Beneficial effects of ‘lamivudine pulse’ therapy in HBeAg-positive patients with normal ALT* 

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Received April 2003; accepted for publication October 2003

SUMMARY. Currently no therapy is given to patients with chronic hepatitis B virus (HBV) infection who are HBeAg positive with normal alanine aminotransferase (ALT) levels. Steroid priming has been shown to enhance T-helper-1 (Th-1) cell response. Lamivudine may restore immunologic competence against HBV by causing a sudden decline in the level of the virus. We examined the efficacy of lamivudine pulse therapy on the seroconversion from HBeAg to anti-HBe. This was a prospective single-blinded trial including 27 patients with chronic hepatitis B, HBeAg positive with ALT £ 1.5 times upper limit of normal (ULN). Lamivudine was administered initially for 4 weeks, then stopped for 2 weeks and later restarted and continued till 3 months after seroconversion or completion of 2 years of therapy. Twenty-six patients completed the study. Lamivudine withdrawal led to a rise in ALT levels above the ULN in 11 (42.3%) patients at 6 weeks; seven of them (63.6%) lost HBeAg compared with only two of the 15 patients (13.3%), in whom ALT levels did not rise (P = 0.011). As one patient showed a relapse, a total of eight (31%) patients responded to lamivudine pulse therapy over a mean period of 17.3 ± 4.5 months. Responders had a higher serum albumin (P < 0.05), a lower fibrosis score (P < 0.05), and a relatively high baseline serum ALT levels (P = 0.024) than the nonresponders. YMDD mutations developed in three patients and none responded. No patient developed hepatic decompensation. Hence lamivudine pulse therapy has potential in converting HBeAg-positive, ‘not-treat-worthy’ (ALT < 1.5 ULN) patients to treat-worthy (ALT > 1.5 ULN) in 42%, with sustained HBeAg and HBV DNA loss in 31% patients. The effects are possibly because of a combination of antiviral and immunomodulating activities of lamivudine.

Keywords: antiviral drugs, chronic hepatitis, cirrhosis, hepatitis B virus, viral replication, YMDD.

INTRODUCTION

Over 400 million people have chronic infection with the hepatitis B virus (HBV), and more than 75% of those affected are of Asian origin [1,2]. Chronic HBV infection can lead to chronic hepatitis, cirrhosis, liver cancer, and even death [3,4]. Patients with chronic HBV infection who have active viral replication and have elevated alanine aminotransferase (ALT), are at risk of progressive liver disease and merit antiviral therapy. For HBeAg-positive patients with an ALT level between two and five times the upper limit of normal (ULN), either interferon or lamivudine may be used [5–7].

However, despite the need, no therapy is currently offered to patients who are HBeAg positive with normal ALT, because of the limited efficacy of drug therapies in such patients [5,6,8–10]. HBeAg positivity has been associated with higher titres of HBsAg, higher levels of viral replication, and less definitively, increased severity of liver disease [8]. Of importance from a public health perspective, HBeAg has been associated with a higher degree of infectivity [9–11]. Moreover, persistence of replicative HBV infection into adulthood is associated with a high mortality from cirrhosis and hepatocellular carcinoma (HCC). Thus, an effective treatment is warranted in patients with chronic HBV infection who are HBeAg positive, even with normal or mildly elevated ALT.

Short course of corticosteroid therapy is known to produce ‘immune rebound’, which causes lysis of hepatocytes expressing HBV antigen, and results in a decrease in HBV replication and a ‘flare’ in the ALT levels [12]. Prednisolone priming has been shown to enhance the T-helper-1 cell (Th-1) response, and efficacy of lamivudine therapy in patients with chronic hepatitis B [13]. Liaw et al. [13] in a study of 30 HBeAg-positive patients with ALT < 5ULN...
observed a response in 12 (43%) patients with steroid priming. An adequate host immune response reflected by elevated ALT levels is needed for the eradication of residual covalently closed circular (ccc) DNA by an antiviral agent [13,14]. In the Asian hepatitis lamivudine trial, it was suggested that manipulation of the host immune response against HBV is required for a better response in patients with lower ALT levels [15]. It has also been suggested that treatment with lamivudine may restore immunologic competence against HBV by decreasing the viral load [16]. It has also been well documented that on withdrawal of lamivudine, a hepatitis ‘flare’ may develop in a few patients, because of the immune rebound [17].

