Original Article

Seroconversion of HBsAg in HBeAg positive and HBeAg negative patients with chronic HBV infection treated with entecavir — a case series from a tertiary care teaching hospital in Eastern India

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The prevalence of chronic HBV infection is increasing in developing countries including India. Experience of seroconversion after treatment with entecavir in patients of chronic HBV infection has been rarely reported. Our aim was to assess the efficacy of HbsAg clearance and persistent seroconversion both in HbeAg positive and HbeAg negative patient after entecavir therapy. This prospective study was conducted in tertiary care hospital in Eastern India from March 2011 to March 2017 on OPD basis. Five HbeAg positive and three HBeAg negative patients (7 males, 1 female, mean age 55.3±14.6 years) amongst 105 patients were eligible for treatment with entecavir 0.5 mg/day. Those patients (n =8) who became HBsAg negative during follow up were included in this case series. Seum alanine transaminase (ALT) levels, HBsAg, Anti-HBsAg, HBeAg and HBV-DNA levels were used to monitor the efficacy of therapy. The main evalution parameters were: time to HBV-DNA clearance, time to HBeAg clearance, time to HBsAg clearance and time to seroconversion (HBsAg clearance followed by appearance of Anti-HBsAg). Detection of HBsAg, Anti-HBsAg, HBeAg in body fluids was performed by Chemilluminescent Microparticle Immunoassay (CMIA). HBV-DNA was measured by real time quantitative PCR. The results were analyzed with descriptive statistics, considering all patients and after stratification for the presence of HBeAg. Overall, the mean time to HBsAg clearance was 33.7±12.8 month. Seroconversion occurred in seven patients (Data of one patient not available), after a mean time of 45.1± 9.3 months. In HBeAg positive, mean time to HBsAg clearance and to seroconversion was 33.2±12.7 and 46±5.4 months, respectively. In HbeAg negative patients, mean time to HBsAg clearance and to seroconversion were 34.6±13.0 and 44±12.7 months respectively. In this case series seroconversion was maintained and was obserbed both in HBeAg positive patients and in HBeAg negative patients. Therefore, it is our observation that suggests treatment with entecavir could be associated to HBsAg seroconversion in a certain period of time, in both HBeAg positive and HBeAg negative chronically HBV infected patients who seldom experience spontaneous seroconversion.

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Chronic hepatitis B virus infecton is worldwide phenomenon affecting more than 350 million people[1,5]. These individuals have an increased risk of potentially life threatening hepatic sequelae, including cirrhosis and hepatocellular carcinoma. Seum alanine transaminase (ALT) levels, HBeAg, HBsAg and HBV-DNA levels are currently used to monitor the efficacy in clinical practice. The detection of these antigens in body fluids has emerged as a powerful predictive tool to evaluate the efficacy of antiviral therapy[2]. After acute HBV infection, HBeAg can be detected up to 12 weeks after exposure to the virus, the clearance of this antigen is generally associated with reduction in viraemia and in ALT flares. This is followed by the appearance of anti-HBeAg ie, HBeAb. The persistence of HBsAg for more than 6 months in body fluids, together with persistent or intermittent elevation of ALT levels and signs of chronic inflammation on liver biopsy, defines the evolution from acute hepatitis B to chronic hepatitis B status[3,4]. The administration of an antiviral

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therapy plays a central role in the reduction of these complications. HBsAg clearance is now considered to be the primary goal of the antiviral treatment. This event may be followed by the seroconversion ie, the appearance of anti-HBsAg antibodies ie, HBsAb. Seroconversion indicates the recovery from the chronic HBV infection and is associated with a life-long immunity against HBV. While the spontaneous seroconversion is sometimes reported in HBeAg positive patients, this event is much less frequent in HBeAg negative subjects. This finding may reflect the lower rates of sustained virological response in HBeAg negative subjects undergoing treatment with anti-viral drugs and possibly, some difference in immune features between the HBeAg negative and the HBeAg positive patients[4]. Entecavir is a novel deoxyguanosine analogue, approved in US and Europe for the treatment of HBV infected patients[1]. One Indian large series did not demonstrate HBsAg clearance in 5 year entecavir treatment[13]. We report here a case series of patients with chronic HBV infection experiencing the seroconversion after a treatment with entecavir.

Materials and Methods

The observation started in March 2011. They were treated in RG Kar medical College OPD basis. In total 105 patients of chronic HBV infection, those were eligible for anti-viral therapy was kept on entecavir. Those patients (n =8) who became HBsAg negative during follow up were included in this case series. Baseline clinical characteristics for the patients included in this analysis are summarized in Table 1. Most patients (n =7) were male; mean age of all patients was 55.3±14.6 years (range 26-74). Mean time from HBV diagnosis was 14.37 months (range 9-24 months). Detection of HBeAg, HbsAg, Anti-HBsAg in body fluids was performed by Chemilluminescent Microparticle Immunoassay (CMIA). HBV-DNA was measured by real time quantitative PCR. In total, HBeAg was identified in five patients. All patients were naive at the time of initiation of therapy. All patients started therapy with entecavir (0.5 mg/day). The main evalution parameters were: time to HBV-DNA clearance, time to HBeAg clearance, time to HBsAg clearance and time to seroconversion. The results of both tests were analyzed with descriptive statistics, considering all patients and after stratification for the presence of HBeAg. Adverse events were also registered, and their correlation with the study was evaluated.

