Durability Of Lamivudine Associated HBe Antigen Seroconversion in Chinese-Canadian Patients with Chronic Hepatitis B Virus Infection

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Citation

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Abstract

Objective: To asses the durability of HBeAg seroconversion in Chinese-Canadian patients treated with lamivudine, and investigate factors predictive of relapse.

Methods: We studied Chinese-Canadian patients with chronic HBV treated with lamivudine monotherapy from 1997 to 2002. Only patients with seroconversion were included, defined as conversion from HBeAg(+) to HBeAb(+) with undetectable HBV DNA, and in the case of pre-core mutants (HBeAg(-) chronic hepatitis B) an undetectable HBV DNA level.

Results: 18 patients seroconverted on lamivudine. Three patients had pre-core mutants. 14 (78%) patients had HBV relapse with a detectable HBeAg and/or HBV-DNA after lamivudine discontinuation. Mean time to seroconversion was 7.4 months. Mean duration of lamivudine therapy was 10.9 months. Lamivudine was continued a mean of 3.5 months post-seroconversion. There was no difference in baseline ALT, HBV DNA titer, or duration of lamivudine in patients who relapsed. Ten of the 14 patients with relapse were re-started on lamivudine, with remission in 7 patients.

Conclusion: Sustained response in the Chinese-Canadian population is poor at 22%. Given the poor sustained response and difficulty in predicting those at risk of relapse it is likely that a prolonged course of lamivudine greater than the suggested one year duration may be needed.

INTRODUCTION

Lamivudine is a nucleoside analogue, causing inhibition of reverse transcription resulting in termination of HBV DNA chain ([1,2]). Lamivudine treatment suppresses HBV replication, and may enhance the T-cell response against hepatitis B, resulting in HBeAg seroconversion. Seroconversion rates with lamivudine have been reported to be approximately 40% after three years of therapy ([3]). This is similar to rates of 33% reported with high-dose interferon therapy for 16 weeks ([4,5,6]). The advantage of lamivudine is superior patient tolerability compared with interferon. This is particularly attractive to an Asian population since interferon is reportedly to less effective in Asians, likely secondary to chronic immune tolerance associated with vertical transmission ([7,8]).

It is generally believed that the HBe seroconversion, HBeAg disappearance with the appearance of HBeAb and undetectable HBV, post-lamivudine is sustained, and that lamivudine can be discontinued after a finite period ([9,10]). These reports have been in a predominantly Caucasian population that acquired HBV through horizontal transmission. A recent study from Korea in an Asian cohort with vertically acquired infection reported a relapse rate of 37.5% and 49.2% after 12 and 24 months after lamivudine discontinuation ([11]).

The aim of our study was to assess the durability of HBeAg seroconversion in a Chinese-Canadian patient population with chronic hepatitis B virus infection treated with lamivudine, and to investigate factors predictive of HBV breakthrough.

METHODS AND MATERIALS

Retrospective analysis of Chinese- Canadian patients with chronic HBV infection residing in British Columbia who

seroconverted during treatment with a lamivudine. Patients were treated between1996 to 2002. Patients were provided treatment if they had elevated transaminase (i.e. serum ALT, AST) levels greater than 1.5 times the upper limit of normal for greater than 6 months. Patients were only included in this study if they seroconverted on lamivudine mono-therapy. Seroconversion was defined as conversion from HBeAg(+) to HBeAg(-) and presence of HBeAb(+), and in patients with HBeAg(-) chronic hepatitis B an undetectable HBV DNA with normalization of the transaminase levels was required. Patients did not have to undergo a liver biopsy prior to therapy. Relapse was defined as re-appearance of HBeAg, and / or detectable serum HBV DNA in association with elevated transaminase levels.

HBV DNA was measured by hybridization assay until and including 1999 (Digene 1 st Generation Hybrid Capture, Digene Diagnostics, Beltsville MD; lower detection limit (LDL) = 5 pg/ml, 1.4 x 10 ^{6} copies/ml). Since 2000 the Ultrasensitive Digene Assay was utilized (LDL=0.017 pg/ml; 4.7 x 10 ^{3} copies/ml).