We investigated the hypothesis of giving ‘pulse therapy’ using lamivudine, to induce immune rebound phenomenon in the subgroup of patients with normal ALT, so as to raise the ALT levels before reintroduction of the drug. We administered lamivudine for initial 4 weeks and then withdrew the drug for 2 weeks. We hypothesized that restarting lamivudine in such patients would amount to administration of lamivudine in naïve patients with chronic HBV infection and raised ALT.

PATIENTS AND METHODS

Patients
All consecutive patients with chronic HBV infection, i.e. detectable serum HBsAg for least 6 months, positive HBeAg, normal ALT (< 1.5 × ULN) on two or more occasions in last 6 months were enrolled. The patients co-infected with hepatitis C, hepatitis D, or human immunodeficiency virus (HIV) and those with antibodies suggestive of autoimmune disease (antinuclear antibody) were excluded from the study protocol. In addition, patients with history or physical findings suggestive of cirrhosis of liver, variceal hemorrhage, ascites, hepatic encephalopathy and/or serum bilirubin >2.5 × ULN were excluded. Administration of any investigational drug, systemic or oral antiviral agent (including lamivudine) and/or immunomodulators (including corticosteroids) within 6 months of enrollment was excluded by a clinical history. The study protocol was approved by the Institutional Ethics Committee and all the patients gave their written informed consent.

A total of 27 patients were enrolled between January 1999 and April 2000, who fulfilled the enrollment criteria.

Study design

The study was a pilot nonrandomized, prospective clinical trial. After fulfillment of the selection criteria, all the patients included in the trial were administered lamivudine 100 mg once daily in adults or 2 mg/kg p.o., once daily in children. Lamivudine was continued for 3 months after achieving seroconversion or for a period of 2 years. At baseline, a complete haemogram, prothrombin time index, liver function tests, renal function tests, HBsAg, HBeAg, anti-HBe, HBV DNA (quantitative assay: Digene Co., Beltsville, MD, USA), anti-nuclear antibody (1:80 dilution) and anti-HCV tests were performed. An ultrasound of the abdomen and alpha-foeto protein estimation were performed to exclude any co-existing hepatocellular carcinoma. Liver biopsy (performed within 6 months before enrollment) was obtained in every patient and histologic activity index (HAI) and the stage of fibrosis were calculated in all the patients before initiation of the therapy [18].

Lamivudine was initially given for 4 weeks (Fig. 1). It was withheld for a period of 2 weeks and was then re-administered in the same dose as before. Patients were closely monitored during this period and liver function tests were performed every week for the first 6 weeks. Patients were closely observed for the development of acute hepatitis or decompensation during the 2-week period of drug withdrawal. We stored the sera of patients for determining HBV DNA levels at the baseline, at 4 weeks after starting lamivudine and at the end of the second week of withdrawal of lamivudine. Thereafter, the liver function tests were performed every month and HBeAg and HBV DNA levels were tested every 6 months. We looked for the development of YMDD mutations in all the patients, including those patients who developed a rise in ALT levels in the absence of seroconversion from HBeAg to anti-HBe. Assay for anti-HBe was performed in patients who lost HBeAg, and if negative, it was repeated after 1 month to reconfirm.

Detection of YMDD mutant

To detect the YM552I/VDD mutation within the catalytic domain ‘C’ of the viral polymerase, we followed the previously described protocol [19]. Briefly the extracted viral DNA from 100 μL of patient serum with the help of standard phenol/chloroform extraction method was subjected to nested polymerase chain reaction (PCR) amplification to amplify the region encoding the catalytic domains of P-open

