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Need of Dual Antiviral Treatment in Chronic Hepatitis B

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1. Abstract

1.1. Introduction: Approximately one third of the world's population has serological evidence of past or present infection with the hepatitis B virus (HBV). An estimated 350-400 million people are surface HBV antigen (HBsAg) carriers**.** India has 40 million HBV carriers i.e. 10–15% share of total pool of HBV carriers of the world. In India.

1.2. Aim: To determine the need of treatment with dual antiviral Tenofovir and Entecavir in Chronic Hepatitis B patients.

1.3. Materials & Methods: This retrospective study was done at Post Graduate Institute of Medical Sciences,Rohtak over a period of nearly eleven years i.e. 01.09.2010 to 15.06.2021, on all HbsAg positive patients who reported for consultation and treatment at Medical Gastroenterology department. In our study total 5300 patients were identified but 30 patients refused to get enrolled in the study, hence total 5270 patients were finally enrolled and their records were collected, regarding their detailed epidemiological profile,clinical profile, investigations and treatment.

1.4. Conclusion: As more and more cases are detected with time, then significant proportion of patients will be on antiviral treatment and virological breakthrough and failure will pose cumbersome challenge. Hence, there is strong need of early detection of cases, followed by regular antiviral where ever indicated with constant vigil for drug resistance.

2. Introduction

An estimated 350-400 million people are surface HBV antigen (HBsAg) carriers [1, 2]. Around one million persons die of HBV-related causes annually.The HBV prevalence rates worldwide varies i.e. from 0.1% up to 20%, probably related to differences in age at infection, which relates with the risk of chronicity. It is 90% for an infection acquired perinatally, and is as low as 5% for adults [3, 4]. In all the cases of chronic hepatitis B (HBV) infection, 15–40% will develop cirrhosis, liver failure and hepatocellular carcinoma [5-8]. There is declining trend in new cases has decreased in most developed countries, most likely due to the implementation of vaccination strategies [9]. However, exact data is difficult to generate as many cases remain undetected due to the asymptomatic nature of many infections [10]. India harbours around 40 million HBV carriers, thus accounting for 10–15% share of total pool of HBV carriers of the world. Every year over 100,000 Indians die due to illnesses related to HBV infection [11, 12] and HBsAg positivity ranges between 2–4.7% [13, 14]. The goal of chronic hepatitis B (CHB) treatment is to achieve early and sustained suppression of hepatitis B virus replication, which prevents progression of liver disease to cirrhosis and development of hepatocellular carcinoma [15, 16]. The availability of nucleos(t)ide analogues such as tenofovir disoproxil fumarate (TDF) and entecavir (ETV), which are more potent than other antiviral drugs, has significantly improved treatment of CHB [17-19]. However, in past, less potent antiviral drugs (i.e., lamivudine (LAM), telbivudine (LdT), and adefovir (ADV) were used as first-line therapy and then with sequential monotherapies, which contributed to the development of multidrug resistance (MDR**)** [20-21]**.** The drug-resistant viral strains results in increased viral loads and serum aminotransferase levels and subsequent progression of liver disease [22-24].In the absence of appropriate rescue treatment therapy based on cross-resistance profiles, patients are at significant risk of hepatic decompensation [25]. The antiviral treatment history may impair the antiviral efficacy of rescue therapy to induce viral suppression; therefore, the choice of optimal treatment in patients with MDR HBV strains is critical to avoid

subsequent treatment failure. To date,clinical data on the efficacy of the rescue therapies in patients infected with MDR HBV strains are limited,thus, recent guidelines, which recommend rescue therapeutic regimens in these patients, lack solid clinical evidences [26-28]. Combination therapy with a nucleoside and a nucleotide is recommended by the European Association for the Study of the Liver clinical practice guideline (Table 1). A European study showed that therapy with ETV plus TDF combination is efficient and safe in patients with viral resistance patterns or with only partial antiviral responses to prior antiviral therapies. However, only 21 of 57 patients included in that study were determined to be infected with MDR HBV strains [26].