Patients with decompensated liver disease, defined as clinical history or findings of a variceal hemorrhage, ascites, encephalopathy or portal hypertension suggested by ultrasound were excluded from this study. Patients were also excluded from analysis if they underwent previous therapy with either interferon or repeated courses of lamivudine, or with co-infection with hepatitis C virus (HCV), or human immunodeficiency virus (HIV).

Lamivudine was used at a dose of 150 mg/day in the patients treated during 1996 and 1997, but thereafter a dose of 100 mg/day was used. During therapy and the first year of follow-up after seroconversion, the transaminase levels, HBeAg, HBeAb and HBV DNA were measured every 2-3 months in all patients. After 1-year of follow-up these parameters were checked every 4-6 months.

Data collected included patient demographics, ALT, bilirubin, HBV DNA titer, HBeAg and HBeAb status at start of therapy, seroconversion, time of lamivudine dis-continuation, relapse and at any subsequent therapy.

STATISTICAL ANALYSIS

Univariate analysis was performed using Chi-square, student t-test, and where appropriate a correlation coefficient was calculated. A two-tailed p value of less than 0.05 was considered significant. The statistical package SPSS 11.0 was utilized.

RESULTS

A total of 21 Chinese –Canadian patients who had undergone lamivudine monotherapy from 1996 to 2002 had a seroconversion from HBeAg(+) to HBeAb(+), and an undetectable HBV DNA with normalization of the transaminase levels in patients with HBeAg(-) chronic hepatitis B. Two patients were excluded due to incomplete records, and one for prior hepatitis B anti-viral therapy with interferon. A total of 18 patients fulfilled the inclusion and exclusion criteria. All patients had vertically transmitted HBV. None of the patients had decompensated liver disease. There were 12 males in the group. The age range at therapy was from 15 years to 58 years. The total follow-up period ranged from 25 months to 73 months, with a mean of 42 months.

All 18 patients had biochemical evidence of seroconversion. Three patients had HBeAg(-) chronic hepatitis B with undetectable HBV DNA and normalization of transaminase levels at seroconversion. The median time to seroconversion was 7.2 months, with a range of 2.5 to 17.8 months. The mean duration of lamivudine therapy was 7 months, with a range from 4 to 56 months. Fourteen of the 18 patients who seroconverted subsequently relapsed (78%). There were no YMDD-motif mutants identified. Baseline characteristics and demographics of the study group are shown in table 1.

Figure 1

Table 1: Baseline characteristics of study group

Parameters	All patients (n=18) mean (range)	Relapse group (n=14) mean (range)
Age (yrs)	36.4 (15-60)	38.2 (15-60)
Gender (male)	12	10
ALT (X limit normal (=40iu/L))	9.7 (2.4-33)	9.7 (2.4-33)
HBV DNA (pg/ml)	528 (14-2002)	591 (14-2002)
HBeAg(-) chronic hepatitis B	3	3

The duration of lamivudine therapy, and its discontinuation after seroconversion was also studied. Lamivudine was used for a minimum of 2 months in 14 (78%) of patients after documented seroconversion. One patient decided to discontinue their lamivudine therapy at the time of seroconversion. In the majority (86%) of patients who had a HBV relapse, it occurred within 1 year of lamivudine discontinuation. Nine patients (64%) relapsed within 6 months of lamivudine discontinuation. Please see table 2.