reading frame (ORF) (nucleotide position 425 to 840). The
amplification step was performed for 30 cycles with the outer
primers SA1: 5'- ATCGC, TGGA, GTGC, TGGG-3', SA2:
5'- GGCAC, CAGCC, TAAAG, GTTCA-3' (position 369 to
388 and 1136 to 1155, respectively) and inner primers SB1:
5'- TTAGG, GTTGA, ATACC, C-3' (position 822 to
842), SB2: 5'- CATCT, TCTTG, TGTGT, TCTTC, TG-3' (position
427 to 448). PCR was carried out using thermal cycler
(Perkin-Elmer, NJ, USA) with denaturation at 94°C for
1 min, annealing at 55°C for 1 min, primer extension at
72°C for 2 min for a total of 30 cycles and finally a single
cycle for primer extension was carried out at 72°C for 7 min.
Thus, generated PCR product of 416-bp size was purified
using a PCR purification kit (Qiagen, Hilden, Germany).
Purified 416-bp fragment was sequenced with both forward
and reverse primers (SB1 and SB2, respectively) in an
automated DNA sequencer (ABI 377-18 sequencing system;
Perkin Elmer) and obtained electrophorogram was compared
with already reported wild-type sequences of HBV DNA of
known genotypes using the 'Multalin' software.

End-points

Primary end-points
Absence of quantifiable serum HBV DNA and seroconversion
to anti-HBe in two consecutive assays, at least 1 month
apart.

Secondary end-points
(i) Development of serious adverse effects, acute hepatitis or
hepatic decompensation, and
(ii) Completion of 2 years of therapy.

Assessment of response

Sustained response
Patients who remained HBeAg and HBV DNA (quantitative
assay) negative 3 months after stopping of therapy.

Seroconversion
Patients in whom HBeAg and HBV DNA became undetect-
able and anti-HBe developed.

Nonresponders
Patients who remained HBeAg positive at the end of
24 months of therapy.

Compliance and adverse effects
Patients were assessed for compliance of the drug therapy by
‘pill-count’. Patients who returned with ≥15% of pills of the
previous visit and/or missed seven consecutive days of
therapy in a month were labelled as ‘noncompliant’. Adverse
effects to lamivudine were carefully monitored and recorded.

Statistical analysis

The descriptive statistics (i.e. mean ± standard deviation) of
continuous variables in responder and nonresponder group
and wherever there was a wide variation of data, the sta-
tistics (median), are presented. The significance of differences
in the variables between responder and nonresponder
group was tested by using chi-square/Fisher’s exact test for
categorical variables, whereas for continuous variables,
parametric two-sample Student’s- t-test and nonparametric
two-sample Wilcoxon–Mann–Whitney and one-sample
Wilcoxon signed-rank test. To compare the change in the
ALT and HBV DNA levels from baseline to week 4 or to week
6, the Student’s t-test/nonparametric, Wilcoxon signed-rank
test for paired sample with two-tailed probability was used.
The percentage increase in ALT and HBV DNA after the ‘rest-period’ between the two groups was compared
using nonparametric two-sample Wilcoxon–Mann–Whitney
U-test. The proportion of patients showing a rise in ALT or
HBV DNA were compared using Fisher’s exact test.

RESULTS

A total of 27 patients were enrolled. One patient was non-
compliant and was lost to follow-up after the third month of
therapy and was therefore excluded. The study group of 26
patients comprised 20 male and six female patients with a
mean age of 28 ± 14.5 years.

Response

Overall, nine (36%) patients lost HBeAg over a mean period
of 17.3 ± 4.5 months. In eight patients this was followed by
seroconversion to anti-HBe and one patient lost HBeAg
at month 16, but failed to develop anti-HBe even after
4 months of HBeAg loss. Five patients who seroconverted
from HBeAg positive to anti-HBe positive status, developed a
mild ‘flare’ in the serum ALT levels (2–5 × ULN) around the
time of seroconversion. HBeAg loss was maintained for up to
a follow-up period of >3 months (mean 5.8 ± 2.4) in all the
patients even after the withdrawal of lamivudine. This would
amount to a total of 6 months of follow-up after response to
therapy, since as a usual practice, lamivudine was continued
for 3 months after seroconversion.

Comparison of responders vs nonresponders

Baseline
The patients who responded to lamivudine therapy were
compared with those who did not respond with respect to
their age, baseline serum bilirubin, serum albumin and the
HAI. In the patients who responded, the baseline ALT levels
were significantly higher than the patients who did not
(38.7 ± 14.4 vs 27.8 ± 8.8 IU/L); the difference was signi-
ficant (P = 0.024). The mean serum albumin level of

responders was significantly higher than the nonresponders (4.2 ± 0.3 vs 3.9 ± 0.4 g/dL; \( P < 0.05 \)). There was no significant difference in the HAI score between the two groups of patients. It was observed that the nonresponders had a higher hepatic fibrosis score than the responders (1.0 ± 0.7 vs 0.2 ± 0.4; \( P = 0.003 \)) (Tables 1 and 2). The baseline serum HBV DNA levels were higher in the nonresponders than responders but the difference was not significant (Table 2).