Table 1: Showing Distribution of Total Chronic Hepatitis B Patients

Total Chronic Hepatitis B Patients	Chronic Hepatitis B Patients Finally Enrolled	Chronic Hepatitis B Patients Requiring Monotherapy	Chronic Hepatitis B Patients Requiring Dual Antiviral
5300	5270	933	3

3. Material and Methods

This retrospective study was done at Post Graduate Institute of Medical Sciences,Rohtak over a period of nearly eleven years i.e. 01.09.2010 to 15.06.2021, on all HbsAg positive patients who reported for consultation and treatment at Medical Gastroenterology department. In our study total 5300 patients were identified but 30 patients refused to get enrolled in the study, hence total 5270 patients were finally enrolled and their records were collected, regarding their detailed epidemiological profile,clinical profile, investigations and treatment. Out of these 5270 patients, 933 (17.70%) needed antiviral treatment and rest 4337 patients were found to be inactive carrier. Out of these 933 patients, only 3 patients (0.32%) required dual treatment in view of virological and biochemical breakthrogh. The virological breakthrough was defined as increase in atleast 1 log of HBV DNA from baseline even after on regular antiviral for three months and biochemical breakthrough was defined as atleat two fold increase in transaminases from baseline (Table 2).

Table 2: Showing Epidemiological Parameters of Patients on Dual Antiviral Treatment

Total Patients	Male	Female	Rural Background	Urban Background	Married	History of Past Surgery
3	3	0	3	0	3	1
Percentage	100%	0%	100%	0%	100%	33.33%

4. Observations

In our study total 5300 patients were identified but 30 patients refused to get enrolled in the study, hence total 5270 patients were finally enrolled. The age distribution was from 1-100 yrs of age and maximum number of patients were between 20-50 yrs of age group (68 %) with lesser representation from extremes of ages. When sex distribution was analyzed then strikingly 3636 patients (69%) were males and only 1634 patients (21%) were females. On analysis of socio-economic background, 3741 patients (71%) were from rural background with poor socio-economic status and rest 1529 patients (29%) belonged to urban population with proper standard of living. In our study, 41% 2161) patients gave history of Parenteral injections, dental or any other surgical interventions & tattooing. Around 168 patients (3.18%) were detected during blood donation and out of total pool of 5270 patients. On analysis of clinical stages of diseases, out of total 5270, maximum number of hepatitis B patients were in inactive carrier state i.e. 4337 patients (82.30%) and did not require any treatment. In total 933 patients (17.70%) of chronic hepatitis B were found to be in active phase and were started on treatment. Out of these total 933 patients, 850 patients (91.10%) were on treatment with Tenofovir and 83 patients were on Entecavir (8.90%) (Table 3). In total treatment group of 933 patients on antiviral treatment, only 3 patients (0.32%) required dual antiviral treatment. All three were males and belonged to urban background (100%) with age group of 38 yrs, 50 yrs and 65 yrs respectively. Out of these 3, 2 patients (66.66%) had past history of surgery and tattoing. All three had incidental detection of hepatitis B, One patient was detected at time of blood donation and rest two during routine check up. None of these three patients had HCV or HIV co-infection. All three patients were hepatitis B e- antigen (Hbe Ag) highly positive with high HBV DNA viral loads i.e. 10^{8-11} I.U. Out of these 3 patients, two were cirrhotic and one had grade 2 fibrosis, hence had higher AST level than AST in two cirrhotic patients wheras in third patient ALT was predominant over AST. The fibroscan score in these three patients was 10.6 KPA, 14.9 KPA and 57.9 respectively. Out of the two cirrhotic patients, one had grade 2 and other grade 1esophageal varices on upper gastrointestinal endoscopy but none had ascites or space occupying leison on ultrasonogram abdomen. All these three patients were fully compliant and after mean of one year became HbeAg negative and viral load dropped significantly to 10^{3-4} I.U. At this point of time, all three are healthy and performing thier normal home and occupation services (Table 4).

