Short Report

YMDD Mutation in Pakistani patients. The comparison of Eastern Response with the Western Response

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Abstract

Lamivudine exhibits potent antiviral activity in chronic hepatitis B. YMDD mutations in west is around 32% (5 years) but reports from East are scarce. To evaluate frequency of lamivudine resistance and compare the results with the West, a total of 100 chronic hepatitis B patients were given Lamivudine 100 mg before breakfast. Out of 81 patients (19 no follow up), (85%) males and (15%) females. Wild type were 69 (85%) and 12 (14.8%) pre-core mutants. At 1 year 25/69 wild type (36.2%) lost their HBeAg and 18 (26%) sero-converted. At 2 years 30 (43.4%) became HBeAg negative and 22(31.8%) had positive anti-HBe. At 3 years 33 (47.8%) became HBeAg negative and 25 (36.2%) sero-converted. Of 12 precore mutants 8 (66.6%) lost HBV DNA within 24 weeks of therapy. At 36 months 44.4% showed sero-conversion with a YMDD mutation rate of 6% which is in contrast to 32% reported from the West.

Introduction

Chronic hepatitis B is a prevalent disease in Asia with over 350 million carriers world over.[1-3] Globally there is a decline in chronic hepatitis B due to effective vaccination strategies especially after its inclusion in the EPI. The exact prevalence of hepatitis B in Pakistan is not known but meta analysis shows that the HBsAg carrier rate is around 3-4%.[4] The vaccine for hepatitis B in Pakistan was included in the EPI in 2002 and to date the coverage is around 70 %.[5]

The discovery of Lamivudine was a break through in the treatment of chronic HBV cases and the drug was used extensively all over the globe with good results. Long term use of the drug showed decreased efficacy of lamivudine due to the emergence of drug resistance.[6-10] Lamivudine-resistant hepatitis B virus (HBV) has been described as replication defect based on early clinical observations and in vitro data for single mutations of M204V or M204I in the YMDD motif of HBV polymerase.[11]

The availability of oral nucleoside analogue — Lamivudine in Pakistan in 1998 was a milestone in the treatment of selected group of chronic HBV cases. In Pakistan the treatment cost is borne by the patient and one tablet of 100 mg costs around Rs 100 and one year cost therefore is approximately Rs 40,000 ($ 650). Adefovir is twice more expensive. Due to poor socioeconomic conditions many patients cannot afford lamivudine on long term basis. Due to the favourable reports of high YMDD mutations with long term use of lamivudine in the west, many of our physicians started to convert our patients to newer drugs, making treatment more difficult and expensive. The present study was therefore done to see the YMDD mutation rate with lamivudine in our population.

This study is a part of a large scale study of over 1500 HBsAg positive patients comprising of (wild/precore mutants), delta positive and negative cases. For the ease of evaluation of disease pattern and treatment response, the data has been divided and analyzed separately.

Patients, Methods and Results

A retrospective analysis of data was done on patients having chronic hepatitis B infection who had either wild type of disease or core/ pre-core mutant type of disease for over 6 months duration. The diagnosis was made on a positive HBsAg, positive HBeAg and HBVDNA along with more than twice raised ALT for over 6 months. For pre-core or core mutants the patients were HBsAg positive, HBeAg negative, HBVDNA positive and had raised ALT for over 6 months. Patients of all ages and both genders were selected for the study and 1 tablet of 100mg lamivudine was given once a day before breakfast till sero-conversion for wild type and normal ALT for over 2 years in mutants.

Co-infection with hepatitis delta virus, hepatitis C virus was excluded. The study was done in one of the largest hepatology units of the medical research centre at Jinnah Post Graduate Medical Centre, Karachi. During therapy HBVDNA was checked at 12 weeks in those patients who could afford it while ALT was checked every 3- 6 months till sero-conversion.

HBeAg was checked at 1 year and then every 6-12 months depending upon the HBeAg values (values drop as sero-conversion starts). Treatment was stopped 3-6 months after sero-conversion.

For core and pre-core mutants the treatment was stopped after 2 years of normalization of ALT because majority of the cases could not afford long term treatment. These patients were followed every 6 months for over 1 year

to see relapse/reactivation. YMDD mutation was suspected when at any times after 6 months of therapy the ALT showed a rise which persisted despite continuing treatment and HBV DNA became positive...

Out of 100 patients who received lamivudine, follow-up was available in 81 cases (males 69, females12) whose mean age was 25.8 years . There were 69 (85%) cases of wild type and 12 (14.8%) of pre-core mutant type. All cases normalized their ALT within 12 months of starting treatment. HBV DNA was done in 28 patients (wild-type) out of whom 13 became negative within 12 months (3 at 3months, 6 at 6months and 4 at 12 months) rest of the patients could not afford the test and were followed by ALT and HBeAg values. Results are shown in Table.

Table: Response over 3 years (69 cases= Wild mutant).

Years	1 year	2 years	3 years
HBeAg -ve (negative)	25 (36.2%)	30 (43.4%)	33(47.8%)
Anti-HBe +ve (positive)	18 (26%)	22(31.8%)	25(36.2%)

No-response in wild-type was seen in 9 patients and relapse in one. The remaining 36 patients are still on treatment and responding .

In the pre-core mutant group, 11 (91.6%) of 12 patients became HBV DNA negative within 3 months of treatment. Their treatment was stopped after 2 years of normalization of ALT and in the follow up two cases relapsed while 66.6% have normal ALT and no disease.

Analysis for YMDD mutant showed that it occurred in 5 cases (6.1%) over 36 months and all these cases belonged to wild category and were males. The mutation was seen in one case at 1 year, 2 cases at 2 years and another 2 at 3 years.

Comments

Lamivudine is a reverse transcriptase inhibitor that is active against the DNA polymerase of hepatitis B virus and inhibits viral replication. Prolonged therapy is required for sustained suppression. However, mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) locus of the HBV-RNA-dependent DNA polymerase confering resistance to lamivudine may emerge after 6 months of therapy with a reported incidence of 24% at 1year and 67% after 4 years of lamivudine therapy[6,11,12] and is considered as an important factor in treatment failure.[12]

In the present study, 5 cases developed mutation during 3 years of therapy. Mutation was suspected when ALT values which had normalized during treatment suddenly went up while the treatment was being continued. These values of ALT did not go beyond the pre-treatment values and HBV DNA which had initially become negative at 12 weeks of therapy, again becomes positive This mutation occurs anytime 6 months after the initiation of the therapy and the chances increase with longer duration of treatment.

Although this is a preliminary data further studies are recommended, nevertheless our study shows that a smaller (6.1%) number of lamivudine mutations in HBeAg positive patients were encountered in our patients than those reported in other studies (32%). About 44.4% cases sero converted during therapy and this response is similar to other studies[3,7] justifying the use of long term lamivudine in treating chronic hepatitis B in our population.

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