**Table 1** Baseline characteristics of patients

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<tbody>
<tr>
<td>Total patients (n)</td>
<td>26</td>
<td></td>
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<tr>
<td>Age (year; mean ± SD)</td>
<td>28 ± 14.5</td>
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<tr>
<td>Male:female</td>
<td>20:6</td>
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<td>Follow-up (months; mean ± SD)</td>
<td>17.3 ± 4.5</td>
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<tr>
<td>Serum bilirubin (mg/dL; mean ± SD)</td>
<td>0.72 ± 0.3</td>
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<td>Serum ALT (IU/dL; mean ± SD)</td>
<td>31.5 ± 11.98</td>
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<td>Serum AST (IU/dL; mean ± SD)</td>
<td>29.3 ± 10.9</td>
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<tr>
<td>Serum albumin (g/dL; mean ± SD)</td>
<td>3.9 ± 0.4</td>
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<tr>
<td>HBV DNA (pg/mL; mean ± SD)</td>
<td>85 (0.6–16 000)</td>
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<tr>
<td>HAI (score)</td>
<td></td>
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<tr>
<td>0–3 (%)</td>
<td>5 (19)</td>
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<tr>
<td>4–6 (%)</td>
<td>18 (70)</td>
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<tr>
<td>7–9 (%)</td>
<td>3 (11)</td>
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<tr>
<td>Fibrosis score</td>
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<td></td>
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<tr>
<td>0 (%)</td>
<td>10 (39)</td>
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<tr>
<td>1 (%)</td>
<td>12 (46)</td>
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<td>2 (%)</td>
<td>4 (15)</td>
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At week 4: beginning of lamivudine withdrawal

A slight decrease in the serum ALT levels was seen in all the patients during the first 4 weeks of lamivudine therapy compared with the baseline (\( P = \text{NS} \)). The difference was also not significant between responders and nonresponders. Serum HBV DNA levels significantly (\( P = 0.035 \)) decreased from the baseline values in both responders and nonresponders at 4 weeks.

At weeks 6: end of withdrawal period

We analysed the effect of lamivudine withdrawal for 2 weeks on the serum ALT levels, serum HBV DNA levels and any influence on response to therapy. The mean ALT levels of all the patients taken together at 6 weeks was significantly higher compared with the baseline (\( P < 0.01 \)).

The mean rise in ALT levels in the patients who responded and those who did not was calculated using two parameters; a rise above the normal ALT levels (>40 IU/L) and the proportionate rise from the baseline ALT level of the patient. Twenty of 26 (77%) patients had, at the start of therapy, ALT levels <40 IU/L. After 2 weeks of rest and lamivudine withdrawal, 19 (73%) patients showed an elevation of >1.5 times of their baseline value. Eight of these 19 (47.4%) patients who had a rise of >1.5 × ALT from the baseline levels responded. Only one of the seven (14%), patients who did not have an increase in ALT of >1.5 × from the baseline level responded (\( P = \text{NS} \)). Of the 26, 11 patients (42%) showed a rise in ALT of >1.5 ULN, i.e. a rise above 40 IU/L. Of these 11, seven (64%) patients seroconverted. Of the 15 patients in whom the rise in ALT levels above the ULN was not