Table 1 — *Baseline characteristics of the eight patients*

Patients	Sex	Age	HBeAg Status	Time from diagnosis	HBV-DNA cp/ml	ALT* IU/ml	Entecavir mg/day
1	M	42	negative	12 months	104	35-72	0.5
2	M	74	positive	15 months	104	40-58	0.5
3	M	26	positive	18 months	108	55-72	0.5
4	M	64	positive	12 months	105	34-108	0.5
5	F	35	negative	24 months	104	48-60	0.5
6	M	57	negative	13 months	106	60-211	0.5
7	M	50	positive	9 months	105	55-65	0.5
8	M	55	positive	12 months	105	80-100	0.5

*ALT: alanine transaminase ; cp : copies ; HBeAg : hepatitis B e antigen

Results

HBsAg clearance was observed in all patients after the initiation of entecavir treatment in this case series. Seroconversion was observed in all patients except one (Data not available). Overall, mean time to HBV-DNA clearance was 8.6±2.9 months, mean time to HBeAg clearance was 23.8±7.6 months; the mean time to HBsAg clearance was 33.7±12.8 months (range – 12 to 50 months). Seroconversion occurred after a mean time of 45.1±9.3 months from the initiation of entecavir therapy. The stratification of the results according to the prevalence of HBeAg reveled that in HBeAg negative patients, mean time to HBsAg clearance was 34.6±13.0 months and mean time to seroconversion was 44±12.7 months. In HBeAg positive patients these times were longer with a mean time HBsAg clearance of 33.2±12.7 months and mean time to seroconversion of 46±5.4 months. Entecavir was well tolerated by all patinnts during the entire treatment period. Two patients had asthenia and myalgia and one patient observed flu like symptoms. All these symptoms resolved spontaneously. No treatment discontinuation required (Tables 2&3).

Discussion

The clearance of HBsAg and detection of antibodies directed against HBsAg, ie, seroconversion, are now considered to be the most desirable clinical endpoints in patients with chronic HBV infection, but are rarely observed[3,12]. The case series described here documents eight cases of HBV infected patients experiencing HBsAg

Table 2 — *Time to HBV- DNA clearance and HBeAg clearance*

	Patients							
	1	2	3	4	5	6	7	8
Time to HBV-DNA loss (months)*	6	4	12	12	8	9	12	12
Time to HBeAg loss (months)*	X	23	36	24	X	X	24	NA

*From initiation of entecavir therapy

Table 3 — *Time to HBsAg clearance and seroconversion (detection of HBsAb in body fluids)*

	Patients							
	1	2	3	4	5	6	7	8
Time to HBsAg loss (months)*	39	36	50	28	17	48	40	9
Time to seroconversion (months)*	52	42	54	40	26	54	48	12

*From initiation of entecavir treatment, NA: Data not available

clerence and seroconversion in association with entecavir therapy in different real life scenario. Although the number of patients included in this analysisis limited, both HBeAg positive and HBeAg negative subjects were observed. Of note, while spontaneous HBsAg seroconversion sometimes occurs in HBeAg positive patients, HBeAg negative patients seldom experience a spontaneous seroconversion[14]. To note that seroconversion was observed both in HBeAg positive and in HBeAg negative patients treated with entecavir alone, therefore suggesting potential effect of entecavir in determining seroconversion, expecially in HBeAg negative patients, in which the spontaneous seroconversion is a very rare event. Seroconversion occurred in all patinnts within 3-5 years. Entecavir treatment was well tolerated, with only minor adverse events potentially related to this drug. These observations must be considered with particular caution. In fact, the observational nature of this analysis does not allow inference of any definite any direct cause/ effect relationship. Moreover , this case series presents several confounding factors that time from diagnosis differing from one patient to another, a large majority of males (only one female) and different ages. However, these limitations may reflect at least in part, the clinical-practice setting considered in this case series.

The observations reported here further strengthen the efficacy of entecavir in the treatment of chronic HBV infection in both HBeAg positive and negative patients. Entecavir is a potent deoxyguanine nucleoside analogue, selectively inhibiting HBV replication, and is characterized by high genetic barrier[6]. Entecavir is currently the most potent anti HBV treatment suppressing viral replication in almost 90% of treatment –naive patients after 96 weeks of therapy[7]. Other studies have demonstrated significantly better rates of histologic, virologic and biochemical improvement when compared with lamivudine in both HBeAg positive and negative patients[8,9]. The efficacy of entecavir is sustained, thus reducing the rate of long-term liver complication[10,11]. HBsAg clearance is a rare event in other studies[13]. Long-term sustained viral suppression may have influence on host immunity.

Conclusion

Despite the limitations discussed, this case series could provide preliminary evidence that a treatment with entecavir may be associated with HBsAg seroconversion, thus indicating a clinical recovery and a long-time immunity from the HBV infection, in a certain period of time. This event was observed in both HbeAg positive and HBeAg negative patients, who seldom experience spontaneous seroconversion. Further clinical trials are warranted to confirm these preliminary observations.

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