therapy. He had HBeAg seroconversion at the second month of therapy. For ethical reasons, therapy was continued for another six months after achievement of HBeAg seroconversion. HBV DNA was again detectable soon after cessation of therapy with reversion of HbeAg, and a liver biopsy performed one year later revealed worsening of disease with moderate necroinflammatory activity. Two other patients in the treated group had increasing levels of ALT starting at the end of the third month of therapy. Their ALT values were 118 and 96 IU/L at the end of the therapy, and 12 months later, ALT values of these patients had normalized (Figure 1). Interestingly, one of these patients had seroconversion of HBeAg with undetectable HBV DNA at the end of the follow-up, whereas the other one had no seroconversion (Figure 2).

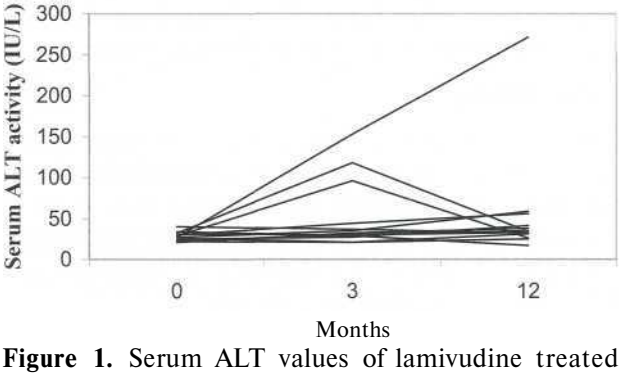

Figure 1. Serum ALT values of lamivudine treated patients in pre-, during and post-treatment periods

HBeAg seroconversion with loss of serum HBV DNA was observed in only one patient in the control group. In this patient, ALT reached the level of 123 IU/L at the third month, consequently with sustained HBeAg seroconversion. In the other patients in the control group, serum ALT concentrations remained in normal ranges except in two during the follow-up period. In these patients, ALT

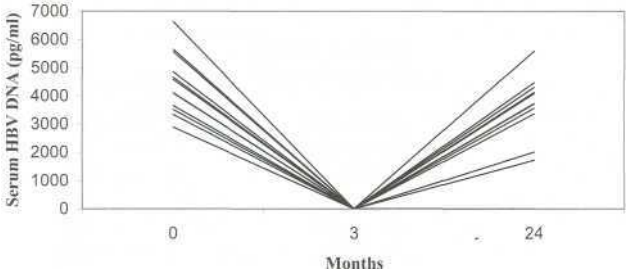

Figure 2. Serum HBV DNA levels of lamivudine treated patients in pre-, during and post-treatment periods

level rose to 94 and 99 IU/L in the follow-up period, with no change in serum HBV DNA levels and in HBeAg status. Loss of serum HBsAg did not occur in any patient in either group.

Sequence analysis of HBV DNA polymerase gene (ABI 310 Genetic Analyzer, Applied Biosystems, Foster City, CA, USA) was performed for only three lamivudine treated patients who had elevated ALT levels, and revealed no emergence of mutant virus with YMDD mutations.

Biochemical findings (ALT changes)

There was no significant change between baseline and post follow-up values of ALT in both treatment and control groups. The number of subjects in whom increased levels of ALT. were determined was three in both groups.

Histologic findings

The initial biopsies of all patients were available and revealed absent or minimal histological activity. Due to ethical considerations, patients were not re-biopsied at the end of the follow-up.

Side effects

The therapy was well tolerated. No serious adverse events nor biochemical or hematologic abnormalities were observed. Post-therapy flare was not observed in any patient after stopping lamivudine therapy. No acute exacerbations of hepatitis and hepatic decompensation were observed in any patient, whether or not they had HBeAg seroconversion.

DISCUSSION

The results of this study showed a non-significant virologic response in the lamivudine treated group compared to the control group (1 of 13, 7.6% vs. 1 of 33, 3.0%, p=0.502). The results, while not encouraging, are interesting and offer some practical information for the care of these patients. Despite the fact that the standard period of lamivudine treatment is at least one year, the reason we utilized a shorter of period of treatment is to observe whether or not suppression of serum HBV DNA and resultantly, diminished viral load, might induce any antiviral response in highly replicative patients with chronic HBV infection. Another reason is to avoid the risk of development of YMDD mutation, which is usually observed after six months of therapy. Nevertheless, there is still an actual risk of it being detected after three months of therapy. Moreover, a short course of therapy in these patients would be a valuable strategy (in terms of costs and case of administration). The main limitation of the study was our inability to perform immunological studies during and after the lamivudine therapy, which would have provided some important clues.