**Table 2** Profile of responders and nonresponders

<table>
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<tr>
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<th>Responder</th>
<th>Nonresponder</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Total patients (n)</td>
<td>9 (36%)</td>
<td>17 (64%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (year; mean ± SD)</td>
<td>30.6 ± 21</td>
<td>26.7 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Male:female</td>
<td>8:1</td>
<td>12:5</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up (months; mean ± SD)</td>
<td>18.1 ± 6.6</td>
<td>16.7 ± 5.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL; mean ± SD)</td>
<td>0.7 ± 0.3</td>
<td>0.6 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>ALT (IU/dL; mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>38.7 ± 14.3</td>
<td>27.8 ± 8.8</td>
<td>0.024</td>
</tr>
<tr>
<td>4 weeks</td>
<td>34 ± 9.2</td>
<td>29.2 ± 8.3</td>
<td>NS</td>
</tr>
<tr>
<td>6 weeks</td>
<td>64.7 ± 39.2</td>
<td>55.4 ± 48.3</td>
<td>NS</td>
</tr>
<tr>
<td>AST (IU/dL; mean ± SD)</td>
<td>33.2 ± 12</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Serum albumin (g/dL; mean ± SD)</td>
<td>4.2 ± 0.3</td>
<td>3.9 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>HBV DNA (mean ± SD; pg/mL)</td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>103.6 ± 144</td>
<td>1392 ± 1918</td>
<td>NS</td>
</tr>
<tr>
<td>4 weeks (after starting lamivudine therapy)</td>
<td>13.7 ± 33.6</td>
<td>637.9 ± 1701</td>
<td>0.035†</td>
</tr>
<tr>
<td>6 weeks (after starting lamivudine therapy)</td>
<td>26.4 ± 61.2</td>
<td>591.6 ± 1336</td>
<td>NS</td>
</tr>
<tr>
<td>HAI (mean ± SD) score</td>
<td>4.4 ± 1.5</td>
<td>4.9 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrosis score (mean ± SD)</td>
<td>0.9 ± 0.3</td>
<td>1.2 ± 0.7</td>
<td>0.003</td>
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†Compared to baseline in each group.

observed, only two (13%) patients responded ($P = 0.011$). However, there was no significant difference in the median ALT level between the responders and the nonresponders (median 57 IU/L vs 35 IU/L, $P = \text{NS}$). None of the patients had a rise in bilirubin or decompensation along with rise in ALT levels.

Serum HBV DNA levels did not rise much at 6 weeks from the levels detected at 4 weeks in both responders and nonresponders (Table 2).

During the treatment period and follow-up
Lamivudine was well tolerated and no significant side-effects were observed. Good compliance was observed in all the patients. None of the patients in the study group showed icteric hepatitis at any time during the study period. YMDD mutations developed in three (12%) patients after a mean of 17.3 ± 4.5 months of drug therapy. None of the patients with YMDD mutations seroconverted. The HBeAg loss and seroconversion was sustained in eight of the nine (88%) patients. In one patient who had not seroconverted, the HBeAg again became positive during the follow-up. Thus, the overall sustained response was seen in eight of 26 (31%) patients.

DISCUSSION
The results of the present study indicate that lamivudine ‘pulse therapy’ is potentially effective in HBeAg-positive patients with normal ALT. A slight elevation in the ALT level following a brief withdrawal of lamivudine and a good response rate of 31% suggests that lamivudine pulse therapy induces immune modulation in the patients with normal ALT. As evident from our results, lamivudine withdrawal, converted 11 (42%) patients from normal ALT to ‘raised ALT’ (>1.5 × ULN) group, a good predictor of response [7]. In other words, lamivudine pulse, converted patients from a ‘not-treat-worthy’ to a ‘treat-worthy’ category. Seven of the 11 (64%) patients who showed a rise in ALT levels, lost HBeAg. Furthermore, this approach was found to be safe as none of the patients showed icteric hepatitis or decompensation. A similar immune rebound and response was observed by Liaw et al. [13] using steroid priming prior to lamivudine therapy in patients with chronic hepatitis B having normal ALT.

In their pilot study, 20 of the 30 (67%) patients showed an increase in ALT levels and 12 (60%) of these patients seroconverted. However, only one of the 10 (10%) patients without an ALT flare showed seroconversion. In our study, an ALT elevation of >2 × ULN was seen in six patients. Three (50%) of these patients lost HBeAg. However, besides determining the rise in ALT levels above the ULN, we also calculated the rise above the baseline ALT value of the subject. We found that the subjects in whom a rise of >1.5 × in ALT levels occurred from the baseline value, the response to lamivudine pulse therapy was good. The slight lower response rate to lamivudine pulse therapy in our patients compared with the steroid priming protocol followed in the study by Liaw et al. [13] could mainly be because of the differences in the selection criteria. We strictly included only those patients who had a persistently normal ALT (<1.5 × ULN). In fact, 20 (77%) of our patients had ALT levels persistently below 40 IU/L. However, Liaw et al. [13] included patients who had elevated ALT up to 5 times ULN.