Figure 2

Table 2: Duration of lamivudine in sustained response and relapse groups

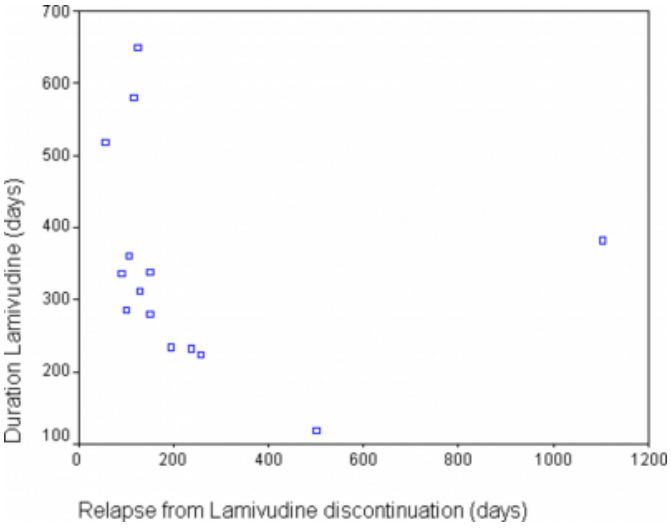
Parameters	Relapse group (n=14) Mean (range)	Sustained Response (n=4) Mean (range)	p value
Time to seroconversion (mon.)	7.9 (2.5-17)	8.2 (2.3-17.8)	0.913
Time from seroconversion to lamivudine discontinuation (mon.)	3.6 (0-7.8)	12.2 (0.9-38)	0.07
Total duration of lamivudine (mon.)	11.5 (4-21.6)	20.5 (6.9-56)	0.176
Lamivudine discontinuation to relapse (mon.)	7.9 (1.8-36.8)		

There was no significant difference between the 2 groups.

The time to relapse from discontinuation of lamivudine did not correlate with the duration of lamivudine therapy. In 64% of patients, regardless of duration of lamivudine, relapses occurred within 6 months of lamivudine discontinuation. Please see figure 1.

Figure 3

Figure 1: Time to relapse from lamivudine discontinuation is not correlated with duration of lamivudine therapy.



On univariate analysis there was no difference in baseline transaminase levels, HBV DNA titer, age or gender between patients who relapsed and those with sustained HBV seroconversion. There was a trend towards an increased total duration of lamivudine in patients who had a sustained response (mean 20.5 months) versus those who had HBV relapse (mean 11.5 months), although this difference was not statistically significant. Similarly there was a trend towards an increased duration of lamivudine treatment post-seroconversion in those patients who had a durable seroconversion (mean 12.2 months) versus those who had HBV relapse (3.6 months), this again was not statistically significant. Therefore, the total duration of lamivudine, or duration of lamivudine after seroconversion did not predict HBV relapse. The HBV DNA titer just prior to seroconversion was predictive of relapse. The HBV DNA titer was lower in those patients with HBV relapse compared to patients with a sustained HBV seroconversion (mean 7.47 pg/ml vs. undetectable, p<0.001 (CI 95% 4.8-10.2). There was no difference in transaminase values at seroconversion. In patients who relapsed, the transaminase level at seroconversion correlated with transaminase level at relapse (correlation coefficient 0.94).

Of the 14 patients who relapsed, 10 patients were re-treated with lamivudine. Seven (70%) of the patients went into remission a second time. Two patients relapsed a second time and were retreated, with one of these patients relapsing a third time. Both are maintained on indefinite lamivudine therapy.

DISCUSSION

The relapse rate of hepatitis B after seroconversion was 78% in our study. A recent study from Korea, by Song et al.([11]), reported a relapse rate of 49.2% at 2 years follow-up. A study by Lee and colleagues ([12]) reports a 57.4% relapse rate at 6 months after treatment in an Asian population. Relapse rates of 43% have been reported in Asian patients treated in Western countries after interferon-a induced HBeAg seroconversion ([5]). It was previously believed that seroconversion after lamivudine monotherapy was durable, and that patients could be withdrawn off lamivudine soon after seroconversion ([9,10]). These studies predominantly involved Caucasian patients from western countries. Therefore, even with documented seroconversion there is a continued substantial risk in the order of 40-80% of relapse in patients with vertically acquired hepatitis B virus in whom lamivudine is withdrawn.

