TREATMENT OF HBV AND HDV CO-INFECTION USING LAMIVUDINE

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Objective: To see effect of Lamivudine on sero conversion of HBeAg positive cases co infected with Delta hepatitis. **Methods**: Hepatitis B positive patients with deranged liver functions for 6 months were tested for HBeAg, HBV DNA and anti-Delta virus (HDV), using ELISA. Patients were divided into 2 groups, group 1: HBeAg, HBV DNA positive (wild type) but delta negative and group 2: HBeAg, HBV DNA positive (wild type) with delta positive. Lamivudine (100 mg) was advised to both groups till sero-conversion. **Results:** Of 124 cases in year 1999–2005, 69 were in (Group 1), and 55 were in (Group 2). Eighty percent were males in both groups. ALT normalisation occurred in 75%, 24% cases within 6 months respectively. At the start of therapy mean HBeAg was 289±189 in group 1 and 142±160 in group 2. With treatment, the values did not change much till 12 months of therapy. The fall was significantly slow in delta positive cases. At 36 months 26 (38%) cases in group 1 and 9 (16.4%) cases in group 2 sero-converted. Nine cases in each group remained non-responders while 2 in each group relapsed. **Conclusion:** Wild type of HBV/HDV co-infected cases have a 16% chance of seroconversion which negates the concept that once infected with delta virus there is not much that can be done.

Keywords: Hepatitis B virus, Delta hepatitis, co-infection, sero-conversion, fulminant hepatitis, lamuvidine, interferon, entecavir

INTRODUCTION

Meta-analysis of data from Pakistan shows that hepatitis B virus is present in about 3–4% of the population.[1] Delta virus which has been eradicated from most of the developed countries is still prevalent in certain areas of Pakistan.[2] Co-infection in most cases results in fulminant hepatitis resulting in high mortality, while super infection results in high chronicity and morbidity.[3] Global data shows some reduction in HDV RNA levels and normalization of ALT in HDV positive cases without clearance of the virus.[4]

The present study was done to see the effect of Lamivudine therapy on the seroconversion of chronic HBeAg positive cases that were co infected with HDV infection.

PATIENTS AND METHODS

Patients having chronic HBV (HBsAg) infection and having deranged liver functions for over 6 months were further worked up for HBeAg, HBV DNA and anti -Delta virus (HDV). These tests were done using ELISA. Using these tests patients were divided into 2 groups, group 1 was HBeAg positive, HBV DNA positive (wild type) with delta infection and group 2 was HBeAg positive, HBV DNA positive (wild type) but anti delta negative. Both groups were advised to take one tablet of 100mg of Lamivudine orally before breakfast till seroconversion. HBV DNA was repeated at 12 to 16 week in both groups and once it became negative it as not repeated. ALT levels were checked every 3–6 months till seroconversion. Seroconversion was checked after 12 months of therapy by HBeAg which became negative overtime and HBe antibody became positive. Treatment was continued till 6 month after seroconversion.

RESULTS

A total of 124 cases during year 1999–2005 were included in the study. Sixty-nine were HBsAg positive, HBeAg positive, and HBV DNA positive (Group 1); and 55 were HBsAg positive, HBeAg positive, HBV DNA positive, and HDV positive (Group 2). Majority (80%) were males in both groups. Seventeen patients in Group 1 and 8 in Group 2 were below 15 years of age while majority (27 cases in Group 1 and 25 in Group 2) were between 15–24 years of age (Table-1).

Table-1: Gender and age distribution in HBV Positive and HBV with Delta Positive cases

	HBV Positive HBeAg +ve (n=69)	HBV with Delta Positive HBeAg +ve (n=55)	*p*-Value
Gender			
Male	58 (84.1%)	46 (83.6%)	0.521
Female	11 (15.9%)	9 (16.4%)	
Age in years			
<15	17 (24.6%)	8 (14.5%)	0.011
15–24	27 (39.1%)	25 (45.5%)	
25–34	10 (14.5%)	8 (14.5%)	
35–44	9 (13.0%)	10 (18.2%)	
45 & above	8 (8.7%)	4 (7.3%)	

Following therapy, the ALT normalisation occurred in 75% cases within 6 months in Group 1 and 23.6% in Group 2. Further 6% normalized their ALT at 12 months in group 1 and 13% in group 2 showing a rapid normalization in those who were not co infected with delta virus and a slow response in those co infected with delta virus (Figure-1 and 2).

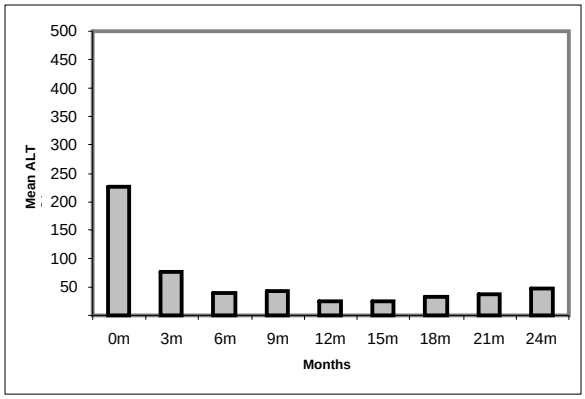
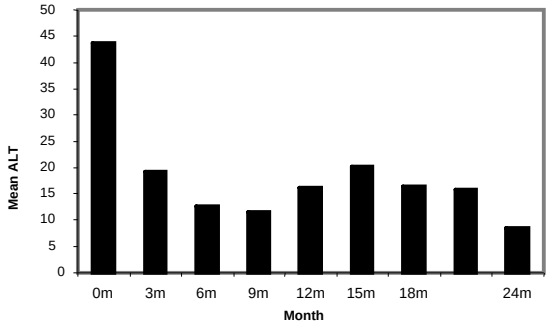