A recent study found that whereas the relative risk of hepatocellular carcinoma (HCC) among men with HBsAg alone was 9.6 compared to those without HBsAg, the risk increased to 60.2 when they were positive for both HBsAg and HBeAg (12). A more interesting finding in this study was that the adjusted relative risk for those who were seropositive for HBsAg and HBeAg and who had a normal serum alanine aminotransferase level was 61 (14). There is also data to suggest that survival among cirrhotic patients is lower among those who are HBeAg positive (15). Although these patients have a lower virologic response to either therapy, one has to raise the question whether or not these patients should be treated to reduce their substantial risk for HCC based solely on the detection of HBeAg (16). Moreover, treatment of hepatitis B patients in the immune-tolerant phase is important because it may eradicate the virus from the body before significant liver damage is caused by inflammation when the body's immune system attempts to clear the virus. Thus, facing an over 60-fold increased risk for HCC despite normal aminotransferase levels, therapy should not be withheld from these patients for ethical reasons irrespective of their chance of virologic response (17).

There are millions of patients worldwide, especially in Asia, with perinatally acquired infection, who show normal aminotransferase levels, but more immune-tolerant patients have been encountered in other parts of the world, including the Eastern Mediterranean and the Middle East regions. These non-Asian patients have the same dise-

ase specifics (18,19) and the same treatment difficulties as the Asian patients. Of particular concern is the fact that until now no drug therapy has actually been effective in achieving a sustained response against the hepatitis B virus in the immune-tolerant phase.

There are some evidences to suggest that in patients with HBV infection in the immune- tolerant phase, the response to antiviral therapy whether with lamivudine or interferon is closely related to the serum ALT values. The preliminary results of the study of Dienstag et al. suggested that a three-month course of treatment could induce prolonged suppression of HBV DNA in only 19% of chronic hepatitis B patients (9). Another three-month lamivudine and a famciclovir study also showed that sustained HBeAg seroconversion and/or HBV DNA suppression were more likely in patients with initially high ALT levels (9,20). In the study of Lai (21), a four-week course of 25 to 300 mg lamivudine was effective in suppression of 94% to 98% of serum HBV DNA in Chinese HBsAg carriers, but with no change in the HBeAg status. HBeAg seroconversion rate after one year of lamivudine treatment is also less than 10% in patients with pre-treatment ALT levels less than two times normal (3,22). Also, in a recent study of four drug trials, after one year of therapy, the HBeAg loss was 0% (0 of 25 patients) with placebo and 4% (2 of 55) with lamivudine in patients with ALT values <lx the ULN (23). Several studies have suggested that pre-treatment with a short course of corticosteroid may augment the response to subsequent interferon therapy (11,24). But patients who have persistently normal ALT levels are unlikely to benefit from interferon therapy even with prednisone priming (10,11,25,26). More recent treatment modalities, such as therapeutic vaccination with a preS2/S HBV vaccine (27,28) and thymosin-alphal and famciclovir combination therapy (29), did not have favorable results. Thus, virtually no treatment has been able to effectively cure hepatitis B in patients in the immune-tolerant phase of the viral infection.

It is important to note that ALT levels went up in the treated group. Although there was no significance, this is clearly due to the small sample size. In our study, increase in biochemical activity after lamivudine therapy resulted in three patients: in one with sustained virologic response, in another with ongoing chronic active hepatitis and in a third with temporarily elevated liver enzymes. The cause of the increase in ALT levels in these patients remained unexplained. The most probable explanation might be lamivudine-induced immune reactivity to the infected liver cells. It can also be speculated that lamivudine has partial effect in restoring T-cell responses in chronic hepatitis B. It was shown that lamivudine treatment in chronic hepatitis B can restore cytotoxic T lymphocyte (CTL) reactivity, making CTL susceptible to exogenous stimulation. Both HBV-specific cytotoxic T cell activity and CD8+ T cell frequency were significantly augmented by a 12-month course of lamivudine therapy (22). It has also been known that lamivudine can overcome CTL hyporesponsiveness (30), and this may serve as a bridge to subsequent HBV-specific immune therapies, which may cause changes in the balance between viral replication and the host's immune response in favor of eradication of chronic HBV infection.

It is therefore likely that lamivudine may have to be administered on a long-term basis. This is feasible because unlike interferon, lamivudine is taken orally once daily and is associated with few adverse events. However, as with all antiviral agents, there is the possibility of escape mutation(s) with prolonged treatment.

In conclusion, in this pilot study, the primary outcome as virological response at month 12 was not affected by the lamivudine treatment. It was observed that a three-month course of lamivudine therapy has a partial and temporary effect on suppression of HBV DNA, probably because of the short course of therapy. A short course of lamivudine monotherapy for patients in the immune-tolerant phase of HBV infection has no far-reaching effect on virologic response. Whether permanent suppression of HBV DNA can be achieved in HBsAg carriers by long-term treatment with lamivudine awaits further controlled trials. But the fact that therapy will inevitably lead to the emergence of the YMDD mutation together with the occurrence of an active liver disease is a limitation for the prolonged therapy. Thus new and safe modalities of therapy are needed for these asymptomatic but viremic patients.

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