Table 3: Showing Age Distribution Of Patients on Dual Antiviral Treatment

Total Patients	0-10 yrs	10-20 yrs	20-30 yrs	30-40 yrs	40-50 yrs	50-60 yrs
3	0	0	0	1	1	1
Percentage	0%	0%	0%	33.33%	33.33%	33.33%

Table 4: Showing Viral Parameters,Compliance and Use of Alternative Medications By Patients

Total Patients	HbeAg Positivity	High HBV DNA Viral Load	AST >ALT	Alternative Medication Used	Compliance
3	3 (>1000)	3 (10^{8-11} I.U)	2	1	3
Percentage	100%	100%	66.66%	33.33%	100%

5. Discussion

In our small study group of three patients who required dual treatment with antiviral, the age distribution varied between 30-60 yrs of age (Table 5). All three patients were male and belonged to rural background with lower socioeconomic status and it corresponds with their representation in total pool of hepatitis B patients. Hence no inference can be made that patients with above features are predisposed to require dual antiviral treatment. One patient each gave history of past surgery and use of alternative medications for treatment of hepatitis B infection. Out of two cirrhotic patient, one each had grade 1 and grade 2 esophageal varices but none had ascites. The HBV infection is most commonly seen in adult patients in the third or fourth decade of life and commonly in males. It suggests close relationship of acquisition of infection in the adults [29, 30] and it corrobates with our study. In about two-thirds of the disease burden in India, it is represented by inactive/immunotolerant phase thus not requiring any treatment [31, 32]. Our total study group of 5270 patients also confirms the same findings, as majority were in inactive carrier state, thus not requiring any treatment. Only 17.70% of chronic hepatitis B were found to be in active phase or cirrhotics and were started on treatment. The more number of cirrhotic patients in older age is due to the fact that it takes prolonged period of years together for developing cirrhosis. In total pool of 933 patients, 850 patients were taking tenofovir and 83 patients were on Entecavir. The majority of patients who were put on antiviral treatment responded to treatment, were fully compliant and had no significant side effects. Only three patients, two on Tenofovir and one on Entecavir developed virological breakthrough as evidenced by increase in HBV DNA by two log despite being on regular treatment. These patients had biochemical breakthrough as evidenced by two fold increase of transaminases and were on treatment for last 6 months-12 months with mean duration of 8 months. All were HbeAg positive (>1000) with high baseline HBV DNA viral load (10^{8-11} I.U). Once these patients were put on dual antiviral treatment i.e. Tenofovir was added to Entecavir or vice-versa, within mean of six months, all of them responded as evidenced by virological and biochemical remission. They had no side effects with combination therapy and repeated biochemical tests especially renal function tests remained normal. The reasons for good compliance rate are easily available free availability of complete treatment including all tests & drugs on daily basis under National Viral Hepatitis Control Program (NVHCP), good connectivity with patients with help of telephonic helpine. The good response and nil side effects with dual therapy in our small study group is in aggrement with larger study of 93 patients in which also Tenofovir and Entecavir was used in resistant patients [26].

Table 5: Showing Distribution of Co-infection in Patients on Dual Antiviral Treatment

Total Patients on Dual Antiviral	Patients with HBV Mono infection	Patients with HBV &HCV/HIV Co-infection	Patients with HBV,HCV &HIV Triple Co-infection
3	3	0	0
Percentage	100%%	0%	0%

6. Conclusion

Hepatitis B is a major health problem in India affecting mainly young males with rural background. Majority of Chronic hepatitis B patients are in inactive stage, thus not requiring treatment. As more and more cases are detected with time, then significant proportion of patients will be on antiviral treatment and virological breakthrough and failure will pose cumbersome challenge. Hence, there is strong need of early detection of cases, followed by regular antiviral where ever indicated with constant vigil for drug resistance. This will substantially decrease the development of long term complications like cirrhosis and hepatocellular carcinoma

7. Limitation of the Study

The limitation of study is that data pertains to smaller study group and large scale researches are required for futher insights in this field.

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