The reason for increased relapse in Asian patients with chronic hepatitis B virus infection is unclear, but may be due to the longer duration of infection. Long-standing HBV infection can result in immune-tolerance, which may be a possible mechanism by which relapse occurs after lamivudine discontinuation ([7,8]). In our study, patient age, and therefore disease duration, was not predictive of relapse. Pichoud et al. ([13]) described the persistence of viral replication even after HBeAg seroconversion, by detection of HBV DNA by polymerase chain reaction, although HBV

DNA was undetectable during hybridization assay. These authors suggested that mutant forms of HBV existed that allowed escape from the anti-HBe immune response and antiviral therapy with continued replication. Although lamivudine inhibits viral replication it does not eliminate hepatocyte covalently closed circular DNA (cccDNA). Therefore the cccDNA can act as a reservoir of chronic infection ([1,2]).

We observed that a detectable HBV DNA at seroconversion predicted a sustained response. This suggests that even though seroconversion with a non-detectable HBeAg occurs, the HBV DNA is detectable for a longer period. This concept is consistent with reports by others ([13]). This lends further evidence towards treatment with a longer duration of lamivudine, beyond HBeAg seroconversion and the detection of HBeAb(+).

Relapse was not predicted by the total duration of lamivudine therapy or the duration of therapy after seroconversion. In the group with loss of seroconversion there was a shorter duration of lamivudine therapy after seroconversion (3.6 months) vs. those with a durable seroconversion (12.2 months lamivudine post-seroconversion), but this did not meet statistical significance ($p=0.07$). Our findings are similar to those published by Song et al. ([11]) who reported a shorter duration of lamivudine therapy after seroconversion predicted relapse. From our study, most patients (86%) who relapse to do in the first year after lamivudine discontinuation. Interestingly, this holds true irrespective of the duration of lamivudine therapy after seroconversion – see figure 1. Therefore, if lamivudine is discontinued the clinician should monitor for relapse frequently within the first year.

Although our study did not report any YMDD mutants, this would be the risk of prolonged lamivudine therapy. Resistance with the YMDD motif is reported to occur at 14% at 1 year, and 38% at 2 years of lamivudine therapy ([3,14]). An Asian study ([14]) which continued lamivudine monotherapy for 2 years reported a seroconversion rate of 27%. In this study, 38% developed YMDD mutants, but continued to remain HBeAg (-), and have lower HBV DNA and ALT levels from baseline. Therefore even though there is a substantial risk of developing a YMDD mutant with prolonged lamivudine, these patients appear to have less inflammation than at baseline.

The increasingly reported high relapse rates after discontinuation of lamivudine raise the question of appropriate duration of lamivudine therapy. The current guidelines in Canada, published by the Canadian Association for Study of the Liver (CASL)([15]), as well as the guidelines from the American Association for the Study of Liver Disease (AASLD) ([16]) both suggest a duration of 12 months of total lamivudine therapy. The high relapse rate of 78% from our study, and others ([11,12,17]), suggests that relapse is a much more common occurrence than previously believed. Further, contrary to present North American guidelines, a prolonged course of lamivudine therapy beyond 1 year and perhaps indefinitely, especially in patients with vertically transmitted HBV, would be beneficial in maintaining seroconversion. The role of newer nucleoside analogues, such as adefovir, in the therapy of HBV when YMDD mutants emerge remains to be determined. A combination of prolonged therapy with 2 or more nucleoside analogues, especially in the context of YMDD mutants, to maintain HBV seroconversion will likely be a future therapeutic consideration.

CONCLUSION

Sustained response after hepatitis B seroconversion in the Canadian-Chinese population is poor at 22%. The initial transaminase and HBV DNA levels do not predict relapse. The majority of relapse episodes occur within the first year, and usually first 6 months after lamivudine discontinuation, and occur irrespective of the duration of lamivudine therapy. Although current guidelines suggest a 1-year course of lamivudine, given the poor sustained response and difficulty in predicting those at risk of relapse it is likely that a prolonged course of lamivudine is needed.

DISCLOSURES

This work was presented as a poster at Canadian Digestive Diseases Week, Banff AB, in February 2003 and at Digestive Diseases Week, Orlando FL, in May 2003. The conference abstracts from these meetings were published in the 2003 supplements of the Canadian Journal of Gastroenterology and Gastroenterology respectively.

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