Figure-1: Mean ALT in Responders (n=69) of



HBV Positive cases

Figure-2: Mean ALT in Responders (n=69) of HBV with Delta Positive cases

HBeAg values were also monitored to see if these could be used as a marker for response. At the start of therapy mean HBeAg values were 289±189 in Group 1 cases and 142±160 in Group 2, with treatment the values did not change much till 12 months of therapy. Then onwards the drop was seen as 50% at 18 months and almost negative at 36 months in Group 1. The fall was significantly slow in delta positive cases (Table-2).

Table-2: HBeAg value from baseline to 36 months in HBV Positive and HBV with Delta Positive cases

	HBV Positive		HBV with Delta Positive		
	HBeAg +ve (n=69)		HBeAg +ve (n=55)		
HBeAg	No.	Mean±SD	No.	Mean±SD	***p*-Value**
Baseline	40	289±189	45	142±160	0.001
6 months	10	166±179	10	84±126	0.259
12 months	23	204±174	17	44±61	0.001
18 months	15	156±156	13	42±78	0.026
24 months	5	38±51	10	71±123	0.581
36 months	3	5±4	4	55±95	0.416

At 36 months, 26 cases (37.7%) cases seroconverted and were labelled as responders in Group 1 and 9 cases (16.4%) in Group 2. Nine cases in each group remained non responders while 2 in each group relapsed after stopping therapy (Table-3).

Table-3: Responder in HBV Positive and HBV with Delta Positive cases

	HBV Positive	HBV with Delta Positive	
	HBeAg +ve (n=69)	HBeAg +ve (n=55)	
Responder	26 (37.7%)	9 (16.4%)	0.008
Non responder	9 (13.0%)	9 (16.4%)	0.602
Relapse	1 (1.4%)	2 (3.6%)	-
On Treatment	32 (46.4%)	26 (47.3%)	0.920
Stop	-	1 (1.8%)	-
Expire	1 (1.4%)	-	-
NFU	-	8 (14.5%)	-

DISCUSSION

The present study showed that wild type of HBV infected cases who are co infected with delta virus have a 16% chance of seroconversion and thus becoming disease free, which is against the general feeling that once infected with delta virus there is not much that can be done to these cases. The study also showed that those who were not co infected with delta virus responded quicker and seroconverted earlier than those who were co infected with delta virus infection. Delta infection was apparently a hindrance in recovery.

For checking the progress in response, the HBeAg values can be serially followed every 6 months; and a steady fall is seen in these values over years, finally becoming negative and then seroconversion occurs. In delta infected cases majority show a steady drop in HBeAg values till about 12 months after which these values tend to lag behind and do not become negative despite continuing treatment for 36 months. The treating physician has problem in deciding here whether to stop therapy as theses cases would not seroconvert or continue treatment for more years, then there is fear of flare and reactivation in those who have not seroconverted and are stopped treatment (HDV RNA in delta positive cases, available in Pakistan since two years, can also be used for follow-up of response).

About 50% cases in both the groups were still on therapy and had not seroconverted despite completing 24 months and there is a chance that some would clear the virus in due course.

Lamivudine therapy was a breakthrough in the management of these selected groups of HBV positive cases and encouraging results were seen world over with therapy.[5,6] Later studies showed a high chances of YMDD mutation while on lamivudine therapy and this frequency increased with the prolongation of therapy.[7–10] Adefovir[11] had similar issues and now it is recommended that Entecavir[12] should be used as it has the lowest mutation rates and higher seroconversion rates. In Pakistan health is not ensured and treatment cost is mostly borne by the patient. The lower

socioeconomic group suffers the most as they can not afford expensive treatment and too for a long time. There is high chance of stopping treatment due to non affordability or transient improvement in the disease. One tablet of lamivudine costs around $ 1.5/day but even this is expensive for majority of our cases.

The fear of YMDD was also studied by us earlier[13] and was reported to be around 6% at 36 months which was much lower than 25–32% reported in the west. This finding is very encouraging as we can now give prolonged treatment with lamivudine without much fear of mutation. Adefovir costs around $ 3 and entecavir $ 3.5 per tablet which are much beyond the reach of our cases. It is suggested that these drugs should be reserved for cases that develop drug resistance. Interferon 5,000,000 units daily for 4 months are very expensive with manifold side effects posing a serious issue of compliance.[14,15] Interferon response is dependent on HBV DNA levels and response is better in individuals who have low levels of HBV DNA while nucleoside analogues have an equally good response in both low and high HBV DNA levels.

CONCLUSION

Wild type of HBV/HDV co-infected cases have a 16% chance of seroconversion which negates the concept that once infected with delta virus there is not much that can be done.

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