Another explanation for a lower response could be due to the fact that the lamivudine withdrawal was only for 2 weeks, in the present study. The drug was reintroduced after 2 weeks. This short period may not be sufficient enough to allow immune rebound. In previous studies, it has been shown that it requires 4–8 weeks after lamivudine therapy before T-cell function returns to normal [17]. It is likely that a longer ‘rest period’ could have given a higher response rate. The reason for a short ‘rest period’ in this study was because of our concern of developing decompensation following lamivudine withdrawal.

The patients who responded to lamivudine pulse therapy had a significantly higher baseline serum ALT level when compared with the nonresponders (38.7 ± 14.4 vs 27.8 ± 8.8 IU/L; $P = 0.02$). It is possible that patients with slightly higher ALT levels, even if within the normal range, may have a stronger endogenous immune response to HBV antigens and may therefore develop a greater degree of immune rebound and respond better to lamivudine pulse. The rise in serum ALT after lamivudine pulse supports the hypothesis of an immune rebound which could be utilized for HBV clearance. It would be worthwhile to study the immunological changes in patients during the initial lamivudine therapy and during the drug free ‘rest-period’. Assessment and documentation of enhanced Th-1 response would have supported the basis of immune modulation by lamivudine pulse therapy.

While our results indicate that short-term lamivudine withdrawal produces similar benefits as could be achieved with corticosteroid priming in patients with normal ALT, they indicate an additional advantage of lamivudine pulse therapy. The HBV viral load is markedly reduced by 4 weeks of lamivudine therapy and the ‘rest-period’ of 2 weeks did not allow the HBV DNA levels to increase.

However, the use of corticosteroid therapy could lead to an increase in the serum HBV DNA levels. It is known that the HBV genome contains a glucocorticoid-responsive element that is responsible for an increase in serum HBV DNA levels and enhanced production of viral transcripts [20–22]. To have an increased viral load at the baseline before starting antiviral therapy with lamivudine, may theoretically pose additional problems. It has been shown that high baseline HBV DNA levels may increase the chance of development of YMDD mutants [23]. In their study, Liaw et al. did not look for emergence of these mutant forms of HBV. While potentially beneficial, it is difficult to justify the use of steroids for chronic HBV [24], as HBV DNA levels increase in all the patients after steroid pulse but at best, only
60% the patients may respond to subsequent lamivudine therapy [13]. However, lamivudine pulse therapy is much more rational, as it not only achieves the much needed immunomodulation; the HBV DNA levels remain low after the 'rest period'. In fact, we observed the emergence of YMDD mutations in only three (12%) patients after a mean duration of 17.3 ± 4.5 months of lamivudine therapy. Our study revealed that serum albumin levels and stage of hepatic fibrosis do have a bearing on the outcome of therapy. Higher serum albumin and lower hepatic fibrosis, would mean a shorter duration of infection with a milder disease. Such patients were found to respond better. Furthermore, patients with the lower HBV DNA levels responded better. This later observation was noted by Liaw et al. [13] as the median baseline HBV DNA in patients who had an 'ALT flare' was 700 pg/mL compared with 2353 pg/mL in those who did not have a flare [13]. In other studies also, a low baseline HBV DNA is reported to be a good indicator of response [20,25].

Except for one patient, the patients who had lost HBeAg on lamivudine pulse therapy, maintained it for a period of >6 months, thereby indicating that the HBeAg loss and seroconversion is stable [1]. The one patient who had a relapse and reappearance of HBeAg, did not develop anti-HBe after stopping therapy. A longer follow-up period is required to accept a sustained response to lamivudine pulse therapy, in view of the high relapse rates reported from East [26].

In conclusion, this pilot study indicates that lamivudine pulse therapy is safe and effective in patients with active viral replication, HBeAg positive, with normal ALT levels. It is quite possible that a similar approach could further enhance the efficacy of lamivudine monotherapy in HBeAg positive patients who have ALT levels between 1.5–5 × ULN. In such patients, it is possible that lamivudine withdrawal could lead to a rise in ALT to >5 × ULN and higher response rates. The underlying mechanisms of response to therapy are possibly related to immune-rebound effects produced by lamivudine withdrawal as well as the antiviral effects of lamivudine. The concept of lamivudine pulse therapy merits further evaluation in large randomized double blind clinical trials, along with studies related to Th-1 cellular responses.

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